BASHAR SAAD
OMAR SAID

GRECO-ARAB AND ISLAMIC HERBAL MEDICINE

Traditional System, Ethics, Safety, Efficacy, and Regulatory Issues




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By

Bashar Saad, PhD
Professor of Cell Biology and Immunology, Arab American University, Jenin, Palestine, and Qasemi Research Center, Al-Qasemi Academic College, Israel

Omar Said, PhD
Pharmacologist, Senior researcher of Arab Herbal Medicine, Antaki Center for Herbal Medicine Ltd, Kufur Kanna and the Galilee Society R&D Center, Israel

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FOREWORD

There was a huge enlightenment in the Arab world at a time when Europe was in the grip of the Dark Ages, stifled by Church authority. A major part of this explosion of intellectual freedom was the creation of an entirely new coherent medical system, based on the medicine of the Greeks, the Egyptians, and even of India, that developed into a rational, experimental, and thorough corpus with its theories and treatment protocols, pharmacies, hospitals, libraries, and thousands of new medicines and combinations used for the first time along with differential diagnosis. It became a foundation stone of modern medicine and also of herbal medicine in the West. And it still exists. Arabic medicine today stands alongside Ayurvedic and Chinese medicine as one of the great traditional medical systems of the world and is popularly used in all Muslim countries from Pakistan to Morocco. However, it is relatively unknown and unappreciated as a system in its own right, and today, at a time when natural medicine is a primary source of new therapies and remedies, there is still a great deal to be learnt from it.

This book sets out to reveal the potential of Arabic medicine and especially medicinal plants as a living and vital medical resource today. In this it is quite unique, especially because of its coverage of research on the herbs, and much of it was carried out in the authors' own labs. As far as I am aware, no other professional-level book covers the pharmacology and science of so many important herbs that are widely used in Arabic countries but are still relatively unknown in the West. Take, for example, *Nigella* (black seed). It is a central herb in Arabic medicine used as a powerful anti-inflammatory and antiseptic. The authors have researched this herb and there are also hundreds of papers, including clinical studies, published on it in the world scientific literature, yet the herb is still unknown and unused in the West except as a spice. This book might well raise its profile worldwide. There has been an assumption in the past that all the herbs of Arabic medicine are already known and used in modern professional herbalism and the health industry. This is not so [1], and this book can be very helpful in introducing a host of novel plants, together with research on them.

Professor Bashar Saad and Dr. Omar Said have written what may well become a classic text on Arabic medicine, not only because of its pharmacological and scientific material, but also because of its interdisciplinary nature. It is a fascinating exploration of the richness of the past knowledge, combined with ethnopharmacology of Arabic medicine today, safety and pharmacology of Arabic medicinal plants, botany, clinical aspects, Arabic medical principles, and so on. The authors are uniquely qualified to write this book, because they themselves embody the interdisciplinary wisdom

needed for it. Indeed, they would stand alongside some of the greats of ancient Arabic medicine, who transcended boundaries of subject and discipline. Many times I have walked with the authors over the Galilee hills and listened as they picked out a small hidden herb, identified it, described its Latin, Arabic, English, Hebrew, and ancient names, described its uses and the debates surrounding it in the ancient literature, told me what is in it chemically, described how it performs in the lab and how it should be formulated into a finished remedy, and told stories of, for example, of how the Bedouin of the Negev desert or the Druze of Syria might use it today. The authors are accomplished scientists in the fields of pharmacology, cell biology, and immunology and bring this unique and original aspect of modern science to the herbal wisdom. Besides, the authors are involved in the Galilee Society's botanical garden of medicinal plants, the largest garden devoted to medicinal plants in the Middle East. Thousands of children go there every year and are taught about the traditional medicine of the region. And it should also be mentioned that working and researching on traditional Arabic medicine in Israel and Palestine, regions of conflict, has not been easy.

Today, it is acknowledged that much of modern drug discovery depends on natural product concepts. The first steps are usually the work by ethnopharmacologists in the field and pharmacologists in the lab. This book breaks new ground in opening up a forgotten resource for both drug discovery and new natural product medicines.

STEPHEN FULDER

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PREFACE

At the beginning of the twenty-first century and despite the great progress in modern medicine, traditional Arab–Islamic medicine continues to be practiced within the Mediterranean as well as most Arab and Islamic countries. A very important factor that has enhanced the present popularity and widespread use of Arab herbal-based medicines is the belief that they are prepared according to the principles of Greco-Arab and Islamic medicine, which was developed during the Golden Age of Arab–Islamic civilization. This civilization spanned from the seventh to the fifteenth century and extended from Spain to Central Asia and India. It became a wellspring of brilliant medical developments and innovations, as well as of great achievements in astronomy, mathematics, chemistry, philosophy, and arts. Arab and Muslim scientists significantly contributed to the development of modern Western medicine, accomplishing far more than mere translation. A closer look at their activity during the medieval period shows that they translated classical medical texts not only from Greece, but also from Persia, India, and China. From this, Arab and Muslim scientists were able to synthesize and develop a rich and universal medical system based on scientific methods and experimentation. The works of Arab and Muslim scholars gained widespread use and were used in European medical schools. For instance, the Arab and Muslim physicians Al Tabbari, Rhazes, Al-Zahrawi (Albucasis), Al-Biruni, Avicenna, Ibn al-Haitham, Ibn al Nafees, Ibn Khaldun, and Ibn Zuhr (Avenzoar) are regarded as among the great medical authorities of the ancient world and the medieval world, physicians whose textbooks were used in European universities up to the sixteenth century. They were among the first to make accurate diagnoses of plague, diphtheria, diabetes, gout, cancer, leprosy, rabies, and epilepsy. Avicenna's and Rhazes's works on infectious diseases led to the introduction of quarantine as a means of limiting the spread of these diseases. Arab physicians laid down the principles of clinical investigation and drug trials, as well as animal tests. They mastered operations for hernia and cataracts, filled teeth with gold leaf, and prescribed spectacles for defective eyesight. The physicians and scientists of the Islamic Golden Age, who were of diverse religious and ethnic backgrounds, passed on rules of health, diet, and hygiene that are still largely valid.

The high degree of development achieved in Greco-Arab and Islamic medicine is observable in a statement of Avicenna (980–1037), who defined medicine in his *Canon of Medicine* as "the science from which we learn the states of the human body with respect to what is healthy and what is not; in order to preserve good health when it exists and restore it when it is lacking." He further stated that "we have to understand

that the best and most effective remedy for the treatment of patients should be through the improvement of the power of the human body in order to increase its immune system, which is based on the beauty of the surroundings and letting him listen to the best music and allowing his best friends to be with him." Another statement concerning therapeutic methods was made by Rhazes (846–930): "if the physician is able to treat with foodstuffs, not medication, then he has succeeded. If, however, he must use medications, then it should be simple remedies and not compound ones." Arab–Islamic medicine influenced Western medical circles to such an extent that it was included in the curriculum of European medical schools for many centuries. It became a foundation stone of modern medicine and also of herbal medicine in the West. And it still exists. Arab-Islamic medicine today stands as one of the great traditional medical systems of the world and is popularly used in all Arab and Islamic countries from Pakistan to Morocco.

The Eastern region of the Mediterranean is covered with at least 3600 plant species of which 700–800 are noted in medieval medical books for their use as medicinal herbs. Recent ethnopharmacological studies have demonstrated that more than 450 medicinal plants have continued to be employed in the treatment and prevention of human diseases within the Mediterranean as well as most Islamic countries. Some of these plant species have been investigated and their bioactive ingredients extracted to treat various human diseases.

This book is the first academic book in the field of Arab herbal medicine that explores and introduces aspects of Arab herbal medicine using original ethnopharmacological surveys conducted by our group in the Mediterranean area. This book includes 19 chapters, embracing particularly historical aspects and present uses of traditional Arab–Islamic herbal medicine. Chapters 1–5 focus on historical background, medical innovations introduced by Arab physicians, common roots of Arab medicine and Western medicine, and methodology of drug discovery and therapy in Arabic and Islamic medicine. Chapters 6–10 present a comprehensive review of the methodology of drug discovery, method of therapy, and commonly used herbal medicines in the Arab–Islamic world and their tremendous potential in modern drug discovery. Chapters 11–14 combine overviews of state-of-the-art *in vitro* and *in vivo* techniques, as well as clinical trials of traditional herbal medicine. Chapters 15 and 16 cover medical ethics in Arabic and Islamic medicine, uses of medicinal plants, and methods of extracting their active ingredients. Chapter 17 examines the use of food therapy in Arab–Islamic medicine. Chapters 18 and 19 focus on demographic and regulatory issues, as well as on drug development from herbal sources.

For convenience, all dates given in book are those of the Christian calendar, unless otherwise specified. The designation AD is used only when there is a need to distinguish a date from an earlier BC date. General references to a century rather than to a specific year refer to centuries of the Christian era.

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CHAPTER 1

An Overview of Greco-Arab and Islamic Herbal Medicine

1.1 INTRODUCTION

Natural products, such as plant, fungal, and bee products, as well as minerals, shells, and certain animal products, represent the oldest form of medical treatment. Currently, many of the commonly used drugs are of herbal origin and about 25% of the prescription drugs contain at least one herbal-derived active ingredient or synthetic compound, which mimics a plant-derived compound. There are over 80,000 plants that have medicinal uses throughout the world and usually a specific part of the plant is used for medical preparations such as tablets, infusions, extracts, tinctures, ointments, or creams. The pharmacological action of these medicines is often described in very general terms, such as carminative (an agent that prevents formation of gas in the gastrointestinal tract or facilitates the expulsion of said gas), laxative (an agent that induces bowel movements or loosens the stools), demulcent (an agent that forms a soothing film over a mucous membrane, relieving minor pain and inflammation of the membrane), antitussive (cough suppressants), or antiseptic (antimicrobial substances that are applied to living tissue/skin to reduce the possibility of infection). Unlike synthetic drugs, which usually consist of a single and often synthetic chemical, herbal-based medicines contain multiple constituents.

In the history of science, Arabic medicine, Islamic medicine, Arab–Islamic medicine, Greco-Arab medicine, or Greco-Arab and Islamic medicine are terms that refer to medicine developed during the Golden Age of Arab–Islamic civilization (seventh to fifteenth century), which extended from Spain to Central Asia and India (Figure 1.1). This civilization became the center of brilliant medical developments and innovations, as well as great achievements in astronomy, mathematics, chemistry, philosophy, and artistic culture. Arab and Muslim scholars translated and integrated scientific knowledge of other civilizations into their own. As will be seen in the following chapters, however, Arab–Islamic medicine was not simply a continuation of Greek ideas but a venue for innovation and change. These included the discovery of

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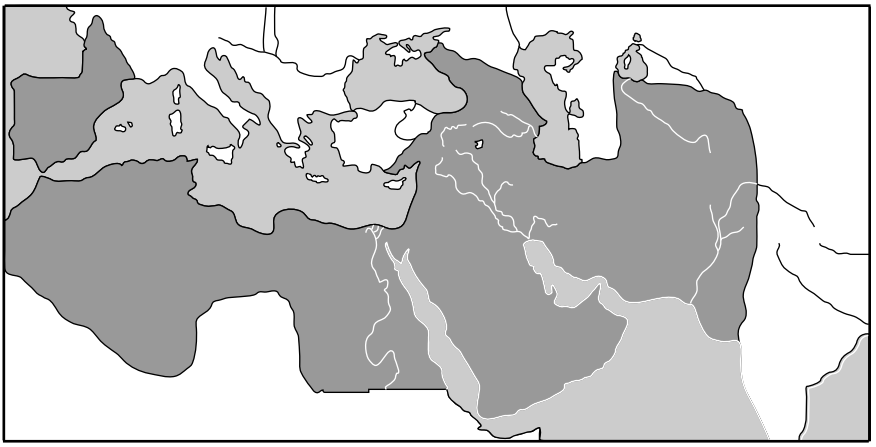

FIGURE 1.1 The medieval Arab–Islamic Empire at its largest extension.

the immune system, the introduction of microbiological science, and the separation of pharmacological science from medicine. Medicine in general is considered to be one of the most illustrious and best known achievements of Arab–Islamic civilization, which influenced Western medical circles to such an extent that it was included in the curriculum of medical schools up to sixteenth century.

Despite great progress in allopathic medicine, Arab–Islamic medicine has continued to be practiced within the Mediterranean as well as most Arab and Islamic countries (Table 10.2), where cultural beliefs and religion often lead to self-care or home remedies in rural areas and consultation with traditional healers. In addition, Arab–Islamic therapies are most often utilized by people who have faith in spiritual healers and herbalists. These people are the first to be consulted for problems such as infertility, impotence, diabetes, obesity, epilepsy, psychosomatic troubles, and many other diseases (see Chapter 10). The popularity of herbal preparations based on Greco-Arab and Islamic medicines has increased worldwide in the past four decades, probably because of the sustainability of this medicine over the years. Other factors include the notion that herbal-based drugs are safe (see Chapter 13), that they are relatively inexpensive, the restricted access to physicians imposed by managed care, and the adverse effects of synthetic drugs.

Chapter 10 provides an overview of Greco-Arab and Islamic medicine practiced in countries other than those in the Middle East, such as Iran, India, Turkey, Maghreb region, and Pakistan [1–10]. India is the only country where Greco-Arab medicine has an official status. It was introduced by Arabs and soon took firm roots in the subcontinent. Greco-Arab and Islamic medicine as practiced in Muslim communities of the Indo-Pakistan subcontinent is known as Unani-Tibb. "Tibb" is an Arabic word meaning "medicine," while "Unani" is thought to be derived from "Ionan" (meaning Greek), acknowledging the influence of early Greek medicine on Greco-Arab and Islamic medicine. A Unani physician is known as a *hakim*. However, the Unani

medicine currently practiced in the Indo-Pakistan subcontinent is vastly different from its Greco-Arab roots. It benefited from the native medical system or folk medicine in practice at the time in various parts of central and southern Asia, mainly Ayurvedic medicine and Chinese medicine.

Herbal medicines are classified in many European countries as drugs; in the United States, they are sold as dietary supplements. Unfortunately, in the Arab–Islamic world as well as in China and India, they are mostly sold over the counter without regulation. As discussed in Chapter 11, safety assessment of herbal products has often been neglected since prolonged and apparently safe use is usually considered as evident. Nevertheless, evidence of the toxicity of such products has accumulated. This is not surprising, since herbal products are complex mixtures of secondary metabolites, many of which are potentially toxic (e.g., hepatotoxic and nephrotoxic). Therefore, the widespread use and popularity of herbal-based medicines raises concerns and fears over the professionalism of practitioners and safety, quality, and efficacy of these products. In regard to safety, biomedical journals have reported serious side effects, particularly hepatotoxicity. These matters are covered extensively in Chapters 11 and 12.

The popularity of natural product-based therapies is rapidly increasing and global sales of herbal products top $100 billion a year. In 2008, $4.8 billion were spent in the United States and a large center of complementary and alternative medicine has been established recently at the NIH (National Institute of Health). And more recently, the NIH has sponsored large clinical trials of botanicals such as St. John's Wort and Ginkgo.

In the course of the following chapters, we intend to reveal the complexities, encourage comparisons, and offer answers to questions such as the following: How did Arab–Islamic medicine reach such high levels of knowledge and practice? How did Arab–Islamic scholars lay the foundations of modern Western medicine and pharmacology? How did Arab and Muslim physicians discover and successfully treat diseases? How did Arab and Muslim scholars lay the foundation for clinical trials and animal testing? And finally we give an overview of currently used medicinal plants in the Arab world and their efficacy and safety. This book is organized around 19 major topics, reflected by the titles of these chapters: (1) An overview of Greco-Arab and Islamic herbal medicine, (2) History of Greco-Arab and Islamic medicine, (3) Herbal medicine, (4) The Arab–Islamic roots of Western medicine, (5) Contributions of Arab and Islamic scholars to modern pharmacology, (6) Natural drugs in Greco-Arab and Islamic medicine, (7) Method of therapy in Greco-Arab and Islamic medicine, (8) Commonly used herbal medicines in the Mediterranean, (9) The current state of knowledge of Arab herbal medicine, (10) Greco-Arab and Islamic medicine practiced outside the Middle East, (11) Biosafety of herbal medicine, (12) Arab medicinal plants: from traditional uses to scientific knowledge, (13) Modern *in vitro* test systems, (14) Modern *in vivo* evaluations and clinical trials, (15) Medical ethics in Arab and Islamic medicine, (16) Medicinal herbs and extracting their active ingredients, (17) Food therapy, (18) Drug development from herbal sources, and (19) Herbal remedies: use and demographic and regulatory issues. In this introductory chapter, we will give a brief overview of the main topics of this book.

1.2 THE GOLDEN AGE OF ARAB–ISLAMIC CIVILIZATION

The development of Arab–Islamic civilization started in the Arabian Peninsula, the homeland of the Arabs. The Peninsula is predominantly deserted and the tribes who inhabited this area were nomadic, that is, they traveled from one grazing land to another. The great unifying power of these nomadic Arabs was clearly the Prophet Mohammad (peace be upon him) (570–632) from the Quraysh tribe that ruled Mecca. Though Mecca was a prosperous caravan city, it was still tied to traditional social customs and was governed by the tribal societies of the desert. Each tribe worshipped its own gods in the form of objects from nature but all Arabs worshipped one object in common, the *Kaaba*, a large black stone at Mecca, which made Mecca significant as a place of worship and pilgrimage. The Prophet was able to unite the nomadic tribes and to create a strong nation, able to defeat the two powerful empires at that time, the Persian and Byzantine Empires.

The Byzantines and Persians were the first to feel the power of unified Arabs. At Yarmuk in 636, the Arabs defeated the Byzantine army (Table 1.1). Syria fell in 640. A decade later, the Arabs had conquered the entire Persian Empire. Egypt, the Maghreb (North Africa), and Spain were all conquered and under Arab rule by the 720s. Arab expansion in Europe ended after the loss of the Battle of Tours in 732. The Arabs not only conquered new lands, but also became scientific innovators through originality and productivity. They preserved the cultures and knowledge of the conquered lands, tolerated religious minorities within land they had conquered, and were careful to protect the purity of their religion, language, and law from any foreign influence.

The first problem after the death of the Prophet was who should be caliph, the spiritual and secular successor to the Prophet (PBUH). The first four caliphs were elected by a tribal council of elders and are referred to as the Orthodox Caliphs, ruling from 632 to 661. However, as the empire grew, this form of government became increasingly inadequate. In addition, tribal and clan rivalries continued. Finally, the Umayyad clan took over and established the Umayyad Dynasty (661–750). From now on, the dynastic principle of one family choosing the caliph would dominate. From the start, the Umayyads saw that they must adapt Byzantine and Persian techniques for ruling their empire. Therefore, they instituted some major changes. They moved the capital from Medina in Saudi Arabia to a much more central location, Damascus in Syria, created the first Muslim coinage, and also adapted and further developed Byzantine and Persian bureaucratic methods as well as postal communication and transmission of news. In 750, a revolt led by Abbas, a governor of Persia, overthrew the Umayyads and established the Abbasid Dynasty (750–1258). The victorious Abbasids moved their capital to Baghdad to signify a break with the Umayyads. However, the reconstituted Umayyads set up a rival Arab state and put their capital at Cordoba. Even as the Abbasids, in particular the Caliphs Harun al-Rashid (ruled from 786 to 809) and Al-Mamun (ruled from 813 to 833) and their heirs, turned Baghdad into the smartest, most creative, and most modern city of the world, the Umayyads led by Abd Al Rahman I and his heirs set out to do the same thing in Cordoba, Grenada, and the other Andalusian cities.

TABLE 1.1 Timeline of Arab Islamic Civilization

Year	Historical Event
570	The Prophet Mohammad is born in Mecca
622	The Prophet and followers emigrate to Medina. The first year of Islamic calendar
632	Death of the Prophet
632	Muslim armies consolidate their power over Arabia
634–644	Muslim forces advance through the Persian and Byzantine empires
636	Battle of Yarmuk. Byzantine emperor Heraclius is defeated by Muslim army in Syria
642	Arabs conquer Byzantine Egypt and expand into North Africa
656	Mohammad's son-in-law, Ali, succeeds to the leadership of Islam
661–750	**Umayyads rule in Damascus**
711	Tariq with a mixed force of Arabs and Berbers invades Spain
712	Muslims advance into Sind (modern-day Pakistan) and Central Asia
725	Muslims occupy Nimes in France
750–945	**Abbasids rule in Baghdad**
756–929	**Umayyad emirs rule in Spain**
762	Al-Mansur founds Baghdad
786	Haroun al-Rashid becomes caliph in Baghdad
792	The first papermaking factory in the Muslim Empire is built in Baghdad
813–823	Al-Mamun reigns in Baghdad. He founds the House of Wisdom
823	Beginning of Muslim conquest of Sicily
909–1171	**Fatimids expand in North Africa**
929–1031	**Umayyad caliphate reigns in Spain**
969	Fatimid conquer Egypt and transfer their capital to Cairo in 973
976	Al-Azhar university is founded in Cairo
1058	Seljuks take Baghdad
1090	Cordoba is sacked by Almoravids
1096	First Crusade. Christians rule in Jerusalem in 1099
1145–1232	Almohads rule in Spain
1171	Saladin overthrows the Fatimids in Egypt
1171–1250	Ayyubid Dynasty rules in Egypt and Syria
1187	Saladin returns Jerusalem to Arab–Islamic rule
1206–1406	**Mongol Empire**
1492	Christian Reconquest of Spain
1453–1922	**Ottoman Empire**
1494–1566	Suleiman I guides the Ottoman Empire to its fullest extent, ranging from Morocco to the Caspian Sea and the Persian Gulf and into Europe through the Balkans to Hungary
1922	End of the Ottoman Empire

All dates given in the table are those of the Christian calendar. Bold entries denote dynastic rule.

Under the Abbasid Caliphs, Islamic civilization entered a Golden Age. And while in Europe, learning seemed to be at its lowest point, the Arabs created a highly sophisticated civilization. The period from the seventh to roughly the end of the fifteenth century is known as the Golden Age of Arab–Islamic civilization. During this period, the vigorous desert tribesman from Arabia assimilated and interpreted the Byzantine, Persian, and Indian cultural traditions into their own. Perhaps the most important catalyst was Islam itself that encouraged study, thinking, and discussion, as well as a scientific understanding of the world. Historians of Arab science point to various statements in the Qur'an and in the body of other statements attributed to the Prophet (PBUH): "Even if you must go to China, seek knowledge." or "Acquire knowledge, because he who acquires it in the way of the Lord performs an act of piety; who speaks of it, praises the Lord; who seeks it, adores God." Another recognized trigger for the rise of Arab intellect was the acknowledged intellectual traditions of the older societies that fell under Arab and Muslim influence. Places such as Alexandria, Damascus, Tunis, Spain, the Byzantine lands, Persia, and India had been urban and intellectual centers for many centuries when the Arab armies arrived. So people who had long been trained in the ways of research, study, debate, and invention were eager to continue their work within the Arab context. Thanks to Arab and Muslim scholars, ancient Greek knowledge, acquired from their contact with Byzantine scholars, was kept alive and was eventually transferred to the West in the twelfth century and after. But not only did Arab and Muslim scholars preserve the heritage of Greek science and philosophy, they added to it by writing commentaries and glossaries, thus adding to what eventually became the Western intellectual tradition.

The Arab–Islamic Empire covered a period of roughly nine centuries, from the middle of the seventh to the end of the fifteenth century, when the Arab–Islamic world was divided into three independent empires, the Ottoman Empire in Turkey, the Safavid Empire in Persia, and the Mughal Empire in the Indo-Pakistan subcontinent. In the eighteenth and nineteenth centuries, Islamic regions fell under the sway of European imperial powers. Following World War I, the remnants of the Ottoman Empire became European protectorates [1–18].

1.3 THE DEVELOPMENT OF ARAB MEDICAL SCIENCES

The health care practices of the medieval Arab–Islamic community over a large area and nine centuries were not uniform. The everyday practices and the public health of the Arab–Islamic world were affected by many factors: fasting laws and dietary regulations during the holy month of Ramadan, hygiene and burying the dead by Muslims as well as by non-Muslims, the climatic conditions of the vast area, the living conditions of nomadic, rural, and urban communities, the amount of travel undertaken for commerce, or for pilgrimage, the maintenance of a slave class and slave trade, the injuries and diseases attendant upon army camps and battles, and the incidence of plague and endemic diseases [4–6].

As mentioned above, the Abbasids moved the Islamic capital to Baghdad by the tenth century. The city became the center of scientific knowledge and research activity

and emerged as the capital of the scientific and cultural world. In addition to Baghdad, Seville, Toledo, Granada, and other cities established themselves as centers for medical sciences, which were strongly supported and promoted by Abbasid Caliphs. The eagerness of the Arabs for learning resulted in the translation of substantial amounts of Greek, Persian, and Indian medical texts into Arabic. In parallel, Arabs established and promoted their own medical sciences in theories and practices that became highly influential in Western science and teaching. During the Arab–Islamic Golden Age, collaborative works of physicians and scientists from different nations and ethnic groups raised the dignity and caliber of the medical profession. Disease was seen by Arab and Muslim physicians as a problem that can be challenged. The Prophet (PBUH) was credited with many statements on health care problems and their treatments. For instance, "The one who sent down the disease sent down the remedy." and "For every disease, God has given a cure." He was also credited with articulating several specific medical treatments, including the use of honey, olive oil, figs, and cupping. But most importantly, whereas other societies usually feared the sick and afflicted, at best isolating them and at worst leaving them somewhere to die, the Prophet had a very compassionate and forgiving view of the sick.

As a result, health care services rose in esteem from that of a menial calling to the rank of a learned profession, which became known as Greco-Arab and Islamic medicine. This medicine had advanced from ephemeral talisman and theology to real hospital wards, mandatory examination for doctors, and the use of technical terminology. Baghdad and Cairo had hospitals that were open to both male and female patients, staffed by attendants of both sexes. These hospitals contained libraries, pharmacies, intern systems, externs, and nurses. There were mobile clinics to reach the disabled, the disadvantaged, and those in distant areas, regulations were imposed by the health authorities to maintain quality control on drugs, medical ethics was introduced, and pharmacy became separated from medicine and a licensed profession.

Baghdad and Cordoba became the main centers for Arab development of herbal medicines. Al-Zahrawi (Albucasis, tenth century) of Cordoba wrote *The Book of Simples*, an important source for European herbal medicine. The Andalusian botanist Abu al-Abbas al-Nabati introduced the use of experimental scientific methods in the thirteenth century. He also introduced empirical techniques in the testing, description, and identification of numerous *materia medica*. Al-Nabati separated unverified reports from those supported by actual tests and observations. This allowed the study of *materia medica* to evolve into the science of pharmacy. Later on, Ibn al-Baitar, who lived in Damascus, published *The Book on Drinks and Foods*, a collection of different drinks and foods. It is considered as one of the most prestigious books in the medieval pharmacopeia in which the drugs are classified in alphabetical order. Other pharmacopoeia books include that written by Abu-Rayhan Biruni in the eleventh century and Ibn Zuhr (Avenzoar) in the twelfth century. Daoud al-Antaki used different herbs for treating patients and published a book on medicinal herbs summarizing the knowledge of his predecessors. Al-Antaki in the sixteenth century described in his book 57 plants that were used as a source for simple drugs, or frequently as one ingredient in complex herbal-based preparations. He

described the plant and the way it was used by physicians. For instance, birthwort, carob, castor oil plant, common fennel, common myrtle, Persian cyclamen, saffron, serapias, sycamore fig, and Syrian bryony. Furthermore, Al-Antaki mentioned foreign plants that were brought to the area for their medicinal properties, such as cornelian cherry, purging croton, and gardenia. He also described pharmacological uses of typical agricultural crops, such as caraway, carrot, wild coriander, pear, quince, sugar cane, and walnut. The traditional and medicinal uses of many of these plants are described in Chapters 3, 8, and 17.

The development of medicine and pharmacy in the Arab–Islamic world laid the foundations for the development of modern Western medicine and pharmacy. Arabs contributed many insights of their own to the development of medicine while acknowledging the knowledge they received from other civilizations. It is important to mention that they translated classical medical texts not only from Greek, but also from Persian, Indian, and Chinese sources. This synthesis resulted in a richer and universal medical system, based on scientific rules and experimentation. Al Tabbari (838–870), Al-Razi (Rhazes, 864–930), Al-Zahrawi (Albucasis, 936–1013), Al-Biruni (973–1050), Ibn Sina (Avicenna, 980–1037), Ibn al-Haitham (960–1040), Ibn al-Nafis (1213–1288), Ibn Khaldun (1332–1395) (Figure 1.2), Ibn al-Baitar (1197–1248), and Ibn Zuhr (Avenzoar, 1091–1161) are regarded as among the great medical authorities of the medieval world and as physicians whose textbooks were used in European universities up to the sixteenth century. They made accurate diagnoses of plague, diphtheria, diabetes, gout, cancer, leprosy, rabies, and epilepsy. Avicenna's and Rhazes's works on infectious diseases led to the introduction of quarantine as a means of limiting the spread of these diseases. Other physicians laid down the principles of clinical investigation, drug trials, and animal tests, and uncovered the secret of sight. They mastered operations for hernia and cataract, filled teeth with gold leaf, and prescribed spectacles for defective eyesight. And they passed on rules of health, diet, and hygiene that are still largely valid today. Physicians of different languages and religions cooperated in building a medical organization whose outlines are still visible in current medical practices. While, as mentioned above, medieval Arab–Islamic medicine laid the foundation of modern medicine, some of the currently practiced therapies may seem irrelevant to the modern world. These include magical procedures and folkloric practices of local tradition.

The development and the recognition of the independent, academically oriented status of pharmacy as a profession charged with the preparation of safe and effective drugs started in Baghdad during Al-Mamun's caliphate (813–833). The main objectives of pharmacists were directed not only toward the translations and interpretations of accumulated data on natural product-based drugs, but increasingly toward the search for the potential of natural products as sources for new drugs, and they even started to elucidate physicochemical properties of these products. Drugs were classified according to their effects on the human body, for example, diuretics (promote urination and thus expel toxins), expectorants (remove mucous accumulation), topical antiseptic cleansers, stimulants (prescribed to increase blood flow and raise energy level), tonics (general strength building and disease prevention), analgesics and anesthetics, digestive aids, and oral health agents. Pharmacists, or

FIGURE 1.2 Ibn Khaldun (1332–1406). The fame of Ibn Khaldun in modern scholarship is due to his writing of the Muqaddimah, or "Introduction." In the Muqaddimah, he laid the foundations of a new science, "Ilm al-Umran," or the science of human social organization.

saydalaneh in Arabic, managed to introduce a large number of new drugs to clinical use, including senna, camphor, sandalwood, musk, myrrh, cassia, tamarind, nutmeg, cloves, aconite, ambergris, and mercury. They also developed syrups, juleps, and pleasant solvents such as rose water and orange blossom water as means of administering drugs. The first pharmacy shop was apparently in Baghdad, founded in 762, and medicines were manufactured and distributed commercially, and then dispensed by physicians and pharmacists in a variety of forms: ointments, pills, elixirs, confections, tinctures, suppositories, and inhalants. *Saydalaneh* were required to pass examinations and be licensed and were then monitored by the state [1–18].

As discussed in detail in Chapter 16, the selection of potential natural products as sources for new drugs was based on traditional knowledge developed in the

pre-Islamic era based on a long history of trial and error, and then by theoretical and practical knowledge introduced by Islam. These include natural products mentioned in the Holy Quran or in the *Hadith* of the Prophet (PBUH), notably honey, milk, dates, black seeds, olive leaf, and olive oil. In addition, theoretical and practical knowledge developed in other medical systems, which became available to Arab–Islamic scholars after the translation of foreign scripts, played a central role in developing new medicines. The works of Galen, Hippocrates, and the Indian physicians Sushruta and Charaka were translated into Arabic. Arab–Muslim physicians developed hundreds of new natural product-based remedies. They were not guided by a long history of trial and error, but mainly by scientific methods, which led to the development of evidence-based medication. Avicenna discussed in his book, on simple drugs (*materia medica*), the nature and quality of drugs (see Chapter 7), and the way that compounding them influences their effectiveness. He stated "You can tell the potency of drugs in two ways, by analogy and by experiment. We say experimenting leads to knowledge of the potency of a medicine with certainty after taking into consideration certain conditions."

Arab–Islamic medicine considers all components of existence with equal importance, from breath and body to the soul and matter; both spiritual and physical health are treated equally. Hence, the body should be treated as a whole and not just as a series of organs and tissues. Physicians noted that there are individual differences in the severity of disease symptoms, and in the individual ability to cope with disease and healing. Hippocrates thus laid the foundations of the modern theory that thoughts, ideas, and feelings, which he proposed to originate in the brain, can influence health and the process of disease. Rhazes supported this concept by his recommendation: "The physician, even though he has his doubts, must always make the patient believe that he will recover, for state of the body is linked to the state of the mind." Later on, Avicenna who defined medicine as "the science from which we learn the states of the human body with respect to what is healthy and what is not; in order to preserve good health when it exists and restore it when it is lacking" supported the views of Rhazes. He stated that "We have to understand that the best and most effective remedy for the treatment of patients should be through the improvement of the power of the human body in order to increase its immune system, which is based on the beauty of the surroundings and letting him listen to the best music and allowing his best friends to be with him."

It is now clear that the mind and the body interact, influence, and regulate each other. The perception of stress can lead to production of "stress hormones" as well as mediators of the immune system, for example, cytokines and free radicals. Stress hormones act in a feedback pathway to regulate their own production and the production of certain immune products. These immune products act on the brain to modify behavior and the ability to perceive and to respond to stressful challenges by inducing lethargy, fever, and nausea.

Based on the recommendations of Rhazes and Avicenna, patients were treated through a scheme starting with physiotherapy and diet, and if this failed, drugs were used. Rhazes's treatment scheme started with diet therapy; he noted that "if the physician is able to treat with foodstuffs, not medication, then he has succeeded. If,

however, he must use medications, then it should be simple remedies and not compound ones." Drugs were divided into two groups, simple and compound drugs. Physicians were aware of the interaction between drugs; thus, they used simple drugs first. If these failed, compound drugs consisting of two or more compounds were used. If these conservative measures failed, surgery was undertaken.

The Greek and Roman humor theory of the human body or humoralism had a great influence on the development of the Greco-Arab medical system. Hippocrates was the first who applied this idea to medicine and it became strongly accepted in the medical canon through the influence of Galen. The humoral theory was adopted and further developed by Arab–Muslim physicians and it became the most commonly held view of the human body among European physicians until the advent of modern medical research in the nineteenth century [1–8]. Chapter 7 provides an overview of method of therapy used in Greco-Arab and Islamic medicine.

1.4 COMMONLY USED HERBAL MEDICINES AND DIETS IN THE ARAB AND ISLAMIC WORLD

Medicinal plants and their products have been used traditionally across the world for the prevention and treatment of almost all known types of diseases. Clinical and basic scientific research confirmed the efficacy and action mechanism of several plants for treating several ailments, including liver disease, diabetes, skin diseases, and hypertension. As a result, about 25% of the currently prescribed drugs are of herbal origin. For instance, milk thistle (*Silybum marianum*) has been shown to have clinical applications in the treatment of liver diseases, including toxic hepatitis, fatty liver, cirrhosis, ischemic injury, radiation toxicity, and viral hepatitis, via its antioxidative, antilipid peroxidative, antifibrotic, and anti-inflammatory properties. Furthermore, milk thistle has shown immunomodulating and liver regenerating effects. Another example is *Nigella sativa* (black seed). The seeds of this plant are known to have many medicinal properties and are widely used in Greco-Arab and Islamic medicine. Therapeutic potential and toxicological properties of the seeds have been extensively studied. A Medline search using "*Nigella sativa*" or "black seed" reveals more than 700 citations, including antioxidant, anti-inflammatory, antimicrobial, hypotensive, antinociceptive, choleretic, uricosuric, antidiabetic, antihistaminic, immunomodulatory, anticancer, and antifertility effects.

Chapter 8 provides an overview of traditional uses, safety, and efficacy of commonly used medicinal plants in the Eastern region of the Mediterranean (Lebanon, Jordan, Israel and Palestine) where more than 3600 plant species are found and about 450–550 plants are noted for their medicinal uses. Plant parts used included leaves, flowers, stems, roots, seeds, and berries [3, 4, 10, 19–21].

Food plays an important role in Arab–Islamic medicine in maintaining a healthy body, soul, and spirit. Muslims are commanded to follow a set of dietary laws outlined in the Holy Quran where almost everything is permitted, except what God specifically prohibited. Later on, when the Islamic empire covered all of Arabia, half of Byzantine Asia, all of Persia, Egypt, the Maghreb (North Africa), and Spain, Arabs and Muslims

became exposed to foreign and multinational culinary heritages. Furthermore, great developments in scientific fields, the establishment of "modern" hospitals, and growing socioeconomic conditions of Islamic empire increased the awareness of the relationship between food and health. During this period, a type of Islamic food therapy developed that was a blend of Quranic teaching and Greek medicine.

As discussed in depth later in Chapter 17, the foods favored by the Prophet were dates, honey, olive oil, and black seeds. Concerning olive oil, he said "Eat olive oil and massage it over your bodies since it is a holy tree." Black seeds were regarded as a medicine that cures and prevents all types of diseases. The Prophet once stated, "The black seed can heal every disease, except death." Dates are mentioned in 20 places in the Quran. The Prophet is reported to have said: "if anyone of you is fasting, let him break his fast with dates. In case he does not have them, then with water. Verily water is a purifier."

1.5 SAFETY AND EFFICACY OF HERBAL MEDICINES

The widespread use and popularity have also brought concerns and fears over quality, efficacy, and safety of the "natural" products available on the market as well as the professionalism of practitioners. It is well known that adulteration, inappropriate formulation, or lack of understanding of plant and drug interactions can lead to adverse reactions that are life threatening or lethal to patients. Safety assessment of herbal-based preparations has often been neglected since traditional and prolonged use is usually considered evidence of its safety. Another important factor is the belief that these medicines are prepared according to the principles of the Greco-Arab tradition that forms the basis for the current conventional product. However, a history of traditional usage is not always a reliable guarantee of safety since it is difficult for traditional practitioners to detect or monitor delayed effects (e.g., mutagenicity), rare adverse effects, and adverse effects arising from long-term use. Most reports concerning toxic effects of herbal medicines are associated with hepatotoxicity although reports of kidney, nervous system, blood, cardiovascular, dermatologic effects, mutagenicity, and carcinogenicity have also been published in the biomedical literature. Chapter 11 gives a systematic safety review of herbal medicine and the contribution of Arab scholars to toxicology. Standards for safety, quality control, use of modern cell biology and biochemistry, and *in vitro* as well as *in vivo* techniques for the evaluation of medicinal plants are also discussed [11, 19–21].

There is little doubt that the use of the concept of Greco-Arab and Islamic herbal therapy has shown remarkable success in healing acute as well as chronic diseases. As mentioned above, Arab and Muslim physicians were the first to use scientific methods in the field of medicine and pharmacy, including the introduction of quantification, animal testing, and clinical trials. Hospitals in the Arab–Islamic world featured the first drug tests, drug purity regulations, and competency tests for physicians. In his *Comprehensive Book of Medicine*, Rhazes documented clinical cases of his own experience and provided very useful recordings of various diseases. He also introduced urinalysis and stool tests. Avicenna (980–1037) introduced experimental

medicine and systematic experimentation and quantification in physiology. He discovered the contagious nature of diseases and described many medical treatments, including clinical trials, risk factor analysis, and the idea of a syndrome in the diagnosis of specific diseases. His book, *The Canon of Medicine*, was the first book dealing with evidence-based medicine, randomized controlled trials, and efficacy tests. Concerning the medical documentation, the first documented description of a peer-reviewed publication process was written by Ishaq bin Ali al-Rahwi (854–931). In his work, *The Ethics of the Physician*, he stated that a physician must always make duplicate notes of a patient's condition. When the patient was cured or had died, the notes of the physician were examined by a local medical council of other physicians, who would review the practicing physician's notes to decide whether the treatment had met the required standards of medical care. Chapter 12 discusses the status of Greco-Arab and Islamic herbal medicine, including the efficacy and safety of specific medicinal preparations, prepared according to scientific and traditional knowledge of Greco-Arab and Islamic medicine.

1.6 MODERN *IN VITRO* AND *IN VIVO* TEST SYSTEMS

Under international regulations, animal tests play a crucial role in developing new knowledge that provides the basis for a new drug development. The appropriate use of animals in biomedical research and safety testing is an indispensable part of the process for acquiring the knowledge necessary to control or treat disease and injury. Regulatory bodies worldwide require preclinical efficacy and safety data for new drugs based on animal tests before human clinical trials can be conducted. Animal studies are mandatory in order to reduce the risks for people and allow the safe creation of new therapies. Drug development is a time-consuming, costly, and complicated research process. Thousands of chemical compounds must be synthesized or purified (in the case of natural products) and tested in order to find a desirable therapeutic result. The Food and Drug Administration in the United States (FDA) estimates that it takes approximately 8.5 years to study and test a new drug before it can be approved for the general public. This estimate includes preclinical *in vitro* studies and animal testing, as well as clinical trials using human subjects. The appropriate and responsible use of animals is a mandatory part of biomedical research and pharmaceutical product safety testing. They significantly reduce the probability of side effects occurring during testing in humans. Around 70% of serious adverse effects that occur in humans are identified at the animal testing stage. In addition, animal tests enable researchers to determine which experimental compounds in advanced development are unsuitable for use in humans either because the risk of potential toxicity is too great or because they do not have the desired pharmacokinetic profile. Therefore, animal testing is extremely beneficial in minimizing the risks to humans in clinical trials. Chapter 14 provides an overview of *in vivo* test methods used for both toxicity and efficacy studies.

Culturing cells is the most widely used *in vitro* method in pharmacology, toxicology, and biomedical research. In general, *in vitro* test systems represent the

first phase of the evaluation procedure. *In vitro* cell culture methods have the advantage of relatively well-controlled variables and are generally accepted as a very effective method for safety testing. Advantages of these systems over classical methods, such as long-term studies on experimental animals, include relatively well-controlled variables, decreased costs, a reduced time to completion, and reduced number of animals necessary to complete the study. Although some advanced *in vitro* systems are available that allow prediction of the local effects of test pharmaceuticals, even the most sophisticated *in vitro* test cannot yet be used to measure systemic effects, for example, blood pressure or fever.

Given the well-known problem of using two-dimensional cell culture pharmaceutical test systems, more realistic three-dimensional tissue constructs are required in order to create more *in vivo*-like cell culture conditions, where cells and tissues do not exist in isolation but communicate with and are interdependent on neighboring tissue. The breakthrough might be to develop human three-dimensional *in vitro* test systems and tissue equivalents that could serve as *in vitro* model systems during the initial stages of drug discovery. Chapter 13 provides an overview of *in vitro* test methods used for both preclinical toxicity and efficacy tests.

1.7 DRUG DEVELOPMENT FROM HERBAL SOURCES AND REGULATORY ISSUES

Herbal-based drug discovery research is a multidisciplinary approach combining ethnopharmacology and traditional knowledge on the one hand and botanical, phytochemical, biological, toxicological, pharmacological, and molecular techniques on the other hand. As mentioned above, about 25% of the currently used prescription drugs contain at least one herbal-derived active ingredient and several herbal-based drugs either have recently been introduced to the market or are currently involved in late-phase clinical trials. Although herbal-derived compounds continue to provide an important source of new drug leads, numerous challenges are encountered including the procurement of plant materials, for example, the selection and implementation of appropriate high-throughput screening bioassays and the scale-up of active compounds.

It is generally believed that the standardization and regulation of plant materials is not required when used by the rural communities for their primary health care. Nevertheless, regardless of whether the medicinal plant is to be used by local communities or by industry, a systematic approach is required for a traditionally used plant, as is done in modern medicine. It is necessary to standardize all stages of herbal-based drug discovery: from cultivation, ethnopharmacology, utilization, isolation, and identification of active constituents to efficacy evaluation, pharmacology, safety, formulation, and clinical evaluation.

In general, many herbs are effective when consumed as whole or as extracts. Current trends, however, are directed toward the use of purified herbal-derived agents that can serve not only as new drugs themselves but also as drug leads suitable for optimization by medicinal and synthetic chemists. Even when new chemical

structures are not found during drug discovery from medicinal plants, known compounds with new biological activity can provide important drug leads. In this respect, the sequencing of the human genome paves the ways for identification of thousands of new pathologically active molecules. With the help of modern *in vitro* and *in vivo* screening assays directed toward these targets, known herbal-derived compounds may show promising and possibly selective activity. Several known herbal-derived compounds have already been shown to act on newly validated molecular targets (e.g., indirubin selectively blocks cyclin-dependent kinases). Other herbal-derived compounds have also been shown to act on novel molecular targets, thus reviving interest in members of these frequently isolated plant compound classes. In Chapter 19, we concentrate on important aspects of the herbal-based drug discovery: from collection of plant material to efficacy and safety evaluation through preclinical studies and phytochemical standardization.

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CHAPTER 2

History of Greco-Arab and Islamic Medicine

2.1 INTRODUCTION

Islamic medicine, also known as Arabic medicine, medieval Islamic medicine, and Greco-Arab and Islamic medicine, refers to medicine developed during the Golden Age of the Arab–Islamic Empire, which extended from Andalusia (Spain) and Maghreb states (North Africa) in the west to Central Asia and India in the east, with the central lands of Egypt, Bilad al-Sham (Greater Syria), and Iraq playing an important role. It spanned a period of roughly nine centuries, from the middle of the seventh to the end of the fifteenth century, by which time it had broken up into three distinct empires, the Ottoman, the Safavid, and the Mughal.

The Arab–Islamic Empire was comprised of Muslims, Christians, Jews, and many different nations with different languages, including Arabic, Persian, Spanish, Turkish, and many other central Asian languages. Islam became the dominant religion, and Arabic served as the scientific language as well as a common language for all educated and official communications, much as Latin did in Europe for several centuries. Use of the Arabic language enabled scholars speaking different languages to communicate with one another. Thus, whether the authors were Persian or Arab, Muslim or Christian, and whether they spoke Arabic, Greek, Persian, or Turkish, for the most part they wrote in Arabic, the *lingua franca* of the Islamic civilization.

Medicine was a central part of medieval Arab–Islamic civilization. Arab and Muslim physicians and scholars developed a large and complex medical literature exploring and synthesizing the theory and practice of medicine. Islamic medicine was initially built on tradition, mainly the theoretical and practical knowledge developed in Arabia, Mesopotamia, Persia, Greece, Rome, and India. The founder of the Arab–Islamic medicine is believed to have been the Prophet himself, as a significant number of Hadith (statement by the Prophet) concerning medicines are attributed to him. His statement that "there is no disease that Allah has created, except that He also has created its treatment" encouraged Arabs and Muslims to engage in medical research and seek out a cure for every disease known to them. Many early authors of

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Arab–Islamic medicine were clerics rather than physicians, and were known to have advocated the traditional medical practices of the Prophet's time, such as those mentioned in the Quran and Hadith.

Later on, Arab and Muslim scholars translated the voluminous writings of Galen and Hippocrates, as well as writings of the Indian physicians Sushruta and Charaka and the Hellenistic scholars in Alexandria, from Greek and Sanskrit into Arabic and then produced innovative medical knowledge and practice based on those texts. In order to make the Greek and Indian traditions more accessible, understandable, and didactical, Arab and Muslim scholars systematically organized the vast and sometimes inconsistent Greco-Roman and Indian medical texts by writing encyclopedias and compendia. In addition, they made many of their own significant advances and contributions to medicine, notably in the fields of anatomy, botany, embryology, immunology, obstetrics, ophthalmology, pathology, pediatrics, physiology, psychiatry, psychology, pulsology, surgery, urology, and pharmacy.

There is no doubt that the West learned of Hellenic medicine through Arabic translations, including the works of Galen and Hippocrates. Of equal if not of greater influence in Western Europe were systematic and comprehensive works such as Avicenna's *Canon of Medicine*, which were translated into Latin and then disseminated in manuscript and printed form throughout Europe. To be sure, the earlier Greco-Roman scholarly medical literature was the wellspring from which much Arab–Islamic medicine grew, just as several centuries later Islamic medicine became the core of late medieval and early European medical education.

The medical practices spanning the vast regions of the Arab–Islamic Empire (is at its greatest extent reaching from Mongolia to Spain) (see Figure 1.1) were of course neither uniform nor unchanging. The everyday practices and the general health of the Islamic community were influenced by many factors, for example, the dietary and fasting rules in the holy month of Ramadan as well as the climatic conditions of the desert, marsh, mountain, and littoral communities; the different living conditions of nomadic, rural, and urban populations; local economic conditions and agricultural successes or failures; the amount of travel undertaken for commerce, for attendance at courts, or during a pilgrimage; the injuries and diseases attendant among army camps and battles; and the incidence of plague and other epidemics, as well as the occurrence of endemic conditions such as dysenteries and certain eye diseases [1–7].

This chapter will provide an overview of Greco-Arab and Islamic medicine including historical background of pre-Islamic and Islamic periods. It will highlight the cultural interaction between prominent ancient civilizations and emerging Islamic values at the level of theory and practice, Arab science in the Golden Age, medical innovations introduced by Arab physicians, hospitals, and the application of clinical studies in development of new medicines.

2.2 DEVELOPMENT OF GRECO-ARAB AND ISLAMIC MEDICINE

The development of Greco-Arab and Islamic medicine was based on four main resources: (1) knowledge developed by traditional healers in the pre-Islamic period

based on a long history of trial and error, (2) knowledge introduced by Islam, (3) theoretical and practical knowledge developed in other medical systems, which became available to Arab–Islamic scholars after the translation of Greek, Indian, and Persian scripts, and (4) theoretical and practical knowledge introduced by Arab and Muslim scholars (Figures 2.1 and 6.1) [1–7].

2.2.1 Ancient Medical Systems

Paleopathological studies reveal that diseases have existed throughout millennia. Archaeologists have unearthed the skeleton of an individual dated 60,000 years ago in a cave in north Iraq. The skeleton shows multiple traumatic injuries, healed

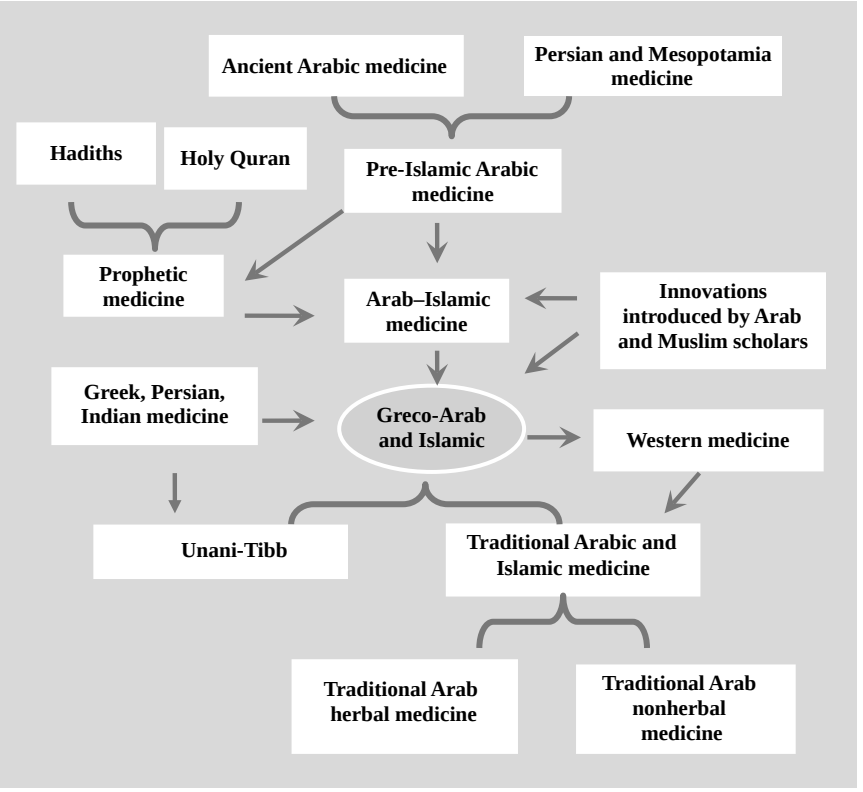

FIGURE 2.1 Development of Arab–Islamic medical science. Mesopotamian medicine was transmitted in part to the Greeks, and together with Egyptian medicine, it paved the way for the great Hippocratic reform. Then, during the rise of the Arab–Islamic Empire, Greek medicine was translated to Arabic. The Arabs improved on Greek medicine as well as made new discoveries over several centuries. In the thirteenth and fourteenth centuries, Greco-Arab medicine was disseminated to Europe again from Arab capitals such as Cordoba and Baghdad.

fractures, and degenerative bone disease. Another skeleton has been found in Mesopotamia dating back as early as 5000 BC. As the Sumerians are credited with the earliest human civilization, it is not surprising that excavations in Mesopotamia reveal the existence of a Sumerian physician's seal as early as 3000 BC. That seal is among the earliest proof of the existence of physicians. Besides the invention of the wheel and writing, the Sumerians are also credited with the first preparations of drugs and cosmetics and brewing of barley beer. Furthermore, it is not surprising that the ancient Mesopotamians perceived that some diseases are contagious. They likely had experience with major contagious diseases such as the plague or minor diseases such as the common cold. One of the Mesopotamian kings, King of Mari (1780 BC), wrote to his wife: "I have heard that the lady Nanname has been taken ill . . . Now then, give severe orders that no one should drink in the cup where she drinks, no one should sit on the seat where she sits, no one should sleep in the bed where she sleeps. She should no longer meet many ladies in her house. This disease is contagious."

Complex medical and philosophical beliefs existed in the Babylonian Empire. They believed that (1) the heart is the seat of the mind, (2) the liver is the seat of emotion, (3) the stomach is the seat of courage, and (4) the uterus is the seat of kindness. These beliefs survived for several millennia. They still exist, not only within Arab culture, but also in many cultures around the world. Some ancient Arab poets associated both the heart and the liver with love.

Similar development was established in Egypt. Egyptian medicine dates from about 2900 BC, but the best known Egyptian pharmaceutical record is the Ebers Papyrus dating from 1500 BC. This documents some 700 herbal- and animal-based medicines and includes formulas such as gargles, snuffs, poultices, infusions, pills, and ointments, with beer, milk, wine, and honey being commonly used as vehicles [5–8].

2.2.2 Medical Practices in Pre-Islamic Times

While the lack of water precluded the rise of large cities and societies, it did not hinder the development of Arabian culture and civilization. By the sixth century, Arabia had established economic links with ancient civilizations such as Egypt, Phoenicia, Assyria, Persia, Greece, India, Rome, and Byzantium with a trade in precious spices, frankincense, and myrrh. Arabs had contact with other civilizations by way of the trade caravans that made biannual trips from Mecca, traveling to Syria in the north (summer journey) and to Yemen in the south (winter journey). There is no doubt that the Babylonian, ancient Egyptian, and Persian medical systems were the foundation for the greater part of pre-Islamic medicine. Medical knowledge in the Arabian Peninsula before Islam (610) consisted of the folk medicine found among the nomadic Bedouin population as well as in the various settlements of the Hejaz (bordering the Red Sea). We know a lot about the nature of this medicine from the Prophet's medicine (*Al-Tibb al-Nabawi*) that was in most cases the medicine practiced in Hejaz

at that time (see Chapters 6 and 7). Ibn Khaldun (1332–1406), a well-known medieval Muslim jurist, historian, and statesman, in his "Muqaddimah" (the Prolegomena) states: "The Bedouins in their culture have a kind of medicine which they base primarily on experience restricted to a few patients only, and which they have inherited from their tribal leaders and old women. In some cases it is correct, but it is not founded on natural laws, nor is it tested against (scientific accounts) natural constitution (peoples). Now the Arabs had a great deal of this type of medicine before the advent of Islam and there were among them well known doctors like al-Harith ibn Kalada and others." As mentioned earlier, Arabs had access to medical practices developed in other civilizations existing at that time. In general, they tended to live frugally, and to eat a simple diet, and this may have well protected them against many diseases. In addition, they used a wide variety of medicinal plants, animal parts and products, and cupping and bloodletting (see Chapters 6 and 7) [5–8].

2.2.3 Contributions of Islam

As discussed in Chapters 6 and 7, the majority of the Muslims believe that the development of Arab and Islamic medicine started at the time (610) when the Prophet Mohammad (PBUH) at the age of 40 began to receive the Holy Quran in visions. He created a strong nation that was able to defeat the Persian and Byzantine Empires, who were the strongest known empires at that time. In Arab–Islamic tradition, the first Muslim physician is believed to have been the Prophet Mohammad (PBUH), as a significant number of *Hadith* concerning medicine are attributed to him. He stated that "There is no disease that Allah has created, except that He also has created its treatment," "Make use of medical treatment, for Allah has not made a disease without appointing a remedy for it, with the exception of one disease, namely old age," "God has sent down both the disease and the cure, and He has appointed a cure for every disease, so treat yourselves medically," "The one who sent down the disease sent down the remedy," and "For every disease, Allah has given a cure." These statements encouraged early Muslims to engage in medical research and seek out a cure for every disease known to them, and hence initiated the foundations of Arab–Islamic medicine.

Early Muslims utilized many plants and animal products mentioned in the Holy Quran and in the *Hadith* of the Prophet for health promotion, for example, dates, black seeds, olive leaf and olive oil, honey, and camel milk. Later on, these products formed the basis for the Prophet's medicine (Al-Tibb al-Nabawi), which includes medical treatments, prescriptions of diseases, prevention, health promotion, and spiritual aspects that were recommended by Prophet (PBUH) to his companions.

The book of medicine (*Kitab al-Tibb*) of Sahih al-Bukhari by Imam Bukhari (810–870) is recognized by the majority of the Muslim scholars to be one of the most authentic collections of what had been said and practiced (*Hadith* and *Sunnah*) by the Prophet (PBUH). The scope of the Prophetic medicine has been explained in the very well known commentaries of Sahih al-Bukhari by Ibn Hajar al-Asqalani (died 1449) and Abu Mohammad al-'Ayni (died 1452). Accordingly, the Prophetic medicine was

not based on medical experiments but rather on inspiration and experience from the previous culture and tradition. According to a *Hadith*, the stomach is the central basin of the body and origin of many diseases: "The stomach is the central basin of the body, and the veins are connected to it. When the stomach is healthy, it passes on its condition to veins, and in turn the veins will circulate the same and when the stomach is putrescence, the veins will absorb such putrescence and issue the same." Indeed, the prophet (PBUH) used to recommend food for ailments (Table 6.1) even more than herbs or animal-based medicines. He used everything from barley soup to honey to camel milk to heal his followers and advised them to eat certain foods to prevent or cure other diseases. In fact, diet is one of the oldest and most respected healing agents available to man. Honey, camel milk, dates, olive oil, and black seeds were the favored foods by the Prophet who regarded food as part of an overall holistic approach. Concerning olive oil, he said "Eat olive oil and massage it over your bodies since it is a holy tree." Black seeds were regarded as a medicine that cures all types of diseases. He once stated "The black seed can heal every disease, except death." Dates are mentioned in 20 places in the Quran. The Prophet is reported to have said: "if anyone of you is fasting, let him break his fast with dates. In case he does not have them, then with water. Verily water is a purifier." Therapeutic significance of the prophetic medicine is highlighted in Chapters 6 and 7 [1,2,8,9].

2.2.4 Theoretical and Practical Knowledge Developed in Other Medical Systems

Recognizing the importance of translating Persian, Indian, and Greek works into Arabic to make them more widely available, the Abbasid Caliphs Harun al-Rashid (786–809) and his son Al-Mamun (813–833) established a translation unit in Baghdad, the *Bait al-Hikmah* (House of Wisdom), and sent emissaries to collect Greek scientific works in the Byzantine Empire. The most important of the translators was Hunayn ibn Ishaq al-Ibadi (809–873), who was reputed to have been paid for his manuscripts by an equal weight of gold. He and his team of translators rendered the entire body of Greek medical texts, including all the works of Galen, Oribasius, Paul of Aegin, Hippocrates, and the *Materia Medica* of Dioscorides, into Arabic by the end of the ninth century. These translations established the foundations of a uniquely Arab medicine. "We should not be ashamed to acknowledge truth from whatever source it comes to us, even if it is brought to us by former generations and foreign peoples." The philosopher Al-Kindi, who wrote those words in the ninth century in Baghdad, was one of the thousands of Arab scholars employed to translate, analyze, and develop Greek learning by the Abbasid Caliphs, rulers of the Arab–Islamic Empire of the seventh to the fifteenth centuries.

As will be seen in later chapters of this book, Arab and Muslim scholars largely accepted Galen's theory of humors. It is important to highlight that this theory formed the basis from which much of Arab–Islamic medicine grew. This theory held that the human body is made up of the same four elements that comprise the world—earth, air, fire, and water (see Chapter 7). These elements can be mixed in various proportions, and the differing mixtures give rise to the different temperaments and "humors."

When the body's humors are correctly balanced, a person is healthy. Sickness is not due to supernatural forces but due to humoral imbalance, and such imbalance could be corrected by the doctor's healing arts. Even before the period of translation declined, advances were made in other health-related fields. As discussed later in this chapter, the first physician to refute Galen's theory of humorism was Rhazes in his *Doubts about Galen* in the tenth century. He criticized Galen's theory that the body possessed four separate "humors," whose balance is the key to health and a natural body temperature. He carried out an experiment that would upset this system by inserting a liquid with a different temperature into the body resulting in an increase or decrease of bodily heat, which resembled the temperature of that particular fluid. Rhazes noted particularly that a warm drink would heat up the body to a degree much higher than its own natural temperature; thus, the drink would trigger a response from the body, rather than transferring only its own warmth or coldness to it. In addition, Ibn Zuhr (Avenzoar) (1091–1161) was one of the earliest physicians known to have carried out human dissection and postmortem autopsy. He proved that the skin disease scabies was caused by a parasite, a discovery that upset the theory of humorism supported by Hippocrates and Galen. The removal of the parasite from the patient's body did not involve purging, bleeding, or any other traditional treatments associated with the four humors [1–9].

2.2.5 Contribution of Arab and Muslim Scholars

The translation of Persian, Indian, and Greek medical scripts represents the first phase in the development of Greco-Arab medical system. Arab and Muslim scholars began developing and promoting their own medical sciences in theories and practices that were highly influential in the development of Western medicine. Like in other fields of science, Arab–Muslim physicians developed the first scientific methods for the field of medicine. This included the introduction of experimentation, quantification, experimental medicine, evidence-based medicine, clinical trials, dissection, animal testing, human experimentation, and postmortem autopsy by Muslim physicians (Figure 2.2). Harun al-Rashid established the first hospital, in the modern sense of the term, at Baghdad around 805. Within a decade or two, 34 more hospitals had sprung up throughout the Islamic world. These hospitals featured drug tests, drug purity regulations, and competency tests for doctors.

In the twelfth century, European scholars who were interested in science and philosophy came to appreciate how much they needed to learn from the Arabs. As such, they set about studying Arab manuscripts in these disciplines and translating the most important ones into Latin. The most outstanding writer on medicine in Arabic was Avicenna. Like Rhazes, Avicenna wrote on many subjects, and was known to have been a greater philosopher than a physician. Nevertheless, his vast *Canon of Medicine* is rightly acclaimed as the "culmination and masterpiece of Arab systematization." It was translated into Latin in the twelfth century and continued to dominate the teaching of medicine in Europe until at least the end of the sixteenth century. There were 16 editions of Avicenna's work in the fifteenth century, 20 editions in the sixteenth century, and several more in the seventeenth century [1–9].

FIGURE 2.2 The diagnostic parameters of the Greco-Arab medicine include the rate, strength, width and depth of the pulse, and the color, odor, and amount of urine and stool.

2.3 SOME NOTABLE SCHOLARS OF THE MEDIEVAL GRECO-ARAB AND ISLAMIC MEDICINE

As mentioned earlier, Muslims believe that the first Muslim physician is the Prophet Mohammad (PBUH), as a significant number of *Hadith* concerning medicine are attributed to him. Later on, the development of Greco-Arab and Islamic medicine was largely influenced by Galenic and Hippocratic ideas. Galen promoted Hippocratic medicine unconstrained by Christian concepts of sin and sacrilege and compiled a vast *corpus* of theoretical and practical medical knowledge. Although some of the Galenic *corpus* is medically relevant, the better part of it is highly inaccurate. Nonetheless, it provided the first attempt to understand the connections between the organs within the body, nutrition, environment, disease, injury, pharmacology, and surgery. Hence, there is no doubt that Galen and Hippocrates were preeminent authorities in the medical field, along with the Indian physicians Sushruta and Charaka and the Hellenistic scholars in Alexandria. Therefore, it is important to highlight that the earlier Greek and Persian medical literature represented the roots from which Arab–Islamic medicine arose, just as several centuries later Greco-Arab and Islamic medicine formed the stem from which late medieval and early European medical education grew. While Galen indeed uses logic, Arab and Muslim physicians are responsible for giving medicine its formal scientific structure. They translated the voluminous writings from Greek and Persian into Arabic and then produced new theoretical and practical medical knowledge based on those texts. Later on, in the ninth century, Galen and Hippocrates for the first time had serious competition from

medical innovators in the Arab world, namely, Al Tabbari (838–870), Al-Razi (Rhazes, 864–930), Al-Zahrawi (Albucasis, 936–1013), Al-Biruni (973–1050), Ibn Sian (Avicenna, 980–1037), Ibn al-Haitham (960–1040), Ibn al-Nafis (1213–1288), Ibn Khaldun (1332–1406), and Ibn Zuhr (Avenzoar, 1091–1161) (Table 2.1). They made significant advances and contributions to medicine in the fields of anatomy, botany, embryology, immunology, obstetrics, ophthalmology, pathology, pediatrics, physiology, psychiatry, psychology, pulsology, surgery, urology, and pharmacy. In the following sections of this chapter, we will try to summarize the sophisticated framework of medical theory and practice developed by the most prominent Arab and Muslim physicians [1,2,9–21].

Al-Razi (Rhazes, 864–930). The first major medical works in Greco-Arab and Islamic medicine were written by Rhazes (Figure 2.3), who was born in Persia in the town of Rayy. After completing his medical studies at the age of 40, he was selected to be the director of a new hospital to be built in Baghdad. He approached the question of where to put the new facility by a simple technique. He hanged pieces of meat in various sections of the city and checked the rate at which they spoiled. He then ordered to build the hospital at the site where the meat showed the least putrefaction.

TABLE 2.1 Some Notable Scholars of the Medieval Arab–Islamic Science

Arabic Name	Latin Name	Period AD	Scientific Specialization
Ibn Sina	Avicenna	980–1037	Medicine, philosophy, mathematics
Al-Razi	Rhazes	864–930	Medicine, ophthalmology, smallpox, chemistry, astronomy
Al-Zahrawi	Albucasis	936–1013	Surgery, medicine (father of modern surgery)
Al-Biruni	Al-Biruni	973–1050	Physic, anthropology astronomy, chemistry, pharmacy
Ibn al-Baitar	Ibn al-Baitar	Died 1248	Pharmacy, botany
Ibn Zuhr	Avenzoar	1091–1161	Surgery, medicine
Al-Antaki	Al-Antaki	Died 1599	Pharmacy, natural product-based drugs
Al-Kindi	Alkindus	800–873	Philosophy, physics, optics, medicine, mathematics, metallurgy
Ibn Khaldun	Ibn Khaldun	1332–1406	Sociology, philosophy, political science
Ibn Jazzar	Ibn Jazzar	898–980	Medicine
Ibn Wahshiyyah	Ibn Wahshiyyah	ca. 900	Alchemy and toxicology
Ibn Hayan	Geber	Died 803	Chemistry (father of chemistry)
Ibn al-Haitham	Alhacen	960–1040	Physics, optics, mathematics
Ibn Rushd	Averroes	1128–1198	Philosophy, medicine, astronomy, theology
Ibn al-Nafis	Ibn al-Nafis	1213–1288	Anatomy

FIGURE 2.3 Rhazes (864–930). He was chief physician at the Baghdad hospital. An observant clinician, he formulated the first known description of smallpox as distinguished from measles in a work known as Liber de pestilentia. His works were widely circulated in Arabic and Greek versions and were published in Latin in the fifteenth century. They include a textbook of medicine called Almansor and an encyclopedia of medicine compiled posthumously from his papers and known as Liber continens.

Rhazes, along with Avicenna and Al-Zahrawi (Albucasis), is considered to be the greatest of all Arab and Muslim scientists. According to Rhazes, disease has specific physical causes. It is not a punishment inflicted upon men by God. He rejected superstition and primitive dogma not based in observable physical reality. These beliefs led him to criticize some of the foundations of Galen in his *Shukuk 'ala alinosor*, or *Doubts about Galen*: "I prayed to God to direct and lead me to the truth in writing this book. It grieves me to oppose and criticize the man, Galen, from whose sea of knowledge I have drawn much. Indeed, he is the Master and I am the disciple. Although this reverence and appreciation will and should not prevent me from doubting, as I did, what is erroneous in his theories. I imagine and feel deeply in my heart that Galen has chosen me to undertake this task, and if he were alive, he would have congratulated me on what I am doing. I say this because Galen's aim was to seek and find the truth and bring light out of darkness. I wish indeed he were alive to read what I have published."

His treatise *The Diseases of Children* has led some medical historians to regard him as the father of pediatrics. Rhazes identified hay fever and its cause and his work on kidney stones is still considered a classic. He was a strong proponent of experimental

medicine and the beneficial use of previously tested medicinal plants and other medicines. A leader in the fight against quacks and charlatans he called for high professional control and standards for practitioners. He also insisted on continuing education for already licensed physicians. Rhazes was the first to emphasize the value of mutual trust and consultation among skilled physicians in the treatment of patients, an unknown practice at that time.

His first major work was a 10-volume treatise entitled *Al-Kitab al-Mansuri*, named for the ruler of Rayy, Mansur ibn Ishaq. In it, he discussed such varied subjects as general medical theories and definitions, diet and drugs and their effect on the human body, mother and child care, skin disease, oral hygiene, climatology and the effect of the environment on health, epidemiology, and toxicology.

Rhazes was the first physician to clinically and scientifically distinguish between smallpox, which is fatal, and measles. In his book *Kitab al-Jadari wa'l Hasbah*, or *The Book of Smallpox and Measles*, he stated: "The eruption of smallpox is preceded by a continued fever, pain in the back, itching in the nose and nightmares during sleep. These are the more acute symptoms of its approach together with a noticeable pain in the back accompanied by fever and an itching felt by the patient all over his body. A swelling of the face appears, which comes and goes, and one notices an overall inflammatory color noticeable as a strong redness on both cheeks and around both eyes. One experiences a heaviness of the whole body and great restlessness, which expresses itself as a lot of stretching and yawning. There is a pain in the throat and chest and one finds it difficult to breath and cough. Additional symptoms are dryness of breath, thick spittle, hoarseness of the voice, pain and heaviness of the head, restlessness, nausea and anxiety. (Note the difference: restlessness, nausea and anxiety occur more frequently with 'measles' than with smallpox. At the other hand, pain in the back is more apparent with smallpox than with measles). Altogether one experiences heat over the whole body, one has an inflamed colon and one shows an overall shining redness, with a very pronounced redness of the gums."

Rhazes's most supreme work was a medical encyclopedia in 25 volumes, *Al-Kitab al-Hawi*, or *The Comprehensive Work*, the *Liber Continens* of Rhazes's later Latin translators. Rhazes spent a lifetime collecting data for the book, which he intended as a summary of all the medical knowledge of his time, augmented by his own experience and observations. In *Al-Hawi*, he emphasized the need for physicians to pay careful attention to patient history, rather than merely consulting the authorities of the past. In a series of diagnosed case histories entitled "Illustrative Accounts of Patients," Rhazes demonstrated this important principle.

Ibn Sina (Avicenna, 980–1037). He was born in Bukhara in Uzbekistan. His preeminence embraced not only medicine, but also the fields of philosophy, science, music, poetry, and statecraft. The son of a tax collector, he was so precocious that he had completely memorized the Holy Quran (about 600 pages) by age of 10. Then he studied law, mathematics, physics, and philosophy. At age of 16 he turned to the study of medicine, and by the age of 20, Avicenna was appointed court physician, and twice served as Vizier to Shams al-Dawlah, the prince of Hamadan, in western Persia. His

remaining years were crowded with adventure and hard scientific work, yet he somehow found time to write 20 books on theology, metaphysics, astronomy, philology, and poetry and 20 more on medicine.

As highlighted in the following chapters, his esteemed work, however, is the monumental *Al-Qanun fi al-Tibb*, or *The Canon of Medicine*. Over one million words long, it was nothing less than a codification of all existing medical knowledge. It summarized Hippocratic and Galenic theories and practices, describing Arab–Islamic and Indo-Persian knowledge and practice and including notes on his own experimental observations and innovations. Avicenna strove to fit each segment of anatomy, physiology, diagnosis, and treatment into its proper niche.

While Galen indeed used logic and a scientific methodology, it was Avicenna who gave medicine its formal scientific structure in his Canon. Avicenna's genius may lie in the fact that he transformed the human body into something that can be understood in terms of causal chains of events that lead to various states of health and disease. Elucidation of diseases and their causes represents the main objective of medicine. He distinguished four kinds of causes for diseases, namely, material, efficient, formal, and final. In this regard, in his Canon Avicenna wrote: ". . .Therefore in medicine we ought to know the causes of sickness and health. In addition, because health and sickness and their causes are sometimes manifest, and sometimes hidden and not to be comprehended except by the study of symptoms, we must also study the symptoms of health and disease. Now it is established in the sciences that no knowledge is acquired save through the study of its causes and beginnings, if it has had causes and beginnings; nor completed except by knowledge of its accidents and accompanying essentials. Of these causes there are four kinds: material, efficient, formal, and final."

The Canon highlights the importance of diet and the influence of climate and environment on health. It includes discussions of rabies, breast cancer, tumors, labor, and poisons, and their treatment. Avicenna distinguished between meningitis and meningismus of other acute diseases, and also described chronic nephritis, facial paralysis, ulcer of the stomach, and the various types of hepatitis, and their causes. He also expounded on the dilation and contraction of the pupils and their diagnostic value, described the six motor muscles of the eye and discussed the functions of the tear ducts, and noted the contagious nature of some diseases, which he attributed to "traces" left in the air by a sick person.

In parallel with Ibn al-Haitham, who was conducting his researches in Cairo at the same time, but from a more detailed anatomical and medical perspective, Avicenna searched deeply into the various parts of the eye, including the cornea, iris, retina, aqueous humor, and optic nerve. He enlarged on Galen's theories in describing much more esoteric and remote optical organs, such as the optic chiasma, a structure in the brain formed by the partial intersection or crossing of the optic nerve fibers on the underside of the hypothalamus. And he confirmed that nerves are critical message paths for virtually all physical functions, in particular muscular contractions, concluding that pain is transmitted from its source via the nerves. He further elucidated how the aorta works, noting that its three valves prevent blood from rushing back into the heart after the heart completes contracting.

As discussed in the following chapters, the Canon also included a description of some 760 medicinal plants and the medicines that could be derived from them. At the same time, Avicenna laid out the basic rules of clinical drug trials, principles that are still followed today (see Chapters 6 and 12).

The Canon made its first appearance in Europe by the end of the twelfth century, and its impact was dramatic. Copied and recopied, it quickly became the standard European medical reference work. In the last 30 years of the fifteenth century, just before the European invention of printing, it was issued in 16 editions; in the century that followed, more than 20 further editions were printed. From the twelfth to the seventeenth century, its *materia medica* was the pharmacopoeia of Europe, and as late as 1537 the Canon was still a required textbook at the University of Vienna.

Avicenna's contributions to anatomy and physiology are of great importance. Galen as well as Chinese physicians believed that there was a unique type of pulse for every organ of the body and for every disease. Galen also believed that "every part of an artery pulsates simultaneously" and that the motion of the pulse was due to natural motions (the arteries expanding and contracting naturally) as opposed to forced motions (the heart causing the arteries to either expand or contract). The first correct explanations of pulsation were given by Avicenna, who refined Galen's theory of the pulse. He stated in his *Canon of Medicine* that "Every beat of the pulse comprises two movements and two pauses. Thus, expansion, pause, contraction, pause. The pulse is a movement in the heart and arteries . . . which takes the form of alternate expansion and contraction." Avicenna also pioneered the modern approach of examining the pulse through the examination of the wrist, which is still practiced. His reason for choosing the wrist as the ideal location is due to it being easily available and the patient not needing to be distressed at the exposure of his/her body. Other contributions of Avicenna to physiology include the introduction of systematic experimentation and quantification into the study of physiology in *The Canon of Medicine* (see Chapters 6 and 7).

Avicenna described in his Canon the contagious nature of infectious diseases, such as phthisis and tuberculosis, the distribution of these diseases by water and soil, and the contagious nature of sexually transmitted diseases. In addition to the classification and description of diseases, the Canon also discusses hygiene, simple and complex medicines, the symptoms and complications of diabetes, and functions of parts of the body. Avicenna even asserted that tuberculosis was contagious, which was later disputed by Europeans, but turned out to be true. Even before discovery of contagious diseases by Avicenna, Rhazes discovered the origin of smallpox and showed that one could acquire it only once in one's life. As a result, hospitals were created with separate wards for specific illnesses, so that people with contagious diseases could be kept away from other patients who do not have any contagious disease. When the Black Death bubonic plague reached Andalusia in the fourteenth century, Ibn Katina hypothesized that infectious diseases are caused by small "minute bodies" that enter the human body and cause disease.

Taken overall, it is hard to describe Avicenna in anything other than superlatives or as his contemporaries called him "*the prince of physicians*" (Figure 2.4).

FIGURE 2.4 Avicenna (980–1037). He is remembered in Western history of medicine as a major historical figure who made fundamental contributions to medicine and the European reawakening. About 100 treatises were ascribed to Avicenna. The best known amongst them is his 14-volume *The Canon of Medicine*, which was a standard medical text in Western Europe for seven centuries. One of the most important citations from Avicenna concerning psychological and organ diseases was: "We have to understand that the best and effective remedy for the treatment of patients should be through the improvement of the power of the human body in order to increase its immune system, which is based on the beauty of the surroundings and letting him listen to the best music and allow his best friends to be with him."

Ibn al-Haitham (Alhacen, 965–1040). Through his extensive studies on optics, he has been considered as the father of modern optics. In his writing, one can see a clear development of the scientific methods as developed and applied by the Muslims and comprising the systematic observation of physical phenomena and their linking together into a scientific theory. This was a major breakthrough in scientific methodology, as distinct from guess and gesture, and placed scientific pursuits on a sound foundation comprising systematic relationships between observation, hypothesis, and verification. Ibn al-Haitham made a thorough examination of the

passage of light through various media and discovered the laws of refraction. He also carried out the first experiments on the dispersion of light into its constituent colors. His book *Kitab-at-Manazir* was translated into Latin in the Middle Ages (Figure 2.5). He dealt in depth with the theory of various physical phenomena such as shadows, eclipses, and the rainbow and speculated on the physical nature of light. He is the first to describe the anatomy of the eye and give a scientific explanation of the process of vision. He also attempted to explain binocular vision and gave a correct explanation of the apparent increase in size of the Sun and the Moon when near the horizon. He contradicted Ptolemy's and Euclid's theory of vision that objects are seen by rays of light emanating from the eyes; according to him, the rays originate in the object of vision and not in the eye.

Ibn al-Haitham wrote more than 200 books, very few of which have survived. His monumental treatise on optics survived in its Latin translation. The Latin translation of his main work, *Kitab-at-Manazir*, exerted a great influence upon Western science, for example, on the work of Roger Bacon and Kepler. His contribution to mathematics

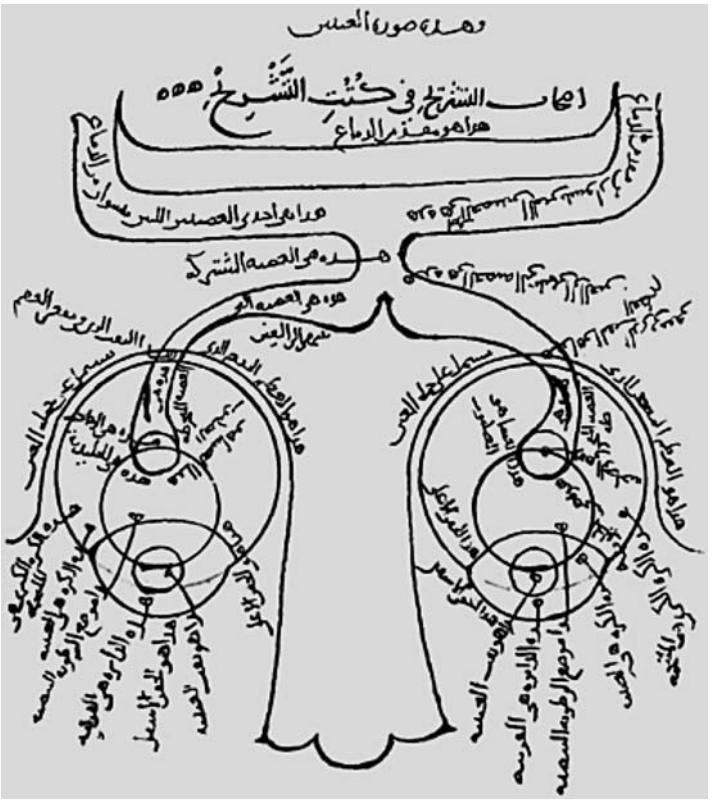

FIGURE 2.5 Diagram from *Kitab al-Manazir* (*Book of Optics*) by Ibn al-Haitham (Alhazen, 965–1038), showing a chiasm, "the joining nerve."

and physics was extensive. In mathematics, he developed analytical geometry by establishing linkage between algebra and geometry. He studied the mechanics of motion of the body and was the first to maintain that the body moves perpetually unless an external force stops it or changes its direction of motion. This would seem equivalent to the first law of motion.

Ibn al-Nafis (1213–1288). Perhaps one of the greatest cardiologists of the Arab–Islamic civilization and pre-modern time. Ibn al-Nafis was born in a small town near Damascus, but after studying medicine there, he spent most of his life in Cairo as the chief physician of Al-Mansuri hospital and head of its school of medicine. And there he made his earthahattering discovery around 1284. He described the true anatomy of the heart and the blood circulatory system.

Ibn al-Nafis was an Arab physician who made several important contributions to the early knowledge of pulmonary circulation. He was the first person to challenge the long-held contention of the Galen School that blood could pass through the cardiac interventricular septum, and in keeping with this he believed that all the blood that reached the left ventricle passed through the lung. He also stated that there must be small communications or pores (*manafidh* in Arabic) between the pulmonary artery and vein, a prediction that preceded by 400 years the discovery of the pulmonary capillaries by Marcello Malpighi.

Until Ibn al-Nafis, the standard explanation of heart anatomy and function was from Galen, who believed that blood moved from the right ventricle to the left through a series of pores or passageways between the two sides. Ibn al-Nafis clarified all that when he studied the heart–lung blood circulation, observed through many surgeries and possibly dissection. In his *Commentary on the Canon of Anatomy of Avicenna* he wrote: "The blood from the right chamber of the heart must enter the left chamber, but there is no direct pathway between them. The thick septum of the heart is not perforated and does not have visible openings as some people thought or invisible pores as Galen thought. The blood from the right chamber must flow through the vena arteriosa (pulmonary artery) to the lungs, spread through its substance, be mingled with air, pass through the arteria venosa (Pulmonary vein) to reach the left chamber of the heart." Ibn al-Nafis's discovery is about as important to modern medicine as Al-Khwarizmi's "zero" is to modern math. Al-Nafis is also the first to map the network of vessels supplying blood to the heart.

Ibn al-Nafis, the father of circulatory physiology, was another early proponent of human dissection. In 1242, he was the first to describe the pulmonary circulation, coronary circulation, and capillary circulation, which form the basis of the circulatory system, for which he is considered one of the greatest physiologists in history. In his *Commentary on Anatomy in Avicenna's Canon*, Ibn al-Nafis completely rejected the Galenic theory of pulsation after his discovery of the pulmonary circulation. He developed his own Nevisian theory of pulsation after discovering that pulsation is a result of both natural and forced motions, and that the "forced motion must be the contraction of the arteries caused by the expansion of the heart, and the natural motion must be the expansion of the arteries." He notes that the "arteries and the heart do not expand and contract at the same time, but rather the one contracts while the other

expands" and vice versa. He also recognized that the purpose of the pulse is to help disperse the blood from the heart to the rest of the body. Ibn al-Nafis briefly summarizes his new theory of pulsation: "The primary purpose of the expansion and contraction of the heart is to absorb the cool air and expel the wastes of the spirit and the warm air; however, the ventricle of the heart is wide. Moreover, when it expands it is not possible for it to absorb air until it is full, for that would then ruin the temperament of the spirit, its substance and texture, as well as the temperament of the heart. Thus, the heart is necessarily forced to complete its fill by absorbing the spirit." Ibn al-Nafis also described the earliest concept of metabolism and developed new Nevisian systems of anatomy, physiology, and psychology to replace the Avicenna and Gaelic doctrines, while discrediting many of their theories on the four humors, pulsation, bones, muscles, intestines, sensory organs, bilious canals, esophagus, stomach, and the anatomy of almost every other part of the human body.

Of all the branches of Islamic medicine, ophthalmology was one of the foremost. Ibn al-Nafis, in *The Polished Book on Experimental Ophthalmology*, discovered that the muscle behind the eyeball does not support the ophthalmic nerve, that it does not come into contact with it, and that the optic nerves transect but do not come into contact with each other. He also discovered many new treatments for glaucoma and the weakness of vision in one eye when the other eye is affected by disease.

Al-Kindi (Alkindus, 800–873). He was born and educated in Kufa (Iraq), before pursuing further studies in Baghdad. His father was an official of Haroon al-Rashid. He was formally employed by the Abbasid Caliphs Al-Mutawakkil as a calligrapher. Al-Kindi was the first of the Muslim Peripatetic philosophers and is known for his efforts to introduce Greek and Hellenistic philosophy to the Arab–Islamic tradition, and as a pioneer in chemistry, cryptography, medicine, music theory, physics, psychology, and the philosophy of science. On account of his works, he became known as the philosopher of the Arabs. Al-Kindi became a prominent figure in the House of Wisdom, and a number of Abbasid Caliphs appointed him to oversee the translation of Greek scientific and philosophical texts into the Arabic language. This contact with "the philosophy of the ancients" (as Greek and Hellenistic philosophy was often referred to by Muslim scholars) had a profound effect on his intellectual development and led him to write original treatises on subjects ranging from Islamic ethics and metaphysics to Islamic mathematics and pharmacology.

In mathematics, Al-Kindi played an important role in introducing Indian numbers to the Islamic and Christian world. He was a pioneer in cryptanalysis and cryptology and devised new methods of breaking ciphers, including the frequency analysis method. As discussed in later chapters, Al-Kindi was the first to systematically determine the doses to be administered for all known drugs at the time. This resolved the conflicting views prevailing among physicians on the dosage that caused difficulties in writing prescriptions. He also experimented with music therapy.

The central theme underpinning Al-Kindi's philosophical writings is the compatibility between philosophy and other orthodox Islamic sciences, particularly theology. Many of his works deal with subjects that concerned theology, including the nature of God, the soul, and prophetic knowledge.

Ibn Zuhr (Avenzoar, 1091–1161). Ibn Zuhr was born in Seville and is considered as one of the greatest physicians of the medieval Arab–Islamic medicine. Contrary to the general practice of the Arab and Muslim scholars of that time, he confined his work to only medicine. This enabled him to produce works of everlasting fame and importance. In his works, Ibn Zuhr lays stress on observation and experiment and his contribution greatly influenced medical science for several centuries both in the East and in the West.

His contribution was mainly contained in his monumental works; out of these, however, only three are extant. *Kitab al-Taisir fi al-Mudawat wa al-Tadbir* (*Book of Simplification Concerning Therapeutics and Diet*), written at the request of Ibn Rushd (Averroes), is the most important work of Ibn Zuhr. It describes several of Ibn Zuhr's original contributions. The book gives detail of pathological conditions, followed by therapy. His *Kitab al-Iqtisad fi Islah al-Anfus wa al-Ajsad* (*Book of the Middle Course Concerning the Reformation of Souls and the Bodies*) gives a summary of diseases, therapeutics, and hygiene written specially for the benefit of the layman. Its initial part is a valuable discourse on psychology. *Kitab al-Aghziya* (*Book on Foodstuffs*) describes different types of food and drugs and their effects on health. His books were translated into Latin and Hebrew and remained popular in Europe as late as the advent of the eighteenth century.

Al-Zahrawi (Abulcasis, 936–1013). Al-Zahrawi was born in Zahra in the neighborhood of Cordova. He became one of the most renowned surgeons of the Arab–Muslim era and was physician to King Al-Hakam-II of Spain. He is best known for his original innovations in surgery as well as for his famous medical encyclopedia *Al-Tasrif*, which is composed of 30 volumes covering different aspects of medical science. The more important part of this series comprises three books on surgery, which describe in detail various aspects of surgical treatment based on the operations performed by him, including cauterization, removal of stone from the bladder, dissection of animals, midwifery, and surgery of eye, ear, and throat. He optimized several delicate operations, including removal of the dead fetus and amputation.

Al-Tasrif contains numerous schematic illustrations of surgical tools, in use or developed by him, and comprised a part of the medical curriculum in European countries for many centuries. Contrary to the view that the Muslims fought shy of surgery, Al-Zahrawi's *Al-Tasrif* provided a monumental collection for this branch of applied science. Al-Zahrawi was the inventor of several surgical tools, of which three are notable: (i) an instrument for internal examination of the ear,(ii) an instrument for internal inspection of the urethra, and(iii) an instrument for applying or removing foreign bodies from the throat. He specialized in curing disease by cauterization and applied the technique to as many as 50 different operations. In his book *Al-Tasrif*, he discussed the preparation of various herbal-based medicines and described in detail the application of such techniques as sublimation and decantation. Al-Zahrawi was also an expert in dentistry, and his book contains sketches of various instruments used therein, in addition to a description of various important dental operations. He discussed the problem of nonaligned or deformed teeth and how to rectify these

defects. He developed the technique of preparing artificial teeth and using them to replace defective teeth. In medicine, he was the first to describe in detail the unusual disease hemophilia.

In conclusion, there can be no doubt that Al-Zahrawi influenced the field of medicine and surgery very deeply and the principles laid down by him were recognized as authentic in medical science, especially surgery, and these continued to influence the medical world for five centuries.

2.4 INNOVATIONS INTRODUCED BY ARAB AND MUSLIM PHYSICIANS

Medical innovations introduced by Arab and Muslim physicians included the discovery of the immune system and the introduction of microbiological science. Avicenna, Rhazes, and others were the first to use ice to treat fever, separate medicine from pharmacological science, introduce the use of animal testing, and combine different sciences such as chemistry, medicine, pharmacology, agriculture, and plant science in order to develop new treatments for their patients. In surgery, Al-Zahrawi was the first to develop various surgical equipments and tools, some of which were unique for surgery on females. Later on, Ibn al-Haitham improved the surgery of eyes and studied the process of sight for the first time. Arab doctors were also aware of the contagious qualities of diseases. Furthermore, every major city of the Arab–Islamic Empire had a hospital; the hospital at Cairo had separate wards for fevers, ophthalmic, dysentery, and surgical cases.

Concerning herbal medicine, Arab physicians introduced many new ideas and upgraded the existing knowledge about herbs and their potential medical uses. For example, Jaber ibn Hayan and others extracted different anesthetic compounds from local herbs for local or general anesthetization. Daoud al-Antaki used different herbs for treating patients and published a book on medicinal herbs summarizing the knowledge of his predecessors. Ibn al-Baitar, in Andalusia, Spain, introduced around 350 new plant species as medicinal herbs for treating human diseases. Abu al-Abbas and other herbalists published several books and dictionaries on the use of medicinal plants describing each plant species, the plant parts used, the preparation procedure used for each remedy, and the treatment procedure of certain diseases. Avicenna's *Canon of Medicine* and Rhazes's *Comprehensive Book of Medicine* were translated into several different languages. Until a few centuries ago, these two books were the focus of medicinal literature, and they are still in use in different libraries in Europe [[7–13].

2.4.1 Development of Pharmacology

As highlighted in Chapters 4 and 5, in the eighth century Arabs and Muslims in the Baghdad region were the first to separate medicine from pharmacological science. At that point, patients started to deal with experts in the pharmaceutical sciences working on the extraction and preparation of remedies, and not with physicians who were

responsible for the diagnosis of diseases and follow-up with the applied treatments. This fact resulted in a huge development in pharmaceutical science; pharmacologists and ethnopharmacologists started to search for different ingredients and extracts to be used as remedies, and they even started to study the chemical properties of the materials used in the treatment of various diseases and ailments. For the first time, chemists such as Jaber ibn Hayan (ca. 776), who is considered the father of Arab–Islamic alchemy, started to search for methods to extract and purify different compounds including alcohol, nitric acids, sulfuric acids, and royal acid (Figure 2.6). The latter was used to dissolve gold. Arab pharmacists, or *saydalaneh*, introduced a large number of new drugs to clinical practice, including senna, camphor, sandalwood, musk, myrrh, cassia, tamarind, nutmeg, cloves, aconite, ambergris, and mercury. The *saydalaneh* also developed syrups, juleps, and pleasant solvents such as rose water and orange blossom water as means of administering drugs. They were familiar with the anesthetic effects of Indian hemp and henbane, both when taken in liquids and inhaled.

By the time of Al-Mamun's caliphate (813–833), pharmacy was a profession practiced by highly skilled specialists. Pharmacists were required to pass examinations and be licensed and were then monitored by the state. At the start of the ninth century, the first private apothecary shops opened in Baghdad. Pharmaceutical preparations were manufactured and distributed commercially, and then dispensed by physicians and pharmacists in a variety of forms: ointments, pills, elixirs, confections, tinctures, suppositories, and inhalants.

FIGURE 2.6 Jabir ibn Haiyan, the Geber (died 803).

Avicenna's contribution to pharmacology and the pharmaceutical sciences in *The Canon of Medicine* includes the introduction of systematic experimentation and quantification into pharmacology and the study of physiology, the introduction of clinical pharmacology, experimental medicine, evidence-based medicine, clinical trials, randomized controlled trials, efficacy tests, the experimental use and testing of drugs, a precise guide for practical experimentation in the process of discovering and proving the effectiveness of medical substances, and the first careful descriptions of skin troubles, sexually transmitted diseases, perversions, and nervous ailments, as well the use of ice to treat fevers, and the separation of medicine from pharmacology, which was important for the development of the pharmaceutical sciences.

The advances made in medicine, botany, and chemistry by medieval Arab and Muslim physicians had stimulating effects on the development of pharmacology. Rhazes (864–930), for instance, acted to promote the medical uses of chemical compounds. Al-Zahrawi (Abulcasis) (936–1013) pioneered the preparation of drugs by sublimation and distillation. His *Liber servitoris* is of particular interest; it contains a large number of recipes and explains how to prepare simple as well as complex drugs. Shapur ibn Sahl (died 869) was, however, the first physician to initiate pharmacopoeia, describing a large variety of drugs and remedies for ailments. Al-Biruni (973–1050) wrote one of the most valuable Islamic works on pharmacology entitled *Kitab al-Saydalah* (*The Book of Drugs*), where he gave detailed knowledge of the properties of drugs and outlined the role of pharmacy and the functions and duties of the pharmacist. Ibn Sina (Avicenna), too, described no less than 700 preparations, their properties, mode of action, and their indications. In fact, he devoted a whole volume to simple drugs in *The Canon of Medicine*. Al-Kindi was a renowned ninth-century Arab doctor who introduced the application of mathematics into medicine, particularly in the field of pharmacology. This includes the development of a mathematical scale to quantify the strength of drugs, and a system that would allow a doctor to determine in advance the most critical days of a patient's illness, based on the phases of the Moon.

2.4.2 Poisons and Antidotes

In parallel with the development of pharmacy and pharmacology in the Arab world, there was also a similar development in alchemy and toxicology (see Chapter 11). The origins of these developments date back to the Greeks and Indians as well as to the empiric knowledge of the indigenous population. Alchemy was commonly practiced during the ninth century and many works have been written on this art. For instance, *Kitab al-Sumum* is a five-volume, independent manual on toxicology that is attributed to Shanaq the Indian. It was translated into Arabic by Al-Jawhari for Caliph Al-Mamun, and was a compilation from Greek and Indian sources of the ninth century. It elaborates on poisons and how they can be detected by sight, touch, taste, or the toxic symptoms they cause. Descriptions are provided of poisoned drinks, foods, clothes, carpets, beds, skin lotions, and eye salves, as well as narcotics and universal antidotes. A similar approach can be found in an early tenth-century book on toxicology by Ibn Wahshiyyah. Another equally important example is the book on

poisons and their antidotes by the famous Arab alchemist, Abu Musa Jabir ibn Hayan. In its six chapters, the author identifies poisons by their traits, natural origins, modes of action, dosages, methods of administration, choice of drugs, and target organ (which is attacked by each particular poison). The latter is a proposition that is modern in its chemotherapeutic application. Ibn Wahshiyyah also discusses general human anatomy and the four humors, detailing how they are affected by purgatives and lethal drugs. He even warns against poisonous or poisoned matter and prescribes antidotes. His discussion of body principles and subordinate organs and their function is similar to the previously mentioned Greek classification. Many of the antidotes described by Arab scientists such as Abu Musa Jabir ibn Hayan (Figure 2.6), Ibn Wahshiyyah, and Avicenna are still used by herbalists in the Arab world.

2.4.3 Surgery

Arab scholars contributed greatly to the development of surgery and were pioneer in applying oral as well as inhalant anesthetics. One of the main figures in surgery was Al-Zahrawi (Abulcasis). He is regarded as the father of modern surgery, contributing greatly to the development of modern surgery with his *Kitab al-Tasrif* (*Book of Concessions* or *The Method of Medicine*), a 30-volume medical encyclopedia published in 1000, which introduced over 200 surgical instruments. These included the first instruments unique to gynecology, as well as the surgical uses of catgut and forceps, ligature, surgical needle, scalpel, curette, retractor, surgical spoon, sound, surgical hook, surgical rod, speculum, bone saw, and plaster. His work also included anatomical descriptions and sections on orthopedic surgery and ophthalmology.

Ibn Zuhr (Avenzoar) is considered the father of experimental surgery, for introducing the experimental method into surgery in his *Al-Taisir*. He employed animal testing in order to experiment with surgical procedures before applying them to human patients. He also performed the first dissections and postmortem autopsies on humans as well as animals.

Ibn al-Haitham (Alhacen) made important advances in eye surgery, as he studied and correctly explained the process of sight and visual perception for the first time in his *Book of Optics*, published in 1021. Avicenna was the first to describe the surgical procedure of intubation in order to facilitate breathing. He also described the first known surgical treatment for cancer, stating that the excision should be radical and that all diseased tissue should be removed, including the use of amputation or the removal of veins running in the direction of the tumor.

Ibn al-Nafis dedicated a volume of *The Comprehensive Book on Medicine* to surgery. He described three stages of a surgical operation. The first stage is the pre-operation period that he calls the "time of presentation" when the surgeon carries out a diagnosis on the affected area of the patient's body. The second stage is the actual operation that he calls the "time of operative treatment" when the surgeon repairs the affected organs of the patient. The third stage is the post-operation period that he calls the "time of preservation" when the patient needs to take care of himself and be taken care of by nurses and doctors until he recovers. *The Comprehensive Book on Medicine* was also the earliest book dealing with the decubitus of a patient.

In parallel with their achievements in surgery, Arab scholars were pioneers in applying oral as well as inhalant anesthetics. Al-Zahrawi and Ibn Zuhr, and other Arab surgeons, performed their operations under inhalant anesthesia with the use of narcotic-soaked sponges that were placed over the face. Arab–Muslim physicians also introduced the anesthetic value of opium derivatives during the medieval time. Laudanum was also used as an anesthetic. Avicenna wrote about its medical uses in his works, which later influenced the works of Paracelsus.

2.4.4 Dentistry

The earliest medical text to deal with dental surgery in detail was the *Al-Tasrif* by Abulcasis. He gave detailed methods for the successful reimplantation of dislodged teeth. Another Arab dentist, Al-Jazzar (tenth century), described methods of dental restoration in his *Kitab Zad al-Musafir wa qut al-Hadir* (*Provision for the Traveller and Nutrition for the Sedentary*), which was later translated into Latin as *Viaticum* by Constantine the African in Salerno (see Chapter 10). He provided the earliest treatment for dental caries: "with caries purging must take place first, and then the teeth can be filled with gallnut, dyer's, buckthorn, terbinth resin (Resin is a hydrocarbon secretion of many plants, particularly coniferous trees), cedar resin, myrrh, pellitory (*Anacyclus pyrethrum*, chamomile, or Mount Atlas daisy is a perennial herb much like chamomile in habitat and appearance) and honey, or fumigated with colocynthis root." He also recommended arsenic compound in his prescription for holes in the teeth, as well as against dental caries, loosening, and relaxing of the nerves as a result of too many fluids.

Avicenna dedicated many chapters of his Canon to dentistry, particularly dental restoration. Influenced by Al-Jazzar, he provided his own treatment for dental caries, stating that carious teeth should be filled with cypress, grass, mastix, myrrh, or styrax, among others, with gallnut, yellow sulfur, pepper, camphor, and with drugs for pain relief, such as arsenic or wolf's milk. He further stated that arsenic boiled in oil should be dripped into the carious defect.

2.4.5 Gerontology and Geriatrics

Avicenna's *Canon of Medicine* was the first book to offer instruction for the care of the aged. In a chapter entitled "Regimen of Old Age," Avicenna wrote that "old folk need plenty of sleep. Time spent on the couch should be liberal—more than is legitimate for adults." He wrote that after waking up, the body should be anointed with oil "to stimulate the sensitive faculties." Regarding exercise, he recommended walking or horse riding. He stated: "The factors to consider in regard to exercise in old people are the various bodily states of different persons; the sequels likely to arise from their ailments; and their previous habits as regards exercise." Accordingly, if the body is healthy, it can perform tempered exercises, but if one part of the body is infirm, "then that part should not be exercised until after the rest," and that exercises are not to be strictly graduated "as if the body were to be strengthened."

The Canon describes four periods of life: the period of growth, prime of life, elderly, and decrepit age. He states that during the last period, "there is hardness of their bones, roughness of the skin, and the long time since they produced semen, blood and vaporal breath." However, he agreed with Galen that the earth element is more prominent in the aged and decrepit than in other periods. Avicenna did not agree with the concept of infirmity, however, stating: "There is no need to assert that there are three states of the human body—sickness, health and a state which is neither health nor disease. The first two cover everything."

The Canon discusses the diet suitable for old people. Avicenna wrote that they should be given food in small amounts at a time and that they can have two to three meals a day, divided up according to the digestive powers and general condition of the old person in question. He also recommended fruits, such as figs and prunes. He also stated: "Some laudable nutrition may be allowed at bedtime, [but] robust old folk may have a more liberal supper, as long as they avoid any gross aliment . . . all hot, sharp or desiccative foods, such as dishes made with vinegar, salt, hot aromatics, seasonings and pickles. [Milk is good for the aged, being] nutritious and humectant in nature. [Yet] articles of food with a laxative action are most appropriate for the elderly."

Ibn al-Jazzar (898–980) also wrote a special book on the medicine and health of the elderly, entitled *Kitab Tibb al-Machayikh* or *Teb al-Mashaikh wa hefz sehatahom*. He also wrote a book on sleep disorders and another one on forgetfulness and how to strengthen memory, entitled *Kitab al-Nissian wa Toroq Taqwiati Adhakira*, and a treatise on causes of mortality entitled *Rissala Fi Asbab al-Wafah*. Another Arabic physician in the ninth century, Ishaq ibn Hunayn (died 910), wrote a *Treatise on Drugs for Forgetfulness* (*Risalah al-Shafiyah fi adwiyat al-nisyan*).

2.4.6 Psychiatry and Psychology

The concepts of mental health and "mental hygiene" were introduced by Ibn Sahl al-Balkhi (850–934). In his *Sustenance for Body and Soul*, he was the first to successfully discuss diseases related to both the body and the mind, and argued that "if the nafs [psyche] gets sick, the body may also find no joy in life and may eventually develop a physical illness." Al-Balkhi was also a pioneer of psychotherapy, psychophysiology, and psychosomatic medicine. He recognized that the body and the soul can be healthy or sick, or "balanced or imbalanced," and that mental illness can have both psychological and physiological causes. He wrote that imbalance of the body can result in fever, headache, and other physical illnesses, while imbalance of the soul can result in anger, anxiety, sadness, and other mental symptoms. He recognized two types of depression: one caused by known reasons such as loss or failure, which can be treated psychologically, and the other caused by unknown reasons possibly caused by physiological reasons, which can be treated through physical medicine.

Avicenna was a pioneer of psychophysiology and psychosomatic medicine. He recognized "physiological psychology" in the treatment of illnesses involving emotions and developed a system for associating changes in the pulse rate with inner

feelings. Avicenna was also a pioneer of neuropsychiatry. He first described numerous neuropsychiatric conditions, including hallucination, insomnia, mania, nightmare, melancholia, dementia, epilepsy, paralysis, stroke, vertigo, and tremor.

Najab Uddin Muhammad (tenth century) described a number of mental diseases in detail. He made many careful observations of mentally ill patients and compiled them in a book that "made up the most complete classification of mental diseases theretofore known." The mental illnesses first described by Najab include agitated depression, neurosis, sexual impotence, psychosis, and mania.

Rhazes and Al-Balkhi were the first known physicians to study psychotherapy. Rhazes in particular made significant advances in psychiatry in his landmark texts *El-Mansuri* and *Al-Hawi* in the tenth century, which presented definitions, symptoms, and treatments for problems related to mental health and mental illness. He also ran the psychiatric ward of a Baghdad hospital. Such institutions could not exist in Europe at the time because of fear of demonic possessions.

Abulcasis developed material and technical designs that are still used in neurosurgery. Avenzoar gave the first accurate descriptions of neurological disorders, including meningitis, intracranial thrombophlebitis, and mediastinal germ cell tumors, and made contributions to modern neuropharmacology.

Ibn al-Haitham is considered by some to be the founder of experimental psychology and psychophysics, for his pioneering work on the psychology of visual perception in the *Book of Optics*. In Book III of the *Book of Optics*, Ibn al-Haitham argued that vision occurs in the brain, rather than the eyes. He pointed out that personal experience has an effect on what people see and how they see, and that vision and perception are subjective. Along with Al-Kindi and Ibn al-Haitham, Al-Biruni was also a pioneer of experimental psychology, as he was the first to empirically describe the concept of reaction time.

2.4.7 Biological Sciences

Other medical contributions first introduced by Arab–Muslim physicians include the discovery of the immune system, the introduction of microbiology, the use of animal testing, and the combination of medicine with agriculture, botany, chemistry, pharmacology, and biomedical sciences.

In botany, they developed a scientific approach based on sophisticated systems of crop rotation, highly developed irrigation techniques, and the introduction of a large variety of crops. Numerous encyclopedias on botany were written, with highly accurate precision and details. Al-Dinawari (828–896) is considered the founder of Arabic botany for his *Book of Plants*, in which he described at least 637 plants and discussed plant evolution, growth, and their flowers and fruits.

In the early thirteenth century, the Andalusian biologist Abu al-Abbas al-Nabati developed an early scientific method for botany, introducing empirical and experimental techniques in the testing, description, and identification of numerous *materia medica*, and separating unverified reports from those supported by actual tests and observations. Later on, his student Ibn al-Baitar wrote the *Kitab al-Jami fi al-Adwiya al-Mufrada*, which is considered one of the greatest botanical compilations in history

and was a botanical authority for centuries. It contains details on at least 1400 different plants, foods, and drugs.

The earliest known treatises dealing with environmental science, especially pollution, were Arabic treatises written by Al-Kindi, Rhazes, Ibn al-Jazzar, Avicenna, and Ibn al-Nafis. Their works covered a number of subjects related to pollution such as air pollution, water pollution, soil contamination, and municipal solid waste mishandling, as well as environmental impact assessments of certain localities. Cordoba, Al-Andalus, also had the first waste containers and waste disposal facilities for litter collection.

In zoology, Arab and Muslim scholars developed theories on evolution and natural selection, which were widely taught in medieval Islamic schools. John William Draper, a contemporary of Charles Darwin, considered the "Mohammedan theory of evolution" to be developed "much farther than we are disposed to do, extending them even to inorganic or mineral things." According to Al-Khazini, ideas on evolution were widespread among "common people" in the Islamic world by the twelfth century.

The first Muslim biologist to develop a theory on evolution was Al-Jahiz (781–869). He wrote on the effects of the environment on the likelihood of an animal to survive, and he described the struggle for existence and an early form of natural selection. Al-Jahiz was also the first to discuss food chains, and was also an early adherent of environmental determinism, arguing that the environment can determine the physical characteristics of the inhabitants of a certain community and that the origin of different human skin colors is the result of the environment.

Ibn al-Haitham wrote a book in which he argued for evolutionism, and numerous other Islamic scholars and scientists, such as Al-Biruni, Nasir al-Din Tusi, and Ibn Khaldun, discussed and developed these ideas. Translated into Latin, these works began to appear in the West after the Renaissance and appear to have had an impact on Western science. Furthermore, Ibn Miskawayh's *al-Fawz al-Asghar* expressed evolutionary ideas on how species evolved from matter, into vapor, to water, then minerals, then plants, then animals, then apes, and, finally, humans.

2.4.8 Hospitals

The hospital was one of the great achievements of medieval Arab–Islamic civilization. It was called a *Bimaristan*, from the Persian words *Bimar*, "ill person," and *stan*, "place." Although the Prophet Mohammad (PBUH) was the first to order the establishment of small mobile military *Bimaristan*, the first proper hospital built in the Arab–Islamic world was in Damascus, by Al-Waleed bin Abdel Malek (ruled from 705 to 715) with the founding of a hospice, possibly a leprosarium, in Damascus. Other versions, however, suggest that he only arranged for guides to be supplied to the blind, servants to the crippled, and monetary assistance to lepers. The earliest documented hospital established by an Islamic ruler was built in the ninth century in Baghdad probably by the Vizier to the Caliph Harun al-Rashid.

In Egypt, the first hospital was built in the southwestern quarter of present-day Cairo in 872 by Ahmad ibn Tulun, the Abbasid governor of Egypt. It is the earliest for

which there is clear evidence that care for the insane was provided. By the end of the century, two hospitals were also said to have been built in Old Cairo (Fustat), though the evidence on this point is questionable. In the twelfth century, Saladin founded the Nasiri hospital in Cairo, but it was surpassed in size and importance by the Mansuri, completed in 1248 after 11 months of construction. The Mansuri hospital (with 8000 beds) remained the primary medical center in Cairo through the fifteenth century. The Nuri hospital in Damascus was a major one from the time of its foundation in the middle of the twelfth century well into the fifteenth century, by which time the city contained five additional hospitals. Besides those in Baghdad, Damascus, and Cairo, hospitals were built throughout Islamic lands. In Al-Qayrawan in Tunisia, a hospital was built in the ninth century, and early ones were established at Mecca and Medina. Ottoman hospitals flourished in Turkey in the thirteenth century, and there were hospitals in the Indian provinces as well as in Islamic Spain.

In addition to the promotion of health and the curing of disease, hospitals served as a place for the expansion and dissemination of medical knowledge. Therefore, medical schools and libraries were attached to the larger hospitals, and senior physicians taught students, who were in turn expected to apply in the men's and women's wards what they had learned in the lecture hall. Hospitals set examinations for their students, and issued diplomas. By the eleventh century, there were even traveling clinics, staffed by the hospitals that brought medical care to those too distant or too sick to come to the hospitals themselves. The *Bimaristan* was, in short, the cradle of Arab medicine and the prototype upon which the modern hospital is based.

The style and location of hospitals were carefully determined and much attention was given to the natural environment and climate with regard to the health conditions. They preferred to build the hospitals over hills or by rivers. Harun al-Rashid asked Rhazes to build the first general hospital, so Rhazes selected the place after putting a few pieces of meat in different places in Baghdad to check which spoiled the least, thus identifying the place with the freshest air. In general, hospitals were built on a cruciform plan with four central *Iwans* or vaulted halls, with many adjacent rooms including kitchens, storage areas, a pharmacy, some living quarters for the staff, and sometimes a library. Each *Iwan* was usually provided with fountains to provide a supply of clean water and baths. There was a separate hall for women patients and areas reserved for the treatment of conditions prevalent in the area, for example, eye ailments, gastrointestinal complaints, and fevers. There was also an area for surgical cases and a special ward for the mentally ill. Some had an area for rheumatics and cold sufferers. There were frequently outpatient clinics with a free dispensary of medicines. The staff included pharmacists and a roster of physicians who were required at appointed times to be in attendance and make the rounds of patients, prescribing medications. These were assisted by stewards and orderlies, as well as a considerable number of male and female attendants who tended the basic needs of the patients. There were also instructors, possibly aspiring medical students, who trained the nonprofessional staff. The budget of such institutions must have been considerable, and in fact the budget of the Mansuri hospital was the largest of any public institution in Cairo. An administrator, who was not usually trained in medicine, was responsible

for the entire staff and the management of the hospital. In most instances, this was a political appointment, subject to the unpredictable fluctuations of political favor, as the position of controller of a hospital was very lucrative. The chief of staff, on the other hand, was a medical officer.

The first psychiatric hospitals were built in Baghdad in 705, Fes (Morocco) in the early eighth century, and Cairo in 800. Other famous psychiatric hospitals were built in Damascus and Aleppo in 1270. Medieval Arab–Muslim physicians relied mostly on clinical psychiatry and clinical observations on mentally ill patients. They made significant advances to psychiatry and were the first to provide psychotherapy and moral treatment for mentally ill patients, in addition to other new forms of treatment such as baths, drug medication, music therapy, and occupational therapy.

To keep within the scope of this chapter, the following points summarize the main characteristics of Arab–Islamic hospitals:

- *Secular*: Hospitals served all people irrespective of ethnic or religious origins. They were run by the state. Physicians of all faiths worked together with one aim in common: the well-being of patients.
- *Separate Wards*: Male and female patients occupied separate wards. Furthermore, different diseases especially infectious diseases were allocated different wards. Male nurses took care of male patients, and female nurses took care of the female patients.
- *Proper Records of Patients*: For the first time in history, hospitals kept records of patients and their medical history.
- *Hygiene*: Praying is an important pillar of Islam. Sick or healthy, it is an Islamic obligation; of course, physical performance depends on one's health, but one can even pray while laying in bed. Therefore, these hospitals had to provide the patients and employees with a plentiful, clean water supply and bathing facilities.
- *Qualifications of Physicians*: Only qualified physicians were allowed by law to practice medicine. In 931, the Caliph Al-Mugtadir from the Abbasid dynasty ordered the Chief Court Physician Sinan ibn Thabit to screen the 860 physicians of Baghdad, and only those qualified were granted license to practice. It is worth mentioning that studying medicine was a long and tedious process. Students had to finish Islamic studies, philosophy, astronomy, art, chemistry, and other subjects before being accepted as medical students. Therefore, the physician was an educated person who had wisdom and knowledge that spanned many fields. In fact, the Arabic translation of a physician is *hakim*, which means sage. Many distinguished physicians, as discussed in other chapters, showed enough talent, social knowledge, political capabilities, and wisdom to be appointed by the Caliphs as Vizier (prime minister).
- *Medical Schools*: The hospital was a place not only for treating patients, but also for educating medical students, exchanging medical knowledge, and developing medicine as a whole. At main hospitals, there were extensive libraries containing the most up-to-date books, auditoria for meetings and lectures, and housing for students and house staff.

- *Ethics and Regulation*: As mentioned above, regulations were introduced in order to ensure that all physicians had received proper education and were qualified. These regulations also ensured that doctors did not cheat their patients when it came to drug composition, for which high levels of efficacy, accuracy, and safety are essential. On a practical level, Rhazes attacked charlatans and fake doctors who roamed the cities and countryside selling their nostrums and "cures." At the same time, he warned that even highly educated physicians did not have the answers to all medical problems and could not cure all sickness or heal every disease. In order to improve their services, Rhazes advised his staff to keep up with advanced knowledge by continually studying medical books and exposing themselves to the latest information and case studies. He distinguished between healable and incurable illnesses. Pertaining to the latter, he commented that in treating advanced cases of cancer and leprosy the physician should not be blamed when he could not find a cure. He wrote the following regarding medical ethics: "The doctor's aim is to do good, even to our enemies, so much more to our friends, and my profession forbids us to do harm to our kindred, as it is instituted for the benefit and welfare of the human race, and God imposed on physicians the oath not to compose mortiferous remedies."
- *Building Hospitals*: The Caliphs of the Arab–Islamic Empire built magnificent hospitals for religious reasons, as Islam teaches that money spent on charity is a good investment for Judgment Day, as well as for political reasons to appease and demonstrate care for their people. Whatever the motive of the ruler, the population benefited and good hospitals were established.
- *Financing to Run the Hospitals*: The Caliphs provided hospitals with generous funds. There was a special system called *Al-Waqf*. A person could donate part or all of their wealth to charity. The donation was cared for and managed by the state, and its revenues help to maintain and build mosques, hospitals, and schools. Another source of funds and an important pillar of Islam is *Al-Zakat* (2.5% of property value).

Thus, the main Arab–Islamic hospitals were models for medieval hospitals built later in Europe. In addition, schools for those seeking advanced medical knowledge existed in the Islamic world and were attended by individuals from the East and Western worlds [1–8].

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CHAPTER 3

Herbal Medicine

3.1 INTRODUCTION

Herbal medicine, also known as botanical medicine, herbalism, herbology, or phytotherapy, is the oldest form of health care known to mankind. Herbal medicine flourishes today as the primary form of medicine for perhaps as much as 80% of the world's population. Over 80,000 species of plants are in use throughout the world. Usually, a specific part of the plant (root, leaves, fruit, flowers, seeds) is formulated into a suitable preparation, for example, compressed as tablets or made into pills, used to make infusions (teas), extracts, tinctures, ointments, or creams.

Many medicines commonly used today are of herbal origin. Indeed, about 25% of prescription drugs contain at least one active ingredient derived from plant material. Some are made from plant extracts others are synthesized to mimic a natural plant compound. As discussed in depth in Chapter 12, the efficacy of herbal medicines is often described in very general terms, such as carminative (an agent that prevents formation of gas in the gastrointestinal tract or facilitates the expulsion of said gas), laxative (an agent that induces bowel movements or loosens the stools), demulcent (an agent that forms a soothing film over a mucous membrane, relieving minor pain and inflammation of the membrane), antitussive (cough suppressants), or antiseptic (antimicrobial substances that are applied to living tissue/skin to reduce the possibility of infection). Unlike orthodox medicines, which usually consist of a single, isolated principle (often synthetic), herbal-based medicines contain multiple constituents.

The popularity of Greco-Arab and Islamic medicine, Ayurveda, Kampo, and traditional Chinese medicine has increased worldwide over the past two decades, probably stimulated by the belief that these systems flourished for hundreds of years, because of their organizational strengths, and because they focus primarily on natural product-based mixtures. Other factors include the perception that herbal remedies are safe (see Chapter 13), sharp increases in prices of prescription drugs, restricted access to physicians imposed by managed care, and media reports of the adverse effects of prescription drugs. The revival of interest in herbal-based medicines at the global level has been so dramatic that sales of herbal products in the world are staggering at

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over $100 billion a year. In 2008, $4.8 billion was spent in the United States on herbs and other botanical remedies. Germany is the leading country in Europe followed by France in the use of herbal medicines. Around 80% of German physicians prescribe herbs, and St John's wort is commonly prescribed for mild to moderate depression. Similarly, *Ginkgo* is experiencing high-volume sales in Europe. The cost of about 40% of the herbal remedies prescribed by German physicians is covered by the health care system. In the United States, a large center of complementary and alternative medicine has been established recently at the NIH, with heavy funding and more recently, NIH has been engaged in sponsoring studies of large clinical trials on botanicals such as St John's wort and *Ginkgo*.

Herbal medicines are classified in many European countries as drugs; in the United States they are sold as dietary supplements, whereas in Arab–Islamic world as well as China and India they are mostly sold over the counter without clear regulations. As discussed in Chapter 11, safety assessment of herbal products has often been neglected since prolonged and apparently safe use is usually considered as evidence of their safety. Nevertheless, evidence of the toxicity of such products has accumulated. This is not surprising, since herbal products are complex mixtures of secondary metabolites, many of which are potentially toxic (e.g., hepatotoxic and nephrotoxic). Therefore, the widespread use and popularity of medicinal plants brought concerns and fears over the professionalism of practitioners and of the safety, quality, and efficacy of these products. In regard to safety, biomedical journals have reported serious side effects, particularly hepatotoxicity. Other cases including kidney, nervous system, blood, cardiovascular, and dermatologic effects, mutagenicity, and carcinogenicity have also been published in the biomedical literature. In some cases, adulteration, inappropriate formulation, or lack of understanding of plant and drug interactions or uses has led to adverse reactions that are life-threatening or lethal to patients. For example, Ephedrine, first isolated in 1887 from *Ephedra sinica*, a plant long used in traditional medicine to treat asthma and other respiratory problems. Ephedrine is added to many supplements marketed to reduce weight and to boost energy. These preparations act as powerful stimulants to both the cardiovascular and the central nervous systems, and their application has been associated with strokes, cardiac arrhythmias, seizures, acute psychosis, myocardial infarction, and death. By 2000, more than 1200 serious side effects related to *Ephedra* had been reported to the FDA, although the actual number of events is undoubtedly far greater. Under current regulations, there is no penalty for withholding reports of adverse effects. However, the Justice Department, at the FDA's request, has initiated a criminal investigation because of false statements that claim an absence of adverse effects. Canadian, but not the United States, health authorities have requested the voluntary recall of health products containing *Ephedra*, noting its enhanced toxicity when combined with caffeine [1–5].

As discussed in later chapters, one of the problems with herbal drugs, especially those with active principles which have well-defined medicinal effects (e.g., *Digitalis*), is that the amount of active principle(s) varies according to the location where the plant is grown, the prevailing weather conditions, and other environmental factors. Therefore, it is vital in these instances that the crude material is assayed appropriately

so that the dosage can be accurately controlled; especially where the therapeutic ratio is low (therapeutic ratio is the ratio of the dose causing toxic effects to that required for treatment).

Another concern surrounding herbal medicine is the availability of wild plants for a growing market; it is feared that the limited supplies of known wild herbs are being threatened by overharvesting and habitat loss. The potential of isolating beneficial drugs from plants, however, has prompted large pharmaceutical companies to contribute to the conservation of the tropical rain forest [1–5].

This chapter will focus on traditional Arab herbal medicine and will highlight medical innovations introduced by Arab and Muslim scholars and a state of the art description of traditional Arab herbal medicine.

3.2 HISTORY OF HERBAL MEDICINE

As will be seen in the following chapters, plants have been used for medicinal purposes for as long as history has been recorded. Mesopotamia, Egypt, China, India, and later on the Arab–Islamic world appear to have been the places which cradled the use of herbs. In addition to plants, other natural products from animals and minerals have also been used as a source of medicines from ancient times. Hundreds of wild plants and wild and domestic animals and their by-products (e.g., milk, blood, urine, bones, feathers, hooves, skins, and tusks) form important ingredients in the preparation of curative, protective and preventive medicine.

Historical evidence shows that the study of herbs dates back over 4000 years to Mesopotamia. The records of King Hammurabi of Babylon (about 1800 BC) include instructions for using medicinal plants. Hammurabi prescribed the use of mint for digestive problems. In addition, Sumerians used the oils of *Cedrus* species (cedar) and *Cupressus sempervirens* (cypress), *Glycyrrhiza glabra* (licorice), *Commiphora* species (myrrh), thyme, and *Papaver somniferum* (poppy juice) all of which are still in use today for the treatment of diseases ranging from coughs and colds to parasitic infections and inflammation. Egyptian medicine dates from about 2900 BC. The best known Egyptian pharmaceutical record is the Ebers Papyrus dating from 1500 BC; this documents some 700 herbal- and animal-based medicines and includes formulas, such as garlic, opium, castor oil, coriander, mint, and indigo. Gargles, snuffs, poultices, infusions, pills, and ointments, with beer, milk, wine, and honey were commonly used as vehicles. Ayurvedic medicine in India (see Chapter 10) has employed herbs such as turmeric possibly as early as 1900 BC. Many other herbs and minerals used in Ayurvedic medicine were later described by Indian herbalists such as Charaka and Sushruta. The *Sushruta Samhita* attributed to Sushruta in the sixth century BC describes 700 medicinal plants, 64 preparations from mineral sources, and 57 preparations based on animal sources. The Chinese *Materia Medica* has been extensively documented over the centuries, with the first record dating from about 1100 BC (*Wu Shi Er Bing Fang*, containing 52 prescriptions), followed by works such as the Shennong Herbal (about 100 BC; 365 drugs), and the Tang Herbal (659 AD, 850 drugs).

Greek and Roman medicinal practices, as preserved in the writings of Hippocrates and Galen, formed the roots for later Greco-Arab and Islamic medicine and modern Western medicine. Theophrastus (about 300 BC), in his *History of Plants*, dealt with the medicinal qualities of herbs, and noted the ability to change their characteristics through cultivation. Dioscorides (100 AD) mentioned the collection, storage, and use of medicinal herbs, and Galen (130–200) wrote 30 books on these subjects, and is well known for his complex prescriptions and formulas used in compounding drugs, sometimes containing dozens of ingredients. Taken together, a large and complex medical literature exploring and synthesizing the theory and practice of medicinal plants was developed. These included their potential medical uses and safety. Numerous encyclopedias on botany were written with highly accurate precision and details of medicinal plants.

The uses of plants for medicine changed little in early medieval Europe. Many Greek and Roman writings on medicine, as on other subjects, were preserved by hand copying of manuscripts in monasteries. The monasteries thus tended to become local centers of medical knowledge, and their herb gardens provided the raw materials for simple treatment of common disorders. At the same time, folk medicine in the home and village continued uninterrupted, supporting numerous wandering and settled herbalists. Among these were the "wise-women," who prescribed herbal remedies often along with spells and enchantments. It was not until the late Middle Ages that women who were knowledgeable in herbal lore became the targets of "witch hysteria." One of the most famous women in the herbal tradition was Hildegard of Bingen, a twelfth century Benedictine nun, she wrote a medical text called *Causes and Cures*.

By the seventeenth century, the knowledge of herbal medicine was widely disseminated throughout Europe. In 1649, Nicholas Culpeper wrote *A Physical Directory*, and a few years later produced *The English Physician*. This respected herbal pharmacopeia was one of the first manuals that the layperson could use for health care, and it is still widely referred to and quoted today. Culpeper had studied at Cambridge University and was meant to become a great doctor, in the academic sense of the word. Instead, he chose to apprentice to an apothecary and eventually set up his own shop. He served the poor people of London and became known as their neighborhood doctor. The herbal medicine he created was meant for the layperson.

The first U.S. *Pharmacopeia* was published in 1820 and became the legal standard for medical compounds in 1906. It included an authoritative listing of herbal drugs, with descriptions of their properties, uses, dosages, and tests of purity.

Undisputedly, the history of herbal medicine is inextricably intertwined with that of modern medicine. Herbal-derived substances represented about 80% of all drugs by the middle of the nineteenth century. At the turn of the twentieth century, synthetic drugs dominated as a result of rapid developments in the pharmaceutical industry, although the use of herbal medicine has never ceased. Even today, at least 25% of sold drugs are plant-derived. In addition, about 75% of plants that provide active ingredients for prescription drugs came to the attention of researchers because of their use in traditional medicine. And among the 120 active compounds currently

isolated from the higher plants and widely used in modern medicine today, 80% show a positive correlation between their modern therapeutic use and the traditional use of the plants from which they are derived [6–13].

3.3 GRECO-ARAB AND ISLAMIC HERBAL MEDICINE

As mentioned in Chapter 2, medicine was a central part of Arab–Islamic civilization. Responding to circumstances of time and place, Arab–Islamic physicians and scholars developed a large and complex medical literature exploring and synthesizing the theory and practice of medicine and pharmacy. They introduced many new ideas and upgraded the knowledge about herbs and their pharmacology and safety. Medical schools began to appear from the ninth century in the Arab-Islamic world, which were generally more advanced than medieval Europe during this era.

As a trading culture, Arab travelers had access to plant material from distant places such as Persia, China, and India. Herbals, medical texts and translations of the classics of antiquity filtered in from east and west. Arabs and Muslims appreciated Greco-Roman culture and learning, and translated tens of thousands of medical texts into Arabic for further study. Botanists and physicians significantly expanded on the earlier knowledge of *Materia Medica*. For example, Al-Dinawari (828–896) is considered as the founder of Arabic botany for his *Book of Plants*, in which he described about 640 plants and described the phases of plant growth and the production of flowers and fruit. Avicenna's *The Canon of Medicine* is considered the first pharmacopoeia, and lists 800 tested drugs, plants, and minerals. Volume two of the canon was devoted to a discussion of the healing properties of herbs, including senna, sandalwood, rhubarb, myrrh, cinammon, and rosewater. In particular, the *Canon* introduced clinical trials, randomized controlled trials, and efficacy tests.

Baghdad was an important center for Arab herbalism, as was Al-Andalus between 800 and 1400. Abulcasis (936–1013) of Cordoba authored *The Book of Simples*, an important source for later European herbals. The experimental scientific methods were introduced into the field of *Materia Medica* in the thirteenth century by the Andalusian botanist Abu al-Abbas al-Nabati. Al-Nabati introduced empirical techniques in the testing, description, and identification of numerous *Materia Medica*, and he separated unverified reports from those supported by actual tests and observations. This allowed the study of *Materia Medica* to evolve into the science of pharmacology. Later on Ibn al-Baitar, who lived in Damascus, Syria (1197–1248), compiled *The Book on Drinks and Foods*, which is a collection of different drinks and foods. It is one of the most prestigious book in the Arabian pharmacopeia; it contains 260 references. The medications were classified in alphabetical order. Other pharmacopoeia books include that written by Abu-Rayhan Biruni in the eleventh century and Ibn Zuhr (Avenzoar) in the twelfth century. Daoud al-Antaki used different herbs for treating patients and published a book on medicinal herbs summarizing the knowledge of his predecessors. Al-Antaki described in his book 57 plants that were used as a source for simple drugs, or frequently as one ingredient in more complex herbal-based

remedies. He described the plant as well as its preparations and form of administration. For instance, birthwort, carob, castor-oil plant, common fennel, common myrtle, Egyptian balsam, great horsetail, Leopardus-bane, autumn mandrake, paper reed, Persian cyclamen, saffron, serapias, sycamore fig, and Syrian bryony. Furthermore, Al-Antaki mentioned nonindigenous plants, which were brought to the area specifically for their medicinal applications, such as Cornelian cherry, purging croton, and gardenia. He also described the pharmacological uses of typical agricultural crops, such as Caraway, carrot, wild coriander, pear, quince, sugar cane, and walnut. The traditional and medicinal use of many of these plants is described in Chapters 8 and 17.

In the medieval Arab–Islamic world, pharmacology was a profession practiced by highly skilled specialists. Medicines were produced in a variety of forms—ointments, pills, elixirs, confections, tinctures, suppositories, and inhalants. Herbal medicines were classified according to their effects on the human body. For example, diuretics (promote urination and thus expel toxins), expectorants (remove mucous accumulation), topical antiseptic cleansers, stimulants (prescribed to increase blood flow and raise energy level), tonics (general strength building and disease prevention), analgesics and anesthetics, digestive aids, and oral health [1–5].

3.4 CURRENT STATUS OF HERBAL MEDICINE

In line with the revival of interest in the herbal remedies known from the ancient medical systems, such as Greco-Arab, Ayurvedic, and Chinese, there is also greater research activity in these medical systems particularly on the biological and molecular aspects of medicinal plants. As discussed in later chapters, there is an increasing trend in the United States and Canada as well as in Europe to incorporate herbal-derived remedies as an essential component in the medical curriculum. As a result, conventional medicine is now beginning to accept the use of herbal remedies once their efficacy and safety are scientifically validated.

Despite drug discovery technology diversification and reduced funding for natural product-based drug discovery, natural products from plants and other biological sources remain an undiminished source of new pharmaceuticals. The World Health Organization (WHO) estimates that about 80% of the world population presently uses herbal-based medicines for some aspect of primary health care. Although industrial funding for natural product-based drug discovery has been declining from 1984 to 2003, the percentage of natural product-derived small molecule patents has remained relatively constant. A comprehensive review of human drugs introduced since 1981 suggests that, of 847 small molecule-based drugs, 43 were natural products, 232 were derived from natural products (usually semisynthetically), and 572 were synthetic molecules. However, 262 of the 572 synthetic molecules had a natural product-inspired pharmacophore or could be considered natural product analogues. Natural products continue to make the most dramatic impact in the area of cancer. From 155 anticancer drugs developed since the 1940s, only 27% could not be traced to natural products, with 47% being either a natural product or a direct derivation thereof. The

above analysis did not include biologics and vaccines, which are, by definition, derived from nature.

The use of, and search for, drugs and dietary supplements derived from plants have accelerated in recent years. Paralleling and even exceeding the growth in popularity of Arab and Islamic herbal medicines is the surge in information available to the public in the media. For example, a Google search using the term "Arab herbal medicine" reveals more than 280,000 citations. Faced with this huge amount of information, people are often left with a desire for guidance and direction. In the past decade, there has been an increase in scientific research activities in the Arab–Islamic world. Pharmacologists, microbiologists, botanists, and natural-products chemists are investigating the pharmacological properties of potential plants in order to identify phytochemicals and leads that could be developed for treatment of various diseases. A Medline and Google Scholar search using the terms "Arab herbal medicine" reveals more than 6000 citations. Examples include the use of traditional Arab and Islamic herbs for treatment of diabetics (1500 citations), cancer (1300 citations), liver diseases, inflammation (1200 citations), and infertility (1400 citations).

According to recent surveys, there are about 450 medicinal plants in the Eastern region of the Mediterranean and about 230 medicinal plants in the coastal Mediterranean region in Egypt. These plants are used by healers for the treatment and prevention of almost all types of human disease (Tables 9.1 and 12.1), such as cancer; skin, respiratory, digestive, and liver diseases; diabetes and others, and are sold or traded in market places in the Mediterranean region or internationally. In many cases, plant extracts are prepared into a mixture (Table 12.2). Plant parts used include leaves, flowers, stems, roots, seeds, and berries. In the following section, we discuss the efficacy of herbal remedies that are prepared according to knowledge of Greco-Arab herbal medicine in the treatment of human diseases, such as diabetics, cancer, infertility, and inflammation.

Most herbalists acknowledge that pharmaceuticals are more effective in emergency situations where time is of the essence. For example, elevated blood pressure posing imminent danger. However, they believe that over the long-term herbs are helpful in treatment as well as in prevention of diseases, and that in addition, they provide nutritional and immunological support that synthetic drugs or purified herbal compounds lack.

Herbalists generally use the whole plant or extracts from parts of plants, for example, the roots or leaves, but do not isolate a particular active compound. Modern medicine prefers single ingredients on the grounds whose dosage can be more easily quantified. They argue that the different phytochemicals present in herbs will interact to potentiate therapeutic effects of the herb and reduce side effects. Potentiation can be defined as positive interactions that intensify the potency of a bioactive ingredient. Additive and synergistic effects are subsets of potentiation, where two or more compounds in a mixture interact to provide a combined effect that is equal to the sum of the effects of the single molecule (additive) or where combinations of bioactive substances exert effects that are greater than the sum of individual molecules (synergistic). Potentiation can exist between two components in a single plant extract, two components from two different plant extracts, or between a phytochemical and

synthetic drug. A good example of the multicomponent nature of botanicals is illustrated in the field of cancer research. Phytochemicals have been shown to affect various parts of signal transduction pathways including gene expression, cell cycle progression, proliferation, cell mortality, metabolism, and apoptosis. Combination chemotherapy has been the mainstay of cancer treatment for 40 years. It is therefore reasonable to assume that a mixture of compounds (phytochemical or synthetic) would have greater bioactivity than a single compound because a mixture of bioactive compounds has the ability to affect multiple targets. Studies have documented synergistic anticancer effects of phytochemicals including quercetin, catechins, resveratrol, and curcumin with various cancer drugs and/or other phytochemicals. In addition, natural products have been shown to overcome multiple drug resistance in tumors when used in combination with other natural products or drugs. Similar observations have been made in the field of antibiotic research. A number of plant extracts and natural products have been shown to work synergistically with existing antibiotics, restoring antibiotic activity against resistant strains of *Staphylococcus aureus* (methicillin resistant), *Escherichia coli*, and *Shigella*.

Human diseases are multifactorial and may be treated by consuming the chemical defenses that herbalists believe to be present in herbs (see Chapter 12). Viruses, inflammation, nutrition, and ROS (reactive oxygen species) may all play a role in cancer. Herbalists claim a single herb may simultaneously address several of these factors. In short, they view their field as the study of a web of relationships rather than a quest for a single cause and a single cure for a single condition.

In selecting herbal treatments, herbalists may use forms of information that are not applicable to pharmacists. Herbalists contend that historical medical records and herbals are underutilized resources. As discussed in details in Chapter 16, the selection of potential medicinal plant in the Greco-Arab and Islamic medicine was based on the following factors: (1) Knowledge developed traditional healers in the pre-Islamic period based on a long history of trial and error. (2) Theoretical and practical knowledge introduced by Islam. These include natural products mentioned in the Holy Quran or in the *Hadith* of the Prophet Mohammad (PBUH), for example, honey, milk, dates, black seeds, olive leaf, and olive oil. (3) Theoretical and practical knowledge developed in other medical system, which became available to Arab–Islamic scholars after the translation of Greek, Indian, and Persian scripts. (4) Theoretical and practical knowledge introduced by Arab and Muslim scholars. In the case of diet therapy, food built a substantial part of pre-Islamic medicine as well as in other traditional medicines, for example, Greek and Ayurvedic. Diet is a matter of faith in Islam, and plays an important role in maintaining healthy body, soul, and spirit, which in turn strengthen the nature of their mutual relationship. The Prophet Mohammad (PBUH) used food more than 1400 years ago. The Prophet also recommended regarding food as part of an overall holistic approach to health and incorporating into one's everyday diet. Muslims should follow a set of dietary laws outlined in the Quran, were almost everything is permitted (halal), except what God specifically prohibited (haram). These facts may explain the remarkable outstanding interest of the Arabic–Islamic world in food therapy [6–17].

3.5 COMMONLY USED MEDICINAL PLANTS IN ARAB–ISLAMIC MEDICINE

As discussed in depth in Chapters 8 and 17, herbs are available in a variety of forms, including fresh, dried, in tablets or capsules, or bottled in liquid form (Table 9.1). Medicinal plants are available as single or in mixtures formulated for specific conditions.

Currently, medicinal plants fall into two categories: wild grown and cultivated. A wild-grown herb is one that grows naturally, without human intervention. As a result of natural selection, plants tend to be found in places with conditions that optimize their growth. The disadvantage of wild-grown herbs is that there is no guarantee the plants have not been exposed to chemicals and pesticides. Herbs harvested from a meadow, for example, may have been exposed to chemical drift from a crop-dusted farm nearby. Exhaust fumes from passing traffic may have settled invisibly on plants growing near a country road.

Because of the possibility of contamination cultivated organic herbs grown commercially may be a better choice. Organic farm-grown herbs are becoming increasingly available, as more and more herb farms are being established. With careful management, organic herb farms can provide a steady supply of quality herbs to the consumer. To produce top-quality products, herb farmers require a great deal of specialized knowledge. For maximum potency, it is important that particular herbs be harvested at the optimum season. For example, echinacea is gathered in the spring, winter, and fall, but not in summer, when the plant's energies are concentrated on growth and flowering.

Chapter 8 provides an overview of traditional uses, safety, and efficacy of commonly used herbal medicines in the Eastern region of the Mediterranean (Lebanon, Jordan, Israel and Palestine) where more than 3600 plant species are found and about 450–550 plants are noted for their uses as medicinal herbs (Figure 3.1). Plant parts used included leaves, flowers, stems, roots, seeds, and berries. In order to reduce the confusions of common names, which can refer to different plants depending on the region where they grow, we used Latin names as well as common Arabic names and common English names (see Appendix I). To keep within the scope of this chapter, we mention here briefly the most commonly used medicinal plants in the Mediterranean region [1–3,6–25].

Nigella sativa, black seed (Figure 8.1), is one of the most commonly used medicinal herbs throughout the Middle East. *N. sativa* seeds have been used for centuries as a spice and food preservative, as well as a protective and curative remedy for numerous diseases have long been prescribed in Greco-Arab and Islamic medicine as well as in Indian and Chinese traditional medicine (Chapter 10) for prevention and treatment of a wide range of diseases, including bronchial asthma, headache, dysentery, infections, obesity, back pain, hypertension, and gastrointestinal problems. It is the black seed referred to by the Prophet (PBUH) (570–632), who once stated that "*the black seed can heal every disease, except death*." Avicenna (980–1037 AD) refers to *N. sativa* in his *Canon of Medicine*, as the seed that stimulates the body's energy and helps recovery from fatigue and dispiritedness.

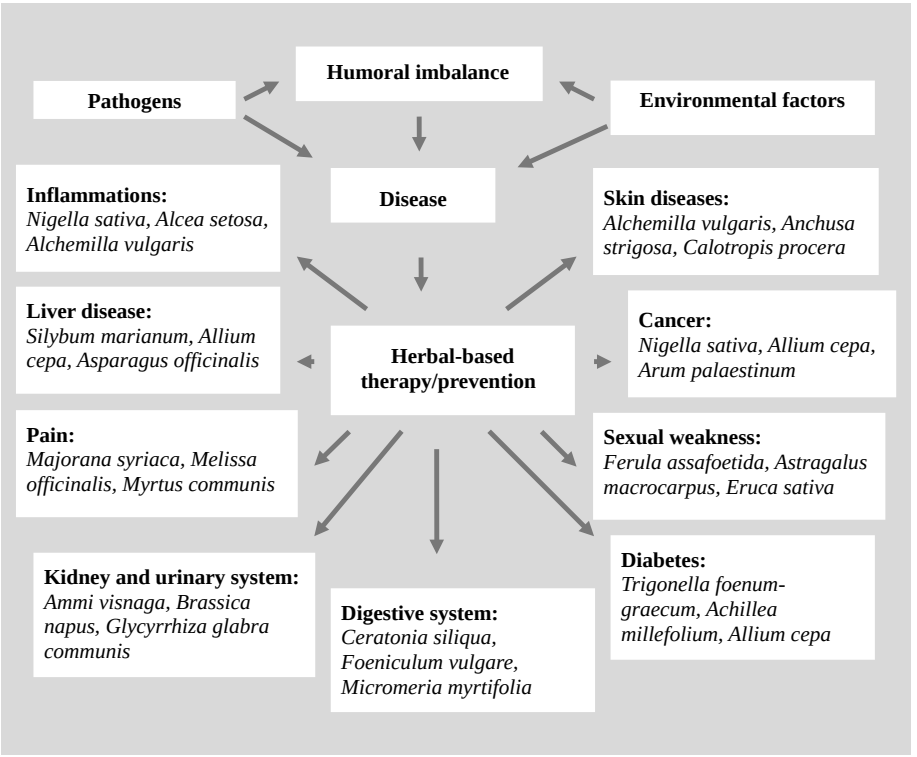

FIGURE 3.1 Diseases and Commonly used medicinal plants. Herbs are used either in their crude forms or as herbal teas, syrups, infusions, and powders in treatment and prevention of diseases. Efficacy and safety medicinal plants in this diagram are discussed in detail in Chapters 8 and 12.

Olea europaea, the Olive, like *N. sativa*, is one of the most commonly used medicinal herbs throughout the Mediterranean. While olive oil is well known for its health benefits, the leaf has been used medicinally in various historical contexts and cultures. Olive leaf and olive leaf extracts are now marketed as antioxidants, antiaging, immunostimulators, and even antibiotics. Clinical evidence has proven the antidiabetes and antihypertension effects of leaf extracts. In addition, several studies support its antibacterial, antifungal, and anti-inflammatory properties. The olive tree is described in the Quran as the holy tree and Prophet (PBUH) said "*Eat olive oil and massage it over your bodies since it is a holy tree*."

Trigonella foenum-graecum, fenugreek, is extensively cultivated in the Mediterranean region. It is a spice used in Indian cooking and commonly used herb in Ayurveda. Defatted seeds of fenugreek, which are rich in fiber, saponins, and protein, have been described in early Greek and Latin pharmacopoeias as antihyperglycemic. In addition to the seed, other parts of the herb have also been investigated. Therapeutic effects include delay of gastric emptying, slowing carbohydrate absorption, and inhibition of glucose transport from the fiber content, as well as increased erythrocyte

insulin receptors and modulation of peripheral glucose utilization. Fenugreek is another herb that was favored by the Prophet (PBUH) and herbalists for thousands of years.

Salvia species, sage, has been used for centuries, especially by the Chinese to promote longevity and in Roman ceremonies as a sacred herb. The positive benefits of *Salvia officinalis* to health are reputed throughout Ancient Roman times and the Middle Ages. A quote such as: "*Cur moriatur homo cui Salvia crescit in horto?*"—"Why should a man die whilst sage grows in his garden?" epitomizes the impact of sage on that society at the time. Most *Salvia* species are inherently linked to local traditional medicine systems in their country of origin. *S. officinalis* is used to treat various conditions such as bronchial infections, colds, and coughs. Furthermore, *S. officinalis* is traditionally used to treat digestive disorders such as dyspepsia, flatulence, poor digestion, and bloating, to reduce excessive perspiration, for example, in the menopause. It is also used as a gargle or mouthwash to treat inflammations of the mouth or throat mucosa, such as pharyngitis, tonsillitis, stomatitis, gingivitis, and glossitis.

Ammi visnaga, khella, has traditionally been used to treat respiratory system diseases such as asthma, bronchitis, emphysema, and whooping cough, as well as cardiovascular disorders, premenstrual syndrome, liver and gallbladder disorders, and to stimulate diuresis. Its purported effect is related to its antispasmodic action on smaller bronchial muscles, coronary arteries, and urinary tract tubules. *A. visnaga* may vasodilate the coronary arteries, which increases the blood supply to the myocardium, and as a result, can be used to treat mild forms of angina. It is also used to treat problems associated with spasms and constriction of the gallbladder and bile duct and facilitates discharge of kidney stones and gallstones.

Silybum marianum, milk thistle, is currently the most scientifically well-investigated medicinal plant in the treatment of liver disease. It has a long history of use in the Greco-Arab and Islamic medicine as well as in the European folk medicine as a liver tonic and in the treatment of chronic or acute liver disease, as well as protecting the liver against toxicity.

Origanum majorana, sweet marjoram, is used as a sedative. Marjoram eases stiff joints and muscle spasms, including tics, excessive coughing, menstrual cramps, and headaches (especially migraines). It also slightly lowers high blood pressure. Testing has shown it to be one of the most effective fragrances in relaxing brain waves. As a result, it makes excellent calming massage oil, delightful when combined with the softer lavender. It has specific properties that fight the viruses and bacteria responsible for colds, flu, or laryngitis. In healing salves and creams, it also soothes burns, bruises, and inflammation. *O. majorana* is also an antioxidant that naturally preserves food.

Inula viscosa, tayun, has been regarded for centuries as one of the most effective medicinal plants in the Mediterranean region. *I. viscosa* is traditionally used to treat infections, inflammations, fever, and external skin irritations. It is also effective in wound healing. The roots are used against cough and catarrh, as an antiseptic and expectorant, which loosens phlegm and supports mucus membranes.

Portulaca oleracea, purslane, is traditionally used in the treatment of a variety of conditions that include headache, painful urination, stomach ache, enteritis, mastitis,

lack of milk flow in nursing mothers, and for postpartum bleeding. Externally, it is used to treat burns, earache, ulcers, pruritis (itching skin), insect stings, inflammations, skin sores, eczema, and abscesses. These conditions are usually treated with the fresh herb used as a poultice or the expressed juice is used. Psoralens as repigmenting agents for vitiligo were described as early as 1400 BC. The Indian sacred book Atharva Veda mentioned the effect of the plant on skin color.

Majorana syriaca, Palestinian thyme, is considered one of the most popular herbs in the Arab world. It is traditionally used to treat asthma, congestion, rheumatism, sore throats, wounds, ulcers, and tumors. A combination of *M. syriaca* dried leaves, salt, sesame seeds, and the fruits of the tree *Rhus coriaria* are called "Zaatar" in Arabic, a very popular mixture that is used almost daily in the Middle East as a food, additive in salads and spice for pastry, and meat. With its high content of volatile oils, the herb leaves are used in Greco-Arab and Islamic medicine as herbal tea to treat cold, flu, and cough.

Eruca sativa, rucola, is traditionally considered as a general tonic and potent aphrodisiac. It is known generally as a food, in which the leaves are eaten as part of salads. It has been known as a garden vegetable since Biblical Times, and there are many records of its household usage from the Hellenistic period onwards. It finds widespread use in Greco-Arab and Islamic medicine. These include antibacterial action (for eye infections), increasing fertility and sperm production, as an aid to digestion, and kidney function. Ibn Wahsiyya is quoted as stating that the ground seeds when mixed in a cream and spread on the face can be used for treatment of acne.

Cichorium intybus, wild chicory, is a well-known food and medicinal herb. It is mentioned in most of the major herb books of the Western world. It is used both in the prevention and treatment of various diseases. It is used much like dandelion in European herbal medicine. That is, it is helpful in cleaning the body and supporting the liver and also in stimulating the eliminative processes both via the intestine and the kidneys. It is a warming and tonifying plant, and the fresh root is used traditionally in chest problems and cold conditions. The plant is classically used in cold countries as part of soup to ward off colds and flu. Professional herbalists also use the plant as part of mixtures for the treatment of dry coughs, chest pain and bronchial problems. Arabic traditional healers today regard chicory as part of a combined treatment of metabolic problems, and a medicine to cleanse the body, and treat colds and flu.

Cyperus rotundus, nut-grass, roots are used in Ayurvedic medicine as an infusion or as a soup for fever, diarrhea, dysentery, dyspepsia, vomiting, and cholera. Fresh tubers are applied on the breast in the form of paste or plaster as galactagogue. Paste is applied to scorpion stings and when dried, to spreading ulcers. In Greco-Arab and Islamic medicine, the root is a diuretic, emmenagogue, diaphoretic, anthelmintic, vulnerary, and useful for ulcers and sores, fevers, and dyspepsia.

Sarcopoterium spinosum, thorny burnet, is used in Greco-Arab medicine for its antidiabetic properties. The plant is also used to treat stomachaches, toothache, gingivitis, oliguria, external inflammation, and as a tranquilizer.

Allium sativum, garlic and onion (*Allium cepa* L.) are used both as a food and for medicinal applications. Garlic has been used for thousands of years for medicinal purposes. Sanskrit records mention its medicinal use about 5000 years ago, and it has

been used for at least 3000 years in Chinese medicine. The Egyptians, Babylonians, Greeks, and Romans used garlic for healing purposes. Garlic and onion are rich sources of several phytonutrients recognized as important elements of the Mediterranean diet, but are also used in the treatment and prevention of a number of diseases, including cancer, coronary heart disease, obesity, hypercholesterolemia, diabetes type 2, hypertension, cataract, and disturbances of the gastrointestinal tract (e.g., colic pain, flatulent colic, and dyspepsia).

Foeniculum vulgare, fennel, is used in Greco-Arab and Islamic medicine as well as in other different medical systems. Fennel is known for its laxative properties. It is also used as a muscle relaxant as well as to treat urinary disorders. In the eastern Mediterranean countries, fennel is used for its therapeutic effects on the gastrointestinal system as a pain reliever as well as for its diuretic properties. Experimental as well as human studies demonstrated that fennel oil had antispasmodic and relaxing effects on smooth muscles.

Eryngium creticum, "*Qors Aanneh*" is used in traditional Arab medicine for a wide range of diseases; in particular, the roots are used against various inflammatory disorders, edema, sinusitis, urinary infections and inflammations, and snake or scorpion bites or goiter; roots and leaves for infertility; and herbs for wound healing as well as food while fresh. Traditional reports stressed the use of *E. creticum* as an antidote for scorpion poison, as well as for its hypoglycemic effects.

Gundelia tournefortii, commonly known as *Akkoub* in the Arab world, is a medicinal plant and also used as a nutritious food. It is recorded that the flowers, leaves, seeds, and stems of *Akkoub* are used as food sources. In the Middle East, the young and still undeveloped flower buds are sold in the local markets just like artichoke hearts; it is a highly sought item. In Arab–Islamic traditional medicine, *Akkoub* is known for its hypoglycemic and laxative properties.

Urtica dioica, stinging nettle, is widely used in Greco-Arab medicine to treat stomachaches, rheumatic pain, colds and cough, and liver insufficiency. It is also used as a hypotensive and anti-inflammatory agent.

Chamomilla recutita, chamomile, is an annual herbaceous plant indigenous to Europe and Western Asia. Also known as German chamomile or wild chamomile, the plant is cultivated for the flower heads. Infusions and essential oils from fresh or dried flower heads have aromatic, flavoring, and coloring properties. Both are used in a number of commercial products including soaps, detergents, perfumes, lotions, ointments, hair products, baked goods, confections, alcoholic beverages, and herbal teas. Chamomile tea, brewed from dried flower heads, has been used traditionally for medicinal purposes. The main constituents of the flowers include several phenolic compounds, primarily the flavonoids apigenin, quercetin, patuletin, and luteolin. The principal components of the essential oil extracted from the flowers are the terpenoids α-bisabolol and its oxides and azulenes, including chamazulene. Chamomile has moderate antioxidant and antimicrobial activities, and significant antiplatelet activity *in vitro*. Animal model studies indicate potent anti-inflammatory action, some antimutagenic and cholesterol-lowering activities, as well as antispasmodic and anxiolytic effects. However, human studies are limited, and clinical trials examining the purported sedative properties of chamomile tea are absent.

Pimpinella anisum, anise, is a member of the Apiaceae family that includes fennel, caraway, cumin, cilantro, dill, and carrots. It is commonly used to flavor candy, foods, and liqueurs. The seeds ("fruits") are used in traditional Arab medicine for a wide range of diseases, particularly for their ability to bring about a reduction in gas and bloating and to settle the problems related to digestion. Seed-based remedies are commonly used with infants and children to induce relief from cases of colic; these remedies are also given to people of all ages to help in relieving the symptoms associated with indigestion and nausea arising from a variety of causes. An additional therapeutic effect of the seeds is their antispasmodic properties, which are effective in reducing the symptoms of menstrual pain, the discomfort during asthma attacks, as well as in the treatment of whooping cough and other spasmodic coughs. Furthermore, remedies made from the seeds are also believed to be able to bring about an increase in the production of breast milk; these remedies may also be beneficial in the treatment of impotence and frigidity. The essential herbal oils derived from anise are also used in the treatment of similar complaints in patients. It is recommended that patients should consume the essential oil while they are under careful and responsible professional supervision. Women in the term of pregnancy must also abstain from taking anise, with the exception of minute amounts, such as those normally used during cooking.

Hypericum triquetrifolium, wavy leaf St John's wort or tangled hypericum, is native to Eastern Europe and the Mediterranean area. *H. triquetrifolium*-derived remedies have been used in traditional Greco-Arab and Islamic herbal medicine to treat inflammatory diseases. The classic Arabic name for this plant species is *Dathi* or *Nabtat Yohanna*. Unfortunately, this plant is no longer used within the practitioner communities in Palestine. This fact reflects a process of extinction of important elements of the Arab herbal medicine heritage.

Ferula asafoetida, devil's dung, is plant native to central Asia and it is held in great esteem among indigenous Indian medicine men. The roots are thick and pulpy and also yield a similar resin to that of the stems, it is said the roots look like "carrots." All parts of the plant have a distinctive stinky smell. In Ayurvedic medicine, it is highly regarded as a condiment and medicinal remedy for various conditions. Traditional Chinese herbalists say this resin enters the liver, spleen, and stomach channels where it stimulates the intestinal, respiratory, and nervous systems. *Asafoetida* has digestive, sedative, stimulant, antispasmodic, expectorant, emmenagogue (promoting menstrual discharge), and vermifuge (expelling worms or other parasites in the intestines) properties.

Zallouh is the common name in the Middle East for the roots of the species *Ferula hermonis* growing on the slopes of Mount Hermon in the Syrian Golan Heights and has been used for centuries as a folk remedy to treat frigidity in women, and erectile and sexual dysfunction in men. Greco-Arab and Islamic medicine supports its use as a sexual tonic to encourage potency. Al-Razi (Rhazes 864–930) reported that Indians use *F. asafoetida* L. as the main botanical aphrodisiac, several centuries before his time. Ibn Sina (Avicenna) and Al-Antaki have also emphasized the aphrodisiac effect of *F. asafoetida* L.

Melissa officinalis, lemon balm, is a perennial herb in the mint family Lamiaceae, native to the Mediterranean region and southern Europe. The therapeutic uses of *this*

plant dates back into ancient times. Greco-Arab and Islamic physicians used the herb to treat heart disorders. In the Middle Ages, a sprig of lemon balm was said to staunch the blood of a sword wound and to help relieve an earache, toothache, pregnancy sickness, fix crooked necks, and prevent baldness. In more recent history, *M. officinalis* was used against catarrh, fevers, and flatulence problems. People realized that the oil makes for great surgical dressing because it kills off germs and while the oil dries, it seals up wounds. Physicians used the herb to entice sweat for fevers and regulating menstrual cycles; however, lemon balm was not as preferred as other mints because it contains less volatile oil. Pharmacological properties of this plant on the nervous system are documented in medicinal history that extending back to the *Materia Medica* in approximately 50–80 BC. *M. officinalis* gained widespread usage throughout Europe by the Middle Ages, with medicinal use during this early epoch including a recommendation by Paracelsus (1493–1541) that balm would completely revivify a man, and as an indication for all complaints supposed to proceed from a disordered state of the nervous system.

Ruscus aculeatus, butcher, is native to the Mediterranean region and Western Europe. The roots and sometimes the young shoots are known for the therapeutic properties of the plant. *R. aculeatus* has been known since ancient times as a medicinal plant and was commonly used in the Greek, Roman, and Greco-Arab traditions. It is used as a diuretic in the treatment of urinary problems. It is also used in the treatment of a variety of inflammatory and circulatory diseases. In modern herbalism, *R. aculeatus* is the most frequently used herb in the treatment of varicose veins, hemorrhoids, and swellings.

Punica granatum, the pomegranate, is a fruit-bearing deciduous shrub or small tree native to the region from Persia to northern India and has been cultivated and naturalized over the whole Mediterranean region and the Caucasus since ancient times. The pomegranate has long been used in traditional medicine to treat a variety of ailments, including sore throat, inflammation, and rheumatism. Additional traditional uses include treatment of diarrhea and colic and to remove intestinal worms in children. The fruit is also used for treating bladder disturbances, strengthening gums, and soothing mouth ulcers. Pomegranates feature prominently in all religions, Judaism, Christianity, Islam, Buddhism, and Zoroastrianism. According to the Quran, pomegranates grow in the gardens of Paradise. The Quran also mentions pomegranates twice as examples of good things that God created. In Ayurvedic medicine, the pomegranate is considered "a pharmacy unto itself," the bark and roots believed to have anthelmintic and vermifuge properties; the peels a powerful astringent and cure for diarrhea and oral aphthae; and the juice a "refrigerant" and "blood tonic." Dried pomegranate peels are decocted in water and employed both internally and externally for numerous problems demanding astringents and/or germicides, especially for aphthae, diarrhea, and ulcers. Mixtures of pomegranate seed, juice, and peel products paradoxically have been reported to not only prevent abortion but also conception. In Greco-Arab and Islamic medicine, pomegranate flowers serve as a remedy for *diabetes mellitus*.

Ruta chalepensis, ruta, is a perennial herb widely distributed in the Mediterranean region. It is one of the commonly used medicinal plants in Greco-Arab and Islamic medicine. Orally, it is used as analgesic, antipyretic, anti-inflammatory, in menstrual

problems, antispasmodic, anthelmintic, and abortifacient, relief of rheumatic pain, and mental disorders. Topically, it is used as hair tonic, insect repellent, and for snakebite.

Conium maculatum, poison hemlock, is a weed known almost worldwide for its toxicity to many domestic animals and to humans. The plant is used in traditional medicine as a sedative and antispasmodic, and in sufficient doses acts as a paralyzer to the centers of motion. Therefore, it has been recommended as an antidote to Strychnine poisoning, and in other poisons of the same class, and in tetanus, and hydrophobia. Because of its sedative action on the motor centers, *C. maculatum* juice is prescribed as a remedy in cases of undue nervous motor excitability, such as teething in children, epilepsy from dentition, in spasms of the larynx and gullet, and in acute mania. As an inhalation it is said to relieve cough in bronchitis, whooping cough, and asthma. *C. maculatum* was formerly believed to exercise an alterative effect in scrofulous disorders. Greco-Arab physicians were in the practice of using it to cure indolent tumors, swellings and pains of the joints, as well as for affections of the skin.

Capparis spinosa, the caper, is a perennial spiny bush that bears rounded, fleshy leaves, and big white to pinkish-white flowers. The plant is best known for the edible bud and fruit (*caper berry*), which are usually consumed pickled. In Greek traditional medicine, an herbal tea made of caper root and young shoots is considered to be beneficial against rheumatism. Dioscoride also provides instructions on the use of sprouts, roots, leaves, and seeds in the treatment of inflammation. *C. spinosa* is used as an analgesic, anthelmintic, antihemorrhoidal, aperient, deobstruent, depurative, diuretic, expectorant, tonic, and vasoconstrictor. Decoctions from the root bark have been used in traditional medicines for dropsy, anemia, arthritis, and gout. The stem bark is bitter and diuretic. If taken before meals, it will increase the appetite. In Ayurvedic medicine *C. spinosa* is recorded with other hepatic stimulants and protectors as improving liver function. It is used internally in the treatment of gastrointestinal infections, diarrhea, gout, and rheumatism. Externally, it is used to treat skin conditions, capillary weakness, and easy bruising. The unopened flower buds are a laxative and are used internally in the treatment of coughs, and externally to treat eye infections. The buds are a rich source of compounds known as aldose reductase inhibitors; it has been shown that these compounds are effective in preventing the formation of cataracts. The buds are harvested before the flowers open and can be pickled for later use—when prepared correctly they are said to ease stomach pain. In Greco-Arab and Islamic medicine, the decoction of root bark is prescribed as deobstruent to liver and spleen, as anthelmintic and anti-inflammatory agents.

Atriplex species, saltbushes are dominant in many arid and semiarid regions of the world, particularly in habitats that combine relatively high soil salinity with aridity. About 40–50 *Atriplex* species are found in the Mediterranean basin. *Atriplex halimus*, Mediterranean saltbush (Kataf in Arabic) is a perennial native shrub of the Mediterranean with an excellent tolerance to drought and salinity. It ramifies almost from the base, can grow 1–3 m high and may reach 3 m in diameter. The plant is commonly used in the Greco-Arab medicine for its antidiabetic effects.

Zingiber officinale, ginger, has been used as a medicine in Chinese, Ayurvedic, and Greco-Arab and Islamic medicine since ancient times. In China, for example, the

underground stem, or rhizome, of the plant ginger has been used to aid digestion and treat stomach upset, diarrhea, and nausea for more than 2000 years. The rhizome of ginger found a widespread use in the Greco-Arab and Islamic medicine. It is one of the plants that are mentioned in the Holy Quran as one of the drinks of Paradise: "*And in it, their drink is mixed with ginger*." Ginger has also been used to help treat arthritis, colic, diarrhea, and heart conditions. In addition to these medicinal uses, ginger continues to be valued around the world as an important cooking spice and is believed to help treat the common cold, flu-like symptoms, headaches, and even painful menstrual periods. Currently, health care professionals recommend ginger for helping prevent or treat nausea and vomiting associated with motion sickness, pregnancy, and cancer chemotherapy. It is also used as a digestive aid for mild stomach upset, as support in inflammatory conditions such as arthritis, and may even be used in heart disease or cancer.

Rosmarinus officinalis, rosemary, is a woody shrub with fragrant evergreen needle-like leaves, and blue flowers which last through spring and summer. The fresh and dried leaves are traditionally used throughout the Mediterranean region; they have a bitter, astringent taste, and are highly aromatic, which complements a wide variety of foods. *R. officinalis* is known for its muscle relaxation effects, including the smooth muscles of the digestive tract and uterus. Because of this property, it is traditionally used to soothe digestive upsets and relieve menstrual cramps. Several studies indicated strong antioxidant and antimicrobial effects of *R. officinalis*.

3.6 ADMINISTERING HERBAL TREATMENT

Several preparation methods were developed in Greco-Arab and Islamic medicine and are still practiced by traditional herbalists to obtain beneficial ingredients from medicinal plants. The majority of herbal preparations are taken orally in the form of tea or other drink containing either diluted or concentrated extracts. Teas are generally produced from the different parts of the plants through infusion or as decoctions. Heating a raw plant in a solvent not only aids the extraction and concentration of curative phytochemicals but also acts to reduce or even to eliminate the amount of poisons and impurities prior to application. The chemical composition of an extract is largely affected by the method of extraction. Hot water extracts of herbs will be rich in polar components because water is a polar solvent. Oil, on the other hand, is a nonpolar solvent and it will absorb nonpolar compounds. Alcohol lies somewhere in between. Other methods include the inhalation of aerosols, essential oils, and vaporized plant juices or teas.

Currently, herbs and prepared herbal compounds are available in different forms, each of which has its own particular characteristics. The main forms are as follows:

Tinctures: Tinctures are preparations containing alcohol. In a tincture, alcohol is used to extract the active properties of the herb. Alcohol is also a very effective natural preservative. Because the body easily assimilates a tincture, it is a very effective way to administer herbal compounds. One of the main concerns when

using tinctures is the presence of the alcohol, which can be reduced by gentle heating of the preparation.

Extracts: Extracts can be made with alcohol, like tinctures, or the essence of the herb can be leached out with water. In this method, varying ratios of water and alcohol, usually ethanol and water, is mixed with the herb. Extracts offer essentially the same advantages and disadvantages that tinctures do, but have a strong herbal taste. The extraction method of herbal compounds is the most used method for research purposes.

Capsules and Tablets: Capsules and tablets contain a ground or powdered form of raw herb. In general, there seems to be little difference between the two in terms of clinical results. Because finely milled herbs degrade quickly, it is important that herbs be freshly grounded and then promptly encapsulated or tableted, within 24 h of being powdered. With the exception of certain herbal concentrates in capsule form, both capsules and tablets tend to be much less strong and potent than tinctures and extracts.

In addition Greco-Arab herbal medicine developed different techniques for drug preparation for external (topical) applications, which are currently used by herbalists in the Arab–Islamic world. These include essential oils, salves, oils, balms, creams and lotions, or poultices, and compresses (Table 16.2). In making a poultice, for example, plant parts are grounded or crushed and combined with hot water or other liquids to create a medicinal paste or plaster. The resulting mixture is placed directly on wounds, bruises, burns, insect and animal bites, rashes, swellings, wrinkles, or dermatological irritations [1–3].

3.7 ESSENTIAL OILS

Essential oils are secondary metabolites synthesized by all plant organs, that is, buds, flowers, leaves, stems, twigs, seeds, fruits, roots, wood or bark, and are stored in secretory cells, cavities, canals, epidermal cells, or glandular trichomes. They are liquid, volatile, limpid and rarely colored, lipid soluble, and soluble in organic solvents with a generally lower density than that of water. Essential oils play an important role in the protection of plants as antimicrobials, antifungals, antivirals, insecticides, and also against herbivores by reducing their appetite for such plants. They also may attract some insects to favor the dispersion of pollens and seeds, or repel undesirable others. They are extracted from various aromatic plants generally localized in temperate to warm climates such as Mediterranean and tropical countries where they represent an important part of the traditional pharmacopoeia.

Essential oils are usually obtained by steam or hydrodistillation, which was first developed by Arab scholars. Avicenna is believed to have been the first person to incorporate the process known as distillation to obtain the essence of rose. Essential oils were used extensively in his practice, and one of his books was devoted entirely to rose oil. Alcohol was also first distilled during his period, and then combined with essential oils, creating the first perfumes. The *Book of Perfume Chemistry and*

Distillation by Al-Kindi (803–870 AD) describes many essential oils. Jabir ibn Hayan (Gerber) wrote in his *Summa Perfectionism* several chapters on distillation. Currently, there are several methods for extracting essential oils. These may include use of liquid carbon dioxide or microwaves, and mainly low- or high-pressure distillation employing boiling water or hot steam. Due to their bactericidal and fungicidal properties, pharmaceutical and food uses are more and more widespread as alternatives to synthetic chemical products to protect the ecological equilibrium. In those cases, extraction by steam distillation is preferred. For perfume uses, extraction with lipophilic solvents and sometimes with supercritical carbon dioxide is favored. Thus, the chemical profile of the essential oil products differs not only in the number of molecules but also in the stereochemical types of molecules extracted, according to the type of extraction, and further the type of extraction is chosen according to the purpose of the use. The extraction product can vary in quality, quantity, and composition according to climate, soil composition, plant organ, age, and vegetative cycle stage. So, in order to obtain essential oils of constant composition, they have to be extracted under the same conditions from the same part of the plant, which has been growing on the same soil, under the same climate and has been picked in the same season.

Essential oils are known for their antiseptic, that is bactericidal, virucidal, fungicidal, and medicinal properties and their fragrance, they are used in embalming, preservation of foods and as antimicrobial, analgesic, sedative, anti-inflammatory, spasmolytic, and locally anesthetic remedies. Currently, about 3000 essential oils are known, 300 of which are commercially important especially for the pharmaceutical, food, cosmetic, and perfume industries. Moreover, essential oils are used in massages as mixtures with vegetable oil or in baths but most frequently in aromatherapy. Some essential oils appear to exhibit particular medicinal properties that have been claimed to cure one or another organ dysfunction or systemic disorder [26].

3.8 HERBAL ACTIVE COMPOUNDS

Plants produce chemical compounds as part of their normal metabolic activities. These include primary metabolites, such as carbohydrates, proteins, and fats, found in all plants; and secondary metabolites found in a smaller range of plants, some useful ones found only in a particular genus or species. The functions of secondary metabolites are varied. For example, some secondary metabolites are toxins used to deter predation, and others are pheromones used to attract insects for pollination. Phytoalexins protect against bacterial and fungal attacks. Allelochemicals inhibit rival plants that are competing for soil and light. Plants upregulate and downregulate their biochemical paths in response to the local mix of herbivores, pollinators, and microorganisms. The chemical profile of a single plant may vary over time as it reacts to changing conditions. It is the secondary metabolites that can have therapeutic actions in humans and which can be refined to produce drugs. Plants synthesize a bewildering variety of phytochemicals but most are derivatives of a few biochemical motifs.

Numerous herbal-derived substances have been evaluated for their therapeutic potential. These include alkaloids, coumarins, saponins, and flavonoids. Flavonoids are probably the best known of these substances due to their antioxidant properties. The therapeutic benefit of several plant species used by traditional herbalists, at least in part, was attributed to their effective inhibition of oxidative processes. Several of these herbs are used traditionally in treating liver diseases, for example, *Pistacia lentiscus* was found to be effective in suppressing oxidative stress. *S. marianum* (milk thistle) is currently the most well-researched plant used traditionally by Arab herbalists in the treatment of liver diseases. The active constituents of milk thistle are flavonolignans including silybin, silydianin, and silychristin, collectively known as silymarin. Silymarin is not water-soluble and so cannot be taken as a tea but as an encapsulated standardized extract.

Thymoquinone has been found to be the main compound responsible for the pharmacological properties of the volatile oil of black seed (*N. sativa*). As discussed in details in Chapters 8 and 16, black seed has been used for hundreds of years in Arab–Islamic medicine for its magic healing properties. Avicenna refers to black seeds in his *Canon of Medicine*, as the seed that stimulates the body's energy and helps recovery from fatigue and dispiritedness. The therapeutic potential and toxicological properties of black seeds are extensively discussed in Chapter 8. In brief, thymoquinone has been reported to have potent anticancer and superoxide anion scavenging abilities in animal models and cell culture systems. It acts as an antioxidant and inhibited iron-dependent microsomal lipid peroxidation, cardiotoxicity induced by doxorubin in rats, and inhibited ifosfamide-induced damage in kidney. It also prevents liver injury induced with carbon tetrachloride, lowered drug-induced toxicity, and causes amelioration in the drug's anticancer activity. There are studies reporting that the anticancer potential of thymoquinone is related to its pro-oxidant activities. In human colon cancer cells and in isolated rat liver mitochondria, thymoquinone induced a significant release of reactive oxygen species and inhibited the activity of aconitase, an enzyme sensitive to superoxide anion generation. One of the most promising effects of thymoquinone is that it exhibits high cancer specificity and low toxicity to normal cells. This has been observed in prostate cancer, colon cancer, canine osteosarcoma, and skin cancer. Many multidrug-resistant variants of human pancreatic adenocarcinoma, uterine sarcoma, and leukemia were found to be sensitive to thymoquinone. These results provide a great potential into the development of synthetic derivatives of thymoquinone as anticancer agents. Thymoquinone induces apoptosis through modulation of multiple targets and hence is a promising phytochemical that could be useful for the killing of many types of cancer cells. These results are also supported by reports in prostate and other cancer cells. Thymoquinone blocked angiogenesis *in vivo*, prevented tumor angiogenesis in a xenograft human prostate cancer model in mouse and inhibited human prostate tumor growth with almost no side effects. *In vivo*, thymoquinone inhibited the growth of prostate and colon tumors implanted in nude mice with no noticeable side effects. In colon xenografts, growth inhibition by thymoquinone was not due to decreased proliferation but rather due to the significant induction of apoptosis. However, in androgen-independent prostate tumor xenografts, the suppression of tumor growth was

associated with a massive apoptosis. These results indicate that the antitumor activity or cell growth inhibition could in part be due to the effect of thymoquinone on cell cycle [18,19].

Today many drugs listed as conventional medications were originally derived from plants. Cinchona bark is the source of malaria-fighting quinine. Vincristine, used to treat certain types of cancer, comes from periwinkle. Prior to the discovery and subsequent synthesis of antibiotics, the herb echinacea (which comes from the plant commonly known as purple coneflower) was one of the most widely prescribed medicines in the United States. For centuries, herbalists prescribed echinacea to fight infection. Today, research confirms that the herb boosts the immune system by stimulating the production of leukocytes. Most of these herbal-derived drugs were discovered through the study of traditional medical knowledge of indigenous people and some of these could not be substituted despite the enormous advances in synthetic chemistry. Aspirin, an acetyl salt of salicylic acid isolated from willow bark, is considered one of the most effective analgesic, antipyretic, and anti-inflammatory agents commonly used in conventional medicine. With the passage of time, multiple therapeutic uses of aspirin have emerged, with the most prevalent use being as an antiplatelet/anticoagulant at low dose to prevent further problems in patients who have already suffered from one heart attack. Another example of herbal-derived medicines is morphine, which is isolated from the opium poppy (*P. somniferum*). It is one of the early molecules that entered into conventional medicine as painkiller. It remains drug of choice today for cancer patients suffering from terminal pain. Indeed, the isolation of morphine from crude opium by Serturner in 1806 stimulated so much wide-spread research on the vegetable drugs that Megendie was able to publish a medical formulary in 1821, which contained only pure chemical agents, thereby laying the foundation for the use of pure compounds instead of medicinal plants and their extracts.

Other herbal-derived compounds have contributed successfully to treatments of cardiovascular diseases. *Digitalis* and the cardiac glycoside derived from the foxglove (*Digitalis purpurea*) are perhaps the most cited examples. They represent a widely used group of clinically effective compounds, which produce positive inotropic effects on the failing heart as well as having value in the treatment of atrial fibrillation. As a group they are unrivalled by any synthetic or semisynthetic substitutes even though they are among the most toxic group of clinically useful drugs and have unique mode of action with selective cardiotonic activity, without accompanying tachycardia. A second discovery of cardiovascular activity in medicinal plants led to the discovery of reserpine over five decades ago. Reserpine, isolated from the roots of the Indian plant *Rauwolfia serpentina*, was brought to the attention of the modern Western world in 1949 by Vakil who described its use in hypertension. In rapid succession between 1952 and 1958, reserpine was isolated from *Rauwolfia*, its structure determined and its total synthesis achieved. Later on, reserpine was found to be a potent agent in treating depression and Parkinson's disease. These findings stimulated further investigation and evidence was found that reserpine depleted not only brain serotonin but also nor-epinephrine and dopamine. This was a major stimulus for continued research on transmitter amine defects in depression and Parkinson's

disease. This in part laid the foundation for the development of many of the modern psychoactive drugs and stimulated a significant interaction between researchers and the drug industry.

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CHAPTER 4

The Arab–Islamic Roots of Western Medicine

4.1 INTRODUCTION

The Mosque in Cordoba, the Alhambra in Granada, and the Giralda in Seville are the reminders of the architectural imprint of the Arab–Islamic civilization left on Western Europe (Figure 4.1). Less well remembered, however, is the impact of this civilization on Western science, philosophy, and medicine between the eighth and fifteenth centuries. Undoubtedly, Arab and Muslim scholars of this period, known as the Islamic Golden Age, laid the foundations of modern pharmacy and medicine. However, a typical medical textbook description of the role of Arab and Muslims in the development of the modern Western medicine might be summarized as follows: The ancient Greco-Roman medical system, from which the modern Western medicine is derived, was lost to Europe during its Dark Ages (fifth to fourteenth centuries). Fortunately, it was translated and preserved by Arab and Muslim scholars, and rediscovered during the Renaissance period with little to no innovations or contributions by Arabs and Muslims or other Eastern healing systems (Figure 4.2). Intentional or not, one of the reasons the history of Western medicine understates the contribution of Arab–Islamic medicine made during the medieval period is a deep-seated prejudice against Arabs and Muslims as being non-Christians. This can be summarized with the following statement by HRH Prince Charles in a speech entitled "Islam and the West," Oxford, October 27, 1993: "If there is much misunderstanding in the West about the nature of Islam, there is also much ignorance about the debt our own culture and civilization owe to the Islamic world. It is a failure, which stems, I think, from the straightjacket of history, which we have inherited. The medieval Islamic world, from central Asia to the shores of the Atlantic, was a world where scholars and men of learning flourished. But because we have tended to see Islam as the enemy of the West, as an alien culture, society, and system of belief, we tended to ignore or erase its great relevance to our history." Sir John Bagot Glubb, British

Greco-Arab and Islamic Herbal Medicine: Traditional System, Ethics, Safety, Efficacy, and Regulatory Issues By Bashar Saad and Omar Said

FIGURE 4.1 The Great Mosque of Cordoba was considered a wonder of the medieval world by both Muslims and Christians. The Great Mosque of Cordoba was built between 784 and 786 during the reign of Abd al-Rahman.

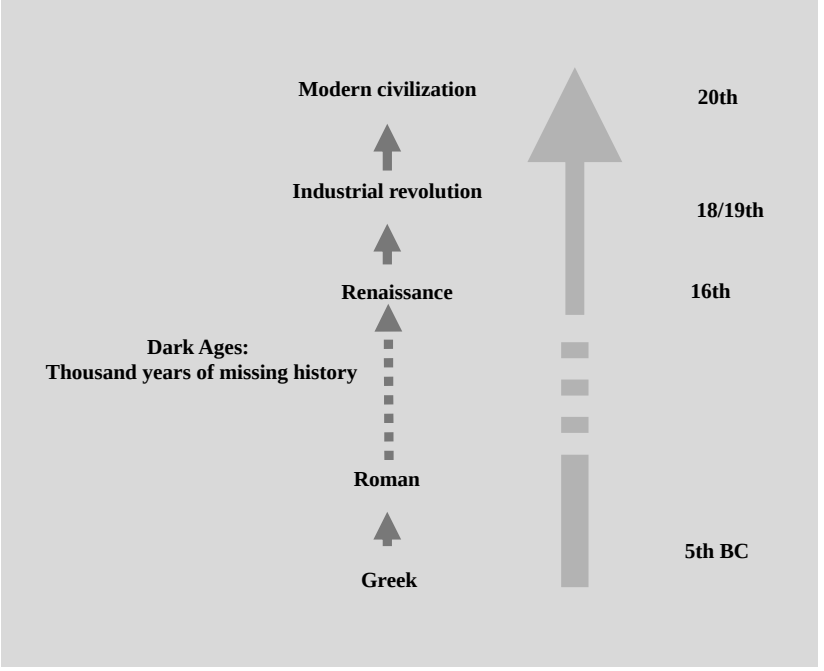

FIGURE 4.2 The history of science and civilization in Western educational systems.

lieutenant general and commander of the Arab Legion who served in the Middle East from 1920 to 1956, gave another statement: "The indebtedness of Western Christendom to Arab civilization was systematically played down, if not completely denied. A tradition was built up, by censorship and propaganda, that the Muslim imperialists had been mere barbarians and that the rebirth of learning in the West was derived directly from Roman and Greek sources alone, without any Arab intervention" [1,2].

As highlighted in the statement by Prince Charles, history indicates that Arab and Muslim scientists significantly contributed to the development of modern Western medicine, accomplishing far more than mere translation. A closer look at their activity during the medieval period shows that they translated classical medical texts not only from Greece, but also from Persia, India, and China. From this, Arab and Muslim scientists were able to synthesize and develop a rich and universal medical system, based on scientific methods and experimentation. The works of Arab and Muslim scholars gained widespread use and were used in European medical schools. For instance, the Arab and Muslim physicians Al Tabbari, Rhazes, Al-Zahrawi (Albucasis), Al-Biruni, Avicenna, Ibn al-Haitham, Ibn al-Nafis, Ibn Khaldun, and Ibn Zuhr (Avenzoar) contributed many of their own insights to the development of medical knowledge, while acknowledging their inheritance from other civilizations. They are regarded as among the greatest medical authorities of the ancient world and the medieval world, physicians whose textbooks were used in European universities up to the sixteenth century. These Arab and Muslim scholars were among the first to make accurate diagnoses of plague, diphtheria, diabetes, gout, cancer, leprosy, rabies, and epilepsy. Avicenna's and Rhazes's works on infectious diseases led to the introduction of quarantine as a means of limiting the spread of these diseases. Arab physicians laid down the principles of clinical investigation, drug trials, and animal tests. They mastered operations for hernia and cataracts, filled teeth with gold leaf, and prescribed spectacles for defective eyesight. The physicians and scientists of the Islamic Golden Age, who were of diverse religious and ethnic backgrounds, passed on rules of health, diet, and hygiene that are still largely valid [1,2].

As noted in earlier chapters, books were the primary means through which knowledge was acquired and transmitted in the Arab–Islamic world and publishing and collecting was a feature of Arab culture. Arabs learned the technique of papermaking from the Chinese in Samarkand in Uzbekistan in 712. The first Arab papermaking plant was opened in Baghdad in 794. Later, the Arabs transmitted the craft to Andalusia by 950, and to Sicily by 1102.

The Caliphs in Baghdad supported the translation and publication of scholarly works and libraries became an important part of civic life. The main cites of Iraq, Mosul in the north and Basra in the south, had libraries in the tenth century. The Arab geographer Yaqut collected the data for his geographical dictionary (which included the travels of Ahmad ibn Fadlan) during a 3-year period of research through libraries in what is now Turkmenistan and Uzbekistan. The main library in Cairo grew from 100,000 to 200,000 volumes during 990–1094 and lent out manuscripts without charge to students. There were about 70 libraries in Andalusia. The Al-Hakam's library at Cordoba alone was said to have about 400,000 titles. In addition, it was

fashionable among wealthy citizens to have an ample collection of books, which led to an uncountable number of private libraries.

But much of this came to an end in the thirteenth century as Mongol invaders ruined everything in their path as they moved eastward. At the time of its destruction in 1258, Baghdad had 36 public libraries. Though few of these institutions survived the Mongol invasion, many copies of Arab works remained in libraries in Egypt, Sicily, and Spain. These works were later available for translators, scribes, and printers.

With the development of print machines in Western Europe, the work of the Arab scribes moved into Western libraries. Latin translations the philosopher Al-Kindi were published in Venice in 1507, in Strasburg in 1531, and in Nuremberg in 1548. The first book printed in England, *The Dictes and Sayings of the Philosophers*, by William Claxton in 1477 was based on a collection of aphorisms and sayings from several Arab philosophers.

Taken together, not only did the Arab–Islamic world provide a successful line of transmission for the medical heritage of ancient Greece and the Hellenic world, but it also updated and enormously expanded that knowledge before passing it on to European universities [1–12].

4.2 MEDICINE DURING THE DARK AGES

During the Dark Ages, Europe lost touch with much of its intellectual heritage. Institutions of learning became virtually extinct throughout Europe after the end of the Western Roman Empire in the fifth century. Without the centralized governing body, security, and international network once provided by the Roman Empire, intellectual discourse in Europe withered and learning became an activity reserved mainly for cloistered monks who had little interaction with the world at large. The church became the center of the European worldview, which exerted profound new influences on health care. Although the church viewed spiritual care with far greater importance than bodily care and medical treatments were of little value, monastic orders ran hospitals that received only those with serious illnesses. Patients were not treated by learned healers, but only by kindly monks who dispensed comfort and the sacraments and not medicines.

Europeans came to look upon illness as a condition caused by supernatural forces. Hence, cures could only be effected by religious means. Every ailment had a patron saint to whom prayers were directed by the affected person and his relatives. A blessing of the throat with crossed candles on the feast of Saint Blaise was believed to be able to cure respiratory infections. Saint Roch became the patron of plague victims. Saint Nicaise was the patron of smallpox. Kings were believed to be able to cure scrofula and skin diseases with the "royal touch." In this era, licensed medicine as an independent profession virtually disappeared. As a result, physicians were mostly connected with monasteries and abbeys. The decline in the medicine continued and in the middle of the seventh century, the Catholic Church banned surgery by monks because it represented a danger to their souls. Since most of the surgeons of that era were clerics, the decree effectively ended the practice of surgery in Europe [6–8].

4.3 THE RISE OF ISLAM AND ARAB–ISLAMIC MEDICINE

At roughly the same time, a new civilization was appearing in Mecca in Arabia. By the eighth century, the Islamic Empire had risen to power and the scientific and intellectual center of the world had shifted completely from the West to the Arab and Islamic world. Uniquely situated at the crossroads between East and West, Arab and Muslim scholars were living in the best geographical location to benefit from cross-cultural intellectual exchange. The formation of the Arab–Islamic Empire led to about seven centuries of continuous geographical expansion and innovations in all branches of known sciences. The Arabs rapidly melded the various cultures of the Islamic domain, and Arabic became the universal language. By the tenth century, a single language linked peoples from Morocco and Andalusia to countries of central Asia, and Arabic became to the East what Latin and Greek had been to the West, the language of literature and sciences.

Unlike their early European counterparts who persecuted people of other religions and nations, such diverse contacts were fostered and encouraged in the Arab–Islamic world. One of the main philosophical differences between Europeans and Arabs of the medieval world focused around the role of sciences, especially medicine. Christian philosophy has always been slanted toward a mind–body split, while Muslim belief is inclined toward a more unified view. Arabs and Muslims, on the other hand, regarded science and civilization as God-given gifts and sought to develop those gifts by integrating and further developing the knowledge of both East and West.

Recognizing the importance of translating Greek and Roman works into Arabic, the Abbasid Caliphs Harun al-Rashid (786–809) and his son al-Ma'mun (813–833) established Bait al-Hikmah, or House of Wisdom, and collected Greek, Roman, Indian, and Persian scientific scripts. Medicine was the first of the Greek sciences to be translated and studied in depth by Arab and Muslim physicians. After Plato's Academy in Athens was closed in 529, some of its scholars found refuge at the university at Jundishahpur in Persia, which was conquered by the Arabs in 636. The medical school at Jundishahpur enabled Arab and Islamic scholars to study the works of Hippocrates, Galen, and other Greek physicians. The most famous translator was Hunayn ibn Ishaq al-Ibadi (809–873). He and his colleagues translated most of the available Greek medical works, including all available scripts of Galen, Hippocrates, and the *Materia Medica* of Dioscorides, into Arabic by the end of the ninth century. These translations built the stem from which much Arab–Islamic medicine grew (Figure 4.3).

4.4 THE ROLE OF ARAB AND MUSLIM SCHOLARS IN PRESERVING AND DEVELOPING WESTERN MEDICINE DURING THE MEDIEVAL PERIOD

As discussed in detail in later chapters, the Arab–Islamic medical system largely accepted Galen's premise of four humors, which held that the human body was made up of the same four elements that comprise the world—earth, air, fire, and water.

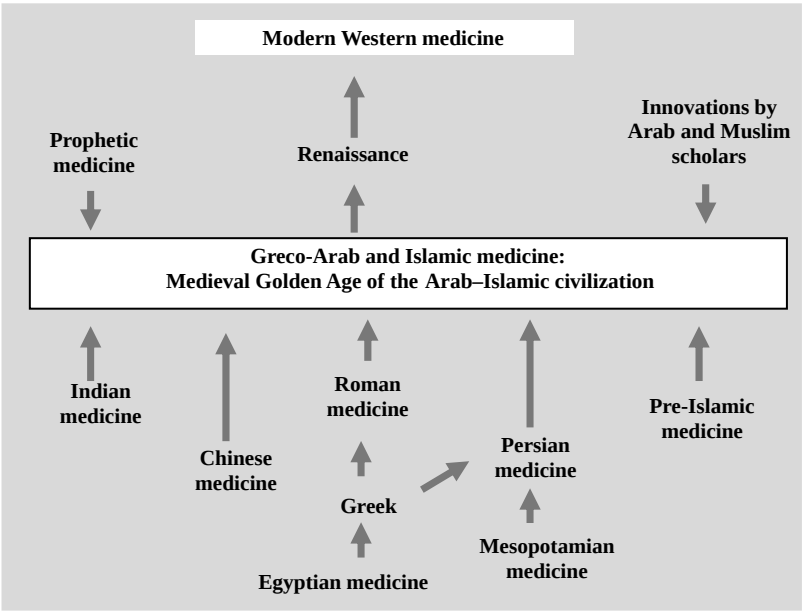

FIGURE 4.3 The role of Greco-Arab and Islamic medicine in the development of Western medicine. Medical knowledge that originated in India, China, and the Hellenistic world was sought out by Muslim scholars and then translated, refined, synthesized, and augmented at different centers of learning in the Islamic world from where the knowledge spread to Western Europe.

Combinations of these elements gave rise to the different temperaments and "humors" found in the human body. When the bodily humors were correctly balanced, a person was healthy. Illness was due not to supernatural forces but to humoral imbalance, and such imbalance could be cured by the physician's healing power.

Even before the period of translation ended, advances and innovations were made in other medical related fields. In 805, Harun al-Rashid established the first hospital, in the modern sense of the term, in Baghdad. Within two decades, 34 more hospitals were established throughout the Arab–Islamic Empire and the number grew rapidly each year. These hospitals bore little resemblance to their European counterparts. The sick saw the hospitals as a place where they could be treated and perhaps cured by physicians. To the physician, hospitals were institutions that were devoted to the promotion of health, the cure of disease, and the expansion and dissemination of medical knowledge. Medical schools and libraries were attached to the larger hospitals, and senior physicians taught students, who were in turn expected to apply in the men's and women's wards what they had learned in the lecture hall. Hospitals set examinations for their students and issued certificates. By the eleventh century, there were even mobile clinics that brought medical services to distant places or to patients who could not come to the hospitals themselves. The *bimaristan* was, in

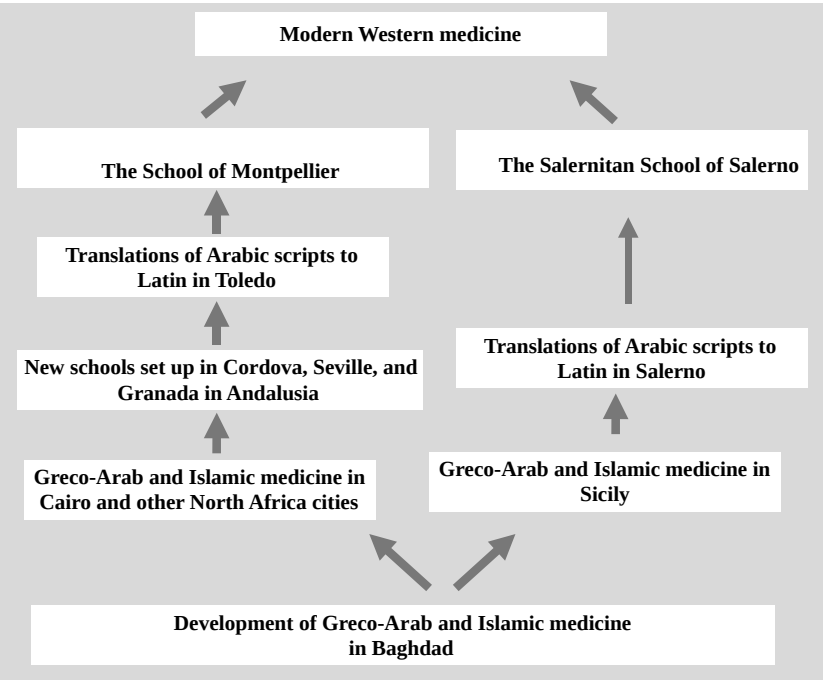

FIGURE 4.4 The rise of European medical schools.

short, the cradle of Arab–Islamic medicine and the prototype upon which the modern hospital is based.

The separation between medicine and pharmacy was an Islamic development. The Prophet Mohammad (PBUH) stated that "God has provided a remedy for every illness" and that Muslims should search for those remedies and use them with skill and compassion. Jabir ibn Hayyan (ca. 776) (Figure 4.4), who is considered the father of Arab alchemy, wrote one of the first pharmacological treatises. By the time of Al-Ma'mun, pharmacists were required to pass licensing examinations. They were then monitored by the state. Hence, pharmacy was a profession practiced by highly skilled specialists. At the beginning of the ninth century, the first private apothecary shops were opened in Baghdad. Both herbal-based and animal-based preparations were manufactured and dispensed by physicians and pharmacists in a variety of forms—ointments, pills, elixirs, confections, tinctures, suppositories, and inhalants. The Arab pharmacopoeia of the time was extensive and gave descriptions of the geographical origin, physical properties, and methods of application of everything found useful in the cure of disease. Pharmacists introduced a large number of new drugs to clinical practice, including camphor, sandalwood, senna, myrrh, cassia, musk, tamarind, nutmeg, cloves, ambergris, and mercury. They were familiar with the anesthetic properties of Indian hemp and henbane, both when taken in liquids and inhaled.

To keep in context of this chapter, we summarize the innovations introduced by Rhazes and Avicenna. As mentioned in Chapters 2 and 3, Rhazes is regarded as the greatest clinician as well as the most original thinker of Greco-Arab and Islamic medicine. A prolific writer, he wrote about 120 books in medicine. His treatise, *The Diseases of Children*, has led some historians to regard him as the father of pediatrics. He was the first to describe hay fever and its cause. Furthermore, he was instrumental in the introduction of mercurial ointments to treat scabies. Rhazes advocated reliance on observation rather than on received authority; he was a strong proponent of experimental medicine and the beneficial use of previously tested medicinal plants and other drugs. His work on kidney stones is still considered a classic. Rhazes also insisted on continuing education for already licensed physicians. He was the first to emphasize the value of mutual trust and consultation among skilled physicians in the treatment of patients, a rare practice at that time.

Al-Kitab al-Mansuri was one of Rhazes's first major works in which he discussed varied subjects, such as general medical theories and definitions, diet and drugs and their effect on the human body, mother and child care, climatology, the effect of the environment on health, epidemiology and toxicology, skin disease, and oral hygiene. *Al-Judari wa al Hasbah* was the first treatise ever written on smallpox and measles. In a masterful demonstration of clinical observation, Rhazes became the first to distinguish the two diseases from each other. At the same time, he provided still valid guidelines for the sound treatment of both.

Rhazes's most esteemed work was *Al-Kitab al-Hawi*, a medical encyclopedia in 25 books, or *The Comprehensive Work*, the *Liber Continens* of Rhazes's later Latin translators. In *Al-Hawi,* he emphasized the need for physicians to pay careful attention to what the patient histories told them, rather than merely consulting the authorities of the past. In a series of diagnosed case histories entitled *Illustrative Accounts of Patients*, Rhazes demonstrated this important tenet. One patient, who lived in a malarial district, suffered from intermittent chills and fever that had been diagnosed as malaria, but nonetheless seemed incurable. Upon noting pus in the patient's urine, Rhazes diagnosed an infected kidney and he treated the patient successfully with diuretics.

Understanding human nature was one of Rhazes's clinical skills, particularly concerning patient attitudes. In a series of short monographs on the doctor–patient relationship, he described principles that are still taught a millennium later: "doctors and patients need to establish a mutual bond of trust," he wrote, "positive comments from doctors encourage patients, make them feel better and speed their recovery," and "he warned, changing from one doctor to another wastes patients' health, wealth and time."

Not long after Al-Rhazes's death, Avicenna (980–1037) was born in Bukhara, in what today is Uzbekistan. It is hard to describe Avicenna in anything other than superlatives. He was to the Arab world what Aristotle was to Greece, Leonardo da Vinci to the Renaissance, and Goethe to Germany. His preeminence embraced not only medicine, but also the fields of philosophy, science, music, poetry, and statecraft. His contemporaries called him "the prince of physicians."

Avicenna's life was in fact the stuff of legend. His supreme work, however, is the monumental *Al-Qanun fi al-Tibb* (*The Canon of Medicine*). Over one million words long, it was nothing less than a codification of all existing medical knowledge. Summarizing the Hippocratic and Galenic traditions, describing Syro-Arab and Indo-Persian practice, and including notes on his own observations, Avicenna strove to fit each bit of anatomy, physiology, diagnosis, and treatment into its proper niche.

The Canon stressed the importance of diet and the influence of climate and environment on health. It included discussions of rabies, hydrocele, breast cancer, tumors, labor, and poisons and their treatment. Avicenna differentiated meningitis from the meningismus of other acute diseases and described chronic nephritis, facial paralysis, ulcer of the stomach, and the various types of hepatitis and their causes. He also expounded on the dilation and contraction of the pupils and their diagnostic value, described the six motor muscles of the eye and discussed the functions of the tear ducts, and noted the contagious nature of some diseases that he attributed to "traces" left in the air by a sick person.

The Canon also included a description of some 760 medicinal plants and the drugs that could be derived from them. At the same time, Ibn Sina laid out the basic rules of clinical drug trials that are still followed.

Not surprisingly, *The Canon* rapidly became the standard medical reference work of the Islamic world. Nizami-i Arudi of Samarkand spoke for generations of physicians when he wrote, in the early twelfth century, "From him who manages the first volume [of *The Canon*], nothing will be hidden concerning the general theory and principles of medicine." *The Canon* was used as a reference, a teaching guide, and a medical textbook until well into the nineteenth century, longer than any other medical work.

During the tenth century, when Arab astronomical texts were first translated in Catalonia, Europe began to reap the intellectual riches of the Arabs and, in doing so, sought out its own classical heritage. The medical works of Galen and Hippocrates returned to the West by way of the Middle East and North Africa, recovered through Latin translations of what had become the Arab medical classics. Through the intellectual fervor of the Islamic present, Europe recovered some of its past.

The two main translators of classical material from Arabic into Latin were Constantine (also known as Leo) Africanus (1020–1087), who worked at Salerno and in the cloister of Monte Cassino, and Gerard of Cremona (1140–1187), who worked in Toledo. It was no accident that both translators lived in the Arab–Christian transition zone, where the two cultures fructified each other. And it was no coincidence that Salerno, Europe's first great medical faculty of the Middle Ages, was close to Arab Sicily, nor that the second, Montpellier, was founded in 1221 in southern France, near the Andalusian border.

Avicenna's *Canon* made its first appearance in Europe by the end of the twelfth century, and its impact was dramatic. It quickly became one of the main European medical textbook. It was issued in 16 editions in the fifteenth century and more than 20 further editions were printed in sixteenth century. And as late as 1537 The Canon was still a required textbook at the University of Vienna.

Translations of Rhazes *Al-Kitab al-Hawi* and other works followed rapidly. Printed, while printing was still in its infancy, all of Rhazes's works gained widespread acceptance. The ninth book of *Al-Kitab al-Mansuri* (*Concerning Diseases from the Head to the Foot*) remained part of the medical curriculum at the University of Tübingen until the end of the fifteenth century.

Contemporary Europeans regarded Rhazes and Avicenna as the greatest authorities on medical matters, and portraits of both men still adorn the great hall of the School of Medicine at the University of Paris. In *The Inferno*, Dante placed Avicenna side by side with antiquity's two greatest physicians, Hippocrates and Galen. Roger Bacon consulted Avicenna to further his own inquiries into vision. But it was not only Rhazes and Avicenna who influenced Europe. Translations of more than 400 Arab authors, writing on such varied topics as ophthalmology, surgery, pharmaceuticals, child care, and public health, deeply influenced the rebirth of European science.

Despite their belief in now superseded theories such as humors and miasmas, the medicine of Avicenna, Rhazes, and their contemporaries is the basis of much of what we take for granted today. It was those Arab physicians who made accurate diagnoses of plague, diphtheria, leprosy, rabies, diabetes, gout, cancer, and epilepsy. Avicenna's theory of infection by "traces" led to the introduction of quarantine as a means of limiting the spread of infectious diseases. Arab doctors laid down the principles of clinical investigation and drug trials, and they uncovered the secret of sight. They mastered operations for hernia and cataract, filled teeth with gold leaf, and prescribed spectacles for defective eyesight. And they passed on rules of health, diet, and hygiene that are still largely valid.

Thus, not only the Islamic world provided a slender but ultimately successful line of transmission for the medical knowledge of ancient Greece and the Hellenic world, but it also corrected and enormously expanded that knowledge before passing it on to a Europe that had abandoned observation, experimentation, and the very concept of earthly progress centuries before [1–9].

4.5 TRANSMISSION OF ARAB–ISLAMIC SCIENCES TO EUROPE

"We have underestimated the importance of 800 years of Islamic society and culture in Spain between the 8th and 15th centuries. The contribution of Muslim Spain to the preservation of classical learning during the Dark Ages, and to the first flowerings of the Renaissance, has long been recognized. But Islamic Spain was much more than a mere larder where Hellenistic knowledge was kept for later consumption by the emerging modern Western world. Not only did Muslim Spain gather and preserve the intellectual content of ancient Greek and Roman civilization, it also interpreted and expanded upon that civilization, and made a vital contribution of its own in so many fields of human endeavour - in science, astronomy, mathematics, algebra (itself an Arabic word), law, history, medicine, pharmacology, optics, agriculture, architecture, theology, music. Averroes and Avenzoor, like their counterparts Avicenna and Rhazes in the East, contributed to the study and practice of

medicine in ways from which Europe benefited for centuries afterwards." A citation from HRH Prince Charles in a speech "Islam and the West," Oxford, October 27, 1993.

Historical evidence suggests that European intellectual life in the Dark Ages was shaped significantly by the flourishing Islamic civilization in Spain. Over a period of roughly 200 years, Europe's encounter with Arab–Islamic civilization enabled it to develop its skills in all scholarly and scientific fields, particularly those of medicine, astronomy, chemistry, and mathematics. It is one of the great successes of Arab–Islamic civilization to have preserved the treasures of ancient Greco-Roman philosophy and science for posterity. European scholars only came to know about the concepts of Aristotelian metaphysics through the Arab and Muslim philosophers in Andalusia and their translations and commentaries. The importance of Andalusia in the transition of science to Europe is highlighted by another statement from the above-mentioned HRH Prince Charles' speech "Islam and the West," Oxford, October 27, 1993: "Islam nurtured and preserved the quest for learning. In the words of the tradition, 'the ink of the scholar is more sacred than the blood of the martyr'. Cordoba in the tenth century was by far the most civilized city of Europe. We know of lending libraries in Spain at the time King Alfred was making terrible blunders with the culinary arts in this country. It is said that the 400,000 volumes in its ruler's library amounted to more books than all the libraries of the rest of Europe put together. That was made possible because the Muslim world acquired from China the skill of making paper more than 400 years before the rest of non-Muslim Europe. Many of the traits on which modern Europe prides itself came to it from Muslim Spain. Diplomacy, free trade, open borders, the techniques of academic research, of anthropology, etiquette, fashion, various types of medicine, hospitals, all came from this great city of cities."

The Arab universities in Cordoba, Seville, Granada, Valencia, and Toledo attracted a great number of European scholars. The *Great Library of Europe* in Toledo, where in 1130 a school of translation was founded, attracted students and researchers from all over Europe. Great European thinkers of that time, such as Albertus Magnus, Roger Bacon, Thomas Aquinas, and William of Ockham, to mention only a few, developed their intellectual skills in these centers of learning. Arab–Islamic medical science had an enormous impact on the development of the Western medical system in Europe. The first professors of medicine at the newly established European universities in the twelfth century were all former students of Arab and Islamic physicians. Avicenna's and Rhazes's treatises were taught in all major European universities for over six centuries. Toward the end of the sixteenth century, King Henry III of France established a chair in Arabic at the College Royal to promote medical education in France. Similar influences on the development of sciences can be traced in the fields of mathematics, astronomy, chemistry, architecture, music, and industrial techniques. The Arab astronomer Al-Battani (Albatenius, 858–929) authoritatively disproved the Ptolemaic dogma of heliocentrism long before Copernicus published his famous treatise *De revolutionibus orbium coelestium* in the sixteenth century. Without going into further detail, one can rightly state that the Arab–Islamic civilization, which flourished in Andalusia until the late twelfth century and in its universal achievements

even surpassed the earlier contribution of the Roman empire to the development of civilization, awakened Europe from its Dark Ages and thus prepared an early European renaissance in the sense of an enlightened, rational, and nondogmatic world vision [1–9].

4.5.1 Arabic to Latin Translations

The repositories of knowledge in Baghdad might have remained out of reach of the West, but for the fact that the Arab empire stretched across North Africa to Spain. From the eighth to the tenth centuries, Arab Spain remained intellectually tied to the Arab heartland. New schools set up in Cordoba, Seville, Granada, and Toledo sent their students to Cairo and Baghdad for advanced studies. The culture and structure of the Arab way of life made books the primary means through which knowledge was acquired and transmitted. Accordingly, returning pilgrims from Mecca and merchants brought newly published books to Arab Andalusia from Baghdad and book collecting was a mark of prestige among the upper classes in Arab Spain. As the West began to show interest in Arabic scripts, the Arab–Islamic world was beginning to enter its own Dark Age. The glory that defined Baghdad in the ninth century went up in smoke when Hulugu destroyed the city in 1258.

Just as the Arabs had sought out Greek and Persian manuscripts from schools in Syria, Asia Minor, and Persia, European scholars sought out Arabic manuscripts from schools and libraries in Toledo, Seville, and, especially, Cordova. In Baghdad, non-Arabs and non-Muslims were often translators. Similarly, in Andalusia often Jews or Muslim converts translated Arabic texts into Hebrew, from which learned Europeans made the first Latin translations.

As had been the case in the East in the eighth and ninth centuries, translation in the West in the twelfth and thirteenth centuries was provided impetus by several strong leaders, leaders interested in the learning of the Arabs both for polemical reasons and for reasons of personal curiosity. Many Western scholars were attracted to the cultural value of the information in Arabic texts, most notably in the intellectual center that was Cordova. Toledo was the first center of translation after Christian forces took control of the city from the Arabs in 1085. One of the earliest translators was Robert of Chester, an English astronomer and mathematician, who worked in Toledo from 1141 to 1147. In addition to translating works on astronomy, he completed the first Latin version of the Holy Quran.

As mentioned above, Constantine Africanus (1020–1087) and Gerard of Cremona (1140–1187) were the two main translators of classical material from Arabic into Latin were. It was no accident that both translators lived in the Arab–Christian transition zone (Salerno and Toledo) where the two cultures fructified each other. And it was no coincidence that Salerno, Europe's first great medical faculty of the Middle Ages, was close to Arab Sicily, nor that the second, Montpellier, was founded in 1221 in southern France, near the Andalusian border.

Gerard began the translation of Avicenna's *Kitab al-Shifa* (*The Book of Healing*), a philosophical treatise consisting of four major books in mathematics, logic, physics,

and metaphysics. This treatise is estimated to be the longest book of its kind written by a single author. Avicenna's Canon was a systemization of the medical knowledge of his age. When it was printed in Rome in 1593, it was 833 pages long and contained about a million words. Copied and recopied, it quickly became the standard European medical reference. In the last quarter of the fifteenth century, just before the European invention of printing, it was issued in 16 editions; in the century that followed, more than 20 further editions were printed. From the twelfth to the seventeenth century, its *materia medica* was the pharmacopoeia of Europe, and as late as 1537 *The Canon* was still a required textbook at the University of Vienna. Avicenna's Canon remained a staple text in Western medical schools for 400 years and in Eastern medical schools for 600 years [10–12].

Another center of translation was established in Seville, where along with Toledo, the scientific works of Hippocrates, Euclid, Ptolemy, Galen, and other Greek scientists were translated from Arabic to Latin, as well as the treatises of Al-Khwarizmi, Rhazes, and Avicenna and the theological works of Ibn Rushd (1126–1198). Ibn Rushd, known to the West as Averroes, is the most notable for his commentaries on Aristotle and it was through him that Aristotelianism was introduced into Western thought. Translations of Ibn Rushd's commentaries eventually became a key component of the studies of the young Thomas Aquinas. In his effort to systematize Catholic theology, Aquinas repeatedly mentions and quotes Avicenna in order to criticize his interpretation. Through Aquinas, Arab philosophy established a firm foothold in the Western Christian tradition. Translations of Rhazes's *Al-Kitab Al Hawi* (The Comprehensive Work) and his other works gained widespread acceptance. The ninth book of *Al-Kitab al-Mansuri* remained part of the medical curriculum at the University of Tübingen until the end of the fifteenth century.

However, Spain was not the only center for translation. In Sicily, Frederick II, ruler of both Germany and Sicily (1215–1250), lived in Sicily and dressed as an Arab. Able to read the Arabic classics in their original, Frederick sought to expand himself in the realm of philosophy and lured the translator Michael Scotus in 1220 from Toledo to Sicily, where he translated Ibn Rushd's commentaries on Aristotle. In 1224, Frederick II founded the University of Naples, the first university founded by royal charter, and the Sicilian translations eventually became the standard text used at the university. It was at Naples that Thomas Aquinas began his studies. Frederick also imported Hermannus Allamanus from Spain in 1240 and continued to sponsor additional translations of most of the other great Arab theologians and philosophers.

Contemporary Europeans regarded Avicenna and Rhazes as the greatest authorities on medical matters, and portraits of both men still adorn the great hall of the School of Medicine at the University of Paris. In *The Inferno*, Dante placed Avicenna side by side with antiquity's two greatest physicians, Hippocrates and Galen. But it was not only Rhazes and Avicenna who influenced Europe. Translations of more than 400 Arab authors, writing on such varied topics as ophthalmology, surgery, pharmaceuticals, child care, and public health, deeply influenced the rebirth of European science.

4.5.2 The Rise of European Medical Schools

It is a historic fact that the first medical schools, the Salernitan School in Italy, Montpellier, and Paris in France, were established thanks to the Arab–Islamic medicine.

4.5.2.1 The Salernitan School The Salernitan School (Schola Medica Salernitana) in the south Italian city of Salerno was the first medieval medical school that provided the most important source of medical knowledge in Western Europe at the time. The school, which found its original base in the dispensary of a monastery founded in the ninth century, achieved its utmost splendor between the tenth and thirteenth centuries, during which its fame began to spread throughout the region. The arrival in Salerno of Constantine Africanus in 1077 marked the beginning of Salerno's classic period. Through the encouragement of Alfano I, Archbishop of Salerno, and translations of Constantinus Africanus, Salerno gained the title of *Town of Hippocrates*. Constantine Africanus practiced medicine as he had learned it in the Arab–Islamic schools. He established the Salernitan School, imitating the Andalusian Arab–Islamic medical schools, where medical teaching took place either in the library or in the hospital and students were directed in their studies by a group of physicians. Arabic medical treatises, including those translated from Greek or other sources and those originally written in Arabic, were translated into Latin. As a result, the medical practitioners of Salerno were unrivalled in the medieval Western Mediterranean. People from all over the world flocked to the "Schola Salerni," both the sick, in the hope of recovering, and students, to learn the art of medicine. In the school, besides the teaching of medicine (in which women were also involved, as both teachers and students), there were courses of philosophy, theology, and law.

In short, we can say that the introduction of Arab–Islamic medicine in Salerno was a fundamental element in the development of the school, in its fruition and in its celebrity. The success of the Salernitan School encouraged the creation of other schools with similar methods; the most famous of these were in Bologna, Padua, Pisa, and Naples in Italy and Montpellier and Paris in France (Figure 4.4).

4.5.2.2 The School of Montpellier Like Salerno, Montpellier existed on the border between the Islamic and Latin worlds. Founded in the eighth or ninth century, Montpellier soon possessed a rabbinical school of Spanish origin that taught grammar and later medicine. In 1220, Cardinal Conrad, the legate of Pope Honorius III, established the medical school of Montpellier and organized it along the lines of the Arab medical schools. At this time, there were 16 teaching books, 13 of which were books of Arab–Islamic medicine, for example, Avicenna's *Canon* and the Al-Mansouri and the Aphorisms of Rhazes. During the thirteenth and the fourteenth centuries, Arab–Islamic medicine was the most important subject in the teaching program of the medical school of Montpellier. Among the most famous teachers, there were Arnaud de Viulleneuve, Ermengaud Blein, Pierre de Capestang, Jean Jacme, and others, who were called the Arabic scholars, as they taught only Arab medicine. Hence, Arab medicine encompassed the school of Montpellier from its creation to the

second half of the sixteenth century. Arab medicine allowed the school of Montpellier to develop, to expand, and to become a scientific center, not only in France but also in Europe, toward which students and patients made their way.

In conclusion, Arab–Islamic medicine played an important role in the creation of European medical schools. We can also say that without Islamic medicine, Islamic hospitals, Islamic pharmacies, and medical schools, the Salernitan School and the school of Montpellier might not have existed. The movement that started in Salerno and Montpellier rapidly covered the whole of Europe and at the end of the Middle Ages, there were eighty universities in Europe, nineteen of which were French.

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CHAPTER 5

Contributions of Arab and Islamic Scholars to Modern Pharmacology

5.1 INTRODUCTION

The development of pharmacy as a profession entrusted with ensuring the safe and effective use of drugs has been shaped by the works of many Arab and Muslim scientists. It is a historical fact that the development and the recognition of the independent, academically oriented status of pharmacy started in Baghdad during the time of Al-Mamun's caliphate (813–833). By that time scholarly interest was directed toward the elucidation of natural products as a source for new drugs and emphasis was placed on translations and interpretations of accumulated data on natural product-based drugs. Pharmacists, or saydalaneh, began to search for potential herbal-derived ingredients and extracts to be used as remedies, and they even started to elucidate their physicochemical properties. They built on the works of other ancient civilizations and on the knowledge that was developing elsewhere in the world. Al-Biruni (973–1051) defined pharmacy as the science of identifying the types, kinds, shapes, and physicochemical properties of crude materials and of practical experience on how to compound them into drugs. A qualified pharmacist should also be able to substitute or discard one drug for another. The selection and identification of potential natural products was based on both knowledge obtained from traditional healers in the pre-Islamic period and knowledge introduced by the Holy Quran or by the Prophet Mohammad (PBUH).

A large number of new drugs were introduced for use in clinical practice, including senna, camphor, sandalwood, musk, myrrh, cassia, tamarind, nutmeg, cloves, aconite, ambergris, and mercury. Drugs were divided according to their medicinal effects into hypnotics, sedatives, antipyretics, laxatives, demulcents, diuretics, emetics, emollients, astringents, and digestants. The first pharmacy shop was most likely founded in 762 in Baghdad. It was here that medicines were first manufactured and distributed commercially, and then dispensed by physicians and pharmacists in a variety of forms: ointments, pills, elixirs, confections, tinctures, suppositories, and

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inhalants [1–3]. Pharmacists were required both to pass examinations and be licensed and monitored by the state, resulting in significant developments in pharmacy. This chapter provides an overview of innovations introduced by Arab and Muslim scholars in the field of pharmacology.

5.2 HISTORICAL BACKGROUND

Pharmacy has always existed as a science, but not so as a profession. Originally, medicine and pharmacy were practiced together by the person making the diagnosis, who also provided the remedy, be it in the form of amulets, prayers, herbs, animal products, or whatever. The physician was a healer without formal education, but with much experience, as an elder or priest. When the physician could no longer cope with his work, he hired a servant to collect herbs and make prescribed medicines.

As highlighted in Chapter 2, archaeologists have unearthed clay tablets from the time of the Mesopotamians (about 5000 BC), which are the earliest known medical texts and pharmaceutical compendia. These early findings suggest that they used natural materials and were able to manipulate them to prepare medicines. There is evidence that even at these times, there were healers who had knowledge of pharmaceuticals and compounding.

Many similarities exist between the techniques and the materials used in Mesopotamia and ancient Egypt. The most relevant to pharmacy was the Ebers Papyrus, written around 1500 BC. It contains prescriptions and medical uses of over 700 different remedies. The preparation and the application of these remedies were rooted firmly in magic and religious practices of the time. A skilled healer chose the correct materials and combined them with the right magic to bring about a desirable therapeutic effect. There were many people who practiced related health care services, such as gathering medicinal plants or preparing drugs, under the supervision of the physician.

Great advances in pharmaceutical sciences were made during the Greco-Roman era. There was a shift toward a rational and empirical approach to the treatment of diseases and their natural causation. As discussed in Chapter 7, there were four primary elements from which all things were thought to be derived—water, air, fire, and earth—which became the foundation of the concept of humoral theory and pharmacotherapy. Accordingly, the humors that corresponded to the four elements (phlegm, blood, yellow bile, and black bile) must be in balance in order to maintain health. It was thus the physician's duty to restore balance, and, to this end, he used a variety of natural products in the form of poultices, gargles, pills, and ointments.

In this regard, the writing of *De Materia Medica* by Pedanius Dioscorides was of great significance to pharmacy during Greco-Roman time. This work built the foundation for all later pharmacopoeias, as it describes the origin, properties, and type of action; medicinal usage and possible side effects; instructions on harvesting, preparation, and storage; and magical and nonmedical uses of over 600 plants, 35 animal products, and 90 minerals. Although great advances were made in pharmacy

during this time, the practice remained the function of the medical practitioner. Galen built on the work of Dioscorides and organized his drug data under the framework of humoral pathology. He developed a system of rules and procedures for using drugs and also experimented with new medicinal preparations. It is evident that he made a significant contribution both to the practice of medicine and to pharmacy.

As highlighted in previous chapters, as Arab–Islamic civilization developed, so did their knowledge of science, literature, and medicine. With their clear insight and mathematical approach, they realized that people who dealt with the health of others ought to acquire a solid education, both professionally and ethically. They also realized that the simultaneous practice of medicine and pharmacy were incompatible. The mutual control between physician and pharmacist provides a much higher degree of safety. Therefore, they demanded that those who prepared medicines would do so as an independent profession, not as a side profession or as the servants of physicians. It was during this time that the first pharmacy was established in Baghdad, and the attainment of professional identity and independence of the pharmacist became recognized. The pharmacist was indeed a new specialist and had command over the ever-increasing number of drugs, and complexity of preparations that were being used. The early rise and development of the professional pharmacy in Baghdad took place over four centuries before such development took place in Europe.

By the ninth century, after the separation of pharmacy from medicine and alchemy, a class of formally educated pharmacists appeared. At the same time, however, they were outnumbered by native drug and spice dealers, and so it became necessary to license proper pharmacy shops. As a result of this great development in pharmacy, physicians began to rely on these services, a system that built the foundations for the current practice, where physicians write prescriptions that are then dispensed by a pharmacy. The development of hospitals had a great impact on the development of pharmacies as well. The ninth century witnessed an increase in the number of pharmacy shops in Baghdad and in other cities of the Arab–Islamic world. By the twelfth century, hospitals were designed to include pharmacies and trained pharmacists were employed. Many of the pharmacists who managed them were skilled apothecaries and quite knowledgeable in the compounding, storing, and the preserving of drugs. State-sponsored hospitals also had their own dispensaries attached to manufacturing laboratories where syrups, electuaries, ointments, and other pharmaceutical preparations were prepared on a relatively large scale. The pharmacists and their shops were periodically inspected by a government appointed official al-Muhtasib and his aides. These officials were responsible for checking weights and measures, as well as the purity and adulteration of the medicines sold. Such supervision was intended to prevent the use of deteriorated compounded drugs and syrups and to safeguard the public. Furthermore, a code of ethics was formulated and accepted at this time, an important step in the development of any profession. The pharmacist was called to “have deep religious convictions, consideration for others, a general sense of responsibility, and be careful and God-fearing.” The shop was to be cleaned and well stocked, and profits were to be kept moderate [1–20].

5.3 THE VALUABLE CONTRIBUTIONS OF ARABS AND MUSLIMS TO THE DEVELOPMENT OF PHARMACY

Rhazes. The contributions of Rhazes to the development of medicine are highlighted in Chapter 2. Here, we will describe his valuable contributions and innovations in the field of pharmacy. He was one of the greatest physicians of Arab–Islamic civilization, as well as he was an enthusiastic supporter of alchemy. To a great extent, he influenced the development of pharmacy and alchemy throughout the medieval period. His interest in alchemy and his strong belief in the possibility of transmutation of lesser metals to silver and gold is observable in his two best known alchemical texts *al-Asrar* (The Secrets) and *Sirr al-Asrar* (Secret of the Secrets). In both the books, he discussed the following three topics: (1) Knowledge and identification of plant-, animal-, and mineral-based drugs and the choicest type of each for utilization in treatment. (2) Knowledge of tools used that are of interest to both the alchemist and the pharmacist. He classifies these tools into those used for the dissolving and melting of bodies such as the furnace, bellows, crucible, holder, macerator, pot, stirring rod, cutter, and grinder, as well as utensils used in the transmutation procedure, such as the retort, alembic, receiver, other parts of the distilling apparatus, oven, cups, bottles, jars, and blowers. (3) Knowledge of the seven alchemical techniques such as sublimation and condensation of mercury, precipitation of sulfur and arsenic, calcination of minerals, salts, glass, talc, shells, and waxing.

Rhazes believed that because of the continuous discovery of new data and new truths, present-day knowledge must, by necessity, surpass that of previous generations. Thus, contemporary scholars, because of the accumulated knowledge at their disposal, are better equipped, more knowledgeable, and more competent than the ancient ones. Indeed, what Rhazes did in attempting to criticize the unchallenged authority of ancient knowledge was, by itself, a great step in the right direction. This impulse stimulated research and advances in medicine, pharmacy, and natural sciences. On the practical level, Rhazes warned that even highly educated physicians could not treat all diseases. Nonetheless, he encouraged physicians to continually study medical books and expose themselves to new information in order to keep up with advanced knowledge.

Rhazes was the first in the Arab–Islamic world to write a book for the general public, entitled *Man la Yahduruhu Tab*. He dedicated it to the poor, the traveler, and the ordinary citizen who could consult it for treatment of diseases, such as headaches, colds, coughing, melancholy, and diseases of the eye, ear, and stomach. In its 36 chapters, he described diets and drugs that were practically available everywhere, in apothecary shops, in the market place, and in military camps. For a feverish headache, for example, he prescribed "two parts of the duhn (oily extract) of rose, to be mixed with part of vinegar, in which a piece of linen cloth is dipped and compressed on the forehead." For a laxative, he recommended "27 grams of dried violet flowers with twenty pears, macerated and mixed well, then strained. To the filtrate, twenty drams of sugar is added for a draf."

In addition to curing bodily diseases, he searched for cures for the failings of the soul. That he was concerned with psychotherapy is quite evident. On completing his

medical encyclopedia, *al-Mansuri*, on the diagnoses and treatment of bodily diseases, he added a counterpart volume *at-Tibb ar-Ruhani*, on the medicine of the soul. In his famous *al-Mansuri*, however, Rhazes devoted 4 out of 10 treatises to diets and drugs, medicated cosmetics, toxicology and antidotes, amelioration of laxatives, and compounded remedies, all of which are of pharmaceutical interest.

Rhazes's last and the largest medical encyclopedia is his *al-Hawi fi-Tibb*, which embraces all areas of medical knowledge of the time. It included sections related to pharmacy in the healing art, *Materia Medica* arranged in alphabetical order, compounded drugs, pharmaceutical dosage forms, and toxicology. It also included numerous medical recipes and tested prescriptions that influenced medical therapy in the Arab–Islamic world and in Europe during the medieval period.

Based on recommendations of Rhazes and later on of Avicenna, treatment scheme should start with physiotherapy and diet; if this failed, drugs were used. Rhazes stated that "if the physician is able to treat with foodstuffs, not medication, then he has succeeded. If, however, he must use medications, then it should be simple remedies and not compound ones." Medicines were divided into two groups, simple and compound drugs. Physicians seemed to be aware of the interaction between drugs; thus, they used simple drugs first. If these failed, compound drugs were used. If these conservative measures failed, surgery was carried out [1–12,16,17].

Ibn al-Ash'ath. Like Rhazes and Avicenna, attention to diet and drug therapy was also emphasized by Ibn al-Ash'ath in his two books *Quwa al-Adwiyyah* and *Al-Ghadhi wal-Mughtadhi*. In his *Quwa*, in three treatises, he discusses general principles and regulations for treatment, as well as the properties of plant-, animal-, and mineral-based medicines. In addition, he explained that the five principles concerned with conditions of sickness and health, the air we breath that surrounds us, sleep and wakefulness, rest and motion, infusion and evacuation, and psychic manifestations, all generate and evolve within our bodies. In addition to these internal factors, he paid attention to what comes into our bodies and affects us from the outside, for example, what we eat and drink as well as the drugs we use to restore health or cure illness. Like Rhazes, he warned against charlatans and ignorant doctors and encouraged practical and theoretical education for healers and continued medical training for hospital internship, residency, and beyond. He concluded, "For those who collect money are always afraid to lose it, but those (like physicians) who accumulate knowledge endeavor to increase it."

Al-Majusi. Ali ibn Abbas al-Majusi (died 994), also known as Masoudi, or Latinized as Haly Abbas, is most famous for the *Kitab al-Maliki* (Complete Book of the Medical Art), consisting of 20 treatises on theatrical and practical aspects of medicine. He encouraged the use of native medicinal plants, as well as animal- and mineral-based products. Al-Majusi divided drugs according to their pharmacological properties into hypnotics, sedatives, antipyretics, laxatives, demulcents, diuretics, emetics, emollients, astringents, and digestants. He described medicinal plants and their parts used as remedial agents, such as seeds, leaves, flowers, fruits, and roots. Concerning the preparation of compounded remedies, he advised physicians to increase or decrease

the amount of each included ingredient according to need. Quantities for dosage in each case, Al-Majusi confirmed, should be determined only by the practitioner himself. Finally, he offered a classification system for drugs based on their properties and also described methods of preparing pills, syrups, powders, ointments, and so forth. Other chapters of the book discuss diet, exercise, and even bathing as they relate to health.

In his *Al-Maliki*, Al-Majusi states that the best way to determine the effects of a drug is to test it on healthy people as well as the sick and to keep careful records of the results. *Al-Maliki* was first translated in part by Constantine Africanus under the title Pantegno. A complete and much better translation, however, was made in 1127 by Stephen of Antioch. It was first printed in Venice in 1492 by Bernard Rici de Novaria and in 1523 in Venice and Lyons. This work, as that of Rhazes, Avicenna, and Al-Zahrawi, continued to circulate and influence medicine and pharmacy in Europe for over five centuries [1–12].

Abu ar-Rayhan al-Biruni (973–1050). Important contributions to pharmacy were also made by Al-Biruni, who studied drugs, physical properties, and their symptoms both in books and by examining available specimens (Figure 5.1). Among Al-Biruni's works, his *as-Saydanah fit-Tib* on pharmacy and *materia medica* are the most notable. It comprises two important, distinct, and separate sections. The first, and the most original, contains authentic definitions of pharmacology, therapeutics, and related fields of the healing arts, lexicology and lexicography, toxicology, omissions and substitutions of drugs, and their synonyms. It also contains important historical and biographical information not found anywhere else in the medieval literature. The second section of *as-Saydanah* is devoted to *materia medica*. In this, Al-Biruni explains over 700 natural remedies, conveniently and scrupulously arranged in alphabetical order.

In addition, in his *as-Saydanah fit-Tib*, Al-Biruni defines the pharmacist as the person who is specialized in the collection of all remedies. It is the responsibility of the pharmacist to choose the best of each simple or compound remedy and prepare good drugs from them, following the most accurate techniques as recommended by skilled physicians. He strongly supported the separation of pharmacy from medicine. He postulated that pharmacy must provide the tools to help in the healing process, but is not a part of medicine. Al-Biruni claimed that many so-called pharmacists were not worthy of the name and that all their knowledge was rooted in hearsay concerning the preparation of drugs. He emphasized that pharmaceutical progress resulted only from academic training and day-to-day practical experiences with remedies. As a result, these trainees would become more and more familiar with the identification of remedies, for example, shapes, physical properties, and kinds of drugs, and would possess skilled and technical knowledge.

According to Al-Biruni, the word *saydanani* is originated from the Indian *jandanani*. In India sandalwood (or *jandan*) was used extensively, more than other aromatic woods. In Arabic, the person who deals with sandalwood or *jandan* was called *sandalani* and later *saydalaneh*. In general, the Arab apothecaries (*al-'attar*), who sold perfumes and aromatics, did not use sandalwood as often as the Indians.

FIGURE 5.1 Abu ar-Rayhan al-Biruni (973–1050): Al-Biruni gave in his *as-Saydanah fit-Tib* on pharmacy and *materia medica* one of the finest definitions of the pharmacist, pharmacy, drugs, and their action. This book represents one of the finest contributions to pharmaceutical science during the medieval period and a great masterpiece of all times. Indeed, it stands as one of the most original texts in Arabic on the subject.

They excluded sandalwood, primarily, because it was not a popular wood in Arab world. The word drug (‘*uqqar*), Al-Biruni stated, comes from the Syriac word for the stump of a tree (root and Greek *rizoma*). This word (uqqar) was later applied to all the parts of the tree and was taken by the Arabs to mean a *materia medica*.

In his *as-Saydanah fit-Tib*, Al-Biruni classified the substances taken internally into three classes: The first class includes foods that are digested and assimilated to replace what has been lost. Thus, foods were first affected by the body and then they affected it for its own nourishment. The second class includes poisons that negatively affect the body’s activities, inducing diseases or death depending on their potency, as well as the body’s resistance. The third class includes drugs that fall between class one and class two and their effectiveness as remedies depends on the capability and qualifications of the physician who prescribes them.

Al-Biruni further defined pharmacy as the art of knowing the types, kinds, shapes, and physicochemical properties of crude materials and of practical experience on

how to compound them into drugs according to physician's prescriptions. Therefore, a qualified pharmacist should also be able to substitute or discard one drug for another. The theoretical knowledge of how drugs affect the body, however, is more important than the mere skill of preparing them. In substituting one drug for another, the various actions of each should be considered and accounted for. Cure can be sought through a draft, ointment, anointing oils, or by fumigation. Therefore, in seeking a substitute, all these and other applications should be taken into account. Without this knowledge, one falls short of professional goals. According to Al-Biruni, enthusiasm for the search for new remedies and their actions was much stronger in the Maghreb (North Africa) and Andalusia than in the Eastern Caliphate. Still greater activities are known to exist in India, but these follow different principles and approaches from those practiced in the Arab–Islamic world. These differences have limited the contact and dissemination of knowledge between Arab–Islamic world and India [1–12].

Ibn al-Baitar (Died 1248). As mentioned in Chapters 2 and 3, Ibn al-Baitar was one of the greatest scholars of Andalusia and was the greatest botanist and pharmacist of the medieval time. His search for medicinal plants extended over a vast area including Arabia and Palestine that he either visited or managed to collect plants from. *Kitab al-Jami fi al-Adwiya al- Mufrada*, the major contribution of Ibn al-Baitar, is one of the greatest botanical compilations dealing with medicinal plants in Arabic. It enjoyed a high status among botanists up to the sixteenth century and is a systematic work that embodies earlier works, with due criticism, and adds a great part of original contribution. It comprises some 1400 different items, largely medicinal plants and vegetables, of which about 200 plants were not known earlier. The book refers to the work of some 150 authors, mostly of Arab origin, and it also quotes about 20 early Greek scientists. *Kitab al-Jami fi al-Adwiya al-Mufrada* was translated into Latin and published in the second half of the eighteenth century.

Kitab al-Mlughni fi al-Adwiya al-Mufrada is an encyclopedia of medicine in which he lists the drugs in accordance with their therapeutic value. Thus, its 20 different chapters deal with the plants bearing significance to diseases of the head, ear, eye, and so on. On surgical issues, he has frequently quoted the famous Muslim surgeon, Abul Qasim Zahrawi. Besides Arabic, Baitar has given Greek and Latin names of the plants, thus facilitating the transfer of knowledge.

Ibn al-Baitar's contributions are characterized by observation, analysis, and classification and have exerted a profound influence on both Eastern and Western botany and medicine [1–12,15].

Al-Kindi (Alkindus). A few books related to pharmacy were written by Al-Kindi (Alkindus, 800–873), known as the philosopher of the Arabs. He became a prominent figure in the House of Wisdom, and a number of Abbasid Caliphs appointed him to oversee the translation of Greek texts into the Arabic. This contact with "the philosophy of the ancients" had a profound effect on his intellectual development and led him to write original treatises on subjects ranging from Islamic ethics and metaphysics to Islamic mathematics and pharmacology. As discussed in later

chapters, Al-Kindi was the first to systematically determine the doses to be administered of all the drugs known at his time. This resolved the conflicting views prevailing among physicians on the dosage that caused difficulties in writing recipes [1,2] (Figure 5.2).

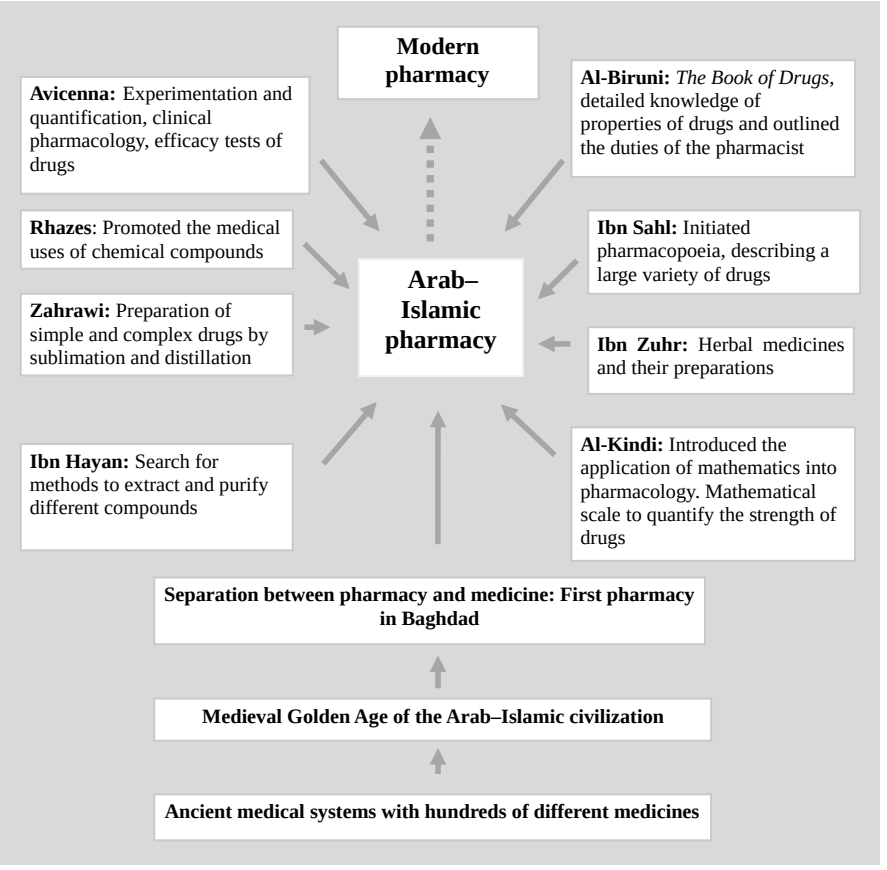

FIGURE 5.2 Development of Arab–Islamic pharmacy. Chemists such as Jaber ibn Hayan started to search for methods to extract and purify different compounds. Avicenna devoted a whole volume to simple drugs in Canon. He described about 700 preparations and introduced systematic experimentation and quantification into pharmacology. Rhazes promoted the medical uses of chemical compounds. Al-Zahrawi described a large number of recipes and explained how to prepare both simple and complex drugs. Shapur ibn Sahl, was, however, the first physician to initiate pharmacopoeia, describing a large variety of drugs and remedies for ailments. Al-Biruni gave in his *as-Saydanah fit-Tib* a detailed knowledge of the properties of drugs and outlined the role of pharmacy and the functions and duties of the pharmacist. Al-Kindi introduced the application of mathematics into medicine.

5.4 METHODS OF DRUG DISCOVERY USED IN THE ARAB AND ISLAMIC PHARMACY

As discussed in detail in Chapter 16, the selection of potential natural products was based on knowledge acquired by traditional healers in the pre-Islamic period through a long history of trial and error and then by theoretical and practical knowledge introduced by the Holy Quran or by the Prophet Mohammad (PBUH), for example, honey, milk, dates, black seeds, olive leaf, and olive oil. Furthermore, the vastness of the Arab empire and the fact that Arabs and Muslims from the farthest corners met each other while on pilgrimage to Mecca provided the exchange of both ideas and goods between people from India and China as well as from Spain. Thus, a lot of new medicines were introduced, such as acajou wood, amber, amomum, ammonia gum, areca, berberis, nux vomica, cassia fistula, cubeba, dragonblood, galenga, ginger, jasmin, jujubae, camphor, clove, manna, nutmeg, mace, musk, myrobalanes, oranges, rhubarb, sandalwood, sarcocolla, senna leaves, refined sugar, tamarind, turbith, zedoaria, and so on [3,4,13–20].

Herbal-Based Remedies. A large and complex pharmaceutical literature of hundreds of medicinal plants and their preparation and applications was introduced by Arab physicians and pharmacists. These works combined theoretical and practical aspects of medicine, pharmacy, and botany with highly accurate precision and detail. They introduced many new concepts and upgraded knowledge about herbs and their potential medical properties. The ninth century in Arab–Islamic world witnessed the richest period thus far in literary productivity insofar as medicine and pharmacy were concerned. This prolific intellectual activity paved the way for still a greater period in the succeeding five centuries of high caliber scholarship. In pharmacy, books on *materia medica* and for instructing the pharmacist concerning the work and management of his shop circulated in increasing numbers. To keep within the scope of this chapter, only a few authors and their important works will be briefly discussed.

As previously mentioned, Al-Kindi (Alkindus) introduced for the first time a scale to define the drug degrees in order to allow physicians to quantify the potency of their prescriptions. In addition, he wrote numerous encyclopedias on herbs and their pharmaceutical properties, with highly accurate precision. Al-Dinawari (828–896) is considered to be the founder of Arabic botany for his *Book of Plants*, in which he described about 640 plants and their growth phases. In 1161, Ibn Abil-Bayan of Spain published *The Bimaristan Law in Pharmacopoeia*, *Materitenses* containing 607 detailed medications. Ibn Zuhr (Avenzoar), who lived in Seville (1091–1161), wrote the *Al Kitab Al Jami*, about liquids and creams. This book includes 230 medications that are mostly herbal, with a few of animal and mineral origin. This book gives a full description of the uses of herbs, including roots, seeds, or leaves. In the early thirteenth century, the Andalusian-Arabian biologist Abu al-Abbas al-Nabati published several books and dictionaries on the use of medicinal plants describing each plant species, the plant parts used, the preparation procedure used for each remedy, and the treatment procedure of certain diseases. Ibn al-Baitar (Figure 16.1)

(1197–1248) published *The Book on Drinks and Foods*, containing 260 references, and it is the most prestigious book in the Arabic pharmacopeia.

Al-Antaki characterized in his *Tadhkirat Uli l-al-Bab wa l-Jami li-L-'Ajab al-'Ujab* 57 plants that were used as sources for simple and complex drugs. These included birthwort (*Aristolochia* sp.), carob (C*eratonia siliqua*), castor oil plant (*Ricinus communis*), common fennel (*Foeniculum vulgare*), common myrtle (*Myrtus communis*), Egyptian balsam (*Balanites aegyptiaca*), great horsetail (*Equisetum telmateia*), Leopardus-bane (*Doronicum scorpioides*), autumn mandrake (*Mandragora autumnalis*), paper reed (*Cyperus papyrus*), Persian cyclamen (*Cyclamen persicum*), saffron (*Colchicum* sp.), serapias (*Polypodium* sp.), sycamore fig (*Ficus sycamorus*), and Syrian bryony (*Bryonia certica*). Furthermore, Al-Antaki mentioned nonindigenous plants that were brought to the area specifically for their medicinal applications, such as Cornelian cherry (*Cornus mas*), purging croton (*Croton tiglium*), and gardenia (*Gardenia* sp.). He also described pharmacological uses of typical agricultural crops, such as caraway (*Bunium pauciflorum*), carrot (*Daucus carota*), wild coriander (*Coriandrum sativum*), pear (*Pyrus communis*), quince (*Cydonia oblonga*), sugarcane (*Saccharum officinarum*), and walnut (*Juglans regia*). The traditional and medicinal uses of many of these plants are described in Chapters 8 and 17.

Abu Hasan al-Tabari (808–870), a younger colleague of Ibn Masawayh, wrote several medical books, the most famous of which is his *Paradise of Wisdom*. It discusses the nature of man, cosmology, embryology, temperaments, psychotherapy, hygiene, diet, and diseases, both acute and chronic, and their treatments. In addition, the book contains several chapters on *materia medica*, diets, utilities, and therapeutic uses of animal and bird organs, as well as of drugs and methods of preparation. Al-Tabari urged the physicians to choose the best of remedies in accordance with the particular case. He was also precise in describing his therapeutics. He said, "I have tried a very useful remedy for swelling of the stomach; the juices of the liverwort (water hemp) and the absinthium after being boiled on fire and strained to be taken for several days. Also powdered seeds of celery (marsh parsley) mixed with giant fennel made into troches and taken with a suitable liquid release the wind in the stomach, joints and back (arthritis)." To strengthen the stomach and to ensure good health, he prescribed "black myrobalan powdered in butter, mixed with dissolved plant sugar extracted from the licorice and that this remedy should be taken daily." He recommended glass or ceramic vessels for storage purposes of liquid drugs, special small jars for storage of eye liquid salves, and lead containers for storage of fatty substances. Furthermore, he highlighted the importance of the origin of the used remedies. For example, black myrobalan comes from Kabul, clover dodder from Crete, aloes from Socotra, and aromatic spices from India. It is likely that Al-Tabari's recommendations built the basis for the current WHO guidelines. As discussed in detail in Chapters 16 and 19, these WHO guidelines include botanical identity, scientific name, including genus, species, subspecies, or variety and family of the potential plant, and, if available, the local name should also be verified. Furthermore, WHO guidelines highlight the importance of obtaining data regarding environmental conditions, such as soil, climate, and vegetation at the collection site.

Al-Aqrabadhin by Sabur ibn Sahl (died 869) represents one of the earliest pharmacopoeias in Arabic. It contains details of pharmaceutical recipes, including methods and techniques of compounding drugs, their actions, dosages, and means of administration. The recipes are organized in accordance with their administration form, for example, tablets, powders, ointments, electuaries, or syrups. Each class of preparation is represented along with a variety of recipes made in a specific form; however, they vary in the ingredients used and their recommended uses and therapeutic effects. Many of these remedies are remindful of similar formulas given in ancient documents from ancient civilizations.

In his *Ten Treatises on the Eye*, Hunayn ibn Ishaq (809–873) devoted one treatise to compounded drugs for the eye. He extracted some recipes from earlier treatises and added more prescriptions recommended by Greek physicians. As one example of the uses and therapeutic values of using compounded drugs, Hunayn gave that of the theriac, the universal antidote against poisoning. Hunayn defined the Greek word theriake as an animal that bites or snaps. Since these antidotes were used against animal bites, the word eventually was applied to all antidotes, especially when snake flesh was incorporated.

Animal-Based Remedies. A wide range of animals and their products were used in the medieval era by physicians and pharmacists as a source for drugs to treat a wide range of symptoms and diseases, such as skin diseases, bleeding, wounds, internal disease, hemorrhoids, animal bites, and sex-related diseases. As discussed in Chapter 6, these substances were divided into wild animals, domesticated animals, parasites of humans or domesticated animals, rare animal substances, and exotic animal substances, such as common beaver, musk, pearl, Spanish fly, and sperm whale that were imported from distant lands via the trade routes and therefore were "exotic." Al-Antaki described in his *Tadhkirat Uli l-al-Bab wa l-Jami li- L-'Ajab al-'Ujab* the therapeutic effects of many animal-based drugs. For instance, cow cheese was used to treat scabies, to relieve burning sensations in the urinary tract, to treat kidney problems, and as an aphrodisiac. The internal organs of the mule were used as painkillers and to prevent inflammation of the joints. Many of the animals that were mentioned in historical texts of the Greco-Arab and Islamic world currently remain in use in traditional medicine in the Arab and Islamic world. For instance, in Iraq 12 kinds of animals are described as medicinal sources, including sea sponge, cow, camel, bee, fish, squid, sheep, nacre, and silkworm.

Minerals and Metals. Like many other early writers, Al-Antaki describes the use of asphalt in medicine. Asphalt was used medicinally to stop a racing heartbeat, strengthen the stomach, treat infections in the spleen and liver, and stop diarrhea. It was also taken as an aphrodisiac. An additional mineral mentioned is the Jew's stone, also called *Zaitun bani Israil*, which Al-Antaki identified as a stone found in Jerusalem and Bilad al-Sham. It dissolves kidney and bladder stones, its powder treats wounds, and when mixed with honey, it softens calluses and hard skin. Iron rust was used to treat skin and eye conditions and was used as a cosmetic. Rust was also used as a contraceptive, as well as to eliminate hemorrhoids and treat diarrhea.

Al-Antaki mentioned the medicinal use of dry earth, particularly the Sidon earth, which comes from a cave outside the city of Sidon in Lebanon. This earth was known for its efficacy in knitting together fractured bones. Another type of earth or clay is the mineral hematite, identified by its red–yellow hues, which was used to stop hemorrhage and diarrhea, to treat skin diseases and high fever, to reduce swellings, and to clean infected sores. Petrified spines of sea urchin were used to open obstructions in the renal system and dissolve renal stones (bladder as well as kidney stones). Other uses included treating stings, bites, and wounds and the softening of hard skin [1–3,14].

5.5 PHARMACEUTICAL REGULATION

Throughout the Arab–Islamic Golden Age, from the ninth through the fifteenth centuries, there were many regulations that were highly regarded and strictly followed by educated pharmacists. These pharmacists were highly esteemed in their communities. In centers of science and culture, such as Baghdad, rulers issued decrees regulating pharmacy practice, whenever the situation demanded it. There were also government officials, such as Al-Muhtasib and his aides, who supervised markets, sales of commodities, weights and measures, and the professions, including pharmacy and medicine, to curb adulteration and social violations and safeguard the public. Both rulers and patrons of learning gave support and protection to health practitioners. Physicians and pharmacists gained great fame and trust among the public. Furthermore, expanding trade in the vast Arab–Islamic world and the great demand for medicines brought added prestige to the profession. Under these circumstances, Arab pharmacy developed and matured. Literary contributions of practitioners were noteworthy. These commendable developments influenced the rise of professional pharmacy in Europe and enriched available literature in pharmacy and related fields [1–12].

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CHAPTER 6

Natural Drugs in Greco-Arabic and Islamic Medicine

6.1 INTRODUCTION

Throughout history, humans have relied on natural products for their health care and basic needs to produce foodstuffs, shelter, clothing, modes of transportation, flavors and fragrances. Hundreds of wild plants and wild and domestic animals and their by-products (e.g., bones, feathers, hooves, skins, and tusks) form important ingredients for the preparation of curative, and preventive medicine. The first records are from Mesopotamia and date from about 2600 BC; among the substances discovered were oils of *Cedrus* species (cedar) and *Cupressus sempervirens* (cypress), *Glycyrrhiza glabra* (licorice), *Commiphora* species (myrrh), and *Papaver somniferum* (poppy juice), all of which are still in use today for the treatment of diseases ranging from coughs and colds to parasitic infections and inflammation. Egyptian medicine dates from about 2900 BC, but the best known Egyptian pharmaceutical record is the Ebers Papyrus dating from 1500 BC; this documents some 700 herbal- and animal-based medicines, and includes formulas, such as gargles, snuffs, poultices, infusions, pills, and ointments, with beer, milk, wine, and honey being commonly used as vehicles. Similarly, Chinese *materia medica* has been extensively documented over the centuries, with the first record dating from about 1100 BC (Wu Shi Er Bing Fang, containing 52 prescriptions), followed by works such as the Shennong Herbal (about 100 BC; 365 drugs), and the Tang Herbal (659 AD; 850 drugs). The Greeks contributed substantially to the rational development of the use of herbal medicines and other natural products. Theophrastus (about 300 BC), in his *History of Plants*, dealt with the medicinal qualities of herbs, and noted the ability to change their characteristics through cultivation. Dioscorides (100 AD) mentioned the collection, storage, and use of medicinal herbs, and Galen (130–200) wrote 30 books on these subjects, and is well known for his complex prescriptions and formulas used in compounding drugs, sometimes containing dozens of ingredients.

Greco-Arab and Islamic Herbal Medicine: Traditional System, Ethics, Safety, Efficacy, and Regulatory Issues By Bashar Saad and Omar Said

Greco-Arab and Islamic medicine, Ayurveda, Kampo, and traditional Chinese medicine have flourished as systems of medicine in use for hundreds of years. They are still in place today because of their organizational strengths, and they focus primarily on multicomponent preparations of natural products. Arab and Muslim scholars introduced hundreds of natural products, mainly medicinal plants and animal parts and products. They also developed a large and complex theoretical and practical knowledge in medicine, botany, and zoology with highly accurate precision and details. They introduced many new ideas and upgraded the knowledge about natural products and their potential pharmacological uses [1–3].

The currently available nonsynthetic and/or semisynthetic pharmaceuticals in clinical use are comprised of drugs derived from higher plants, followed by microbial, animal, and mineral products, in that order. This chapter highlights the importance of natural products as a source for new medicines as well as strategies used in selecting new potential natural products in Greco-Arab and Islamic medicine.

6.2 DRUG DEVELOPMENT IN THE GRECO-ARAB AND ISLAMIC MEDICINE

As discussed in details in Chapter 16, the selection of potential natural products was based on accumulated knowledge developed in the pre-Islamic period based on a long history of trial and error, and then by knowledge introduced by Islam. These include natural products mentioned in the Holy Quran or in the *Hadith* of the Prophet Mohammad (PBUH). Foreign developments in medicine also became available to Arab–Islamic scholars following the translation of Greek, Indian, and Persian texts. Additionally, physicians in the Islamic world introduced many innovative theoretical and practical ideas to the fields of medicine and pharmacy throughout this period [1–3] (Figure 6.1).

6.2.1 Medical Practices in Pre-Islamic Times

Medical knowledge in the Arabian peninsular before Islam (610) was the folk medicine found in all human communities. We know a lot about the nature of this medicine from the Prophet's medicine (Al-Tibb al-Nabawi), which was in most cases the medicine practiced in Hejaz at that time. Ibn Khaldun (1332–1406) (Figure 1.2), a well-known medival Muslim jurist, historian, statesman in his "Mqaddimah" states: "The Bedouins in their culture have a kind of medicine which they base primarily on experience restricted to a few patients only, and which they have inherited from their tribal leaders and old women. In some cases it is correct, but it is not founded on natural laws, nor is it tested against (scientific accounts) natural constitution (peoples). Now the Arab had a great deal of this type of medicine before the advent of Islam and there were among them well known doctors like al-Harith ibn Kalada and others." The harsh environment, isolation in the desert, the nomadic Bedouin life, and general illiteracy explain the low level of medical knowledge among Arabs before Islam. They used a wide variety of herbal and animal-based remedies. In general, they tended

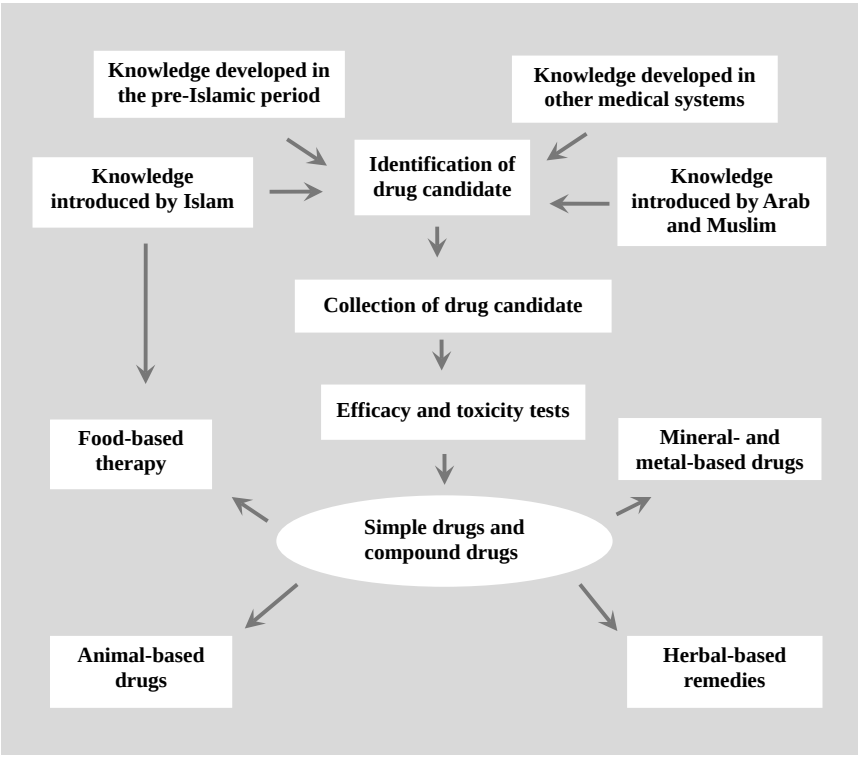

FIGURE 6.1 Drug discovery in Greco-Arab and Islamic medicine. Selection of potential natural products was based on (1) knowledge developed traditional healers in the pre-Islamic period based on a long history of trial and error; (2) knowledge introduced by the Islam; (3) Greek and Persian medical knowledge; and (4) theoretical and practical knowledge introduced by Arab and Muslim scholars. At present, herbal-based drug discovery continues to provide new and important leads against various ailments, for example, cancer, psoriasis, diabetes, malaria, and pain. With only 5–15% of the approximately 250,000 species of higher plants systematically investigated, and the potential of the marine environment barely tapped, these areas will remain a rich source of novel bioactive compounds.

to live frugally, and to eat a simple diet, and this may well have protected them against many diseases. Pre-Islamic Arabs used hijamah (cupping), kayy (cautery), and washim (branding with fire) (see Chapter 7). Among medical practitioners in the pre-Islamic era were Ibn Huzeem, Nadr Ibn Harith, and Ramtha al Tamiimi [3–5].

6.2.2 Theoretical and Practical Knowledge Introduced by the Islam

Many plants and animal products are mentioned in the Holy Quran and in the *Hadith* of the Prophet Mohammad (PBUH) (570–632), for example, dates, black seeds, olive leaf and olive oil, honey, and camel milk. These products were part of the everyday

diet, as well as used for the treatment of various diseases. Later on these products were utilized in the *Medicine of the Prophet* (Al-Tibb al-Nabawi), which includes medical treatments, descriptions of diseases, prevention, health promotion, and spiritual aspects that were recommended by Prophet (PBUH) to his companions. Two *Hadiths* of the Prophet (PBUH), "The one who sent down the disease sent down the remedy." and "For every disease, Allah has given a cure" encouraged Muslims to search for possible remedies for each diseases and greatly influenced the development of Greco-Arab and Islamic medicine during the Golden Age of the Arab–Islamic civilization.

The Book of Medicine (*Kitab al-Tibb*) of Sahih al-Bukhari (810–870) is recognized by the majority of Muslim scholars as one of the most authentic collections of what had been said and practiced (*Hadith* and *Sunnah*) by the Prophet (PBUH). The scope of Prophetic medicine is discussed in the very well known commentaries of Sahih al-Bukhari by Ibn Hajar Al-Asqalani (d. 1449) and Abu Muhammad Al-'Ayni (d. 1452), both were living in the Golden Age of the Arab–Islamic civilization, which witnessed the overlap of medical literature with other forms of science, literature, and culture. At the time, and influenced by these works, Prophetic medicine was understood to be relevant, not only during the life of the Prophet (PBUH), but within their era and within their experience [6,7].

Prophetic medicine is not based on medical experiments but rather on inspiration and accumulated medical knowledge from ancient culture and tradition. According to a *Hadith*, the stomach is the core of the body and origin of many diseases: "The stomach is the central basin of the body, and the veins are connected to it. When the stomach is healthy, it passes on its condition to veins, and in turn the veins will circulate the same and when the stomach is putrescence, the veins will absorb such putrescence and issue the same." Indeed, the Prophet used to recommend food for ailments (Table 6.1) even more than herbs or animal-based medicines. He used everything from barley soup to honey to camel milk to heal his followers and advised them to eat certain foods to prevent or cure other diseases. In fact, food is one of the oldest and most respected healing agents available to man. Honey, camel milk, dates, olive oil, and black seeds were the favored foods by the Prophet (PBUH) who regarded food as part of an overall holistic approach. Concerning olive oil, he said "Eat olive oil and massage it over your bodies since it is a holy tree." Black seeds were regarded as a medicine that cures all types of diseases. He once stated, "The black seed can heal every disease, except death." Dates are mentioned in 20 places in the Quran. Prophet (PBUH) is reported to have said "if anyone of you is fasting, let him break his fast with dates. In case he does not have them, then with water. Verily water is a purifier." To keep within the scope of this chapter we will discuss the therapeutic values of honey and camel milk. Traditional and medicinal values of black seeds, dates, and olive leaf and oil are discussed in Chapters 8 and 17.

6.2.2.1 Camel Milk Milk is rich in proteins and peptides, which play a crucial role in innate immunity when transferred to offspring and may accelerate maturation of the immune system in newborns. The immune properties of these molecules prompted investigators to assess their potential application in prevention and therapy for newborns and adults. For instance, lactoferrin exhibits antimicrobial, antifungal,

TABLE 6.1 Natural Products Used by the Prophet Mohamed and Their Current Pharmacological Uses

Product	Traditional Uses	Pharmacological Uses
Black seeds	Bronchial asthma, headache, dysentery, infections, obesity, back pain, and hypertension	Antioxidant, anti-inflammatory, antimicrobial, hypotensive, antinociceptive, uricosuric, antidiabetic, anticancer, antihistaminic, immunomodulatory
Olive Oil	Treatment and prevention of many diseases and as excellent diet	Anti-inflammatory, antihypertensive, antihypercholesterolemic, and antithrombotic,
Olive leaf	Olive leaf finds a widespread uses, treatment, and prevention of many diseases	Antioxidant, anti-inflammatory, antimicrobial, antinociceptive, choleretic, anticancer, antidiabetic, antihistaminic, antihypercholesterolemic
Honey	According to Avicenna, it preserves activity in old age and for wound healing	Wound healing, burns and serious infections, antimicrobial, antioxidant, anticancer, and anti-inflammatory
Camel milk	Hepatitis, autoimmune diseases osteoporosis, tuberculosis, asthma, flu, hypertension, and diabetes	Metabolic and autoimmune diseases, antidiabetic
Pomegranate	Inflammation, diarrhea colic, cancer, and rheumatism	Anti-inflammation, antioxidant, cardiovascular protection, oral hygiene, and weight loss
Figs	Prevention from hemorrhoids	Anti-inflammatory, antioxidant, anticancer
Dates	Generally accepted as an excellent protective and curative diet for large number of diseases	Stimulation of digestion due to high dietary fibers, antioxidants, and antimutagenic properties

antiviral, antiparasitic, and antitumoral activities. It is found in the intestinal epithelium, promotes bone growth, and accelerates the recovery of immune system function in immunocompromised animals. Casein is the predominant phosphoprotein that accounts for nearly 80% of proteins in cow milk. Casein and casein-derived peptides showed protective activities in enamel demineralization and as caries-preventing agents. They were also protective in diabetic animals, reduced tumor growth, demonstrated antihypertensive activity, and diminished colic symptoms in infants. Glycomacropeptide, a peptide derived from kappa-casein, exhibited various antibacterial and antithrombotic activities. Alpha-lactalbumin demonstrated antiviral, anticancer, and antistress properties. Lysozyme found application in infant formulas, in treating periodentitis, and the prevention of tooth decay.

Camel milk is different from other ruminant milk; it exhibits low cholesterol, low sugar, high minerals (sodium, potassium, iron, copper, zinc, and magnesium), high vitamin A, B2, C, and E, low protein and high concentrations of insulin. It has no allergic properties and it can be consumed by lactase deficient persons and those with week immune systems. Camel milk is considered to have medicinal properties. In the Sahara, fresh camel butter is often used as a base for medicines and it is also used to develop medicines and cosmetics. Additionally, a series of metabolic and autoimmune diseases are successfully being treated with camel milk. In India, camel milk is used therapeutically against dropsy, jaundice, problems of the spleen, tuberculosis, asthma, anemia, piles, and diabetes. A beneficial role of raw camel milk in chronic pulmonary tuberculosis patients has been observed. In repeated clinical trials, it was observed that there was 30–35% reduction in daily doses of insulin in patients with type 1 diabetes who were treated with raw camel milk. The Prophet (PBUH) mentioned that camels milk and urine have medical effects, so Islam encourages and permits the drinking of camel milk and camel urine in case of necessary medical treatment. Bedouins treat many diseases and disorders with camel milk. This range from osteoporosis, rickets, hepatitis, digestive ulcers and disorders, spleen problems, tuberculosis, asthma, flu, and other respiratory diseases to controlling heartbeat, hypertension, and diabetes [6–8].

6.2.2.2 Honey As described in detail in Chapter 17, honey has been known since ancient times as a glorified food, an ingredient of favored drinks, a popular medicine and the principal agent of liniments and plasters. It is frequently mentioned in early pharmacopeia, although more usually as an ingredient or carrier vehicle rather than a specific treatment. Dioscorides (40–80 AD) often mentioned honey as a vehicle for carrying therapeutic agents in *de materia medicis*. Hippocrates (460–377 BC), often cited as advocating honey for wound care, simply listed it as one of many ingredients in a multitude of unguents. Galen (130–200) recommended warming up the honey or cooking it, then using it to treat hemorrhoids and deep wounds.

In the Arab–Islamic medical system, as in other medical systems, including Ayurvedic, Chinese, and Roman traditions, honey is considered as healthy drink. The Holy Quran describes its potential therapeutic value in the bee verse: "And thy Lord has inspired the Bees, to build their hives in hills, on trees and in man's habitations, from within their bodies comes a drink of varying colors, wherein is healing for mankind, Verily in this is a Sign, for those who give thought."

Al-Basri (Ali Bin Hamzah Al-Basri), a tenth century Arab philosopher, mentioned uncooked honey for swollen intestine, whereas cooked honey was good for inducing vomiting when a poison was ingested. For that purpose, he recommended mixing one pound of sesame oil with one-third pound of cooked honey. Rhazes claimed that a mixture made of flour and honey vinegar was good for skin disease and nerve injuries and recommended the use of honey water for bladder wounds. In his book, *Al Hawi* (Encyclopedia of Medicine), he stated "Honey is the best treatment for the gums. To keep the teeth healthy mix honey with vinegar and use as mouth wash daily. If you rub the teeth with such

a preparation, it will whiten the teeth. Honey does not spoil and could also be used to preserve cadavers."

Avicenna recommended to use honey as part of an overall holistic approach to health and should be incorporated into one's everyday diet. He stated in his Canon "Honey is good for prolonging life, preserve activity in old age. If you want to keep your youth, take honey. If you are above the age of 45, eat honey regularly, especially mixed with chestnut powder. Honey and flour could be used as dressing for wounds. For lung disease, early stage of tuberculosis, use a combination of honey and shredded rose petal. Honey can be used for insomnia on occasions."

6.2.3 Theoretical and Practical Knowledge Developed in Other Medical System

The development of Arab and Islamic medicine started with the Prophet (PBUH). He was able to unite the Arab tribes who had been divided by revenge, rivalry, and internal fights. He created a strong nation who was able to defeat the Persian and Byzantine Empires. The Golden Age of Arab–Islamic civilization lasted roughly nine centuries—from the middle of the seventh to the end of the fifteenth century and in geographical terms covered nearly two-thirds of the known world. Arab and Muslims not only conquered new lands, while preserving indigenous culture, but also became scientific innovators with originality and productivity. The Arab–Islamic Empire was one of the most technologically and scientifically advanced nations in the world. By the tenth century, their zeal and enthusiasm for learning resulted in the translation into Arabic of many important Persian, Indian, and Greek medical writings in Damascus, Cairo, and Baghdad. The Caliph Al-Ma'mun in Baghdad became aware of what was to be learned from other civilizations, and therefore, he founded for this purpose, "*The House of Wisdom*," an academy for the translation of texts into Arabic. The most famous of all the translators was Hunayn ibn Ishaq. He and his colleagues translated a large number of medical manuscripts by Hippocrates and Galen, philosophical works by Plato and Aristotle, and mathematical works by Euclid and Archimedes [1–4].

6.2.4 Theoretical and Practical Knowledge Introduced by Arab and Muslim Scholars

The translation of Persian, Indian and Greek medical texts represents the first phase in the development of the Greco-Arab medical system. During the second phase of the development, Arab and Muslim scholars established and promoted their own medical theories and practices that became highly influential in Western science and teaching. Like in other fields of science, Arab–Muslim physicians developed the first scientific methods for the field of medicine. This included the introduction of experimentation, quantification, experimental medicine, evidence-based medicine, clinical trials, dissection, animal testing, human experimentation and postmortem autopsy by Muslim physicians, while hospitals in the Arab–Islamic world featured the first drug tests, drug purity regulations, and competency tests for doctors.

Arab–Muslim scholars were not guided by a long history of trial and error, but mainly by scientific methods, which has led to production of evidence-based medication. Avicenna discussed in his second book, on simple drugs (*materia medica*), the nature and quality of drugs (see Chapter 7), and the way that compounding them influences their effectiveness. He stated "You can tell the potency of drugs in two ways, by analogy (qiyas) and by experiment (tajribah). We say experimenting leads to knowledge of the potency of a medicine with certainty after taking into consideration certain conditions."

Avicenna then specified seven rules that need to be taken into account in the drug discovery process. These rules demonstrate the emphasis placed on evidence-based medication in the Greco-Arab medical system. If examines closely, one may identify modern notions about testing drugs in each of Avicenna's rules:

1. The drug must be free from any extraneous accidental quality. "This can occur if the drug is exposed to temporary heat or cold, if there is a change in the essence of the drug, or if the drug is in close proximity to another substance. Water, although cold by nature, will give warmth as long as it is heated; euphorbium, although hot by nature, will have a cold effect when cold; almond, although naturally neutral, will have a strong effect of heat if it turns rancid; and fish, although cold, is a strong source of heat if salt is added to it."
2. Drugs must be tested on a simple, not a composite, disease. "The experiment must be done on a single, not a composite, condition. In the latter case, if the condition consists of two opposite diseases and the drug is tried and found beneficial in both, we cannot infer the real cause of the cure. For example, if we treat a patient suffering from phlegmatic fever with agaric and the fever abates, this does not mean that because it was useful for a hot illness agaric possesses the property of coldness. It is possible that the drug was effective because it dissolved the phlegm or removed it; when the phlegm disappeared the fever disappeared. This action represents both the direct and the accidental benefit of the drug. The direct benefit relates to the phlegm, and the indirect refers to the fever."
3. The drug candidate must be tested with two contrary types of diseases. "The drug must be tested on two contrary conditions. If it is effective on both, we cannot judge which condition benefited directly from the drug. It is possible that the drug acted directly against one disease, and acted against the symptom of the other. Scammony, if used to treat a cold disease, would no doubt have a warming effect and bring benefit. If we try it on a hot disease, such as diurnal fever, it would also have a beneficial effect because it gets rid of yellow bile. In these cases, an experiment would be of no help in deciding whether the drug is hot or cold, unless we could know that it acted directly on one disease and acted on a symptom of the other." In the third rule, he stressed that a drug can affect the disease itself directly, and thus can cure it, but that it can also have a secondary, accidental effect, and that it would then cure a symptom only without removing the cause of the problem.

4. The potency of the drug must correspond to the strength of the disease. "The potency of the drug should be equal to the strength of the disease. If some of the drugs are inadequate with regard to heat when compared to the coldness of an illness, they will not be able to affect a cure. Sometimes during their application against coldness, their function for producing warmth is weakened. So it is best to experiment first using the weakest dosage and then increase it gradually until you know the potency of the drug, leaving no room for doubt."
5. The time of action must be observed, so that essence and accident are not confused. "One should consider the time needed for the drug to take effect. If the drug has an immediate effect, this shows that it has acted against the disease itself. If its initial effect is contrary to what comes later, or if there is no initial effect at first and the effect shows up later, this leads to uncertainty and confusion. Actions in such cases could be accidental: their effect is hidden at first and later comes into the open. The confusion and uncertainty relate to the potency of the drug."
6. The effect of the drug must be seen to occur constantly or in many cases. "The effect of the drug should be the same in all cases or, at least, in most. If that is not the case, the effect is then accidental, because things that occur naturally are always or mostly consistent."

The experimentation must be done with the human body "Experiments should be carried out on the human body. If the experiment is carried out on the bodies of other animals it is possible that it might fail for two reasons: the medicine might be hot compared to the human body and be cold compared to the lion's body or the horse's body ... The second reason is that the quality of the medicine might mean that it would affect the human body differently from the animal body." Currently, the development of new drugs is suffering from two major limitations. First, none of the animal species or *in vitro* test systems can properly mimic the complexity of the human body. A new developed drug can induce unprecedented positive or negative biological effects involving systemic interactions specific to humans. This phenomenon was first described by Avicenna's seventh rule and thus it remains relevant today. Second, systematic comparisons of drug studies done in animals and humans showed substantial differences, due to the failure of animal models to adequately mimic human disease (see Chapters 13 and 14 for further discussion) [1–9].

6.3 NATURAL MEDICINAL SUBSTANCES

In general, natural products can be classified as herbal-based, animal-based, or mineral-based products. It is believed that the vast majority of the world's natural compounds have not been tested for their therapeutic value and that several novel sources of biodiversity are potentially available. These include a broader range of plant species than traditionally sampled, animals, marine organisms, and microbial diversity. Two examples of recently developed natural product-based drugs, one from a plant and one from an animal, deserve mention. Taxol, isolated from the Pacific yew,

is a substance that kills cancer cells by a mechanism unlike that of other known chemotherapeutic agents: it prevents cell division by inhibiting the disassembly of the mitotic spindle. The discovery of the complex molecule taxol, and its novel mechanism of action, has led to the synthesis of several taxol-like compounds that are even more effective than the natural taxol. The other example that deserves mention are the peptide compounds in the venom of cone snails, a genus of predatory snails numbering about 500 species that inhabit tropical coral reefs. The diversity of these compounds is so great that it may rival that of alkaloids in higher plants and secondary metabolites in microorganisms. Some of these peptide compounds, which have been shown to block a wide variety of ion channels, receptors, and pumps in neuromuscular systems, have such selectivity that they have become important tools in neurophysiological research and may become invaluable to clinical medicine. One voltage-sensitive calcium-channel blocker, omega-conotoxin, binds with enormous specificity to neuronal calcium channels and has been found to have potent activity in animals both as an analgesic and as a means of keeping nerve cells alive following ischemia.

Comparisons of the information presented on sources of new drugs from 1981 to 2007 indicate that almost half of the drugs approved since 1994 are based on natural products. The list of recently approved natural product-based drugs include compounds from plants (elliptinium, galantamine, and huperzine), microbes (daptomycin) and animals (exenatide and ziconotide), as well as synthetic or semisynthetic compounds based on natural products (e.g., tigecycline, everolimus, telithromycin, micafungin, and caspofungin). They cover a range of therapeutic indications: anticancer, anti-infective, antidiabetic, among others [9–13].

6.3.1 Herbal-Based Remedies

Arab and Muslim scholars introduced hundreds of medicinal plants and developed a large and complex medical literature during the Golden Age of Arab–Islamic civilization. These works explored and synthesized the theory and practice of medicine and botany with highly accurate precision and detail. They introduced many new ideas and upgraded knowledge about herbs and their potential pharmacological effects. Al-Kindi (Alkindus) (800–873) introduced for the first time a scale to define the meaning of drug "degrees" in order to allow physicians to quantify the potency of their prescriptions. In addition, numerous encyclopedias on botany were written, with highly accurate precision and detail concerning medicinal plants. For instance, Al-Dinawari (828–896) is considered to be the founder of Arabic botany for his *Book of Plants*, in which he described about 640 plants and described the phases of plant growth and the production of flowers and fruit. In 1161, Ibn Abil-Bayan of Spain published *The Bimaristan Law in Pharmacopoeia*, *Materitenses* containing 607 detailed medications. Ibn Zuhr (Avenzoar), who lived in Seville (1091–1161), wrote the *Al Kitab Al Jami*, about liquids and creams. This book includes 230 medications that are mostly herbal, with a few of animal and mineral origin. This book gives a full description of the uses of herbs whether they are roots, seeds, or leaves. In the early thirteenth century, the Andalusian-Arabian biologist Abu al-Abbas al-Nabati pub-

lished several books and dictionaries on the use of medicinal plants describing each plant species, the plant parts used, the preparation procedure used for each remedy, and the treatment procedure of certain diseases. Ibn al-Baitar (Figure 16.1), who lived in Damascus, Syria (1197–1248), published *The Book on Drinks and Foods*, containing 260 references, it is the most prestigious book in the Arabic pharmacopeia.

Al-Antaki described in his book 57 plants (about 79% of all the medicines mentioned) that were used as a source for simple drugs, or frequently as one ingredient in more complex herbal-based remedies. He described the plant and the way it was used by Greco-Arab and Islamic Arab physicians. Furthermore, Al-Antaki mentioned nonindigenous plants that were brought to the area specifically for their medicinal applications and also described pharmacological uses of typical agricultural crops (Figure 6.2).

FIGURE 6.2 Daud al-Antaki/David of Antioch (d. 1599) was born blind in Antioch. Despite his disability, he became a famous pharmacist in the 16th century and learned many foreign languages (in addition to Arabic), including Greek. His life was dedicated to traveling across Turkey, Syria, and Egypt to seek knowledge. He finally resided in Egypt and worked as a senior pharmacist. Al-Antaki produced a number of medical books and his famous writing was entitled Tadhkirah or "Memorandum Book," is still available today in bookstalls in Egypt in modern printings.

Selection Methods. In general, the correlation between morphological features, for example, size, shape, color, texture, and taste of herbs and the anatomy of the affected organ led to the identification on new potential medicine. For instance, seeds with kidney shape are used for treating kidney stones, for example, *Alhagi maurorum* and *Astragalus macrocarpus*. Roots with shapes similar to the human body or fruits that resemble the human testis are used traditionally for stimulating sexual desire or treating sexual weakness. This doctrine of signatures is reflected in the usage of certain herbs, for example, the yellow decoction obtained from leaves of *Rhamnus alaternus* and the yellow juice from the fruits of *Ecbalium elaterium* are used for treating jaundice and liver diseases. For several herbs, the plant's common name in Arabic refers to its medicinal applications [1–3,9–13].

Current Strategies in Plant Selection. As discussed in detail in Chapters 16 and 19 and the WHO guidelines (2003), complete taxonomical identification is an important factor during selection process. These include botanical identity, scientific name, including genus, species, subspecies or variety and family of the potential plant, and, if available, the local name should also be verified. Furthermore, WHO guidelines highlight the importance of obtaining data regarding environmental conditions, such as soil, climate, and vegetation at the collection site. They also demand that a voucher specimen be deposited in a national or regional herbarium for authentication and further consultation by other researchers.

There are certain differences in approaches in selecting plants for industrial or rural applications. On one hand, the rural community applies natural products for treatment of common diseases. According to our recent survey, the majority of the Arab community in Palestine do use medicinal plants for treatment of common diseases such as diarrhea, pneumonia, and wound infections and healing (Chapter 9). On the other hand, the pharmaceutical industry requires medicinal plants for formulation of herbal-based remedies for commercial gain and hence focuses more on urban problems such as metabolic disorders, chronic diseases, and multidrug resistance with infectious pathogens. Whether for the rural community or for industrial application the selection of natural-based products should be based on their safety and effectiveness in prevention and/or treatment of a given illness.

Currently, natural product selection generally follows five main routes: (1) random selection followed by chemical screening; (2) activity-based random selection; (3) ethnobotanical and ethnopharmacological knowledge; (4) traditional knowledge obtained from ancient medical systems; and/or (5) ecological search.

1. *Random Selection Followed by Chemical Screening*: These so-called phytochemical screening approaches have been used in the past and are currently pursued mainly in developing countries. The tests are simple to perform, but false-positive and false-negative tests often render results difficult to assess. More important, it is usually impossible to relate one class of herbal-derived agents to specific biologic targets; for example, the alkaloids or flavonoids produce a vast array of biologic effects that are usually not predictable in advance.

2. *Activity-Based Random Selection*: Safety and efficacy of plant extracts are evaluated both in experimental animals and *in vitro* using cultured cells. During the last four decades, thousands of plant species have been screened *in vitro* and *in vivo* for several biologic activities, including antibacterial, antidiabetic, antifertility, antifungal, antihypercholesteremic, anti-inflammatory, antitumor, cardiovascular, central nervous system depressant, cytotoxicity, diuretic, and others (see Chapter 8).
3. *Ethnobotanical and Ethnopharmacological Studies*: The ethnobotanical and ethnopharmacological approach uses information obtained from an ethnobotanical survey such as traditional medical uses, preparation techniques, geographical distribution of the plant, its abundance, whether it is threatened or endangered, a shrub or fast growing tree, easily cultivable, easily identifiable, and so on. Information such as the season of collection, parts that are used and whether those parts are seasonal/replenishable and if there is any reported toxicity, are also required. The information can be obtained from traditional medical practitioners and other experts such as village elders who are traditional users of medicinal plants. It is highly recommended that the ethnobotanical surveys are carried out by a team of botanists, traditional healers, and medical practitioners. In this manner the traditional healers would identify medicinal plants for treatment of different diseases, the botanist can carry out appropriate taxonomical and botanical characterization of these medicinal plants, whereas the medical practitioners would help in proper identification of potential medical applications. These practitioners can help to evaluate whether an herbal remedy has curative properties, if it is merely alleviating the symptoms, or if it is exhibiting a placebo effect. However, information obtained from ethnobotanical surveys is not always reliable. It is possible that people may cite a particular plant more frequently since it is easily available, easily recognizable or resembles a certain disease feature. People may also mention plants about which they have gained information from personal communication, books, from the media, or from the Internet. In addition, publications concerning medicinal plants are often compilations from other texts and seldom stem from personal experience, making evaluation difficult.
4. *Knowledge Obtained from Ancient Medical Systems*: A huge amount of medical information is available in ancient texts from different sources such as Greco-Arab and Islamic medicine. However, while studying ancient medical texts, one must consider the fact that the plants may have evolved over a period of time resulting in changes in their phytochemical composition and hence their medicinal properties and therefore validation is required. Nevertheless, the success rates of the traditional-based approaches are substantially higher than those of random screening since the continued use of crude preparations are, in fact, comparable to small scale clinical trials. In general, the search for the medicinal plants can follow three main routes: random, ethnobotanical, and ethnopharmacological, traditional knowledge obtained from ancient medical systems, and ecological search.

5. *Ecological Approach*: Pharmacologically active plants can also be identified using an ecological approach. The absence of predation in areas infested with herbivores, for example, can indicate the presence of toxic compounds. Selection can also be based on an approach called zoopharmacognosy, a variation to the ecological approach, which proposes the selection of plant species regularly ingested by animals, mostly primates for reducing pain, microbial or worm infestations.

6.3.2 Zootherapy

The treatment of human ailments by using medicines that are obtained from animals or ultimately are derived from them is known as zootherapy. Animal-based medicines have been elaborated from parts of the animal body, from animal metabolites (corporal secretions and excrements), or from animal products (nests and cocoons). Data have been found on such usages in ancient civilizations, such as Egypt and Mesopotamia, which left their mark on the various civilizations that later arose in these regions. Historical sources of ancient Egypt mention the medicinal uses of animal-derived products, such as, bee honey, cattle milk, ox organs, lizard blood, bat limbs, ambergris from the sperm whale, and the glands of the musk deer. Historical scripts of civilizations of ancient Mesopotamia, mainly the Assyrian and the Babylonian, contain descriptions of beeswax and honey, mongoose blood, turtle shell, fish oil, goat skin, bird excrement, and animal fat. In India, the Hindu religion has used five products of the cow for purification since ancient times. In ancient China, among many other substances of animal origin, the glands of the musk deer were used. Hippocrates (460–377 BC) used among many other animal substances cattle milk, chicken eggs, mammal horns, and sea sponge as remedies. About one-tenth of the remedies mentioned in Dioscorides's (100 AD) *Materia Medica* were animal parts and products. The ancient Jewish scripts mention several animals and their medical uses: honey was used to treat bulimia and goat milk was used to cure coughing. Snakes, human urine, pearls, mammal glands, and several other substances were used for their therapeutic effects.

Zootherapy in Greco-Arab and Islamic Medicine. Medieval Greco-Arab and Islamic literature offers a huge amount of data about natural products in general, with emphasis on herbal as well as animal-based remedies in particular. As discussed in Chapter 7, the medicine of the Prophet (*tibb al-nabawi*) indicates intensive medicinal use of milk, cattle cheese, and bee honey. Early Arab and Muslim physicians such as Rhazes (864–930), Avicenna (980–1037), Al-Kindi (800–873), and Al-Antaki (d. 1599), prescribed many animal-based remedies. These included camel milk, cattle fat, coral, crab, dog, fish stone, horse, lizard, medical skink, mouse, pearl, pigeon, rabbit, rhino and goat horns, scorpion, snake, squid, turtle, and wolf, and animal products such as honey, wax, milk, and eggs. About 10% of all the medicinal substances used in the Arab–Islamic world during the Middle Ages were of animal origin. Most animal products, such as milk, cheese, and honey, were used in the diet for the prevention and treatment of various diseases (see Chapter 17).

Detailed information on animals and animal-based products are found in various encyclopedias such as Daud al-Antaki's book, *Tadhkirat Uli l-al-Bab wa l-Jami li-L-'Ajab al-'Ujab,* and *Hayat al-Hayawan* (life of animals) by Al-Damiri (1344–1405), an Egyptian zoologist. The latter is one of the most well-known medieval works on zoology and animals. The work is a compilation of over 500 prose writers and nearly 200 poets. The correct spelling of the names of the animals is given with an explanation of their meanings. The use of the animals in medicine, their lawfulness as food and their position in folklore are the main subjects explained, alongside long, irrelevant stretches of political history. Al-Damiri describes in his lexicon hundreds of animals, tens of which were used for remedies.

One of the most important sources for learning about medicinal substances of natural origin used among physicians and inhabitants of the Bilad al-Sham (Bilad al-Sham is the medieval Arabic name for a large area including the majority of present-day Syria, Israel, Lebanon, and Jordan also known as the Levant) is the work of the physician, Daud al-Antaki, who lived and practiced during the second half of the sixteenth century. Al-Antaki's book, *Tadhkirat Uli l-al-Bab wa l-Jami li-L-'Ajab al-'Ujab*, is a medical and pharmaceutical encyclopedia, containing detailed descriptions of natural-based remedies in use in the Bilad al-Sham. The book consists of an introduction and four parts. In the introduction, he listed the sciences addressed in the main body of the work, and explains the connection of each to medicine. Part one is a general preface on medical wisdom and discusses various diagnostic methods. Al-Antaki opens part two with a historical survey of the development of pharmaceutical science, beginning with Dioscorides and ending with Al-Antaki's contemporaries. This part of the text also describes the nature of simple and complex drugs and gives general instructions to pharmacists. Part three lists medicinal substances in Arabic alphabetical order and describes their application as well as their use as an ingredient in complex drugs. The list includes hundreds of plants, minerals, and animals (and their organs). Part four describes diseases, their causes and symptoms, and various specific treatments.

Animal-Based Remedies. A remarkably wide range of animals and their parts were used therapeutically in the medieval era by physicians, pharmacists, and patient. These included (1) wild animals such as ant, bee eater, cuttlefish, desert partridge, earthworm, fish, firefly, flycatcher, fox, frog, gazelle, hedgehog, lizard, scarabee, scorpion, sea shell, and snail; (2) domesticated animals such as ass, cattle, hen, honey and wax, goat, goose, lamb, mule, and silkworm; (3) parasites of humans or domesticated animals, such as louse, mouse, and stinkbug; (4) rare animal substances such as adder, bustard, coral, kermes, lacca, ostrich, triton, and squid. These animals were hunted in season or collected in the desert, on the seashore, or in remote areas; (5) exotic animal substances, such as common beaver, musk, pearl, Spanish fly, sperm whale, which were imported from distant lands via the trade routes and therefore were exotic.

Animal substances were utilized to treat a wide range of symptoms and diseases such as skin diseases, bleeding, wounds, internal disease, hemorrhoids, animal bites, and sex-related diseases. Al-Antaki described in his book the therapeutic benefits of

a number of animals and their products. Accordingly, the cow cheese was used to treat scabies, to relieve burning sensations in the urinary tract, to treat kidney problems, and as an aphrodisiac. The internal organs of the mule were used as painkillers and to prevent inflammation of the joints. Eating a mule's heart was supposed to purify the body, eating its liver prevented pregnancy, and drinking its urine stopped excessive tears. Silkworm treated several medicinal properties. For instance, its ashes were used to treat wounds; its liquids were used to eliminate scars; whereas its boiled body was used to treat swellings, throat infections, and racing heartbeat. The stinking bug, a common parasite at that time, was used to treat headaches, uterine problems, coughing, and fever, to dissolve kidney stones, and to open blocked a urinary tract. Al-Antaki mentioned three wild birds: the bee eater, the flycatcher, and the bustard. The bustard's flesh, fat, blood, and internal organs (such as the stomach), ashes from its feathers, its eyes, and claws were used to prevent or eliminate phlegm, treat pneumonia, dissolve kidney stones, and remove cataracts. Products of the flycatcher were used as a drug to dissolve blood clots, to treat jaundice and infected spleens, to dissolve kidney stones, and to cure eye and skin diseases. The bee eater was used to eliminate odor, treat colds and skin diseases, and remove phlegm. The firefly is identified as possessing special medicinal properties, and was used to dissolve kidney stones and to heal hemorrhoids. Theriak (theriac), a mixture of many plants, poisonous minerals, and extracts of animals generally poisonous such as snakes and scorpions, was used as an antidote to snakes bites, scorpion stings, animal bites, and poisoning by different kinds of poisons.

Many of the animals were mentioned in historical scripts of the Greco-Arab and Islamic world are currently still in use in traditional medicine in the Arab and Islamic world. For instance, in Iraq 12 kinds of animals are described as medicinal sources, including sea sponge, cow, camel, bee, fish, squid, sheep, nacre, and silkworm, and they constitute 5% of all the natural products mentioned. Similarly, surveys conducted in Syria during the 1970s found that about 5% of the natural remedies sold in the markets were animal based. A survey of traditional medicines in use in the markets of Israel recorded 20 substances of animal origin. Similar data are derived from surveys conducted in Jordan. In Pakistan, for instance, 31 animal parts and products are used, constituting 9% of all the medicinal substances used in traditional medicines. A survey of traditional medicines in use in the markets in Sudan has recorded 23 animals that are used as sources of remedies in Sudanese traditional medicine. For example, the fresh manure of a dromedary (*Camelus dromedaries*) is applied externally on the affected parts to alleviate arthritis; honey is used in the treatment of hepatic and gastrointestinal disorders, gastric ulcers, as well as to heal wounds; the fats of the lion (*Panthera leo*) and hyena (*Crocuta crocuta*) are used topically to alleviate abdominal pains.

Current Trends. Leeches are undergoing a triumphant resurgence in medicine, particularly in microsurgery. Traditionally, leeches are usually used in conditions such as abnormal swellings, piles, inflammatory abscess, skin diseases, rheumatoid arthritis, eye diseases, poisonous bites, erysipelas, and so on. The first recorded use of leeches in medicine was in 200 BC by Greek physicians and was later reintroduced by Avicenna in *The Canon of Medicine*. Leech therapy became a popular practice in

medieval Europe, namely the leeches from Portugal and France, due to the influence of *The Canon*. Like Avicenna, Abu al-Qasim al-Zahrawi (known as Albucasis 936–1013) recommended the use of leeches on parts of the body for which application of cupping-vessels is impossible, either because of part is bare of flesh, like the nose. A more modern use for medicinal leeches was introduced by Abd el-Latif al-Baghdadi in the twelfth century, who wrote that leeches could be used for cleaning tissues after surgical operations. He did, however, understand that there is a risk over using leech, and advised patients that leeches need to be cleaned before use and that the dirt or dust "clinging to a leech should be wiped off" before application. The revival of interest in leech therapy was caused due to the unsatisfactory results of conventional treatment of many cardiovascular diseases, and to new findings about the leech's salivary components and its influence on the human organism. During the blood-sucking process, leeches produce an anticoagulant, a local anesthetic, a vasodilator, and an antibiotic, all of which are useful to their blood-sucking propensities and are capable of being turned into therapeutic advantage. Leech secretions are more effective than heparin at inhibiting fibrin formation because, being smaller, they penetrate the clot more effectively. Also, whereas heparin acts indirectly by activating the anticoagulant antithrombin III, leech anticoagulants inhibit specific steps in the coagulation cascade.

One of the best-known examples of a successful animal-based drug is that of the angiotensin-converting enzyme (ACE) inhibitor, a component of snake venom (*Bothrops jararaca*). This enzyme is responsible for converting an inactive precursor into the locally active hormone angiotensin, which causes blood vessels to constrict and hence raises blood pressure. By pharmacologically blocking the enzyme's activity, blood pressure can be reduced, and agents with this activity are commonly used to treat people with hypertension. Currently, ACE inhibitors like captopril, enalapril, and lisinopril are among the top 20 best selling medicines in the world.

Several compounds have been extracted from fish and these are employed as remedies in the medical cannon. Today, some of these compounds are important as tools for biochemical research or as new leads for the development of anticancer and antiviral drugs. Oily fish, like cod, herring, salmon, and turbot, have a great medicinal value to human beings due to a polyunsaturated compound known as Omega-3. This substance helps the prevention of arthritis. The presence of an anticoagulant system in the plasma of Atlantic salmon (*Salmo salar*) and rainbow trout (*Oncorhynchus mykiss*) has been confirmed; similarities exist with the protein C found in the mammal anticoagulant system. Tetrodotoxin (TTX), a water-soluble guanidinium derivative, is an example of a bioactive compound produced by marine organisms such as the puffer fish that resembles procaine in its ability to inhibit transmission of nerve cells. When diluted it acts as an extraordinary narcotic and analgesic.

Amphibians have provided compounds that demonstrate a therapeutic advantage. Peptides extracted from the scraped secretions of *Phyllomedusa bicolor*, for instance, are used in the treatment of depression, stroke, seizures, and cognitive loss in ailments such as Alzheimer's disease. Some of these compounds are important tools for biochemical research or as new leads for the development of anticancer or antiviral drugs. The number and diversity of compounds produced by amphibians in their

granular glands is surprisingly high, even within single species. The main categories of secretions include biogenic amines, bufogenines and bufotoxins (steroids), alkaloids and peptides (including smaller oligopeptides, polypeptides, and proteins), and the as yet uncharacterized zetekitoxins found in the Middle and South American harlequin frogs, genus *Atelopus*. Most alkaloids of amphibian skin appear to be sequestered from dietary arthropods. Many of the compounds contained in granular gland secretions have a defensive role. Their pharmacological effects include cardiotoxic, myotoxic, and neurotoxic activities, some are vasoconstrictive and hypotensive agents while others have hallucinogenic effects—all properties that would adversely affect a potential predator. Dermmophin, a novel opioid heptapeptide produced in the skin of the South American leaf frogs, genus *Phyllomedusa*, has a 1000-fold greater effect than morphine at the same concentration. It is therefore possible that molecules derived from amphibian sources might provide useful alternative or supplementary treatments, primarily as antimicrobial and antifungal agents. The presence of a wide range of peptides with unknown properties enhances the prospects of using peptide vaccines for viral diseases.

Insects have proven to be very important as sources of drugs for modern medicine since they have immunological, analgesic, antibacterial, diuretic, anesthetic, and antirheumatic properties. Chitosan, a compound derived from chitin, has been used as an anticoagulant and to lower serum cholesterol level, as well as to repair tissues, and even in the fabrication of contact lenses. The major component of bee venom, the tetrameric polypeptide melittin, may be responsible for the often-reported antiarthritic and anti-inflammatory effects. A toxin named margatoxin has been isolated from the venom of the scorpion *Centruroides margaritatus*. This chemical compound blocks lymphocyte activation and the production of interleukin-2 by human T-lymphocytes. The Merck Company has filed a patent application for the use of margatoxin as an immunosuppressant, which may be potentially useful in treatment of autoimmune diseases or in preventing the rejection of organ transplants. The use of animal toxins to determine nerve action mechanisms could prove to be the starting point for designing new treatments for Alzheimer's disease [9–15].

6.3.3 Minerals and Metals

Al-Antaki described five minerals that were used medicinally. Like many other early writers, he discussed the use of asphalt in medicine. Asphalt was used medicinally to stop racing heartbeat, strengthen the stomach, treat infections in the spleen and liver, and stop diarrhea. It was also taken as an aphrodisiac. An additional mineral mentioned is the Jew's stone, also called *Zaitun bani Israil*, which Al-Antaki identified as a stone found in Jerusalem and Bilad al-Sham. It dissolves kidney and bladder stones, its powder treats wounds and when mixed with honey it softens calluses and hard skin. Iron rust was used to treat skin and eye conditions and was used as a cosmetic. Rust was also used as a contraceptive and to eliminate hemorrhoids, and in treatments against diarrhea.

Al-Antaki mentioned the medicinal use of dry earth (*Turab*), particularly the Sidon earth, which comes from a cave outside the city of Sidon. This earth was known its

efficacy in knitting together fractured bones. Another type of earth or clay is the mineral hematite, which is identified by its red/yellow hues, and was used to stop hemorrhaging and diarrhea, to treat skin diseases and high fever, to reduce swellings, and to clean infected sores. Petrified spines of sea urchin (*Cidaris* sp.) were used to open obstructions in the renal system and dissolve renal stones (bladder as well as kidney stones). Other uses included treating stings, bites, and wounds, and the softening of hard skin [9–11].

6.4 CURRENT TRENDS IN NATURAL PRODUCT-BASED DRUG DISCOVERY

Just over 200 years ago, Friedrich Sertürner isolated the first pharmacologically active pure morphine compound from opium produced by cut seed pods of the poppy, *P. somniferum*. This initiated an era wherein drugs from plants could be purified, studied, and administered in precise dosages that did not vary with the source or age of the material (e.g., plant). Pharmaceutical research expanded after the Second World War to include massive screening of microorganisms for new antibiotics following the discovery of penicillin. By 1990, about 80% of drugs were either natural products or analogs inspired by them. Antibiotics (e.g., penicillin, tetracycline, erythromycin), antiparasitics (e.g., avermectin), antimalarials (e.g., quinine, artemisinin), lipid control agents (e.g., lovastatin and analogs), immunosuppressants for organ transplants (e.g., cyclosporine, rapamycins), and anticancer drugs (e.g., taxol, doxorubicin) revolutionized medicine. Life expectancy in much of the world lengthened from about 40 years early in the twentieth century to more than 77 years today.

As discussed above, natural products have provided the inspiration for most of the active ingredients in drugs: about 80% of medicinal products up to 1996 were either directly derived from naturally occurring substances or were inspired by a natural product. In an extensive review of new drugs introduced between 1981 and 2002, 28% of the 868 new chemical entities were natural products or derived from natural products, with another 24% created around a pharmacophore from natural substances. In addition to launched products, at least 70 natural product-related compounds were involved in clinical trials in 2004, and exploration of the bioactivity of natural products continues to provide novel chemical scaffolds for further drug discovery. Various reasons have been put forward to explain the success of natural products in drug discovery: their high chemical diversity, the effects of evolutionary pressure to create biologically active molecules, the structural similarity of biomolecular targets across many species, and so on. Evidence for many of the suggested explanations is hard, if not impossible to obtain. However, analysis of the structural diversity of natural products does support the belief that collections of natural products are not only more varied than those made up of synthetic compounds, particularly those produced by combinatorial chemistry, but also that natural products are more similar than synthetic compounds to the “chemical space” occupied by drug molecules. Further analysis of the structural features of natural products has led to ways to describe the regions of chemical space they occupy. From such approaches, it may be

possible to guide the synthesis of libraries of new molecules that will occupy parts of chemical space predicted to be associated with drug-like biological activity.

Although the expansion of synthetic medicinal chemistry in the 1990s caused the proportion of new drugs based on natural products to drop to about 50%, 13 natural product-derived drugs were approved in the United States between 2005 and 2007, with five of them being the first members of new classes. With such a successful record, it might be expected that the identification of new metabolites from living organisms would be the core of pharmaceutical discovery efforts. However, many pharmaceutical firms have eliminated their natural product research during the last decade. Although more than 100 natural product drugs are currently undergoing clinical trials and at least a 100 similar projects are in preclinical development, this represents about a 30% drop between 2001 and 2008. This is because of the perceived disadvantages of natural products (e.g., difficulties in access and supply, complexities of natural product chemistry and inherent slowness of working with natural products, and concerns about intellectual property rights), and the hopes associated with the use of collections of compounds prepared by combinatorial chemistry methods [11–15].

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CHAPTER 7

Method of Therapy in Greco-Arab and Islamic Medicine

7.1 INTRODUCTION

In Islam, all components of existence are treated with equal importance, from breath and body to the soul and matter; both spiritual and physical health is essential. As a result, many Arab and Muslim physicians, such as Rhazes and Avicenna, proposed that the body should be treated as a whole and not just as a series of parts and organs, and that it was endowed with an ability of natural healing that depended on rest, a good diet, fresh air, and cleanliness. Avicenna noted that there were individual differences in the severity of disease symptoms and in the individual ability to cope with disease and healing. Hippocrates thus laid the foundations of the modern theory that thoughts, ideas, and feelings, which he proposed to originate in the brain, can influence the health and the process of disease. Rhazes supported this concept by his recommendation: "The physician, even though he has his doubts, must always make the patient believe that he will recover, for state of the body is linked to the state of the mind." Later on, Avicenna who defined medicine as "the science from which we learn the states of the human body with respect to what is healthy and what is not; in order to preserve good health when it exists and restore it when is lacking" supported the views of Rhazes. He stated that "We have to understand that the best and most effective remedy for the treatment of patients should be through the improvement of the power of the human body in order to increase its immune system, which is based on the beauty of the surroundings and letting him listen to the best music and allowing his best friends to be with him."

It is now clear that the mind and the body interact, influence, and regulate each other. The perception of stress can lead to production of both "stress hormones," and mediators of the immune system. These "stress hormones" act in a feedback mechanism to regulate their own production and the production of certain immune mediators. These immune products (e.g., Cytokines) act on the brain to modify

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behavior and the ability to perceive and respond to stressful challenges by inducing lethargy, fever, and nausea (i.e., sickness behavior).

On the basis of the recommendations of Rhazes and Avicenna, patients were treated through a scheme starting with physiotherapy and diet; if this failed, drugs were used. Rhazes's treatment scheme started with diet therapy. He noted that "if the physician is able to treat with foodstuffs, not medication, then he has succeeded. If, however, he must use medications, then it should be simple remedies and not compound ones." Drugs were divided into two groups, simple and compound drugs. Physicians were aware of the interaction between drugs; thus, they first used simple drugs. If these failed, compound drugs, consisting of two or more compounds, were used. If these conservative measures failed, surgery was undertaken.

The Greek and Roman humor theory or humoralism of the human body had a great influence on the development of the Greco-Arab medical system. Hippocrates was the first to apply this idea to medicine and it became strongly accepted in the medical canon through the influence of Galen. The humoral theory was adopted and further developed by Arab–Muslim physicians, and it became the most commonly held view of the human body among European physicians until the advent of the modern medical research in the nineteenth century [1–8]. This chapter highlights both the basic concepts of the humoral theory and the methods of therapy of the Greco-Arab and Islamic medicine.

7.2 THE FOUR HUMORS THEORY

7.2.1 Concept

Hippocrates laid the foundations of the Greco-Arab theory that thoughts, ideas, and feelings, which he proposed to originate in the brain, can influence health and the process of disease. In Hippocrates's view, the process of healing and the purpose of medicating held one and the same goal, to assist the patient in regaining harmonious balance of the tendencies within him/herself and external forces. He formulated a set of principles that helped to define the tendencies (i.e., temperaments) of each patient, and he claimed that the root of one's temperament was derived from the four humors dominant in the body.

Essentially, this theory held that the human body contains four basic fluids, called humors, that are in balance in healthy persons. Imbalances, for example, an excess or deficit in one of the four humors, results in the development of a disease state. The four humors in the body are blood, phlegm, yellow bile, and black bile. Each humor has its specific temperament, for example, blood is hot and moist, phlegm is cold and moist, yellow bile is hot and dry, and black bile is cold and dry. The humors are held in balance when a person is in a healthy state, which is controlled by self-preservation power called *medicatrix naturae*. Every healthy person is supposed to have a unique humoral constitution. Accordingly, diseases are the result of imbalance in the humor composition. Medicines and correct diet are helpful in regaining the preserving power in order to restore normal humor balance.

According to the "humor theory," the drugs themselves have unique temperaments derived from their chemical composition. Curing can be achieved by using drugs with antagonistic temperaments against the unbalanced humor responsible for the specific disease. Herbal remedies are classified according to their spicy qualities, touch, and temperature (hot, cold, dry, and moist), paralleling the four earthy elements—fire, air, earth, and water. Theophrastus and others developed a set of characters based on the humors. Those with too much blood were sanguine. They typically demonstrate quick, impulsive, and relatively brief reactions. Those with too much phlegm were phlegmatic. They are characterized by a longer response delay, but the response typically is short lived. Those with too much yellow bile were choleric. They show a short response time delay, but the response typically is sustained for a relatively long time. Those with too much black bile were melancholic. They exhibit a long response time delay, and the response typically is sustained at length, if not, seemingly, permanently. According to the Hippocratic model, these patterns of response translated into the ability/inability to ward off diseases and infections, as well as describing emotions, fears, and depression. From pre-Christian Rome until the nineteenth century, Western medicine was dominated by the humoral theory, which was taught in all Western medical schools from Salerno and Montpellier to Paris and Oxford.

7.2.2 Development of Four Humor Theory by Arab–Muslim Scholars

The mainstream of Arab–Muslim physicians and pharmacologists, represented by Rhazes and Avicenna, adopted Greek medical methodologies, which were based on the four-humor theory. Whereas other scholars represented by Al-Zahrawi adopted a nonphilosophical and practical theory medicine, both groups, however, accepted only the logical parts of the philosophical theory of the four humors and deeply contributed to the development of Greco-Arabic medicine. Only aspects that could be experimentally confirmed were accepted by scholars of the Greco-Arabic medicine. Avicenna developed the humor theory further by adding new concepts such as "secondary humors" (which represent in modern biology intercellular and extracellular fluids) and clarified their roles in pathogenic and healing processes. Expansion of the theory became an urgent need to follow up on the huge developments in medical fields, and at the same time Avicenna criticized many of Galen statements and medical concepts regarding theoretical and applied ideas. Rhazes (864–930) was the first physician to update the theory of four humors in his *Doubts about Galen*. Although he accepted the general pattern that had been introduced earlier by Galen, Rhazes attempted to correct several points made by Galen himself. As an experiment-oriented chemist and physician, he believed that many chemical reactions take place in the body and that drugs act by modifying these chemical reactions. To confirm his hypothesis, he carried out an experiment that affected one of the four humors. Therefore, he gave test persons a liquid with a different temperature that was expected to alter the bodily heat (resembling the temperature of that particular fluid). Rhazes noted that a warm drink would heat up the body to a degree much higher than its own

natural temperature, and thus the drink would trigger a response from the body, rather than merely transferring its warmth or coldness. In addition, he introduced the use of controls in his clinical experiments that were never practiced before. Rhazes classified diseases into three categories: those that are curable, those that can be cured, and those that are incurable. Referring to the latter, he cited advanced cases of cancer and leprosy that were almost incurable and where the physician could not be at fault.

Other aspects of the four humors theory were challenged by experiments carried out by Avenzoar (1091–1161). By dissection and autopsy, he proved that the skin disease scabies was caused by a parasite, a discovery that upset the prevailing theory. The removal of the parasite from the patient's body did not involve purging, bloodletting, or any other traditional treatments associated with the body fluids (four humors). Furthermore, Ibn al-Nafis (1213–1288) discredited the theory of four humors after his discovery of pulmonary circulation and coronary circulation [1–8].

7.2.3 Practical Aspects of Humoral Theory in the Greco-Arab and Islamic Medicine

As discussed in Chapter 10, Greco-Arab and Islamic medicine is still practiced in most Arab and Islamic countries (Table 10.2). It is practiced in Muslim communities of the Indo-Pakistan subcontinent, where it is known as Unani-Tibb. Unani and Tibb are Arabic words meaning Greek and medicine, respectively. However, the currently practiced Unani medicine is vastly different from its Greco-Arab roots. It benefited from Ayurvedic medicine and Chinese medicine that was, and continues to be, practiced in various parts of the Indo-Pakistan subcontinent [7–10]. The following points characterize the four-humor theory in both the Greco-Arab medical system and the currently practiced Unani system: (a) The human body is a single unit consisting of seven components known as Umoor-e-Tabiya. These seven components have the Arabic names Arkan (elements), Mizaj (temperament), Akhlaat (humors), Arwaah (life force), Afa'al (functions), Aaza (organs), and Quwa (faculties). (b) The body is made up of the four basic elements that have different temperaments, that is, earth (cold), air (hot), water (wet), and fire (dry). (c) Mixing and interactions of the four elements result in the creation of new compounds having new Mizaj (temperament), that is, hot wet, hot dry, cold wet, and cold dry. (d) The body has simple and compound organs that receive their nourishment through four Akhlaat (humors), that is, Dam (blood), Balgham (phlegm), Safra (yellow bile), and Sauda (black bile). (e) Each humor has its own temperament: blood is hot and moist, phlegm is cold and moist, yellow bile is hot and dry, and black bile is cold and dry. (f) Every healthy person attains a temperament according to the preponderance of the humors in the body. The temperament of a person may be sanguine, phlegmatic, choleric, or melancholic (Figure 7.1).

The Greco-Arab adopted the Greek theory in which health represents a balance of the four humors and functions of the human body. To maintain an optimal balance, there is a power of self-preservation or adjustment called Quwwat-e-Mudabbira (*medicatrix naturae*) in the body. A disease is a result of a quantitatively or qualitatively imbalance in the equilibrium of the humors. Therefore, the duty of a

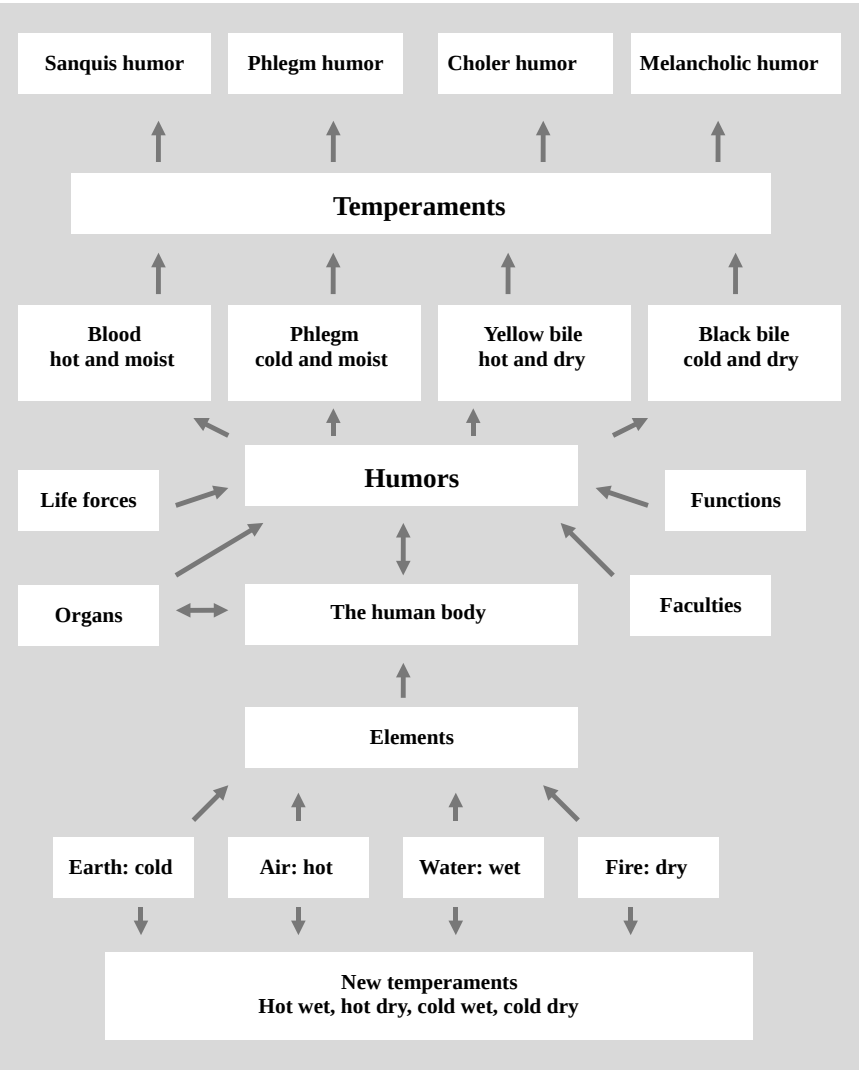

FIGURE 7.1 The Greek and Roman humor theory or humoralism of the human body had a great influence on the development of the Greco-Arab medical system. Hippocrates was the first who applied this idea to medicine and it became strongly accepted in the medical canon through the influence of Galen. The humoral theory was adopted and further developed by Arab–Muslim physicians. Essentially, this theory held that the human body contains four basic fluids, called humors, that are in balance in healthy persons. Imbalances, for example, an excess or deficit in one of the four humors, results in the development of a disease state.

physician is to determine the cause of the underlying imbalance of humors, so that it can be corrected and disease can be cured. Imbalance of humors may be due to external factors such as an injury, incorrect diet, environmental factors, and so on, internal factors such as improper digestion, or both. External environmental factors

and daily lifestyle can affect the human body, for example, air quality, food and drink, movement and rest, sleep and wakefulness, and emotions. It is believed that each of these five factors must be balanced in terms of quality, quantity, and sequence in order to sustain good health. Imbalance of humors tends to occur as a result of thinning of humor (the consistency of humor becomes thinner), thickening of humor (the consistency of humor becomes thicker), hyperactivity of a humor, or putrefaction of a humor [1–10].

7.2.4 Signs of Humoral Imbalances

An excess or over activity of one of the four humors can be detected according to the following symptoms:

Sanguis Humor (Ghalba-e-Dam). When there is excess of blood in the body, the color of skin appears red, veins appear more prominent, pulse seems to be full, and urine becomes dark colored. Patients complain of breathlessness, headache, and scenes of blood in their dreams.

Phlegm Humor (Ghalba-e-Balgham). In the case of excess of phlegm in the body, skin becomes whitish and cold, pulse becomes slow and deep, and urine becomes thick and light colored. Patients complain of forgetfulness, loss of appetite, increased sleep, laziness, and scenes of water in their dreams.

Choler Humor (Ghalba-e-Safra). An excess in the choler humor results in yellowness of the skin, swifter pulse than ordinary, and dark colored urine. Patients appear irritated without any apparent cause and complain of headache, disturbed sleep, bitterness in throat, and scenes of fire, lighting, anger, fighting in their dreams.

Melancholer Humor (Ghalba-el-Sauda). When there is excess of black bile in the body, the skin appears rough, pulse becomes weak, urine becomes thin, patients complain of loss of appetite and soreness in throat. Patients remain busy with foolish imaginations and appear fearful without any cause.

7.3 METHODS OF THERAPY

The diagnostic parameters of both the Greco-Arab medicine and the Unani system of medicine are the rate, strength, width, and depth of the pulse, as well as the color, odor, and amount of urine and stool. In addition, the deposits in the urine sample are also observed. After confirming the cause of the disease, the physician starts the treatment by recommending the diets or drugs that have temperament opposite to the prevailing abnormal temperamental condition of the affected organ or system (Figure 7.2). It is important to note that each and every diet or drug has its own temperament [1,4,9,10].

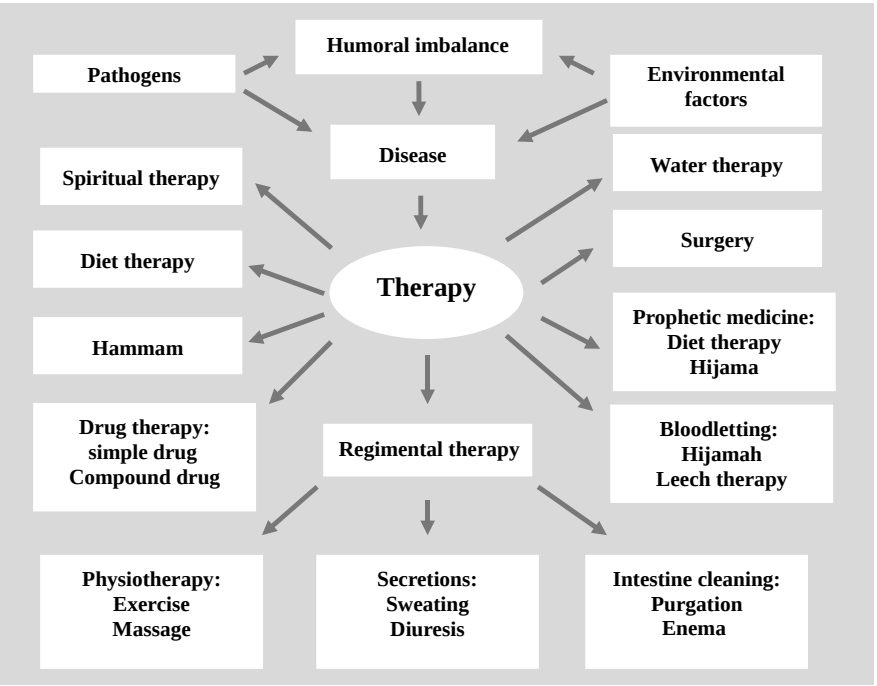

FIGURE 7.2 Greco-Arab and Islamic medicine apply three types of therapies. These include the diet, drug, and regimental therapies. The diagnostic parameters of the Greco-Arab medicine include the rate, strength, width, and depth of the pulse and the color, odor, amount of urine and stool. After confirming the cause of the disease, the physician starts the treatment by recommending the diets or drugs that have temperament opposite to the prevailing abnormal temperamental condition of the affected organ or system.

7.3.1 Diet Therapy

Diet therapy is one of the oldest methods of healing known to man and built a substantial part of the pre-Islamic medicine as well as other ancient medicines, such as Greek and Ayurvedic. Nowadays, there are clear associations between intake of fruits and vegetables and reduced rate of heart disease mortality, common cancers, and other degenerative diseases as well as ageing. This is attributed to the fact that these foods may provide an optimal mix of dietary fiber, natural antioxidants, and other biotic compounds. Various constituents in the food can control the physiological functions of the body and modulate immune responses. Immune functions are indispensable for defending the body against attack by pathogens or cancer cells and thus play a pivotal role in the maintenance of health. However, the immune functions are disturbed by malnutrition, aging, physical and mental stress, or undesirable lifestyle. Therefore, the ingestion of foods with immunomodulating activities is considered an efficient way to prevent immune functions from declining and reduce the risk of infection or cancer [11–17].

Both Rhazes and Avicenna recommended a treatment scheme that started with diet therapy. In Thesis III of the *Canon*, Avicenna discussed diet therapy in general and gave specific therapy recommendations such as diet for old people. He recommended that they should be given food in small amounts at a time and that they can have two to three meals a day, divided according to the digestive capacity and general condition of the old person in question. He discussed the beneficial effects of fruits, such as figs and prunes. He also stated "Some laudable nutrition may be allowed at bedtime, but robust old folk may have a more liberal supper, as long as they avoid any gross aliment . . . all hot, sharp or desiccative foods, such as dishes made with vinegar, salt, hot aromatics, seasonings and pickles. [Milk is good for the aged, being nutritious and humectant in nature. Yet articles of food with a laxative action are most appropriate for the elderly."

7.3.2 Bloodletting

7.3.2.1 Cupping (Hijamah) Hijamah is the sucking of blood by cupping, which is commonly practiced in the Arab world [8,18,19]. The Prophet stated that there are three methods to cure diseases: "a drink of honey, a scratch of hijamah and cautery." But, notably, he was not too keen on the latter.

Hijamah is a method used for local evacuation or diversion of morbid blood in which a horn is attached to the surface of the skin of the diseased part through negative pressure created by vacuum. The vacuum is created by the introduction of suction. Now, this horn is replaced by a glass cup, and hence the procedure is known as cupping. Cupping is of two types; wet cupping, that is, cupping with bloodletting and dry cupping, that is, cupping without bloodletting.

In the wet cupping, the skin site is shaved, cleaned, and marked by placing the mihjamah such as a bull horn on the site and sucking the mouth end of the horn to mark the site for extraction (Figure 7.3). The horn is removed and superficial incisions are made within the marked area. Then, the horn is reapplied and the horn's mouthpiece is vigorously sucked. Blood accumulates within the horn. After that, the wound is cleaned with dry cloth and either left uncovered or herbal powder is applied. The patient is instructed to keep the wound dry for one day.

The best season for cupping is in spring or fall to avoid extremely cold or hot temperatures. According to Avicenna, the best time is by full moon at early morning. He also devised clear times during the month when the procedure is appropriate: "Some authorities advise against the procedure at the beginning of the lunar month, because the humors are not yet on the move or not in a state of agitation; he also was against performing it at the end of the lunar month, because at that period (of the cycle) the humors are less plentiful. The proper time according to them is the middle of the month (when the humors are in a state of agitation) and during the time when the moonlight is increasing (when the humors are on the increase). During that period the brain is increasing in size within the skull, and the river-water is rising in tidal rivers. The best time of the day for hijamah is at second or third hours," that is, 2–3 h after sunrise.

For each complaint, there is a specific site for hijamah. For instance, for headache, the location is behind the head. For chest pain, the location is on the shoulder, dorsally.

FIGURE 7.3 Horns and glass cup used for mihjamah. Horns (left) and glass cup with build-in sucking tube (right) used for mihjamah.

Albucasis described in his 30-volume medical encyclopedia, *The Methods of Medicine*, his surgical techniques with about 200 illustrations of medical instruments that he made and drew. He described the technique of hijamah, the timing, and the tools. Albucasis listed several points at which hijamah is performed. He mentioned that "The application of cupping to the shoulders helps in palpitation of the heart arising from plethora and heat." He also said, "What Hijamah does is to draw blood out of the fine vessels dispersed over the flesh; for this reason it does not cause the strength to decline as does venesection; nor may use Hijamah, in any disease due to plethora, until the whole body has been evacuated. If the disease or custom prescribe Hijamah, we may apply it at any hour, at the beginning or the end of the month, at wherever time it may be. For there are some people who, when there is an abundance of blood in them, so as to need Hijamah, feel heaviness and pain in the head. Some find they have fullness and redness of the face and also the head and neck. We therefore prescribe Hijamah after the second or the third hour of the day has passed."

7.3.2.2 Bloodletting (Fasd) Fasd, which is phlebotomy or venesection, is rarely practiced nowadays in the Arab world. Fasd is a procedure in which an incision is made to any of the superficial veins, and blood containing "waste material" is allowed to flow. It removes excess humors in the same proportion as present in the blood vessels, abnormal humor, or both. It is applied for purification of vitiated humors in meningitis, pneumonia, pleurisy, sciatica, gout, rheumatic arthritis, diphtheria, piles, and amnesia [8,18,19].

Bloodletting was used by the Greeks who thought that veins contained blood and arteries air "pneuma." There were two key concepts: the first is that blood was created and then used up. During the time of Galen, the Greeks believed that humoral balance was the basis of illness or health and that blood was used up after its creation. Furthermore, they did not know that the blood circulated, and therefore they thought it could "stagnate" and cause illness. Galen regarded bleeding as the appropriate treatment for almost every disorder, including hemorrhage and fatigue. The Arab

scholars adopted the concepts of Galen and only Ibn al-Nafis (Father of Circulation) dared to say that Galen was wrong about the flow of the blood in the heart. Bloodletting was used by Greco-Arab physicians to "treat" a wide range of diseases, becoming a standard treatment for almost every ailment. They used it to treat headache, eye disease, sciatica, and gout. A number of different methods were employed. The most common was phlebotomy or venesection, in which blood was drawn from one or more of the larger external veins. Avicenna recommended using bloodletting either when the blood is superabundant that a disease is about to develop or when disease is already present. He stated that "The object in both cases is to remove the superabundant blood, to remove the unhealthy blood, or both. Examples of the first category are incipient sciatica and gout ..." Avicenna mentioned that bloodletting should not be performed before the age of 14 or after 70, as well as in those patients who were very emaciated. Furthermore, he mentioned that the best time to conduct venesection is "Before mid-day if the procedure is elective, when digestion is completed and when the bowels are empty. When it is urgent, then it could be done any time."

Phlebotomy could act as painkiller when carried out aggressively enough to induce fainting. Such bleeding was used in preparation for childbirth, reducing dislocation, and setting fractures. The Arab Andalusian surgeon, Al-Zahrawi (Albucasis), mentioned about 30 blood vessels as suitable for venesection. He mentioned 16 vessels in the head, 5 in each arm and hand, and 3 veins in each leg and foot. He devised and illustrated fine scalpels or lancets for veins, and he called one such lancet the *olivary* scalpel.

7.3.2.3 Leech Therapy (Taleeq) Leech therapy is a unique method of removal of bad matters from the body. Leeching is better than cupping for drawing the blood from deep tissues. The first recorded use of leeches in medicine was in 200 BC by Greek physicians and was later reintroduced by Avicenna in his Canon. He considered the use of leech therapy to be more effective than hijamah in "letting off the blood from deeper parts of the body." He also introduced the leech as treatment for skin disease. Leech therapy became a popular practice in medieval Europe, namely, the leeches from Portugal and France, due to the influence of Avicenna's Canon. A more modern use for the medicinal leech was introduced by Abd el-latif al-Baghdadi in the twelfth century, who wrote that leech could be used for cleaning tissue after surgical operations. He did, however, agreed that there is a risk over using leech and advised patients that leech need to be cleaned before being used and that the dirt or dust "clinging to a leech should be wiped off" before application. He further recommended that after the leech has sucked out the blood, salt should be "sprinkled on the affected part of the human body." The use of leeches began to become less widespread toward the end of the nineteenth century. Like Avicenna, Albucasis recommended the use of leeches to the part of the body to which application of cupping vessels is impossible, because the part is bare of flesh, such as the nose. He recommended freshwater leeches "Leave them in fresh water for a day and a night until they are hungry and nothing is left in their bellies. Scrub the afflicted part until it is flushed; and then place the leeches on it. When they are full they will fall off."

Medicinal leeches are now making a comeback in microsurgery. They provide an effective means to reduce blood coagulation (they produce an anticoagulant molecule called hirudin), relieve venous pressure from pooling blood (*venous insufficiency*), and stimulate circulation in reattachment operations for organs with critical blood flow, such as eyelids, fingers, and ears, in reconstructive surgery. The therapeutic effect is not from the blood taken in the meal, but from the continued and steady bleeding from the wound left after the leech has detached. The most common complication from leech treatment is prolonged bleeding, which can easily be treated, although allergic reactions and bacterial infections may also occur [8,18,19].

7.3.3 Cauterization (Kayy)

The medical practice or technique of cauterization is a medical term describing the burning of part of a body to remove or close off a part of it in a process called cautery. It destroys some tissue, in an attempt to mitigate damage, remove an undesired growth, or minimize other potential medical harmful possibilities such as infections when antibiotics are not available. It is also useful in stopping severe blood loss to close amputations and in preventing infections. Special medical instruments called cauters were used to cauterize arteries. These were first described by Al-Zahrawi (Abulcasis) in his *Kitab al-Tasrif*. He also introduced the technique of ligature of the arteries as an alternative to cauterization [8–10].

7.3.4 Exercises and Massage

Moderate exercises were applied by Arab–Muslim physicians to increase the "vital force of body" and eliminate waste products through urine, stool, and sweat. Furthermore, moderate exercises strengthen the organs and increase the appetite.

Massage is any method of applying pressure on or friction against, or stroking, kneading, rubbing, tapping, pounding, vibrating, or stimulating of the external soft parts of the body with the hands. Usually, rough cloth with or without rubbing oils, creams, lotions, ointments, or other similar preparations are used to enhance the therapeutic effects of massages. Massage therapy improves functioning of circulatory, lymphatic, muscular, skeletal, and nervous system and improves the rate of body's recovery from injury or disease. Massage therapy may be useful in several symptoms and diseases such as anxiety, tension, depression, insomnia, stress, backache, headache, muscular pain, and some forms of chronic pain. Hard friction or massage makes the body firm, soft massage relaxes the body, and prolonged massage reduces the fat of the body and enhances weight gain in premature infants [8–10].

7.3.5 Sweating and Fomentation

Diaphoresis is a medical term for profuse sweating. It can be normal (physiological) brought on by physical activity, emotional response, or high environmental temperature or a symptom of a pathological condition. Sweat therapy simply means the use of heat and humidity to cause the body to perspire freely. The method used for sweat

therapy varies depending on body temperament. Greco-Arab physicians have described therapeutic methods of diaphoresis, in which excessive sweating is produced. It plays an important role in expulsion of waste product through skin, especially if kidneys are not functioning properly. Several drugs exist that when used internally or externally may cause profound sweating for example, *Allium sativum*, *Raphanus sativus*, and *Aconitum napellus*.

Fomentation is process in which warm covers are laid on a part of the body to relieve pain and inflammation. This diathermy method should always be restricted to a patient's tolerance. Hot fomentation treatments can be used in a variety of acute conditions including chest colds, muscle spasms, gallstones, insomnia, and backache [8–10].

7.3.6 Diuresis

The method is used to excrete poisonous matters, waste products, and excess of humors through urine and to purify blood. It is also helpful in the treatment of cardiac, hepatic, and renal diseases. There are many herbal remedies used for this purpose, for example, *Cichorium intybus*, *Gentiana dahurica*, and *Cuscuta reflexa*.

7.3.7 Purgation (Ishaal), Enema (Huqna), and Emesis (Qai)

Purgation is a process in which the whole body or intestines are cleansed of accumulated toxins through the use of laxatives and purgatives. Mild, moderate, and strong laxatives may be used depending upon the prevailing condition. Various medicines used for purgation are *Operculina turpethum*, *Agaricus alba*, *Convolvulus scammonia*, and *Cuscuta epithymum*. It is used to achieve detoxicating effect, resolve the body matter, and treat chronic constipation.

Enema therapy is a method used for the removal of the superfluities from the intestines. Enema is used in the case of constipation (a condition of the digestive system in which a person experiences hard feces that are difficult to expel). Avicenna dedicated several sections of Thesis III to elderly patients who become constipated and wrote: "Strong clysters (enemata) must be avoided because they dry up the gut. An unctuous enema is beneficial in cases where the bowels have been constipated for several days. . . . Evacuations must be procured with as little stress as possible in the aged and decrepit, for it is to their advantage to get bowels opened gently." Greco-Arab physicians apply a variety of natural medicines, which can be used for this purpose, for example, saline water, and oil of castor plant (*Ricinus communis*).

Emesis (Qai) is the reflex act of ejecting the contents of stomach through the mouth. The main purpose of vomiting is to eliminate toxic substances from the stomach. Many drugs can be used for this purpose, for example, *Raphanus indicus* and *Oroxylum indicum*.

7.3.8 Steam and Vaporization Therapy

This therapy is a process in which steam from a bowl of boiling water is allowed to seep into the face or any area of the skin. It is applied for 5–10 min, and an essential oil,

menthol, or incense is added to the boiling water. The top of the head and sides of the face are covered with a towel to prevent evaporation. Vaporization is useful for colds, flu, acne lesions, and as a freshener. This method is still commonly used in the Arab Islamic world.

7.4 WATER THERAPY

Water is a natural gift and is a part of the act of purification found in the major religions. The Pharaohs worshiped the Nile River because they believed it to have supernatural powers and the ability to cure diseases. The Ganges River has significance in the Hindu religion, just as the Jordan River has importance to Christianity. Water from the Zamzam well in Mecca is considered holy, and millions of Muslim believers use it to cure diseases. The Prophet described the water of the well of Zamzam saying, "It is blessed! It is a kind of food and cure for illness." Muslims believe that this water is proper for whatever purpose it is drunk for, and the Prophet said, "So, if you drink it in order to be cured of illness, God cures you; if you drink it in order to satisfy your appetite, God satisfies your appetite for you; and if you drink it in order to quench your thirst, God quenches your thirst for you. It was dug up by Gabriel and provided by God to Ishmael to drink." Muslims believe in the performance of rituals of ablution by washing five times a day before each of the daily prayers. The hammam is an example of the bathing establishments that inherited the tradition of the Greco-Roman thermal baths adapted to the requirements of the civilization of the countries dominated by Islam. The baths in fact took a dominant place in the Islamic world where body hygiene is directly associated with the prayer ritual. From the Umayyad period, independent baths or baths connected to civil or religious structures such as the mosques were constructed, as attested by the large estates in Arab–Islamic world.

Thermal and Mineral Waters. Since ancient times, drinking or bathing in mineral waters has been known to cure a variety of illnesses, including heart diseases, joint disorders, respiratory inflammation, and kidney stones. While there have been few scientific studies of these postulated effects, there is no doubt of the benefits of warm water therapy in pain relief, joint mobility, and relaxation. Naturally occurring hot springs were particularly valued in colder climates; for example, springs were developed by the ancient Romans in Europe. The Baden-Baden springs in Germany, developed by the Romans as Aquae Aureliae, are the hottest in Europe and, like most other thermal springs, are slightly radioactive. There are many health spas and clinics around the world offering a wide range of natural treatments that may be combined with a relaxing vacation. Many of these centers are used simply for restoring health. Thermal and mineral waters are considered curative due to their physical and chemical properties and also through psychological effect. Thermal and mineral spas are believed to help relax muscles and the mind, provide relief from muscular and joint pains, respiration, and heal infections. Water containing hydrogen, sulfur, carbon dioxide, and bromides are useful as a tranquilizer and a relaxant. Some waters are

radioactive and contain high levels of iodides, iron, calcium, and magnesium and are useful for the body as a whole. It is believed that mineral water exerts an effect on the immunological and neuropeptidergic systems of the skin beyond the antibacterial, antifungal, and keratolytic effects. Water plays an important role in dermatological therapy through its hydrating, cooling, and cleansing effects and as a vehicle for more effective delivery of active agents.

Hammam (Turkish Bath). The hammam retains the traditions of the Arabic bathhouse known today as Turkish bath. It is a steam room where facilities are available for a bath followed by shower and massage. The positive effect of the hammam was described by Avicenna. He appreciated the bath for its powerful, healthful, and cleansing effect both in a physical and a spiritual sense. Avicenna especially emphasized the positive effect of bath on the blood circulation, lymph circulation, breathing, and neural systems, as well as for the regulation of weight.

Climatotherapy at the Dead Sea. The healing aspects of Dead Sea water were known for thousands of years and were mentioned in the Old Testament. Warm spas activate the sweat glands, dilate cutaneous blood vessels, and stimulate intestinal peristalsis. They also have vagotonic action and augment blood pH levels. Exposure to sunlight to treat different ailments and skin conditions and the use of natural health spas and mud have been used for ages to treat psoriasis and other diseases. Skin shows marked improvement in many cases with a longer delay of relapses, less need to use conventional medications such as corticosteroids, and eventually fewer adverse effects. In addition, this proves to be a very inexpensive method.

The Dead Sea is one of the most popular sites for climatotherapy. This area is unique for its combination of natural effects that are unparalleled anywhere else on earth. They include sun rays that are weakened due to the longer path they have to travel to reach the lowest point on earth, 415 m below sea level, and the dispersion of the sun rays on their way by a misty cloud overhanging the sea most of the year. This attenuation is inversely related to the length of the ray; as a result, the shorter ultraviolet B rays are shortened to greater extent than the longer UVA rays (12% and 3.8% on average, respectively). This difference in solar radiation intensity provides a major therapeutic advantage, since damage to the skin after solar exposure increases as the UVB solar rays become shorter. However, the effective wavelength for suppressing psoriatic skin lesions is around 311 nm, a range at the longer wavelength end of the UVB scale. In addition to the unique composition of sun rays, the low altitude of the area results in a high atmospheric pressure (37 mmHg), which is approximately 5% higher than that at sea level. As a result, the partial oxygen tension at the Dead Sea is about 7–8 mmHg higher than at zero altitude; this has important therapeutic implications for patients with hypoxic heart and lung diseases, as will be specified later. The Dead Sea is the world's second most saline lake (after Lake Assal, Djibouti), with salinity reaching 290 g/L, compared to that of the Red Sea, whose salinity is only 40 g/L. The water contains an unusual composition, including high concentrations of cations, for example, magnesium, sodium, calcium, and anions such

as phosphorus, bromide, and chloride. These raise the density of the water to about 1.237 kg/L, causing people bathing in the lake to float on rather than swim in the water. Certain minerals in the water have been shown to penetrate the skin, which may contribute to its healing effect. Mineral and sulfur-containing natural springs are found along its shores. Also, black mud, which contains medicinal antibacterial and hyperemic properties, is extracted from the shores of the lake. With regard to climate, a dry stable temperature reaches high levels during midsummer, while an extremely low rainfall is recorded in the very moderate winter. The elevated barometric pressure, high temperature, and low humidity have been shown to have a favorable effect on patients with various rheumatic diseases.

The Dead Sea was described by both Greeks and Arabs and was given many names, including Sedom, Dragon, Araba, Asphilt Sea, and Lot Sea (Lot, that is, the nephew of Abraham, who lived at Sodom and Gomorrah). The Dead Sea water contains a natural tar called asphalt or tar sea. This natural tar is believed to function as an anti-inflammatory and keratolytic agent to the skin. In general, it is possible that the water of the Dead Sea functions as a major factor in slowing down the rapid turnover process of skin cells in patients with psoriasis, a possibility that should be further investigated. The mud in the Dead Sea is rich in magnesium, natural tar (bitumen), and silicates (silicon compounds); the latter is often used as a mask for the skin. The black color of mud absorbs much of the solar radiation, hence acting as a photosensitizer when applied to the skin. Mud baths are mainly useful for arthropathy because they aid in stimulating blood circulation around the affected joints; thus, mud packs are effective for individuals with psoriatic arthropathy [1,20,21].

7.5 DRUG THERAPY

If the deviation from balanced humors is high so that diet therapy alone is not sufficient, then pharmacotherapy is advised in addition to the diet therapy. The drugs may be derived from plants, minerals, or animals.

Drug Temperament. According to Greco-Arab medicine, every drug has its specific temperament based on its ingredients. The temperament of drugs is classified into five classes: hot, cold, dry, wet, and sometimes neutral. A drug may be hot and dry, hot and wet, cold and dry, or cold and wet. A drug used in a given pathological condition should have temperament opposite to the prevailing temperament of the affected organ.

Potency of Drugs. The concept "temperament" by Hippocrates and Galen discussed only the qualitative and not the quantitative nature of the temperaments of simple drugs (single plants). The term "degree" was considered as a sensation effect of a drug without any quantitative scale based on scientific methods. The four degrees of each drug temperament, which represent the strength of the drug, or maybe, the pharmacological and toxicological effects, were understood as mathematical sum of each degree, so second degree meant double of first degree and third degree meant

three times of the first degree, and so on. They could not determine the main temperament of a drug mixture with complicated factors.

Al-Kindi (803–873, known as Al-Kindus) was the first to distinguish and quantify the "drug degrees" concept and developed a mathematical method to determine the strength and quality of compound drugs. This crucial contribution was achieved owing to original development in Arab pharmacognosy and chemistry by Jaber ibn Hayan, alongside new mathematical concepts by Al-Khwarizmi. These innovations allowed pharmacology to stand on scientific foundations and built the roots of pharmacy. Al-Kindi was a pioneer in linking theoretical concepts to applied sciences and deeply influenced the development of biomedical system in the Middle Ages. The temperament of a drug, according to Al-Kindi, means the chemical properties, toxicity, drug interactions, mechanism of action, and efficacy. The temperaments were determined following their physiological action examined and observed by physicians, animal tests, and clinical trials using both single and compound drugs. Correct diagnosis is the ultimate condition for successful treatment and choice the right medication and mainly was achieved through naked eye examination of urine and stool, pulse reading, and other conventional methods, such as, auscultation, palpation, and percussion with the help of some modern tools. Thus, the spot diagnosis was made very easy.

"Hot drugs," for instance, indicate drugs that can stimulate and enhance body temperature in the first and second degrees during activating basic metabolic rates. The third "hot" degree is quite toxic and the fourth one is highly toxic with severe side effects and should be controlled using ingredients with antidote or antagonistic effects based on the Al-Kindi method.

Herbal Remedies. Herbs are used either in their crude forms or as herbal teas, syrups, infusions, and powders in the treatment and prevention of diseases. Owing to a statement (*Hadith*) by the Prophet Mohammad (PBUH), "The one who sent down the disease sent down the remedy." and "For every disease, God has given a cure." every Muslim is encouraged to search for those remedies and use them with skill and compassion. Herbal remedies are discussed in detail in Chapters 8 and 12.

7.6 SPIRITUAL THERAPY IN ISLAM

Spiritual medicine refers to the belief in a spiritual, ethical, or psychological cure for diseases that may have physical or mental origin. Thus, a physical illness may be cured, for example, by recitation of the Quran or other prayers (Du'a). First noted by Avicenna, most modern health practitioners in the Arab–Islamic world still respect this method for the treatment of certain aliments.

Arab and Muslim physicians practiced various forms of psychotherapy such as shock therapy for treating mental illnesses. Rhazes wrote an important text on this subject called *al-Tibb al-Ruhani* (Spiritual Medicine), which has been translated into English as *The Spiritual Physick of Rhazes*. In this work, he described in detail moral diseases and discussed with acute perception their effect on human behavior.

Avicenna noted in his Canon the close relationship between emotions and the physical condition and felt that music had a definite physical and psychological effect on patients. Avicenna was the pioneer of neuropsychiatry. He first described numerous neuropsychiatric conditions, including hallucination, insomnia, mania, nightmare, melancholia, dementia, epilepsy, paralysis, stroke, vertigo, and tremor. He was also a pioneer in psychophysiology and psychosomatic medicine, and the first to recognize "physiological psychology" in the treatment of illnesses involving emotions and developed a system for associating changes in the pulse rate with inner feelings, which is seen as a precedent for the word association test attributed to Carl Jung. Avicenna identified love sickness when he was treating a very ill patient by "feeling the patient's pulse and reciting aloud to him the names of provinces, districts, towns, streets, and people." He noticed how the patient's pulse increased when certain names were mentioned, from which Avicenna deduced that the patient was in love with a girl. Avicenna was able to locate by the digital examination. He advised the patient to marry the girl he was in love with, and the patient soon recovered from his illness after his marriage. Concerning psychological and organ diseases, Avicenna stressed that "we have to understand that the best and effective remedy for the treatment of patients should be through the improvement of the power of the human body in order to increase its immune system, which is based on the beauty of the surroundings and letting him listen to the best music and allow his best friends to be with him."

Volumes of spiritual prescriptions for cures exist in the Arab–Islamic world. Most prayers and amulets contain verses from the Holy Quran, to which high curative powers are ascribed. It is often recommended that the patient shall write down certain Qur'anic verses on a piece of paper or on a glass (ceramic plate) and after soaking these writings in water, drink the water. In Southeast Asian countries, it is customary for sick people to stand outside mosques and await the believers who, upon finishing prayer and exiting the mosque, blow air onto them [1,4,6,22].

7.7 MEDICINE OF THE PROPHET (AL-TIBB AL-NABAWI)

The medicine of the Prophet (al-Tibb al-Nabawi) includes medical prescriptions of diseases, prevention, health promotion, and spiritual aspects that were recommended by Prophet Mohammad (PBUH) to his companions. This medical practice adopted many medical practices that existed in pre-Islamic period. Therefore, it is clear that the medicine of the Prophet played an important role in the development of the Greco-Arab and Islamic medicine. Owing to *Hadith*s of the Prophet, "The one who sent down the disease sent down the remedy." and "For every disease, Allah has given a cure." every Muslim is obligated to search for those cures and use them with skill and compassion. In this respect, pharmacists introduced a large number of preparation methods of new drugs into clinical use, including senna, camphor, sandalwood, musk, myrrh, cassia, tamarind, nutmeg, cloves, aconite, ambergris, and mercury. They also developed theoretical and practical knowledge on various forms of administration of medicinal plants, for example, syrups and juleps and pleasant solvents such as rose water and orange blossom water as means of administering drugs.

The *Book of Medicine* (*kitab al-tibb*) of Sahih al-Bukhari reflects the view of Imam Bukhari (810–870) on the scope of medicine in Islam. This book is recognized by the majority of the Muslim scholars to be one of the most authentic collections of what had been said and practiced (*Hadith* and *Sunnah*) by the Prophet (PBUH). The scope of Islamic medicine has been explained in the very well known commentaries of Sahih al-Bukhari by Ibn Hajar al-Asqalani (died 1449) and Abu Muhammad al-'Ayni (died 1452); both were living in the Golden Age of Arab–Islamic civilization at a time when medical literature included broad disciplines from various sources.

In his commentary, Ibn Hajar divided Prophetic medicine into two types: physical or body medicine and spiritual medicine. There is a symbiotic relationship between the two kinds of medical knowledge, as one would find it impossible to achieve one form of medical science without the other. This implies that Muslims should be fully aware of their spiritual and physical health, because in Islam the mind and the body are inseparable.

Ibn al-'Ayni divided the science of medicine into two main parts, theoretical and practical science. He emphasized that a physician must master the practical part. Accordingly, practical medicine is comprised of two braches, namely, preventive medicine and therapeutic medicine. The former includes preventing of diseases and preserving the natural state (homeostasis) of the body, the state in which human beings function normally, and the sound and perfect condition of a healthy body, mind, and spirit. It is generally acknowledged that disease prevention is the most important branch of Islamic medicine since it is primarily concerned with the prevention and preservation of health rather than with finding a cure. Imam Bukhari also mentioned *Hadiths* relating to the treatment of diseases that were practiced during the time of Prophet (PBUH). In this regard, the medicine of the Prophet is not only history but also an applied history with relevance today. Prophetic medicine is not based on medical experiments but rather on inspiration and experience from both pre-Islamic and Islamic culture and tradition. In many obvious cases, many companions of Prophet (PBUH) could treat a patient suffering from certain diseases during that time successfully without any knowledge of medicine as practiced today. They merely followed his instruction relating to the treatment of disease.

According to a *Hadith*, the stomach is the central basin of the body and the origin of many diseases: "The stomach is the central basin of the body, and the veins are connected to it. When the stomach is healthy, it passes on its condition to veins, and in turn the veins will circulate the same and when the stomach is putrescence, the veins will absorb such putrescence and issue the same." Indeed, the Prophet (PBUH) used to recommend food for ailments even more than he prescribed herbs or medicines. He used everything from barley soup to honey to camel milk to heal his followers; he advised them to eat certain foods to prevent or cure other diseases. In fact, diet is one of the oldest and most respected healing agents available to man. Dates, honey, olive oil, and black seeds were the favored foods by the Prophet (PBUH), who regarded food as part of an overall holistic approach. Concerning olive oil, he said, "Eat olive oil and massage it over your bodies since it is a holy (mubarak) tree." Black seeds were regarded as a medicine for they cure all types of diseases. He once stated, "The black seed can heal every disease, except death." Dates are mentioned in 20 places in the

Quran. Prophet (PBUH) is reported to have said, "If anyone of you is fasting, let him break his fast with dates. In case he does not have them, then with water. Verily water is a purifier."

In addition to diet, fasting is one of the five basic elements of Islam. It is considered one of the means of providing the ideal conditions necessary for the repair of bodily damages and for the elimination of toxins. Fasting is an exercise in which a Muslim purifies the body and soul by feeling hunger and thus sympathizes with those who are hungry and cannot afford to buy food. Fasting during Ramadan every year includes meditation, contemplation, and cogitation. In addition to Ramadan fasting, the Prophet (PBUH) used to fast on Mondays and Thursdays.

As mentioned previously, the Prophet (PBUH) stated that there are three methods to cure diseases: "a drink of honey, a scratch of hijamah and cautery." But he was not too keen on the last one. The therapeutic and prophylactic properties of honey are discussed in detail in Chapter 17, and hijamah and cautery are discussed above.

Furthermore, the Prophet Mohammad (PBUH) taught that oral hygiene is essential for a healthy body. The prophet noted the benefits of Siwak or Miswak (Figure 7.4), a twig from the arak tree (*Salvadora persica*), for cleaning the teeth. Highly abundant around Mecca and the Middle East, it is widely used among Muslims today and is the most widely used tree twig since the time of the Prophet who emphasized the use of Siwak by a *Hadith* "If it were not too much burden on the believers, I would prescribe that they use the Siwak before each prayer."

Siwak contains about 20 beneficial ingredients. Most important among them are antibacterial acidic inhibitors that fight decay and diarrhea. They are natural disinfectants and can be used to stop bleeding. It also contains minerals such as sodium chloride, potassium, sodium bicarbonate, and calcium oxides.

In conclusion, the treatment of diseases as stated in the *Hadiths* gives us insight into how the sick were treated during the time of the Prophet, given the medical knowledge

FIGURE 7.4 Siwak, the natural brush from a branch of the *Salvadora persica*. The Prophet noted the benefits of Siwak or Miswak, which it is still widely used among Muslims. Siwak contains antibacterial acidic inhibitors that fight decay and diarrhea. It is used as natural disinfectants.

available at the time. It is apparent that treatments were causal rather than based upon various symptoms. Thus, the conditions for which these remedies were prescribed may not be the same as those found today. Likewise, the medicine of the Prophet, when applied today, should be based upon empirical research due to possible changes in medicinal plants, the environment, and the pathology of diseases, in addition to changes in linguistic terms. Therefore, we must not be satisfied with referring to the writings of traditionalist scholars without referring to new medical discoveries [22,23].

7.8 SURGERY

Abu al-Qasim al-Zahrawi (Albucasis) (Figure 7.5), born in 936 in Zahra, Cordoba (Andalusia), is regarded as the pioneer of modern surgery who contributed greatly to the discipline with his *Kitab al-Tasrif* (Book of Concessions or The Method of Medicine), a 30-volume medical encyclopedia published in 1000. It was the first book

FIGURE 7.5 Abu al-Qasim al-Zahrawi (Abulcasis, 936–1013) became one of the most renowned surgeons of the Muslim era of Spain. He is best known for his early and original breakthroughs in surgery as well as for his famous medical encyclopedia called *Al-Tasrif*, which is composed of 30 volumes covering different aspects of medical science. The more important part of this series comprises three books on surgery that describe in detail various aspects of surgical treatment based on the operations performed by him.

in Arabic to treat surgery independently and comprehensively. It included many pictures of surgical instruments, most invented by Al-Zahrawi himself, and explanations of their use. There are approximately 200 such drawings ranging from a tongue depressor and a tooth extractor to a catheter and an elaborate obstetric device. The variety of operations covered is remarkable. In this treatise, Al-Zahrawi discussed cauterization, bloodletting, midwifery, and obstetrics and the treatment of wounds. He described the exposure and division of the temporal artery to relieve certain types of headaches, the diversion of urine into the rectum, and the removal of cataracts. He wrote extensively about injuries to bones and joints, even mentioning fractures of the nasal bones and the vertebrae. Al-Zahrawi outlined the use of caustics in surgery, fully described tonsillectomy, tracheotomy, and craniotomy operations he had performed on a dead fetus. Al-Zahrawi was the first to describe the so-called "Walcher's position" in obstetrics, the first to depict dental arches, tongue depressors, and lead catheters, and the first to describe clearly the hereditary circumstances surrounding hemophilia. He also described ligaturing of blood vessels. Once al-Tasrif was translated into Latin in the twelfth century, Al-Zahrawi had a tremendous influence on surgery in the West. The French surgeon Guy de Chauliac in his *Great Surgery*, completed in ca. 1363, quoted Al-Tasrif over 200 times. Al-Zahrawi was described by Pietro Argallata (died 1423) as "without doubt the chief of all surgeons." Jaques Delechamps (1513–1588), another French surgeon, made extensive use of al-Tasrif in his elaborate commentary, confirming the great prestige of Al-Zahrawi throughout the Middle Ages and up to the Renaissance [2,3,24].

7.9 SELECTED DISEASES AND THEIR THERAPY

To stay within the scope of this chapter, we will take cancer and bladder diseases as an example and discuss diagnostic methods and remedies used for prevention and treatment of these two diseases.

7.9.1 Cancer Therapy

Many of the famous Arab–Muslim physicians, for example, Rhazes, Al-Zaharawi, and Avicenna, studied cancer and suggested various therapy methods. They identified many cancer types, for example, stomach (gastric) cancer, liver tumor and cancer, spleen tumor, nerve tumor, urinary system cancer, kidney cancer, testis cancer, eye cancer, nasal cancer, tongue cancer, and breast cancer. Kidney's cancer was mentioned clearly, for the first time, by Al-Zaharawi who had distinguished between kidney acute inflammation and kidney cancer. Both Rhazis and Avicenna described cancer as a tumor that is an extremely difficult disease to treat. They noted that a "cancerous tumor progressively increases in size, is destructive and spreads roots which insinuate themselves amongst the tissue elements." Both Rhazes and Avicenna described most types of cancers known at their time and suggested several therapies based on their belief that cancer is a result of excess of black bile in the affected tissue, leading to an excessive heat in the body. Therefore, they recommended evacuation of

the organ from black bile by excessive vomiting and use of laxatives, as well as by using cold medications and food. Avicenna recognized that if one of the body's humors was out of balance, then all four of them were unbalanced. He said a benign tumor could be distinguished from a cancerous one by certain symptoms such as pain, throbbing, and rapid growth. He also stated that cancers often strike muscles, tendons, and lymph nodes. Many scholars believed that cancerous tumors send out "crablike tracks," occurred more often in "hollow" organs, and are more common in women.

Rhazis, Albucasis, Avicenna, and many of the earlier Arab and Muslim scholars realized that a cure is most likely if the cancer is identified at its earliest stage. The first goal of a treatment strategy should be to halt the cancerous growth. They suggested surgical removal if the tumor is small and accessible, and not close to major organs. Avicenna noted that the tumor "can be arrested with anything, it can be so by vigorous excision . . . including all the [blood] vessels supplying the tumor so that nothing of these will be left." Avicenna also wrote that ". . .. it was told by one of the predecessors that a physician had excised a cancerous breast radically then cancer developed in the other breast. My opinion is that the second breast might have been on its way to cancerization (a dormant cancer) which fits this case and it is possible to be a spread of the material (cancerous from the first breast) and this is more evident (opinion) . . .." He also recommended that surgery be preceded by purifying the body of excess black bile. This could be achieved by providing a nutritious and balanced diet to the patient to maintain purity and strengthen his or her organs and immune system. Avicenna most often treated cancer patients with drug remedies. He also advised cancer patients to change their diets. Avicenna also attempted the earliest known pharmacological treatments for cancer. One drug he discovered was "Hindiba" (*Chicorium intybus*), a herbal compound drug that Ibn al-Baitar later identified as having anticancer properties and that could also treat other tumors and neoplastic disorders. Another method for treating cancer first described in the *Canon of Medicine* was surgical excision. It stated that the excision should be radical and that all diseased tissue should be removed, which included the use of amputation or the removal of veins running in the direction of the tumor.

More than one hundred of medicinal plants and tens of animal-, mineral-derived materials were applied to treat cancer. As mentioned above, the main medical stream (including Rhazis and Avicenna) within the Arab–Islamic medical system was restricted to the four humors theory (Figure 7.1) that explained cancer to be caused as a result of burned black bile diffusion to the body organs leading to "boiling" of the black bile in that cancerous site. The first step in cancer treatment cancer was to take the black bile out of the body using methods and medications to induce vomiting and diarrhea, along with the removal of veins running in the direction of the tumor. As a logical outcome of that theory, all the plant-based medications were plants with cold temperaments in order to antagonize the cancer's hotness. Rhazis and as well as many previous scholars had recommended cold plants in the third and fourth degrees such as *Lactuca seriolla*, *Lactuca sativa*, *Bryonia syriaca*, *Linum usitatissimum*, *Arum palaestinum*, *Brassica oleracea*, and *Portulaca oleracea*. "Cold" food, such as milk, beans, *Hordeum vulgare*, *Portulaca oleracea*, and chicory, was also recom-

mended. Mineral-derived materials were mainly used to stop and prevent cancer development, in a manner that may remind us of modern chemotherapy. Minerals (zinc, blue vitriol, iron) were applied on the developed cancer or immediately after the surgical removal.

According to Avicenna, cancer medications have four purposes: "the total arrest of cancer and this is difficult, preventing its progress, preventing ulceration, and the treatment of ulceration. And those [medications] aiming at arrest of cancer are those aiming at reversal of what happened through the bad material (atrabile) and preventing its effect on the organ (involved)." Avicenna recommended that these measures should not be of much strength and mobilization (stimulation) "since strong medications increase cancer evil." He indicated that "one should avoid irritant medications. And for this, good medications are: washed (pure) minerals like washed pure tutty mixed with greases (oils) like rose grease (oil) and the oil of yellow gillyflower mixed with it."

It is worth mentioning that our ethnobotanical findings show that many of the main herbs currently used in the Arab communities are completely new herbs and do not belong to the herbs used in classic Arab–Islamic medicine. Some of these new anticancer medicinal plants are not in direct line with the four humors theory. They have hot temperaments, and are not cold; examples are *Eryngium creticum* and *Ziziphus spina-christi*. This may indicate the importance of the nonphilosophical public wisdom and knowledge as a source for potential treatments of the cancer disease [25–27].

7.9.2 Bladder Diseases

Avicenna described in his Canon almost all the diseases of the bladder. His approach to diagnosis complies with the modern methodology, and even in some interventions such as routes of drug administration and catheterization, his points are astonishing. In chapter seven of Book III, Part 19, entitled "Warm inflammation and Abscess in Bladder," he listed the symptoms and signs of warm inflammation and abscess in bladder. These are fever, urinary retention, difficulty voiding, dribbling, and concentrated urine.

> Less frequently, there is warm inflammation in the bladder that is accompanied by the excretion of blood . . . This often affects children, but it can affect adults too. Bladder calculus can cause this condition. Calculus scratches the bladder and leads to pain and warm inflammation. Its signs are fever, urinary retention or difficult voiding, and urinary dribbling. The patient cannot void in the flank position and only amount of urine is excreted in the standing position. Occasionally, the concentrated urine may be trapped in the bladder. There is inflammation in the flank and suprapubic area. There is pain in the flank area that is similar to needle insertion. It is sometimes throbbing accompanied by redness in the perirenal area. Another sign is that pain is alleviated if you bandage the area. Symptoms of warm inflammation in bladder are: 1) severe thirst, 2) vomiting of bile, 3) dyspnea similar to that of asthma, 4) cold extremities, 5) delirium, 6) blackness of tongue, 7) worsening of disease by any astringent and diuretic food, and 8) relation of the disease and the patient's age. The worst signs of warm inflammation in the bladder are

> severe persistent fever, retention of urine, fecal impaction, severe constipation, and worsening pain . . . If warm inflammation of the bladder converts to abscess, it is much more dangerous, but if urinary sediment of the patient is clear, there is hope of recovery. Otherwise, cloudy sediment is a sign of patient's death.

Avicenna also describes signs of kidney abscess, including inflammation in the flank and redness of that area due to renal or perirenal abscess, and signs of urinary retention. In the final stage, there is coldness of the extremities, confusion, vomiting, and acute respiratory distress syndrome. Severe thirst can be a symptom of hypotension and early stages of septic shock. Also, diabetes mellitus that induces thirst is a predisposing factor for severe urinary tract infection and abscess. Neurogenic bladder due to diabetes mellitus can be another predisposing factor for urinary tract infection in these patients. "In bladder abscess, there are several types of rigor, various types of fevers, and signs similar to those described for kidney abscess. If the abscess bursts into the bladder, its sign is the pus that passes through urine. If the abscess . . . does not burst, the patient dies in 1 week. Discharges of bladder in abscess often appear in bladder neck and occasionally may flood to other surrounding tissues. Bladder abscess can be opened and drip its content to the abdominal cavity or places other than the abdomen."

In Chapter 8 of Book III, Part 19, entitled "Management of Bladder Inflammation," Avicenna first describes some of the therapeutic methods that are outdated and we have to set them aside. Then, he points to the following four important therapeutic methods that he uses for bladder inflammation in addition to oral drugs:

1. Transurethral injection of drugs by a hollow instrument: "In early stages of the disease, inject these drugs transurethrally into the bladder by a hollow cylindrical instrument, if the patient can tolerate."
2. Rubbing the drug onto the skin over the bladder or topical administration of drugs: "If the pain of the inflamed bladder aggravates to a severe level that could induce [shock and] death, you must prescribe narcotics. You can prescribe it locally by rubbing onto the skin over the bladder or inject it into the bladder."
3. Sitting the patient in sitz bath: "You should know that asking the patient to sit in sitz bath is always useful even if the patient wants to void in the water. Let the patient do this because it is therapeutic and useful."
4. Transrectal administration of analgesics: "There are some solutions that are compatible and useful for patients with bladder inflammation. There are solutions that are mixed with various drugs. And this method relieves the pain due to inflammation. You must dissolve these drugs in water and soak a handkerchief in it until the handkerchief absorbs the drug, and then, insert the handkerchief into the patient's anus until he pain is alleviated. The patient will immediately sleep. In this stage, if the patient tolerates, inject some of these narcotics through penile urethra with a hollow cylindrical instrument into the bladder. At this time, if you rub the narcotics on the patient's bladder topically you can boost the effects of these drugs."

It is notable how Avicenna was familiar with intravesical drug injection. Today in modern urology, this method is prescribed for the local treatment of superficial transitional cell carcinoma of the bladder. Also, some drugs are prescribed by this method for the treatment of interstitial cystitis. Avicenna also names local drug therapy that is the cornerstone of *iontophoresis* in modern drug administration. Iontophoresis is a noninvasive method of propelling high concentrations of a charged substance, medications, or bioactive agents transdermally by repulsive electromotive forces using a small electrical charge. Another interesting point is Avicenna's indication of the use of sitz bath in some disease. In modern urology, a hot sitz bath is used for the treatment of some disorders such as amicrobic cystitis and chronic prostatitis. Finally, Avicenna points to the rectal route of drug administration. It is astonishing that he was familiar with all these methods of drug administration [28].

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CHAPTER 8

Commonly Used Herbal Medicines in the Mediterranean

8.1 INTRODUCTION

Medicinal plants have been used traditionally by herbalists and indigenous healers across the world for the prevention and treatment of almost all types of pathological conditions. Clinical research has confirmed the efficacy of several plants for treating several ailments, including liver disease, diabetes, skin diseases, and hypertension. Basic scientific research has elucidated the mechanisms by which some plants afford their therapeutic effects. For instance, *Silybum marianum* (milk thistle) has been shown to have clinical applications in the treatment of toxic hepatitis, fatty liver, cirrhosis, ischemic injury, radiation toxicity, and viral hepatitis via its antioxidative, antilipid peroxidative, antifibrotic, anti-inflammatory, immunomodulating, and liver regenerating effects. Another example is *Nigella sativa* (black seed). The seeds of this plant are of the most commonly used herbal medicines across the Middle East. They are known to have many medicinal properties and are widely used in Greco-Arab and Islamic medicine. Therapeutic potential and toxicological properties of *N. sativa* seeds have been extensively studied. A Medline search using "*N. sativa*" or "black seed" reveals more than 700 citations, including antioxidant, anti-inflammatory, antimicrobial, hypotensive, antinociceptive, choleretic, uricosuric, antidiabetic, and antihistaminic, immunomodulatory, anticancer, and antifertility effects (Table 8.1).

This chapter will provide an overview of traditional uses, safety, and efficacy of commonly used herbal medicines in the Eastern region of the Mediterranean (Lebanon, Jordan, Israel, and Palestine) where more than 3600 plant species are found and about 450–550 plants are noted for their uses as medicinal herbs. Plant parts used included leaves, flowers, stems, roots, seeds, and berries [1,2].

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TABLE 8.1 Commonly Used Medicinal Plants and Their Pharmacological Properties

Medicinal Plant	Antioxidant	Antihypheninflammatory	Immunomodulatory	Hypotensive	Antidiabetic	Antimicrobial	Anticancer	Antiallergic	Hypolipidemic	Vasoconstrictive	Cardiovascular	Sexual Functioning	Hepatoprotective	Nervous System	Antiobesity	Others
Nigella sativa	+	+	+		+	+	+	+								+
Olea europaea	+	+	+	+	+	+	+		+	+	+				+	
Hypericum triquetrifolium	+	+														
Urtica dioica	+	+			+											
Ferula asafoetida									+			+				
Trigonella foenum-graecum		+			+											
Melissa officinalis						+								+		+
Salvia fruticosa	+					+								+		
Portulaca oleracea		+				+										
Ammi visnaga						+				+						
Silybum marianum	+												+			
Cuminum cyminum							+								+	

Ruscus aculeatus											+								
Inula viscosa		+				+													
Majorana syriaca						+													
Eruca sativa						+	+												
Cichorium intybus	+		+		+					+					+				
Punica granatum	+	+					+	+				+							+
Ruta chalepensis		+				+					+					+			
Conium maculatum																+			
Capparis spinosa	+	+						+	+	+			+	+					
Cyperus rotundus				+		+								+					
Sarcopoterium spinosum	+	+			+														
Atriplex halimus					+														
Origanum majorana	+			+		+										+			
Foeniculum vulgare																			

FIGURE 8.1 *Nigella sativa*, black seed (Alhaba Alsawadaa or Habbatul-Barakah). (*See the color version of this figure in Color Plates section.*)

8.2 *Nigella sativa*, BLACK SEED (ALHABA ALSAWADAA OR HABBATUL-BARAKAH)

N. sativa of the Ranunculaceae family is one of the most commonly used medicinal plants throughout the Middle East. *N. sativa* seeds have been used for centuries as protective and curative remedy for numerous diseases as well as a spice and food preservative. The seeds are known to have many medicinal properties and are widely used in Greco-Arab and Islamic medicine as well as in the Prophetic medicine. The plant is found wild in North Africa, the Mediterranean region, Asia Minor, and in Southern Europe. It grows to 20–30 cm tall, a bushy and self-branching plant with white or pale-to-dark blue flowers. *N. sativa* forms a fruit capsule, which consists of many white seeds (Figure 8.1). After maturation, the fruit capsule opens up and the seeds contained within are exposed to the air, becoming black colored. The seeds are the main source of the active compounds of the plant [2,3].

8.2.1 Phytochemistry

Thymoquinone, dithymquinone, thymohydroquinone, and thymol, are the main active compounds responsible for the therapeutic effects of *N. sativa* seeds. The seeds contain other compounds, including nutritional components such as carbohydrates, fats, vitamins, mineral, and essential amino acids. In addition, they are rich in the essential and unsaturated fatty acids linoleic acid and oleic acid. They also contain phospholipids, such as phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, and phosphatidylinositol. The seeds also contain calcium, iron, potassium, and carotene, which are converted by the liver to vitamin A [2,4,5].

8.2.2 Traditional Uses

N. sativa was used by Ancient Egyptian and Greek physicians to treat nasal congestion, toothache, as a diuretic to promote menstruation, and to increase milk

production. The seeds, known as black seed, black cumin, or "Habbatul-Barakah" in Arabic, have long been prescribed in Greco-Arab and Islamic medicine as well as in Indian and Chinese traditional medicine (Chapter 10) for prevention and treatment of a wide range of diseases, including bronchial asthma, headache, dysentery, infections, obesity, back pain, hypertension, and gastrointestinal problems. It is the black seed that is referred to by the Prophet Mohammad (PBUH), who once stated that "*the black seed can heal every disease, except death*." Avicenna (980–1037) refers to *N. sativa* in his *Canon of Medicine*, as the seed that stimulates the body's energy and helps recovery from fatigue and dispiritedness. In the Unani Tibb system of medicine (Chapter 10), seeds are regarded as a valuable remedy for a number of diseases. The seed's oil has been used to treat skin conditions such as eczema and boils and to treat cold symptoms. In conclusion, its many uses have earned *N. sativa* the Arabic name "Habbatul-barakah," meaning the *seed of blessing* [2,3,6,7].

8.2.3 Pharmacological Activities

Therapeutic potential and toxicological properties of the seeds have been extensively studied. In recent years, scientific journals have published numerous articles pointing to potential therapeutic properties *N. sativa*, including antioxidant, anti-inflammatory, antimicrobial, hypotensive, antinociceptive, choleretic, uricosuric, antidiabetic, and antihistaminic, immunomodulatory, anticancer, and antifertility effects [2].

8.2.3.1 Antioxidant Activity Oxidative damage to macromolecules and cellular structures is implicated in the pathophysiology of several diseases. The cause of this oxidative damage has been connected to imbalance in the prooxidant (free radicals) and the antioxidant (scavenging) factors, either as a result of increased generation of free radicals caused by excessive oxidative stress, or due to the poor scavenging capability in the body. Reactive oxygen radicals (ROS), produced mainly by macrophages and neutrophils, are electrically charged molecules that attack cells, tearing through cellular membranes to react and create havoc with the nucleic acids, proteins, and enzymes present in cells and tissues. Therefore, the interest in herbal-derived antioxidant agents and their use in preventing and treating these diseases have recently increased. One of the potential properties of *N. sativa* seeds is the ability of one or more of its constituents to reduce toxicity due to its antioxidant activities. *In vitro* investigations reveal that the seeds have the following properties [2,8]:

- Protection of erythrocytes against lipid peroxidation and protein degradation.
- Protection of laryngeal carcinoma cells from LPS/cortisol-induced apoptosis.
- Inhibition of the hemolytic activities of snake and scorpion venoms.

The following *in vitro* studies indicate that the observed antitoxic effects of the seeds could be attributed to their antioxidant properties [2,9]:

- Pretreatment of LPS-activated peritoneal macrophages with aqueous extract of the seeds caused a significant decrease in nitric oxide (NO) production.

- Thymoquinone efficiently inhibited iron-dependent microsomal lipid peroxidation *in vitro* in a concentration-dependent manner.
- Thymoquinone induced significant protection of isolated hepatocytes against *tert*-butyl hydroperoxide induced toxicity evidenced by decreased leakage of L-alanine aminotransferase (ALT) and alkaline phosphatase (AP).
- Thymoquinone reduces at no toxic concentrations, NO synthesis, and decreases both gene expression and protein synthesis levels of inducible nitric oxide synthase (iNOS) in supernatants of LPS-activated macrophages.
- Activation of polymorphonuclear leukocytes with thymoquinone showed protective effects against superoxide anion radical either generated photochemically, biochemically, or derived from calcium ionophore, indicating to its potent superoxide radical scavenger.

Antioxidant activities of *N. sativa* seed oil were found in the following *in vivo* studies using different hepatic and kidney toxicity murine models [2,10,11]:

- The oil protected against carbon tetrachloride (CCl_4)-induced hepatotoxicity coinciding with decreasing the elevated serum potassium and calcium levels; improvement in serum lipid profile; elevating the reduced erythrocyte, leukocytes, and hemoglobin levels; decreasing the increased liver enzyme levels; and increasing the reduced antioxidant enzyme levels. Other studies indicate that treatment with the oil prevents CCl_4-induced liver fibrosis in rabbits and improves the antioxidant status.
- The oil-produced amelioration of the biochemical and histological markers of gentamicine-induced nephrotoxicity coincided with the increase in the scavenger defense system, including glutathione (GSH) concentration and the total antioxidant status in renal cortex.
- Oral administration of ethanol in rats (gastric ulcer model) causes a significant reduction in the levels glutathione and free acid. Pretreatment of rats with *N. sativa* before induction of ulcer results in a significant increase in glutathione level and free acid.
- Pretreatment of mice with thymoquinone before CCl_4 injection ameliorated hepatotoxicity of CCl_4 as evidenced by the significant reduction of the elevated levels of serum enzymes and significant increase in the hepatic glutathione content.
- Thymoquinone administration counteracted the development of nephrotoxicity, cardiotoxicity, and oxidative stress induced by doxorubicin (DOX) in rats.
- Thymoquinone administration counteracted the development of nephrotic hyperlipidemia, and hyperproteinuria; and restored the biomarker's values of oxidative stress toward normal.
- *Schistosoma mansoni* infection induces marked alteration in the liver function. Administration of *N. sativa* oil markedly reduced the worm and egg burden, coincided with partial amelioration of the *schistosoma*-induced liver fibrosis and changes in ALT, GSH, AP activities in serum. Furthermore, treatment with

N. sativa oil decreased the hepatocellular necrosis, degeneration, and advanced fibrosis in CCl_4-induced liver fibrosis in rabbits. Similarly, treatment of *S. mansoni*-infected mice with *N. sativa* oil or purified thymoquinone induced a protective effect on the infection-induced genotoxicity evidenced by reduction in the percentage of chromosomal aberrations and the incidence of chromosome deletions and tetraploidy.

Coupling the fact that black seeds have been widely used in Greco-Arab and Islamic medicine as well as in other traditional medicines with the above-mentioned antitoxic properties, it is apparent that the seed's crude oil and its active compounds can reduce oxidative stress-mediated toxicity induced accidentally by environmental or infectious factors, or by anticancer drugs. Since chemotherapy induces massive expansion of the immature granulocytes, which produce large amounts of NO, it might be feasible to follow chemotherapy with thymoquinone treatment that might alleviate the suppressive effects on the immune responses by chemotherapy-induced NO [2].

8.2.3.2 Anti-Inflammatory Properties As discussed in Chapters 12 and 13 inflammation is mediated by cytokines, eicosanoids, oxidants, and lytic enzymes secreted by macrophages and neutrophils. Nitric oxide, initiates a wide range of toxic oxidative reactions causing tissue injury. In addition, inflammation is also mediated by two main enzymes: cyclooxygenase (COX) and lipoxygenase (LO). COX catalyzes the formation of prostaglandins (PGE) and thrompoxane, while LO catalyzes the formation of leukotrienes (LT). Both PGE and LT function as the main mediators of allergies and inflammation [2,12,13].

Inhibitory effects of *N. sativa* oil and its active ingredients on the production of inflammatory mediators have been reported in several *in vitro* studies. For instance, thymoquinone and the crude fixed oil inhibited both COX and LO pathways of arachidonate metabolism in rat peritoneal leukocytes stimulated with calcium ionophore and inhibited nonenzymatic peroxidation in brain phospholipid liposomes. Furthermore, *in vitro* treatment of calcium- or ionophore-stimulated neutrophils with either crude extract or thymoquinone inhibited the formation of leukotrienes by LO. Thus, inhibition of both COX and LO pathways are key factors mediating the anti-inflammatory effects of the crude oil of *N. sativa* and its active ingredients. These finding were confirmed in several *in vivo* studies. For instance,

- Experimental allergic encephalomyelitis (EAE) is an autoimmune demyelinating disease of the central nervous system that is widely used as a test model for the human multiple sclerosis that is mediated by T lymphocytes. Oxidative stress plays a central role in the onset and progression of this disease. Treatment of EAE animals with thymoquinone results in higher glutathione level, no perivascular inflammation, or any disease symptoms.
- Anti-inflammatory effects were seen in ulcerative colitis, an inflammatory disease characterized by cycles of acute inflammation, ulceration, and bleeding of the colonic mucosa. Several factors, such as eicosanoids, leukotrienes, platelet activating factor, and ROS have been implicated in the pathogenesis of this

disease. Other investigations in rats showed that pretreatment of animals with thymoquinone led to complete protection against acetic acid-induced colitis with comparable or even higher effects than sulfasalazine, an anticolitis drug.

- Arthritis is another inflammatory disease. It has been observed for a long time that *N. sativa* oil has an anti-inflammatory effect relieving the effects of arthritis. Consistent with these observations, recent studies have reported also that externally in an ointment form, the anti-inflammatory activity of the *N. sativa* was found to be of the same range as that of other similar commercial products without induction of skin allergy.

Taken collectively, in recent years, medical journals have published various articles pointing to a potential therapeutic effect of *N. sativa* and its active ingredients, in particular thymoquinone, against murine colitis, EAE, and arthritis inflammatory diseases, which would be translated to the clinical settings of these diseases in humans. However, it still remains unknown if the anti-inflammatory effects discussed above are merely attributed to nonspecific inhibitory effects on macrophages and neutrophils, or also involve inhibitory effects on T cell populations. Further studies, therefore, should be precisely designed to dissect the impact of thymoquinone on the cytokines that drive Th1- and Th2-mediated inflammatory immune diseases, since these cytokines have reciprocal inhibitory effects. In addition, more attention is needed to test if thymoquinone can modulate dendritic cells [2].

8.2.3.3 Antiallergic Properties The effectiveness of *N. sativa* oil in the treatment of allergic diseases was confirmed in a clinical study in which treatment of patients with allergic diseases, including allergic rhinitis, bronchial asthma, and atopic eczema. The oil decreased the IgE level, eosinophil count, and endogenous cortisol in plasma and urine. Dithymquinone was found to suppress symptoms in the majority of patients suffering from bronchial asthma.

The antiallergic effect of *N. sativa* seed components could be attributed to its antihistaminic effects. *In vitro* studies support this notion. Aqueous extract of *N. sativa* has shown relaxant and antihistaminic effects on precontracted guinea pig tracheal chains. Moreover, thymoquinone caused a concentration-dependent decrease in the tension of the tracheal smooth muscle precontracted by carbachol and totally inhibited effects of histamine and serotonin on the guinea pig isolated tracheal and ileum smooth muscles. It is suggested that these effects of thymoquinone can be mediated, at least in part, by inhibition of lipoxygenase products of arachidonic acid metabolism and possibly by nonselective blocking of the histamine and serotonin receptors. Preclinical and clinical studies have also shown antihistaminic effects for *N. sativa* seeds. Using gastric ulcer model induced by oral administration of ethanol, which caused a significant increase in mucosal histamine content, rat pretreated with *N. sativa* oil before induction of ulcer induced a significant decrease in gastric mucosal histamine content [2,13,14].

8.2.3.4 Immunomodulatory Properties Generation of effective immunity requires both nonspecific innate immunity that builds the first line of defense in

the body and adaptive immunity that recognizes specific antigens. Innate immunity consists of anatomical barriers, physiological barriers, and nonspecific cells, including macrophages, granulocytes, natural killer cells, and dendritic cells. Adaptive immunity is comprised of a humoral arm mediated by B cells that secrete antigen specific antibodies, and cellular arm mediated by helper and cytolytic T cells. T helper cells are responsible for orchestrating an immune response, whereas cytolytic T cells are the killer cells that traffic to sites of infection or cancer and lyze infected or tumor cells. Together, these two types of T lymphocytes play critical roles in eliminating foreign antigens and self altered cells, for example, cancer and virus-infected cells. One of the precious properties of *N. sativa* is the immunomodulatory effect of its ingredients. Various *in vitro* and *in vivo* studies reveal enhancing effects of *N. sativa* on T-cell immunity. For example, 1 week of oral administration of aqueous extracts of *N. sativa* seeds significantly increased the number of splenic natural killer cells, and their cytotoxicity against YAC-1 tumor targets when compared with control cells. In addition, oral administration of *N. sativa* oil commenced 6 weeks after induction of streptozotocin (STZ)-induced diabetes significantly induced beneficial effect, coincided with elevation in the phagocytic activity of peritoneal macrophages, and lymphocyte count in peripheral blood compared with untreated diabetic hamsters, indicating the potential of *N. sativa* oil to enhance cell functions of innate immunity, including macrophages and natural killer cells, as well as cellular immunity. Another example for enhancing immunity by *N. sativa* is its ability to ameliorate age-associated decline in T-cell functions. Nutritional supplementation can enhance the immune response in elderly humans by changing both the total amount and the type of dietary lipids. The oil is rich in the linoleic acid, the linolenic acid, and a small amount of stearidonic acid. Dietary supplementation with the *N. sativa* oil has found to improve the immune response of healthy elderly subjects, which is mediated by a change in the factors closely associated with T-cell activation.

In contrast to its enhancing effect on the T-cell mediated immune response, *in vivo* studies with *N. sativa* constituents have shown a tendency to downregulate B cell-mediated immunity. The effect of the volatile oil of *N. sativa* seeds was studied on the antigen-specific response induced by vaccinating rats with the typhoid TH antigen. Treatment with *N. sativa* oil induced about twofold decrease in the antibody production in response to typhoid vaccination as compared to the control rats. Thus, based on the *in vitro* and *in vivo* data, it is likely that *N. sativa* constituent may enhance cellular immunity, while suppressing humoral immunity. Further studies, however, are required to validate this hypothesis, and to define the components responsible for each effect.

Cytokines are critical in initiation and execution of immunity. Several experiments have shown that excessive or insufficient production of cytokines may significantly contribute to the pathophysiology of a range of disease responses and are thought to be decisive for pathological or physiological consequences. After activation, T helper cells differentiate into either TH1-type cells, secreting IL-2, IL-12, IFN-γ, and TNF-α, or TH2-type cells secreting IL-4, IL-5, IL-10, and IL-13. Indeed, the balance between TH1 and TH2 cytokines is critical for the orientation of the inflammatory

response toward cell- or humoral-mediated responses. Thus, any factors that can interfere with TH1/TH2 axis might affect the outcome of the response. By investigating the effects of *N. sativa* seed proteins on cytokine production by human peripheral blood mononuclear cells, the proteins enhanced the production of IL-3 and IL-1 by lymphocytes when cultured with or without allogeneic cells, suggesting the stimulatory effects of *N. sativa* seed proteins on the naive cells itself. However, under the same culture conditions, crude extract of *N. sativa* seeds or their soluble fractions did not show any effect on the production of IL-2 and IL-4. In a recent study, *N. sativa* oil exhibited a striking antiviral effect against murine cytomegalovirus infection coincided with elevation of IFN-γ in serum, which lasted for a prolonged time. Thus, it is apparent that the effect of *N. sativa* on cytokine production depends on the nature and doses of ingredients and the nature of cytokines itself [2,15–18].

8.2.3.5 Hypoglycemic Effects In view of the traditional use of plant mixtures for treatment of diabetes, many scientific investigations have addressed the antidiabetic effects of plant mixtures containing *N. sativa*. These studies revealed that the blood glucose lowering effect was due to the inhibition of hepatic gluconeogenesis. For instance, an aqueous extract of a plant mixture containing *N. sativa* was found to lower the blood glucose level significantly after oral administration. In addition, intraperitoneal administration of *N. sativa* seed's oil produced a significant hypoglycemic effect in normal and alloxan-induced diabetic rabbits. Similar results were seen in rats treated with a mixture of *N. sativa* and other plant extracts.

Another study was designed to investigate the possible insulinotropic properties of *N. sativa* oil in streptozotocin and nicotinamide-induced diabetes mellitus in hamsters. After 4 weeks of treatment with *N. sativa* oil, significant decrease in blood glucose level together with significant increase in serum albumin level were observed, indicating that the hypoglycemic effect of *N. sativa* oil is, at least partially, mediated by a stimulation of beta cells coincident with an increase in serum insulin level and possess insulinotropic properties in type II like model. In another study, the hypoglycemic effect of *N. sativa* was supposed to be mediated by extrapancreatic actions rather than by stimulated insulin release. A recent clinical study on human volunteers showed that 1 g of *N. sativa* twice daily caused a decrease in blood glucose level after 2 weeks of oral treatment [2,19,20].

8.2.3.6 Antimicrobial Properties *N. sativa* seed oil and active ingredients have been found to exert antimicrobial activities, including antibacterial, antifungal, antiparasitic, and antiviral effects. Some of these antimicrobial effects have been attributed to the immunomodulatory properties of *N. sativa* seed components [2,19–21].

8.2.3.7 Antibacterial Effects *N. sativa* was found to exhibit antibacterial activity against several bacterial strains, such as *Escherichia coli*, *Bacillus subtilis*, *Streptococcus faecalis*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa*, as well as against the pathogenic yeast *Candida albicans* and fungus. Diethyl ether extract of *N. sativa* caused concentration-dependent inhibition of the Gram-positive bacteria *S. aureus*, and of Gram-negative bacteria *P. aeruginosa* and *E. coli.*

Furthermore, *in vivo* treatment with this extract successfully eradicated a nonfatal subcutaneous staphylococcal infection in mice when injected at the site of infection. This might indicate that the microbial activity of the seed components observed *in vivo* is mediated by different host factors. Inoculum of *C. albicans* into mice produces colonies of the organism in the liver, spleen, and kidneys. By studying antifungal effect of the aqueous extract of *N. sativa* seeds using this model, treatment of the infected mice with *C. albicans* markedly inhibited the growth of the fungus in all organs studied. All the findings discussed above show that *N. sativa* seed constituents possess antimicrobial effects against different pathogens, including bacteria, viruses, parasites, and fungus.

8.2.3.8 Antiviral Effects Murine cytomegalovirus (MCMV) is a herpes virus that causes disseminated and fatal disease in immunodeficient animals similar to that caused by human cytomegalovirus in immunodeficient humans. *In vivo* treatment with *N. sativa* oil induced a striking antiviral effect against MCMV infection, indicating a promising therapeutic potential of *N. sativa* oil as an antiviral remedy. Both the nonspecific cells, including natural killer cells and macrophages, and specific cells including T-helper and T-cytotoxic cells control immunity generated toward viral infection. Each cell population plays a central antiviral role at a certain time postinfection, where natural killer cells and macrophages are important during the early phase, while T cells are crucial for clearance of the virus at late stages. Leukocyte-derived cytokines mainly IFN-γ are seminal factors in mediating the antiviral response. Interestingly, the antiviral effect of the *N. sativa* oil was found to be associated with enhancing response of T-helper and T-cytotoxic cells, and macrophages, augmenting their ability of IFN-γ production that is known to render mice more resistance to MCMV infection. It has been reported that viral infection induces apoptosis leading to lymphocyte depletion in the host, and that antioxidant agents can inhibit virus-induced apoptosis as well as the viral replication in target cells. Eventually, the antioxidant effect of the *N. sativa* oil may represent another mechanism that contributes to its antiviral activity [2,19–21].

8.2.3.9 Antiparasitic Properties The essential oil from the seeds showed pronounced antiparasitic effects against tapeworms, earthworms, nematodes, and antischistosome effects. Schistosomiasis, a tropical parasitic disease, is endemic in the third world countries. Although vaccine trials have been tested, chemotherapy is still the only choice regimen to the human host. Treatment of *S. mansoni* infected mice with *N. sativa* oil induced reduction in the number of *S. mansoni* worms in the liver, coincided with a decrease in the egg burden in both the liver and the intestine. Administration of *N. sativa* oil to *S. mansoni*-infected mice partially corrected the infection-caused alterations biochemical and pathological in ALT, GGT, and AP activities, as well as the albumin content in serum. In murine schistosomiasis, a variety of cytokines are implicated as mediators of the granulomatous inflammatory response. Accordingly, modulation of cytokine levels can modify the intensity of the inflammatory response. Since *N. sativa* seeds increased the ratio of helper to cytotoxic T cells, and enhanced macrophages and natural killer cell activities in

normal volunteers, its antischistosome effect could in part be attributed to modulation of the immune response to schistosome eggs trapped in the liver.

8.2.3.10 Antitumor Properties In both *in vivo* and *in vitro* studies *N. sativa* seeds were found to exhibit antitumor effects [2,19,22–25]. These studies are presented in Chapter 12. In brief, proliferation of cells from a breast cancer cell line was completely inhibited after treatment with aqueous or alcohol extracts *of N. sativa*. Other studies show that *N. sativa* extracts induced inhibition of the metastasis-induced factors, including type IV collagenase, metalloproteinase, and serine proteinase inhibitors, angiogenic protein-fibroblastic growth factor, tissue-type plasminogen activator, urokinase-type plasminogen activator, and plasminogen activator inhibitor type 1. It seems that the antitumor activity of *N. sativa* oil might be mediated through antiangiogenic effects through inhibition of local tumor invasion and metastasis. In addition to the antitumor effects of the whole extract of *N. sativa*, thymoquinone, dithymquinone, and other active ingredients also showed cytotoxic effects. Both thymoquinone and dithymquinone were equally cytotoxic against different human tumor cells lines, including the pancreatic adenocarcinoma, human uterine sarcoma, and human leukemic, triggering their apoptosis through arresting the growth of these cells in G1 phase of the cell cycle associated with increase in the gene and protein expression of p53 and inhibition of the antiapoptotic Bcl-2 protein. This indicates that the antineoplastic effect of thymoquinone is mediated by proapoptotic effects modulated by Bcl-2 protein and is linked to and dependent on p53.

Antitumor effects have also been confirmed in different tumor models in animals. For instance, topical treatment with *N. sativa* inhibited two-stage initiation/promotion of skin carcinogenesis induced in mice by anthracene/croton oil in mice. Furthermore, oral feeding with *N. sativa* extract suppressed hepatic tumor in rat induced by diethylnitrosamine or by partial hepatectomy. In addition, the oil suppressed colon carcinogenesis induced by methylnitrosourea or by dimethylhydrazine. These antitumor effects of *N. sativa* oil might be attributed to the effect of thymoquinone, since administration of thymoquinone in drinking water resulted in significant suppression of forestomach tumor induced by benzo(α)pyrene. These findings indicate that thymoquinone, in addition to its prophylactic and therapeutic antitumor effects; can be a potential chemotherapeutic adjuvant to standard chemotherapy. This might lower the dose of standard chemotherapeutic drugs, while augmenting their antitumor efficacy. Suppression of immune cell function associated with chemotherapy, radiotherapy, and late stages in tumor-bearing hosts is mediated, at least in part, by NO produced by immature granulocytes that are massively generated under these conditions. Therefore, it is possible that the antitumor effects reported for *N. sativa* oil and thymoquinone are mediated by their abilities to scavenge the NO produced by these cells. The impact of *N. sativa* ingredient, in particular thymoquinone, on these cells in the tumor-bearing hosts needs to be explored. In addition, since chemotherapy induces massive expansion of the immature granulocytes, which produce large amount of NO, it might be feasible to follow chemotherapy with thymoquinone treatment that might alleviate the suppressive effects on the immune responses by chemotherapy-induced NO. In addition to the possible antioxidant mediating

antitumor effects of thymoquinone, it is also possible that its antitumor effects are mediated by the ability to suppress PEG and LT [2,19,22–25].

8.2.4 Potential Toxicity

All the information discussed above reveal the beneficial immunotherapeutic potentials of the crude oil and extracts of *N. sativa* seeds and its active ingredient thymoquinone toward several disease settings. However, toxicity of medicinal plants is central for acceptance of their therapeutic application in human (Chapter 11). Various studies have addressed the possible toxicity of *N. sativa* seeds and their components. For instance, potential toxicity of the fixed oil of the seeds was investigated in mice and rats through determination of LD_{50} values and examination of possible biochemical, hematological, and histopathological changes. LD_{50} values, obtained by single doses (acute toxicity) in mice, were 28.8 mL/kg body with oral administration, and 2.06 mL/kg body with intraperitoneal administration. Chronic toxicity was studied in rats treated daily with an oral dose of 2 mL/kg body weight for 12 weeks. Changes in key hepatic enzymes levels, including ALT, AST, and GSH, and histopathological modifications (heart, liver, kidneys, and pancreas) were not observed in rats treated with *N. sativa* oil after 12 weeks of treatment. It is important to mention, however, the serum cholesterol, triglyceride and glucose levels and the count of leukocytes and platelets decreased significantly, compared to control values, while hematocrit and hemoglobin levels increased significantly. A slowing of body weight gain was also observed in *N. sativa* treated rats compared to control animals.

Taken together, the parameters emerging from these studies indicate that *N. sativa* is not toxic, as evidenced by high LD_{50} values, hepatic enzyme stability and organ integrity, suggesting a wide margin of safety for the therapeutic doses of *N. sativa* fixed oil. However, the changes in hemoglobin metabolism and the fall in leukocyte and platelet count must be taken into consideration. In addition, the route of administration of *N. sativa* seems to be crucial for its toxicity, since the LD_{50} was higher with oral administration (a 20-fold higher) than with intraperitoneal route, indicating that oral intake is safer than the systemic one [2,19,26].

In contrast to the above-mentioned studies, *in vitro* toxicological properties and potential antimutagenic effects aqueous extracts of the *N. sativa* were tested in primary rat hepatocyte cultures against *N*-methyl-*N*-nitro-*N*-nitrosoguanidine (MNNG). MNNG represents a standard alkylating agent that preferentially methylates the O_6 position of deoxyguanosine residues in DNA causing DNA adducts. It has also proven to induce massive chromosomal damage in rat hepatocytes. Hepatocytes were chosen as indicators of genotoxicity because of their high metabolic capacity, which enables a highly sensitive test system for antimutagenicity and detoxification properties. Results obtained in this study indicate that *N. sativa* did not protect hepatocytes from the clastogenic effect of MNNG. Instead, it led to a significant increase of chromosomal aberrations in the case of pretreatment. This effect therefore has to be considered as synergistic, probably due to the induction of metabolic enzymes favoring the generation of reactive metabolites of

MNNG. Taking into consideration that the *N. sativa* extract itself significantly increased the level of chromosomal aberrations, these findings most likely indicate a direct interaction of components contained in the *N. sativa* extract with MNNG. On the other hand, all three modes of treatment caused a significant reduction of micronuclei, an observation eventually pointing to an antimutagenic potential of the *N. sativa* extract. To prove this assumption, cell proliferation has to be taken into consideration since the appearance of cells with micronuclei strictly depends on cell division. Hence, the number of cells with micronuclei will decline if cell proliferation is lowered even when DNA damage has occurred. Since the mitotic indices are also reduced, the reduction of micronuclei cannot be attributed to protective properties of the extract [27]. Taken together, a degree of caution is necessary with larger amounts of *N. sativa* due to the presence of thymoquinone and other active ingredients.

8.3 *Olea europaea*, THE OLIVE (*ALZAITUN*)

Olea europaea (the olive) is a species of the family Oleaceae. The olive tree is an evergreen tree or shrub native to the Mediterranean, Asia, and the Maghreb region. The silvery green leaves are oblong in shape, measuring 4–6 cm long and 1–2 cm wide. Its fruit, the olive, is of major agricultural importance in the Mediterranean as the source of olive oil (Figure 8.2). While olive oil is well known for its flavor and health benefits, the leaf has been used medicinally in various historical contexts and cultures. Olive leaf and olive leaf extracts are now marketed as antioxidants, antiaging, immunostimulators, and even antibiotics. Clinical evidence has proven the antidiabetic and antihypertension effects of leaf extracts. In addition, several studies support its antibacterial, antifungal, and anti-inflammatory properties [28–30].

8.3.1 Traditional Uses

Recorded evidences of olive leaf's therapeutic uses date back thousands of years: It was used by an ancient Egyptian and Mediterranean cultures to treat a variety of health conditions. There are tens of ancient olive trees throughout Palestine. Specifically, two giant olive trees in the Arab town of Arraba and five trees in Deir Hanna, both in Galilee region, have been determined to be over 3000 years old. All seven trees continue to produce olives. Olive leaf is the first herb cited in the Bible as a natural remedy "*The fruit thereof shall be for meat and the leaf thereof for medicine*." Olive tree is described in the Holy Quran as the holy tree and Prophet Mohammad (PBUH) (570–632) said "*Eat olive oil and massage it over your bodies since it is a holy (Mubarak) tree*." Olive leaf finds a widespread use in the Greco-Arab and Islamic medicine in the treatment and prevention of many diseases. Leaf extracts can be taken in powder, liquid concentrate, or capsule form though the fresh-picked leaf liquid extracts are quickly gaining popularity due to the broader range of healing compounds they contain [2,28–33].

FIGURE 8.2 *Olea europaea*, the olive (*Alzaitun*). (*See the color version of this figure in Color Plates section.*)

8.3.2 Pharmacological Activities

The primary medical constituents of olive leaf are the antioxidants oleuropein, hydroxytyrosol, hydroxytyrosol acetate, and the flavonoids luteolin, and luteolin-glucosides. Oleuropein and its hydrolysis products are those of the greatest therapeutic potential. Oleuropein has a vasodilator effect, increases blood flow in the

coronary arteries and improves arrhythmia. It has proven to be a potent antioxidant, anti-inflammatory, antiviral, and antibacterial compound. Various scientific reports show that oleuropein also exhibits in antimicrobial activity against viruses, retroviruses, bacteria, yeasts, fungus, molds, and other parasites. Other clinical properties of oleuropein are anti-inflammatory effects through macrophage activation, the inhibition of plaque aggregation, and eicosanoid production, and a reduction in the level of low-density lipoproteins (LDL) [2,28–33].

8.3.2.1 Cardiovascular Properties Atherosclerosis of the coronary arteries represents a major cause of cardiovascular mortality and morbidity. Dietary fat may influence the risk of coronary heart disease by several pathways. One such pathway is the effect of dietary fat on the susceptibility of LDL to oxidation. According to the oxidation hypothesis, one of the initial steps in atherogenesis is the oxidative modification of lipoproteins, mainly LDL, in the arterial wall. The oxidized LDL is taken up by macrophages, which in turn become lipid-laden foam cells. Autoantibodies to oxidized LDL have been found in the blood, and LDL extracted from human atherosclerotic lesions demonstrates many of the physical, chemical, and biological properties of *in vitro* oxidized LDL. The susceptibility of LDL to oxidation correlates independently with the extent of atherosclerosis. Several studies have shown that diets rich in monounsaturated fatty acids lead to the production of LDL that is more resistant to oxidation than that found in persons consuming a diet rich in polyunsaturated fatty acids. However, in some regards the interaction of dietary fat and LDL composition and oxidizability is poorly understood.

A strong connection between Mediterranean diets and lower rates of heart disease is evident through many scientific reports. The most important health-promoting substance in olive oil is oleic acid, which is a monounsaturated fatty acid. In addition, oleuropein may play a role in the prevention of cardiovascular diseases through a decreased formation of atherosclerotic plaques by inhibiting LDL oxidation. Traditional uses support olive leaf and olive oil in cardiovascular disease prevention. Animal experiments in rabbit and rat preparations found a hypotensive effect of oleuropein, possibly through a direct action on smooth muscle. Oleuropeoside also may exert vasodilator activity. Additionally, olive leaf extracts may possess antispasmodic, vasodilator, and antiarrhythmic properties [28,29,34–37].

8.3.2.2 Hypotensive Properties As with other aspects of cardiovascular diseases, there is a reduced incidence of hypertension in populations that consume olive oil-rich diet. Epidemiological data from studies in three Mediterranean countries (Italy, Greece, and Spain) as well as non-Mediterranean countries, suggest a protective effect for monounsaturated fatty acids or olive oil, while non-Mediterranean countries show little or no positive effects. A diet rich in monounsaturated fatty acids (from olive oil) reduced the dosage of antihypertensive medication in patients taking these medications. [28,29,34–37].

8.3.2.3 Antioxidant Properties Antioxidant activity of the olive has been attributed by phenols content particularly to hydroxytyrosol, oleuropein, and caffeic

acid. Caffeic acid was also reported to have antioxidant activity through the scavenging of superoxide anion. In rat, epithelial cells stimulated with cytokines, a concentrated polyphenol extract reduced nitrite concentration and free radical production. Rabbits with induced diabetes showed a decrease in oxidative stress markers when treated with oleuropein. Other experiments support the antioxidant activity of the phenols oleuropein and hydroxytyrosol. A recent study has evaluated the antioxidant potency of water and methanol olive leaves extracts and of the main compounds. Oleuropein, phenols and flavonoids demonstrated strong antioxidant potency [28,29,38].

8.3.2.4 Hypolipidemic Effect As mentioned above, oxidation of LDL cholesterol has been identified as one of the first steps in the development of atherosclerotic lesions by promoting injury to the arterial wall through several mechanisms, including growth factor and chemotactic protein expression, inflammation, and increased local macrophages. Phagocytosis of oxidized LDL by macrophages, an innate immune response to tissue damage, produces a fatty foam cell, which, when combined with other cells, produces a fatty streak in the blood vessel. Oxidized LDL can also be taken up directly by endothelial and smooth muscles cells, leading to formation of fatty streaks, which is the first sign of atherosclerosis. The lesions forming atherosclerotic plaques are made up of lipids, endothelial and smooth muscle cells, and extracellular matrix. The plaque environment is proinflammatory. Inflammation occurring prior to the formation of fatty streaks and atherosclerotic lesions causes alterations to the endothelial cell wall, which increases the adhesion of leukocytes, LDL cholesterol, and platelets. This contributes to the development of atherosclerosis and cardiovascular disease. Olive leaf has been reported to inhibit platelet aggregation and production of thromboxane A2 (a stimulator of platelet aggregation with vasodilatory effects). Also of interest, is a recent study reporting that olive leaf extract inhibited both angiotensin-converting enzymes. *In vitro* studies have demonstrated hydroxytyrosol and oleuropein are capable of inhibiting production of isoprostanes, a marker of LDL oxidation. It has been suggested that phenols present in olive oil may act synergistically with these constituents to prevent LDL oxidation. Animal tests have shown hypoglycemic and hypolipidemic activity of olive leaf. The active constituent was reported to be oleuropein, with a proposed mechanism of action of potentiation of glucose-induced insulin release, and an increase in peripheral blood glucose uptake [28,32].

In keeping with its long history of safe usage of plant mixtures for treatment of hypercholesterolemic conditions, many scientific investigations carried out in order to evaluate hypolipidemic activity of plant mixtures containing leaf extracts of *O. europaea*. For instance, based on traditional Greco-Arab and Islamic medicine knowledge, we have evaluated the effects of extracts *of O. europaea* and *Eriobotrya japonica* in lowering fat levels in the blood. Antioxidant and antihypercholesterolemic properties of this mixture were assessed in a clinical study carried out among 41 human volunteers with hyperlipidemia values. The volunteers were divided into three groups and were asked to continue their usual diet and medications unchanged and were evaluated for efficacy and tolerability of the mixture (tablets 1×3 daily for

3 months). Group 1 included 12 persons who were at a fixed dose of statins therapy without fully responding to their medications. Group 2 included 20 volunteers who consumed only the mixture. Group 3 (control group) included nine volunteers who consumed placebo tablets 1×3 daily for 3 months. The mixture was well tolerated by all subjects and no side effects were reported. Cholesterol levels were significantly reduced in Groups 1 and 2 by 24% and 14.3% after 3 months of consumption, respectively. Parallel reductions in both LDL and triglycerides levels and increments in HDL levels were observed. The results demonstrate safety, tolerability, and efficacy of the mixture that seems to have dual inhibition on both the absorption and production of cholesterol [39].

8.3.2.5 Antioverweight Properties Overweight is a major health challenge in the Western world with serious clinical complications such as type 2 diabetes mellitus, cerebrovascular and ischemic heart diseases. Available pharmacological therapy of obesity is limited to anorexics such as amfepramon and sibutramin. When added to a diet, such therapy is expected to yield a weight loss of 0.2–0.4 kg/week, but only for few weeks due to tolerance and side effects. Effective management of overweight seems to be of the utmost importance especially if modern science can utilize safe plants derived from traditional medicine to fill the gap and supplement currently employed pharmacological products. Mild overweight was generally accepted in ancient Arab societies and considered a reflection of a high socioeconomic level and part of the desired beauty standards in those days. This fact was expressed in the minimal effort to discover antioverweight/obesity remedies compared to other medical fields. Only severe obesity was considered suitable for treatment using specific medicinal plants, body exercises, and control of food consumption. In a recent study, a mixture of extract of leaves of *Alchemilla vulgaris*, *O. europaea* and *Mentha longifolia*, as well as seeds of *Cuminum cyminum,* used in Greco-Arabic and Islamic medicine as well as in European herbal medicine, was assessed for its safety and efficacy in weight loss. Cultured human fibroblasts treated with this mixture did not exhibit any sign of toxicity as evidenced by LDH-release. These results were confirmed in experimental studies on rats where a LD_{50} of 15.3 g/kg was observed. In addition, a clinical study was carried out among 80 human volunteers with a body mass index (BMI) of $30.67 \pm 2.14\ kg/m^2$. All 80 subjects were asked to continue their usual diet but to eat only 3 main meals daily and to take one mixture tablet 30 min before each meal. Fourteen subjects were excluded for not following the protocol, and 66 subjects were all evaluated for efficacy and tolerability of the mixture. The mixture was well tolerated by all subjects and no side effects were reported. A progressive and significant weight loss was seen in these subjects during the whole study period. Higher levels of weight loss were seen in people with BMI of $25–30\ kg/m^2$ (overweight) compared to people with BMI higher than $30\ kg/m^2$ (obese). The BMI was reduced after three months from $28.5 \pm 1.2\ kg/m^2$ and $32.1 \pm 1.8\ kg/m^2$ to $24.5 \pm 1.4\ kg/m^2$ and $27.5 \pm 2.2\ kg/m^2$ in overweight and obese group, respectively. Results indicate safety, tolerability, and efficacy of the mixture. The combination of the four plants seems to increase both satiety and thermogenesis in brown adipocytes by measuring thermogenesis in male Sprague-Dawley rats. This system is generally

accepted as a model for fat depletion ("fat burning"). The amines of *A. vulgaris*. are mainly the tannins reported to increase the metabolic rate in cold environments and the flavonoids reported to regulate digestive enzymes and to have cardioprotective effects. Beside metabolic stimulation, olive leaves-extracts were shown to inhibit intestinal glucose absorption and thereby, a hypoglycemic effect was reported together with hypotensive and hypolipidemic properties. Olive leaves are thus known to reduce fat load and circulatory fat levels. Wild mint was reported to relax the stomach and increase gastric emptying and the passage of food throughout the digestive system. Cumin was also reported to improve glucose utilization, reduce raised blood sugar and promote digestion by stimulating gastrointestinal mucosa and pancreatic digestive enzymes [40].

8.3.2.6 Antidiabetic Properties Diabetes is a predominant public health concern and has increased steadily worldwide. The disease causes substantial morbidity, mortality, and remains an important risk factor for cardiovascular disease. With increasing rates of childhood and adult obesity, diabetes is likely to become even more prevalent over the coming decade. There are two types of diabetes: type 1 and type 2. Type 1 juvenile diabetes is known as an autoimmune disease resulting in extensive destruction of the beta cells in the pancreas. While the cause of type 2 adult-onset diabetes remains poorly understood, all patients with type 1 diabetes and part of type 2 diabetes require daily insulin shots, replacement of the destroyed beta cell mass via islets or transplant of pancreas in order to survive.

Diabetes mellitus with retinopathic, neuropathic or nephropathic complications is a common debilitating and often life-threatening disease that constitutes a significant risk factor in atherosclerosis. It is well known that diabetes mellitus is associated with an increased production of reactive oxygen species and a reduction in antioxidative defenses. The diabetic-induced oxidative stress is pathogenetically important in diabetic complications. Antioxidant micronutrients may thus significantly contribute to, reduce, or prevent diabetic complications and atherosclerosis. Diabetes has been recognized since ancient times, its main symptoms were increased thirst, frequent urination and tiredness. Arab and Muslim physicians and practitioners had used a series of plants for treating these combined symptoms (named Zarab) beside several instructions for consumption of specific food and mild practices. For the treatment of diabetes mellitus *O. europaea* leaf is part of the strongly recommended medicinal plant list. The hypoglycemic activity of olive leaf has been demonstrated in animals. In rabbits with induced diabetes, an ethanol extract of olive leaf decreased blood glucose. Suggested mechanisms include potentiation of glucose-induced insulin release and increased peripheral uptake of glucose. Other studies have shown that intragastrically administration of 500 mg/kg of aqueous extracts of dried *O. europaea* leaf to male rats reduced the blood glucose levels of normal or alloxan-induced diabetic rats. In addition, aqueous decoctions of *O. europaea* leaf, administered intragastrically to the rat at a dose of 32 mg/kg, showed activity against alloxan-induced hyperglycemia [28,32,41].

In a recent study, safety and antidiabetic effects of a mixture (Glucolevel) of dry extracts from the leaves of *Juglans regia*, *O. europaea*, *Urtica dioica*, and *Atriplex*

halimus was evaluated here using *in vivo* and *in vitro* test systems. No sign of toxic effects were seen in cultured human fibroblasts treated with increasing concentrations of the mixture. Similar observations were seen in *in vivo* studies using rats (LD_{50}: 25 g/kg). Antidiabetic effects were evidenced by the augmentation of glucose uptake by yeast cells and by inhibition of glucose intestinal-absorption in a rat gut-segment. Furthermore, treatment with Glucolevel of streptozotocin-induced type 2 diabetes mellitus rats for 2–3 weeks showed a significant reduction in glucose levels to normal levels. In addition, the glucose levels were tested in 16 human volunteers with recent onset of type 2 diabetes mellitus who received Glucolevel tablets 1×3 daily for a period of 4 weeks. Within the first week of Glucolevel consumption, baseline glucose levels were significantly reduced from 290 ± 40 to 210 ± 20 mg/dL. At baseline, a subgroup of 11 of these subjects had glucose levels below 300 mg% and the other subgroup had levels $\geq$300 mg%. Clinically acceptable glucose levels were achieved during the 2–3 week of therapy in the former subgroup and during the 4th week of therapy in the latter subgroup. No side effect was reported. In addition, significant reductions in hemoglobin A1c values were found in six patients treated with Glucolevel. Results obtained in the present study demonstrate safety, tolerability, and efficacy of such herbal combination of the four plants that seem to act differently but synergistically to regulate glucose-homeostasis [41].

8.3.2.7 Anticancer Properties Epidemiological studies provide robust evidence for a protective effect of the Mediterranean diet against cardiovascular disease and cancer. These findings prompted scientists to search Mediterranean flora as a rich source of bioactive phytochemicals with a potential to evolve into preventive and possibly therapeutic agents. Many epidemiological evidences suggest that people who consume the olive oil-rich diet have a lower incidence of certain cancers, including breast, skin, and colon. The anticancer properties of olive leaf and oil are discussed in details in Chapter 12. In brief, the lower incidence of certain cancers is most likely associated with the antioxidant activity of active ingredients of the olive oil. Oxidative stress has been shown to contribute to cancer development, and antioxidants are believed to reduce the risk of mutagenesis and carcinogenesis. Hydroxytyrosol has been found to be capable of protecting cells from hydrogen peroxide damage and DNA from peroxynitrite-induced damage, blocking cell cycle progression at the G1 phase, and inducing apoptosis. *In vivo* and *in vitro* studies on the activity of oleuropein have found, in addition to antioxidant properties, it has antiangiogenic action and inhibits cell growth, motility, and invasiveness. Oleuropein has also been found to cause cell rounding, which disrupts the cell actin cytoskeleton. Oleuropein also affects and disrupts purified actin filaments, providing direct antitumor effects due to cell disruption. In *in vivo* animal studies, rapid tumor regression was observed when mice were given 1% oleuropein in drinking water. Saturated animal fats and polyunsaturated plant fats in the diet have been implicated in colon, breast, prostate, and ovarian cancers. The substitution of olive oil in the Mediterranean diet may explain its apparent cancer-protective effect and accentuate the importance of the type, rather than the amount, of fat consumed. A recent study has evaluated the antioxidant potency and antiproliferative activity against cancer and

endothelial cells of water and methanol olive leaves extracts. Olive-leaf crude extracts were found to inhibit proliferation of cell from a human breast adenocarcinoma, cells from human urinary bladder carcinoma (T-24), and cells from bovine brain capillary endothelial (BBCE) [28,32,42–44].

8.3.2.8 Antimicrobial Activity As aforementioned, *O. europaea* preparations are used in the Greco-Arab and Islamic medicine in a variety of diseases, including skin infections. *O. europaea* extracts and some of its pure compounds have shown antimicrobial activity *in vitro*. *O. europaea* leaf extracts and active compounds have been found to exhibit effective antimicrobial properties against a variety of microbes, including and *S. aureus*, *Klebsiella pneumonia*, *Salmonella typhimurium*, *Vibrio parahaemolyticus*, and *E. coli*. Indicating that leaf's extracts could be considered as antimicrobial agent for the treatment of intestinal or respiratory tract infections. Oleuropein is usually associated with antimicrobial properties of *O. europaea* leaf. It has also been reported to directly stimulate macrophage activation in *in vitro* studies. Hydroxytyrosol demonstrated broader antimicrobial activity than oleuropein and is comparable to ampicillin and erythromycin in spectrum and potency. *In vitro* studies have showed the antimicrobial activity of hydroxytyrosol, tyrosol, and oleuropein against several strains of bacteria implicated in intestinal and respiratory infections. Hydroxytyrosol and oleuropein have antimicrobial action against both laboratory and patient-derived clinical bacterial strains, with slightly greater activity against laboratory strains [28,32].

8.4 *Hypericum triquetrifolium*, WAVY LEAF ST JOHN'S WORT (*DATHI*)

Hypericum triquetrifolium, wavy leaf St John's wort or tangled hypericum, is native to Eastern Europe and the Mediterranean area. It is a perennial herb of the Hypericaceae, growing to 45 cm high with, as its name suggests, intertwining and tangled branches. Herbal medicines containing *H. triquetrifolium* have been used in traditional Greco-Arab herbal medicine to treat inflammatory diseases. The classic Arabic name for this plant species is *Dathi* or *Nabtat Yohanna* (Figure 8.3). Unfortunately, this plant is no longer used within the practitioner communities in Palestine. This fact reflects an extinction process of important elements of the Arab herbal medicine heritage [3,31,45].

8.4.1 Pharmacological Properties

8.4.1.1 Anti-Inflammatory Properties According Greco-Arab and Islamic medicine and recent *in vivo* and *in vitro* studies, *H. triquetrifolium* extract exhibit anti-inflammatory properties. We have explored the anti-inflammatory mechanism of *H. triquetrifolium* in cells from human monocyte cell line (THP-1). We measured the expression and release of proinflammatory cytokines tumor necrosis factor-α (TNF-α) and interleukine 6 (IL-6), and the iNOS. *H. triquetrifolium* inhibited the

FIGURE 8.3 *Hypericum triquetrifolium*, wavy leaf St John's wort (*Dathi*). (*See the color version of this figure in Color Plates section.*)

production of NO and TNF-α, and the expression of iNOS and TNF-α, but not of IL-6. Another *in vivo* study evaluated anti-inflammatory effect of *H. triquetrifolium* in a rat model of carrageenan-induced inflammation. Male Wistar rats were treated intraperitoneally with dimethylsulphoxide (DMSO) (as control group) and *H. triquetrifolium* extract 30 min before carrageenan injection. The intraplantar injection of carrageenan caused a time-dependent paw edema in the rat although saline injection caused no swelling. Intraperitoneal administration of *H. triquetrifolium* extract (25, 50, 60 mg/kg) inhibited paw swelling dose-dependently 2 h after carrageenan injection, indicating that *H. triquetrifolium* extract may exert an anti-inflammatory effect in rats [46,47].

8.4.1.2 Antioxidant Activity The principle medicinal secondary metabolites present in *Hypericum* species are thought to be naphthodianthrones hypericin and pseudohypericin. A recent study has investigated the antioxidative potential of ethanol extracts of *H. triquetrifolium* using diphenyl-picrylhydrazyl (DPPH), metal chelating, reducing power, hydroxyl radical, total antioxidant activity, and lipid peroxidation inhibition assays. Extracts were found to be highly active in the DPPH radical scavenging assay. The IC_{50} values of *H. triquetrifolium* in the DPPH radical scavenging assay were 39 μg/mL. The amounts of total phenolic compounds were also determined, and total phenolic content of 1 mg *H. triquetrifolium* were equivalent to 267 μg gallic acid. Metal chelating ability was found to be low compared with EDTA. Extracts of *H. triquetrifolium* exhibited a high reducing power, suggesting that extracts had strong electron-donating capacity. The degradation of deoxyribose by hydroxyl radicals is inhibited by *H. triquetrifolium* extracts, acting mainly by scavenging hydroxyl radicals rather than as chelators of iron ions. Total antioxidant

activity of ethanol extracts of *H. triquetrifolium* was tested by using ferric thiocyanate (FTC) and thiobarbituric acid (TBA) methods. Antioxidative activities of the extracts were found to be comparable with vitamin E. Moreover, extracts showed notable capacity to suppress Fe^{2+}-induced lipid peroxidation in rat brain homogenate. These results indicate that ethanol extracts of *H. triquetrifolium* are a potential source of natural antioxidants [47].

8.5 *Urtica dioica*, STINGING NETTLE (*QUERAIS*)

U. dioica, (The local species is *U. pilulifera*) commonly known as stinging nettle, is an herbaceous perennial flowering plant. The leaves and stems of *U. dioica* are very hairy with both, nonstinging and stinging hairs, whose tips come off when touched, transforming the hair into a needle that will inject several chemicals acetylcholine, histamine, serotonin, and possibly formic acid. This mixture of chemical compounds causes a sting from which the species derives its common name.

8.5.1 Traditional Uses

U. dioica herbs are widely used in Greco-Arab medicine, commonly to treat stomachache, rheumatic pain, colds and cough, and liver insufficiency. It is also used as a hypotensive and anti-inflammatory agent (Figure 8.4).

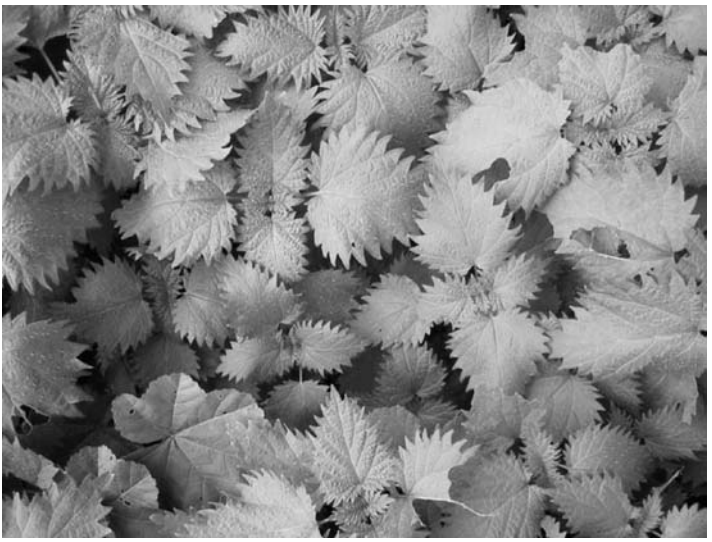

FIGURE 8.4 *Urtica dioica*, stinging nettle (*Querais*). (*See the color version of this figure in Color Plates section.*)

8.5.2 Pharmacological Properties

It is known in traditional therapy that *U. dioica* has a hypotensive and anti-inflammatory effects. Some other actions of this plant have also been reported such as antioxidant, antidiabetic, and stimulation of proliferation of human lymphocytes. The effects of the nettle are also evoked in the therapy of prostatic hyperplasia and this plant has been used in the traditional therapy of hypertension.

8.5.2.1 Anti-Inflammatory Effects Rheumatoid arthritis is an autoimmune disease characterized by chronic inflammation, hyperproliferation of the synovial lining and cartilage destruction. Cytokines, in particular TNF-α, are elevated in the synovial fluid and presumably involved in the disease process by upregulation of a multitude of inflammatory mediators. The success of anti-TNF antibodies in clinical trials underlines that TNF-α is a major pathogenic factor in rheumatoid diseases. Activation of transcription factor NF-κB is elevated in several chronic inflammatory diseases and is responsible for the enhanced expression of many proinflammatory gene products. Extracts from leaves of *U. dioica* are known to exert anti-inflammatory effects in rheumatoid arthritis, most likely through inhibition of NF-κB activation. An inhibitory effect was observed in response to several stimuli, suggesting that *U. dioica* extracts suppressed a common NF-κB pathway. Inhibition of NF-κB activation by *U. dioica* extracts was not mediated by a direct modification of DNA binding, but rather by preventing degradation of its inhibitory subunit IκB-α. These results suggest that part of the anti-inflammatory effect of *Urtica* extract may be ascribed to its inhibitory effect on NF-κB activation. Other studies indicate that aqueous *U. dioica* extract stimulated the proliferation of T-lymphocytes and suppressed NO production in lipopolysaccharide-stimulated macrophages without affecting cell viability [48].

8.5.2.2 Antioxidant Activity *U. dioica* extracts have a powerful antioxidant activity. The antioxidant properties of water extract of *U. dioica* were evaluated using different antioxidant tests, including reducing power, free radical scavenging, superoxide anion radical scavenging, hydrogen peroxide scavenging, and metal chelating activities. *U. dioica* extract (250 μg/mL) totally inhibited peroxidation of linoleic acid emulsion [49].

8.5.2.3 Antidiabetic The blood glucose lowering effect of *U. dioica* as a medicinal plant has been noted in old writings such as those of Avicenna. Recently, there have also been other investigators that indicated the hypoglycemic effect of *U. dioica*. But so far, the mechanism of this effect has not been deduced. In a recent study, islets of Langerhans have been exposed to several fractions of extracts of *U. dioica*. The active ingredient fraction named F_1 caused a marked increase in insulin secretion. A simultaneous assay of glucose showed that the increase in insulin level was associated with a decrease in glucose level. Furthermore, the active component of *U. dioica* was found to increase the insulin content of blood sera in normal and streptozotocin diabetic rats that were injected intraperitoneally (i.p.) with the active ingredient of the extract. Other *in vivo* studies indicate that not only an increase in

insulin level of blood sera was observed in rats after 30 min from the initial point of injection but a simultaneous decrease of blood sugar was detected when similar sera was tested for glucose. The increase in insulin level was six times during the 120 min of our determination. The decrease in blood sugar was found to be similar both in the level and time of initiation. The results show that the blood lowering effect of the extract was due to the enhancement of insulin secretion by islets of Langerhans [50].

8.6 *Ferula asafoetida*, DEVIL'S DUNK (*ANDUJAN, HILTIT OR ZALLOUH*)

This plant is native to central Asia (Iran and Afghanistan) and it is held in great esteem among indigenous Indian medicine men. It is the sharp odor of this resin that is the cause for some of its strange names, such as Devil's Dung, Stinking Gum, Zallouh, and Giant Fennel. The name *asafoetida* is derived from the Latin word for "stinking." The roots are thick and pulpy and also yield a similar resin to that of the stems, it is said the roots look like "carrots." All parts of the plant have a distinctive stinky smell.

8.6.1 Traditional Uses

In Ayurvedic medicine, *asafoetida* is used to treat hysteria, nervous disorders, flatulence, flatulent colic, digestion, and spasmodic affections of the bowels. It is also used to treat pneumonia, bronchitis, and asthma as well. In Ayurvedic, Western, and Chinese medicine this resin is effective in treating worms and other intestinal parasites. *Asafoetida* has a reputation for expelling wind from the stomach and relieves stomach spasms. In Ayurvedic medicine, it is highly regarded as a condiment and medicinal remedy for various conditions. Traditional Chinese herbalists say this resin enters the liver, spleen, and stomach channels where it stimulates the intestinal, respiratory, and nervous systems. *Asafoetida* has digestive, sedative, stimulant, antispasmodic, expectorant, emmenagogue (promoting menstrual discharge), and vermifuge (expelling worms or other parasites in the intestines) properties.

Hiltit and Zallouh are the common name in the Middle East for the roots of the species *Ferula hermonis* growing on the slopes of Mount Hermon in the Syrian Golan Heights and has been used for centuries as a folk remedy to treat frigidity in women, and erectile and sexual dysfunction in men. This plant is botanically quite close to *Ferula communis*, the Giant Fennel. Ferula is the Latin name for "walking stick," a word mentioned in the Old Testament as the Hebrew name "kelech," in the context that its stem was used as a walking stick. There are several species of Ferula that grow throughout the world including the species *F. asafoetida*. This plant is native to central Asia (Iran and Afghanistan), however it was well integrated in the Greco-Arab medicinal system and still employed in all Arab countries. According to the Greek herbalists, Dioscorides and Galen, this plant is used for the treatment of tiredness and impotence. The rich traditional knowledge of Greco-Arab medicine gives support to its use as a sexual tonic to encourage potency. Rhazes (841–926) reported that Indians use *F. asafoetida* as the main botanical aphrodisiac, several centuries before his time. Avicenna and Al-Antaki have also emphasized the aphrodisiac effect of *F. asafoetida*.

There is considerable confusion in the identification of aphrodisiac species of plants especially due to their extensive use as aphrodisiac agents, plant part used and relatively similar smell. They are called names such as "Heltit," "Andujan," "Kallch," "Aqir Qarha," or "Oud alkerach algabali." All the well-known traditional herbalists agree that these species are used to manage tiredness and impotence and they describe a unique method of preparation, which includes boiling of the roots to dryness sometimes with oil addition [51–54].

The roots of *F. asafoetida* produce the well known spice asafoetida used to flavor foods all over the world. The plant is approved for food use in both the European Union and the United States. The use of *F. asafoetida* seems thus to be without safety concerns as was confirmed in two clinical studies in India and in Germany.

8.6.1.1 Aphrodisiac Properties Based on the above-mentioned traditional knowledge from the Greco-Arab and Islamic herbal medicine, we examined the effects of extracts from *F. asafoetida* on male fertility and sexual functioning in rats and in man. Results obtained in our study showed that *F. asafoetida* extracts exhibit high levels of safety in both cultured human fibroblasts and in experimental studies on rats with a LD_{50} of 5 g/kg. Antioxidant properties were substantial both in rat liver cells and in human sperm cells at a concentration of 50 µg/mL. Experiments with rat arterial rings with and without their endothelial tissue revealed, that Masculine is a potent vasodilator due to an endothelia-mediated effect rather than a direct effect on smooth muscle cells. Episodes of penile erection were studied in two groups of rats and were significantly augmented in the extract-treated group. Furthermore, two groups of healthy young men were studied and followed for 3 months. *F. asafoetida* extracts were well tolerated by all men and no side effects were reported. Both groups were recruited from fertility clinics, the first group ($n = 60$) was recruited due to incomplete azospermia that was medically untreatable, and the second group ($n = 25$) was recruited due to erectile dysfunction and impotence of no treatable cause. Quantitative and qualitative improvements of sperm counts were reported after 2 months of treatment in 17% and 60%, in the first and second group, respectively. In addition, 60% of the second group reported remarkable improvements in both their libido and erectile function. In relation to possible mechanism of action, *F. asafoetida* extract seems to encourage endothelial cells to release nitric oxide, which stimulates the synthesis of cyclic guanosine monophosphate in the penile corpus cavernosum. A contributing role for an effect upon prostacycline synthesis seems possible. Extracts of asafoetida contain volatile oil, resin, and gum. The resinous constituents include asaresinol ferulate, free ferulic and umbellic acids as well as sesquiterpene coumarines identified as asa-fetidnol A and B. Asafoetida sesquiterpene coumarines may act similar to those present in *F. hermonis* sesquiterpenes (ferutinin, teferdin, and tenuferidine), which have been shown to have estrogenic activity and may contribute to its aphrodisiac activity. It also contains ferulic acid that is present in other plants such as *Angelica sinensis*, which is used for female tonic effects [54].

8.6.1.2 Other Pharmacological Properties The plant disclosed hypolipidemic properties in patients and was a useful treatment of irritable bowel syndrome,

with no side effects. Supportive action of *asafoetida* in the digestive process was also evidenced in animal studies suggesting the spice as a carminative that is able to stimulate pancreatic digestive enzymes.

8.7 *Trigonella foenum-graecum* L, FENUGREEK (*HILBE*)

Trigonella foenum-graecum (fenugreek) is a legume, which is extensively cultivated in India, North Africa, and the Mediterranean (Figure 8.5). It is a spice used in Indian cooking and commonly used herb in Ayurveda. Defatted seeds of fenugreek, which are rich in fiber, saponins, and protein, have been described in early Greek and Latin pharmacopoeias as antihyperglycemia. In addition to the seed, other parts of the herb have also been investigated. Therapeutic effects include delay of gastric emptying, slowing carbohydrate absorption, and inhibition of glucose transport from the fiber content, as well as increased erythrocyte insulin receptors and modulation of peripheral glucose utilization. Many studies in alloxan-rat models have shown modulated exocrine pancreatic secretion.

8.7.1 Traditional Uses

Most of the medicinal properties of *T. foenum-graecum* are found in the seeds, which have been used for thousands of years in Greco-Arab and Islamic medicine as well as in Indian and Chinese medicine. Fenugreek is another herb that was favored by the Prophet Mohammad (PBUH) and herbalists for thousands of years. It is also related in the collection of *Hadith* (statement by the Prophet Mohammad) that the Prophet visited one of his blessed companions, Sa'ad bin Abi Waqqass, who had

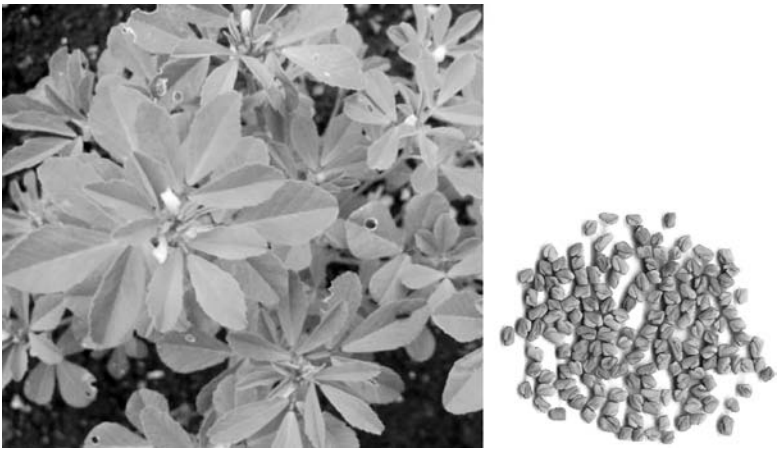

FIGURE 8.5 *Trigonella foenum-graecum*, fenugreek (*Hilbe*). (*See the color version of this figure in Color Plates section.*)

contracted an illness during his stay in Mecca, and then requested that a physician examine him. After a diagnosis was made, the Prophet (PBUH) said, "*He will be fine. Give him the soup of a concoction of dates and fenugreek*." In another *Hadith*, he said, "*If my community had only known what there is in fenugreek they would have paid its weight in gold*." Crushed or powdered, these seeds can be used externally and applied as poultices for boils, hives, ulcers, and eczema. Internally, the seeds have been used in traditional medicine to reduce blood sugar, increase lactation and treat pellagra, appetite loss, indigestion, dyspepsia, bronchitis, fever, hernia, impotence, vomiting, catarrh of the respiratory tract, and stomach ulcers. Fenugreek seed is also known to make women more buxom and treat hormonal imbalances [3,31,45,51–53].

8.7.2 Phytochemistry

T. foenum-graecum seed contains galactomannans, proteins high in lysine and tryptophan, lipids, pryridine-type alkaloids mostly trigonelline, choline, gentianine, carpaine, flavonoids (apigenin, luteolin, orientin, quercetin, vitexin, and isovitexin), free amino acids, calcium and iron, saponins, glycosides yielding steroidal sapogenins on hydrolysis (diosgenin, yamogenin, tigogenin, neotigogenin), cholesterol and sitosterol, vitamins A, B1, C, nicotinic acid, and volatile oils [55].

8.7.3 Pharmacological Properties

According to the German Commission E, fenugreek seeds have secretolytic (antimucous) and mild antiseptic properties. The British Herbal Pharmacopoeia states that the seeds have hypoglycemic actions. Scientific studies have shown that for adults, taking one-half teaspoon of fenugreek seeds with water three times daily often produces a quick relief. Other reports indicate that fenugreek seeds have significant hypoglycemic effects in type 1 diabetes patients. Many animal studies have documented the same. Other studies established anti-inflammatory effects of the seeds and strong activity against abnormal growths [51–57].

8.7.3.1 Hypoglycemic Properties There are several clinical studies available for fenugreek in type 2 diabetes; however, most are noncontrolled, generally poorer-quality studies with small numbers, and from a single investigator group. Nonetheless, these trials, including a single trial in type 1 diabetes, have reported improved glycemic control using seed powder incorporated into unleavened bread. Another trial in healthy volunteers ($n = 38$) incorporated several short-term randomized crossover experiments administering different preparations of fenugreek. In these series of trials, whole raw seeds, extracted seed powder, gum isolate of seeds, and cooked whole seeds seemed to decrease postprandial glucose levels. Other studies have followed patients on fenugreek for up to 6 months with reported benefits in glycemic control. No adverse effects were reported in these trials [55–57].

8.8 *Melissa officinalis*, LEMON BALM (*MELISSA*)

Lemon balm (*Melissa officinalis*) is a perennial herb in the mint family Lamiaceae, native to the Mediterranean region and Southern Europe. It grows 70–150 cm tall. The leaves have a gentle lemon scent, related to mint. At the end of the summer, little white flowers full of nectar appear. These attract bees, hence the genus name *Melissa* (Greek for "honey bee"). Its flavor comes from the terpenes citronellal, citronellol, citral, and geranio (Figure 8.6).

8.8.1 Traditional Uses

The therapeutical use of *M. officinalis* dates back into ancient times. Dioscorides used balm for dog and scorpion bites and also in wine to relieve pains. The Greco-Arab physicians used the herb to treat heart disorders. In the middle ages, a sprig of lemon balm was said to staunch the blood of a sword wound and to help relieve an earache, toothache, pregnancy sickness, fix crooked necks, and prevent baldness. In more recent history, *M. officinalis* was used against catarrh, fevers, and flatulence problems. People realized that the oil makes for great surgical dressing because it kills off germs and while the oil dries, it seals up wounds. Physicians used the herb to entice sweat for fevers and regulating menstrual cycles; though, lemon balm was not as preferred as other mints because it contains less volatile oil. Pharmacological properties of this plant on the nervous system are documented in medicinal history that extending back

FIGURE 8.6 *Melissa officinalis*, lemon balm (*Melissa*). (*See the color version of this figure in Color Plates section.*)

to the "*Materia Medica*" in approximately 50–80 BC. *M. officinalis* gained widespread usage throughout Europe by the middle ages, with medicinal use during this early epoch including a recommendation by Paracelsus (1493–1541) that balm would completely revivify a man, and as an indication for all complaints supposed to proceed from a disordered state of the nervous system. Several herbal apothecaries of the time also attributed balm tea not only with general beneficial effects upon the brain but also specific memory improvements [3,31,58].

8.8.2 Phytochemistry

M. officinalis leaves contain no more than 0.1% of essential oil, which is of complex and variable composition. Constituents that have been identified include a number of monoterpenoid aldehydes (including citronellal, neral, and geranial), flavonoids, and polyphenolic compounds, most notably rosmarinic acid and monoterpene glycosides. Among the compounds identified more than 50 aroma compounds are citronellal, β-caryophyllene, neral, geranial, citronellol and geraniol, these amount to about 70% of the oil [59,60].

8.8.3 Pharmacological Uses

Currently, *M. officinalis* is still widely used in medicine. The herb works as a useful astringent to cleanse pores for people with acne. Furthermore, a recent study shows the herb has a sedative effect on the central nervous system of mice, which explains its use as a type of valium by several cultures. *M. officinalis* oil has also been found to reduce bacteria and viruses. When the herb is combined with St John's wort or Echinacea, a topical application of the mixture is effective in treating cold sores of the Herpes simplex virus. The herb also inhibits thyroid functioning so it works to combat hyperthyroidism and as a mood enhancer for depressed patients. While studies are still inconclusive, there is very strong evidence to suggest that lemon balm is also effective in decreasing symptoms of Alzheimer's and dementia such as memory loss. There are no known side effects or symptoms of toxicity from taking lemon balm.

8.8.3.1 Cognitive Function Contemporary reports suggest that, in addition to possessing spasmolytic and antibacterial properties, *M. officinalis* can modulate a number of behavioral measures, with indications including administration as a mild sedative, in disturbed sleep, and in the attenuation of the symptoms of nervous disorders, including the reduction of excitability, anxiety, and stress. In keeping with its long history of safe usage, no adverse side effects have so far been reported for the herb. *M. officinalis* is predominantly sold in combination with other herbs. It is most often combined with *Valeriana officinalis*, and this combination has been reported to have as positive an effect on the sleep quality of poor sleepers as 0.125 mg of Triazolam. Similarly, a placebo-controlled trial found significant improvements in the quality of sleep during 30 days of treatment with 600 mg/day of a *Melissa–Valeriana* combination.

8.8.3.2 Calming Effects Several studies suggest specific sedative, antiagitation, and "calming" effects of *M. officinalis* alone. These include, in mice, a reduction in spontaneous movement following administration of both the whole volatile oil of *M. officinalis* and individual isolated terpenes of the extract, and reductions in behavioral activity in exploratory and aversive situations following administration of a hydro-alcoholic extract of *M. officinalis*. In the latter study, the extract also increased pentobarbital-induced sleep parameters. A recent double-blind, placebo-controlled study examined the effect of *M. officinalis* essential oil aromatherapy on ratings of agitation and quality of life of 71 patients suffering from severe dementia. Following 4 weeks of treatment, patients in the active treatment group were rated, in comparison to the placebo group, as being less agitated, less socially withdrawn, and as engaging in more time spent in constructive activities in comparison to the placebo group. Behavioral consequences such as these may be attributed to a number of possible active components of the dried leaf and essential oil of the herb.

8.8.3.3 Alzheimer's Disease It has previously been suggested, on the basis of a retrospective review of the historical role of a number of European plant species in the enhancement of memory, that *M. officinalis* and *Salvia officinalis*, another plant in the Labiatae family, might potentially provide novel natural treatments for Alzheimer's disease. This approach has generated research showing that *M. officinalis* exhibits central nervous system acetylcholine receptor activity, including nicotinic and muscarinic binding properties in human cerebral cortex tissue. The cholinergic receptor-binding properties in particular suggest the possibility that *M. officinalis* may provide a potential treatment for the cholinergic dysfunction in Alzheimer's disease, while contemporary use of the herb as a mild sedative may provide a concomitant beneficial effect on the severe agitation often associated with severe dementia. Additionally, its antioxidant properties suggest that *M. officinalis* may also provide some protection against the putative etiological free radical damage in dementia. A first investigation of the possibility of modulation of cognitive performance and mood following oral administration of *M. officinalis* was recently reported. The acute dose (three separate doses plus placebo), multiple time-point (1, 2.5, 4, and 6 h postdose) experiment showed that the ingestion of single doses of a commercial *M. officinalis* extract by healthy young volunteers was associated with striking dose dependent impairments on a "Quality of Memory" measure derived by factor analysis from the Cognitive Drug Research (CDR) computerized assessment battery. More specifically, decrements were most pronounced for all the three doses utilized on two timed memory tasks (delayed word recognition and a spatial memory task). The overall pattern of results also indicated that, while the memory task decrements increased with dose, the lowest dose (300 mg) engendered increased "calmness" at the first two postdose testing sessions (1 and 2.5 h), and the middle dose (600 mg) led to improved performance on attention tasks. The highest dose, however, was not associated with any benefits, and led to the most pronounced decrements on the memory tasks along with reduced "alertness" at all postdose testing sessions. This pattern of results is broadly in line with the contemporary role of *M. officinalis* as a

calming agent and mild sedative, but it is disappointing in as much as it is not in keeping with beneficial modulation of cholinergic activity. However, an *in vitro* analysis conducted after the behavioral experiment showed that, unlike previous such investigations, the extract in question showed negligible displacement of [3H]-(*N*)-nicotine from nicotinic receptors, and comparatively low displacement of [3H]-(*N*)-scopolamine from muscarinic receptors. This leaves open the question of the cognitive and mood effects of a cholinergically active *M. officinalis* treatment, which ideally may engender increased calmness with concomitant improvements in cognitive performance [58–63].

8.8.3.4 Other Uses The crushed leaves, when rubbed on the skin, are used as a repellent for mosquitoes. Lemon balm is also used medicinally as an herbal tea, or in extract form. It is claimed to have antibacterial, antiviral properties.

8.9 *Salvia fruticosa*, COMMON SAGE (*MAIRAMIA*)

Salvia species (sage) belong to the Lamiaceae family. The genus name *Salvia* is derived from the Latin *salvare* meaning "to heal or to be safe and unharmed" referring to the therapeutic properties of some of the species. It has been used for centuries, especially by the Chinese to promote longevity and in Roman ceremonies as a sacred herb. Sage encompasses about 900 species, widespread throughout the world and includes several ornamental, culinary, and medicinal species (Figure 8.7).

FIGURE 8.7 *Salvia fruticosa*, common sage (*Mairamia*). (*See the color version of this figure in Color Plates section.*)

8.9.1 Traditional Uses

The positive benefits of *S. officinalis* to health are reputed throughout Ancient Romans times and the Middle Ages. A quote such as: "*Cur moriatur homo cui Salvia crescit in horto?*"—"Why should a man die whilst sage grows in his garden?" summarizes the impact of this sage on that society at the time. Apart from general scientific curiosity, understanding the chemistry of *S. officinalis* is important for several commercial industries because these plants are utilized for flavoring food, used in cosmetic formulations, aromatherapy, and insecticides. Most *Salvia* species are inherently linked to local traditional medicine systems in their country of origin. *S. officinalis* is used to treat various conditions such as treating bronchial infections, colds, and coughs. Furthermore, *S. officinalis* is traditionally used to treat digestive disorders such as dyspepsia flatulence, poor digestion and bloating, to reduce excessive perspiration, for example, during the menopause. It is also used as a gargle or mouthwash to treat inflammations of the mouth or throat mucosa, such as pharyngitis, tonsillitis, stomatitis, gingivitis and glossitis [3,31,45].

8.9.2 Phytochemistry

The strongest active constituents of sage are within its essential oil, which contains cineole, borneol, and thujone. Sage leaf contains tannic acid, oleic acid, ursonic acid, ursolic acid, cornsole, cornsolic acid, fumaric acid, chlorogenic acid, caffeic acid, niacin, nicotinamide, flavones, flavonoid glycosides, and estrogenic substances.

8.9.3 Pharmacological Uses

Therapeutic potential and toxicological properties of *S. officinalis* leaf have been extensively studied. *S. officinalis* is considered to be antioxidant, anti-inflammatory, antimicrobial, carminative, weakly spasmolytic, astringent, and antihidrotic (inhibits perspiration). *S. officinalis* is also considered to be a stimulant and tonic to the digestion and nervous system. Clinical studies have demonstrated beneficial therapeutic properties of *S. officinalis* leaf on cognitive performance and mood in healthy young volunteers and cognitive function in elderly patients with mild to moderate Alzheimer's disease [64–66].

8.9.3.1 Antioxidant Activity *In vitro* studies indicate that *S. officinalis* leaf extracts exhibit strong antioxidant activity, largely attributable to various phenolic constituents including phenolic diterpenes such as carnosol and hydroxycinnamic acid derivatives, notably rosmarinic acid. In a carotene-bleaching test, the antioxidative activity of a dry acetone extract from *S. officinalis* leaf was found to be similar to that of the synthetic antioxidant butylated hydroxytoluene. Lipid peroxidation in both enzyme-dependent and enzyme-independent test systems was inhibited more effectively by a dry methanolic extract from aerial parts of sage leaf than by α-tocopheryl acid succinate (as a positive control). The antioxidant activity was attributed mainly to phenolic compounds, rosmarinic acid being the main contributor due to its high concentration in the extract [67,68].

8.9.3.2 Cognitive Performance and Mood in Healthy Young Volunteers

In a double-blind, placebo-controlled study, 30 healthy young volunteers (mean age 24 years) was given, on three separate days at 7-day intervals 300 mg or 600 mg of dried *S. officinalis* leaf, or placebo. On each test day, predose and at 1 h and 4 h postdose, each participant underwent mood assessment, requiring completion of Bond–Lader mood scales and the State Trait Anxiety Inventory before and after a 20 min performance on the Defined Intensity Stress Simulator (DISS) computerized multitasking battery. The last comprised a set of four cognitive and psychomotor tasks presented concurrently on a split (quartered) screen layout, to which responses had to be made with an external mouse, giving attention simultaneously to all four tasks while monitoring the cumulative score (reflecting accuracy and speed of response) in the center of the screen. The DISS engenders increases in self-ratings of negative mood, arousal, and stress-related physiological responses. Results obtained indicate that single doses of *S. officinalis* leaf can improve cognitive performance and mood in healthy young participants, although the lower dose (300 mg) appeared to fall somewhat below the level required for beneficial effects. It is possible that inhibition of cholinesterases by *S. officinalis* leaf (demonstrated only *in vitro*) could be involved in the mechanism causing these effects [69].

8.9.3.3 Cognitive Function in Elderly Patients with Mild to Moderate Alzheimer's Disease

In a randomized, double-blind, placebo-controlled clinical study, patients aged 65–80 years of age with a diagnosis of mild to moderate dementia and probable Alzheimer's disease were treated for 4 months with 60 drops/day of either a *S. officinalis* leaf liquid extract or a placebo liquid. Compared with the placebo group, patients in the sage leaf group experienced significant benefits in cognitive function by the end of treatment, as indicated by improved scores in the Clinical Dementia Rating and the Alzheimer's disease Assessment Scale. Within the limitations of a fairly small number of patients and short period of follow-up, the results suggested efficacy of the *S. officinalis* leaf extract in the management of mild to moderate Alzheimer's disease [70].

8.9.3.4 Antimicrobial Properties

S. officinalis oil has strong antimicrobial properties, attributed principally to the presence of thujones. Inhibitory activity of the oil against Gram-positive and Gram-negative bacteria and against a range of fungi has been demonstrated. Antiviral activity (against vesicular stomatitis virus) was exhibited by a methanolic extract from sage aerial parts and two phenolic diterpene constituents (safficinolide and sageone). *S. officinalis* oil had only a relatively weak spasmolytic effect on isolated guinea pig tracheal and ileal smooth muscle in comparison with oils from other Labiatae such as lemon balm or thyme [71,72].

8.9.4 Potential Toxicity

S. officinalis leaf has been consumed as a culinary herb for centuries without toxic effects. However, a degree of caution is necessary with larger amounts due to the presence of α-thujone, β-thujone, and camphor in the essential oil. The pure essential

oil should never be used. *S. officinalis* leaf preparations should be avoided during pregnancy and lactation. In a randomized clinical study, 15 elderly patients treated with 60 drops/day of a sage leaf liquid extract for 4 months experienced slightly more mild gastrointestinal complaints than those receiving placebo, but the differences were not significant. The oral LD_{50} of the essential oil in rats was found to be 2.6 g/kg. α-Thujone, which is more toxic than β-thujone and is present as a higher proportion of the essential oil and is a neurotox. Its intraperitoneal LD_{50} in mice is about 45 mg/kg, while 60 mg/kg causes a tonic convulsion leading to death within 1 min. The mechanism of α-thujone neurotoxicity has been shown to be a modulation of the γ-aminobutyric acid (GABA) type A receptor. However, α-thujone is rapidly detoxified in mice by conversion to less toxic metabolites. In tests for mutagenicity neither ethanolic extracts nor the essential oil from sage leaf showed any mutagenic potential [73–75].

8.10 *Portulaca oleracea*, PURSLANE (*FARFAHENA*)

Portulaca oleracea, purslane, is an annual succulent in the family Portulacaceae, which can reach 40 cm in height (Figure 8.8). About 40 varieties are currently cultivated. It has an extensive old-world distribution extending from North Africa through the Middle East and the Indian Subcontinent to Malesia and Australasia.

FIGURE 8.8 *Portulaca oleracea*, purslane (*Farfahena*). (*See the color version of this figure in Color Plates section.*)

8.10.1 Traditional Uses

P. oleracea is used traditionally in the treatment of a variety of conditions that include headache, painful urination, stomachache, enteritis, mastitis, lack of milk flow in nursing mothers, and in postpartum bleeding. Externally it is used to treat burns, earache, ulcers, pruritis (itching skin), insect stings, inflammations, skin sores, eczema, and abscesses. These conditions are usually treated with the fresh herb used as a poultice or the expressed juice is used. *P. oleracea* is eaten as a salad and vegetable across the world.

Psoralens as repigmenting agents for vitiligo were described as early as 1400 BC. The Indian sacred book Atharva Veda mentioned the effect of the plant on the skin color. Ancient Egyptians identified *Psoralea corylifolia* and *Amni majus* as psoralen, and they used it for vitiligo. Psoralens are furocoumarin compounds, photodynamically active drugs that are capable of absorbing radiant energy.

8.10.2 Phytochemistry

P. oleracea contains large amounts of L-norepinephrine (L-noradrenaline; 0.25% in fresh herb), a neurohormone that has vasopressor and antihypotensive activities and reduces hemorrhage at the tissue level. It also contains numerous common nutrients, including: vitamins (A, B_1, B_2, C, niacinamide, nicotinic acid, α-tocopherol, β-carotene, etc.); minerals (especially potassium); fatty acids, especially omega-3 acids whose concentration in *P. oleracea* is the highest found in leafy vegetables; glutathione; glutamic acid; and aspartic acid. Other constituents include calcium oxalate, malic and citric acids, dopamine and dopa, coumarins, flavonoids, and alkaloids. Recent research has shown that the plant also contains saponins [76].

8.10.3 Pharmacological Uses

An aqueous extract of purslane was shown to have skeletal muscle relaxant effects both *in vitro* and *in vivo*; it also relaxed guinea pig gastric fundus, taenia coli, and rabbit jejunum as well as contracted the rabbit aorta and raised blood pressure. Topical application of the aqueous extract onto the skin was effective in relieving muscle spasms. Other effects include antibacterial and antifungal, wound healing, anti-inflammatory, uterine stimulant, and diuretic in rabbits. Although norepinephrine may account for some pharmacologic activities, the active principle for most of the biological activities and medicinal properties of purslane are still unidentified [76].

8.11 *Ammi visnaga*, KHELLA (*KHELLA*)

Ammi visnaga is a species of flowering plant in the carrot family known by many common names, including bisnaga, toothpick weed, and khella (Figure 8.9). It is native to Europe, Asia, and North Africa. *A. visnaga* is an annual or biennial herb

FIGURE 8.9 *Ammi visnaga*, khella (*Khella*). (*See the color version of this figure in Color Plates section.*)

growing from a taproot erect to a maximum height near 80 cm. Leaves are up to 20 cm long and generally oval to triangular in shape but dissected into many small linear to lance-shaped segments. *A. visnaga* and other *Ammi* species are sources of khellin, a diuretic extract. Khella was used in Ancient Egypt as an herbal remedy for renal colic.

8.11.1 Traditional Uses

The whole fruit has traditionally been used to treat respiratory system diseases such as asthma, bronchitis, emphysema, and whooping cough, as well as cardiovascular disorders, premenstrual syndrome, liver and gallbladder disorders and to stimulate diuresis. Its purported effect is related to its antispasmodic action on smaller bronchial muscles, coronary arteries, and urinary tract tubules. *A. visnaga* may vasodilate the coronary arteries, which increases the blood supply to the myocardium, and as a result, can be used to treat mild forms of angina. It is also used to treat problems associated with spasms and constriction of the gallbladder and bile duct and facilitates discharge of kidney stones and gallstones.

8.11.2 Phytochemistry

A. visnaga contains coumarins and furocoumarins (psoralens), the most important of which are khellin and visnagin. Khellin is present in fruits in a concentration of approximately 1% and visnagin in a concentration of approximately 0.3%. The fruits contain also xanthotoxin (methoxsalen) and ammidin (imperatorin), furocoumarins. In addition, marmesin, ammoidin, and ammidin have been found in the fruits [76].

8.11.3 Pharmacological Uses

8.11.3.1 Vasodilatory Properties Acting at multiple sites, visnagin inhibited induced contractile responses in rat vascular smooth muscle. Similarly, visnadin demonstrated peripheral and coronary vasodilatory activities in isolated rat vascular smooth muscle. The clinical and therapeutic effectiveness of khellin, with respect to the coronary, respiratory, and urologic indications, have been demonstrated in many experiments. Current khella indications include mild angina complaints, postoperative treatment of urinary calculus, and supportive treatment of mild forms of obstructive pulmonary diseases. Khellin is commercially available in several multi-ingredient European proprietary preparations for oral and parenteral administration as a vasodilator. It is used in the management of bronchial asthma and angina pectoris. The structure of cromolyn sodium, used in the management of allergic respiratory illness, was based on components derived from *A. visnaga*. Lipophilic extracts from the plant, including the active components visnadin, khellin, and visnagin, exhibited calcium channel-blocking actions, with visnadin being the most active [77,78].

8.11.3.2 Antimicrobial Properties *A. visnaga* extract showed marked antimicrobial activity against Gram-positive bacteria and *Candida* species. Constituent khellin from *Ammi* fruit parts inhibited the mutagenicity of certain promutagens in *S. typhimurium* [79].

8.11.3.3 Vitiligo Interest in khellin as an adjunct to ultraviolet (UV) light therapy in the treatment of vitiligo is based on the structural similarity between khellin and the psoralens. Success has been reported using oral and topical khellin in clinical studies, and a mechanism of action has been studied in cultured human cells [80]. Studies using oral (100 mg) or topical khellin (0.005% encapsulated in liposomes and 5% khellin in water/oil emulsion) plus UVA therapy achieved success rates comparable to those seen with standard psoralen plus UVA (PUVA) therapy. In addition, topical therapy with the khellin–UVA combination not only required longer duration to achieve treatment goals but also demonstrated fewer side effects. Follow-up (mean, 40 months) of patients who received oral khellin showed no long-term side effects [81,82].

8.12 *Silybum marianum*, MILK THISTLE (*KHURFAISH*)

S. marianum is a flowering plant of the Asteraceae. It is native to the Mediterranean area. The plant is a stout thistle, growing one to three meters tall in rocky soils, with

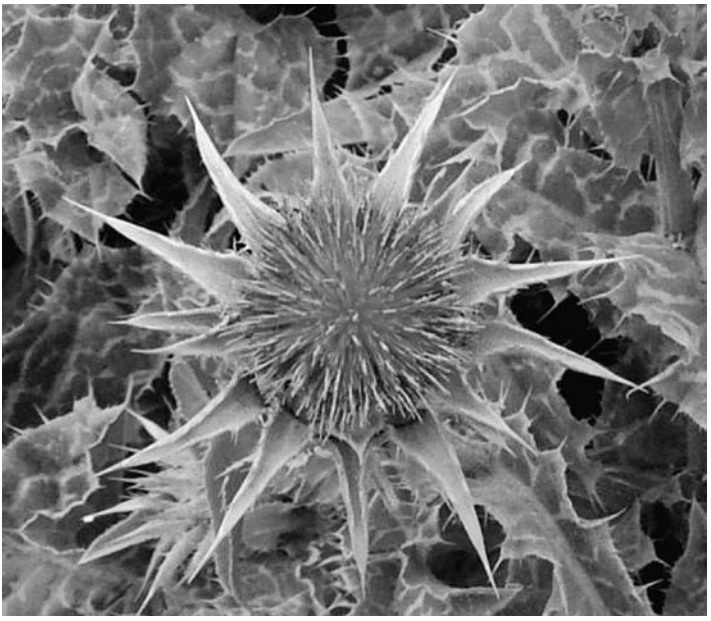

FIGURE 8.10 *Silybum marianum*, milk thistle (*Khurfaish*). (*See the color version of this figure in Color Plates section.*)

large purple flowering heads (Figure 8.10). The name "milk thistle" derives from two features of the leaves: they are mottled with splashes of white and they contain a milky sap. However, it is the seeds of this plant that have been used for over 2000 years to treat liver disease and protect the liver against toxins. *S. marianum* is currently the most well scientifically investigated medicinal plant in the treatment of liver disease.

8.12.1 Traditional Uses

S. marianum has a long history of use in the Greco-Arab and Islamic medicine as well as in the European folk medicine as a liver tonic. *Silybum* is cited as one of the oldest known herbal medicines. Dioscorides first described the plant. In Roman times, Pliny the Elder (77 AD), a noted naturalist, described the medicinal uses of this plant, indicating it was "excellent for carrying off bile." Culpeper (1650) wrote of its effectiveness in removing obstructions of the liver and spleen. But it has been relatively recent clinical research, especially in Germany, which has brought the use of *Silybum* to prominence in the treatment of chronic or acute liver disease, as well as protecting the liver against toxicity.

8.12.2 Phytochemistry

The active compounds of *S. marianum* are flavonolignans including silybin, silidianin, and silichristine, collectively known as silymarin. Silybin is the component

with the greatest degree of biological activity, and *S. marianum* extracts are usually standardized to contain 70–80% silybin. Silymarin is found in the entire plant but is concentrated in the fruit and seeds. The seeds also contain betaine (a proven hepatoprotector) and essential fatty acids, which may contribute to silymarin's anti-inflammatory effect. Other components include tyramine, histamine, essential oils, lipids, sugars, alkaloids, saponins, mucilages, organic acid, vitamins C, E, and K, and other flavonoids such as quercitin, taxifolin, and dehydrokaempferol.

Silymarin is not water-soluble and so cannot be taken as a tea. It is typically administered as an encapsulated standardized extract. The absorption with oral administration is rather low. The peak plasma levels after an oral dose are achieved in 4–6 h in both animals and humans. Silymarin is cleared from the body predominantly via the bile and to a lesser extent the kidney. The clearance half-life is 6–8 h [83].

8.12.3 Pharmacological Uses

Silymarin from *S. marianum* has shown a protective effect against many types of chemical toxins, as well as alcohol. An extract of milk thistle is used to improve liver function, protect against liver damage and enhance regeneration of damaged liver cells. Clinical studies have confirmed the usefulness of standardized milk thistle extracts in cases of cirrhosis, toxic liver, and other chronic liver conditions [3,31,45].

8.12.3.1 Antitoxic Properties The most remarkable therapeutic properties of silymarin are its antitoxic effects in the treatment of *Amanita* mushroom poisoning. The *Amanita* genus is widespread in Europe and North America, and mushroom collectors consider several species choice items. Unfortunately, this mushroom contains two extremely powerful hepatotoxins, amanitin (LD_{50} is 100 μg/kg body weight) and phalloidin. In mice, silymarin was 100% effective in preventing liver toxicity if given before or up to 10 min after *Amanita* toxin poisoning. Severe liver damage was avoided if silymarin was administered within 24 h. In a study with dogs none of the dogs died when given silymarin 5–24 h after ingesting an LD_{50} dose of *Amanita phalloides* (85 mg/kg). In comparison, untreated dogs experienced a mortality rate of 33%. Liver enzyme studies and liver biopsies in the controls and treated dogs demonstrated a significant hepatoprotective effect for the silymarin. The hepatoprotective effects of silymarin in humans after ingestion of *Amanita* toxins have been repeatedly demonstrated. In one series of 18 patients treated with silymarin, all patients survived except one particularly high-dose suicide. The authors concluded, "Administration of silymarin even up to 48 h after mushroom ingestion appears to be an effective measure to prevent severe liver damage in *A. phalloides* poisoning." In a 1995 study of 41 mushroom poisoning victims, none died in the group, which included silymarin in the treatment regimen. A 1996 report made the case that silymarin may be useful even 3 days posttoxification. A family of four poisoned by *Amanita* mushrooms was admitted to the hospital with severe liver damage. Although all were treated with standard therapy, there was a worsening of the clinical picture until the third day, when it was decided to add silybin dihemisuccinate intravenously

to the therapy. After the beginning of silybin administration the patients showed a favorable course with a rapid resolution of the clinical picture, although the prognosis appeared severe on the basis of hepatochemical examination results. A particularly dramatic case of a very severe accidental poisoning in a 7-year old girl resulted in her entering a hepatic coma. The authors reported the girl's survival was due in large part to treatment with silymarin in combination with high doses of G-penicillin [83].

8.12.3.2 Hepatoprotective Properties Many studies have demonstrated the beneficial hepatoprotective effects of treatment with silymarin. *S. marianum* and its derivatives have been used for centuries for the treatment of liver disease. Many studies have been published in scientific literature pertaining to the potential use of *S. marianum* or its derivatives for the treatment of alcoholic liver disease [83].

8.12.3.3 Alcoholic Liver Disease The metabolism of ethanol is primarily through conversion into acetaldehyde by three enzyme systems. These include catalase (CAT), alcohol dehydrogenases (ADHs), and the microsomal ethanol oxidizing system (MEOS). Acetaldehyde is more hepatotoxic in its effects than ethanol. Acetaldehyde produces multiple effects in the body. Binding with proteins, glycoproteins, and membrane phospholipids results in cellular dysfunction such as swelling, impairment of the mitochondrial electron transport chain, and upregulation of protein kinase. Maintenance of cell structure is impaired due to altered formation and function of microtubules. Acetaldehyde also increases the production of cytokines IL-1a, IL-6, and TNF-α and promotes inflammatory responses via activation of necrosis factor kappa beta (NF-κB). Furthermore, TNF-α promotes free radical production by mitochondria, activated neutrophils, and hepatic Kupffer cells.

Numerous *in vitro* studies of Kupffer cells and other types of immune cells investigated the effect of *S. marianum* or its derivatives on the formation of the nitric oxide, TNF-α, prostaglandin E2 (PGE2), and leukotriene B4 (LTB4) found beneficial effects of *S. marianum* its active compounds. For instance, controlled *in vitro* studies have demonstrated that silymarin inhibits NF-κB activation in a variety of cell lines. TNF-mediated NF-κB activation was inhibited in a dose-dependent manner. In addition, silymarin appeared to block the activation of NF-κB by phorbol ester, LPS, okadaic acid, and ceramide, partially inhibited NF-κB induction by H_2O_2, and was found to inhibit NF-κB activation in all cell types studied [83].

8.12.3.4 Liver Regeneration Silymarin at a concentration of 100 mg/kg was shown to enhance liver regeneration in hepatectomized rats, as shown by increased weight for treated rats as compared with controls. Proliferative activity as measured by the stathmokinetic test (counting numbers of mitotic cells in prepared slides of liver tissue from hepatectomized rats) was increased in treated animals as compared with controls. The rate of DNA synthesis in rats treated with silibin following partial hepatectomy was increased from 23% to 35% compared with controls. No change in DNA synthesis was seen in normal livers.

Clinical studies have varied greatly in quality, with the majority limited by inadequate sample size, lack of uniformity in the population treated, lack of

standardization of preparations studied, and variability in dosing regimens, inconsistent outcome measures, and a lack of information on concurrent use of alcohol during the treatment period. While *S. marianum* and its derivatives appear to be safe and the available evidence on the mechanisms of action appears promising, there is currently insufficient data from well-conducted clinical trials to recommend their use in patients with alcoholic liver disease [83].

Taken together, although silymarin is safe and may have several properties that make it a potentially attractive therapy for alcoholic liver disease, such as effects on liver regeneration, lipid peroxidation, inflammation, and hepatic fibrogenesis; there are insufficient data from well-conducted clinical trials at present to routinely recommend the use of this agent for patients with alcoholic liver disease. The widespread availability for clinical trials of a standardized pure *Silybum*/silymarin/silybin product as proposed by the National Institutes of Health will be an important first step to the systematic study of whether this herbal compound may be an effective therapy for alcoholic and other liver diseases [83].

8.12.4 Potential Toxicity

S. marianum and its active compounds appear safe with relatively few side effects reported in the scientific literature. One case of severe gastroenteritis was reported following ingestion of capsules containing a variety of ingredients, including milk thistle. It is unclear whether the reaction may have been an idiosyncratic response to milk thistle or a reaction to another ingredient in the formulation. In general, the safety of both *S. marianum* and silymarin has been well established. No mortality or any signs of side effects were observed in a review of toxicological studies performed in various animals [83].

8.13 *Cuminum cyminum*, CUMIN (*KAMON*)

C. cyminum is a flowering plant of the Apiaceae, native to the east Mediterranean region and from Iran to East India. It is an herbaceous annual plant, with a slender branched stem 20–30 cm in height (Figure 8.11). English "cumin" derives from the Arabic *Kammon*. Cumin appears to originate from Egypt and is mentioned in ancient Egyptian scripts as a spice and medicine. It is a flavoring agent, which belongs to a group of digestive or carminative umbelliferous fruits, which include fennel, caraway, aniseed, and cumin.

8.13.1 Traditional Uses

C. cyminum seeds have been in use since ancient times. They were excavated at the Syrian archeological site Tell ed-Der and have been dated to the second millennium BC. They were also found in several ancient Egyptian archeological sites. Cumin is mentioned in both the Old Testament and the New Testament. It was also known in ancient Greece and Rome. This is a plant with a strong history and extensive use

FIGURE 8.11 *Cuminum cyminum*, cumin (*Kamon*). (*See the color version of this figure in Color Plates section.*)

across the world both as a food and as a medicine against indigestion, dyspepsia, to treat stomach complaints, to reduce appetite by making the digestive process more efficient, and to ease cramps and flatulence. It is part of a group of carminative spices, which are included in foods to aid digestion and reduce flatulence and cramps. It is used in traditional remedies against overeating in the same way as fennel, which reduces appetite by creating a sensation of fullness after eating and so reducing overeating. It is used extensively in Arabic medicine as a remedy for the stomach and for reducing overeating and appetite [45,51–53].

8.13.2 Phytochemistry

The main active ingredients are found in essential oils, which can reach 5% by weight. These include components such as cymol or cymene, and cyminol, and smaller quantities of antheone, fenchone chalvicol, and others. There are also flavonoids and flavone glycosides. The seeds are a good source of iron. Iron is an integral component of hemoglobin, which transports oxygen from the lungs to all body cells, and build the active site of key enzyme, such as cytochrome, cytochrome P450 [84].

8.13.3 Pharmacological Uses

8.13.3.1 Digestion Cumin, like other carminative seeds such as, caraway, fennel, dill, and anise, has been acknowledged to have stomach-calming effects to improve digestion and regulate appetite especially for children. They all have similar

properties of stimulation of the intestinal mucosa, increasing local blood supply and increasing digestive acid production, and also digestive enzymes such as lipase, trypsin, and chymotrypsin. There is clear evidence that cumin increases the biological value and utilization of protein in the diet, thus requiring less food for the same nutritional value [85].

8.13.3.2 Antiobesity Properties In addition to the digestive effects, there is evidence that cumin can significantly reduce cholesterol and various forms of fats in the blood and other tissues, with obvious implications for obesity. For instance, we evaluated in a clinical study the antioverweight properties of a mixture of *A. vulgaris*, *O. europaea*, and *M. longifolia* as well as seeds of *C. cyminum*. These plants are used in traditional Arabic and Islamic medicine as well as in European herbal medicine in the treatment of excessive body weight. The study was carried out among 80 human volunteers with a BMI of $30.67 \pm 2.14\,kg/m^2$. The mixture was well tolerated by all volunteers and no side effects were reported. A progressive and significant weight loss was seen in these subjects during the whole study period. Higher levels of weight loss were seen in people with BMI of 25–30 kg/m^2 (overweight) compared to people with BMI higher than $30\,kg/m^2$ (obese). The BMI was reduced after 3 months from $28.5 \pm 1.2\,kg/m^2$ and $32.1 \pm 1.8\,kg/m^2$ to $24.5 \pm 1.4\,kg/m^{22}$ and $27.5 \pm 2.2\,kg/m^2$ in overweight and obese groups, respectively [40].

8.14 *Ruscus aculeatus*, BUTCHER'S BROOM (*UHRF ALDEEK*)

Ruscus aculeatus is a spiny, small-leaved evergreen bush of the Lily family. It is native to the Mediterranean region and Western Europe. The mature branches used to be bundled and made into brooms by butchers, hence its popular name. The roots and sometimes the young shoots are known for the therapeutic properties of the plant (Figure 8.12).

8.14.1 Traditional Uses

R. aculeatus therapeutic properties have been known since ancient times. It was commonly used in the Greek, Roman, and Greco-Arab traditions. It is used as a diuretic in the treatment of urinary problems. It is also used in the treatment of a variety of inflammatory and circulatory diseases. The Roman scholar Pliny reported the use of this plant to treat varicose veins in 60 AD, and this has been the dominant use until today. In modern herbalism, *R. aculeatus* is the most frequently used herb in the treatment of varicose veins, hemorrhoids, and swellings [3,31,45].

8.14.2 Phytochemistry

The main ingredients of *R. aculeatus* are two steroidal saponins (ruscogenin and neoruscogenin). It also contains a number of other steroidal saponins, sterols,

FIGURE 8.12 *Ruscus aculeatus*, butcher's broom (*Uhrf Aldeek*). (*See the color version of this figure in Color Plates section.*)

triterpenes, flavonoids, coumarins, chrysophanic acid, euparone, sparteine, tyramine, and glycolic acid [86].

8.14.3 Pharmacological Uses

8.14.3.1 Vasoconstrictive Properties There is considerable clinical and pharmacological research on *R. aculeatus*, which indicate that saponins have vasoconstrictive effects. Animal studies show clearly how these compounds also reduce vascular permeability, and could therefore reduce the permeability and swelling associated with the inflammatory reaction. There are several mechanisms that have been proposed for this, the main evidence suggesting that saponins activate or stimulate the alpha-1 and alpha-2 postjunction adrenergic receptors. However, other studies have shown that saponins inhibit elastase enzyme, which is involved in maintaining the structural integrity of the blood vessels [3,31,45].

8.14.3.2 Varicose Veins Clinical studies assessed the efficacy of *R. aculeatus* in the treatment of varicose veins, venous insufficiency combined with lower leg edema, and similar problems. For instance, a recent double-blind randomized, multicenter trial with 166 women with venous insufficiency, demonstrated that *R. aculeatus* was significantly better than placebo in reducing edema, measured by leg circumference, as well as other parameters such as quality of life and symptoms. A similar double-blind study in Argentina confirms the effectiveness of *Ruscus* in chronic venous lymphatic insufficiency. A connected health problem is orthostatic hypotension, in which low blood pressure creates dizziness and other symptoms, especially in certain postures. *R. aculeatus* seems to be one of the safest and best available treatments for this problem. A recently published review of *R. aculeatus* demonstrates that its effects in stimulating venous constriction, improving venous tone, and exerts a protective, strengthening effect on capillaries, veins, and the vascular endothelium and muscle wall make it the ideal and safest remedy for orthostatic hypotension [87].

8.14.3.3 Antiarthritis Properties There is apparently no clinical or biomedical research on the effect of *R. aculeatus* on arthritis as such. However there has been research on some of the symptoms associated with arthritic inflammation. In particular, there is evidence that *R. aculeatus* can reduce edema and swelling that is associated with problems in lymph drainage or other causes. A double-blind clinical trial on 140 patients suffering from edema as a result of blood clots, venous insufficiency or other reasons found that *R. aculeatus* was effective in reducing edema by increasing lymphatic drainage and sealing capillaries. An external application of Butchers Broom cream was used to treat sports injuries such as sprains and contusions in a double-blind randomized clinical trial. There was a clear improvement in swelling of the injured leg, compared to the uninjured leg, and a reduction in the subjective perception of pain [88].

8.14.3.4 Antihemorrhoids Properties *R. aculeatus* is well known in the treatment of hemorrhoids, which is due to reduced venous return as well as an inflammatory response. In one open trial, 75% of patients with acute hemorrhoids rated the efficacy of the treatment with *R. aculeatus* extract as good or excellent. *R. aculeatus* is commonly accepted as an extremely safe over-the-counter remedy. No toxicity is known, although nausea is reported rarely [88,89].

8.15 *Inula viscose*, TAYUN (*TAYON*)

Inula viscosa has been regarded for centuries as one of the most effective medicinal plants in the Mediterranean region. *I. viscosa* of the compositae family is a sturdy perennial shrub that grows in the wild around the Mediterranean basin (Figure 8.13). It is an aromatic plant that disperses a strong smell of camphor. The leaves and stems of the plant are coated with a sticky resin from September through the winter months, the plant blooms with clusters of small yellow flowers, providing one of the few food sources available to honey bees during winter.

FIGURE 8.13 *Inula viscosa*, tayun (*Tayon*). (*See the color version of this figure in Color Plates section.*)

8.15.1 Traditional Uses

I. viscosa is traditionally used to treat infections, inflammations, fever, and external skin irritations. It is also effective in wound healing. The roots are used against cough and catarrh, as an antiseptic and expectorant, which loosens phlegm and supports mucus membranes [3,31,45].

8.15.2 Phytochemistry

The leaves contain essential oils, flavonoids such as rhamnocitrin, glycosyl analogue of diacylglycerol, sakuranetin, methylaromadendrin, acetyl-methylaromadendrin, and sesquiterpene lactones [90].

8.15.3 Pharmacological Uses

I. viscosa is well documented to have antiulcerogenic effects, to cause abortion or inhibition of zygote implantation in mammals, to inhibit growth of pathogenic fungi, to be a strong anti-inflammatory, antioxidant, and to be a hypoglycemic agent to treat diabetes. For these reasons, this species is of major interest for many pharmaceutical research and industries [90–93].

8.15.3.1 Anti-Inflammatory Properties The anti-inflammatory properties of three flavanones isolated from *I. viscosa*, sakuranetin, methylaromadendrin, and acetyl-methylaromadendrin, have been tested both *in vitro* and *in vivo*. Acute

inflammation *in vivo* was induced by means of topical application of tetradecanoyl-phorbol-acetate (TPA) to mouse ears or by subcutaneous injection of phospholipase A (PLA) into mouse paws. The test compounds were evaluated *in vitro* for their effect on both the metabolism of arachidonic acid and on the release and/or activity of enzymes involved in the inflammatory response such as elastase, myeloperoxidase (MPO), and protein kinase C (PKC). The most active compounds *in vivo* against PLA-induced paw oedema were methylaromadendrin and sakuranetin. In contrast, the most potent compound against TPA-induced ear oedema was acetyl-methylaromadendrin, followed by sakuranetin. *In vitro*, the latter compound was the most potent inhibitor of leukotriene production by peritoneal rat neutrophils and it was also the only compound that directly inhibited the activity of lipoxygenase. Acetyl-methylaromadendrin also inhibited leukotriene production, but had no effect on lipoxygenase activity. The only flavanone that inhibited the secretory PLA(2) activity *in vitro* was methylaromadendrin. This finding may partly explain the anti-inflammatory effect observed *in vivo*, although other mechanisms such as the inhibition of histamine release by mast cells may also be implicated. Sakuranetin was found to inhibit elastase release, although this result is partly due to direct inhibition of the enzyme itself. At the same concentration, methylaromadendrin only affected the enzyme release. Finally, none of the flavanones exhibited any effect on MPO or PKC activities. Taken together, these findings indicate that sakuranetin may be a selective inhibitor of lipoxygenase [90–93].

8.15.3.2 Antimicrobial Properties Activity against bacteria and fungi is also evident. Alcoholic and water extracts of above ground parts showed significant activity against some bacteria, and especially against the yeast *C. albicans*. A further study has shown that this plant has powerful antifungal effects against dermatophytes [90–93].

8.16 *Majorana syriaca*, PALESTINIAN THYME (*ZAATAR*)

Majorana syriaca (Zaatar in Arabic) is a grayish shrub herb that belongs to the mint family Labiatae is native to the Eastern Mediterranean, Southern Europe, and Western Asia, and is cultivated in many parts of the world and commonly called Syrian oreganum (Figure 8.14). It grows wild in the mountains of the Eastern Mediterranean between the months of April–May. Palestinian thyme, *M. syriaca*, is considered one of the most popular herbs in the Arab world. The herb possesses a distinctive aroma with a slight warm pungent taste. The green leaves of the herb are rich in essential oil, which is responsible for its characteristic flavor and fragrance.

8.16.1 Traditional Uses

M. syriaca has been used for thousands of years. Hippocrates used to prescribe it for bronchitis and pleurisy. Traditionally, *M. syriaca* has been used to remedy asthma, congestion, rheumatism, sore throats, wounds, ulcers, and tumors. A combination of *M. syriaca* dried leaves, salt, sesame seeds, and the fruits of the tree *Rhus coriaria* are

FIGURE 8.14 *Majorana syriaca*, Palestinian thyme (*Zaatar*). (*See the color version of this figure in Color Plates section.*)

called "Zaatar" in Arabic, a very popular mixture that is used almost daily in the Middle East as food, additive in salads, and spice for pastry, and meat. With its high content of volatile oils, the herb leaves are used in Greco-Arab and Islamic medicine as herbal tea to treat cold, flu and cough. It has been reported that thyme in general comprises various medicinal benefits. For example, a solution of thyme's most active ingredient, with antibacterial and antifungal properties thymol, is used as an over-the-counter antiseptic mouthwash product. Moreover, thyme extracts are frequently included in popular cough syrups and prescribed to clear respiratory difficulties, including bronchial problems and coughs. The antimicrobial properties of thyme essential oils are related to their high phenolic content. It is used as a powerful disinfectant in oral pharmaceutical preparations and flavoring agent of many food products [3,31,45,94–96].

8.16.2 Phytochemistry

The content of essential oil depends on soil, climate, and season. It contains monoterpene hydrocarbons: α-pinene, myrcene, α-terpinene, *p*-cymene, and γ-terpinene. Oxygenated monoterpenes: linalool—terpinen-4-ol, α-terpineol, thymol methyl ether, carvacrol methyl ether, thymol, and carvacrol [94].

8.17 *Eruca sativa*, ROCKET (*JARJEER*)

Eruca sativa (rucola, arugula) is an annual plant approximately 20–50 cm high, with dull-green leaves, which have a distinct spicy-pungent flavor. It is native to Western

FIGURE 8.15 *Eruca sativa*, rocket (*Jarjeer*). (*See the color version of this figure in Color Plates section.*)

Asia and the Mediterranean region. It is an annual herbaceous plant belonging to the family Brassicaceae (Figure 8.15).

8.17.1 Traditional Uses

E. sativa is traditionally considered as a general tonic and potent aphrodisiac. It is known generally as a food, in which the leaves are eaten as part of salads. It has been known as a garden vegetable since Bible Times, and there are many records of its household usage from the Hellenistic period onwards. It finds widespread uses in Greco-Arab and Islamic medicine. These include antibacterial action (for eye infections), increasing fertility and sperm production, as an aid to digestion, and kidney function. Maimonides and Ibn Wahshiyyah are quoted as stating that the ground seeds when mixed in a cream and spread on the face can be used for treatment of acne.

8.17.2 Pharmacological Properties

E. sativa extract was found to possess a potent antioxidant effect, with a large amount of polyphenols and a high reducing ability. Glucoerucin and flavonoids are the major antioxidants present in it. *E. sativa* extract and they significantly scavenged several reactive oxygen species (ROS) and reactive nitrogen species (RNS). Feeding of *E. sativa* extract to rats induced a significant protection against HgCl induced renal toxicity. In addition, there are several scientific publications that indicate that *E. sativa* has a weak antimicrobial effect.

8.17.2.1 Tonic Properties We prepared a mixture containing active fractions of *E. sativa and Cichorium intybus* which are known in the Eastern and Western tradition as energizing plants. They are food plants suitable for daily use and enjoy impressive traditional and scientific backing and were highly recommended by the Arab and Islamic medical literature against chronic fatigue and for increasing sexual, mental, and physical performance. The energizing activity of this mixture has been assessed cell culture system, in animal models, and human volunteers. It was found that this mixture possess remarkable antioxidant, blood lactate elimination, liver and sexual tonic, cell oxygenation, body endurance, and adaptogenic activities. For instance, results obtained in forced swimming capacity test in mice showed that mice swimming capacity was significantly increased after 7 days oral ingestion of the mixture (5 mg/kg) compared with the placebo and caffeine groups. Furthermore, it was also found that 7 days prefeeding of the mice with *E. sativa* and *C. intybus* extracts (5 mg/kg), significantly reduced the mice blood lactate levels compared with the placebo and caffeine groups. In another experiment, preconsumption of this mixture for 3 weeks in human healthy male volunteers, have, significantly, reduced the blood lactate levels following excessive exercises, compared with the control group. These results can be explained by the powerful liver stimulant activity of *E. sativa* and *C. intybus* extract which may lead to high efficient elimination of lactate from the bloodstream, breakdown of liver glycogen, improvement of antioxidant activity, and increasing of mitochondrial oxidative phosphorylation [3,31,45,97].

8.17.2.2 Antigenotoxic Properties In recent years, *E. sativa* has gained greater importance as a vegetable and spice, especially among Europeans. *E. sativa* is a member of the Brassicaceae, which is considered to be an important chemopreventive plant family. A recent study assessed the chemopreventive potency and underlying mechanisms of extracts of *E. sativa* in HepG2 cells. No genotoxic effect could be observed in HepG2 cells treated with up to 50 μL/mL plant juice for 24 h when using the comet assay. In antigenotoxicity experiments, *E. sativa* extract reduced the benzo(*a*)pyrene-induced genotoxicity. This effect was accompanied by a significant induction of glutathione *S*-transferase. No significant suppression of B(*a*)P-induced CYP1A1 protein expression or enzyme activity could be observed. These results indicate a strong antigenotoxicity of the plant material [98].

8.18 *Cichorium intybus*, WILD CHICORY (*HINDIBAA*)

C. intybus is a bushy perennial herb of the Asteraceae family with blue, lavender, or occasionally white flowers (Figure 8.16). The whole plant has been known for its curative benefits since the first century. It is a powerful hepatic stimulant, general and brain tonic, and appetizer. It is a hypoglycemic, increases bile secretion, hepatoprotective, acts on liver glycogen, and promotes digestion.

FIGURE 8.16 *Cichorium intybus*, wild chicory (*Hindibaa*). (*See the color version of this figure in Color Plates section.*)

8.18.1 Traditional Uses

C. intybus is a well-known food and medicinal herb. It is mentioned in most of the major herb books of the Western world. It is a perennial, with a large taproot like that of dandelion. It is used both in the prevention and treatment of various ailments. It has a bitter taste. *C. intybus* is cultivated widely throughout Europe for use in salads. It is used much like dandelion in European herbal medicine. That is, it is helpful in cleaning the body and supporting the liver and also in stimulating the eliminative processes both via the intestine and the kidneys. It is a warming and tonifying plant, and the fresh root is used traditionally in chest problems and cold conditions. The plant is classically used in cold countries as part of soup to ward off colds and flu. Traditional herbalists also use the plant as part of mixtures for the treatment of dry coughs, chest pain, and bronchial problems. Arab traditional healers today regard chicory as part of a combined treatment of metabolic problems, and a medicine to cleanse the body, and treat colds and flu [3,31,45].

8.18.2 Phytochemistry

The roots of chicory contain inulin and oligofructose polysaccharides, which are typical to the plant and of interest as a source of medicinally important probiotic fiber. The plant as a whole contains several guaianolide sesquiterpene lactones. Similar compounds in other plants such as feverfew are known to have anti-inflammatory activity [99].

8.18.3 Pharmacological Properties

Chicory, like many plants that support liver function and immunity, has strong antioxidant effects *in vitro*, but the clinical significance of this has not been tested.

However, there have been several studies in humans on the therapeutic effects of the inulin and oligofructan polysaccharides. They have been shown to pass through the stomach and undergo fermentation in the colon. This leads to the selective stimulation of the healthy bifidobacteria population. The health consequences of this include the reduction of colonic diseases and diabetes, as well as support for the immune system. These polysaccharide components of chicory also have a significant effect on cholesterol levels, especially on reducing LDL cholesterol and increasing HDL cholesterol. In addition other improvements in lipid metabolism, which may be signs of "blood purification" in the traditional herbal terminology, are caused by consuming chicory, along with a clearing out of body fat, bile, and cholesterol through fecal excretion. It is known that these changes can support general health and disease prevention. There is very little scientific evidence on the general benefits to health and resistance of chicory. One study has demonstrated that elderly patients given chicory improve their hepatic function and rehabilitation [3,31,45,99–101].

8.19 *Punica granatum*, THE POMEGRANATE (*RUMMAN*)

The pomegranate (*Punica granatum*) is a fruit-bearing deciduous shrub or small tree growing to between 5 and 8 m tall (Figure 8.17). This tree is native to the region from

FIGURE 8.17 *Punica granatum*, the pomegranate (*Rumman*). (*See the color version of this figure in Color Plates section.*)

Persia to Northern India and has been cultivated and naturalized over the whole Mediterranean region and the Caucasus since ancient times. The fruit is covered by a leathery pericarp, contained within are numerous *arils*, each a single seed surrounded by a translucent juice-containing sac. Thin acrid-tasting membranes extend into the interior of the fruit from the pericarp, providing a lattice work for suspending the arils. *P. granatum*, especially its fruit, possesses a vast ethnomedical history and represents a phytochemical reservoir of heuristic medicinal value. The tree/fruit can be divided into seven anatomical compartments: seed, juice, peel, leaf, flower, bark, and roots, each of which has interesting pharmacologic activity.

8.19.1 Traditional Uses

The pomegranate is a symbol of life, longevity, health, femininity, fecundity, knowledge, morality, immortality, and spirituality. It has long been used in traditional medicine to treat a variety of ailments, including sort throat, inflammation, and rheumatism. These folk uses of the pomegranate are common throughout the Arab world, Iran, and India. Additional traditional applications include treatment of diarrhea and colic and to remove intestinal worms in children. The fruit is also used for treating bladder disturbances, strengthening gums, and soothing mouth ulcers. In India, the leaf of the pomegranate is used to treat cuts, as it contains a natural healing and soothing agent. Pomegranates feature prominently in all religions, Judaism, Christianity, Islam, Buddhism, and Zoroastrianism. According to the Holy Quran, pomegranates grow in the gardens of paradise. The Quran also mentions pomegranates twice as examples of good things God creates. In Ayurvedic medicine, the pomegranate is considered "a pharmacy unto itself," the bark and roots believed to have anthelmintic and vermifuge properties, the peels a powerful astringent and cure for diarrhea and oral aphthae, and the juice a "refrigerant" and "blood tonic." Dried pomegranate peels are decocted in water and employed both internally and externally for numerous problems demanding astringents and/or germicides, especially for aphthae, diarrhea, and ulcers. Mixtures of pomegranate seed, juice, and peel products paradoxically have been reported to not only prevent abortion but also conception. In Greco-Arab and Islamic medicine, pomegranate flowers serve as a remedy for diabetes mellitus [3,31,45,102].

8.19.2 Phytochemistry

While detailed knowledge of relationships of the chemical content of pomegranates and their desirable pharmacologic endpoints has yet to be obtained, significant progress has been made over the past two decades toward a much more comprehensive understanding of some of the important pharmacologic active components of pomegranate. The most abundant polyphenols in pomegranate juice are the hydrolyzable tannins called punicalagins, which show free-radical scavenging properties in *in vitro* tests experiments. Punicalagins are absorbed into the human body and may have dietary value as antioxidants. Other phytochemicals include beta-carotene, and polyphenols catechins, gallocatechins, and anthocyanins such as prodelphinidins,

delphinidin, cyanidin, and pelargonidin. The fruit also contains vitamin C at 0.47 mg/100 g [102].

8.19.2.1 Seed *P. granatum* seed oil comprises 12–20% of total seed weight. The oil consists of approximately 80% conjugated octadecatrienoic fatty acids, with a high content of *cis* 9, *trans* 11, *cis* 13 acid (i.e., punicic acid). The fatty acid component of the seeds comprises over 95% of the oil, of which 99% is triacylglycerols. Minor components of the oil include sterols, steroids, and a key component of mammalian myelin sheaths, cerebroside. Seed matrix includes lignins and potently antioxidant lignin derivatives.

8.19.2.2 Juice Anthocyanins, potent antioxidant flavonoids, provide *P. granatum* juice with its brilliant color, which increases in intensity during ripening, and declines after pressing. Minerals in the juice and seed include Fe, relatively prevalent, and Ca, Ce, Cl, Co, Cr, Cs, Cu, K, Mg, Mn, Mo, Na, Rb, Sc, Se, Sn, Sr, and Zn.

8.19.2.3 Pericarp (Peel, Rind) Both flavonoids and tannins are more abundant in the peels of wild-crafted fruit as compared to cultivated fruits. Complex polysaccharides from the peels have been studied and partially characterized.

8.19.2.4 Leaf Unique tannins occur in pomegranate leaves, as well as in peel. Leaves also contain glycosides of apigenin, a flavone with progestinic and anxiolytic properties.

8.19.2.5 Flower The flowers contain compounds also found in peels (e.g., gallic acid) and seed (e.g., ursolic acid), and quite possibly unique, distinctive compounds as well.

8.19.2.6 Tree Bark and Roots Extracts prepared from the rougher parts of the tree also have potent physiological effects and a long medical history. Their chemistry is notable against that of other tree parts mainly for the extensive presence of alkaloids.

8.19.3 Pharmacological Properties

Therapeutic potential and toxicological properties of *P. granatum* have been extensively studied. A Medline search using *P. granatum* reveals more than 300 citations, including antioxidant, hormone replacement therapy, resolution of allergic symptoms, cardiovascular protection, oral hygiene, ophthalmic ointment, weight loss soap, and as an adjunct therapy to increase bioavailability of radioactive dyes during diagnostic imaging. *P. granatum* mediated antioxidant activity can be considered a means of lowering the threshold for inflammation. Antioxidant activity, as well as suppression of inflammation, may contribute to chemotherapeutic and chemopreventive utility against cancer [102].

While multiple mechanisms reflect the fruit's chemical complexity, major themes of increased apoptosis, decreased inflammation, decreased metastasis and invasion, as well as a decrease in drug resistance, are evident. For example, compounds such as ursolic acid, ellagic acid, quercetin, ellagitannins, luteolin, and apigenin have all been associated with tumor cell apoptosis. This is achieved through a decline in activation of NF-κB, a decrease in fatty acid synthase activity, and tumor necrosis factor, increased caspase activities and upregulation of p21 and p53 expression. Pomegranate component control of inflammation involves inhibition of both COX and LOX enzymes and a decline in prostaglandin release from cells. Pomegranate components decrease tumor cell invasion into normal tissue and metastasis to distant sites. Mechanisms explaining these actions include inhibition of selected metalloproteinase activity, reduced VEGF expression, and decreased focal adhesion kinase activity. Key pomegranate components (e.g., catechins) may also reduce drug resistance through interaction with p-glycoprotein expression, relevant to potential employment of pomegranate juice or extracts as helpful adjuncts to traditional cytotoxic agents, the latter often compromised by rapid development of tumor cell resistance.

Recent studies have also begun to suggest possible synergistic interactions between aqueous and lipid phases of the fruit, and between different chemicals in each phase. Though, undoubtedly, much more is still unknown than known about the pomegranate's chemistry and medicinal potential, the beginnings of a possible use for the fruit in cancer chemoprevention and chemotherapy, largely deriving from the anti-inflammatory properties of both the aqueous and lipid phases, is in the earliest stages of being appreciated. Clinical trials with pomegranate materials, though, particularly with regard to inflammation and cancer, are still sorely lacking. Much of the work completed on pomegranate during the past decade has focused on antioxidant activity of *P. granatum*.

8.19.4 Potential Toxicity

P. granatum has been widely consumed in many different cultures for thousands of years, largely without untoward incident, and thus is considered generally safe. However, some toxicity is known, and undoubtedly, more remains to be discovered. Consumption of decoction of the tree bark, and to a lesser extent, pericarps of the fruit, may cause severe acute gastric inflammation due to the presence of both tannins and alkaloids. Whole fruit extracts have been shown to cause congestion of internal organs and elevated creatinine *in vivo* [102].

8.20 *Ruta chalepensis* L., RUTA (*FAIJAN*)

Ruta chalepensis, *Ruta* (Faijan in Arabic) is a perennial herb characterized by glabrous, alternate leaves with narrow oblong-lanceolate or obovate segments and cymose inflorescence. *R. chalepensis* is widely distributed in the Mediterranean region (Figure 8.18).

FIGURE 8.18 *Ruta chalepensis*, *Ruta* (*Faijan*). (*See the color version of this figure in Color Plates section.*)

8.20.1 Traditional Uses

Ruta graveolens is used for several therapeutic purposes worldwide it is one of the commonly used medicinal plants in Greco-Arab medicine. Orally, it is used as analgesic, antipyretic, anti-inflammatory, in menstrual problems, antispasmodic, anthelmintic and abortifacient, relief of rheumatic pain, and mental disorders. Topically, it is used as hair tonic, insect repellent, and for snakebite [3,31,45,103].

8.20.2 Phytochemistry

R. chalepensis is a rich source of several acridone and quinoline alkaloids. Some quinoline alkaloids isolated from *Ruta* species display mutagenic, ganglionic-blocking, curare-like, and spasmolytic activities. The plant contains coumarins that exhibit antifertility properties [103,104].

8.20.3 Pharmacological Uses

R. chalepensis has wide range of pharmacological properties, attributed to the high content of alkaloids, flavonoids, phenols, amino acids, furocoumarins, and saponins found in the leaves and young stems of the plant. Pharmacological studies carried out with different extracts of *R. chalepensis* reported anti-inflammatory, antipyretic, antifertility, antifungal, and antibacterial properties as well antivascular diseases [103–106].

8.20.3.1 Vascular Diseases It is well known that many pathologic conditions of the cardiovascular system are affected by an increase or dysfunction of the blood

platelet activity, mainly in the arterial thrombi, since these play a major role in thrombotic disorders. Several edible plants and spices have the reputation of being used to prevent or at least to decrease the incidence of different vascular diseases based on their ability to prevent platelet aggregation. Garlic, onion, ginger, strawberries, and tomatoes are well known and well studied representatives in this aspect. Compounds responsible for the inhibition of platelet aggregation have been determined and reported, such as sulphurous compounds in garlic and onion; gingerol and zingiberine in ginger; and phenolics in strawberries. Several medicinal plants with diverse active constituents such as alkaloids, flavonoids, tannins, and coumarins have shown promising results in inhibition of the platelet aggregation. A recent study investigated the inhibitory effect induced by two isolated coumarin derivatives, namely bergapten and chalepensin. Both molecules inhibited in a dose-dependent manner platelet aggregation. Indicating for potential use of this plant in the treatment of vascular disease.

8.20.3.2 Effects on the Central Nervous System The effects of an ethanol extract of the aerial parts of *R. chalepensis* on the central nervous system (CNS) were studied in mice. A crude extract was given systemically and its effects were tested on pentylenetetrazole (PTZ)-induced seizures, sodium pentobarbital-induced hypnosis, exploratory activity, anxiety, and nociception. Results from the mice models tested showed (1) a delay in the onset of seizures and a dose-dependent suppression in the tonic phase and mortality induced by PTZ; (2) a prolongation of the time of sodium pentobarbital-induced hypnosis; (3) a significant attenuation in the anxiety–response; and (4) a reduction in the licking time and shaking behavior in the formalin-induced nociception test. The sedative–hypnotic potentiation, anxiolytic, anticonvulsant, and antinociceptive effects suggest that *R. chalepensis* induces a depressant activity on the CNS.

8.20.4 Possible Toxicity

Contact dermatitis and photoxicity characterized by erythema, itching, and burning of the skin is a common toxic effect, which is usually associated with all *Ruta* species. Mutagenicity of this plant has been found to be mediated by furoquinoline alkaloids and furocoumarins upon prolonged exposure to sunshine [103–106].

8.21 *Conium maculatum*, POISON HEMLOCK (*SAYKARAN*)

Conium maculatum, poison hemlock (Saykaran in Arabic), is a weed known almost worldwide by its toxicity to many domestic animals and to humans. It is an Umbelliferae, characterized by long, hollow stems, reaching up to 2 m height at maturity, producing a large amount of lush foliage during its vegetative growth (Figure 8.19). The flowers are white, grouped in umbels formed by numerous umbellules. It produces a large number of seeds that allow the plant to form thick stands in modified soils, sometimes encroaching on cultivated fields, to the extent of

FIGURE 8.19 *Conium maculatum*, poison hemlock (*Saykaran*). (*See the color version of this figure in Color Plates section.*)

impeding the growth of any other vegetation inside the *C. maculatum* area of growth. The entire plant has a bitter taste and possesses a disagreeable mousy odor, which is especially noticeable when bruised. When dry, the odor is still disagreeable, but not as pronounced as in the fresh plant.

8.21.1 Traditional Uses

C. maculatum is mentioned in early Greek literature for its poisonous nature. The juice of *C. maculatum* was frequently administered to criminals, most famously as the fatal poison that Socrates was condemned to drink. The plant is used in traditional medicine as a sedative and antispasmodic, and in sufficient doses acts as a paralyzer to the centers

of motion. In its action it is, therefore, directly antagonistic to that of strychnine (a very toxic crystalline alkaloid used as a pesticide, particularly for killing small vertebrates such as birds and rodents. It causes muscular convulsions and eventually death through asphyxia or sheer exhaustion. The most common source is from the seeds of the *Strychnos nux vomica* tree). Therefore, it has been recommended as an antidote to strychnine poisoning, and in other poisons of the same class, and in tetanus, and hydrophobia. On account of its sedative action on the motor centers, *C. maculatum* juice is prescribed as a remedy in cases of undue nervous motor excitability, such as teething in children, epilepsy from dentition, in spasms of the larynx and gullet, and in acute mania. As an inhalation, it is said to relieve cough in bronchitis, whooping cough, and asthma. *C. maculatum* was formerly believed to exercise an alterative effect in scrofulous disorders. Greco-Arab physicians were in the practice of using it for the cure of indolent tumors, swellings, and pains of the joints, as well as for affections of the skin. The entire plant has a bitter taste and possesses a disagreeable mousy odor, which is especially noticeable when bruised [3,31,45,107].

8.21.2 Photochemistry

Eight piperidinic alkaloids have been identified in *C. maculatum*. Two of them, gamma-coniceine and coniine are generally the most abundant and they account for most of the plant acute and chronic toxicity [107,108].

8.21.3 Possible Toxicity

The *C. maculatum* has to be administered with care, as narcotic poisoning may result from internal use, and overdoses produce paralysis. In poisonous doses, it produces complete paralysis with loss of speech, the respiratory function is at first depressed and ultimately ceases altogether and death results from asphyxia. The acute toxicity is observed when animals ingest *C. maculatum* vegetative and flowering plants and seeds. In a short time, the alkaloids produce a neuromuscular blockage conducive to death when the respiratory muscles are affected. The chronic toxicity affects only pregnant animals. When they are poisoned by *C. maculatum* during the fetus's organ formation period, the offspring is born with malformations, mainly palatoschisis and multiple congenital contractures (MCC; frequently described as arthrogryposis). Acute toxicity, if not lethal, may result in spontaneous recovery of the affected animals provided further exposure to *C. maculatum* is avoided. It has been observed that poisoned animals tend to return to feed on this plant. *C. maculatum* alkaloids can be transferred to milk and to fowl muscle tissue through which the former can reach the human food chain [107,108].

8.22 *Capparis spinosa* L., THE CAPER (*KABAR*)

Capparis spinosa, the caper (Kabar in Arabic), is a perennial spiny bush that bears rounded, fleshy leaves, and big white to pinkish-white flowers (Figure 8.20). The bush is native to the Mediterranean basin, growing wild on walls or in rocky coastal areas

FIGURE 8.20 *Capparis spinosa*, the caper (*Kabar*). (*See the color version of this figure in Color Plates section.*)

throughout. The plant is best known for the edible bud and fruit (*caper berry*), which are usually consumed, pickled.

8.22.1 Traditional Uses

In Greek traditional medicine, an herbal tea made of caper root and young shoots is considered to be beneficial against rheumatism. Dioscoride also provides instructions on the use of sprouts, roots, leaves, and seeds in the treatment of inflammation. *C. spinosa* is used as an analgesic, antihelmintic, antihemorrhoidal, aperient, deobstruent, depurative, diuretic, emmenagogue, expectorant, tonic, and vasoconstrictor. Decoctions from the root bark have been used in traditional medicines for dropsy, anemia, arthritis, and gout. The stem bark is bitter and diuretic. If taken before meals, it will increase the appetite. One of the reasons for its effectiveness for these purposes may be the fact that the plant contains the antioxidant bioflavinoid rutin, which also contributes to the flavor. In Ayurvedic medicine, *C. spinosa* is recorded with other hepatic stimulants and protectors, improving liver function. It is used internally in the treatment of gastrointestinal infections, diarrhea, gout, and rheumatism. Externally, it is used to treat skin conditions, capillary weakness, and easy bruising. The unopened flower buds are a laxative and are used internally in the treatment of coughs, and externally to treat eye infections. The buds are a rich source of compounds known as aldose reductase inhibitors—it has been shown that these compounds are effective in preventing the formation of cataracts. The buds are harvested before the flowers open and can be pickled for later use—when prepared correctly they are said to ease stomach pain. In Greco-Arab and Islamic medicine, the decoction of root bark is prescribed as deobstruent to liver and spleen, as anthelmintic and anti-inflammatory agents [3,31,45,109].

8.22.2 Phytochemistry

The cortex and leaves contain stachydrine and 3-hydroxy stachydrine. The roots contain glucobrassicin, neoglucobrassicin, and 4-methoxy-glucobrassicin. The crude

extract of the flower buds contains 162 volatile constituents of which isothiocyanates, thiocyanates, sulphides and their oxidative products have been identified as the major components. The seeds and leaves contain glucocapparin and glucocleomin. The root bark contains stachydrine and rutic acid [109–113].

8.22.3 Pharmacological Uses

Medical uses of *C. spinosa* include reduction of flatulence, as an antirheumatic. It has been used as a diuretic, vermifuge, hepatoprotective, antioxidant, and tonic. The leaves are bruised and applied as a poultice in the treatment of gout. In a recent study a methanolic extract of *C. spinosa*, rich of flavonoids, showed a noteworthy antiallergic effect against bronchospasm in guinea pigs, also confirmed in an *in vivo* study performed in human volunteers; the same extract possessed strong antioxidant/free radical scavenging effects in different *in vitro* tests and, when topically applied, it afforded significant *in vivo* protection against UVB light-induced skin erythema in healthy human volunteers [109–113].

8.22.3.1 Hepatoprotective Properties *p*-Methoxy benzoic acid isolated from the methanolic soluble fraction of the aqueous extract of *C. spinosa* was found to possess significant hepatoprotective activity against carbon tetrachloride and paracetamol induced hepatotoxicity *in vivo*. In addition, this compound significantly reduced thioacetamide- and galactosamine-induced hepatotoxicity in isolated rat hepatocytes.

8.22.3.2 Hypolipidemic Properties The effect of single and repeated oral administrations of aqueous extract of *C. spinosa* on lipid metabolism in normal and streptozotocin-induced diabetic rats was assessed in a recent study. In normal rats, the aqueous extract of *C. spinosa* induced a significant decrease on plasma triglyceride concentrations one week and two weeks after once daily repeated oral administration. A significant decrease of plasma cholesterol levels was also observed four days and one week after repeated oral administration. In diabetic rats, *C. spinosa* treatment caused a significant decrease of plasma triglycerides levels after repeated oral administration. Four days after repeated oral administration of aqueous *C. spinosa* extract, the plasma cholesterol levels were significantly decreased and still dropped after 2 weeks. On the other hand, the repeated oral administration of *C. spinosa* aqueous extract caused a significant decrease of body weight 4 days after repeated oral treatment in diabetic rats. These results indicate that the aqueous extract of *C. spinosa* (20 mg/kg) exhibits a potent lipid lowering activity in both normal and severe hyperglycemic rats after repeated oral administration of *C. spinosa* aqueous extract.

8.22.3.3 Chondroprotective Properties Degenerative arthropathies such as osteoarthritis are characterized by the presence of degenerative and oxidative/inflammatory mediators. Osteoarthritis appears to be the result of an imbalance between the destructive and reparative/synthetic processes of the articular cartilage due to the destructive effects of free radicals (ROS and NO), inflammatory cytokines

(e.g., IL and TNF-α), and metalloproteinases (MMP). Cytokines, such as interleukin-1 interfere in extracellular matrix turnover, accelerate the degradation of cartilage matrix, and induce chondrocytes apoptosis. Moreover, it has been shown that IL-1 induces the production of NO that react rapidly with superoxide anions to form peroxynitrite, which is a strong oxidant and other oxidants such as hydrogen peroxide and hydroxyl radicals. NO inhibits proteoglycans synthesis and stimulates the chondrocyte production of proenzymes which are converted into active enzymes as metalloproteases (MMPs). These enzymes have been reported to play significant roles in the destruction of the cartilage matrix in arthritic diseases. Furthermore, MMP-3 is the major metalloprotease in cartilaginous tissue that can degrade matrix components leading to the cleavage of collagen and proteoglycans, fundamental constituents of cartilage. During the inflammatory processes, PGE2 production is intensified and this contributes to synovial inflammation by increasing local blood flow and by potentiating the effects of mediators such as bradykinin, responsible for relevant vasopermeability. It has been shown that PGE2 was able to inhibit chondrocyte growth, and upregulate IL-1. A recent *in vitro* study evaluated chondroprotective effects of the lyophilized methanolic extract from flowering buds of *C. spinosa*. Results obtained suggest that the extract may be able to prevent cartilage destruction. It has been demonstrated that the extract possesses an antiproteolytic action; it inhibited, in fact, the effect and production of the metalloproteinase enzymes, which are directly involved in osteoarthritis disease. The employment of the extract can downregulate the production of pro-MMP and PGE2 in chondrocytes, suggesting that it may serve as a novel anti-inflammatory drug to maintain articular cartilage in osteoarthritis.

8.22.3.4 Female Sexual Dysfunctions We assessed safety and efficacy of a concentrated dry extract of *F. asafoetida* roots and *C. spinosa* buds in enhancing female libido. As mentioned in details in Chapter 12, this mixture exhibited high levels of safety with an LD_{50} of 15 g/kg and antioxidant properties. Furthermore, the mixture revealed to be a potent vasodilator due to an endothelial-mediated effect rather than a direct effect on arterial smooth muscle cells. Two groups of married and healthy females were followed for 6 months while consuming one dose of the mixture daily. The mixture was well tolerated by all females and no side effect was reported. The one group ($n = 32$) was studied due to difficulties in their sexual activity and the other ($n = 28$) was studied due to infertility that could not be helped further by medical evaluations or treatment. Twenty-seven women of the first group (84%) reported significant improvements in their sexual difficulties and their libido while the remaining five women reported no remarkable change. Twenty-one women of the second group (75%) reported that their libido was improved within 1 month of feminine consumption and 11 women became pregnant.

8.23 *Cyperus rotundus*, NUT-GRASS (*SUEDA*)

Cyperus rotundus, nut-grass (Suada in Arabic) is a perennial plant that may reach a height of up to 40cm. The name "nut grass" is derived from its tubers that somewhat

FIGURE 8.21 *Cyperus rotundus*, nut-grass (*Sueda*). (*See the color version of this figure in Color Plates section.*)

resemble nuts, although botanically they have nothing to do with nuts (Figure 8.21). As in other Cyperaceae, the leaves of the *C. rotundus* sprout in ranks of three from the base of the plant. A young plant root system initially forms white, fleshy rhizomes. Some rhizomes grow upward in the soil, and then form a bulb-like structure from which new shoots and roots grow, and from the new roots—new rhizomes grow. Other rhizomes grow horizontally or downward, and form dark reddish-brown tubers or tuber-chains.

8.23.1 Traditional Uses

According to the Ayurveda, roots are useful as an infusion or as a soup in fever, diarrhea, dysentery, dyspepsia, vomiting, and cholera. Fresh tubers are applied on the breast in the form of paste or plaster as galactagogue. Paste is applied to scorpion stings and when dried, to spreading ulcers. In the Greco-Arab and Islamic medicine, the root is a diuretic, emmenagogue, diaphoretic, anthelmintic, vulnerary, and useful for ulcers and sores, fevers, and dyspepsia [3,31,45,114].

8.23.2 Phytochemistry

C. rotundus contains a wide variety of pharmacological active compounds that includes sesquiterpene, oxidoeudesm, cyperenes, cyperenone, mustakone, β-selinene, sugetriol triacetate, and sugeno. The essential oil contains copadiene, epoxyguaiene rotundone, cyperenol, cyperolone, eugenol, cyperol, isocyperol, α- and β-rotunol, kobusone, isokobusone, δ-cadinene, and calamenone [114,115].

8.23.3 Pharmacological Uses

The acetone and ethanol extracts of *C. rotundus* tubers were found to possess antibacterial activity. They are also used as anthelmintic, antihistaminic, antiemetic, antipyretic, hypotensive, smooth-muscle relaxant, and emmenagogue in uterine complaints. The plant has also been reported to have antimalarial, tranquilizing, hepatoprotective against carbon tetrachloride induced liver damage, wound healing, lipolytic action, and reduced obesity by releasing enhanced concentration of biogenic amines from nerve terminals of the brain, which suppressed the appetite center [113,114].

8.24 *Sarcopoterium spinosum*, THORNY BURNET (*NATSH*)

Sarcopoterium spinosum, thorny burnet (Natsh in Arabic), is a bush of the Rosaceae family growing throughout the Mediterranean region. The plant can also be found in the desert. The branches are wooden, ending in branched thorns. The leaves are compound and pinnate; winter leaves are relatively large compared to the smaller summer leaves. Flowering season is from March to April. The flowers are monosexual, the inflorescence are torrent like with the flowers arranged at the top. The fruit is round with a brown-red color. The plant is collected throughout the year.

8.24.1 Traditional Uses

S. spinosum is one of the thorn plants mentioned in the Bible, expressing desolation and ruin. The plant is used in Arab countries for the construction of fences and hedges. It is also used as a source of kindle. In Greco-Arab medicine *S. spinosum* is known for its antidiabetic properties. The plant is also used to treat stomachaches, toothache, gingivitis, oligouria, external inflammation, and as a tranquilizer [3,31,45].

8.24.2 Pharmacological Uses

Most scientific reports support the antidiabetic effects of *S. spinosum*. Other reports indicate antioxidant properties of this plant.

8.25 *Atriplex halimus*, MEDITERRANEAN SALTBUSH (*KATAF*)

Atriplex species (saltbushes) are dominant in many arid and semiarid regions of the world, particularly in habitats that combine relatively high soil salinity with aridity.

Most saltbush species prosper in areas with annual rainfall ranging from 200 to 400 mm. Over 400 species of *Atriplex* have been identified on all continents. About 40–50 *Atriplex* species are found in the Mediterranean basin. *A. halimus*, Mediterranean saltbush (Kataf in Arabic) is a perennial native shrub of the Mediterranean with an excellent tolerance to drought and salinity. It ramifies almost from the base, can grow 1–3 m high and may reach 3 m in diameter. It is monoecious and inflorescences are in dense spikes.

8.25.1 Traditional Uses

A. halimus is commonly used in the Greco-Arab medicine for its antidiabetic effects [3,31,45].

8.25.2 Pharmacological Uses

Scientific reports support the antidiabetic properties of *A. halimus.* Results of animal studies and preliminary human trials suggest that *A. halimus* does indeed have antidiabetic effects. The antidiabetic effects may be partly due to the chromium it contains. Considerable evidence indicates that chromium supplementation can improve blood sugar control, especially in type 2 diabetes. However, there could be other active ingredients in *A. halimus* as well. We tested the antidiabetic effects of a mixture of dry extract of leaves of *J. regia* L., *O. europaea*, *U. dioica*, and *A. halimus*. Antidiabetic properties were evaluated using *in vivo* and *in vitro* test systems. Treatment of streptozotocin-induced type 2 diabetes mellitus rats for 2–3 weeks with the four-plant mixture showed with the plant mixture normalized glucose levels. In addition, the glucose levels were tested in 16 human volunteers with recent onset of type 2 diabetes who received the mixture for a period of 4 weeks. Within the first week of four-plant mixture consumption, baseline glucose levels were significantly reduced from 290 ± 40 to 210 ± 20 mg/dL. At baseline, a subgroup of 11 of these subjects had glucose levels below 300 mg% and the other subgroup had levels $\geq$300 mg%. Clinically acceptable glucose levels were achieved during the 2–3 weeks of therapy in the former subgroup and during the fourth week of therapy in the latter subgroup. In addition, significant reductions in hemoglobin A1c values were found in six patients treated with the mixture. These results indicate safety, tolerability, and efficacy of such herbal combination of the four plants that seem to act differently but synergistically to regulate glucose-homeostasis. Additional considerable evidence proves that saltbush is an extremely effective antidiabetic herb and shows an insulin potentiating effect [3,31,45,91].

8.26 *Origanum majorana* L., SWEET MARJORAM (*MARDAGOUSH*)

Origanum majorana is a low, bushy perennial native to Asia but naturalized in Europe, where singers learned to preserve and strengthen their voices with the

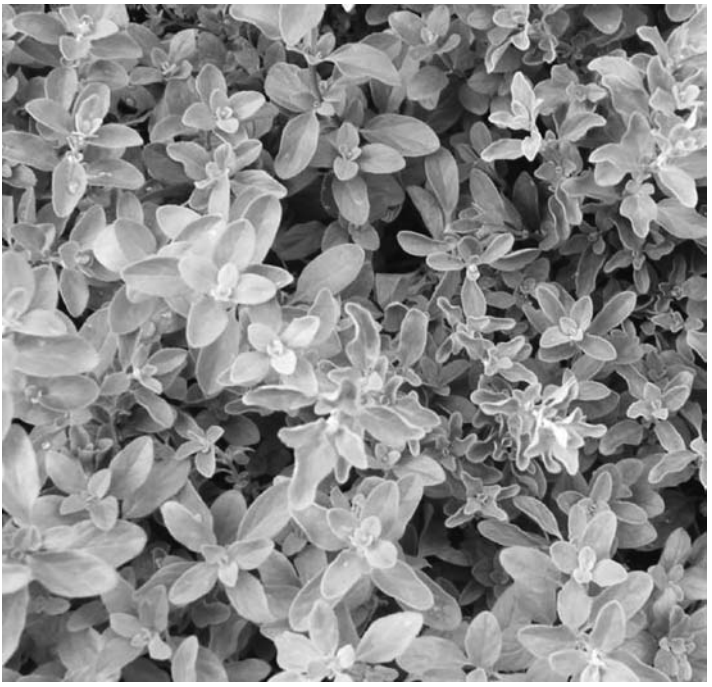

FIGURE 8.22 *Origanum majorana*, sweet marjoram (*Mardagoush*). (*See the color version of this figure in Color Plates section.*)

honeyed tea. Traditionally, it was given to those who felt unstable, physically debilitated, or irritable. Ancient Greeks planted the herb on their ancestors' graves to ensure them a peaceful sleep. *O. majorana* is probably what is called "hyssop" in the Bible, where it is noted for personal cleansing and purification of the temples. The plant had a reputation for endowing longevity and was an antidote to snake poison. The greenish-yellow essential oil is distilled from the plant's flowering tops. Its taste and properties are milder than the closely related oregano, which is so strong and potentially toxic that it is seldom used in aromatherapy (Figure 8.22).

8.26.1 Traditional Uses

O. majorana is used as a sedative, marjoram eases stiff joints and muscle spasms, including tics, excessive coughing, menstrual cramps, and headaches (especially migraines). It also slightly lowers high blood pressure. Testing has shown it to be one of the most effective fragrances in relaxing brain waves. As a result, it makes an excellent calming massage oil, delightful when combined with the softer lavender. It has specific properties that fight the viruses and bacteria responsible for colds, flu, or laryngitis. In healing salves and creams, it also soothes burns, bruises, and inflammation [3,31,45].

8.26.2 Phytochemistry

Carvacrol, thymol, borneol, camphor, linalol, linalyl acetate, cineol, cymeme, sabinene, and terpineol.

8.26.3 Medical Uses

Antioxidant, calms nerves, clears mucous from the lungs, relieves pain, improves digestion, brings on menstruation, lowers high blood pressure, stops bleeding.

8.27 *Allium sativum*, GARLIC AND ONION (A*LLIUM cepa* L.)

Allium sativum, garlic and *Allium cepa*, onion are used both as a food and for medicinal applications. Garlic has been used for thousands of years for medicinal purposes. Sanskrit records mention its medicinal use about 5000 years ago, and it has been used for at least 3000 years in Chinese medicine. The Egyptians, Babylonians, Greeks, and Romans used garlic for healing purposes. Garlic and onion are rich sources of several phytonutrients recognized as important elements of the Mediterranean diet, but are also used in the treatment and prevention of a number of diseases, including cancer, coronary heart disease, obesity, hypercholesterolemia, diabetes type 2, hypertension, cataract, and disturbances of the gastrointestinal tract (e.g., colic pain, flatulent colic, and dyspepsia).

8.28 *Foeniculum vulgare*, FENNEL (*SHOMAR*)

Foeniculum vulgare, fennel, is used in Greco-Arab and Islamic medicine as well as in other different medical systems. Fennel is known for its laxative properties. It is also used as a muscle relaxant as well as to treat urinary disorders. In the Eastern Mediterranean countries, fennel is used for its therapeutic effects on the gastrointestinal system as a pain reliever as well as for its diuretic properties. Experimental as well as human studies demonstrated that fennel oil had antispasmodic and relaxing effects on smooth muscles (Figure 8.23).

8.29 *Chamomilla recutita*, CHAMOMILE (*BABONEJ*)

Chamomilla recutita (synonymous with *Matricaria recutita* L., and *Matricaria chamomilla*), Chamomile, is an annual herbaceous plant indigenous to Europe and Western Asia. Also known as German chamomile or wild chamomile, the plant is cultivated for the flower heads. Infusions and essential oils from fresh or dried flower heads have aromatic, flavoring, and coloring properties. Both are used in a number of commercial products including soaps, detergents, perfumes, lotions, ointments, hair products, baked goods, confections, alcoholic beverages, and herbal teas. Chamomile tea, brewed from dried flower heads, has been used traditionally for medicinal

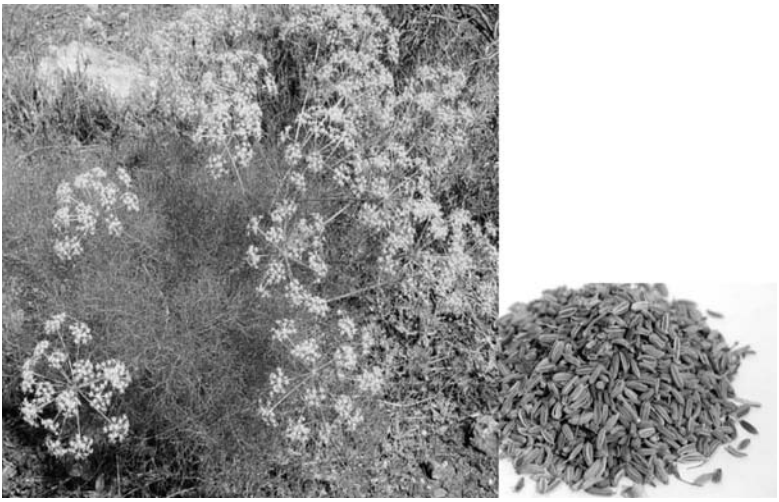

FIGURE 8.23 *Foeniculum vulgare*, fennel (*Jansoon*). (*See the color version of this figure in Color Plates section.*)

purposes. The main constituents of the flowers include several phenolic compounds, primarily the flavonoids apigenin, quercetin, patuletin, and luteolin. The principal components of the essential oil extracted from the flowers are the terpenoids α-bisabolol and its oxides and azulenes, including chamazulene. Chamomile has moderate antioxidant and antimicrobial activities, and significant antiplatelet activity *in vitro*. Animal model studies indicate potent anti-inflammatory action, some antimutagenic and cholesterol-lowering activities, as well as antispasmotic and anxiolytic effects. However, human studies are limited, and clinical trials examining the purported sedative properties of chamomile tea are absent (Figure 8.24).

8.30 *Pimpinella anisum*, ANISE (*JANSOON*)

Pimpinella anisum, anise, is a member of the Apiaceae family that includes fennel, caraway, cumin, cilantro, dill, and carrots. It is commonly used to flavor candy, foods, and liqueurs. The seeds ("fruits") are used in traditional Arab medicine for a wide range of diseases, particularly for their ability to bring about a reduction in gas and bloating and to settle the problems related to digestion. Seed-based remedies are commonly used with infants and children to induce relief from cases of colic; these remedies are also given to people of all ages to help in relieving the symptoms associated with indigestion and nausea arising as a result of different reasons. An additional therapeutic effect of the seeds is their antispasmodic properties, which are effective in reducing the symptoms of menstrual pain, the discomfort during asthma attacks, as well as in the treatment of whooping cough and other spasmodic coughs. Furthermore, remedies made from the seeds are also believed to be able to bring about

FIGURE 8.24 *Chamomilla recutita*, chamomile (*Babonej*). (*See the color version of this figure in Color Plates section.*)

an increase in the production of breast milk; these remedies may also be beneficial in the treatment of impotence and frigidity. The essential herbal oils derived from anise are also used in the treatment of similar complaints in patients. It is recommended that patients should consume the essential oil while they are under careful and responsible professional supervision. Women in the term of pregnancy must also abstain from taking anise, with the exception of minute amounts, such as those normally used during cooking.

8.31 *Zingiber officinale*, GINGER

Zingiber officinale, ginger, has been used as a medicine in Chinese, Ayurvedic, and Greco-Arab and Islamic medicine since ancient times. In China, for example, the underground stem, or rhizome, of the plant ginger has been used to aid digestion and treat stomach upset, diarrhea, and nausea for more than 2000 years. The rhizome of ginger found widespread uses in the Greco-Arab and Islamic medicine. It one of the plants that are mentioned in the Holy Quran as one of the drinks of Paradise: "*And in it, their drink is mixed with ginger*." Ginger has also been used to help treat arthritis, colic, diarrhea, and heart conditions. In addition to these medicinal uses, ginger continues to be valued around the world as an important cooking spice and is believed to help treat the common cold, flu-like symptoms, headaches, and even painful menstrual periods. Currently, health care professionals recommend ginger for helping prevent or treat nausea and vomiting associated with motion sickness, pregnancy, and

FIGURE 8.25 *Zingiber officinale*, ginger (*Zanjabeel*). (*See the color version of this figure in Color Plates section.*)

cancer chemotherapy. It is also used as a digestive aid for mild stomach upset, as support in inflammatory conditions such as arthritis, and may even be used in heart disease or cancer (Figure 8.25).

8.32 *Rosmarinus officinalis*, ROSEMARY (HASALBAN AND IKLIL JABAL)

Rosmarinus officinalis, rosemary, "Hasalban and Iklil jabal" (means crown of the mountain), is a woody shrub with fragrant evergreen needle-like leaves, and blue flowers that last through spring and summer. It is native to the Mediterranean region. It is a member of the mint family Lamiaceae (Figure 8.26). The fresh and dried leaves are traditionally used throughout the Mediterranean region; they have a bitter, astringent taste and are highly aromatic, which complements a wide variety of foods.

R. officinalis contains high levels of iron, calcium, vitamin B6, and a number of potentially biologically active compounds, including antioxidants such as carnosic acid and rosmarinic acid. Other bioactive compounds include camphor (up to 20% in dry rosemary leaves), caffeic acid, ursolic acid, betulinic acid, rosmaridiphenol, and rosmanol.

Rosemary is known for its relax muscle relaxation effects, including the smooth muscles of the digestive tract and uterus. Because of this property it is traditionally used to soothe digestive upsets and relieve menstrual cramps. When used in large amounts it can have the opposite effect, causing irritation of the intestines and cramps. A tea made from the leaves is also taken as a tonic for calming nerves and used as an

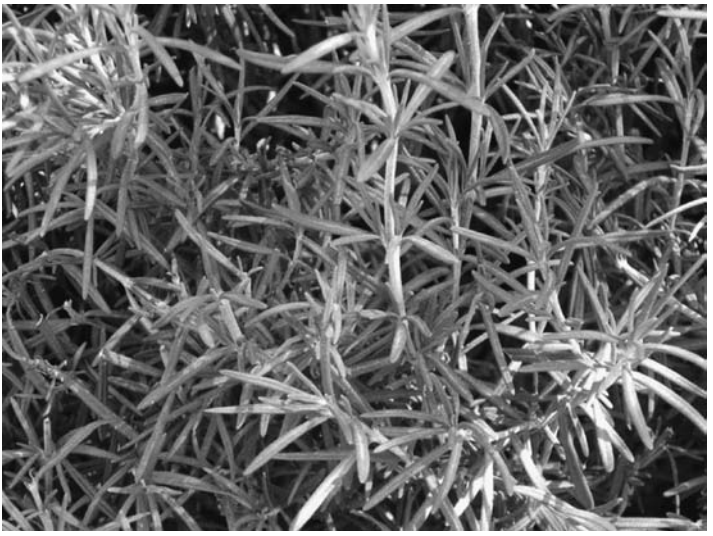

FIGURE 8.26 *Rosmarinus officinalis*, rosemary (*Iklil Jabal*). (*See the color version of this figure in Color Plates section.*)

antiseptic. Several studies indicated that carnosic acid, found in rosemary, exhibit a strong antioxidant and antimicrobial properties [116].

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CHAPTER 9

The Current State of Knowledge of Arab Herbal Medicine

9.1 INTRODUCTION

The Eastern region of the Mediterranean (Syria, Israel, and Palestine) contains at least 3600 plant species of which about 800 are mentioned in medieval medical books for their use as medicinal herbs or botanical pesticides. Recent ethnopharmacological studies have demonstrated that more than 450 medicinal plants are still employed in treating human diseases and are sold or traded in marketplaces in the Mediterranean region and internationally. Usually, herbal-based remedies are administered by practitioners in a standard decoction prepared by boiling plant parts in hot water, infusion in water or oil, or inhalation of essential oils. Other forms of administration include juice, syrup, roasted material, fresh salad or fruit, macerated plant parts, oil, milky sap, poultice, and paste.

Growing public interest in herbal-based remedies is supported by the belief that they are prepared according to the principles of Greco-Arab and Islamic medicine. As a result, many purveyors and institutions of Arab–Islamic herbal medicine are named after the famous scholars Avicenna, Rhazes, Ibn al-Baitar, Al-Zahrawi, or Al-Antaki. Parallel to the increase in the use and popularity of herbal-based therapies, there has been much recent research into the efficacy, the safety, and the practice of medicinal plants, particularly in the Middle East. Some of these plant species have been investigated and their bioactive ingredients extracted to treat various human diseases. In this regard, researchers have published numerous articles and review papers in peer-reviewed journals on this subject. These articles highlight the importance of traditional Arab–Islamic medicine and indicate that the eastern region of the Mediterranean is distinguished from other regions by a rich inventory of herbal-based medicines. As a result, several herbal-based preparations have been tested in cooperation with physicians and have started to be routinely prescribed in Europe and in Mediterranean countries.

Ethnopharmacological studies conducted by different groups in the Middle East support the necessity of proper handling of herbal medicine, which requires both

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national regulation and licensing in order to ensure the supply of appropriate and safe products. Today there are increasing efforts toward the preservation of medicinal plant resources through an increasing emphasis on conservation by way of botanical gardens, greenhouses, herbariums, tissue culture propagation, and seed banks. In addition, several national and international conferences on the current state of research and practice of herbal medicine were organized during the last few years. For instance, in 2007 the authors of this book organized the first regional conference on Arab–Islamic medicine in Amman, Jordan. The conference was designed for research scientists, local and regional traditional healers, international pharmaceutical and medical research companies, medical doctors, ethnopharmacologists, and other parties interested in the study of traditional Arabic and Islamic medicine. Discussions touched on the historical and cultural aspects of Arab–Islamic medicine and its contribution to modern medicine and to human well-being. The latest scientific research on medicinal and aromatic plants, pharmaceutical research, clinical trials, and international legislation and intellectual property rights on Arab–Islamic medicinal plants of the region were also discussed. The conference highlighted the importance of exploring the economically sustainable aspects of Arab–Islamic medical heritage and encouraged investment to develop pharmaceutical products based on this medical system [1–9].

On the basis of the results obtained in our recent survey and other ethnopharmacological potential studies, this chapter provides an overview of the herbal remedies in the Mediterranean. The impact that Arab herbal medicine has on providing general health care for the people in the Mediterranean is also discussed.

9.2 COMMONLY USED MEDICINAL PLANTS IN THE MEDITERRANEAN

The Mediterranean contains approximately 700 medicinal plants that were mentioned in historical Arab medical texts for their use as medicinal herbs. A comprehensive ethnopharmacological study published in 2000 by Lev and Amar from Bar-Ilan University covered selected medicinal plant markets in Israel, belonging to various religious and ethnic communities, and also included a survey of dealers and consumers concerning the healing properties of the herbal-based preparations. The survey yielded information on diverse medicinal materials, of which 310 were identified according to the following classifications: 264 species of plants, 20 species of animals, 19 kinds of minerals, and 7 materials of other or mixed origin. About 50% of the used materials were of local origin, whereas the others were imported from other countries. Similar observations were published in 2003 by Said et al. at the Galilee Society, who conducted a survey on the practice of traditional Palestinian medicine, in which herbal-based medicines comprise a significant and indispensable part of public health care. Furthermore, a recent comprehensive ethnopharmacological survey by the authors of this book reveals that about 450 medicinal plants are in use by Palestinians. Table 9.1 summarizes commonly used medicinal plants in Palestine.

TABLE 9.1 Commonly Used Medicinal Plants and Their Traditional Application by the Palestinian People

Latin Name	English Name	Family	Arabic Name
Erodium malacoides	Mallow leaved storksbill	Geraniaceae	ابرة العجوزة
Brassica oleracea	Kohlrabi	Cruciferae/Brassicaceae	ابو ركبة (فجل غير حار)
Tamarix aphylla	Giant tamarisk	Tamaricaceae	اثل
Pyrus communis	Pear	Rosaceae	اجاص
Emex spinosa	Spiny dock	Polygonaceae	اركيبة (صحراوي)
Myrtus communis	Common myrtle	Myrtaceae	اس
Ruscus aculeatus	Common butchers	Alliaceae/Liliaceae	اس شائك (عرف الديك)
Persea americana	Avocado	Lauraceae	افوكادو
Matricaria recutita	Wild chamomile	Asteraceae/Compositae	اقحوان
Varthemia iphionoides	Common Varthemia	Asteraceae/Compositae	اكتيلا (اشتيليا)
Commiphora myrrha	Bola/myrrh	Burseraceae	المر (مره)
Haplophyllum tuberculatum	Warty rue	Rutaceae	ام جناح / مجننة
Anana comosus/sativus	Pineapple	Bromeliaceae	انانـاس
Origanum vulgare	Oregano/wild marjoram	Lamiaceae/Labiatae	انزار
Oryza	Rice	Poaceae/Gramineae	أرز
Eriobotrya japonica	Medlar tree/loquat	Rosaceae	أسكدنيا
Lantana camara	Red sage/Spanish flag	Verbenaceae	أم كلثوم
Geranium robertianum	Purple Crane's-bill	Geraniaceae	إبرة الراعي
Pyrus syriaca Boiss	Syrian pear	Rosaceae	إجـاص سـوري
Achillea millefojiun	Millfoil/yarrow	Asteraceae/Compositae	إخيليا ام الف ورقة
Matricaria aurea	Wild chamomile	Asteraceae/Compositae	بابونج (قريعة)
Abelmoschus esculentus	Lady's finger/okra	Malvaceae	بامياء
Carica papaya	Papaya	Rutaceae	بباية
Linum pubescens/sativum	Hairy flax	Linaceae	بذر كتان
Citrus aurantium	Orange	Rutaceae	برتقال
Medicago sativa	Alfalfa	Papilionaceae	برسيم حجازي
Prunus section *Prunus*	Plum/gage	Rosaceae	برومياء (جرنك)
Chrysanthemum coronarium	Common Chrysanthemum	Asteraceae/Compositae	بسباس/أقحوان أصفر
Scorzonera papposa	Oriental viper's grass	Asteraceae/Compositae	بشع
Allium cepa	Onion/garden onion	Alliaceae/Liliaceae	بصل
Urginea maritima	Maritime squill	Hyacinthaceae	بصيل (بصل الفار)
Solanum tuberosum	Potato	Solanaceae	بطاطا
Pistacia palaestina	Terebinth tree	Anacardiaceae	بطم فلسطيني
Citrullus vulgaris	Water melon	Cucurbitaceae	بطيخ
Artemisia judaica	Judean wormwood	Asteraceae/Compositae	بعيثران
Petroselinum crispum	Parsley	Apiaceae/Umbelliferae	بقدونس
Sarcopoterium spinosum	Spiny burnet	Rosaceae	بلان (نتش)
Astoma seselifolium	Astoma	Apiaceae/Umbelliferae	بلبسون (بلبلوس)
Quercus calliprinos	Kermes oak	Fagaceae	بلوط
Corylus avellana	Common hazel	Betulaceae	بنـدق
Lycopersicon esculentum	Tomato	Solanaceae	بندورة
Viola tricolor/odorata	Wild pansy	Violaceae	بنفسج
Imperata cylindrica	Cogon grass	Poaceae/Gramineae	بني الشام
Verbascum eremobium	Mullein	Scrophulariaceae	بوصير بريينا
Citrus maxima	Pomelo	Rutaceae	بومـلـه
Sambucus nigra	Elder/black elder	Caprifoliaceae	بيلسان
Sambucus ebulus	Danewort/European dwarf	Caprifoliaceae	بيلسان صغير

(*continued*)

TABLE 9.1 (*Continued*)

Latin Name	**English Name**	**Family**	**Arabic Name**
Nicotiana tabacum	Tobacco	Solanaceae	تبغ (دخان)
Lupinus albus/pilosus	Lupines/wild lupin	Papilionaceae	ترمس / ترمس بري
Citrus medica	Citron	Rutaceae	ترنج
Pyrus malus/Malus sylvestris	Apple	Rosaceae	تفاح
Calotropis procera	Sodom apple	Asclepiadaceae	تفاح سدوم (عشّر)
Phoenix dactylifera	Date palm	Palmae/Arecaceae	تمر
Tamarindus indica	Tamarind tree	Caesalpiniaceae	تمر هندي
Morus nigra	Mulberry	Moraceae	توت
Fragaria grandiflora	Strawberry	Rosaceae	توت أرضـي
Ficus carica	Common fig tree	Moraceae	تين
Allium ampeloprgsurn	Great round-headed garlic	Alliaceae/Liliaceae	ثوم الحيـة
Allium sativum	Garlic	Alliaceae/Liliaceae	ثوم بستاني
Allium schoenoprasum	Chive	Alliaceae/Liliaceae	ثوم معمر
Thuja occidentalis	Tree of life	Pinales/Coniferales	ثويا، عفص
Eruca sativa	Garden rocket	Cruciferae/Brassicaceae	جرجير
Smilax aspera	Rough bindweed	Alliaceae/Liliaceae	جريح
Daucus carota	Carrot	Cruciferae/Brassicaceae	جزر بستاني
Teucreium creticum	Germander	Lamiaceae/Labiatae	جعدة الأفعى
Teucrium capitatum/polium	Mountain germander	Lamiaceae/Labiatae	جعدة (جعدة الصبيان)
Teucrium divaricatum	Astride germander	Lamiaceae/Labiatae	جعدة بلوطية (كماندرة)
Lathyrus aphaca	Yellow vetchling	Papilionaceae	جلبان
Ficus sycomorus	Sycamore fig/fig-mulberry	Moraceae	جميـز
Panax ginseng	Asiatic ginseng	Araliaceae	جنسنغ
Psidium guajava	Guava/apple guava	Myrtaceae	جـوافا
Juglans regia	Walnut	Juglandaceae	جوز
Ayristica fragrans	Nutmeg tree	Myristicaceae	جوز الطيب
Cocos nucifera	Coconut palm	Palmae/Arecaceae	جـوز الهند
Lepidium sativum	Garden cress	Cruciferae/Brassicaceae	حب الرشاد
Cyperus esculentus	Chufa sedge/tigernut sedge	Cyperaceae	حـب العـزيـز
Mentha pulegium	Pennyroyal	Lamiaceae/Labiatae	حبق
Ajuga iva	Herb ivy	Lamiaceae/Labiatae	حرص (شندقورة)
Barbarea Vulgaris	Variegata	Cruciferae/Brassicaceae	حرف بري
Peganum harmala	Peganum/wild rue	Zygophyllaceae	حرمل ، حرملان
Eremostachys laciniata	Common caper bush	Lamiaceae/Labiatae	حزنبل
Galium aparine	Goosegrass/catchweed	Rubiaceae	حشيشة الافاعي (دبيق)
Oenothera drummondii	Evening primrose	Onagraceae	حشيشة الحمار
Echinacea purpurea	Echinacea	Asteraceae/Compositae	حشيشة الذهب
Valeriana officinalis	Common valerian	Valerianaceae	حشيشة القط
Rosmarinus officinalis	Rosemary	Lamiaceae /Labiatae	حصلبان (إكليل الجبل)
Hypericum triquetrifolium	Tumble St. John's- wort	Hypericaceae/Clusiaceae	حلاوة الخرفان (داذي)
Trigonella foenum/ graeceum	Fenugreek	Papilionaceae	حلبة (حند قوق, رومية)
Euphorbia hierosolymitana	Jerusalem spurge	Euphorbiaceae	حلبلوب

TABLE 9.1 (*Continued*)

Latin Name	English Name	Family	Arabic Name
Ferula asafoetida	Asafetida	Apiaceae/Umbelliferae	حلتيت ,صمغ الانجدان
Desmostachya bipinnata	Lovegrass	Poaceae/Gramineae	حلفا
Picris sprengeriana	Yellow succory	Asteraceae/Compositae	حلوان
Cicer arietinum	Chick pea	Leguminosae/ Fabaceae	حمص
Rumex acetosa	Common sorrel/spinach dock	Polygonaceae	حميض
Oxalis pes-caprae	Cape sorrel	Oxalidaceae	حميض صغير
Rumex cyprius	Pink sorrel	Polygonaceae	حميضة
Moricandia nitens	Moricandia	Cruciferae/Brassicaceae	حميم (حاميم)
Lawsonia alba	Henna plant/Judas tree	Lythraceae	حنّاء (حنّة)
Melilotus albus	White melilot	Papilionaceae	حندقوق شائع
Melilotus officinalis	Sweet glover	Papilionaceae	حندقوق شائع
Citrullus colocynthis	Bitter apple/bitter gourd	Cucurbitaceae	حنظل
Turincia tuberosa	Tuberous dandelion	Asteraceae/Compositae	حنونة صفرة
Bidens pilosa	Spanish needle	Asteraceae/Compositae	حوسيكه
Diplotaxis erucoides	White wall-rocket	Cruciferae/Brassicaceae	حويرة
Sedum hispanicum	Biting stonecrop	Crassulaceae	حي العالم
Plumbago europaea	Khamsheh	Plumbaginaceae	خامشة
Althaea rosea	Hollyhock	Malvaceae	خباز ي (خبازى برية)
Malva micaemis/nicaensis	Common mallow	Malvaceae	خبيزة
Lavatera trimestris	Queen mallow	Malvaceae	خبيزة الفار
Brassica nigra	Black mustard	Cruciferae/Brassicaceae	خردل أسود
Sinapis arvensis	Charlock	Cruciferae/Brassicaceae	خردل بري
Atractylis comosa	Beantifue distaff thistle	Asteraceae/Compositae	خرشف بري
Cymara scolymus/Helianthus tuberosus	Artichoke/Jerusalem artichoke	Asteraceae/Compositae	خرشوف (أرضي شوكي, خب)
Silybum marianum	Holy thistle/milky thistle	Asteraceae/Compositae	خرفيش جمال
Notobasis syriaca	Syrian thistle	Asteraceae/Compositae	خرفيش حمير (غزلان)
Ceratonia siliqua	Carob/locust tree	Caesalpiniaceae	خروب
Ricinus communis	Castor oil plant	Euphorbiaceae	خروع
Lavandula officinalis	Lavender	Lamiaceae/Labiatae	خزامى
Lactuca virosa/serriola	Wild lettuce/prickly lettuce	Asteraceae/Compositae	خس بري
Lactuca sativa	Lettuce	Asteraceae/Compositae	خس بستاني
Papaver somniferum	Poppy seed	Rutaceae	خشخاش
Astragalus macrocarpus	Milk vetch	Leguminosae/Fabaceae	خصي الثعلب
Althaea officinalis	Marshmallow	Malvaceae	خطمة
Althaea rosea/Alcea setosa	Hollyhock/marshmallow	Malvaceae	خطمية (خبيزة منورة)
Avena sterilis	Wild oat	Poaceae/Gramineae	خفور (شوفان)
Ammi visnaga	Toothpick	Apiaceae/Umbelliferae	خلة (خلة شيطانية ,برية)
Prunus persica	Peach	Rosaceae	خوخ (دراق)
Salvia dominica	Dominica sage	Lamiaceae/Labiatae	خويخة
Cucumis sativus	Cucumber	Malvaceae	خيار
Datura stramonium	Thorne apple	Solanaceae	داتورة
Nerium oleander	Oleander/rose bay	Apocynaceae	دفلة
Platanus orientalis	Oriental plane tree	Platanaceae	دلب

(*continued*)

TABLE 9.1 (*Continued*)

Latin Name	English Name	Family	Arabic Name
Adonis aleppica	Aleppo adonis	Ranunculaceae	دم الحنونة
Zea mays	Corn/maize	Poaceae/Gramineae	ذرة
Sorghum vulgare	Kaffer corn/broom corn	Poaceae/Gramineae	ذرة بيضاء (ذرة مكانس)
Equisetum arvense	Horsetail	Equisetaceae	ذنبة الفرس
Retama raetam	White broom	Papilionaceae	رتيم (رثم)
Paronychia argentea	Mountain knotgrass	Caryophyllaceae	رجل الحمامة
Nasturtium officinale	Watercress	Cruciferae/Brassicaceae	رشاد ماء (جرجير مائي)
Verbena officinalis	Common vervain	Verbenaceae	رعي الحمام
Punica Granatum	Pomegranate	Punicaceae	رمان
Hammada salicornica	Hammada	Chenopodiaceae	رمث
Ocimum basilicum	Sweet basil	Lamiaceae/Labiatae	ريحان / حبق
Plantago ovata	Ovate plantain	Plantaginaceae	زبّاد / ينامة (بذر قاطونا)
Majorana syriaca	Wild thyme/marjoram	Lamiaceae/Labiatae	زعتر
Satureja thymbra	Summer savory	Lamiaceae/Labiatae	زعتر حمير
Coridothymus capitatus	Capitate thyme	Lamiaceae/Labiatae	زعتر فارسي
Micromeria nervosa	Thyme	Lamiaceae/Labiatae	زعتر ناعم
Crataegus aronia	Spiny hawthorn	Rosaceae	زعرور شائك
Calamintha incana	Gray calamint/Italian	Lamiaceae/Labiatae	زعطمان (نعنعة البلاط)
	senna		
Crocus sativus	Saffron	Iridaceae	زعفران
Achillea ptarmica	Sneezewort	Asteraceae/Compositae	زعوط (عود العطـاس)
Lavandula coronopifolia	Lavender	Lamiaceae/Labiatae	زعيتران
Origanum dayi	Desert origanum	Lamiaceae/Labiatae	زعيترة
Citrus aurantium	Bitter orange	Rutaceae	زفـر
Balanites aegyptiaca	Jericho balsam	Zygophyllaceae	زقوم
Ferula hermonis	Lebanese viagra	Apiaceae/Umbelliferae	زلوع
Androcymbium palaestinum	Desert bulb	Alliaceae/Liliaceae	زنبقة الغور
Zingiber officinale	Common ginger	Zingiberaceae	زنجبيل
Melia azedarach	Azedarach	Meliaceae	زنزلخت
Passiflora edulis	Blue passion flower	Passifloraceae	زهرة الساعة
Micromeria myrtifolia	Savory	Lamiaceae/Labiatae	زوفا
Olea europaea	Olive tree/common olive	Oleaceae	زيتون
Elaeagnus angustifolia	Oleaster/Russian olive	Elaeagnaceae	زيزفون
Spinacia oleracea	Spinach	Chenopodiaceae	سبانخ
Ziziphus spina-christi	Christ thorn jujube	Rhamnaceae	سدر(دوم ,نبق المسيح)
Polypodium vulgare	Common polypody/fern	Polypodiaceae	سرخس حلو
Cupressus sempervirens	Funeral cypress	Cupressaceae	سرو
Arisarum vulgare	Friar's cowl	Araceae	سريج الغولة (دنيدلة)
Pistacia lentiscus	Mastic	Anacardiaceae	سريس (مستكة)
Cyperus rotundus	Carrot/nutgrass	Poaceae/Gramineae	سعد (سعيدة)
Cydonia vulgaris	Quince tree	Rosaceae	سفرجل
Vicia hybrida	Hairy yellow vetch	Papilionaceae	سقاق ابو لبن
Hyoscyamus aureus	Golden henbane	Solanaceae	سكران (بنج)
Cassia italica	Italian senna/turnip	Caesalpiniaceae	سلامكة (سنامكة)
Lonicera etrusca	Italian honeysuckle	Caprifoliaceae	سلطان الغابة
Taraxacum cyprium	Dandelion	Asteraceae/Compositae	سلطة الرهبان
Beta vulgaris	Beet/red beet	Chenopodiaceae	سلق بري / شمندر

TABLE 9.1 (*Continued*)

Latin Name	English Name	Family	Arabic Name
Juncus acutus	Sharp rush	Juncaceae	سمار
Rhus coriaria	Sumach	Anacardiaceae	سماق (مخانش)
Sesamum indicum/ orientale	Sesame	Pedaliaceae	سمسم
Solanum nigrum	Black nightshade	Solanaceae	سموة (عنب الثعلب)
Cleome droserifolia	Spider flower	Capparaceae	سموه
Eminium spiculatum	Wake robin	Araceae	سميعة (جعدة مرقطة)
Silybum marianum	Milk thistle	Asteraceae/Compositae	سنارية
Quercus ithaburensis	Tabor oak	Fagaceae	سنديان (ملّ, الملول)
Symphytum officinale	Common comfrey	Boraginaceae	سنفيطون
Salvadora persica	Toothbrush tree	Salvadoraceae	سواك
Glycyrrhiza glabra	Liquorice/licorice	Leguminosae/Fabaceae	سوس (عرق سوس)
Lilium candidum	Madonna lily	Alliaceae/Liliaceae	سوسن أبيض
Hyoscyamus niger	Henbane	Solanaceae	سوكران (بنج)
Rhamnus palaestina	Palestine buckthorn	Rhamnaceae	سويد فلسطيني
Acacia raddiana	Twisted acacia	Mimosaceae	سيال
Conium maculatum	Mother die/poison hemlock	Apiaceae/Umbelliferae	سيكران
Camellia sinensis	Tea plant	Theaceae	شاي
Anethum graveolens	Dill	Apiaceae/Umbelliferae	شبت (عين جرادة)
Ononis spinosa	Spiny restharrow	Papilionaceae	شبرق
Acacia farnesiana	Needle bush	Mimosaceae	شجر السنط (عنبـر)
Hordeum vulgare	Barley	Poaceae/Gramineae	شعير
Terminalia chebula	Black myrobalan	Combretaceae	شعـير هنـدي
Anemone coronaria	Crown anemone	Ranunculaceae	شقائق النعمان
Cucumis melo	Melon	Cucurbitaceae	شمام (بطيخ أصفر)
Foeniculum vulgare	Florence fennel	Apiaceae/Umbelliferae	شومر
Artemisia arborescens	Shrubby wormwood	Asteraceae/Compositae	شيبة
Artemisia absinthium	Absinth/wormwood	Asteraceae/Compositae	شيبــة النبـي (افسنتين)
Artemisia herba/alba	White wormwood	Asteraceae/Compositae	شيح
Seneca vernalis	Spring groundsel	Asteraceae/Compositae	شيخ الربيع
Cyclamen persicum	Persian cyclamen	Primulaceae	صابون راعي (زقوقيا)
Saponaria officinalis	Soapwart	Caryophyllaceae	صابونية (شرش الحلاوة)
Aloe vera	Aloe	Alliaceae/Liliaceae	صبار (ألوفيرا)
Opuntia ficus-indica	Prickly pear/Indian fig	Cactaceae	صبر
Salix alba	White willow	Plumbaginaceae	صفصاف
Isatis lusitanica	Aleppo woad	Cruciferae/Brassicaceae	صفير(عشبة الصفر)
Mesembryanthemum forsskalii	Forskal fig/marigold	Aizoaceae	صمغ (غاصول)
Santalum album	Sandalwood	Santalaceae	صندل
Pinus halepensis	Aleppo pine	Pinaceae	صنوبر / صـنوبـر حلبـي (حـب قريـش)
Pinus pinea	Stone pine	Pinaceae	صنوبر صخري
Ridolfia segetum	Bishop's weed	Apiaceae/Umbelliferae	ضراط الشومر
Artemisia dracunculus	Tarragon/estragon	Asteraceae/Compositae	طرخون
Inula viscosa	Inula/lesser elecampane	Asteraceae/Compositae	طيون
Alhagi maurorum	Camel thorn/alhagi manna	Papilionaceae	عاقول
Helianthus annuus	Sunflower	Asteraceae/Compositae	عباد الشمس

(*continued*)

TABLE 9.1 (*Continued*)

Latin Name	English Name	Family	Arabic Name
Styrax officinalis	Styrax	Styracaceae	عبهر
Anabasis articulata	Jointed anabasis	Chenopodiaceae	عجرام
Lens culinaris	Lentils	Papilionaceae	عدس
Ajuga chamaepitys	Ground pine/bugle	Lamiaceae/Labiatae	عرصف (حشيشة الجرح)
Juniperus phoenicea	Red juniper	Cupressaceae	عرعر
Cercis siliquastrum	Judas tree/cumin seed	Caesalpiniaceae	عروس الغابة
Mercurialis annua	Annual mercury	Euphorbiaceae	عشبة الجارات
Sanguisorba minor	Burnet/salad burnet	Rosaceae	عشبة الجراح
Ajuga orientalis	Eastern bugle	Lamiaceae/Labiatae	عشبة الدم الشرقية
Ceterach officinarum	Finger fern	Aspleniaceae	عشبة الذهبية
Micromeria fruticosa	White savory/thyme	Lamiaceae/Labiatae	عشبة الشاي
Rhamnus alaternus	Alaternus/Barren privet	Rhamnaceae	عشبة الصفار
Leontice leontopetalum	Lion's leap	Berberidaceae	عشبة الطجطيجة
Cymbopogon citratus	Lemongrass	Poaceae/Gramineae	عشبة الليمون
Polygonum equisetiforme	Horsetail knotweed	Polygonaceae	عصا الراعي (مكسرالنير
Carthamus tinctorius	Safflower	Asteraceae/Compositae	عصفر
Pelargonium graveolens	Pelargonium	Geraniaceae	عطرة
Rheum palaestinum	Rhubarb	Polygonaceae	عطرفان (ريباس)
Asphodeline lutea	Jacob's rod/yellow asphodel	Alliaceae/Liliaceae	عطعاط (أبو صوي)
Zygophyllum dumosum	Syrian bean caper	Zygophyllaceae	عغبة
Polygonum aviculare	Common knotgrass/birdweed	Polygonaceae	عقيدي
Gundelia tournefortii	Tumble thistle/gundelia	Asteraceae/Compositae	عكوب (كعوب)
Cichorium pumilum	Dwarf chicory	Asteraceae/Compositae	علت (هندباء)
Ephedra foemina	Sand cherry	Ephedraceae	علد
Clematis cirrhosa	Virgin's bower	Ranunculaceae	علندا (شرش الريح)
Pituranthos tortuosus	Zaguh/gazuh	Apiaceae/Umbelliferae	عليجيان (زجوح)
Rubus sanguineus	Holy bramble	Rosaceae	عليق بري (توت بري)
Viscum cruciatum	Mistletoe	Loranthaceae	عناب (دبيق الزيتون)
Vinca rosea	Rose periwinkle	Apocynaceae	عناقية (فينكا)
Vitis vinifera	Grapevine	Vitaceae	عنب
Bryonia syriaca	Syrian bryone	Cucurbitaceae	عنب الحية
Nitraria retusa	Common nifrafia	Zygophyllaceae	عورجود (غردق)
Verbascum sinaiticum	Scallop/leaved mullein	Scrophulariaceae	عورور
Lycium europaeum	European boxthorn	Solanaceae	عوسج (عرقد ,غرقد)
Asphodelus ramosus	Tall asphodel	Alliaceae/Liliaceae	عوصلان (عصا الراعي)
Silene aegyptiaca	Egyptian catchfly	Caryophyllaceae	عونية، أحلوان
Anagallis arvensis	Red pimpernel	Primulaceae	عين الجمل
Abrus Precatorius	Jequirity/crab's eye/saga tree	Leguminosae/Fabaceae	عين الديك
Laurus nobilis	Sweet bay	Lauraceae	غار
Vitex agnus/castus	Chaste tree/lilac chaste tree	Verbenaceae	غار الوديان (كف مريم)
Pulicaria desertorum	Common fleabane	Asteraceae/Compositae	غيل
Amaranthus retroflexus	Reflexed amaranth	Amaranthaceae	غبيرة (عرف الديك)
Geranium molle	Dove's foot cranesbill	Geraniaceae	غرنة
Tamus communis	Common black bryony	Dioscoreaceae	فاشرشين
Phaseolus vulgaris	Bean	Leguminosae/Fabaceae	فاصولياء

TABLE 9.1 (*Continued*)

Latin Name	English Name	Family	Arabic Name
Raphnus sativus	Radish	Cruciferae/Brassicaceae	فجل
Armoracia lapathifolia	Horseradish	Cruciferae/Brassicaceae	فجل حار
Portulaca oleracea	Garden purslane	Portulacaceae	فرفحينة (رجلة, البقلة الحمقاء)
Chenopodium murale	Nettle-leaved goosefoot / black mustard	Chenopodiaceae	فسا الكلب
Arachis hypogea	Peanut	Leguminosae/Fabaceae	فستـق
Nepeta curviflora	Catnip	Lamiaceae/Labiatae	فعلجي
Ecballium elaterium	Squirting cucumber	Cucurbitaceae	فقوس (قثاء) الحمار
Capsicum annuum	Sweet pepper	Solanaceae	فلفل
Piper nigrum	Black pepper	Rutaceae	فلفل اسود
Capsocum frutescens	Cayenne pepper	Solanaceae	فلفل أحمر
Pimenta officinalis	Pimento/allspice	Myrtaceae	فليفلة شائعة
Vanilla planifolia	Vanilla	Orchidaceae	فنيلة
Rubia tenuifolia	Eaved madder	Rubiaceae	فوّة
Vicia faba	Broad bean	Leguminosae/Fabaceae	فول
Ruta chalepensis	African rue/common rue	Rutaceae	فيجن (سذاب)
Tropaeolum majus	Nasturtium	Tropaeolaceae	قابوسين
Catha edulis	Khat	Celastraceae	قات
Phagnalon rupestre	Wooly fleabane	Asteraceae/Compositae	قديحة (جديح, قديح)
Eryngium creticum	Field eryngo	Apiaceae/Umbelliferae	قرصعنة (شوك العقربة)
Eryngium maritimum	Sea holly	Apiaceae/Umbelliferae	قرصعنة ساحلية (عانة)
Cinnamomum zeylanicum	Cinnamon	Lauraceae	قرفة (دار صيني)
Brassica oleracea	Cauliflower	Cruciferae/Brassicaceae	قرنبيـط
Eugenia caryophyllata	Cloves tree	Myrtaceae	قرنفل
Cerastium glomeratum	Sticky mouse-ear	Caryophyllaceae	قرنيـه
Urtica pilulifera	Roman nettle	Urticaceae	قريص
Lamium moschatum	Musk deadnettle	Lamiaceae/Labiatae	قريص كاذب (ثم السمكة)
Stellaria media	Common chickweed	Caryophyllaceae	قزازة (نجمية)
Nigea sativa/Nigella Sativa	Black cumin/Nigella	Ranunculaceae	قزحة (حبة البركة)
Parietaria diffusa/judaica	Wall pellitory	Urticaceae	قزيزه (قزاز)
Saccharum officinarum	Sugarcane	Poaceae/Gramineae	قصب السكر
Arundo donax	Cyprus cane	Poaceae/Gramineae	قصب شائع
Cnicus benedictus	Blessed thistle	Asteraceae/Compositae	قصوبة
Glaucium corniculatum	Red horned poppy	Rutaceae	قطرة العين
Atriplex halimus	Shrubby saltbush	Chenopodiaceae	قطف (مالحة)
Arbutus andrachne	Eastern strawberry tree	Ericaceae	قطلب
Euphorbia tirucalli	Pencil cactus	Euphorbiaceae	قلم الرصاص
Triticum aestivum	Common wheat	Poaceae/Gramineae	قمح
Calicotome villosa	Spiny broom	Papilionaceae	قندول (قنديل)
Cardaria draba	Hoary pepperwort	Cruciferae/Brassicaceae	قنيبرة
Coffea arabica	Coffee	Rubiaceae	قهوة (بن)
Echinops adenocaulos	Carthamus	Asteraceae/Compositae	قوص
Calendula officinalis	Marigold	Asteraceae/Compositae	قوقحان
Achillea fragrantissima	Yarrow/lavender cotton	Asteraceae/Compositae	قيصوم (جيصوم)
Anacardium occidentalis	Cashew/cashew nut	Anacardiaceae	كاشـو
Cinnamomum camphora	Camphor	Lauraceae	كافور

(*continued*)

TABLE 9.1 (*Continued*)

Latin Name	English Name	Family	Arabic Name
Threobroma cacao	Cacao	Sterculiaceae	كاكاو
Capparis spinosa	Common caper/thorny caper	Capparaceae	كبار شوكي (قبار)
Allium porrum	Leek	Alliaceae/Liliaceae	كراث
Carum carvi/Bunium elegans	Caraway/turmeric	Apiaceae/Umbelliferae	كراوية
Prunus avium/Prunus mahaleb	Cherry/mahaleb cherry	Rosaceae	كرز (محلب)
Apium graveolens	Wild celery	Apiaceae/Umbelliferae	كرفس
Hibiscus sabdariffa	Roselle	Malvaceae	كركدية (الشاي الأحمر)
Curcuma longa	Long rooted curcuma	Zingiberaceae	كركم
Vitis vinifera	Common grape vine	Vitaceae	كرمة
Marrubium vulgare	White horehound	Lamiaceae/Labiatae	كريهة (حشيشة الكلب)
Coriandrum sativum	Coriander	Apiaceae/Umbelliferae	كزبرة (كسبره)
Adiantum capillus-veneris	Venus hair/maidenhair fern	Adiantaceae	كزبرة البئر
Pancratium maritimum	Sea pancratium	Amaryllidaceae	كعبول
Alchemilla vulgaris	Lady's mantle/lion's foot	Rosaceae	كف الاسد (رجل الأسد)
Anastatica hierochuntica	Rose of jericho	Cruciferae/Brassicaceae	كف مريم (كف العذراء)
Ferula communis	Common giant fennel	Apiaceae/Umbelliferae	كلخ
Triticum aestivum	Common wheat	Poaceae/Gramineae	كمأه (كميه)
Cuminum cyminum	Cumin seed	Apiaceae/Umbelliferae	كمون
Cucurbita pepo	Courget	Cucurbitaceae	كوسا
Capsella bursa-pastoris	Shepherd's purse	Cruciferae/Brassicaceae	كيس (جراب) الراعي
Eucalyptus camaldulensis	Red river gum	Myrtaceae	كينا
Lamium album	White archangel/dead nettle	Lamiaceae/Labiatae	لاميون أبيض
Boswellia carterii	Boswellia serrata	Burseraceae	لبان ذكر (بخور، كندر)
Trichodesma africanum	African trichodesma	Boraginaceae	لزيقة
Anchusa strigosa	Prickly alkanet/bugloss	Boraginaceae	لسان الثور (حمحم)
Onopordum cynarocephalum	Cotton thistle	Asteraceae/Compositae	لسان الجمل
Plantago major	Greater plantain/soldier herb	Plantaginaceae	لسان الحمل (أذن الجدي)
Scorpiurus muricatus	Prickly scorpion tail	Papilionaceae	لسان الكلب
Cynoglossum creticum	Hound's tongue	Boraginaceae	لسان الكلب
Salvia hierosolymitana	Jerusalem sage	Lamiaceae/Labiatae	لسينة
Brassica campestris	Cabbage	Cruciferae/Brassicaceae	لفت
Cistus creticus	Soft-hairy rockrose	Cistaceae	لوبد
Amygdalus communis	Almond	Rosaceae	لوز
Arum palaestinum	Palestinian Arum	Araceae	لوف فلسطيني
Lippia citriodora	Lemon verbena	Verbenaceae	لويزة
Citrus paradisi	Grapefruit	Rutaceae	ليمون الجنة (جريفوت)
Citrus limon	Lemon	Rutaceae	ليمون الحامض
Mangifera indica	Mango	Anacardiaceae	مانجا
Umbilicus intermedius	Pennywort/navelwort	Crassulaceae	مخلد
Centaurea iberica	Shrubby centaury	Asteraceae/Compositae	مرار
Origanum majorana	Sweet marjoram	Lamiaceae/Labiatae	مردقوش (زوباع)
Sonchus oleraceus	Common sow thistle	Asteraceae/Compositae	مرير

TABLE 9.1 (*Continued*)

Latin Name	English Name	Family	Arabic Name
Brassica oleracea	Turnip/cabbage /caraway	Cruciferae/Brassicaceae	ملفوف
Corchorus olitorius	Jew's mallow	Tiliaceae	ملوخية
Melissa officinalis	Common balm	Lamiaceae/Labiatae	مليسا (ترنجان)
Musa paradisiacal	Banana	Musaceae	مـوز
Thymelaea hirsuta	Hairy thymelaea	Thymelaeaceae	ميتنان
Salvia officinalis	Common sage	Lamiaceae/Labiatae	ميرمية
Salvia fruticosa	Three-lobed sage	Lamiaceae/Labiatae	ميرمية (جعساس,شجيرة)
Celtis australis	European nettle tree	Ulmaceae	ميس (ميس الريم)
Stellaria media	Common chickweed	Caryophyllaceae	نجمية
Asteriscus graveolens	Stinkwort	Asteraceae/Compositae	نجود صحراوي
Cynodon dactylon	Bermuda grass	Poaceae/Graminae	نجيل
Phoenix dactylifera	Date palm	Palmae/Arecaceae	نخيل
Satureja hortensis	Summer savory	Lamiaceae/Labiatae	ندغ
Narcissus tazetta	Primrose peerless	Amaryllidaceae	نرجس
Mentha spicata/piperita	Mint/peppermint	Lamiaceae/Labiatae	نعناع (نعنع)
Mentha longifolia	Horse mint	Lamiaceae/Labiatae	نعنعة القناة (نعنـع بـري)
Mentha aquatica	Water mint	Lamiaceae/Labiatae	نعنعة الماء (القاق)
Trifolium purpureum	Purple clover	Papilionaceae	نفلة (خبز القاف)
Datura innoxia	Hairy thornapple	Solanaceae	نفير
Cistanche tubulosa	Broomrape	Orobanchaceae	هالوك
Cuscuta campestris	Clover dodder	Convolvulaceae	هالوك (حامول)
Asparagus aphyllus	Prickly asparagus	Alliaceae/Liliaceae	هليون
Elettaria cardamomum	Cardamom	Zingiberaceae	هيل
Rosa centifolia	Rose phoenicia	Rosaceae	ورد جوري
Rosa canina	Dog rose	Rosaceae	ورد سيـاج (ورد بري)
Ononis natrix	Sticky restharrow	Papilionaceae	وسبة رفيعة
Ononis pubescens	Glandular restharrow	Papilionaceae	وسبة غدية
Jasminum fruticans	Bush jasmine/wild jasmine	Oleaceae	ياسمين
Jasminum officinale	Jasmine of poetry	Oleaceae	ياسمين أبيض
Pimpinella anisum	Anise/seed/henna plant	Apiaceae/Umbelliferae	يانسون (أنيسون)
Mandragora officinalis	Mandrake	Solanaceae	يبروج (تفاح المجن)
Prosopis farcta	Dwarf mesquite	Leguminosae	ينبوت (عقول)

Abu-Irmaileh and Afifi from Jordan University in Amman surveyed the situation of herbal medicine sales in Jordan, where herbal medicine is practiced by a rapidly diminishing number of experienced traditional healers and is currently increasing among mainly untrained individuals. The authors interviewed more than 100 herbalists throughout the country. The data included the types of herbs present in the market, recommendations made by herbalists for the treatment of specified ailments, the level of education and training of the herbalists, and other miscellaneous observations. More than 150 herbal-based preparations were available in natural products shops (attarah). Twenty-seven plant species were found to be common medicinal plants and are sold in most attarah shops in Jordan. Nine plant species were categorized as most prevalent, since they are very well known in local traditional medicine and sold in all attarah shops, and they are considered safe without documented adverse effects, except when misused or not properly handled. The

remaining 17 plant species, to a certain extent considered as less commonly used plants, are also sold. This group includes some plants that contain harmful compounds. Included among them are *Peganum harmala* and the seeds of *Ricinus communis* (see Chapter 8 for more details). *Peganum harmala* is traditionally used in the form of a decoction in the treatment of male impotence. Overdose of the decoction can be harmful as the plant contains many potent alkaloids such as harman, harmalan, and harmalin, which are highly toxic and may accumulate to dangerous concentrations in the body of the patient; in most cases of traditional medicine, the recommended treatment period spans 3–12 months. The seeds of *Ricinus communis* contain the toxic polypeptide ricin, a heat-labile compound that is removed from the medicinally used fixed oil obtained from *Ricinus communis*, which is very well known for its laxative properties. In addition to the usage stated above, oral intake of the seeds is recommended by some traditional healers in Jordan as a female contraceptive, despite the fact that five to eight seeds may kill a mature person.

As in most Arab countries, medicinal herbs are sold in attarah shops in Jordan and are either requested specifically by the patient or recommended by the herbalist. Their widespread use and popularity have raised concern regarding the professionalism of practitioners, as well as fears about the quality, efficacy, and safety of "natural" products available on the market. Many herbalists promote the herbs they have in their shops regardless of their appropriateness to the disease. In some cases, the herb is recommended to the patient by a community member who had received the same treatment. The plant and herbal-based remedies are sold as single plant, prepacked mixtures, or freshly mixed preparations. An additional observation by Abu-Irmaileh and Afifi was that unsuitable storage conditions for plant materials exist in some attarah shops. In a few cases, plant materials were stored in inadequately ventilated stores with poor hygiene conditions, where they are liable to rodent attack; similarly, some plant material was found to be rotten or infested with insects [4–12].

Several ethnopharmacological surveys from other Arab countries such as Syria, Morocco, Yemen, and Egypt have been recently published. For instance, a survey on the uses of medicinal plants in the coastal Mediterranean region of Egypt recorded 230 plant species belonging to eight families. The families of high representation are Compositae (17%), Leguminosae (11.4%), Gramineae (10.5%), and Chenopodiaceae (7.9%). Of the studied species, 62% are common and about 24.9% are occasional, while 13% are rare; 60% of the studied species are perennials and 2.2% are biennials while 40.2% are annuals; 89% percent of the studied plants have multipurpose medicinal uses.

Despite the prevalence of modern medicine, traditional herbal medicine continues to be a viable health alternative for the large and underprivileged sector of the Moroccan population. Heterogeneous ecological conditions in Morocco have favored the growth of approximately 42,000 plants species, divided into 150 families and 940 genuses, spread throughout the entire country with an area of 715,000 km^2. The Moroccan pharmacopoeia dates back to 711 AD, which marks the Arab–Islamic expansion in Europe (see Chapters 1 and 10), and was further developed and enriched by the knowledge introduced by various ethnic groups that migrated to Morocco from many areas, including the Arabs from the Middle-East, the Andalusians and Jews

from Europe, and the Blacks from Sudan, Senegal, and Niger. Noteworthy, Arab–Islamic medicine was taught in Moroccan universities at Quarawin and Zaytouna until 1893, when the practice was stopped by the French colonialists. Several ethnopharmacological studies indicate that the traditional medicine of different Moroccan ethnic groups (such as the Arabs, Sahraouis, Soussis, and Rifains) is still popular and relatively well preserved, being passed on from generation to generation by oral communication and through the written record.

As discussed in Chapter 10, some institutions of higher learning expressed great interest in the field of herbal-based medicines. As a result, numerous medicinal plants and their traditional uses have been documented and published. An ethnopharmacological study published in 2007 by Lyoussi and coworkers at the University of Fez in the Errachidia province in southeastern Morocco surveyed the main medicinal plants used in folk medicine to treat arterial hypertension and diabetes mellitus. Four hundred individuals, who knew about and/or had used the medicinal plants for the indicated diseases, including some herbal healers, were interviewed throughout different regions of the province. Results obtained indicate that 64 medicinal plants belonging to 33 families are used. Of these, 45 are used for diabetes, 36 for hypertension, and 18 for both the diseases. Of these plants, 34% grow in the wild, 44% are cultivated, and 22% are not indigenous to the area and are brought from other parts of Morocco or from outside the country. In addition, results show that 78% of the patients regularly use these medicinal plants. In this region, the most frequently used plants to treat diabetes include *Ajuga iva*, *Allium cepa*, *Artemisia herba-alba*, *Carum carvi*, *Lepidium sativum*, *Nigella sativa*, *Olea europaea*, *Peganum harmala*, *Phoenix dactylifera*, *Rosmarinus officinalis*, and *Zygophyllum gaetulum*, and those used to treat hypertension include *Ajuga iva*, *Allium cepa*, *Allium sativum*, *Artemisia herba-alba* Asso, *Carum carvi*, *Nigella sativa*, *Olea europaea*, *Rosmarinus officinalis*, *Origanum majorana*, *Peganum harmala*, and *Phoenix dactylifera*. The local people recognize the plants that are toxic, such as *Citrullus colocynthis*, *Datura stramonium*, *Nerium oleander*, *Peganum harmala*, and *Zygophyllum gaetulum*, and are very careful in using them.

Another earlier ethnobotanical survey, published in 2003 by Lyoussi and coworkers, indicates that 102 medicinal plants belonging to 48 families are found in northern Morocco. The majority of these medicinal plants grow in the wild (61%), while others are cultivated (37%), and some (1.9%) are domesticated. In addition, herbal-based preparations are widely used in indigenous pharmacopoeia to alleviate the common symptoms of cardiovascular (5.8%), gastrointestinal (24.9%), bronchopulmonary (9.8%), and urogenital systems (12.2%), as well as skin diseases (9.2%). Among the 102 species inventoried, 13 medicinal plants are widely commercialized in the region and exploited outside the province. Several plants included in this survey have been found to be useful in renal disease and have been shown to have a diuretic effect in experimental studies (see Chapters 8 and 12): *Centaurium erythraea*, *Rosmarinus officinalis*, *Zea mays*, and *Foeniculum vulgare*. The antidiabetic and hypoglycemic plants reported in the present study, *Trigonella foenum-graecum*, *Ammi visnaga*, *Nigella sativa*, and *Ajuga iva*, have proven to have such properties. Some of the plants reported in this survey are

also used in treating animals (*Chamaerops humilis* and *Urginea scilla*) and as preservatives for foodstuffs (*Myrtus communis* for meat, *Calamintha officinalis*, *Origanum compactum*, and *Thymus* sp. for milk and olive, and *Nerium oleander* for grain) [13,14].

The above-mentioned ethnopharmacological studies note that all rare species, most of the occasional species, and even certain common species face potential extinction as a result of habitat loss, habitat degradation, overharvesting due to the increased trade of herbal-based preparations, ongoing destruction of their natural habitat, and detrimental climatic and environmental changes. As a result, it is predicted that in semiarid regions, such as the Middle East, a number of species will disappear within the next decade, particularly in desert or dry areas.

9.3 THE STATUS OF HERBAL MEDICINE IN THE MEDITERRANEAN

Although most herbalists in the Mediterranean claim to have much expertise in traditional medicine, the majority of them are not licensed as herbalists, and many are not well educated in herbal medicine or health care. According to the survey discussed above by Abu-Irmaileh and Afifi, over 70% of the interviewed Jordanian herbalists did not have a high school degree, and a considerable percentage had no schooling at all. Hence, the scientific background of the herbalists is clearly insufficient to comprehend the etiology of diseases, to perform diagnoses, and to prescribe herbal medication. Nevertheless, Abu-Irmaileh and Afifi noticed that some practitioners are highly successful in treating conditions such as hysteria, neurotic cases, madness, and other psychotic disorders using the above-mentioned herbal medicines.

In 2002, similar observations were reported by Said et al. of the Galilee Society. They conducted an extensive ethnopharmacological survey among the most well-known Arab indigenous herbal practitioners in the Israel–Palestine region and the Golan Heights to evaluate the potential of local plants used in treating different diseases and illnesses. Thirty-one indigenous practitioners were interviewed using a previously prepared questionnaire. Results revealed that 129 plant species were in use in Arabic traditional medicine for the treatments of various diseases. Among these plants, 40 species are used for treating skin diseases, 27 species for treating diseases of the kidney and urinary system, 26 species for treating diabetes, 23 species for treating the digestive system including stomach and intestinal pain and inflammation, 22 species for treating liver diseases, 16 species for treating respiratory system and coughing, 13 species for treating forms of cancer, and 9 species for treating weight loss and cholesterol reduction. Each interviewed practitioner has his own methods of preparation, following the tradition of his parents or teachers. The process of transmitting knowledge from one generation to the next is a complex one, and the end result is not always identical.

As in the Jordanian survey, Said and his colleagues also found that Palestinian traditional herbalists were not licensed for this particular purpose. The scope of experience of those surveyed practitioners varied greatly, depending upon their

location. In the Golan Heights, there is only one practitioner who works part-time, in comparison to the West Bank and Galilee region, in which more practitioners were found to depend on their practice as a sole source of income. The status of the Arab herbalists according to this survey is (1) most practitioners have very limited knowledge of the identification of species and procedures for preparing medicinal remedies. They buy ready-made or partially prepared remedies from attarah shops, where plant materials are sold, and do not collect plants from natural sources. (2) Younger practitioners were even less experienced than their older counterparts, indicating that traditional knowledge is being partially lost with new generations. (3) Many practitioners are turning to "mystical" or "magical" methods of healing, indicating a loss of the rich knowledge of practical plant medicine. (4) The level of education of practitioners is in decline, where many practitioners often rely on shepherds for knowledge, identification, and collection of plant materials. (5) Plant mixtures are of poorer quality and less variety in comparison to the past. (6) A very limited exchange of information takes place between healers in the same area. Moreover, plants used in certain regions are not used in others. For example, local practitioners from the Negev region of Israel use only plant species found in the desert. The occupation of the traditional healer is a family trade and is passed on by inheritance, so when the present generation of healers die, the know-how may die with them because children of the practitioners have no or little interest in the subject [4–12].

To evaluate the current status of Arab–Islamic herbal medicine, the authors of this book conducted in 2010 a comprehensive survey covering most regions of historic Palestine. We assess the following four points: (1) Qualification of the traditional Palestinian herbal medicine practitioners, (2) the people's attitude toward herbal medicine and their knowledge of specific therapies, (3) physicians attitudes toward herbal medicine and their knowledge of specific therapies, and finally (4) pharmacists' attitudes toward herbal medicine and their knowledge of specific therapies. We will discuss the main findings of our survey below.

Qualification of Traditional Palestinian Herbal Medicine Practitioners. In contrast to the above- mentioned surveys and in parallel with the observed increasing popularity of herbal-based medicines, the qualification of traditional Palestinian herbal medicine practitioners seems to be improving. Our comprehensive survey of traditional Palestinian herbal medicine practitioners found that about 53% of the practitioners claim to have an academic education and half of them have more than 10 years of experience. We noticed that 62.5% practitioners are highly successful in treating cases using only medicinal plants. About 70% of the attendant healers claim that they were able to identify the plants they use in nature and to identify different parts of the plant used to treat different diseases. Furthermore, most of them consider diet as part of the treatment. Table 9.2 summarizes the main findings of our study.

Most of the interviewed practitioners consider media programs as an important source for their knowledge of herbal medicine. Other healers use written texts as their main source of knowledge. Unfortunately, there are many books about herbal

TABLE 9.2 Traditional Healers' Responses to Questions Regarding Herbal Medicine

Question	Response (%)
How long have you been working with medicinal plants?	
0–10 years	50
10 + years	50
Is this your main profession and does it provide an adequate income?	
Yes	37
No	63
Do you consider television programs as a knowledge source?	
Yes	68.8
No	31.2
Where do you receive patients?	
Clinic	43.8
At home	37.5
Special room	12.5
Other	6.2
Can you identify the plants you use in nature?	
Yes	69
No	31
Has there been a case where you were able to cure a patient using only medicinal plants?	
Yes, many cases	62.5
Yes, few cases	28.1
No	9.4
Have you noticed an increase of patients recently?	
Yes	62.5
No	37.5
Can different parts of the same plant be used to treat different diseases?	
Yes	84.4
No	12.5
Not certain	3.1
Are people sufficiently aware of medicinal plant treatments?	
Very aware	15.6
Aware	40.6
Little	43.8
Is there a preference for using one part of the plant over another?	
Yes	62.5
No	37.5
Have you used plants to disengage magic?	
Yes	12.5
No	84.4
A few times	3.1
Do you provide treatments using the Holy Quran?	
Yes	34.4
No	53.1

TABLE 9.2 (*Continued*)

Question	Response (%)
A few cases	12.5
Do consider diet as part of the treatment?	
Yes	84.4
No	3.1
A few cases	12.5

Thirty-one Arab traditional healers (9 females and 22 males) from different regions in Israel were asked to answer questions in a preprepared questionnaire.

medicine on the market written in Arabic by nonspecialized authors, who often employ outdated texts by medieval Islamic physicians and herbalists such as Ibn al-Baitar and Al-Antaki. These texts are then used by current practitioners in directing treatment and prescribing herbal medicines (see Chapter 3). One serious error in relying on these texts is the possible misnaming of the plant species in question. Presumably, misidentification of the intended plant could lead to mistreatment and could subject the patient to harmful effects. Furthermore, in classical references, medicinal plants were known only by their local common names. Based on the fact that one plant can have many names, both locally and regionally, recognition of the correct species can be exceptionally problematic. In addition, different plant species in many cases share the same common name. For instance, *Rosmarinus officinalis* is known by two different local names: "Hasalban" and "Iklil jabal." The name "Hasalban" is also known for the resin produced from the plant *Boswellia carterii* (Table 9.1). Another example is the use of the Arabic name "Rijl El hamameh" for *Paronychia argentea* and also for the less commonly used plants *Verbena officinalis* and *Anchusa officinalis*. Neither the consumer nor the herbalists were aware of the fact that these plants have different uses.

People's Attitude Toward Herbal Medicine. Herbal medicines have gained enormous popularity in the Mediterranean and across the world over the past 30 years. Three of the main factors that explain the current popularity in the Mediterranean are (1) the belief that these medicines are prepared according to the principles of the Greco-Arab tradition. Herbal-based medicines are presumed to be safe and effective in the treatment and prevention of diseases because they are prepared according to the principles of the great Arab and Muslim scholars, such as Avicenna, Razes, Ibn al-Baitar, and Ibn-Zuhr. Indeed, 93% of the interviewed persons in our study do believe that herbal-based remedies are effective (Table 9.3). About 95% of them were content with the result of medicinal plant treatments and 53% confirm that the herbal treatment did indeed alleviate their aliment. Noteworthy, 72% do regularly use medicinal plants at home, (2) with the belief that these products are natural and therefore safe. About 30% of the asked people in our survey believed that all medicinal plants are safe. While 65.5% believe that not all plants are safe. Almost all interviewed people as well as traditional healers do support scientific research into the safety and efficacy of medicinal plants, and (3) the belief that synthetic medicines

TABLE 9.3 People's Attitudes Toward Herbal Medicine

Question	Response (%)
Do you believe that medicinal plants can effectively treat diseases?	
Yes	92.7
Sometimes	7.3
If you have the choice, what would you prefer to use?	
Herbal-based drug	86.9
Synthetic drug	1.9
Both	9.7
Do not care	1.5
Do you think that medicinal plants are safe?	
Yes	29.6
No	4.6
Some of them	65.5
Do you regularly use medicinal plants at home?	
Yes	72.3
Sometimes	24.8
No	2.9
Are you content with the result of medicinal plant treatments?	
Highly content	49
Content	45.6
Somewhat	4.9
Do not care	0.5
Did the treatment alleviate your aliment?	
Yes	53.1
No	7.5
A few times	37.4
What is your attitude toward traditional healers?	
Very positive	9.2
Positive	58.7
Negative	20.9
No opinion	11.2
Do you think that folk medicine is still medically relevant?	
Yes	71.8
Somewhat	25.7
No	2.4
Do you support scientific research into medicinal plants?	
Yes	97.6
No	0.5
Unsure	1.9
Do you think plant remedies can be used as an alternative to modern medicine?	
Yes	26.7
Sometimes	58.3
No	13.6
Other response	1.5

Two hundred and six Arabs (101 females and 105 males, in the ages between 28 and 78 years) from different regions in Israel were asked to answer questions in a preprepared questionnaire.

are often limited in their efficacy and accompanied by unfavorable side effects. 87% of the surveyed persons prefer herbal-based medicines to synthetic drugs.

Physicians' Attitudes Toward Herbal-Based Medicine. The purpose of this study was to evaluate the physicians' attitudes toward traditional herbal medicine as well as other common complementary and alternative medicine practices. Physicians were asked about their attitudes toward herbal-based remedies in general and their knowledge regarding these therapies. 83% believe that medicinal plant remedies can complement synthetic medicines and 85% think that some medicinal plant remedies should be integrated with modern medicine (Table 9.4). Noteworthy, 91% support scientific research to develop herbal medicines and 43.8% would like to learn more about medicinal plants and their traditional applications. Furthermore, 54.2% think that their patients are interested in medicinal plants and 77.1% believe that this interest relates to serious aliments. However, only 20% of the physicians are willing to recommend such therapies to patients with intractable or chronic diseases. Whereas, 39.6% think that medicinal plants treat only very simple diseases. This study highlights the need for educational intervention and the importance of providing physicians ready access to evidence-based information regarding medicinal plants.

Pharmacists' Attitude Toward Herbal Medicine. One of the most effective methods of assessing the popularity of herbal-based medicines is to examine the sale of these products in the pharmacy. Almost all pharmacies included in our survey do have herbal products and 57.4% of the surveyed pharmacists mentioned that natural products represent a high proportion of sales. About 64% expressed a negative attitude toward traditional healers and 80% were not satisfied with the level of control and regulation of plant and folk medicine. Similar to physicians, almost all pharmacists support scientific research into medicinal plants and 66.3% would like to learn more about medicinal plants and folk medicine (Table 9.5).

9.4 CONCLUSION

Ethnopharmacological surveys from the Mediterranean as well as from other regions of the world emphasize the necessity for the proper handling and licensing of herbal medicines. The increasing popularity of herbal-based medicinal products or other natural sources indicates that the public is not satisfied with modern medical treatment. It is necessary that not only new synthetic drugs, but also herbal remedies must fulfill international requirements on quality, safety and efficacy. As we have seen in our survey, all those surveyed would like to see more research activities in the field of medicinal plants in order to insure the quality, safety, and efficacy of herbal-based remedies.

Although many herbal-based medicines are safe and effective, there are many caveats concerning their use, especially in view of the recent rise in the sale and administration of herbal medicine by inexperienced herbalists. Several surveys showed that due to a lack of proper education, herbal medicines are prescribed by

TABLE 9.4 Physicians' Responses to Questions Regarding Herbal Medicine

Question	Response (%)
Can medicinal plant remedies complement modern medicine?	
Yes	83.3
No	4.2
Sometimes	12.5
Should medicinal plant remedies be integrated with modern medicine?	
Yes	52.1
No	14.6
Sometimes	33.3
Where did you acquire your knowledge of medicinal plants?	
University	10
Practitioners/community members	37.5
Personal interest	50
All of the above	2.5
Are you and your colleagues interested in medicinal plants?	
Yes	45.8
No	12.5
Very few	41.7
Do you think that your patients are interested in medicinal plants?	
Yes	54.2
No	4.2
Very few	41.7
Does their interest relate to serious aliments?	
Yes	77.1
No	16.7
Other response	6.3
For which types of cases do you recommend medicinal plants?	
Intractable diseases	12.5
Intractable, very simple, and chronic diseases	18.9
Chronic disease	8.4
Very simple diseases	39.6
Other aliments	20.8
Are you satisfied with the current regulations concerning medicinal plants?	
Yes	8.3
No	77.1
Somewhat	14.6
Do you support scientific research to develop this heritage?	
Yes	91.7
Do not know	8.3
Would you like to learn more about medicinal plants?	
Yes	43.8
No	16.7
Other	39.6

Forty-eight Arab physicians (3 females and 45 males) from different regions in Israel were asked to answer questions in a preprepared questionnaire.

TABLE 9.5 Pharmacists' Attitudes Toward Herbal Medicine

Question	Response (%)
Do you have drugs or preparations from medicinal plants?	
Yes	98
No	2
Are natural products a high proportion of sales?	
Yes	57.4
Low proportion	36.6
No	5.9
Do think that medicinal plants are effective?	
Effective	55
Not effective	2
Sometimes	40
Other response	3
Should medicinal plant treatments be integrated into the modern system of health care?	
Yes	63.4
Sometimes	29.7
No	6.9
Should HMOs support medical plants and traditional remedies along with modern medicine?	
Yes	80.2
Unsure	11.9
No	7.9
What is your attitude toward traditional healers?	
Positive	23.8
Negative	64.4
No opinion	11.9
Are you satisfied with the level of control and regulation of plant and folk medicine?	
No	80.2
Yes	3
Somewhat	15.8
Other response	1
Do you think that folk medicine is still medically relevant?	
Yes	50.5
No	9.9
Somewhat	38.6
Other response	1
Would you like to learn more about medicinal plants and folk medicine?	
Yes	66.3
Unsure	25.7
No	7.9
Do you support scientific research into medicinal plants?	
Yes	99
No	1

Hundred and one Arab pharmacists (12 females and 89 males) from different regions in Israel were asked to answer questions in a preprepared questionnaire.

traditional healers symptomatically rather than as a result of a full and holistic determination of the underlying disease.

As discussed in Chapter 6, medicinal plants contain many substances. Both activity and concentration of these compounds are subject to change due to changing conditions of the environment, especially storage. If not properly stored, the pharmaceutically active compounds in plants could degrade by hydrolysis or oxidation and could be transformed into rather toxic compounds or degradation products. In certain simple to mild diseases, herbal medicine could be useful, independent of diagnosis, but this is unlikely in the majority of cases that require a complex history of the patient, a thorough physical examination and proper laboratory data for the correct diagnosis, and an adequate treatment. Also, many cultivated medicinal herbs went through different breeding procedures throughout the years with the aim of increasing their yield. Presumably, the newly cultivated and hybridized strains of the same species may not correspond to the plants described in the old books. Despite potentially harmful information, herbalists in the Arab world rely on these books, which could be the source of differences among the documented and recommended uses of commonly used medicinal plants. Such books often did not provide clear descriptions of preparation methods accompanying the herbalists' recommendations. Such findings support the necessity of regulations concerning the proper handling of herbal medicines, which requires proper oversight and licensing. WHO regulations (see Chapters 18 and 19) can be considered a good basis for such regulations.

Medicinal plants in the Mediterranean are becoming increasingly rare, due to the ongoing destruction of their natural habitat, overharvesting of wild species, and detrimental climatic and environmental changes. This gives an added sense of urgency to the task of recording their identity and use, as well as initiating programs of preservation of the genetic resources of medicinal plants of the region. This is especially relevant due to the growing interest in herbal medicines globally, accompanied by increased laboratory investigation into the pharmacological properties of the bioactive ingredients used to treat various diseases.

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CHAPTER 10

Greco-Arab and Islamic Medicine Practiced Outside the Middle East

10.1 INTRODUCTION

Arab and Islamic medicine is widely used in most Arab and Islamic world that forms about one-fifth of the world's population (about 1.4–1.5 billion people). The Arab and Muslim world refers in geopolitical sense to Muslim majority countries or countries in which Islam dominates politically (Tables 10.1 and 10.2). This community is spread across many different nations and ethnic groups connected only by religion (Figure 10.1). Medicine in general is considered to be one of the most illustrious and best-known facets of Arab–Islamic civilization. It influenced Western medical circles to such an extent that it was included in the curriculum of medical schools for many centuries. In the discipline of medical history, Islamic medicine is often referred to as Arabic medicine, Greco-Arab, or Islamic medicine. Developed in the Golden Age (from seventh to fifteenth century) of Arab–Islamic civilization, the medicinal sources are written in Arabic, the lingua franca of the Islamic civilization [1–4].

As discussed in Chapter 2, the development of Arab and Islamic medicine is simultaneous to that of Prophet Mohammad (PBUH), who, at the age of 40, received the Holy Quran in verses. He was able to unite the Arab tribes who had been isolated by revenge, rivalry, and internal fights. He created a strong nation, able to defeat the two powerful empires at that time, the Persian and Byzantine Empires. By the time of his death, all of Arabia had adopted Islam and a century later his followers had conquered half of Byzantine Asia, all of Persia, Egypt, the Maghreb (North Africa), and Spain. The Muslims not only conquered new lands, but also became scientific innovators through originality and productivity. They preserved the cultures of the conquered lands. In temporal terms, this civilization covered a period of roughly nine centuries, from the middle of the seventh to the end of the fifteenth century, by which time the empire was divided into three independent empires, the Mughal empire in India, the Ottoman empire centered in Turkey, and the Safavid empire in Persia. The Arab–Islamic Empire was one of the most advanced and civilized nations in the world.

Greco-Arab and Islamic Herbal Medicine: Traditional System, Ethics, Safety, Efficacy, and Regulatory Issues By Bashar Saad and Omar Said

TABLE 10.1 List of Muslim Majority Countries

Arab states	Algeria, Bahrain, Comoros, Djibouti, Egypt, Iraq, Jordan, Kuwait, Lebanon, Libya, Mauritania, Morocco, Oman, Palestine, Qatar, Saudi Arabia, Somalia, Sudan, Syria, Tunisia, United Arab Emirates, Yemen
Muslim states	Afghanistan, Albania, Azerbaijan, Bangladesh, Benin, Brunei, Burkina Faso, Cameroon, Côte d'Ivoire, Maldives, Chad, Gabon, Gambia, Guinea, Guina-Bissau, Guyana, Indonesia, Iran, Kazakhstan, Kyrgyzstan, Malaysia, Mali, Mozambique Niger, Nigeria Pakistan, Senegal, Sierra Leone, Suriname, Togo, Turkey, Turkmenistan, Uganda, Uzbekistan

In a geopolitical sense, these countries are often considered to form the Muslim world. The list only contains countries that are predominantly Muslim dominated, meaning the Muslim population constitutes at least 50% of the total population.

This is because Islam stressed the importance and respect of learning, forbade destruction, and stressed tolerance for other religions. Medicine flourished because it was promoted by Caliphs, while Baghdad, Seville, Toledo, Granada, and other cities were well known as main centers for Arab–Islamic medical sciences and culture. By the tenth century, their zeal and enthusiasm for learning resulted in the translation of essential Greek medical writings into Arabic in Damascus, Cairo, and Baghdad. Arabic became the international language of learning and diplomacy. The Abbasid Caliphs moved the center of scientific knowledge and activity eastward, and Baghdad emerged as the capital of the scientific world. Greco-Arab and Islamic medicine was a result of Roman, Greek, Persian, and Indian theories and practices, within the general context of Islam's system of ethics (Figure 10.2). Arabs then established and promoted their own medical sciences in theories and practices that became highly influential in Western science and teaching. Physicians, whether they were Muslims, Christians, or Jews, under the umbrella of Islam raised the dignity and caliber of the

TABLE 10.2 Top 10 Largest Muslim Populations

Number	Country	Muslims (millions)
1	Indonesia	199
2	Pakistan	160
3	India	151
4	Bangladesh	131
5	Egypt	72
6	Turkey	70
7	Iran	70
8	Nigeria	54
9	Algeria	32
10	Morocco	31

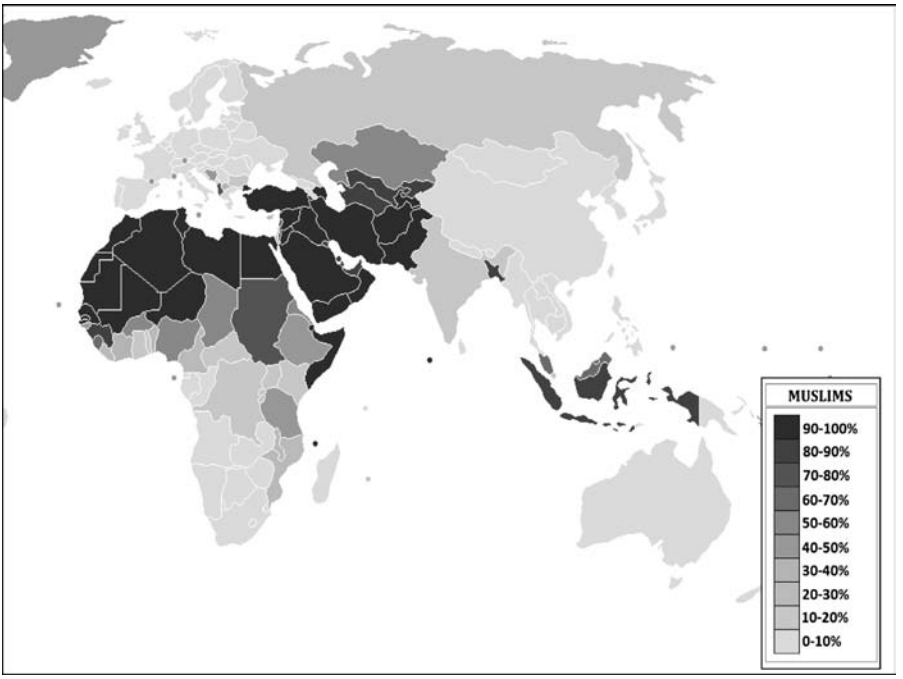

FIGURE 10.1 Map of the Arab–Islamic world. Arab and Islamic world forms about one-fifth of the world's population (about 1.4–1.5 billion people). It refers in geopolitical sense to Muslim majority countries or countries in which Islam dominates politically. This community is spread across many different nations and ethnic groups connected only by religion.

medical profession. During the Islamic Golden Age, the medical sciences rose in esteem from that of a menial calling to the rank of a learned profession. Greco-Arab and Islamic medicine had advanced from ephemeral talisman and theology to tangible hospital wards, mandatory testing for doctors, and the use of technical terminology. Baghdad and Cairo had hospitals open to both male and female patients, staffed by attendants of both sexes. These medical centers contained libraries, pharmacies, intern systems, externs, and nurses. There were mobile clinics to reach the disabled, the disadvantaged, and those in remote areas. There were regulations to maintain quality control on drugs. Pharmacists became licensed professionals and were pledged to follow the physician's prescriptions [1–4].

The health care practices of the medieval Arab–Islamic community over a large area and nine centuries were, in fact, neither uniform nor stable. The general health of the medieval people was affected by many factors: dietary and fasting rules during the holy month of Ramadan; rituals and burying the dead by both Muslims and non-Muslims; the climatic conditions of the vast area; the living conditions of nomadic inhabitants of the desert, rural, and urban populations; agricultural skills; the amount of travel undertaken for commerce, for attendance at courts, or as a pilgrimage; the

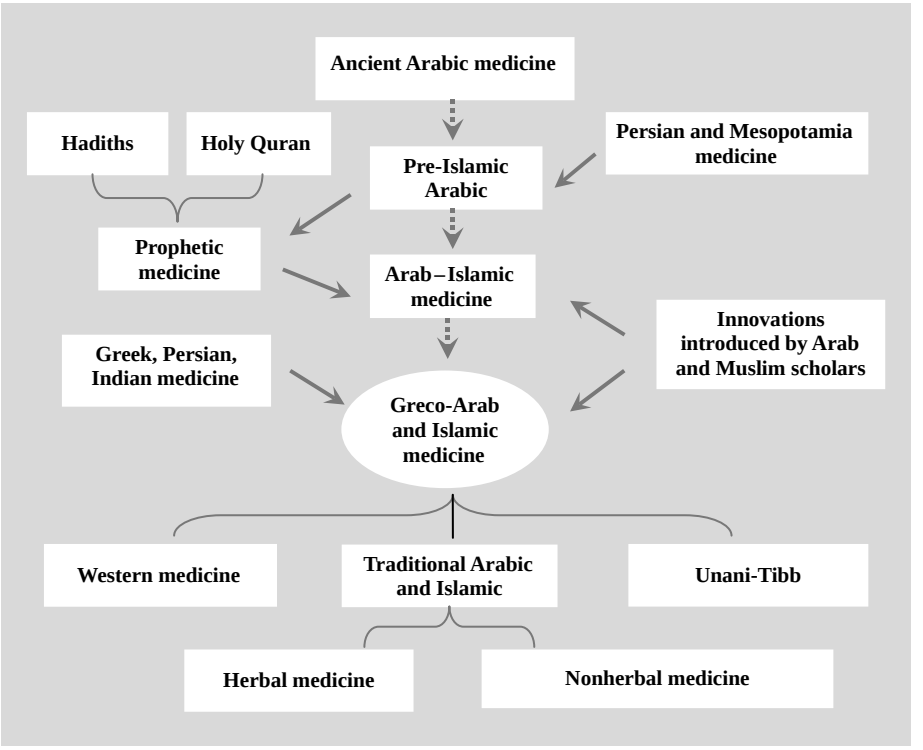

FIGURE 10.2 Development of Greco-Arab and Islamic medicine. Greco-Arab and Islamic medicine became one of the most famous and best-known achievements of Arab–Islamic civilization. Greco-Arab and Islamic medicine was a result of Roman, Greek, Persian, and Indian theories and practices, within the general context of Islam's system of ethics.

injuries and diseases attendant upon army camps and battles; and the incidence of plague and endemic conditions [4–6].

In the eighteenth and nineteenth centuries, Islamic regions fell under the sway of European imperial powers. Following World War I, the remnants of the Ottoman Empire were parceled out as European protectorates. There has been no major widely accepted claim to the caliphate since this time (which had been last claimed by the Ottomans). Despite this political partition and the great progression of modern medicine, Greco-Arab medicine has always been practiced in the Arab–Islamic world. Cultural beliefs and practices often lead to self-care or home remedies in rural areas and consultation with traditional healers. Traditional therapies have been utilized by people who have faith in spiritual healers, homeopaths, or even many herbalists for treatment of diseases such as infertility, impotence, diabetes, obesity, epilepsy, and psychosomatic troubles. This chapter will provide an overview of Greco-Arab and Islamic medicine practiced in countries other than those in the Middle East, such as Iran, India, Turkey, Maghreb region, and Pakistan.

10.2 GRECO-ARAB AND ISLAMIC MEDICINE PRACTICED IN INDIA

While Greco-Arab and Islamic medicine is still practiced in most Arab and Islamic countries (Table 10.2), the only country where it has an official status is India (about 150 million Muslims), where it was introduced by Arabs (in about 1100) and soon took firm roots in the soil. When Mongols ravaged Persian and Central Asian cities, such as Shiraz, Tabrez, and Geelan, scholars and physicians of Greco-Arab and Islamic Medicine fled to India. The physicians who came to India from foreign countries also took advantage and derived benefits from indigenous or local systems of medicine, that is, Ayurveda. Greco-Arab and Islamic medicine practiced in Muslim communities of the Indo-Pakistan subcontinent (about half a billion Muslims in India, Pakistan, and Bangladesh) is known as Unani-Tibb. "Tibb" is an Arabic word meaning "medicine," while "Unani" is thought to be derived from "Ionan" (meaning Greek)—acknowledging the influence of early Greek medicine on Greco-Arab and Islamic medicine. A Unani physician is known as a *hakim*. However, the currently practiced Unani medicine in Indo-Pakistan subcontinent is vastly different from its Greek–Arab roots. It benefited from the native medical system or folk medicine in practice at the time in various parts of central and southern Asia, mainly Ayurvedic medicine and Chinese medicine [7–10].

Concepts. As discussed in Chapter 7, Unani Medicine considers the human body as a single unit, consisting of the following seven components (Figure 7.1):

- Elements (Arkan)
- Temperament (Mizaj)
- Humors (Akhlaat)
- Life force (Arwaah)
- Organs (Aaza)
- Power (Quwa)
- Functions (Afa'al)

In addition, the body is made up of the four basic elements, that is, earth, air, water, and fire, which have different temperaments, that is, cold, hot, wet, and dry, respectively. Mixing and interactions of the four elements results in a new compound having new temperament (Mizaj), that is, hot–wet, hot–dry, cold–wet, and cold–dry. The body has simple and complex organs that receive their nutrition through four humors (Akhlaat), that is, blood (Dam), phlegm (Balgham), yellow bile (Safra), and black bile (Sauda). Each of the humors has its own temperament:

- Blood is hot and moist
- Phlegm is cold and moist
- Yellow bile is hot and dry
- Black bile is cold and dry

Every person attains a temperament according to the dominance of the humors in his/her body and it represents the person's healthy state. The temperament of a person may be sanguine, phlegmatic, choleric, or melancholic. According to Unani-Tibb, health is a state of the body in which there is a balance in the humors and functions of the body. To maintain the correct humoral homeostasis, there is a power of self-preservation or adjustment (Quwwat-e-Mudabbira) in the body. A disease state occurs when this power weakens, the balance of the humors is disturbed quantitatively or qualitatively, and physiological functions of the body are deranged due to the abnormal temperament of an affected organ or system. Therefore, the aim of a Unani physician is to find out the cause of the underlying disruption of humors, so that it can be corrected and disease can be cured. Imbalance of humors may be due to external factors, such as an injury, incorrect diet, environmental factors, or internal factors, such as improper digestion. Signs of humoral diseases are as follows:

Ghalba-e-Dam: When there is excess of blood in the body, the color of skin appears red, veins appear more prominent, pulse seems to be full, and urine becomes high colored. Patient complains of breathlessness, headache, and scenes of blood in his/her dream.

Ghalba-e-Balgham: In the case of excess of phlegm in the body, skin becomes whitish and cold, pulse becomes slow and deep, urine becomes thick and low colored. Patient complains of forgetfulness, loss of appetite, increased sleep, laziness, and scenes of water in his/her dream.

Ghalba-e-Safra: Choler humor results in yellowness of the skin, swifter pulse than ordinary, and high-colored urine. Patient appears irritated without any apparent cause and complains of headache, disturbed sleep, bitterness in throat, and scenes of fire, lighting, anger, fighting, and so on in his/her dream.

Ghalba-e-Sauda: When there is excess of black bile in the body, the skin appears rough, pulse becomes weak, urine becomes thin, patient complains of loss of appetite and soreness in throat. Patient remains busy with foolish imaginations and appears fearful without any cause.

Imbalance of Humors. Imbalance of humors tend to occur in four ways:

- *Thinning of humor (Riqqat-e-Khilt)*: The consistency of humor becomes thinner.
- *Thickening of humor (Ghilzat-e-Khilt)*: The consistency of humor becomes thicker.
- *Plethora (Ghalba-e-Khilt)*: The humor becomes over active.
- *Decay of homors (Afunat-e-Khilt)*: The humor becomes putrefied.

Unani medicine also considers the external environment and its effect on the body and divides these influences into five categories. It is believed that each of these five

categories must be fulfilled adequately for a person to be able to maintain a proper balance of both the four humors and the state of health. The external environment and daily lifestyle choices that are considered major influences in the ability to sustain and maintain good health are

- Air quality
- Food and drink
- Movement and rest
- Sleep and wakefulness
- Emotions

Unani medicine states that these factors should be balanced in terms of quality, quantity, and sequence in order to sustain good health.

Treatment. The diagnostic parameters of the Unani system are the rate, strength, width, and depth of the pulse, as well as the color, odor, and the amount of urine and stool. In addition, deposits in the urine sample are also observed. After confirming the cause of the disease, the Unani physician starts the treatment by recommending the diet or drugs that have temperament opposite to the prevailing abnormal temperamental condition of the affected organ/system. It is important to note that each and every Unani diet or drug has its own temperament. Drug therapy includes naturally occurring drugs derived from plants, animals, and minerals and used singly and in combination. Selection of a suitable method of treatment depends upon the degree of shift from the normal healthy condition. Diet therapy is advised when the shift is of lesser degree from the normal healthy condition, but if the shift is of greater degree and cannot be corrected by diet therapy alone, then drug therapy is advised and drugs having temperament opposite that of the prevailing diseased condition are selected. Sometimes, regimental therapy and surgery are also advised along with diet therapy and drug therapy.

As mentioned, the basic philosophy of Unani-Tibb is that the body, composed of matter and spirit, is taken as a whole because harmonious life is possible only when there is proper balance between the bodily (physical) and spiritual functions. Unani-Tibb has been influenced by Ayurvedic medicine and to some extent by Chinese medicine.

10.3 BASIC PRINCIPLES OF AYURVEDIC AND CHINESE MEDICINE

Ayurveda and Chinese medicine focus on the patient rather than disease. Both systems fundamentally aim to promote health and enhance the quality of life with therapeutic strategies for treatment of specific diseases or symptoms in a holistic fashion. Ayurveda and Chinese medicine have many commonalities. Almost half of the

botanical sources used as medicines have similarities; moreover, both systems have similar philosophies geared toward enabling classification of individuals, materials, and diseases.

Ayurvedic Medicine. Traditional Indian medicine, known as "Ayurveda," which means the science of longevity or "medicine of the gods," was originally a Hindu medical system and its beginning can be traced to the sixth century. It was well known for the science of poisons and was based on the theory of the components of the human body by the six balanced materials: blood, flesh, muscles, marrow, mucus, and semen. Ayurveda believes in "five great elements" (earth, water, fire, air, and space) forming the universe, including the human body. Blood, flesh, fat, bone, marrow, chyle, and semen are believed to be the seven primary constituent elements of the body. Ayurveda is basically a humoral medical system that maintains that there are three essential humors that cause disease if they become imbalanced—wind, bile, and phlegm, each representing divine forces. In Ayurveda, the human body has 20 *Guna* (meaning quality). It is believed that building a healthy metabolic system, attaining good digestion and maintaining proper excretion, leads to vitality. Ayurveda also focuses on exercise, yoga, meditation, and massage. One of the main aspects of Ayurveda is aromatic massage. Indians used a lot of herbal medicine, including cannabis for anesthesia and belladonna for pain. One of the most well-known Indian medical books was *Wisdom of the Indians*, which was translated to Arabic and then to Greek by Simon Antioch in 1070 AD [7,10,11].

Traditional Chinese Medicine. Chinese medicine is rooted in the philosophy of Confucius, who called for the promotion of social and ethical standards in societies. The pattern of Chinese medical practice is based on the use of herbs, dietary therapy, massage, and acupuncture. Chinese medicine is a wide-ranging subject and is practiced by millions of people throughout China and East Asia. Shen Nung's herbal book, *The Divine Farmer's Herb-Root Classic*, dated 2700 BC is considered the oldest Chinese medical text and contains details on more than 300 plants. Traditional Chinese medicine places the human at the center of the universe as an antenna between celestial and earthly elements. Water, earth, metal, wood, and fire are the five elements of the material world. The world is a single unit and its movement gives rise to yin and yang, the two main antithetic aspects. The actual meaning of the term yin and yang is "opposites." However, Chinese believe that yin and yang are not absolute but relative. Consistent with the modern view of homeostasis, yin and yang are interchanged to meet the view that "yang declines and yin rises" or "yang is raised to produce a decline of yin." The four bodily humors (qi, blood, moisture, and essence) and internal organ systems (zang fu) play an important role in balancing the yin and yang in human body. Proper formation, maintenance, and circulation of these energies are essential for health. When the two energies fall out of harmony, disease develops. The physician takes into account this concept while treating patients. Drugs or herbs are used to correct this imbalance of yin–yang in the human body.

Acupuncture. Acupuncture is considered to be the most important old/new Chinese alternative medicine worldwide. 4700 years old, it was described by Huang Ti Nei Ching Wen in *The Yellow Emperor's Classic of Internal Medicine*, considered the most important early Chinese medical book. The most interesting part of this book is the *Sun Wên*, "Familiar Conversations," between the emperor and his physician Ch'i Pai, because it develops into a lucid and an attractive story of humans in health and disease and articulates a theory of medicine.

Acupuncture or "needling" is a method of using fine needles to stimulate the body's own healing process through the body lines of energy. A symptom manifests because the free flow of this energy is obstructed. Consequently, the aim of acupuncture is to remove these obstructions and to encourage the energy to flow smoothly. The Chinese believe that each symptom is only the result of a series of disturbances in the proper functioning of the body and mind. Each symptom has a cause and that cause has a deeper root cause and so on until one gets back to what is termed the constitutional factor. In Chinese medicine, each organ is responsible for maintaining specific aspects of physical and emotional health. The acupuncture point is a precise anatomical location where the energy can be contacted by inserting a needle. Acupuncture works through the following five theories:

- The augmentation of immunity, which raises the level of triglycerides, prostaglandins, white blood cells, and antibody.
- The endorphin theory, by stimulation of enkephalin secretions in the body.
- As a neurotransmitter, in which certain neurotransmitter levels (serotonin and noradrenaline) are affected.
- As circulatory theory, with the effect of constricting or dilating blood vessels through the release of histamines.
- As gate control theory, in which the perception of pain is controlled by a part of the nervous system that regulates the impulse, which will later be interpreted as pain. This part of the nervous system is called the gate. If the gate is hit with too many impulses, it is overwhelmed and thus closes. This prevents some soft impulses from getting through. The first gates to close are the smallest. The nerve fibers that carry the impulses of pain are rather small nerve fibers called C fibers. These are the gates that close during acupuncture [7,11].

10.4 GRECO-ARAB AND ISLAMIC MEDICINE PRACTICED IN PAKISTAN

As aforementioned, the Unani system of medicine came to the Indo-Pakistan subcontinent via Arab and Muslim physicians in the twelfth century. In Pakistan, over half the population (66%) lives in rural areas. Poverty, high rates of illiteracy, limited knowledge of health and disease, low status of women, and inadequate water and sanitation facilities have a negative impact on health status. Pakistan has a very rich tradition in the use of medicinal plants for the treatment of various ailments, based

predominantly on the Unani system of medicine. This traditional medicine has become an important source of health care, especially in rural and tribal areas of the country. Most of the medicinal plants are found in the temperate climates and subtropical forests of northern Pakistan. According to a WHO report entitled "The Legal Status of Traditional Medicine and Complementary/Alternative Medicine: A Worldwide Review" published in 2001 [11], the status of traditional health system in Pakistan can be summarized as follows:

- Most Pakistanis rely on Unani medicine, finding it efficacious, safe, and cost-effective.
- Unani medicine is widely used throughout the country. About 70% of the populations, particularly in rural areas, use traditional and complementary/alternative medicine.
- Approximately 53,000 registered Unani medical practitioners serve the nation through both the public and private sectors in urban and rural areas.
- About 360 Unani-Tibb dispensaries and clinics provide free medication to the public under the control of the health departments of provincial governments.
- About 95 dispensaries have been established under provincial departments of Local Bodies and Rural Development.
- A separate Directorate of Hakims (physicians) has also been established under the Federal Ministry of Population Welfare Programme, and 16,000 diploma-holding Unani physicians of traditional medicine have been involved in the National Population Welfare Programme.

Both the types of symptoms experienced and the duration of an illness are major determinants of health seeking behavior and choice of care provider. In the case of a mild single symptom such as fever, home remedies or folk prescriptions are visited, whereas with multiple symptoms and a longer duration of disease, allopathic physicians are more likely to be consulted. Alternative therapies have been utilized by people with faith in spiritual healers, clergymen, *hakeems*, homeopaths, or even many quacks. These are the first choices for problems such as infertility, epilepsy, psychosomatic troubles, depression, and so on. Other reasons for consulting a Unani healer are the proximity, affordable fee, availability of the provider, family pressure, and the strong opinion of the community. The literature reveals that the patients who use allopathic medicines as well as alternative medicines concomitantly are reluctant to reveal to their allopathic physician that they are also using alternative medicines. This communication barrier augments the risk of developing complications from the combination of allopathic and alternative therapy.

In addition to other traditional systems such as Ayurvedic and homeopathic, the Unani system has been accepted and integrated into the national health system. Pakistan is the only country in the eastern Mediterranean region where formal Unani teaching institutions are recognized. According to the WHO report (2001) [11], Pakistan's Unani teaching institutions (Tibbia colleges) are recognized by the

Government and are under the direct control of the National Council for Tibb within the Ministry of Health, which is responsible for maintaining standards of education in recognized teaching institutions, revising/modifying curricula and syllabuses, and holding annual examinations. Twenty-six colleges in the private sector and one college in the public sector offer 4-year diploma courses in Pakistani traditional Unani and Ayurvedic systems of medicine that follow the prescribed curriculum and conditions laid down in the regulations. Hamdard University has recently introduced a 5-year programme to follow intermediate (FSc) training. About 5000 students are enrolled in its Faculty of Unani Medicine. Annually, about 950 students graduate from the programme. Seventy-six colleges of homeopathic medicine offer officially recognized programmes for the 4-year Diploma of Homeopathic Medical Science. Several hospitals, outpatient clinics, and dispensaries are attached to the homeopathic medical colleges [11–16].

Commonly Used Medicinal Plants in Pakistan. Some 2000 plant species are known for their therapeutic value, out of which only 400 are being used extensively in traditional medicine. A recent ethnobotanical survey of Samahni valley in Kashmir (Pakistan) indicates the following [17]:

- About 95 species of 38 families were recorded to be an important part of the traditional herbal medicine of Samahni valley.
- The distinctive geographic position and historic demological background of the area keep the traditional herbal medicine potential alive.
- Medicinal plants are used in various forms, as regular herbal medicines prescribed by hakims (herbal practitioners) and as food (medicines) recipes suggested by elder people.
- Some herbs are used as single remedy, while others depict better curative effects in synergistic mode against various diseases (Table 10.3).
- Many wild plants are eaten green and raw as salad or in boiled form as soup to cleanse the blood and intestines.

10.5 HEALTH CARE OF THE MOTHER AND CHILD IN UNANI MEDICINE

Among the hundred of plants used in Unani medicine, a number of them are used in the health care of the mother and the child. These plants are commonly used in Iran and the Indo-Pakistan subcontinent. For example, the following plants have been documented in a recent survey [18]:

Viola odorata: A perennial herb commonly found in Iran and India. Its flowers are effective in coryza, cough, congestion, and inflammation of the respiratory tract. The plant is safe for children and pregnant mothers.

TABLE 10.3 Some of the Commonly Used Medicinal Plants in Pakistan (Samahni valley in Azad Kashmir) [17]

Plant	Medicinal Uses
Sisymbrium irio	Measles and asthma
Solanum miniatum	Urinary calculi, heart pain, and rheumatism
Momordica balsamina leaves	Wound healing
Allium sativum bulb juice	Anticancer, contraceptive, and blood pressure
Boerhavia diffusa roots	Antijaundice, anemia, and edema
Capsicum annuum fruit	Omen against evil eye and giant, and yellow fever
Coriandrum sativum seeds	Diuretic and antispermatogenesis
Raphanus sativus seeds	Syphilis
Solanum miniatum fruit	Enlarged spleen and liver
Seed oil of *Pisum sativum*	Antispermatogenesis
Bauhinia variegata	Skin diseases, ulcers
Malva sylvestris	Cough, bladder ulcer
Phoenix sylvestris kernels	Anti-aging tonic
Phyllanthus emblica	Diuretic, anemia, biliousness
Terminalia chebula	Chronic ulcers, carious teeth pain

Cichorium intybus: It is a perennial herb. It is a good diuretic, antipyretic, and analgesic and protects the liver from various indigenous and exogenous toxins.

Glycyrrhiza glabra: It is a perennial herb. Its rhizome is expectorant, demulcent, anti-inflammatory and is commonly used for cough and catarrhal infections. In recent studies, it has also been found useful in peptic ulcers.

Physalis alkekengi: It is a perennial herb with creeping roots. Its fruits are good diuretic and useful in urinary tract infections in females and children.

Carum carvi: A biennial herb native to high altitudes in Iran and India. It is aromatic, carminative, good galactagogue and emmenagogue, and also useful in intermittent fevers and intestinal worms.

Cyperus rotundus: It is a perennial herb. Tuber roots are used. It is a good diaphoretic, diuretic, emmenagogue, and galactagogue. It is also useful in anorexia and diarrhea in children.

Zataria multiflora: A perennial herb, the best quality is from Iran. The aromatic leaves are carminative, antitussive, antiflatulence, and useful in hiccup and early stages of asthma.

Foeniculum vulgare: It is a perennial herb. The fruits are carminative, antiflatulence, and safe for children and pregnant mothers and may protect them from iodine deficiency as the fruit contains iodine.

Ocmium sanctum: It is an aromatic perennial herb. Its leaves and seeds are used as antipyretic, antibacterial, carminative, cardiotonic, and expectorant. It is also good in treating colds and coryza.

Paeonia officinalis or Paeonia femina: It is a perennial herb. Its roots/tuber are used. It is a good diuretic, emmenagogue, and antispasmodic. It is useful in epilepsy, hysteria, paralysis, and so on.

Lepidium iperis: This is a perennial herb commonly grown in Iran and India. It is a good galactagogue and improves the general health during lactation.

Asparagus racemosus: The root/tuber of the plant is used. It is a carminative and a good appetizer, useful in diarrhea and dysentery. It is a general tonic and acts as galactagogue.

10.6 TRADITIONAL MEDICINE IN TURKEY

As aforementioned, the geographical borders of the Islamic empire extended from Spain and Morocco in the west to Central Asia and India in the east, with the central lands of Egypt, Syria, Iraq, and Persia playing a central role (Figure 10.1). By the end of the fifteenth century, the Arab–Islamic Empire was divided into three distinct empires: the Safavid Empire in Persia (modern Iran), the Mughal Empire in India, and the Ottoman Empire. The Ottoman dynasty (1299–1923) in fact arose at the end of the thirteenth century, but the theoretical and practical approaches to medicine in the areas under its domain during the first two centuries of its existence firmly belonged to the medieval Islamic medical tradition. The region comprising modern Turkey has a long and rich Islamic tradition stretching back to the dawn of the Seljuk period and Ottoman Empire. Islam is the main religion of the Turkey (99.8% of Turkey's population are Muslims). Due to its strategic importance, the region has been dominated during history by Western (Greeks, Romans) or Eastern (Turks, Mongolians) civilizations. The Greek physicians of Anatolian, Hippocrates (460–377) from the Island of Kos (a Greek island on the east of the Aegean Sea by the Anatolian peninsula) and Dioscorides (1 AD) from Anarzabos (in south Anatolia), were some of the first physicians to write and describe certain plant remedies. Most of the 600 plants documented in the book of Dioscorides, *Materia Medica*, had originated from the Anatolian peninsula. A recent survey of traditional and folk medicine in Turkey has revealed that most of these plants are still in use by the local inhabitants. Therefore, *Materia Medica* may be assumed to be the oldest comprehensive document on Anatolian folk medicine. For example, fruit juice of squirting cucumber (*Ecballium elaterium*; Cucurbitaceae) is still widely used to treat sinusitis in Anatolia. There has been no other document that has reported such usage, except for that by Dioscorides. In other words, this application has been practiced by the inhabitants of Anatolia for at least 2000 years.

Among the countries in the Middle East, the richest flora has been reported in the Anatolian peninsula (Asian part of Turkey). According to recent surveys, the number of species growing in Anatolia and Thrace (the European part of Turkey) is estimated to be about 11,750. However, toward the southern part of the region, the flora becomes less varied and diverse. In this part of the world, plants have been used as a source of medicines from ancient times onward. Plant species may have different uses in different countries as well as different areas of the same country. In spite of such a rich cultural heritage and relatively rich flora, the number of scientific ethnobotanical field

TABLE 10.4 Medicinal Plants Used in Turkey

Disease	Number of Plants Used	Most Commonly Used Plants
Gastrointestinal disorders	450	*Rosa canina*, *Juniperus* species (*communis*, *nana, drupacea*, *oxycedrus*, *Sabina*), *Teucrium* species (*chamaedrys*, *polium*)
Respiratory ailments	184	*Pinus* species (*brutia*, *nigra*, *pallasiana*, *sylvestris*) Juniperus species (*communis*, *nana, drupacea*, *excelsa foetidissima*)
Skeletomuscular problems	170	*Urtica* species (*dioica*, *haussknechtii*, *Pilulifera*, *urens*), *Ranunculus* species (*arvensis*, *muricatus*, *neopolitanus*, *repens*, *sericeus*), *Sambucus* species (*ebulus*, *nigra*)
Urogenital system complaints	48	*Juniperus* species (*oxycedrus*, *drupacea*), *Zea mays*, *Helichrysum plicatum*
Infectious diseases	64	*Ecballium elaterium*, *Pinus* species (*nigra*, *pallasiana*, *Holmboe*, *sylvestris*), *Berberis* species (*vulgaris*, *crataegina*)
Central nervous system-related disorders	51	*Juglans regia*, *Solanum tuberosum*, *Arctium minus*
Immunological conditions	51	*Urtica* species (*dioica, pilulifera*), *Pinus* species (*nigra, pallasiana*), *Arceuthobium oxycedri*
Metabolic diseases	38	*Rosa canina*, *Cornus mas*, *Morus nigra*

Among the countries in the Middle East, the richest flora has been reported from the Anatolian peninsula. According to recent surveys, the number of species growing in Turkey is estimated about 11,750.

surveys, at least published in the international journals, among the regional communities is very low. Meanwhile, the global factors threatening traditional knowledge and heritage are at play in this region, and a wealth of information has been lost due to certain attributes of modernization, such as urbanization, migration, development of roads and communication media, easier access to allopathic medicine and drugs, and so on [19–26]. Table 10.4 summarizes some of the commonly used plants in the treatment and prevention of different ailments.

10.7 GRECO-ARAB AND ISLAMIC MEDICINE IN THE MAGHREB COUNTRIES

Maghreb, meaning "place of sunset" in Arabic, is a region in North Africa that includes Morocco, Algeria, and Tunisia. Historically, some writers also included Spain, Portugal, Sicily, and Malta in this region, especially during the periods of Arab and Muslim domination. Partially isolated from the rest of the continent by the Atlas

Mountains and the Sahara, the Maghreb has long been closely tied in terms of climate, landforms, population, economy, and history to the Mediterranean. The development of Arab and Islamic culture in the Maghreb region started during the seventh century when the region fell under Islamic statehood and people began their conversion to Islam. The Muslims not only conquered new lands, but also became scientific innovators with originality and productivity by preserving the cultures of the Maghreb. They built many cities with cultural and educational centers, for example, Qairouan in Tunisia. It was founded by the Arabs in around 670 and became an important center for Islamic and Quranic learning and thus attracted a large number of Muslims from various parts of the world, next only to Mecca and Medina. At the end of the ninth century, a Bait al-Hikmah (House of Wisdom) was established in Qairouan and rivaled its counterpart in Baghdad in the study of medicine, astronomy, engineering, and translation [3–6,27].

At Qairouan, classes in medicine were delivered by Ziad bin Khalfun, Ishak bin Imran, and Ishak bin Sulayman, whose works were subsequently translated by Constantine the African in the eleventh century. They were taught in the first faculty of medicine in Europe: Salerno, in the south of Italy, which became the first institution of higher learning in Latin Europe (see Chapter 4). Public education and al-Qairouan were so deeply entwined that even women actively participated in the pursuit of learning, and scholars, reigning monarchs, and men from all walks of life seemed to have supported eagerly the library of their town's grand mosque (The holy Mosque of Uqba is situated in the city). One of the most famous scholars of al-Qairouan was Ibn al-Jazzar, born in the city, hailing from a family of physicians; he studied with the famous philosopher and physician Ishaq bin Sulayman al-Isra'ili and then started a practice in Qairouan, where he died at an advanced age in the year 980. Ibn al-Jazzar was a prolific author in the field of medicine; his writings *Kitab al-adwiya al-mufrada* (*Treatise on Simple Drugs*), *Tibb al-fuqara*' *wa al-masakin (Medicine for the Poor)*, and *Zad al-musafir wa-qut al-hadir* (*Provisions for the Traveller and the Nourishment of the Settled*) earned him great fame and made him very influential in medieval Western Europe.

- *Kitab al-adwiya al-mufrada* (*Treatise on Simple Drugs*) was translated into Greek, Latin, and Hebrew and was frequently copied. But its Latin translation by Constantine the African, under the title *Liber de gradibus*, was of special importance, since it was in this version that the text became one of the most popular pharmacopeia in the Latin West.
- *Tibb al-fuqara*' *wa al-masakin (Medicine for the Poor)* represents a literary topic that became especially popular during the Middle Ages, when works of this type were written by different authors, for instance, Al-Rhazes and Peter of Spain.
- *Zad al-musafir wa-qut al-hadir* (*Provisions for the Traveller and the Nourishment of the Settled*) was Ibn al-Jazzar's most important and most influential work. This work, consisting of seven books, is not, as the title suggests, a guide for the traveler, but a systematic medical handbook, discussing the different

diseases and their treatment "*capite ad calcem*" (from head to toe) in a concise form. The work contains many valuable quotations from the works of famous physicians and philosophers, such as Hippocrates, Aristotle, Rufus, Galen, Paul of Aegina, Palladios, Polemon, and so on. Already in the beginning of the eleventh century, it was translated into Greek and widely distributed. Ibn al-Jazzar's *Zad* became one of the most influential medical handbooks in medieval Europe. The book on fevers and the book on sexual diseases have been recently edited and translated into English. Once accepted into the so-called *Articella* or *Ars medicinae*, a well-devised compendium of medical textbooks, it was widely used in medical schools (Salerno, Montpellier) and in universities (Bologna, Paris, Oxford).

- Ibn al-Jazzar also wrote a treatise on the treatment of forgetfulness (*Risalah fi al-nisyan wa-'ilajihi*), which has recently been edited and translated into English.

Current Status of Herbal Medicine in Morocco. Morocco is a Mediterranean country that is bisected from east to west and from south-west to north-east by four mountain ranges, the Rif, the Middle Atlas, the High Atlas, and the Anti-Atlas. The Mediterranean Sea in the north, the Atlantic Ocean in the west, and the desert in the south have a strong climatic influence that divides the country into many climatic regions. The heterogeneous ecological conditions have favored the proliferation of more than 42,000 species of plants, divided into 150 families and 940 genus, spread over the entire country with an area of 715,000 km^2. Since ancient times, this diverse flora has constituted the main source of products used in folk medicine. The Moroccan pharmacopoeia dates back to 711, the year of the expansion of Muslim influence on Europe. The Moroccan pharmacopoeia was further developed and enriched by the knowledge brought in by various ethnic groups that migrated to Morocco from many areas, including the Arabs from the Middle East, the Andalusians and Jews from Europe, and the Africans from Sudan, Senegal, and Niger. Interestingly, Greco-Arab and Islamic medicine was taught in Moroccan-Islamic universities, such as Quarawin and Zaitouna, until 1893, when the practice was banned by the French colonialists. The common ethnopharmacological legacy of the various Moroccan ethnic groups (such as the Sahraouis, Soussis, Rifains, and Arabs) is well preserved and passed on from generation to generation by oral tradition and through written records and is still flourishing. In the last decades, some institutions of higher learning have shown great interest in the field of ethnopharmacology, and their efforts have borne fruit by bringing to light the primary medicinal plants found in several regions of Morocco [28–31].

Ethnobotanical Studies. An ethnobotanical survey was carried out among the Taounate population in Northern Morocco to identify plants used in folk medicine [29]. Two distinct physiographic regions of the province, populated by two ethnic groups, were surveyed. Extensive investigation undertaken during the past 5 years has brought to light 102 medicinal plants belonging to 48 families. The scientific and vernacular names of plants, their ecological distribution, and the popular uses of the plant, the part

of the plant used, the preparation, and mode of administration were evaluated. Results obtained indicate that plants are widely used in indigenous pharmacopoeia to alleviate the common symptoms of cardiovascular (5.8%), gastrointestinal (24.9%), and bronchopulmonary systems (9.8%); urogenital (12.2%) and skin (9.2%) diseases; and other disorders often associated with magic. In addition, the majority of medicinal plants grow in the wild (61%), while others are cultivated (37%) and some (1.9%) are domesticated. These plants are more abundant in the northern part (62%) of the province where they grow in forested areas. Another recent survey has been carried out in the Errachidia province in south-eastern Morocco in order to inventory the main medicinal plants used in folk medicine to treat arterial hypertension and diabetes mellitus [30]. Four hundred individuals, who knew about and/or had used the medicinal plants for these two diseases, including some herbal healers, were interviewed throughout different regions of the province. The inventory of medicinal plants was summarized in a synoptic table, containing the scientific, vernacular, and common names of the plant, its ecological distribution, the part of the plant, the preparation used, and the therapeutic indication. Results obtained in these extensive investigations indicate 64 medicinal plants belonging to 33 families; of these, 45 are used for diabetes, 36 for hypertension, and 18 for both diseases. Of these plants, 34% grow in the wild, 44% are cultivated, and 22% are not indigenous to the area and are brought from other parts of Morocco or from outside the country. The survey shows that 78% of the patients regularly use these medicinal plants. In this region, the most frequently used plants to treat diabetes and hypertension include the following:

Diabetes Mellitus: *Ajuga iva*, *Allium cepa*, *Artemisia herba-alba*, *Carum carvi*, *Lepidium sativum*, *Nigella sativa*, *Olea europaea*, *Peganum harmala*, *Phoenix dactylifera*, *Rosmarinus officinalis*, and *Zygophyllum gaetulum*.

Hypertension: *Ajuga iva*, *Allium cepa*, *Allium sativum*, *Artemisia herba-alba Asso*, *Carum carvi*, *Nigella sativa*, *Olea europea*, *Rosmarinus officinalis*, *Origanum majorana*, *Peganum harmala*, and *Phoenix dactylifera*.

The local people recognize the toxic plants and are very careful in using them. These plants include *Citrullus colocynthis*, *Datura stramonium*, *Nerium oleander*, *Nigella sativa*, *Peganum harmala,* and *Zygophyllum gaetulum*. This survey shows that traditional medicine in the southeastern Moroccan population not only has survived but also has thrived in the transcultural environment and intermixture of many ethnic traditions and beliefs.

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CHAPTER 11

Biosafety of Herbal Medicine

11.1 INTRODUCTION

Greco-Arab and Islamic medicines have gained enormous popularity in the Mediterranean and across the world over the past 30 years. This popularity has also brought concerns and fears over professionalism of practitioners, quality, efficacy, and safety of the "natural" products available on the market (see Chapter 9). In some cases, adulteration, inappropriate formulation, or lack of understanding of plant and drug interactions have led to adverse reactions that are life-threatening or lethal to patients. Safety assessment of herbal products has often been neglected since prolonged use is usually considered evidence of its safety. Another important factor is the belief that these medicines are prepared according to the principles of the Greco-Arab tradition that forms the basis for the current conventional product. Therefore, most producers and caregiver institutions of Arab herbal medicines are named for famous scholars like Avicenna, Rhazes, Al-Zahrawi, and Al-Antaki. However, a history of traditional usage is not always a reliable guarantee of safety since it is difficult for traditional practitioners to detect or monitor delayed effects (e.g., mutagenicity), rare adverse effects, and adverse effects arising from long-term use. Most reports concerning toxic effects of herbal medicines are associated with hepatotoxicity (HT) although reports of kidney, nervous system, blood, cardiovascular, dermatologic effects, mutagenicity, and carcinogenicity have also been published in the biomedical literature. For example, *Glycyrrhiza glabra*, which is used for conditions like bronchitis and peptic ulcers causes not only hypertension, weight gain, and hypokalemia but also low levels of aldosterone, an antidiuretic hormone, with excessive or prolonged usage.

Based on our recent survey (Chapter 9) as well as other regional surveys, the interest in Arab and Islamic herbal medicines by professionals and lay public is based on the following points:

(a) The belief that these products are "natural" and have long history of safe use.
(b) The belief that these medicines are prepared according to the principles laid by the great Arab and Muslim scholars such as Avicenna and

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Rhazes, and that they are effective in the treatment and prevention of diseases.

(c) Users have a feeling of better control of the disease and its management.

(d) The holistic philosophy behind herbal medicines.

(e) Most countries of the Arab–Islamic world do not impose prescription regulations upon herbal preparations and, therefore, access to this kind of therapy is unrestricted and affordable.

(f) Therapies developed through conventional medicine are often limited in efficacy, unaffordable for many individuals throughout the developing world and also result in unfavorable side effects.

This chapter will give a systematic safety review of Greco-Arab herbal medicine and the contribution of Arab scholars to toxicology. Standards for safety, quality control, use of modern cell biology and biochemistry, and *in vitro* as well as *in vivo* techniques for the evaluation of medicinal plants will be also discussed [1–7].

11.2 EARLY WORKS OF ARAB AND MUSLIM SCHOLARS ON POISONS AND ANTIDOTES

Origins of the discussion on poisons and antidotes date back to the Greeks and Indians, as well as to the empiric knowledge of the indigenous population in the Arabic/Islamic world. One of the most important scholarly contributions is *The Book on Poisons and Antidotes* by the famous Arab alchemist, Abu Musa Jabir ibn Hayyan (Figure 11.1). Based in Kufa, Iraq, he established himself as one of the leading scientists practicing medicine and alchemy in the eighth century. In the six chapters of his book, he identifies poisons by their traits and natural origins, modes of action, dosages, methods of administration, and choice of drugs. He also identifies the target organ attacked by each poison, a proposition that is modern in its chemotherapeutic application.

Another example of an independent manual on toxicology is *Kitab as-Sumum*, written in five volumes by Shanaq the Indian, and translated into Arabic by al-'Abbas bin Sa'id al-Jawhari in the ninth century. The work discusses how various poisons could be detected by sight, touch, taste, or by toxic symptoms developed during the treatment. A similar analysis is found in a later book on toxicology by Ibn Wahshiyyah during the early tenth century. Many of the antidotes described by Arab scientists, like Abu Musa Jabir ben Hayyan and Ibn Wahshiyyah, are still used today by herbalists in the Arab–Islamic world (Table 11.1).

11.3 MODERN TOXICOLOGY AND SAFETY ASSESSMENT OF HERBAL PRODUCTS

Toxicology is the study of the adverse effects of chemicals on living systems, whether they are human, animal, plant, or microbe. "Adverse effect" can range from

FIGURE 11.1 Abu Musa Jabir ibn Hayyan, the Geber, (c. 721–c. 815) is considered by many to be one of the fathers of chemistry. The corpus of Jabir Ibn Hayyan is widely credited with the introduction of the experimental method in alchemy, and with the invention of numerous important processes still used in modern chemistry today. He established himself as one of the leading scientists practicing medicine and alchemy in the eighth century. In *The Book on Poisons and Antidotes* he identifies poisons by their traits and natural origins, modes of action, dosages, methods of administration, and choice of drugs. He also identifies the target organ attacked by each poison, a proposition that is modern in its chemotherapeutic application.

a life-threatening injury to a minor annoyance. For example, a mild irritant that causes watering of the eyes may not seem like a significant effect, but for the person operating fine equipment, such effect can be not only deleterious but potentially dangerous. There are three principles of toxicology.

1. *The dose makes the poison*, is attributed to Paracelsus, a fifteenth-century German physician. The concept that all chemical agents are toxic at some dose is central to a respect for the inherent hazard of all chemicals.
2. *The biologic actions of chemicals are specific to each chemical* has been attributed to Ambroise Paré, a sixteenth-century French surgeon who recognized that toxic substances have different effects dependent upon their inherent nature. Understanding the specific action of chemicals depends upon recognizing the structural domain of the activity of chemicals and the biological structure with which chemicals interact. Very subtle changes in chemical structure can make an enormous difference in biological effects.

TABLE 11.1 Poisons and Antidotes Used in the Greco-Arab and Islamic Medicine

Poison	Antidotes
Lead	Nauseant and then treatment with water extracts from seeds of *Ficus carica* (wild fig tree), *Apium graveolens* (wild celery), *Anethum graveolens* (dill), and then water extracts from *Smilax officinalis* (sarsaparilla), *Triticum vulgare* (common wheat), *Hyssopus officinalis* (common hyssop)
Mercury	Nauseant and then treatment with water extracts of *Smilax officinalis* (sarsaparilla) mixed with honey
Iron	*Rosa canina* (dog rose) and *Viola odorata* (sweet violet), *salix alba* (white willow) mixed with small amounts of vinegar
Convolvolus scammonia	Extracts from *Cydonia vulgaris* (quince tree), *Rheum ribes* (current-fruited rhubarb), and *Rhus coriaria* (sumach)
Nerium oleander	*Vitis vinifera* (common grape), *Phoenix dactylifera* (dates), and *Ficus carica* (wild fig tree)
$CuSO_4$, $FeSO_4$, $ZnSO_4$	Extracts from *Micromeria fruticosa*
Hyoscyamus aureus	Extract from the bark of *Quercus calliprinos*
Toxic plants, for example, *Nerium oleander*	*Artemesia absinthium*

3. *Humans are Animals*: Protection against toxicity of chemicals today would be impossible without the ability to study the effects of toxic agents *in vivo* using test animals.

Toxicology is an interdisciplinary science that integrates the principles and methods of many fields: chemistry, biology, pharmacology, molecular biology, physiology, and medicine. By combining the study of the physiological effects of certain chemical structures and the molecular biological mechanisms that explain those effects, toxicology can provide better understanding of the mechanisms of these substances. For example:

- Understanding chemical mutagenesis and carcinogenesis has permitted the development of bacterial mutagenesis assays, such as the Ames test and other short-term assays for toxic effects. These tests are routinely used during the development phase of new drugs. Before marketing, additional extensive toxicity and efficacy data are required, including studies in humans. Such agents are expected, at anticipated human dose levels, to have a biological effect of benefit to the consumer.
- Long-term animal tests, usually 2-year studies in male and female mice and rats, are very important in assessing new medicines, particularly the assessment of carcinogenesis and other chronic effects. Therefore, a multiple-dose 90-day study is performed in order to choose the maximum tolerated dose (MTD). This dose is then used for a 2-year study. Sole reliance on standard safety-assessment approaches carries a small but finite risk of missing a potentially toxic agent.

This risk can be reduced by assessing the mechanism of toxicity of the chemical. A major goal of toxicological research is a better understanding of the processes by which chemical agents produce adverse biological effects, which will lead to the development of better safety-assessment tests.

- Absorption, distribution, metabolism, and excretion of chemicals are also considered in safety assessment of new drugs. Absorption, the process by which an external dose is converted to an internal dose, occurs by ingestion, inhalation, or through the skin. Distribution of a chemical depends in part on the pathway of entry and on specific chemical and biological factors; for example, only certain types of chemicals are able to penetrate the blood–brain barrier and enter the central nervous system.

11.4 SAFETY OF HERBAL MEDICINES

There are many reasons why herbal toxicity or side effects may occur: lack of pharmaceutical-level quality control at all stages of production; confusing nomenclature and inaccurate plant identification; variations in concentrations of active ingredients in different plant parts, plants harvested at different times or stages of development; or the geography, weather, soil, and other conditions specific to individual plants. The complex chemical mixtures of plants and interactions with other herbs, drugs, adulterants, or contaminants; accidental or deliberate; unprofessional, unwise or careless practitioner treatments or recommendations; or incorrect patient use also contribute to safety issues and increase the risk of adverse reactions. Also, contamination of herbals with microorganisms, fungal toxins such as aflatoxin, pesticides, heavy metals, and synthetic drugs has been described. Another problem is that herbals are usually mixtures of several ingredients or plants harvested during different seasons and extracted through variable procedures, which makes the identification of both the pharmacologically active and toxic compounds difficult.

In general, herbs can be classified into three safety categories:

1. The “food herbs” or GRAS herbs (Generally Regarded As Safe by the FDA) are gentle in action, have very low toxicity, and are unlikely to cause an adverse side effects. Examples of “food herbs” include peppermint, olive, ginger, garlic, chamomile, nettles, and the extracts of these herbs. GRAS herbs can be utilized in substantial quantities over long periods of time without any acute or chronic toxicity.
2. The “medicinal herbs”. These herbs are stronger—they need to be used with greater knowledge (dosage and rationale for use) for specific conditions after a medical diagnosis. Usually, they are to be used for a limited period of time. These herbs have a greater potential for side effects and in some cases, drug interactions. According to recent surveys, there are about 450 medicinal plants in the Eastern region of the Mediterranean. Safety and efficacy of many of these plants have been confirmed with modern biomedical test systems (Chapter 12).

3. The "poison herbs." These herbs have strong potential for either acute or chronic toxicity and should only be utilized by clinicians who are trained to use them and clearly understand their toxicology and appropriate use.

As mentioned above, the increasing popularity of herbal medicines is based on the belief that these treatments are safe. The access to these therapies is unrestricted and cheap because most countries in the Arab and Islamic world do not impose prescription regulations upon herbal preparations.

Potential toxicity and adverse effects of medicinal plants may be related to the mixtures of active compounds that they contain; their interactions with other herbs and drugs, contaminants, adulterants; or their inherent toxicity. For example, plants have complex mixtures of terpenes, alkaloids, saponins, and other chemicals that increase the risk of adverse reactions as well as the additive or synergistic effects of chemical interactions. Furthermore, most individuals who take herbals do not admit their intake because they do not consider herbals as "drugs." Physicians and patients often advocate the long-standing use of herbals in traditional medicine as proof of safety. Therefore, self-medication is frequent and patients may even increase the dosage as liver disease or other ailments worsen.

There are general and herb-specific concerns regarding toxicity and adverse effects. Missuse of nomenclature, issues of quality control and the accurate identification of plants are important concerns. The common names of plants and herbal remedies can be outdated and variable depending on the geographic region [8,9]. There are no governmental regulations on the manufacture, purity, concentration, or labeling claims of herbal remedies and dietary supplements. Thus, it is always "buyer beware" in this marketplace.

Based on obtained results from several recent studies [4,9,10], the status of the knowledge of the safety and efficacy of medicinal plants in the Mediterranean region can be summarized as follows:

1. Most practitioners have very limited training and knowledge. Some practitioners have even turned to "mystical" or "magical methods of healing."
2. Traditional knowledge is not being passed down from generation to generation.
3. Lack of pharmaceutical quality control in harvesting and preparation procedures for medicinal remedies. Practitioners buy ready-made or partially prepared remedies from "Attarah" shops, where plant materials are sold, rather than collecting the plants directly from nature.
4. Plants used in certain regions are not used in others. For example, local practitioners from the Negev region of Israel use plant species found in the desert, overlooking plant varieties and knowledge spanning the entire Middle Eastern region.

Therefore, appropriate regulation guidelines have to be implemented due to the undisputed fact that herbs may contain active ingredients that either treat diseases or cause unwanted adverse effects.

Herbal products are labeled in most Arab and Islamic countries as dietary supplements that are not expected to meet the standards for conventional drugs (see Chapter 18). This simplified licensing practice does not guarantee high quality, safety, or efficacy. Herbal products are exempt from rigorous regulations leading to considerable variation in the composition of herbal remedies that leaves the door open for low quality adulterated herbal products. Therefore, for safety and quality assurances, chemical analytical techniques should be applied at different stages for best practices in quality assurances of medicinal plants, including agricultural practice by the farmers, sourcing and laboratory practices by the pharmaceutical companies, manufacturing practices, and innovative clinical trial practices by researchers and physicians [11,12]. Toxicology studies should include tests such as acute, subchronic, and specific toxins that are impossible to detect clinically such as immunotoxicity, genotoxicity, carcinogenicity, and reproductive toxicity. These tests help in the identification of possible target organs involved and the toxic symptoms. Studies of special toxicology such as carcinogenesis are very important if the herbs contain compounds with known mutagenic or carcinogenic activities.

Therefore, advanced cell biology, biochemistry, molecular biology, and *in vitro* cell culture techniques should be applied in order to prove the safety of herbal medicines (Table 11.2).

Dosage of Phytochemicals. Like conventional medicines, medicinal herbs can be therapeutic in one dose and toxic at another. Therefore, the concept of dose is a basic principle in safety assessments of herbal products. Dose is the amount of chemical that comes into contact with the body or gets inside the body. Exposure is the amount of chemical that is directly available to the body. Exposure includes both the concentration of the chemical in the media and the length of time such chemical is available to the body (concentration $\times$ time). Although exposure is important in determining dose, other factors also come into play. For example, if two individuals are exposed to the same amount of chemical in the air—same concentration and for same length of time—one will inhale a much higher dose than the other if that person is exercising more vigorously. Even though exposure is identical for the two individuals, the faster and deeper breathing of the first individual will pull more chemical (i.e., dose) into the lungs.

The concentration of active ingredients and other chemicals in plants varies by the parts of the plant harvested and sold; the maturity of the plant at the time of harvest; the time of year during harvest; geography and soil conditions; soil composition and its contaminants; and year-to-year variations in soil acidity, water, weather conditions, and other growth factors. For example, a recent study has reported that fertilization affects the antioxidant activity of four medicinal plants used in traditional Arab medicine. They found that increasing the amount of fertilizer caused a significant concentration dependent increase in antioxidant activity of cultivated *Teucrium polium* compared with the wild type. In contrast, increasing the amount of fertilizer caused a significant concentration-dependent reduction in the antioxidant activity of powders prepared from cultivated *Eryngium creticum* when compared with wild plants. Therefore, the actual dose of active ingredients being consumed is

TABLE 11.2 LD_{50} Values of Traditional Medicinal Plants

Plant Species	Parts Tested	Uses	LD_{50} (g/kg weight)
Alchemilla vulgaris	Leaves	Weight loss, stomach pain	17.3
Atriplex halimus	Leaves	Diabetes, heart diseases	21.5
Cichorium pumilum	Leaves	Rheumatism, bacterial and fungal infections	23.6
Crataegus azarolus	Leaves	Cardiovascular diseases, cancer, diabetes	23.4
Eruca sativa	Leaves	Stimulant, aphrodisiac, skin diseases	21.6
Eryngium creticum	Leaves	Liver diseases, antidote, fertility problems	20.7
Ferula hermonis	Roots	Sexual weakness, infertility, asthma	8.8
Hypericum triquetrifolium	Leaves	Anti-inflammatory, depression	14.7
Inula viscosa	Leaves	Muscle relaxations, infertility, stomach pains	11.9
Juglans regia	Leaves	Diabetes, asthma, aphrodisiac	16.9
Nigella sativa	Seeds	Blood pressure, heart diseases, skin diseases	19.8
Olea europaea	Leaves	Diabetes, high blood pressure, viral infections	19.3
Portulaca oleracea	Above ground parts	Kidney stones, diabetes, skin diseases	23.8
Saponaria officinalis	Roots	Acne, antimicrobial	5.1
Silene aegyptiaca	Above ground parts	Fever	25.2
Urtica dioica	Leaves	Cancer, stomach, liver diseases	22.1
Ziziphus spina-christi	Leaves	Hair loss, cancer	22.2

LD_{50} is defined as the quantity of chemical estimated to be fatal to 50% of organisms under stated conditions of the test. Water extracts were prepared from dried plant material were used. Values presented are the mean results of 30–35 rats tested.

often variable, unpredictable, or simply unknown [13]. Dosage variation has larger effects on children due to their smaller size and different capacity for detoxifying chemicals [13,14].

Contaminations. The use of synthetic pesticides during the last half century has often been careless and indiscriminate, and has led to a number of well-known problems. Synthetic pesticides have caused contamination of the environment with toxic residues in many regions around the world, as well as side effects on nontargeted insects and other organisms, an increase in the number of pest species resistant to pesticides, and pest resurgence. Many accidents have occurred due to unsuitable storage conditions and high temperatures during the summer season in the Mediterranean as well as the

mishandling of highly toxic synthetic pesticides, causing deaths and injuries. Pesticides may be introduced to plants from various sources such as direct application, residue absorption from water and soil biochemical processes. Contaminants of medicinal plants can be pharmacologically active and responsible for unexpected toxicity. Plants may be harvested from contaminated soils or cleaned improperly such that they may contain illness-producing microorganisms. Ayurvedic medications have been known to cause lead poisoning in children because of their contamination with lead as well as other heavy metals, such as arsenic and mercury. Contamination of crop and medicinal plant samples with organic chemicals is a pressing problem in many Arab countries. Low contamination levels were detected in cucumbers and tomatoes in Palestine, Jordan, and Egypt. Elevated levels of contamination were detected in vegetables from Pakistan, Egypt and in grapes from Jordan. Several poisonous plant food contamination cases were reported in Morocco, Egypt, Iraq, Saudi Arabia, Sudan, Syria, Jordan, UAE, Pakistan, and Yemen in the past years. For example, Selim and his colleagues [15] found that common Egyptian foods such as nuts and seeds, cereal grains were contaminated with aflatoxins. Twenty-nine percent of medicinal plants were found to be contaminated with aflatoxin B1. The highest mean concentration of aflatoxin B1 was in herb and medicinal plants (49 ppb).

Drug Interactions with Herbal Products. Interactions between herbs and conventional drugs are another source of challenges associated with the intake of herbal medicines, which are often administered in combination with therapeutic drugs, raising the potential of herb-drug interactions. Herbal medicines are often mixtures of more than one active ingredient. The multitude of pharmacologically active compounds obviously increases the likelihood of interactions taking place. Hence, the likelihood of herb–drug interactions is theoretically higher than drug–drug interactions, if only because conventional drugs usually contain single chemical entities. Case reports and clinical studies have highlighted the existence of a number of clinically important interactions, although cause-and-effect relationships have not always been established. Herbs and drugs may interact either pharmacokinetically or pharmacodynamically.

Concurrent use of herbs may mimic, magnify, or oppose the effect of drugs. Cases of herb–drug interactions include the following:

- Bleeding when warfarin is combined with ginkgo (*Ginkgo biloba*), garlic (*Allium sativum*), dong qual (*Angelica sinensis*), or danshen (*Salvia miltiorrhiza*).
- St John's wort (*Hypericum perforatum*) that is promoted for the treatment of depression interacts with numerous conventional drugs including cyclosporin, simvastatin, warfarin, and digoxin due to its inducing properties on cytochrome P450 3A4, 2C9, and the drug transporter MDR1 [16].
- Induction of mania in depressed patients who mix antidepressants and *Panax ginseng*.
- Exacerbation of extrapyramidal effects with neuroleptic drugs and betel nut (*Areca catechu*).

- Increased risk of hypertension when tricyclic antidepressants are combined with yohimbine (*Pausinystalia yohimbe*).
- Potentiation of oral and topical corticosteroids by liquorice (*G. glabra*).
- Decreased blood concentrations of prednisolone when taken with the Chinese herbal product xaio chai hu tang (sho-saiko-to).
- Decreased concentrations of phenytoin when combined with the Ayurvedic syrup shankhapushpi.
- Anthranoid-containing plants (including *Cassia senna* and *Rhamnus purshiana*) and soluble fibers (including guar gum and psyllium) can decrease the absorption of drugs.

The aforementioned interactions between herbal medicines and conventional drugs can occur and may lead to serious clinical consequences. Both pharmacokinetic and/or pharmacodynamic mechanisms have been considered to play a role in these interactions, although the underlying mechanisms for the altered drug effects and/or concentrations by concomitant herbal medicines are yet to be determined. The clinical importance of herb–drug interactions depends on many factors associated with the particular herb, drug, and patient. For example, systems such as the cytochrome P450 (CYP) may be particularly vulnerable to modulation by the multiple active constituents of herbs, as it is well known that the CYPs are subject to induction and inhibition by exposure to a wide variety of xenobiotics. Using *in vitro* and *in vivo* approaches, many herbs and natural compounds isolated from herbs have been identified as substrates, inhibitors, and/or inducers of various CYP enzymes. For example, St. John's wort is a potent inducer of CYP3A4, which is mediated by activating the orphan pregnane X receptor. It also contains ingredients that inhibit CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Many other common medicinal herbs also exhibited inducing or inhibiting effects on the CYP system, with the latter being competitive, noncompetitive, or mechanism based. It appears that the regulation of CYPs by herbal products is complex, depending on the herb type, their administration dose and route, the target organ and species. Due to the difficulties in identifying the active constituents responsible for the modulation of CYP enzymes, prediction of herb–drug metabolic interactions is difficult. However, herb–CYP interactions may have important clinical and toxicological consequences. For example, induction of CYP3A4 by St. John's wort may partly provide an explanation for the enhanced plasma clearance of a number of drugs, such as cyclosporine and innadivir, which are known substrates of CYP3A4, although other mechanisms including modulation of gastric absorption and drug transporters cannot be ruled out.

11.5 HERBAL HEPATOTOXICITY

The liver is the central drug-metabolizing organ and is, therefore, a prime target of drug-related toxicity. Because of its position between the digestive tract and the rest of the body, the liver occupies a central role in major organism functions. It receives large

amounts of nutrients and noxious compounds entering the body through the digestive tract and portal vein. Among the major hepatic functions of the liver are uptake of amino acids, lipids, carbohydrates, and vitamins, and their subsequent storage, metabolic conversion, and release into the blood and bile. The liver is the predominant organ in which biotransformation of foreign compounds (Xenobiotics) takes place, although other organs may also be involved in biotransformation of foreign substances. The capacity of a chemical to produce liver damage often results from the interaction of a series of complex cellular processes that are involved in the uptake, biotransformation, and elimination of these potentially toxic compounds (Figure 11.2). Xenobiotics are predominantly biotransformed in the liver by the action of drug-metabolizing enzymes (DMEs) including microsomal cytochrome P450, sulfotransferases, mixed-function mono-oxygenases, glutathione-*S*-transferases, and UDP-glucuronosyltransferases. Some of these enzymes are inducible through variable pathways, which may result in large interindividual variability in susceptibility for drug-related liver damage.

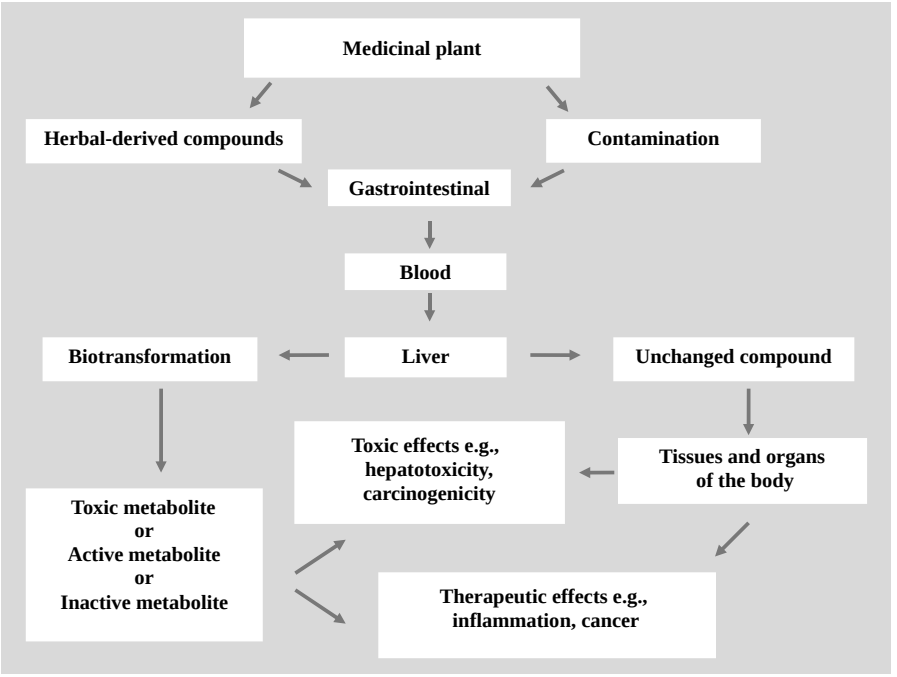

FIGURE 11.2 Safety and efficacy of herbal medicines. The liver is the central drug-metabolizing organ and is a prime target of drug-related toxicity. It occupies a central role in major functions of the organism including biotransformation of foreign substances. The capacity of a chemical to produce liver damage often results from the interaction of a series of complex cellular processes that are involved in the uptake, biotransformation, and elimination of these potentially toxic compounds.

Herbal-derived molecules have only recently been recognized as a cause of adverse hepatic reactions. The occurrence of herbal-induced hepatic injury, while relatively uncommon, is a serious problem that is very difficult to manage, based on the following factors:

- The use of herbal products is extremely widespread (and often unreported), and, based on the common perception of safety, products may be taken at high doses and over a long period of time.
- The complexity and variability of herbal products.
- The lack of rigorous quality controls in manufacturing.
- Variations in susceptibility due to genetic or pathophysiological factors or coexposures to other agents that impact susceptibility.

Certain phytochemicals have been identified as a cause of acute and chronic hepatitis, cholestasis, vascular leasions drug-induced autoimmunity, and even hepatic failure and cirrhosis. Risk factors for herbal toxicity have not been well identified, largely since hepatotoxic incidents have mostly been published as isolated case reports or small series. However, a certain risk pattern has become evident, beginning with the observation that most affected individuals were females. This gender difference does not reflect a higher likelihood of women to use these preparations, but their higher susceptibility toward herb-induced liver damage [11], as is observed for the majority of adverse hepatic reactions induced by conventional drugs. As with chemically defined drugs, adverse hepatic reactions toward herbals cannot be predicted through diagnostic means, which makes the early recognition of liver damage important.

Most reports of toxic effects due to the use of herbal medicines and dietary supplements are associated with hepatotoxicity although reports of other toxic effects including kidney, nervous system, blood, cardiovascular, and dermatological effects, mutagenicity, and carcinogenicity have also been published in medical literature. Hepatic impairment resulting from the use of conventional drugs is widely acknowledged, but there is less awareness of the potential HT of herbal preparations and other botanicals, many of which are believed to be harmless and are commonly used for self-medication without supervision. Although regulation by the Food and Drug Administration may be part of the solution, increasing public awareness and education programs for health care professionals about the potential dangers of herbal preparations will need to be implemented [17,18]. The reported toxicity of herbal formulations may be the result of several factors, including the contamination with pesticides, microbes, heavy metals, toxins, or adulteration with orthodox drugs [19,20]. On the basis of various case reports, the liver injury from herbal remedies has ranged from mild elevations of liver enzymes to fulminated liver failure requiring liver transplantation [13]. For example, veno-occlusive disease may be caused by pyrrolizidine alkaloids, such as *senecio* species, *heliotropium* species, and Comfrey (*Symphytum officinale*). Chapparal (*Larrea divaricata*) leaf ingestion can lead to the development of either fulminant hepatic failure or cirrhosis. Kava (*Piper*

methysticum) has been identified as causing an acute hepatitis. Many traditional Chinese herbal preparations have also been described to cause HT and rarely liver failure [13].

Assessment of Hepatotoxicity. It seems unlikely that a single screening approach is able to predict hepatotoxic potential since the mechanisms of action involved are so varied and complex. However, the development of a battery of tests, based on the thorough characterization of known hepatotoxic plants and correlation to liver injury *in vivo*, might be possible. These tests might be used to screen against the major categories of harmful agents. Toward this end, research efforts are required on DMEs, liver cell cultures, and validation in animal models or from human exposure data.

- *Drug-Metabolizing Enzymes*: Systematic evaluations of the impact of herbal-based products on drug-metabolizing enzymes should be assessed, including elucidation of the inhibition/induction of various Phase I and Phase II enzyme systems from the gut epithelium and liver. A battery of *in vitro* tests might allow the development of a database including this information. One problem is establishing the applicability of such tests to human consumption. What concentrations for the cellular or enzyme testing are relevant for oral bioavailability or hepatic exposure *in vivo*?
- Related to the question of DME interactions is the potential conversion of herbal-derived constituents that may be substrates for CYP450s to intermediates that cause liver injury. Research is needed on the identification of the specific isoforms that mediate such conversions and how these may vary in human populations to determine susceptibility to these agents.
- *Liver Cell Cultures*: Screening for hepatotoxicity using human primary hepatocytes appears to offer distinct advantages over established cell lines (see Chapter 13). Development and use of stable hepatocyte cell lines expressing representative human DMEs would provide a valuable tool for screening. Mechanistic characterization of known herbal-derived hepatotoxins could allow the design of specific screens for detection of a particular activity profile.
- Because heterogenous cell–cell as well as cell–substrate interactions mediate/affect toxic responses for many chemicals, current *in vitro* systems cannot be expected to predict all responses that occur *in vivo*. Systems designed to allow for interactions of different cell types or mediators may be required for some modes of injury. For example, liver slice systems might be used to assess contributions of vascular or stellate cells to parenchymal cell damage. Cocultures (applying two different cell types) of activated inflammatory cells or coincubation with immune/inflammatory mediators may help to simulate some of the complex interactions that can be critical *in vivo* for the expression of hepatotoxic injury.
- *Validation in Animal Models or from Human Exposure Data*: The correlation of *in vitro* findings to appropriate animal models or, where possible, to humans is critical. This type of work has already been implemented for pharmaceuticals in

some of the toxicogenomics database development and can be implemented systematically with other assay systems. It seems likely that correlations must first be developed using herbal-derived pure chemical entities known to cause injury. In this way, the models could be validated and then serve as tools for tracing the entities to the plant and herbal-derived commercial preparations.

11.6 SAFETY ASSESSMENT

Safety assessment is the process that results in an "acceptable daily intake" (ADI) of specific xenobiotics. Safety assessment starts with the underlying premise that exposure to a chemical, be it a drug, food additive, cosmetics ingredients, or consumer product, will occur. It also relies on animal toxicology studies. The assumption made is that humans are more sensitive to these chemicals than the most sensitive animal species tested. Safety assessments for new drugs are based on animal toxicity, doses to be used, and the diseases to be treated. Safety assessment of an over-the-counter drug is often more stringent than for a drug to be used for the treatment of life-threatening diseases. A therapeutic index is developed for almost all drugs and is based on the ratio of the toxic dose to the efficacious dose: The greater the ratio, the greater the margin of safety in use of the drug. A drug being used for cancer chemotherapy can have a greater toxicity and a much smaller therapeutic index than a drug for the common cold. The other issue in this example is that there is a much larger consumer population for over-the-counter preparations than for chemotherapeutic products, and the risks of over-the-counter drugs may not be as well appreciated. Safety measurements have, for decades, been carried out *in vivo* on test animals. Starting in the early 1970s, *in vitro* testing was initiated and added to the tests used to evaluate the safety and action mechanisms of test substances (Figure 11.3). It is very important, however, to mention the following:

1. *In-vitro* methods are not primarily "replacements" of *in vivo* methods. Some of the most common side effects found in *in vitro* models are difficult to recognize, for example, nausea, nervousness, lethargy, heartburn, headache, depression, and so on. Furthermore, extrapolation of *in vitro* dose to humans is difficult.
2. Typically these methods have different roles in research, and they are complementary for each others. Some compounds that show promising activity *in vitro* may be metabolized *in vivo* into inactive metabolites. Alternatively, chemicals may only show *in vivo* activity due to the metabolism of inactive compounds into active forms

For instance, in the intact liver it is difficult *in vivo* to distinguish the primary effects of a compound from those induced secondarily because liver functions are under the influence of various endogenous and exogenous factors that result in complex interactions with other organs. Moreover, most of our understanding of liver injury induced by chemicals remains confined to animal models. Data obtained in animals cannot be extrapolated with certainty to the human situation. Because of the

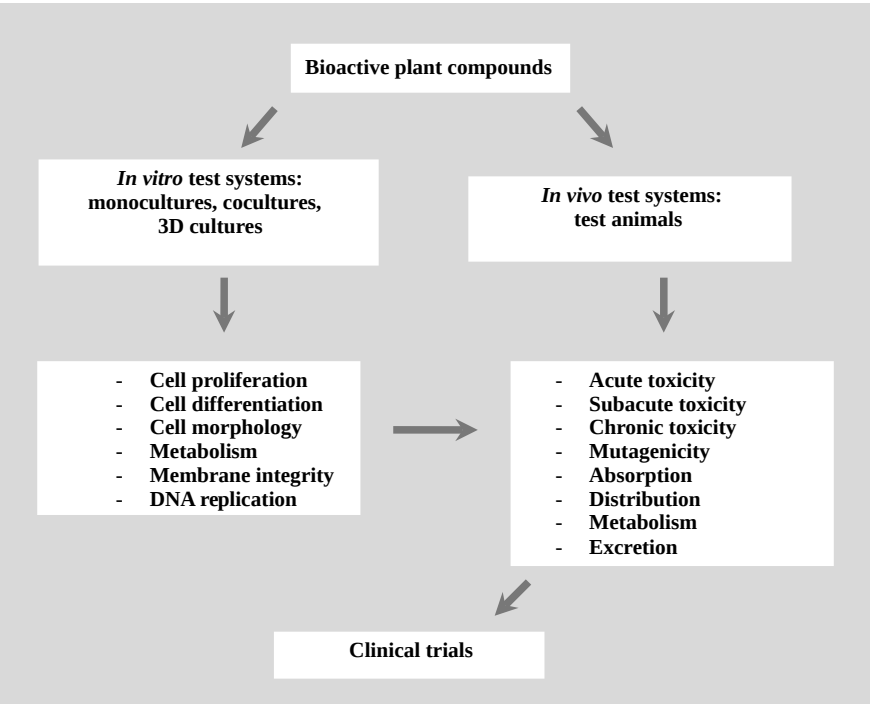

FIGURE 11.3 Safety measurements have, for decades, been carried out *in vivo* on test animals. It is important to note that *in vitro* techniques are not "replacements" for *in vivo* methods. Typically these methods have different roles in research, acting to compliment each other. The most stringent tests are reserved for drugs and foodstuffs.

drawbacks of *in vivo* studies of drug- and chemical-induced hepatotoxicity, *in vitro* liver systems represent a better experimental approach to screen potential hepatotoxic compounds and investigate mechanism(s) by which chemicals induce liver lesions. The most frequently used isolated liver preparations include isolated perfused organ, tissue slices, subcellular fractions, and isolated and cultured hepatocytes. The latter model is the most popular system and is widely used for toxicity studies.

In Vivo Assessments. *In vivo* tests are carried out in laboratory animals for the development of conventional drugs, herbal-derived medicines, food additives, pesticides, and industrial chemicals. *In vivo* tests are usually conducted under the Good Laboratory Practices (GLP) guidelines. These guidelines, issued by the national and international regulatory agencies, lay out the rules within which toxicity assessments that are to be used for regulatory purposes will be conducted. *In vivo* studies range from short-term to lifetime exposure. Around one million animals are used every year in Europe in toxicology tests. In the UK, about 20% of animal experiments are toxicology tests.

In the process of drug development, a number of preclinical tests must to be performed, lasting less than a month (acute), 1–3 months (subchronic), and more than 3 months (chronic) to test general toxicity (damage to organs), eye and skin irritancy, mutagenicity, carcinogenicity, teratogenicity, and reproductive problems. Most toxicity tests involve testing ingredients rather than finished products. The cost of the full complement of tests is several million dollars per substance and it may take 3 or 4 years to complete.

ACUTE STUDIES Short-term, acute studies are usually conducted in one or more rodent species with the aim to assess the dose range for lethality of a test substance. In addition to the LD_{50} (the dose lethal to half the animals), the results of the acute studies are prerequisite for longer term, subchronic experiments. Acute studies can determine toxicity, time of onset of toxic signs, and recovery in the surviving animals. This data is crucial in an emergency situation where humans or animals are exposed to high concentrations of a toxic molecule. Occasionally, acute toxicity studies are used in the search for antidotes to a given toxicant.

SUBCHRONIC STUDIES Subchronic studies are generally conducted in both sexes of two laboratory animal species, one of which is a nonrodent species. These studies are of longer duration, generally 3–6 months, and are conducted using multiple doses. The purpose of the subchronic assessments is to determine target–organ toxicity, to determine the effects of prolonged dosing, and to help establish margins of safety for food additives and drugs. At the end of the study all test animals are autopsied, with complete gross and microscopic examination of tissues. Complete blood chemistries are evaluated and an overall clinical assessment is made on each animal.

CHRONIC STUDIES The next level of toxicity study is the chronic bioassay. As for subchronic studies, the study is conducted in multiple species, in both sexes, and for duration that approaches the life-span of the animal. These are very large and complex studies that necessitate a great deal of day-to-day management. There are multiple intermediate clinical tests, including daily observations, weekly food and water consumption, and body weight determinations. At the end of the study, or at times of interim sacrifices, all animals are autopsied. Chronic toxicity studies provide a thorough examination of the dose effect of a given chemical on homeostasis, bodily function, induced diseases, and the effect on life-span. Chronic toxicity studies provide the bulk of the preclinical information used for assessing safety and risk.

In Vivo Test Systems.

LD_{50} Quantity of chemical estimated to be fatal to half of organisms under stated conditions of the test. LD_{50} assessments are frequently used as a general indicator of a substance's acute toxicity. The LD_{50} values are usually given as the mass of substance administered per unit mass of test animal, such as grams of substance per kilogram of body mass. Stating it this way allows the relative toxicity of different substances to

be compared, and normalizes for variation in the size of the animals exposed (although toxicity does not always scale simply with body mass). Typically, the LD_{50} of a substance is given in milligrams per kilogram of body weight (e.g., 11,900 mg vitamin C/kg tested in rat after oral administration). In the case of some substances such as Botulinum toxin, one of the most deadly toxins known, the LD_{50} may be more conveniently expressed as micrograms or nanograms per kilogram of body mass. The estimated LD_{50} for Botulinum toxin in humans is 1 ng/kg.

The LD_{50} test was created by J.W. Trevan in 1927. As a measure of toxicity, LD_{50} is somewhat unreliable and results may vary greatly between testing facilities due to factors such as the genetic characteristics of the sample population, environmental factors and mode of administration. For instance, many substances are less toxic when administered orally than when intravenously administered. For this reason, LD_{50} figures are often qualified with the mode of administration, for example, "LD_{50} i.v." The substances are applied to the skin or eyes; injected intravenously, intramuscularly, or subcutaneously; or administered orally, through a tube into the stomach, or placing them in the animals' food. Doses may be given once, repeated regularly for many months, or for the life-span of the animal. The test is conducted without anesthesia, since drugs can change test results. LD_{50} is often criticized by Animal-rights and animal-welfare groups for being needlessly cruel, as more modern methods of classifying toxicity, such as the use of computer generated molecular models or testing on cell cultures, are available. LD_{50} still remains popular, despite its general weakness in providing a useful measure in safety assessments of herbal medicines. Table 11.2 summarizes the LD_{50} values of 18 different plant species as well as their traditional uses. The LD_{50} values of 30–35 rats were recorded for different plant parts (as used by the herbalists) under controlled conditions. The values showed that all the plants tested have high LD_{50} values and are considered as safe for use. Therefore, data on the toxicity of each plant species should be available to practitioners before they prescribe any remedies to their patients. Table 11.3 summarizes the LD_{50} values of commonly used herbal mixtures as discussed in details in Chapter 12.

DRAIZE TEST The Draize test is an acute toxicity test developed by toxicologist John H. Draize in 1944. The test involves applying 0.5 mL or 0.5 g of a substance to an animal's eye or skin (usually albino rabbits who are conscious and held immobilized in stocks) for 4 h. The animals are observed for up to 14 days for signs of erythema and edema on the skin, and redness, swelling, discharge, ulceration, hemorrhaging, cloudiness, or blindness in the eye. The animals are killed after the test. The test is controversial. It is viewed as cruel by critics, as well as unscientific because of the differences between rabbit and human eyes, and the subjective nature of the visual evaluations. Despite two decades of research into alternatives to this test, no nonanimal alternatives have yet been successful, although the low-volume eye test is being investigated as an alternative that may reduce, but not eliminate, animal suffering. Because of its controversial nature, the use of the Draize test in the United States and Europe has declined in recent years and is sometimes modified so that

TABLE 11.3 LD_{50} Values of Traditional Medicinal Plant Mixtures Used in the Treatment and Prevention of Diseases

Herbal Mixtures	Treatment of	LD_{50} (g/kg)
Inula helenium, *Saponaria officinalis*, *Citrus limonum*	Acne	10.5
Citrus medica extract., *Negilla sativa* oil	Hemorrhoids	18.8
Extract of leaves of *Eribotrya japonica* (Loquat) and *Olea europaea*	Reducing raised blood cholesterol and fats	17.3
Juglans regia, *Olea Europaea*, *Urtica dioica*, *Atriplex halimus*	Diabetes	25.0
Ferula foetida and *Capparis spinosa*	Female infertility and sexual problems	15.0
Alchemilla vulgaris, *Olea Europaea*, *Cuminum cyminum*, *Mentha longifolia*	Weight problems and obesity	15.3
Cichorium intybus and *Silene aegyptica*	Common cold and flu	27.7
Ocimum basilicum, *Urtica dioica* and *Melissa officinalis*	Migraines and headaches	18.3
Nigella sativa; *Eruca sativa*; *Citrus limonum*; *Hypericum perforatum*	Psoriasis and inflammation	20.6

Water extracts prepared from dried plant material were used. Values presented are means of 30–35 rats tested.

anesthesia is administered and lower doses of the test substances used. Chemicals already shown to have adverse effects *in vitro* are not currently used in a Draize test, thereby reducing the number and severity of tests carried out. The Draize test has been extensively used in the assessment of allergic effects of herbal products used in the cosmetic industry.

TERATOGENIC EFFECTS The effects of contaminations and dosage variations are higher in children than in adults [13]. The teratogenic effects of herbs are not known in many cases. It is possible that herbal chemicals may be transported through the placenta to cause toxic effects on the sensitive growing fetus. For example, Roulet et al. [14] reported the case of a newborn whose mother drank senecionine-containing herbal tea daily for the duration of her pregnancy. The infant was born with hepatic vaso-occlusive disease and died; senecionine is one of the pyrrolizidine alkaloids associated with hepatic venous injury. The potential to induce adverse birth outcomes is tested in several species. Rodents, rabbits, and sometimes dogs are used depending on the end use of the candidate chemical. The studies are designed to determine if the chemical alters the reproductive cycle of the female or spermatogenesis in the male. The studies also examine the effects of the chemical during the first, second, and third trimester of pregnancy, and during parturition and lactation. Multigenerational studies are conducted to determine the overall effects of a given chemical on the parent generation, the offspring, and on the ability of the offspring to reproduce normally.

Other In Vivo Tests.

1. *Ninety-day repeat-dose test*, administered by mouth, inhalation, or skin to 30–80 rats, rabbits, or guinea pigs.
2. *Ninety-day repeat-dose test by mouth in non-rodents*. Usually, dogs are used in this test.
3. *Teratogenicity test*, which tests for the effects of a substance on a fetus, and involves at least 80 mice, rats, hamsters, or rabbits.
4. *Chronic toxicity test*, which involves at least 160 rats, who are given daily doses of the substance for most of their life-span.
5. *Carcinogenicity test*, another lifetime study for cancer in 400–500 rodents.
6. *One- and two-generation reproduction toxicity test*, which involves more than 100 rats or mice.
7. *Test for embryonic genetic damage*, which involves 10–60 rats, hamsters, mice and their offspring.
8. *Toxicokinetic study*, which involves 8–10 animals to study the absorption, metabolism, distribution, and excretion of a substance.

Predictability and Utility. Currently, the development of new drugs (e.g., herbal-derived drugs) is suffering from two major obstacles. First, none of the animal species or *in vitro* tests can properly mimic the complex reactions of the human body. Treatment with newly developed drugs can have unprecedented positive or negative biological effects involving systemic interactions specific to humans. Although, there is a strong similarity among mammalian species, extrapolation of data from laboratory animals to humans, and from high to low doses is central to modern toxicology. In addition to understanding dose–response relationships, knowledge about differences among species in the uptake, metabolism, and disposition of chemicals is also of importance. Where differences between different species do exist, attention to the kinetics of the processes that determine how an external exposure level is translated to the dose of a chemical at a target organ provides information of value to cross-species extrapolation. Questions have been raised about the predictability and overall utility of toxicology testing. Most animal tests either over- or underestimate risk, or do not reflect toxicity in humans particularly well. This variability stems from attempting to apply the results of high chemical doses in a small number of laboratory animals in order to predict the effects of low chemical doses in a large number of humans. Although relationships do exist, opinion is divided on how to use data on one species to make exact predictions about the level of risk in another species. This problem was first described by Avicenna (980–1037). In his voluminous Canon, he laid out the following principle for testing the toxicity and efficacy of a new drug or medication: "The experimentation must be done with the human body, for testing a drug on a lion or a horse might not prove anything about its effect on man." This principle still forms the basis of modern clinical trials.

In Vitro Techniques.

In vitro toxicology simply describes a field of endeavor that applies isolated organs, isolated tissues, cell culture, biochemistry, and chemistry to evaluate toxic effects or adverse reactions to xenobiotics (e.g., herbal-derived medicines). In the early 1970s, *in vitro* studies were used to determine the potential of a chemical or a mixture to induce point mutations in engineered strains of bacteria. These studies indicated that the mutagenic potency of a chemical was a reasonable predictor of its mutagenic and carcinogenic potential. The overall hypothesis was later shown to be less predictive than first thought, depending on the class of chemical tested, but the strength of the tests kept them in the battery of safety evaluation tests. Subsequently, *in vitro* tests have been developed to assess potential hepatotoxicity, mutagenesis, hormone action, immunotoxicity, eye irritation, and cellular and molecular events that are correlated with end-stage disease. Advantages of these systems over classical methods, such as long-term studies on experimental animals, include relatively well-controlled variables, relative affordability, reduced completion time, ability to study specific mechanisms of action, and reduced numbers of animals necessary to complete the study. These tests are generally accepted as a very effective method for safety assessment. The disadvantage of these tests is that the homeostatic mechanisms and pathways found in animals are not present. For instance, *in vitro* assessment of adverse reactions to xenobiotics can only be measured to a limited extent. Although some advanced *in vitro* systems are available that allow prediction of the local effects of test pharmaceuticals, even the most sophisticated *in vitro* test cannot yet be used to measure systemic effects (e.g., blood pressure or fever). Culturing cells is the most widely used *in vitro* method in safety assessment of new medicines. In general, *in vitro* test systems represent the first phase of the evaluation procedure.

TISSUE CULTURE SYSTEMS In order to determine the effects of plant extracts, cell culture model systems are used. In most of these culture systems, vertebrate cells cultured *in vitro* have been grown in monolayer on artificial substrate. However, it has long been realized that while growth in two dimensions is a convenient way of preparing and observing a culture and allows a high rate of cell proliferation, it lacks the cell–cell and cell–substrate interaction characteristic of whole tissue occurs *in vivo*. The interactions of a cell with substratum play an important role in the development, differentiation, and regeneration of multicellular organisms. In cultured rat hepatocytes, morphology, basal functions such as growth [21,22] or protein synthesis and secretion [23] are affected by cell–substratum interactions [22]. For toxicity testing *in vitro* and for studying mechanisms involved in the response of liver cells to xenobiotics, the maintenance, expression and regulation of P450 isoenzymes is of primary interest [24–26].

THREE-DIMENSIONAL TISSUE CULTURES Currently, the available conventional tissue culture polystyrene (TCPS) are not suitable to form tissue-like aggregates *in vitro* that require high cell density. In contrast to the *in vivo* situation, cells cultured on these flat TCPS built a monolayer of cells with flat cell morphology. In addition, all cell types, except those grown in suspension, are in contact with an environment including

some type of topography. The substrate that shows this topography may be made of other cells or of extracellular material. Therefore, the engineering of a new generation of substrates that enables cultured cells to grow at a higher cell density and to maintain more *in vivo* like cell-to-cell interactions is very important in order to obtain more reliable results *in vitro*. Therefore, in our cell culture laboratories, we apply a newly developed cell carrier called DegraPol. DegraPol represents a versatile biodegradable class of multiblock copolymeric elastomers. This polymer has been developed for use as a tissue engineering scaffold as well as for implantable medical devices [27]. Using cell culture techniques, the newly developed, biodegradable, elastic, and porous (pore size 200–400 μm) polyesterurethane foams (DegraPol-foam) were found to be compatible for various cell types. Macrophages seeded on the DegraPol-foam were not activated and no cytotoxic effects were detected in these cells. Osteoblasts and fibroblasts seeded on the DegraPol-foam showed high cell adhesion and preserved their phenotype [23,28,29].

In Vitro Test Systems.

For toxicological studies, some of the common standardized test methods are used in our laboratories (Table 11.4). These methods are based on the extraction of the active compounds. The extracts are applied to cells in different dilutions. After exposition of the cells to the extracts, cytotoxicity is assessed by various methods including microscopic evaluation of cell morphology, methyltetrazolium assay (MTT test), measurement of DNA and protein synthesis, lactate dehydrogenase (LDH) activity, neutral red uptake, and apoptosis tests [23,29–31]. The MTT and LDH assays are

TABLE 11.4 *In Vitro* Test Methods Used in Order to Evaluate the Toxic Effects of Medicinal Plants

Test System	End Points Measured	Applications
MTT	Metabolic activity of a mitochondrial enzyme, succinate dehydrogenase	Cell viability, cell toxicity, cell number
LDH	Lactate dehydrogenase activity	Cell viability, toxicity
Cell counting	Cell number	Cell proliferation, cytostatic effects
Trypan blue	Trypan blue diffusion into the cells	Cell viability
DNA synthesis	^{3}H-Thymidine incorporation or bromodeoxyuridine (BrdU)	Cell proliferation, cytostatic effects
Neutral red uptake	Dye uptake	Cell proliferation, cytostatic effects
Cell morphology	Morphological appearance of cells and tissues	Cytotoxicity, cell proliferation, cell differentiation
Protein synthesis	35S-Methionine and 3*H*-prolline; ELISA	Cell function
Ames test	Mutations	Carcinogenesis

well-established methods used to assess mitochondrial competence and cell membrane integrity, respectively [32].

MTT TEST This test is widely used to assess the viability and/or the metabolic state of the cells [32]. This assay detects the reduction of MTT [3-(4,5-dimethythiazol-2-yl)-2,5-diphenyl-tetrazolium bromide] by mitochondrial dehydrogenase to blue formazan product, which reflects the cell viability, as well as the actual cell number of the culture. Following a 48 h incubation of the cells with the extracts, the culture medium is replaced with MTT dissolved at a final concentration of 1 mg/ml of culture medium for a further 4–6 h incubation. Then, the MTT-formazan is solubilized in isopropanol and the optical density is measured at a wavelength of 550 nm and a reference wavelength of 690 nm. The results are assessed based on IC_{50}, the concentration reduced by 50% the optical density of treated cells with respect to untreated controls.

DNA SYNTHESIS In this assay, the rate of novel DNA synthesis in the cell nuclei is monitored based on the incorporation of radio-labeled thymidine. Following a 24 h incubation of the cells with a test substance, fresh culture medium is added along with [3*H*]-thymidine (0.15 mCi/ml, 25 Ci/mmol). After incubation for a further 14 h, the radioactivity incorporated in the DNA is counted by fixing the cells with trichloroacetic acid (10% w/v), washed copiously under running tap water and air-dried. Then the DNA is solubilized by the addition of 0.3 N NaOH–1% SDS and the lysates is subjected to scintillation counting.

LACTATE DEHYDROGENASE The lactate dehydrogenase assay measures the leakage amount of cytoplasm enzyme LDH into the extracellular medium. The presence of the exclusively cytosolic enzyme, LDH, in the cell culture medium is indicative of cell membrane damage [33]. Cells are seeded in 96-microtiter plates. Twenty-four hours after cell seeding, cells are exposed to varying concentrations of the test substance. After 24 h of treatment, the supernatants are collected from each well. Cell monolayers will be then treated with a cell lysis solution for 30 min at room temperature to lyse. The cells and the lysate are collected and LDH activity is measured in both the supernatants and the cell lysate fractions by using CytoTox 96, a nonradioactive cytotoxicity assay kit in accordance with the manufacturer's instruction. The intensity of the color is proportional to LDH activity. The absorbance is determined at 490 nm with 96-well plate ELISA reader. The percent of LDH release from the cells is determined using the formula: LDH release = (absorbance of the supernatant)/(absorbance of the supernatant and cell lysate) $\times$ 100.

Both MTT and LDH assays have been extensively used to assess cytoxicity of herbal extracts. For instance, using MTT and the LDH assays, eight plant species used in traditional Arabic medicine were tested to evaluate their cell integrity and cytotoxicity using two different types of cultured cells: rat pheochromocytoma PC12 cells and human hepatoblastoma HepG2 cells [34]. The results have indicated that the six aqueous plant extracts (*Asphodelus microcarpus*, *E. creticum*, *Mercurialis annua*, *Rhamnus alaternus*, *T. polium*, *Urtica pilulifera*) did not suppress mitochondrial respiration or increase LDH leakage in PC12 and HepG2

cultured cells with the exception of those prepared from *Ecballium elaterium* and *Pistacia lentiscus* and only at the higher concentrations, namely 500 and 1000 μg/mL. In another study [35], the biosafety of three plant extracts were evaluated *in vitro* using cocultures of cells from the human hepatocyte cell line (HepG2) and the human monocyte cell line (THP1). The hepatocyte monoculture was used as the control. The monocultures and cocultures were maintained under well-controlled *in vitro* cell culture conditions. Cells were treated with various concentrations of extracts from *Pistacia palaestina*, *Juglans regia*, and *Quercus ithaburensis*. All three-plant extracts exhibited biosafe properties in the hepatocyte monoculture. In contrast, *P. palaestina* extract significantly reduced the cell viability in the coculture as measured with the MTT test and the LDH assay. It seems that the observed reduction in the cell viability in the coculture is a result of monocyte-derived factors.

THE AMES This test is a biological assay to assess the mutagenic potential of chemical compounds and to identify chemicals that affect the structure of DNA. A positive test indicates that the chemical might act as a carcinogen. As cancer is often linked to DNA damage, the test also serves as a quick assay to estimate the carcinogenic potential of chemicals in light of the difficulty in ascertaining whether standard carcinogen assays on rodents were successful. The procedure is described in a series of papers from the early 1970s by Bruce Ames and his group at the University of California, Berkeley. In this test, *Salmonella* bacteria are exposed to test chemicals and changes in bacterial growth are assessed. These changes result from mutations that occur when the structure of DNA is altered in certain places. Many chemicals that cause mutations can cause cancer in animals and humans. When the test was developed, it was thought that most of the chemicals that produce results in the Ames test could also cause cancer. It was hoped that this simple test would be an easy way to find cancer-causing chemicals. Over time, the test was found to be a less reliable predictor of carcinogenesis than had been hoped. Some chemicals that are known to cause cancer are not positive in the Ames test and other chemicals that show positive results are not carcinogens. Nonetheless, the test is still considered an important part of assessing the safety of new chemicals. In brief, the Ames test uses strains of *Salmonella* that have been altered to make them more susceptible to mutation than normal *Salmonella*. To perform the test, the altered *Salmonella* strains are treated in a test tube with the test chemical. Because *Salmonella* bacteria lack the enzymes that animals use to metabolize chemicals animal liver enzymes are often added to the test tube. The test is then able to detect what might happen if the chemical entered a human body. The *Salmonella* are then transferred to a Petri dish to grow for 1 or 2 days. The altered *Salmonella* used for the test require the amino acid histidine to grow, and a positive result in the test is indicated when, in response to mutation, the *Salmonella* no longer require histidine to grow (Figure 11.4).

A positive result in an Ames test alone does not indicate that a particular chemical is capable of causing cancer. It does suggest that a chemical can produce mutations and that more extensive testing is needed to determine whether the chemical is likely to produce cancer in humans. The test is useful as a screening tool for setting priorities because it is an inexpensive and quick way to single out chemicals that

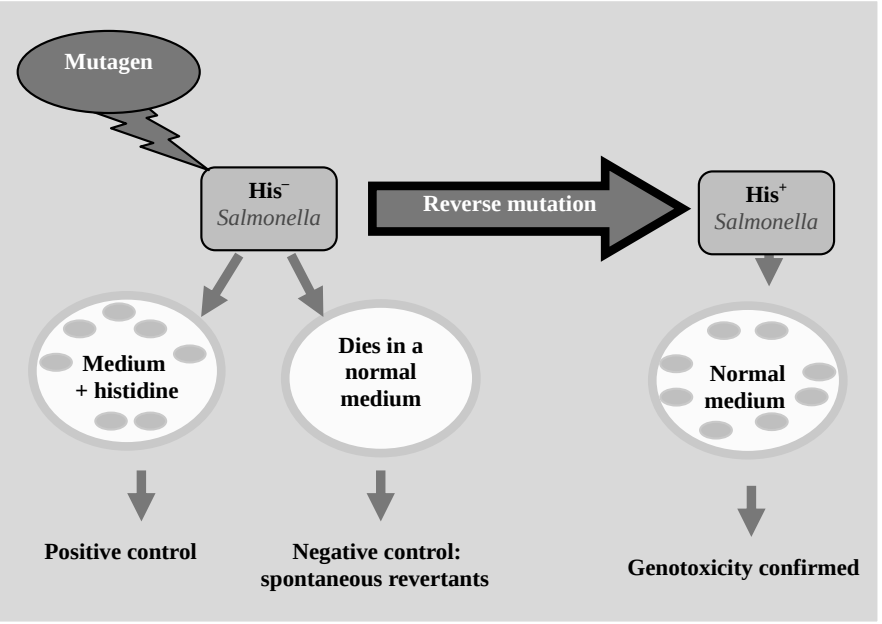

FIGURE 11.4 The Ames test is a biological assay to assess the mutagenic potential of chemical compounds. The Ames assay is based upon the reversion of mutations in the histidine (his) operon in the bacterium *Salmonella typhimurium*. His^- are unable to grow without added histidine. Revertants that restore the His^+ phenotype will grow on minimal medium plates without histidine. This provides a simple, sensitive selection for revertants of his mutants. Potential mutagen induces His^+ revertants during the initial few cell divisions, then each of the resulting revertants will continue to divide and form a colony. The number of colonies produced is proportional to how efficiently the mutagen reverts the original mutation.

should be targeted for further testing. It is also used in industry as a primary preventive approach to eliminate potential carcinogens early in the process of developing new commercial chemicals. The Ames test has been extensively used in the assessment of mutagenic or antimutagenic and carcinogenic or anticarcinogenic effects of medicinal plants. For example,

1. Amin and his colleagues [36] studied the antiproliferative, antioxidant, and antimutagenic activities of flavonoid-enriched extracts from Tunisian *Rhamnus alaternus*. They found that a pronounced antiproliferative effect on human leukemia K562 cells was shown with flavonoid-enriched extracts from *R. alaternus* roots and leaves, with, respectively, IC_{50} values of 165 and 210 µg/mL. High DPPH radical-scavenging activity and antioxidative effects using the xanthine oxidase assay were detected in the presence of the two tested extracts. No mutagenic effect was observed in the Ames test. In addition, they found that the two tested extracts exhibited a high-level protection toward the direct mutagen, sodium azide-induced response.

2. The group of Chekir-Ghedira [37] in Tunis assessed the antimutagenic, antigenotoxic, and antioxidant activities of *Acacia salicina* extracts (ASE) and modulation of cell gene expression by H_2O_2 and ASE treatment. They investigated the total oligomers flavonoids (TOF), chloroform, petroleum ether and aqueous extracts from *A. salicina*, for antioxidative, cytotoxic, antimutagenic and antigenotoxic activities. The viability of K562 cells were affected by all extracts after 48 h exposure. Using the Ames test they showed that *A. salicina* extracts have antigenotoxic and/or antimutagenic activities. TOF and chloroform extracts exhibit antioxidant properties, expressed by the capacity of these extracts to inhibit xanthine oxidase activity. To further explore the mechanism of action of *A. salicina* extracts, we characterized expression profiles of genes involved in antioxidant protection and DNA repair in the human lymphoblastic cell line K562 exposed to H_2O_2. Transcription of several genes related to the thioredoxin antioxidant system and to the DNA base-excision repair pathway was upregulated after incubation with chloroform, TOF and petroleum ether extracts. Moreover genes involved in the nucleotide-excision repair pathway and gene coding for catalase and Mn-superoxide dismutase, two important antioxidant enzymes, were induced after incubation with the chloroform extract. These observations provide evidence that the chloroform and TOF extracts of *A. salicina* leaves contain bioactive compounds that are able to protect cells against the consequences of an oxidative stress.

11.7 INTEGRATION OF TRADITION WITH MODERN TECHNOLOGY

As aforementioned, Greco-Arab and Islamic herbal medicine has gained enormous global and regional popularity over the past three decades [38–40]. This increase in popularity introduces concerns and fears over professionalism of practitioners, quality, efficacy, and safety of the "natural" formulations available on the market. In some cases, adulteration, inappropriate formulation, or lack of understanding of plant and drug interactions or uses has led to adverse reactions that are life-threatening or lethal to patients. Therefore, it has become important to standardize the quality control and safety measures so as to ensure supply of good quality herbal products. Therefore, the following points are of crucial importance in order to ensure high quality and safety of herbal remedies:

1. Proper botanical identification, WHO guidelines should be followed for collecting plant material in terms of proper seasonal and climatic conditions and usage of the correct plant part. Furthermore, plants should be collected from "clean" regions in order to prevent contamination from soil, toxic weeds, or microbes.
2. Postcollection, appropriate processing, and storage conditions are required to reduce drying time, which results in reduced side effects, enhancement of therapeutic value of the plant material, and in improving its shelf life.

3. Preclinical biological studies are important not only for establishing the therapeutic efficacy of the medicinal plants but also to validate their historical utilization by traditional healers and herbalists. This is especially important since the plants may have evolved over a period of time leading to changes in their chemical composition and thus the biological activity. Safety assessments need to be done even if the plants have a history of long usage or do not have any documented adverse or toxic effects, as they can lead to unrelated toxicity especially during long-term treatment for chronic conditions.

We believe that any plant, herb, or ingredients taken from plants should be tested before use as a remedy. Hence, various advanced cell biological, biochemical, molecular biological, and *in vitro* cell culture techniques should be applied with different medicinal herbs in order to test their safety before testing their efficacy. *In vitro* cell culture methods have the advantage of relatively well-controlled variables and are generally accepted as a very effective method for safety testing. Advantages of such systems over classical methods (such as long-term studies on experimental animals) include decreased costs, a reduced completion time, and reduced numbers of animals necessary to complete the study. Because of the complicating secondary effects encountered *in vivo*, it is often difficult to evaluate the mechanism of action of an active medicinal plant compound in a specific cell type or tissue. The fact that cells and tissues *in vivo* do not exist in isolation, but communicate with and are interdependent on neighboring tissue makes it essential in the research of herbal remedies and their active compounds in order to simulate the *in vivo* situation, where, for example, the microenvironment of the hepatocytes within the liver acinus involves gradients in oxygen tension, hormones, extracellular matrix components, nonparenchymal cells and effective exposure levels of xenobiotics from the periportal to the pericentral compartment. Hence, to simulate the *in vivo* situation a higher degree of complex *in vitro* methodology is required, such as the construct of cocultures.

Future efforts in the development of biosafe and active medicinal plant compounds will probably be directed toward the application of modern techniques of cell and molecular biology in the field of medicinal plant research. The determination of gene activity at both the transcriptional and translational level is important in the context of mutagenesis and carcinogenesis. Furthermore, sample preparation is the crucial first step in the analysis of herbs. Currently, however, quality-related problems seem to be overshadowing the potential genuine health benefits of various medicinal plants. Thus, the development of "modern" sample-preparation techniques with significant advantages over conventional methods for the extraction and analysis of herbal remedies is likely to play an important role in the overall effort of ensuring and providing high-quality medicinal plants to consumers worldwide. In addition, advances in biotechnology, particularly methods for culturing plant cells and tissues, should provide new means for the commercial processing of even rare plants and the chemicals they produce [41–64].

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CHAPTER 12

Arab Medicinal Plants: From Traditional Uses to Scientific Knowledge

12.1 INTRODUCTION

Based on scientific and traditional knowledge, there is little doubt that the concept of Greco-Arab and Islamic herbal medicinal therapy has shown remarkable success in healing both acute and chronic diseases. As mentioned in the first five chapters, Arab and Muslim physicians were the first to use scientific methods in the field of medicine, including the introduction of quantification, animal testing, and clinical trials. Hospitals in the Arab–Islamic world featured the first drug tests, drug purity regulations, and competency tests for physicians. The earliest known medical experiment was carried out by Rhazes (865–925). To locate the most hygienic place to build a hospital, he hung pieces of meat in places throughout Baghdad and built the hospital where the meat decomposition was the least. In his *Comprehensive Book of Medicine*, Rhazes documented clinical cases of his own experience and provided very useful recordings of various diseases. He also introduced urinalysis and stool tests. Avicenna (980–1037) introduced experimental medicine and systematic experimentation and quantification in physiology. He discovered the contagious nature of diseases and described many medical treatments, including clinical trials, risk factor analysis, and the idea of a syndrome in the diagnosis of specific diseases. His book, *The Canon of Medicine*, was the first book dealing with evidence-based medicine, randomized controlled trials, and efficacy tests. Concerning the medical documentation, the first documented description of a peer-reviewed publication process was written by Ishaq bin Ali al-Rahwi (854–931). In his work, *the Ethics of the Physician*, he stated that a physician must always make duplicate notes of a patient's condition. When the patient was cured or had died, the notes of the physician were examined by a local medical council of other physicians, who would review the practicing physician's notes to decide whether the treatment had met the required standards of medical care.

Greco-Arab and Islamic Herbal Medicine: Traditional System, Ethics, Safety, Efficacy, and Regulatory Issues By Bashar Saad and Omar Said

Currently, we notice an increasing interest in Greco-Arab and Islamic herbal medicine and an increasing trend in research activities dealing with the safety and efficacy of medicinal plants throughout the Mediterranean region. As mentioned above, this region has been distinguished for long periods with a rich inventory in fields of humane medicine in general and medicinal plants in particular. Greco-Arab and Islamic herbal medicine is the first choice for many in dealing with ailments such as infertility, epilepsy, psychosomatic troubles, and depression. It is a part of modern life in the Middle East, and it is acquiring worldwide respect, with growing interest among traditional herbalists and the scientific community [1–3]. It is expected to become more widely integrated into the modern medical system, including the medical curriculum. In this chapter, we discuss the status of Greco-Arab and Islamic herbal medicine, including the efficacy and safety of specific medicinal preparations, prepared according to scientific and traditional knowledge of the Greco-Arab and Islamic medicine.

12.2 REVIVAL AND PRESERVATION OF GRECO-ARAB AND ISLAMIC HERBAL MEDICINE KNOWLEDGE

Paralleling and even exceeding the growth in utilization of Arab herbal medicine is the surge in information available to the public in the media, health food stores, and the Internet. For example, a Google search using the term "Arab herbal medicine" reveals more than 280,000 citations. Faced with this huge amount of information, people are often left with a desire for guidance and direction. In the past few years, there has been an increase in quality and quantity of scientific research in this area. A Medline and Google Scholar search using the terms "Arab herbal medicine" reveals more than 6000 citations. Examples include the use of traditional Arab herbs for treatment of diabetics (1500 citations), cancer (1300 citations), liver diseases, inflammation (1200 citations), and infertility (1400 citations).

In an effort to help revive and preserve the knowledge of Greco-Arab and Islamic herbal medicine, an international conference on the current state of research and practice in the field was organized in 2007. This 3-day conference took place in Amman, Jordan, and included an exhibition and poster session. The conference intended to (a) establish an institution to serve as a network for all stakeholders in Greco-Arab and Islamic herbal medicine, as a prerequisite to revitalizing this important subject and to coordinate research and different activities in this field; (b) revive the heritage of Greco-Arab and Islamic herbal medicine to present it in its normal environment, in order to release it from the political restrictions of the Middle East; (c) revitalize this heritage as a scientific discipline and raise awareness of Greco-Arab and Islamic herbal medicine; (d) explore the economic and sustainability aspects of this heritage and encourage investment to develop pharmaceutical products based on this culture; and (e) increase the number of practitioners and quality of the practice of Greco-Arab and Islamic herbal medicine by training new and existing practitioners. The conference was designed for research scientists, local and regional traditional healers, international pharmaceutical and medical research companies,

medical doctors, ethnopharmacologists, and other parties interested in the study of traditional Arabic and Islamic medicine. All bodies and institutions, research centers, and interested parties working in the field of Arab medicinal plants were invited to participate in the conference. Discussions touched on the historical and cultural aspects of Arabic Islamic medicine and its contribution to modern medicine and human well-being. The global scientific research on medicinal and aromatic plants, pharmaceutical research, clinical trials, and international legislation and intellectual property rights on Arabic and Islamic medicinal plants of the region were also reviewed. Each of the six sections discussed a different issue related to Greco-Arab and Islamic herbal medicine. Another conference was held in 2008 in Fez, Morocco, with the main aim to preserve, revive, and confirm traditional knowledge by modern biological and medical studies [1–5].

According to recent surveys, there are about 450 medicinal plants in the Eastern Mediterranean region and about 230 medicinal plants in coastal Mediterranean region in Egypt. These plants are used by healers for the treatment and prevention of almost all types of human diseases (Table 12.1), such as cancer; skin, respiratory, digestive, and liver diseases; diabetes; and others, and sold or traded in marketplaces in the Mediterranean region or internationally (Figure 12.1). In many cases, plant extracts are prepared into a mixture (Table 12.2). Several plant species have been investigated and bioactive ingredients extracted to treat various human diseases. Plant parts used

TABLE 12.1 Medicinal Plants and Their Uses to Treat Various Diseases According to Arab Medicine

Disease	Number of Plants Used	Examples
Inflammations	31	*Alcea setosa*, *Alchemilla vulgaris*, *Amygdalus communis*
Fever	17	*Anabasis articulata*, *Anchusa strigosa*, *Artemisia judaica*
Skin diseases	40	*Alchemilla vulgaris*, *Anchusa strigosa*, *Calotropis procera*
Kidney and urinary system	27	*Ammi visnaga*, *Brassica napus*, *Glycyrrhiza glabra*
Diabetes	26	*Achillea millefolium*, *Allium cepa*, *Allium cepa*
Sexual weakness	15	*Astragalus macrocarpus*, *Crataegus azarolus*, *Eruca sativa*
Digestive system	23	*Ceratonia siliqua*, *Foeniculum vulgare*, *Micromeria myrtifolia*
Liver disease	22	*Allium cepa*, *Asparagus officinalis*, *Cynara scolymus*
Pain	19	*Majorana syriaca*, *Melissa officinalis*, *Myrtus communis*
Respiratory system	16	*Anchusa strigosa*, *Anchusa strigosa*, *Brassica oleracea*
Cancer	13	*Allium cepa*, *Arum palaestinum*, *Brassica oleracea*

FIGURE 12.1 An attarah shop.

included leaves, flowers, stems, roots, seeds, and berries. In the following, we will discuss the efficacy of herbal remedies that are prepared according to knowledge of Greco-Arab herbal medicine in the treatment of human diseases, such as diabetics, cancer, infertility, and inflammation [4,6].

TABLE 12.2 Commercially Available Herbal Mixtures Used to Treat Various Diseases

Condition	Herbal Mixtures
Acne: inhibition of sebum production	*Inula helenium*, *Saponaria officinalis*, *Citrus limonum*
Hemorrhoids	*Citrus medica*, *Nigella Sativa* oil
Sunscreen herbal combination	*Nigella sativa*, *Portulaca oleracea*
Raised blood cholesterol and fats	Leaves of *Eriobotrya japonica*, *Olea europaea*
Diabetes	*Juglans regia*, *Olea Europaea*, *Urtica dioica*, *Atriplex halimus*
Reduced male sexual vitality	*Ferula foetida*
Female infertility and sexual problems	*Ferula foetida*, *Capparis spinosa*
Overweight and obesity	*Alchemilla vulgaris*, *Olea europaea*, *Cuminum cyminum*, *Mentha longifolia*
Common cold and flu	*Cichorium intybus*, *Silene aegyptiaca*
Migraines and headaches	*Ocimum basilicum*, *Urtica dioica*, *Melissa officinalis*
Arthritic problems	*Ruscus aculeatus* for internal use and the oil of *Laurus nobilis* for external use
Heartburn	*Eryngium creticum*
Psoriasis and inflammation	*Nigella sativa*, *Eruca sativa*, *Citrus limonum*, *Hypericum perforatum*

12.3 DIABETES

Diabetes is a syndrome of disordered metabolism, usually caused by a combination of hereditary and environmental factors, which results in hyperglycemia (abnormally high blood sugar levels). Blood glucose levels are controlled by a complex interaction of multiple hormones in the body, including insulin made in the beta cells of the pancreas. Type I juvenile diabetes is known as an autoimmune disease thought to be caused by an over-immune reaction that results in extensive destruction of the insulin-producing β cells in the islets of Langerhans in the pancreas. Type II—the adult-onset diabetes, also known as diabetes mellitus—refers to the group of diseases that lead to high blood glucose levels due to defects in either insulin secretion or insulin action. The causes of type 2 diabetes remain poorly understood, and all patients with type 1 diabetes require daily insulin shots. The main pathological effects of diabetes mellitus consist of excessive hepatic glucose production, peripheral insulin resistance, and defective β-cell secretory function. Available oral hypoglycemic agents are directed at stimulating insulin secretion (sulfonylureas). These impair excessive hepatic glucose production (metformin or biguanides) and delay the absorption of carbohydrates in the gut by inhibiting α-glucosidase (acarbose), or reducing insulin resistance (troglitazone), primarily in skeletal muscle and also in adipose tissue.

Diabetes has been recognized since ancient times, and its main symptoms were known by the increased thirst, frequent urination, and tiredness experienced by diabetics. Greco-Arab physicians and practitioners had used a series of medicinal plants for treating these combined symptoms (named Zarab), in addition to several instructions for consumption of specific food and mild exercise. According to recent surveys carried out among practitioners of Arabic medicine in the Middle East, 26 plant species for the treatment of diabetes mellitus have been disclosed (Table 12.3). *Juglans regia* (walnut), *Atriplex halimus* (saltbush), *Olea europaea* (olive), and *Urtica dioica* (nettle) are just a few of the medicinal plants that are strongly recommended as antidiabetic.

A mixture of these four antidiabetic herbs was developed according to the extensive herbal knowledge of the Greek–Arab medical system [1,7]. The safety and efficacy of this mixture was tested in our laboratories. The main findings of our *in vitro* and *in vivo* studies with this mixture, named Glucolevel, are discussed in the following sections.

Preparation of the Plant Mixture (Glucolevel) Leaves of *Juglans regia* (walnut), *Atriplex halimus* (saltbush), *Olea europaea* (olive), and *Urtica dioica* (nettle) were collected, dried under shade, cleaned, and sterilized by steam for 2 h and powdered, extracted with 50% ethyl alcohol, and filtered through the batch centrifuge. We used concentrations according to the traditional uses, where the total amount in the tablets given for each diabetic patient per day is equivalent to 7–10 g dried plant leaves.

Safety Studies The safety of Glucolevel was evaluated both *in vitro* by measuring the LDH release (Chapter 13) from cultured fibroblasts and *in vivo* by measuring the LD_{50} in rats. No significant change in LDH release was seen, whether as a function

TABLE 12.3 Medicinal Plants Used to Treat Diabetes Based on the Traditional Arab Medicine

Plant Species	Preparation	Additional Uses
Astragalus macrocarpus	Leaf decoction	Heart diseases
Ceratonia siliqua	Leaf decoction	Herpes and lip sores
Cichorium pumilum	Foliage decoction	Bacterial infection and rheumatism
Cupressus sempervirens	Fruit decoction	Antiseptic and nervous system
Eryngium creticum	Foliage decoction	Liver diseases, poisoning, anemia, and infertility problems
Juglans regia	Leaf/flower decoction	Asthma and sexual weakness
Lupinus varius	Soaked seeds	Kidney stones
Mercurialis annua	Leaf decoction	Cancer and skin diseases
Morus nigra	Leaf, stem, and fruit decoction	Teeth and gum inflammation and cholesterol
Paronychia argentea	Leaf and flower decoction	Stones in kidney and heart diseases
Pinus halepensis	Leaf and seed decoction	Sexual weakness
Prosopis farcta	Foliage decoction	Menstrual cramps and kidney stones
Quercus calliprinos	Fruit and bark decoction	Cancer, bedwetting, and ulcer
Salvia fruticosa	Foliage infusion	Stomach ache, intestinal gas, and inflammation
Sarcopoterium spinosum	Leaf/seed/root decoction	Intestine pain and kidney diseases
Smilax aspera	Fruit and root decoction	Poisoning
Teucrium polium	Foliage decoction	Kidney stones, liver diseases, stomach and intestine inflammation
Trigonella foenum-graecum	Seed decoction	Sexual weakness and intestinal pain

of increasing of the concentrations or as a function of increasing the incubation period. The mixture showed an LD_{50} by concentration of about 25 g/kg. Similar results were reported for the plants used for the preparation of Glucolevel. For example,

1. A long-term clinical study revealed that a daily dose of 320 mg was well tolerated by patients with benign prostatic hyperplasia (BPH) and there was no evidence of adverse effects
2. Extracts of walnut leaves have been shown to protect against cellular toxicity and to reduce cyclophosphamide-induced biochemical toxicity
3. Several extracts of saltbush have been reported to be nontoxic to the stored plant insect
4. As for olive leaves, doses as high as 1200 mg/kg for 60 days in rats were completely nontoxic and aqueous extracts from these leaves were given to two

groups of hypertensive patients with no side effects and with a promising clinical efficacy

As experienced in good clinical practice, smaller doses of synergistic drugs may yield a better therapeutic efficacy with minimal side effects. This could explain the fact that Glucolevel was well tolerated by all our subjects and no adverse effects could be traced.

Efficacy Studies Sixteen test persons were recruited for our study. Their ages ranged from 48 to 67 years and their compliance with the study protocol was excellent. No test person took any pharmacological drug during the study period. They were asked to continue their daily activities and diet habits unchanged and to take one tablet of Glucolevel three times daily. They were also asked to restrain from consuming any medications during the study period of 4 weeks. An informed consent was obtained from each subject who was given a free-of-charge box containing 90 tablets of Glucolevel.

No minor or major adverse effect was noted and the Glucolevel was well tolerated by all subjects. During the first week of Glucolevel consumption, baseline glucose levels were reduced from 290 ± 40 to 210 ± 20 mg/dL in these subjects. According to baseline glucose levels, a subgroup of 11 subjects had glucose levels below 300 mg/dL and the other subgroup had levels $\geq$300 mg%. As shown in Figure 12.2, the former subgroup achieved clinically acceptable glucose levels during the second and third weeks of Glucolevel consumption while the latter group needed 1 week more to achieve clinically acceptable glucose levels.

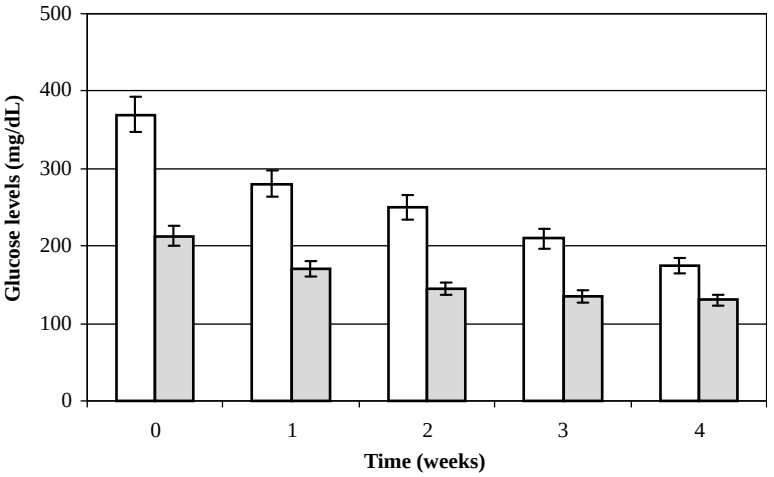

FIGURE 12.2 Glucose levels during 4 weeks period of Glucolevel consumption one tablet three times daily in those subjects with baseline glucose levels below 300 mg/dL (right bulks) and in those with baseline glucose levels $\geq$300 mg/dL (left bulks).

TABLE 12.4 Antidiabetes Effects of Glucolevel

#	Used Drugs	Glucose Values Without Glucolevel	Glucose Values with Glucolevel	HbA1c-A with Drugs	HbA1c-B with Drugs	HbA1c-C with Drugs and Glucolevel
1	Glucophage + Glubin	180–250	90–130	7.8	8	6.3
2	Glucophage + Glubin + Avandia	200–290	110–140	7.5	7.9	6.5
3	Insulin 45 units	200–270	120–150	9.5	8.7	7.3
4	Glucophage	130–150	80–120	7.9	7.7	6.7
5	Insulin 100 units	180–200	90–140	10	10	8.7
6	Glucophage + Glubin	250–200	100–120	7.9	7	6.2
7	Glucophage + Glubin	210–250	140–160	8.8	8.4	7.1
8	Glubin + Avandia	170–230	120–150	8.3	8.2	7.3
9	Glucophage	150–220	110–160	7.9	7.5	6.5
Average				8.4 ± 0.86	8.16 ± 0.85	6.96 ± 0.77

Tests were conducted in 31 diabetic patients who did not fully respond to conventional therapeutics and remained with high glucose levels. The patients were allowed to continue taking their medication while the sugar levels were continually monitored and HbA1c value was determined after 3 months.
HbA1c-A: Values of A1c of the patients were determined during treatments by their doctors (using only conventional drugs).
HbA1c-B: Values of A1c of the patients were determined during treatments by their doctors (using only conventional drugs) in order to make medical comparison to the treatment efficacy (drugs have to reduce A1c values).
HbA1c-C: Values of A1c after taking diabetes drugs and Glucolevel capsules.

Table 12.4 shows the effects of Glucolevel on the glucose level and hemoglobin A1c (HbA1c) in six diabetic patients, who did not fully respond to conventional therapeutics and remained with high glucose levels. The test aimed to clarify whether Glucolevel supplementation can contribute to reduce the glucose levels in this group. The patients were allowed to continue taking their medication during the whole test period. The sugar levels were continually monitored and HbA1c values were determined after 3 months. The results indicating a significant reduction in HbA1c values compared to conventional treatment and showed positive synergetic effect.

Possible Action Mechanism of Glucolevel Scientific evidences obtained so far indicate hypoglycemic and antioxidant properties of each of the four herbs contained in Glucolevel [7].

Olea europaea (Olive): The main active ingredient in olive leaf is oleuropeoside that disclosed a distinct hypoglycemic effect at a dose of 16 mg/kg, together with hypotensive and hypolipidemic properties. The interference of oleuropein aglycone with human islet amyloid polypeptide (hIAPP) aggregation and its protection against aggregate cytotoxicity have been reported using a RIN-5F rat insulinoma cell model, an effect possibly beneficial against type 2 diabetes.

Oleic acid has been shown to increase insulin production and to reverse the inhibitory insulin effect of tumor necrosis factor alpha (TNF-α) in the rat pancreatic beta cell line INS-1. Antioxidant effect of olive oil in pancreatic β cell has been also documented. In islets of Langerhans from mice supplemented with extra virgin olive oil, the expression of antioxidant enzyme catalase (CAT) was 98% greater and catalase and glutathione peroxidase (GPx) had greater activity than that in the control group. Furthermore, after incubation with hydrogen peroxide, islets from extra virgin olive oil-supplemented mice had a higher glucose-stimulated insulin secretion glucose compared to the control group. The *Olea europaea* L. leaf extract significantly increased the number of living cells, reduced necrotic cell number, protected GPx, and overactivated CAT, but had insignificant effect on a drop of insulin secretion in H_2O_2-treated INS-1E cells. Oleuropein recovered insulin release by partly increasing the number of living cell, activated CAT, but had no effect on GPx. In type 1 diabetes models, *in vivo* administration of dried leaf extract significantly reduced clinical signs of diabetes and led to a complete suppression of histopathological changes in pancreatic islets. Incubation with a flavonoid constituent luteolin resulted in a significant reduction in cytokine-induced nitric oxide (NO) production in RIN β cells, a finding that correlated well with reduced levels of the inducible form of NO synthase messenger RNA and protein. The molecular mechanism by which luteolin inhibited iNOS gene expression appeared to involve the inhibition of nuclear factor kappa B (NF-κB) activation [7–9].

Juglans regia (Walnut): Tannins and polyphenolics in walnut leaves were found to be potent antioxidants and reveal a strong scavenging activity against both superoxide and hydroxyl radicals [7–10].

Atriplex halimus (Saltbush): An animal model for diabetogenesis and obesity proved that saltbush is an extremely effective antidiabetic herb and shows an insulin potentiating effect. There is also evidence that nettle extracts possess hypoglycemic properties and improve glucose tolerance. In addition, *in vitro* experiments have shown that Glucolevel facilitates glucose entry into yeast cells during anaerobic fermentation. This observation may be attributed to an effect of saltbush content on Glucolevel [7,11].

Urtica dioica (Nettle): The nettle component is supposed to decrease glucose production by the liver, whereas oleuropein and tannins in olive and walnut leaves are supposed to act as α-glucosidase inhibitors, thus reducing the absorption of carbohydrates in the gut.

Such an effect was evidenced in our experiments with the inverted intestine segment. We measured the glucose concentrations inside and outside the inverted intestine at baseline and during the addition of 10, 20, and 30 mg Glucolevel/mL. Glucolevel at concentrations of 20 and 30 mg/mL significantly decreased the glucose values inside the inverted intestine, whereas slight but insignificant reductions of these values were obtained outside the inverted intestine.

12.4 BEING OVERWEIGHT AND OBESITY

Being overweight is generally defined as having more body fat (adipose tissue) than is optimally healthy. Being overweight is a common condition, especially where food supplies are plentiful and lifestyles are sedentary. It is commonly defined as a body mass index (BMI = weight divided by height squared) of 25–29.9 kg/m^2. Being overweight is a major health challenge in the Western World, with serious clinical complications such as type 2 diabetes mellitus, as well as cerebrovascular and ischemic heart diseases. Obesity is a condition in which excess body fat is accumulated to such an extent that health may be negatively affected with BMI of 30 kg/m^2 or higher. Available pharmacological therapy of obesity is limited to anorexics, such as amfepramon and sibutramin, and one malabsorptive drug orlistat. When added to a diet, such therapy is expected to yield weight loss of 0.2–0.4 kg/week, but only for a few weeks due to tolerance and side effects [12].

Being mildly overweight was generally accepted in ancient Arab societies; it reflected a high socioeconomic level and part of the desired beauty standards in those days. This fact was expressed in the minimal effort to discover antioverweight remedies compared to other medical fields. Only severe obesity was considered suitable for treatment using specific medicinal plants, body exercises, and control of food consumption. *Cuminum cyminum* (Cumin), *Mentha longifolia* (sorting menthe), *Olea europaea* (olive) leaf, and *Alchemilla vulgaris* (lady's mantle) are deeply rooted in Arabic medicine and still used to treat obesity and the condition of being overweight. *Alchemilla vulgaris* has been used for treating obesity, gastrointestinal pain, and inflammation [6,13,14]. Olive leaves are a typical herbal remedy of the Mediterranean area and reported to possess hypoglycemic, hypotensive–diuretic, and antioxidant properties. Extracts from both these plant leaves have been shown to increase the basal metabolic rate. For centuries, mint and cumin have been used to reduce appetite to improve digestion by relieving digestive symptoms such as pain, spasm, gas, and dyspepsia, and creating a sensation of fullness. The group of carminative seeds, such as cumin, caraway, fennel, dill, and anise, have all been acknowledged to have stomach calming effects to improve digestion and regulate appetite, especially for children. We prepared a mixture of extracts of *Cuminum cyminum*, *Mentha longifolia*, *Olea europaea* leaf, and *Alchemilla vulgaris*, as well as tablets of this mixture. Each tablet contained 60 mg *Alchemilla vulgaris*, 50 mg *Olea europaea*, 20 mg *Mentha longifolia*, 25 mg *Cuminum cyminum*, 7 mg vitamin C, and 148 mg tricalcium phosphate. This mixture was named Weighlevel. Safety and efficacy of Weighlevel were assessed in both *in vitro* and *in vivo* test systems [15].

Safety Studies: An extremely high dose of Weighlevel (15.3 g/kg) was necessary to obtain an LD_{50} in rats. On a body weight basis, this would correspond to the human consumption of more than a kilogram.

Efficacy Studies: The effects of Weighlevel on thermogenesis are shown in Figure 12.3. Weighlevel extracts stimulate interscapular rat brown adipose

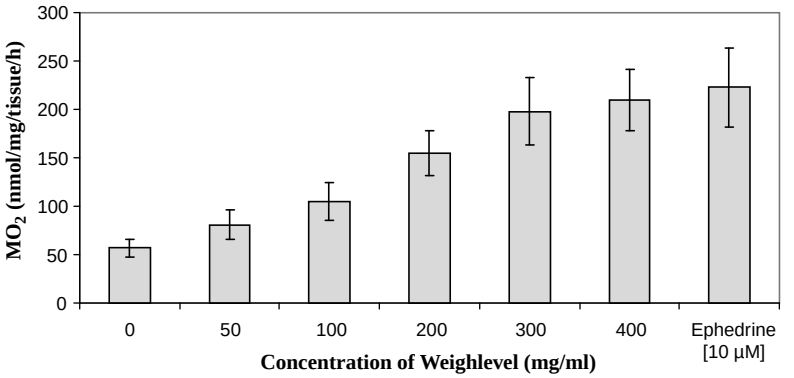

FIGURE 12.3 Thermogenesis effects of Weighlevel were determined in strips of IBAT. Values given represent the mean ± SEM of three independent experiments carried out in triplicates.

tissue (IBAT) respiration rate in a dose-dependent manner up to more than threefold higher than basal MO_2 values.

Clinical Investigations Eighty subjects were recruited for the study. They had an average age of 34.3 ± 9.68 (range 19–53) years, an average weight of 90 ± 5 kg, and an average height of 169 ± 5 cm corresponding to a body mass index of 31.3 ± 1.1 kg/m^2. Women composed 48% of subjects with an age range of 49–67 years. Almost half of all subjects were on some medications mainly for ischemic heart disease, diabetes mellitus, and/or hypertension. All medications were kept unchanged during the study period as patients were in a stable clinical condition. Fourteen subjects were excluded as they violated the protocol, 8 due to lack of compliance, and 6 due to absence from scheduled visits. Therefore, efficacy and tolerability is given for the remaining 66 subjects.

Weighlevel was well tolerated in all 66 subjects and no minor or major adverse effect was noted by any of them. Weighlevel was well tolerated with other medications for diabetes mellitus, hypertension, cholesterol, and ischemic heart disease. Figure 12.4 summarizes the efficacy of Weighlevel in these 66 subjects. Significant and progressive weight reductions of about 1 kg/week were observed over a period of 3 months. The weight was reduced from baseline of 90.5 ± 1.2 to 78.5 ± 1.4 kg at 3 months. Higher levels of weight loss were seen in people with BMI of 25–30 kg/m^2 (overweight) compared to people with BMI higher than 30 kg/m^2 (obese). The BMI was reduced after 3 months from 28.5 ± 1.2 and 32.1 ± 1.8 kg/m^2 to 24.5 ± 1.4 and 27.5 ± 2.2 kg/m^2 in the overweight and obese groups, respectively. No significant effects were seen in the control group, who were asked to restrict it to three main meals.

Possible Action Mechanism of Weighlevel The following scientific evidences support our hypothesis that the combination of the four plants in Weighlevel acts to

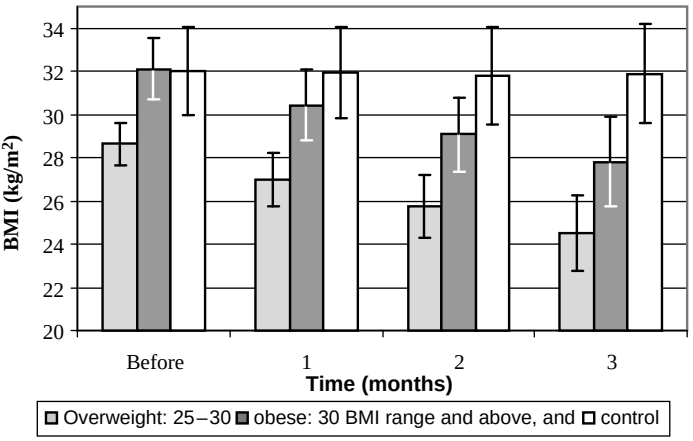

FIGURE 12.4 Clinical efficacy studies of Weighlevel in 66 human. The people were divided into three groups: BMI of 25–30 kg/m^2, BMI higher than 30 kg/m^2, and the control group. Values given represent the mean ± SEM.

increase both satiety and thermogenesis in brown adipocytes (this system is generally accepted as a model for fat depletion known as "fat burning"):

- *Alchemilla vulgaris*: The amines of *Alchemilla vulgaris* L. are the main tannins reported to increase the metabolic rate in cold environments, and the flavonoids are reported to regulate digestive enzymes and have cardioprotective effects.
- *Olea europaea*: Beside metabolic stimulation, olive leave extracts were shown to inhibit intestinal glucose absorption, and thereby a hypoglycemic effect was reported together with hypotensive and hypolipidemic properties. Olive leaves are thus known to reduce fat load and circulatory fat levels [7,15].
- *Mentha longifolia*: Wild mint was reported to relax the stomach and increase gastric emptying and the passage of food throughout the digestive system.
- *Cuminum cyminum*: Cumin was also reported to improve glucose utilization, reduce raised blood sugar, and promote digestion by stimulating gastrointestinal mucosa and pancreatic digestive enzymes.

In addition to the antioverweight effects of our plant combination, a positive and desired antioxidant activity was observed. This finding is of great importance for people suffering from obesity, which is usually accompanied by high levels of oxidative stress [15].

12.5 SKIN DISEASES

Acne It is a chronic inflammatory disease unique to human sebaceous glands and the infundibulum of pilosebaceous follicular units (PFUs) through which sebum

makes its exit to the skin surface. Current acne therapy varies from topical applications of antibacterial, comedolytic, and sebostatic medications to systemic therapy with antibiotics, antiandrogenic hormones (estrogens), and retinoids, depending on the extent and severity of the lesions. However, their use in antiacne therapy would likely produce significant side effects and thus could not be justified as a matter of course. Greco-Arab and Islamic herbal medicine has achieved remarkable progress in the field of dermatology and presented numerous effective plants for treating acne. A large screening to identify the most important plants traditionally used by the Palestinian communities for treating acne was conducted by our group. Thirty-three plant species were selected and tested for their antiacne activities. Each plant was extracted using different solvents. All plant extracts were then tested to evaluate their effects on sebum secretion, as well as their antimicrobial and anti-inflammatory effects, using the following biological test systems:

1. Sebaceous glands organ culture: Sebaceous glands were obtained by microsurgery from skin and each extract was tested on 10–20 glands for decreasing sebum production using radioactive sodium acetate as a marker
2. Antimicrobial screening methods for *Propionibacterium acnes*
3. Nitric oxide determination as test for inflammation detection in HepG2 culture cells

Results indicate that *Inula viscosa* alcoholic extract quickly stops excessive sebum and oil production at very low doses in a nontoxic manner, whereas *Saponaria officinalis* water extract and lemon peel oil possess strong antimicrobial and anti-inflammatory effects. The safety of the active extracts was evaluated *in vitro* using LDH assay on cultured fibroblasts. The most safe and effective extract in each biological experimental system was chosen for creating a cream product prototype, as a combination of the three extracts of *Saponaria officinalis*, *Inula viscosa*, and lemon peel oil, and was tested clinically. Clinical results obtained from 16 acne patients indicate that the cream has unique synergistic effects that dramatically halt sebum production from sebaceous glands, combined with highly antiseptic and anti-inflammatory activity, in which 50% of acne inflammatory spots almost disappeared after 2 weeks of application with 70% efficacy at the seventh week.

Psoriatic Form Conditions These are skin disorders that can be defined by three main conditions: increased levels of cytokines (mediated by T cells), accelerated proliferation of dermal cells, and presence of chronic inflammation. In psoriasis, an activated immune system triggers the skin to reproduce every 3–4 days, building up on the outer layers. The epidermis thickens, blood flow increases and reddens the skin, and silver-gray scales cover it. Psoriasis can be itchy and sore. In general, psoriasis is treated in three steps: topical therapy (topical steroids, tar compounds, vitamin D_3, retinoids, and salicylic acid), phototherapy (climatotherapy, ultraviolet therapy (UVA and UVB), and PUVA), and systemic therapy (cyclosporine for suppressing the immune system). Patients and physicians are not satisfied with these medications, especially due to their severe side effects and partial efficacy.

The most important 25 medicinal plant species, traditionally used by the Arab population to treat psoriasis, were identified and selected. Each plant was extracted using different solvents and tested in unique biological experimental systems as needed. In order to find the potential plant extract that could be used as a cytostatic agent in psoriasis and other dermatoses, we have used cell cultures of keratinocytes cell line (HaCat) and organ culture of skin (Chapter 13). As for organ culture studies, we have used organ culture of pieces of whole skin incubated at 37°C for 16 h with various concentrations of plant extract; the effect of the plant extract on epidermal cell proliferation was evaluated by measuring 3H-thymidine incorporation into DNA in the epidermis (Chapter 13). The cytostatic effect was evaluated by determining the inhibitory concentration leading to 50% reduction in the incorporation of 3H-thymidine into epidermal cells (IC_{50}). Some of the plant extracts showed highly effective cytostatic effects against excessive cell proliferation with minimum cytotoxicity. Since psoriasis is a T cell-mediated inflammatory disease in humans, the effects of plant extracts on the secretion of cytokines by primary isolated T cells were examined. The production of interleukin-2 (IL-2), IFN-γ, and IL-10 was measured after a 24 h treatment of the T cells with various concentrations of plant extract. Several plant extracts exerted downregulation of the Th1-derived IL-2 and IFN-gamma and upregulation of the Th2-derived IL-10. The anti-inflammatory effect was performed using nitric oxide determination test in HepG2 of cell culture (Chapter 13). The results indicate a significant anti-inflammatory effect of antipsoriasis extract. Based on the preclinical results, four plants were selected and an antipsoriasis cream was prepared and tried in a clinical observation study with 17 patients over a period of 3 months. Patients demonstrated significant remissions. A Phase II clinical trial protocol has been prepared.

12.6 LIVER DISEASES

Globally, liver diseases present a growing health problem for all societies. Hepatitis is a general term that refers to inflammation of the liver. This condition may result from various infectious and noninfectious etiologies. Infectious etiologies include viral, bacterial fungal and, parasitic organisms. Xenobiotics, drugs, toxins, and autoimmune disorders may cause noninfectious hepatitis.

Many hepatic active herbals are currently used traditionally by herbalists for the prevention and treatment of liver diseases (Table 12.5). *Silybum marianum*, *Cichorium pumilum*, *Urtica pilulifera*, and *Rhamnus alaternus* are well known as hepatic active herbals and are used traditionally for the prevention and treatment of liver diseases [1,2,13,14,17].

Cichorium pumilum is a well-known food and traditional remedy. The plant as a whole contains several guaianolide sesquiterpene lactones. Similar compounds in other plants such as feverfew are known to have anti-inflammatory activity. *Cichorium pumilum* is known in European herbal medicine as helpful in cleaning the body and supporting the liver. It also stimulates the eliminative processes vis-à-vis both the intestine and the kidneys. Arabic traditional healers regard *Cichorium pumilum* as

TABLE12.5 Medicinal Plants Used in the Traditional Arab Medicine to Treat Liver Diseases

Plant Species	Preparation	Additional Uses
Allium cepa	Bulb juice	Diabetes, loss of appetite, prostate cancer, coughing, external infections
Artemisia officinalis	Young shoots or decoction of above ground parts	Diabetes, urinary system, lack of appetite
Asphodelus microcarpus	Juice or tincture from bulbs and roots, tincture	Ectoderm parasites, psoriasis
Cistance tubulosa	Decoction of leaves	Urinary system and stones in kidney
Citrullus colocynthis	Decoction from seeds	Diabetes
Cynara scolymus	Decoction of leaves/flowers/seeds	Cholesterol regulation
Daucus carota	Root juice	Anemia, urinary system
Ecballium elaterium	Fruit juice into the nose	Sinusitis
Eremostachys laciniata	Decoction of leaves	Allergy, headache
Eryngium creticum	Whole plant decoction	Poisoning, anemia, infertility
Nerium oleander	Infusion of wooden stem	Skin diseases (foliage)
Pistacia lentiscus	Leaf infusion	Bedwetting, respiratory problems
Rosmarinus officinalis	Leaf infusion	Kidney diseases and arteriosclerosis
Saponaria mesogitana	Leaf and root decoction	Acne, stomach ache, kidney stones, joint inflammation
Urtica pilulifera	Foliage decoction	Stomach, intestine pain and inflammation, cancer, bedwetting
Verbena officinalis	Foliage infusion	Stomach pain, fever, menstrual cramps

part of a combined treatment of metabolic problems, as well as a medicine to cleanse the body and treat colds and flu.

Urtica pilulifera is a local Middle Eastern and Mediterranean species of the stinging nettle. The plant has a long history of consumption as both food and medicine. The *Urtica pilulifera* leaf is rich in silicon, minerals, and large quantities of flavonol glycosides, as well as phenolic acids. The stinging properties have been used in the treatment of rheumatic conditions, and *Urtica pilulifera* is regarded as an anti-inflammatory. Local traditional healers regard *Urtica pilulifera* as part of a combined treatment of blood sugar problems. There are a number of studies on immunological stimulation caused by plant lectins that provide some general support for the use of the plant to support resistance. Some of these studies relate to cytokines, lymphocytes, complement, and other immune factors in human volunteers. There are a number of clinical studies on nettle. The most frequent and convincing controlled

clinical studies relate to the use of *Urtica pilulifera* root to treat benign prostatic hyperplasia, in which the nettle had convincing effects on symptoms. There are also positive open clinical studies on the antiarthritic and the anti-inflammatory effects of this plant.

Rhamnus alaternus is an evergreen shrub that grows throughout the Mediterranean region. Local herbalists use *Rhamnus alaternus* traditionally as an herb for the treatment of hepatitis and inflammation in general.

As discussed in details in Chapter 8, silymarin, the active compound of *Silybum marianum* (milk thistle), was found to exhibit many liver protective effects, to improve liver function, to protect against liver damage, and to enhance regeneration of damaged liver cells. Clinical studies confirmed the efficacy of milk thistle extracts in cases of cirrhosis, toxic liver, and other chronic liver conditions. The most remarkable therapeutic properties of silymarin are its antitoxic effects in the treatment of Amanita mushroom poisoning. This mushroom contains two extremely powerful hepatotoxins, amanitin (LD_{50} is 100 μg/kg body weight) and phalloidin. In mice, silymarin was 100% effective in preventing liver toxicity if given before or up to 10 min after Amanita toxin poisoning. Severe liver damage was avoided if silymarin was administered within 24 h. In a study with dogs, none of the dogs died when given silymarin 5–24 h after ingesting an LD_{50} dose of *Amanita phalloides* (85 mg/kg). In comparison, untreated dogs experienced a mortality rate of 33%. Liver enzyme studies and liver biopsies in the controls and treated dogs demonstrated a significant hepatoprotective effect for the silymarin.

Sylamarin was Found to Play a Significant Protective Role in Alcoholic Liver Diseases Ethanol is primarily metabolized to acetaldehyde by three liver enzymes. These include catalase, alcohol dehydrogenases, and the microsomal ethanol oxidizing system. Acetaldehyde binding to proteins, glycoproteins, and membrane phospholipids results in cellular dysfunction such as swelling, impairment of the mitochondrial electron transport chain, and upregulation of protein kinase. Maintenance of cell structure is impaired due to altered formation and function of microtubules. Acetaldehyde also increases the production of proinflammatory cytokines IL-1α, IL-6, and TNF-α and promotes inflammatory responses via activation of necrosis factor kappa beta (NF-κB). Furthermore, TNF-α promotes free radical production by mitochondria, activated neutrophils, and hepatic Kupffer cells.

Numerous *in vitro* types of immune cells found beneficial effects of *Silybum marianum* and its active compounds. For instance, controlled *in vitro* studies have demonstrated that silymarin inhibits NF-κB activation in a variety of cell lines. TNF-mediated NF-κB activation was inhibited in a dose-dependent manner. In addition, silymarin appeared to block the activation of NF-κB by phorbol ester, LPS, okadaic acid, and ceramide; partially inhibited NF-κB induction by H_2O_2; and was found to inhibit NF-κB activation in all cell types studied [48, 49].

Silymarin was shown to enhance liver regeneration in hepatectomized rats, as shown by increased weight for treated rats compared with controls. Proliferative activity as measured by the stathmokinetic test (counting numbers of mitotic cells in prepared slides of liver tissue from hepatectomized rats) was increased in treated

animals compared to controls. The rate of DNA synthesis in rats treated with silybin following partial hepatectomy was increased 23–35% compared to controls. No change in DNA synthesis was seen in normal livers.

Clinical studies have varied greatly in quality, with the majority limited by inadequate sample size, lack of uniformity in the population treated, lack of standardization of preparations studied, variability in dosing regimens, inconsistent outcome measures, and a lack of information on concurrent use of alcohol during the treatment period (see Chapter 8).

12.7 MALE SEXUAL DYSFUNCTIONS

In sexual health, Arab–Muslim physicians, such as Rhazes, Thabit bin Qurra, Ibn al-Jazzar, Avicenna, Averroes, Ibn al-Baitar, and Ibn al-Nafis, identified sexual dysfunctions and erectile dysfunction, and they were the first to prescribe medication for the treatment of these problems [1,2,13,16,17]. They developed several methods of therapy for these diseases and methods to improve male sexuality in general. Sexual dysfunctions were being treated with tested drugs (single drug or in combination with other drug or diet).

The most common plants used in Arabic medicine for sexual dysfunctions are *Trigonella foenum, Eruca sativa, Clematis cirrhosa, Pistacia palaestina, Zingiber officinale, Smilax aspera, Salvia dominica, Nasturtium officinale, Raphanus raphanistrum, Phoenix dactylifera*, and *Allium cepa*. Zallouh is the common name in the Middle East for the roots of the species *Ferula hermonis* growing on the slopes of Mount Hermon in the Syrian Golan Heights. It has been used for centuries as a folk remedy to treat sexual dysfunction in women and erectile and sexual dysfunction in men. This plant is botanically quite close to *Ferula communis*, the giant fennel. Ferula is the Latin name for "walking stick," a word mentioned in the Old Testament as the Hebrew name "kelech," in the context that its stem was used as a walking stick. There are several species of *Ferula* that grow throughout the world including the species *Ferula asa-foetida*. This plant is native to central Asia; however, it was well integrated in the Greek–Arab medicinal system and is still used in most Arab countries. According to the Greek herbalists Dioscorides and Galen, this plant is used for the treatment of tiredness and impotence. The rich traditional knowledge of Greco-Arab medicine gives support to its use as a sexual tonic to encourage potency. Rhazes reported that Indians use *Ferula asa-foetida* as the main botanical aphrodisiac several centuries before his time. Avicenna and Al-Antaki have also emphasized the aphrodisiac effect of *Ferula asa-foetida*. There is considerable confusion in the identification of aphrodisiac species of plants, especially due to their extensive use as aphrodisiac agents, plant parts used, and relatively similar smell. They are called by names such as "Heltit," "Andujan," "Kallch," "Aqir Qarha," or "Oud alkerach algabali." All the well-known traditional herbalists agree that these species are used to manage tiredness and impotence and they describe a unique method of preparation that includes boiling the roots to dryness, sometimes with the addition of oil. On the basis of the knowledge from traditional Greco-Arabic and Islamic herbal medicine,

we studied the effects of extracts from *Ferula assa-foetida* on male fertility and sexual functioning in rats and in man. Therefore, ethanol extract from seeds and 50% water–ethanol root were prepared into so-called "Masculine" tablets and assessed for their safety and efficacy in enhancing male libido.

Safety Studies Results obtained show that Masculine exhibits high levels of safety in both cultured human fibroblasts and experimental studies on rats with a LD_{50} of 5 g/kg. Other studies, however, reported toxic effects in rats treated for a long period and with high concentrations of oil extracts of *Ferula hermonis.* Such long-term administration of high doses of *Ferula hermonis* has also been reported to reduce testosterone and copulatory performance in rats, whereas acute administration of the plant improved sexual functioning in these rats. We used a much safer *Ferula* species and a different and less concentrated extract.

Efficacy Studies Results of lipid peroxidation in rat liver cells are shown in Figure 12.5 as the extent of malondialdehyde (MDA) production at baseline (0) and during the addition of several Masculine concentrations. Low dose of Masculine (0.01 mg/mL) significantly reduces MDA release from 0.27 to 0.17 ng/mg protein (Figure 12.5 right bulks). Higher concentrations (0.05 mg/mL) further reduce MDA release to 0.13 ng/mg proteins. Figure 12.5 (left bulks) shows the extent of lipid peroxidation in human sperm cells. The addition of a low concentration of 0.01 mg/mL reduces MDA release from 0.52 to 0.31 ng/mg proteins. A higher concentration (0.05 mg/mL) further reduces the released MDA to 0.16 ng/mg proteins, but no further antioxidant effect is obtained at the concentration of 0.1 mg/mL of the studied extract.

Aphrodisiac Effects Figure 12.6 shows the episodes of penile erection in control and "Masculine"-treated rats within 3 h. These episodes increase from 4.7 in controls to 19.1 in the treated rats within the first hour and from about 4 to about 23 and 22 episodes within the second and third hours, respectively. In addition, we tested the efficacy of Masculine on 85 young healthy males with a mean age of 37 (range 24–47) years. Masculine (one tablet/daily for 3 months) was well tolerated by all men and no adverse effects were reported. Sixty men were studied for infertility due to azoospermia. They had no sexual complaints. No significant increase in the sperm count of 50 subjects was seen after 3 months of Masculine consumption. However, the sperm count in the remaining 10 men (17%) increased after 3 months from zero to 8×10^5/mL and their sperm motility increased to 19%. At 3 months of "Masculine" dosage, 5 of the 25 men with sexual complaints experienced a slight improvement in their sexual performances and 5 others experienced no change. The remaining 15 men (60%) reported considerable improvements in both libido and erectile function. Ten of these 25 men had normal sperm counts, while the other 15 men were oligospermic and their sperm count increased from a baseline value of 2.2 to 2.8 millions/mL and additionally their sperm motility increased from 23.8% at baseline to 43.2% after 3 months of Masculine consumption. These changes in sperm counts and motility were accompanied by a remarkable improvement in the sperm microstructure and by

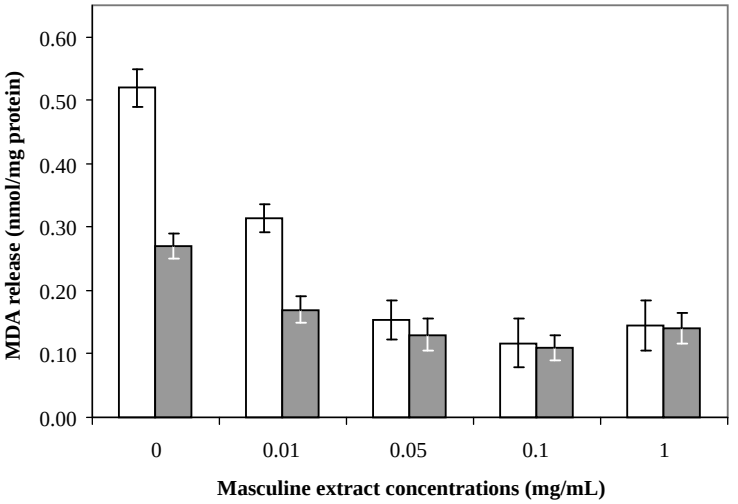

FIGURE 12.5 Effects of "Masculine" extract at different concentrations upon MDA released and produced by lipid peroxidation in rat liver (right bulks) and in human sperm cells (left bulks) cells incubated with 100 µM ferrosulfate. Values given represent the mean ± SD ($^*P < 0.05$ significant compared to controls) of three independent experiments carried out in triplicates.

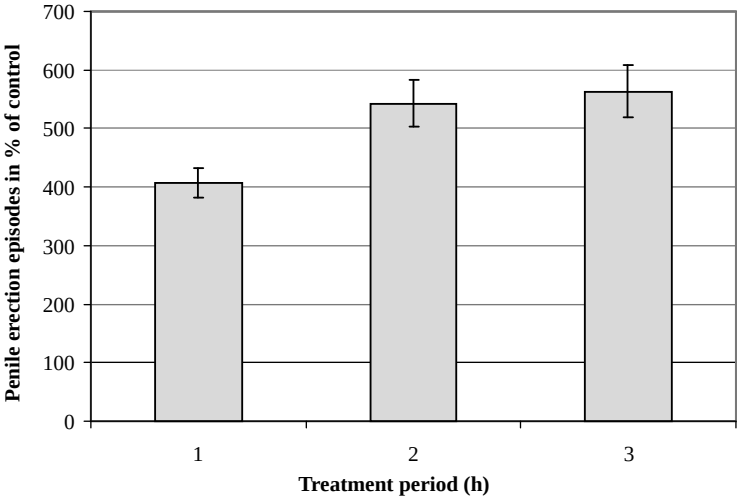

FIGURE 12.6 Episodes of penile erection in control rats and in rats treated with "Masculine" extract within 3 h of sexual stimulation. Values given represent the mean ± SD ($^*P < 0.05$ significant compared to controls) of three independent experiments carried out in triplicates.

significant reductions in white blood cell counts in both these 15 men and the other 10 infertile men (Figure 12.7).

Substantial antioxidant and vasodilatation properties of Masculine were seen at concentrations of 0.05 and 0.2 mg/mL, respectively. Our recommended dose in men is about 1.5 mg/kg corresponding to one tablet of Masculine per day, assuming an average weight of 70 kg. In good clinical practice, an optimal dose of a drug or an herb is the minimal dose that yields therapeutic efficacy with least side effects. We used a relatively small daily dose of extract and found a complete absence of side effects in the 85 men during 3 months of Masculine consumption. Improvements in both the libido and the erectile function were disclosed in 80% of the studied men. Moreover, a substantial augmentation of sperm counts was noticed in all oligospermic men and in 17% of azoospermic men, and it was accompanied by remarkable improvements in sperm motility and microstructure [19].

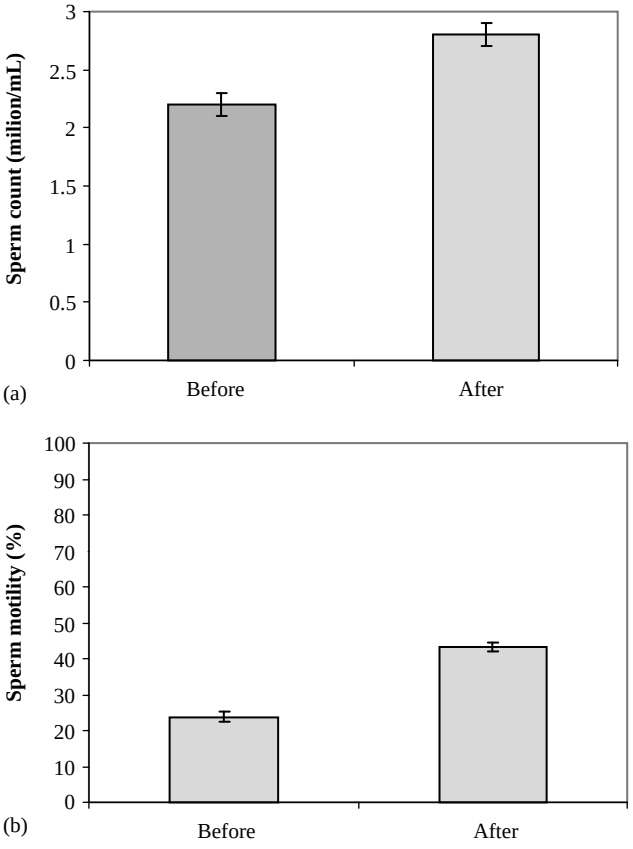

FIGURE 12.7 Effect of Masculine consumption (one tablet/day for 3 months) on sperm count in 15 oligospermic volunteers (a) and on sperm motility in 15 oligospermic volunteers (b).

12.8 FEMALE SEXUAL DYSFUNCTIONS

A concentrated dry extract of *Ferula assa-foetida* roots and *Capparis spinosa* buds was prepared into so-called Feminine tablets and assessed for safety and efficacy in enhancing female libido. Experimental studies on rats disclosed a high level of safety of this extract with an LD_{50} of 15 g/kg. Cultured human fibroblasts incubated with increasing concentrations of the extract did not exhibit any sign of cellular toxicity as evidenced by LDH release.

Efficacy Antioxidant properties were demonstrated using the lipid peroxidation method and were substantial at very low concentrations of this extract when incubated with rat liver cells and ferrosulfate. Derived from Sprague Dawley rats, arterial rings with and without their endothelial tissue were contracted under controlled conditions and during the addition of different extract concentrations. These experiments revealed the Feminine extract to be a potent vasodilator due to an endothelial-mediated effect rather than a direct effect on arterial smooth muscle cells. Two groups of married and healthy females were followed for 6 months while consuming one Feminine tablet daily. Feminine was well tolerated by all females and no side effect was reported. One group ($n = 32$) was studied due to difficulties in the sexual activity and the other ($n = 28$) was studied due to infertility that could not be helped further by medical evaluations or treatment. Twenty-seven women of the first group (84%) reported significant improvements in their sexual difficulties and libido, while the remaining five women reported no remarkable change. Twenty-one women of the second group (75%) reported that their libido was improved within 1 month of Feminine consumption, and 11 women became pregnant. The results indicate that Feminine is a safe sexual tonic enhancing female fertility and sexual functioning.

12.9 STABILIZATION OF FAT LEVEL IN THE BLOOD

Hypercholesterolemia (high levels of cholesterol in the blood) is often associated with obesity, diabetes mellitus, and hypertension. Each contributes to elevated cardiovascular mortality. There is a general consensus that these metabolic disorders share hyperinsulinemia and insulin resistance as a common link, leading to both micro- and macroangiopathies. Atherogenesis is a multifactor process that includes oxidatively modified LDL that triggers pathological events through multiple pathways leading to atherosclerosis. Research in recent years has been directed toward dietary antioxidants of plant-derived products to normalize the augmented levels of cholesterol atherogenic fractions, mainly LDL, and of glucose in an attempt to reduce the cardiovascular risk. Recent data have evidenced antiatherogenic and antioxidant activities of extracts from both olive and loquat leaves [18].

The safety of both herbs (olive and loquat leaves) used in our study is documented by their use in folk medicine through centuries. The leaves of loquat are well-known and safe household remedy, especially in the Far and Middle East [4,6,18]. Extracts from these leaves have been reported to exhibit a significant hypoglycemic effect

both in Italy and in Pakistan. They were also reported to have antiviral and antitumor effects, and to be selectively cytotoxic against tumor cell lines but not against normal cells. Moreover, they have been evidenced as potent natural antioxidants. In this scientific literature, no evidence of any adverse effect of loquat leaf extracts has been indicated, and on the contrary, liver protective effects of seed extracts have been evidenced in animals. As for safety of olive leaf extracts, it has been widely documented both in Europe and in the Middle East, and their antiatherogenic, antioxidant, and antidiabetic properties have been evidenced in Germany [6,18–21]. We investigated the safety and efficacy of a fixed mixture of both olive and loquat leaves named Cholevel. Safety studies were carried out in animals and *in vitro*, whereas therapeutic efficacy was evaluated in human volunteers [22].

Safety: An extremely high dose of the product corresponding to 17.3 g/kg was necessary to obtain the LD_{50} in rats.

Efficacy: Lipid peroxidation induced by incubating rat liver homogenates with ferrosulfate is expressed in Figure 12.8 as the extent of MDA production. The addition of very low dose of the product (0.01 mg/mL) to the medium significantly reduced MDA release from 0.88 to 0.62 nM/mg protein. Higher concentrations of the product (0.05 mg/mL) further reduced MDA release to 0.32 nM/mg protein. No further antioxidative effect of the product was noted by increasing its concentration to 0.1 mg/mL (Figure 12.8).

The results disclose that Cholevel is safe and well tolerated by all 34 studied subjects and is therapeutically efficient as substantial and incremental reductions of cholesterol levels were observed (Table 12.6). After 3 months, baseline cholesterol

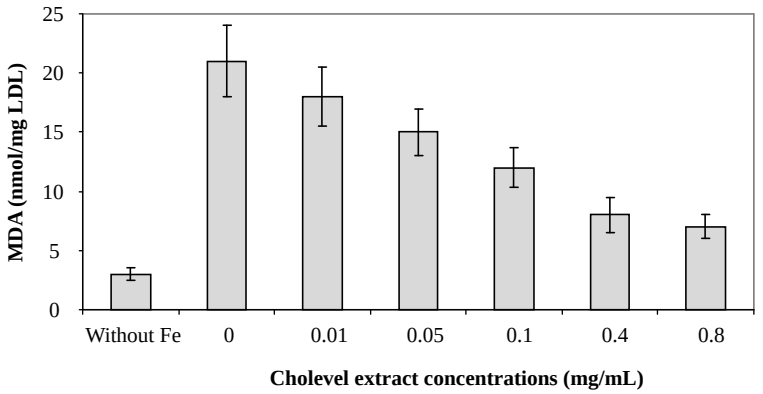

FIGURE 12.8 Effects of Cholevel extract at different concentrations upon MDA released and produced by lipid peroxidation in rat liver cells incubated with 100 μM ferrosulfate. Values given represent the mean ± SD ($^{*}P < 0.05$ significant compared to controls) of three independent experiments carried out in triplicates.

TABLE 12.6 Fasting Lipid Levels in the 34 Subjects at Baseline, 1 Month, and 3 Months While Consuming One Stroll-Down Tablet Three Times Daily

	Baseline	1 month	3 months
Cholesterol (mg%)	289.6 ± 4.1	267.8 ± 5.1	227.3 ± 9.4
LDL (mg%)	158.8 ± 3.2	149.8 ± 4.1	143.1 ± 1.1
HDL (mg%)	39.8 ± 2.2	45.1 ± 1.5	48.8 ± 1.6
Triglycerides (mg%)	274.2 ± 13.1	239.0 ± 7.1	216.8 ± 7.4

levels in these subjects were reduced by 22%, which is comparable to that of 25% observed during simvastatin therapy.

Extracts of loquat leaves have been evidenced as the natural antioxidants superior to other tested antioxidant herbs. Antioxidant properties of olive leaf extracts have been widely documented, and such antioxidant properties of both herbs contribute to the reported hypoglycemic effects of loquat and olive leaves [14,18]. We propose that the loquat component of Cholevel is in accordance with recommendations in traditional Arabic herbalism [2,4,6] and has primarily a statin-like effect that reduces cholesterol production in the liver. The olive component of Cholevel seems to have primarily a Zetia-like effect that reduces cholesterol intestinal absorption. The main active ingredient in olive leaf was reported to be oleuropeoside that disclosed distinct hypolipidemic, hypotensive, and hypoglycemic properties at a dose of 16 mg/kg.

As experienced in good clinical practice, smaller doses of synergistic drugs may yield a better therapeutic efficacy with the fewest side effects. This could explain the fact that Cholevel was well tolerated by all studied subjects and no adverse effect could be traced.

12.10 INFLAMMATION

Inflammation is the first response of the immune system to infection or irritation. It is caused by cytokines. There are two types of cytokines: proinflammatory and anti-inflammatory. Thus, inhibitors of the proinflammatory cytokines have been considered as a candidate of anti-inflammatory drugs. Inflammatory responses are advantageous for eradicating bacteria, as long as they are under control. When out of control, however, deregulated inflammation leads to the massive production of proinflammatory cytokines, such as TNF-α, IL-1, and IL-6 by macrophages, which can cause tissue injury and multiple organ failure. The inflammatory process is controlled by immunosuppressant cytokines such as IL-10 and IL-4 [23–28].

Arabic medicine had shown remarkable achievements in curing inflammatory diseases in general, and clearly distinguishing between several subtypes of inflammatory diseases has offered numerous plants for treating various types of inflammations. Herbal medicines containing *Hypericum triquetrifolium* and *Peganum harmala* have been used in traditional Arab herbal medicine to treat various inflammatory diseases. The classic Arabic name for *Hypericum triquetrifolium* is

Dathi or *Nabtat Yohanna*. Our surveys show that *Hypericum triquetrifolium* is not used any more within the practitioner communities in the Galilee and in the West Bank. This fact reflects an extinction process of important elements of the Arab herbal medicine heritage. This utilizes the knowledge derived from traditional Greco-Arab herbal medicine and a recent *in vivo* report in which *Hypericum triquetrifolium* extract exhibited anti-inflammatory activity in rats.

Lipopolyssacharide (LPS)-activated macrophages are usually used for evaluating the anti-inflammatory effects of various materials. LPS is a principal component of the outer membrane of Gram-negative bacteria and an endotoxin that induces septic shock syndrome and stimulates the production of inflammatory mediators such as nitric oxide, TNF-α, interleukins, prostanoids, and leukotrienes. Therefore, LPS plays a key role not only in eliciting an inflammatory response but also in causing septic shock during a Gram-negative bacterial infection. Our study explored the anti-inflammatory mechanism of *Hypericum triquetrifolium* and *Peganum harmala*. Therefore, the expression and the release of proinflammatory cytokines TNF-α and IL-6 in LPS-activated human monocytic (THP-1) cells were measured [1–6,29].

Safety We applied the MTT test to evaluate the safety of extracts from *Hypericum triquetrifolium* and *Peganum harmala* in cells from the humane monocyte cell line THP-1. Cells were exposed to increasing concentrations (1–500 µg/mL of culture medium) of *Hypericum triquetrifolium* and *Peganum harmala* extracts for 24 h. No sign of any negative effects was observed after treatment with concentrations up to 250 µg/mL (Figure 12.9). Concentrations higher than 250 µg/mL caused a significant reduction in the cell viability.

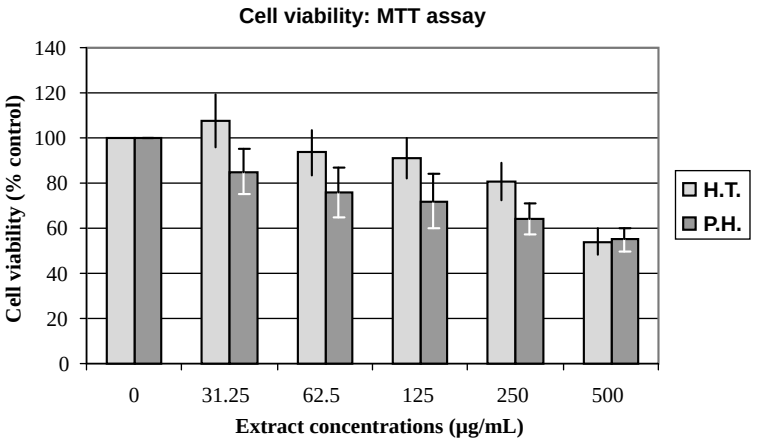

FIGURE 12.9 MTT assay in THP-1 cells after an overnight treatment with various concentrations of extract from *Hypericum triquetrifolium* and *Peganum harmala*. Cell viability was defined as the ratio (expressed as a percentage) of absorbance of treated cells to untreated cells. Values represent mean ± SD of three independent experiments carried out in triplicates.

Efficacy The inhibitors of these cytokines have been considered as a candidate for anti-inflammatory drugs. Monocytes/macrophages are key mediators of inflammation and widely distributed in the body. Therefore, monocytic cell line THP-1, which represents an appropriate model system to study immune responses, was utilized to investigate the anti-inflammatory effects of *Hypericum triquetrifolium* and *Peganum harmala* extracts. Herbal medicines containing *Hypericum triquetrifolium* and *Peganum harmala* extracts have been used in traditional Arab herbal medicine to treat various inflammatory diseases. However, only few studies have been conducted to evaluate the effects of these two plants on inflammation. In our study, we show that both extracts could modulate the regulatory mechanism of proinflammatory cytokines (TNF-α and IL-6) in the LPS-activated THP-1 cells. *Hypericum triquetrifolium* inhibited the production and expression of TNF-α but not of IL-6. *Peganum harmala* inhibited the production of both IL-6 and TNF-α (Figures 12.10 and 12.11).

The Effect on the Production of Proinflammatory Cytokines Several cytokines are deeply associated with inflammatory diseases. In particular, TNF-α and IL-1 are prominent contributors to chronic inflammatory disorders. TNF-α and IL-1 receptor antagonists have been clinically successful in improving the symptoms of rheumatoid arthritis patients. NSAIDs, such as prednisolone and dexamethasone, are known to reduce the production of these cytokines. In recent years, various medicinal plant-derived factors have been reported to regulate the production of proinflammatory cytokines. Flavonids, such as amoradicin, genistein, and silybin, were proved to inhibit TNF-α production from LPS-treated RAW 264.7 cells. Baicalin inhibited the induction of IL-1, IL-6, TNF-α, IFN-γ, monocyte chemotactic protein-1 (MCP-1),

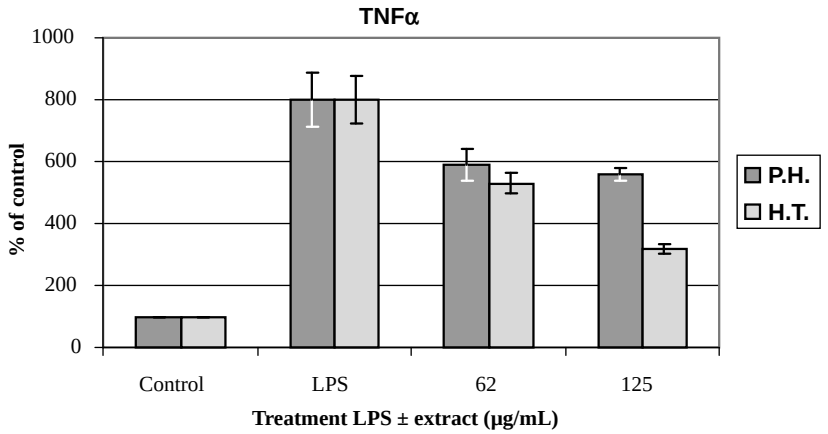

FIGURE 12.10 Dose-dependent inhibition of LPS-mediated production of TNF-α by *Hypericum triquetrifolium* and *Peganum harmala* extracts. For each concentration treatment, the level of TNF-α release is represented as a percentage of the control set at 100%. The bar heights represent the values of mean ± SD of three independent ELISA experiments carried out in triplicates.

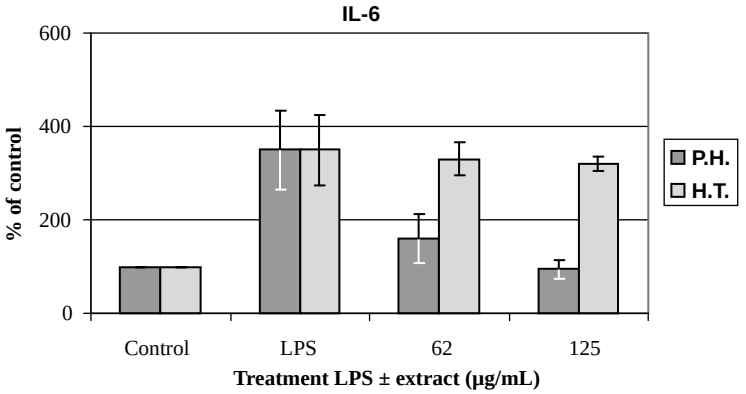

FIGURE 12.11 Dose-dependent inhibition of LPS-mediated production of IL-6 by *Hypericum triquetrifolium* and *Peganum harmala* extracts. For each concentration treatment, the level of TNF-α release is represented as a percentage of the control set at 100%. The bar heights represent the values of mean ± SD of three independent ELISA experiments carried out in triplicates.

macrophage inflammatory protein-1 (MIP-1), and MIP-1 at protein as well as at RNA levels from human blood monocytes treated with staphylococcal enterotoxin. We demonstrate that *Hypericum triquetrifolium* and *Peganum harmala* inhibit the production of LPS-induced TNF-α by downregulating the transcription of the TNF gene. Similar results were found using different medicinal plants. For example, feverfew extracts were found to effectively reduce lipopolysaccharide (LPS)-mediated TNF-α and CCL2 (MCP-1) releases by THP-1 cells. Moutan Cortex extracts were reported to exhibit anti-inflammatory effects through the inhibition of iNOS and COX-2 expression by suppressing the phosphorylation of IkBa and the activation of NF-κB. *Uncaria tomentosa* extracts inhibited the MAP kinase signaling pathway and altered cytokine expression in THP-1 monocyte-like cells with *Uncaria tomentos*. *Hypericum triquetrifolium* inhibits the production of LPS-induced TNF-α by downregulating the transcription of the TNF gene, but has no significant effects on the production levels of IL-6. These results suggest that the anti-inflammatory effects of *Hypericum triquetrifolium* and *Peganum harmala* are mediated via the downregulation of the transcription of the TNF gene [29].

12.11 MODULATION OF IMMUNE FUNCTION

The immune system is increasingly found to be involved in the development of several chronic illnesses, for which allopathic medicine has provided limited tools for treatment and especially prevention. In this context, it appears worthwhile to target the immune system in order to modulate the risk of certain chronic illnesses. It is believed that tumor development, outgrowth, and metastasis are under the surveillance of the immune system. Although both innate and acquired immune systems play

roles, innate immunity is the spearhead against tumors. Recent studies have revealed that natural killer (NK) cells play a critical role in immune surveillance and that NK cell activity is considerably influenced by various agents, such as environmental factors, stress, foods, and drugs. Some of these NK cell stimulants have been used in complementary and alternative medicine (CAM) since ancient times. Therefore, the value of CAM should be reevaluated from this point of view. For the past few decades, scientific investigations on herbal medicines have remarkably advanced and partly supported their medical efficacy through preclinical and clinical experiments. Many studies have suggested that NK cell activation is one of the critical mechanisms for the biological effects induced by various herbal agents. For example, intake of green tea, *Nigella sativa* seeds, *Allium sativum* bulb, *Allium cepa* bulbs, *Cichorium intybus*, and *Viscum album* significantly augmented NK cytotoxicity or restored NK cell activity in some immunosuppressive conditions. Oral administration of *Phyllanthus emblica*, which is known as an excellent source of vitamin C, enhanced NK cell activity and antibody-dependent cellular cytotoxicity (ADCC); thus, supplemental nutrients might enhance NK cell activity [30,31].

12.12 CANCER

Cancer is a group of diseases characterized by uncontrolled cell proliferation. When cells divide without control, the excess tissue that develops is called a tumor or neoplasm. The development of cancer (carcinogenesis) is a long and multistep process that includes selection of a mutated cell (initiation), selective expansion of the initiated cell (promotion), and progression as a consequence of an imbalance between cell proliferation and cell death. More genetic and epigenetic events are required to drive initiated cells to malignant tumors, each conferring one or another type of growth advantage, leading to the progressive conversion of normal human cells into cancer cells. The establishment of a mutation is a prerequisite of cancer. Several factors may trigger a normal cell to lose control and become cancerous (e.g., environmental agents, activation of oncogenes). Most notable among proneoplastic mutations are those that result in increased expression of oncogenes (e.g., myc, ras, bcl-2) or decreased activity of tumor suppressor genes (e.g., p53), conferring a selective growth or survival advantage to the cell. Phenotypic changes representative of preneoplastic mutations include a decreased need for metabolites and growth factors, abnormal signal transduction, inappropriate expression of receptors for available growth factors (epidermal growth factor receptor, HER2/neu), dysregulation of cell cycle checkpoints, and resistance to apoptosis. At this point, any agent that causes increased cell proliferation increases the risk of neoplastic transformation. The damage to the DNA must survive the many DNA repair processes and must be readable by DNA polymerase, which creates and locks in the mutation. If, by chance, this damage to the DNA results in a selective growth or survival advantage to the cell, it may become a precancerous lesion [32–34].

In the Greco-Arab medicine, Avicenna described cancer as a tumor in his Canon. He noted that a "cancerous tumour progressively increases in size, is destructive and

spreads roots which insinuate themselves amongst the tissue elements." Avicenna noted that cancers were caused by an excess of black bile, which caused excessive heat in the body. Like the ancient Greeks, he believed that if one of the body's humors was out of balance, then all four of them were unbalanced. As a result, Avicenna and his contemporaries understood cancer to be an extremely difficult disease to treat. He said a benign tumor could be differentiated from a cancerous one by certain symptoms such as pain, throbbing, and rapid growth. He also noted that cancerous tumors send out "crablike tracks" and occurred more often in "hollow" organs, which is why they were more common in women. Avicenna also stated that cancers often strike muscles, tendons, and lymph nose.

Avicenna realized that a cure is most likely if the cancer was identified at its earliest stage. The first goal of a treatment strategy should be to halt the cancerous growth. He suggested surgical removal if the tumor was small and accessible and not close to major organs. He noted "can be arrested with anything, it can be so by vigorous excision . . . including all the [blood] vessels supplying the tumor so that nothing of these will be left." Avicenna also recommended that surgery be preceded by purifying the body of excess black bile. This could be achieved by providing a nutritious and balanced diet to the patient to maintain purity and strengthen his or her organs and immune system. Avicenna most often treated cancer patients with drug remedies. He also advised cancer patients to change their diets. Avicenna also attempted the earliest known treatments for cancer. One method he discovered was the "Hindiba" (*Chicorium intybus*), an herbal compound drug that Ibn al-Baitar later identified as having "anticancer" properties and that could also treat other tumors and neoplastic disorders. Another method for treating cancer first described in the *Canon* was a surgical treatment. It stated that the excision should be radical and that all diseased tissue should be removed, which included the use of amputation or the removal of veins running in the direction of the tumor. In advanced cases, Avicenna advices against excision, saying the tumor would only grow back.

On the basis of the knowledge of the old literature and the experience of the local herbalists in the treatment of cancer using Arab medicinal plants, we selected the most effective medicinal plants for the treatment of neoplastic diseases (Tables 12.7 and 12.8). We tested the effectiveness of extracts from these selected plants on preventing the proliferation of human cancer cells in an *in vitro* system (Chapter 13).

To test the toxicity of the medicinal plant extracts, the integrity of the plasma membrane was determined following exposure of cultured cells to different amounts (0.1–2 mg/mL) of plant extracts for 48 and 72 h. This was done by measuring LDH activity, in which LDH is released from the cells into the culture medium when plasma integrity is destroyed by necrotic rupture. Using this system, the results indicated that the plant extracts are not toxic.

The effect of plant extracts on cell proliferation induces apoptosis in human breast cancer (MCF7 and T47D) and colon cancer (HT-29, Colo-320) cell lines. Treatment of the cells with these extracts induced significant inhibition of DNA synthesis and affected cell survival. These effects were found to be dose and time dependent. Moreover, our results indicate that treatment of the cells with these extracts induces apoptosis, which was detected by DNA fragmentation, Tunel assay,

TABLE 12.7 Medicinal Plants Used to Treat Cancer Based on Traditional Arab Medicine

Plant Species	Preparation	Additional Uses
Allium cepa	Bulb juice	Diabetes, loss of appetite, liver disease, coughing, external infection
Arum palaestinum	Foliage decoction	Internal bacterial infections, poisoning, and circulatory system
Brassica oleracea	Whole plant juice	Respiratory system, asthma, joint inflammation, bacterial infection
Crataegus azarolus	Fruit and flower decoction	Cardiovascular diseases, sexual weakness, diabetes
Quercus calliprinos	Fruit and bark decoction	Bedwetting, ulcer, diabetes, skin diseases
Quercus ithaburensis	Stem, bark, and fruit decoction	Fever, bedwetting, high blood pressure, ulcer
Triticum aestivum	Shoot decoction	Anaemia, skin disease (seed decoction)
Urtica pilulifera	Foliage decoction	Stomach, intestine pain and inflammation, liver disease, bedwetting (seed)
Zea mays	Kernel and fiber decoction	Urinary system and stones in kidney, blood pressure, joint inflammation, and weight loss

and morphological changes. For the first time, we performed an animal experiment where the cancer cells were injected subcutaneously into immunologically deficient (SCID) mice. Once the tumor had established itself in these animals, the tumors were then injected with plant extract with monitoring of the resultant changes in tumor size. Interestingly, we found that these extracts have anticancer properties, inhibit cell division, induce programmed cell death (apoptosis), and reduce tumor size *in vivo*. Moreover, our herbalists reported that these plants are effective in the treatment of cancer patients.

In a recent study, the chemopreventive activities of *Trigonella foenum graecum* (Fenugreek) against breast cancer were examined. Results obtain suggest that seed extract significantly inhibited the DMBA-induced mammary hyperplasia and decreased its incidence. Epidemiological studies also implicate apoptosis as a mechanism that might mediate the Fenugreek's anti-breast cancer protective effects. To our knowledge, this is the first study that suggests significant chemopreventive effects of Fenugreek seeds against breast cancer [35]. The anticancer properties of *Nigella sativa*, *Phoenix dactylifera*, *Ficus carica*, and *Punica granatum* are discussed in Chapters 8 and 17 [47].

Anticancer Properties of Nigella sativa In both *in vivo* and *in vitro* studies, *Nigella sativa* seeds were found to exhibit antitumor affects [36–41]. For instance,

TABLE 12.8 Effects of Food and Herbal-Derived Compounds in Cancer Chemoprevention

Sources	Active Principle	Antiangiogenesis	Apoptosis Induction	Antimetastasis Effect	Antioxidant Properties	Anti-inflammatory Properties
Olive	Oleuropein	+	+	+	+	+
Black seeds	Thymoquinone	+	+	+	+	+
Onion	Quercetin	+	+		+	+
Garlic	Diallyl sulfide	+	+		+	+
Tumeric	Curcumin	+	+		+	+
Figs	Several flavonoids			+	+	+
Pomegranate	Several polyphenols	+	+	+	+	+
Honey	Several active compounds			+	+	+
Milk thistle	Silymarin	+	+		+	+
Chicory	Inulin-type fructans (beta(2,1) fructans)	+		+	+	+
Bread wheat	Fibers, lignans, isoflavones, and phenolic acids		+			

treatment of cells from the breast cancer cell line with aqueous and alcohol extracts completely inhibited proliferation of these cells. Other studies attempted to define the antitumor mechanisms of *Nigella sativa* oil show that *Nigella sativa* extracts induced inhibition of the metastasis-induced factors, including type IV collagenase, metalloproteinase, serine proteinase inhibitors, angiogenic protein-fibroblastic growth factor, tissue-type plasminogen activator, urokinase-type plasminogen activator, and plasminogen activator inhibitor type 1. It seems that the antitumor activity of *Nigella sativa* oil might be mediated through antiangiogenic effects through inhibition of local tumor invasion and metastasis. In addition to the antitumor effects of the whole extract of *Nigella sativa*, thymoquinone, dithymquinone, and other active ingredients also showed cytotoxic effects. For instance, α-hedrin, another ingredient of the crude extract of *Nigella sativa* oil, expressed antitumor effects against different cancer cell lines with selectivity against hepatocellular carcinoma, leukemic cell, Lewis lung carcinoma, and leukemia cells through a rapid depletion of intracellular GSH and disruption of mitochondrial membrane potential with subsequent increase in the production of reactive oxygen species. Both thymoquinone and dithymquinone were equally cytotoxic against different human tumor cells lines, including the pancreatic adenocarcinoma, human uterine sarcoma, and human leukemia, triggering their apoptosis through arresting the growth of these cells in G1 phase of the cell cycle associated with increase in the gene and protein expression of p53 and inhibition of the antiapoptotic Bcl-2 protein. This indicates that the antineoplastic effect of thymoquinone is mediated by proapoptotic effects modulated by Bcl-2 protein and is linked to and dependent on p53.

Anticancer effects have also been confirmed *in vivo* in different cancer models. For instance, topical treatment with *Nigella sativa* inhibited two-stage initiation/promotion of skin carcinogenesis induced in mice by anthracene/croton oil, where the onset of papilloma formation was delayed and the mean number of papillomas was reduced. The active principal fatty acids derived from *Nigella sativa* completely inhibited the growth of Ehrlich ascites carcinoma and Dalton's lymphoma ascites cells. Moreover, oral feeding with *Nigella sativa* extract suppressed hepatic tumor in rat induced by diethylnitrosamine or by partial hepatectomy. Furthermore, the oil suppressed colon carcinogenesis induced by methylnitrosourea or dimethylhydrazine. These antitumor effects of *Nigella sativa* oil might be attributed to the effect of thymoquinone, since administration of thymoquinone in drinking water resulted in significant suppression of forestomach tumor induced by benzo[α]pyrene. Using the same fibrosarcoma tumor model, administration of *Nigella sativa* extract 30 days after subcutaneous administration of methyclonathrene restricted fibrosarcoma tumor incidence to 33.3%, compared to 100% in control tumor-bearing mice, indicating to therapeutic potentials. These observations demonstrate that thymoquinone, in addition to its prophylactic and therapeutic antitumor effects, can be a potential chemotherapeutic adjuvant to standard chemotherapy. This might lower the dose of standard chemotherapeutic drugs, while augmenting their antitumor efficacy. Suppression of immune cell function associated with chemotherapy, radiotherapy, and late stages in tumor-bearing hosts is mediated, at least in part, by NO produced by immature granulocytes that are massively generated under these conditions. Therefore, it is possible that the

antitumor effects reported for *Nigella sativa* oil and thymoquinone are mediated by their abilities to scavenge the NO produced by these cells. The impact of *Nigella sativa* ingredient, in particular thymoquinone, on these cells in the tumor-bearing hosts needs to be explored. In addition, since chemotherapy induces massive expansion of the immature granulocytes, which produce a large amount of NO, it might be feasible to follow chemotherapy with thymoquinone treatment that might alleviate the suppressive effects on the immune responses by chemotherapy-induced NO. In addition to the possible antioxidant-mediated antitumor effects of thymoquinone, it is also possible that its antitumor effects if mediated by the ability to suppress PEG and LT.

Taken together, the findings of these studies indicate to the potential of the active ingredients of *Nigella sativa* oil, in particular thymoquinone, as a powerful chemopreventive agent against several experimental cancers, including forestomach, fibrosarcoma, colon, skin, and hepatic tumors. In spite of these obvious antitumor effects of *Nigella sativa* oil and thymoquinone, it still remains to be known whether these effects are immune mediated through modulation of antitumor immune responses. CD8+ T cells mainly mediate antitumor immune responses, while help of CD4+ cell is also required for the optimal antitumor immune response. Therefore, further studies are required to define tumor-specific cytotoxic T cell responses under the effects of thymoquinone. This will allow insight into the issue of thymoquinone's benefit for antitumor immunotherapeutic approaches [36–41].

Anticancer Properties of Olive Leaf Epidemiological studies provide robust evidence for a protective effect of the Mediterranean diet against cardiovascular disease and cancer. These findings prompted scientists to search Mediterranean flora as a rich source of bioactive phytochemicals with a potential to evolve into preventive and possibly therapeutic agents. Many epidemiological evidences suggest that people who consume the olive oil-rich diet have a lower incidence of certain cancers, including breast, skin, and colon. This phenomenon is most likely associated with the antioxidant activity of active ingredients of the olive oil. Oxidation of proteins, DNA, and lipids has been shown to contribute to cancer development, and consumption of antioxidants is believed to reduce the risk of mutagenesis and carcinogenesis. Hydroxytyrosol has been found to be capable of protecting cells from hydrogen peroxide damage and DNA from peroxynitrite-induced damage, blocking cell cycle progression at the G1 phase, and inducing apoptosis. *In vivo* and *in vitro* studies on the activity of oleuropein have found that in addition to antioxidant properties, it has antiangiogenic action and inhibits cell growth, motility, and invasiveness. Oleuropein has also been found to cause cell rounding, which disrupts the cell actin cytoskeleton. Oleuropein also affects and disrupts purified actin filaments, providing direct antitumor effects due to cell disruption. In *in vivo* animal studies, rapid tumor regression was observed when mice were given 1% oleuropein in drinking water. Saturated animal fats and polyunsaturated plant fats in the diet have been implicated in colon, breast, prostate, and ovarian cancers. The substitution of olive oil in the Mediterranean diet may explain its apparent cancer protective effect and accentuate the importance of the type, rather than the amount, of fat consumed. A recent study has

evaluated the antioxidant potency and antiproliferative activity against cancer and endothelial cells of water and methanol olive leave extracts. Olive leaf crude extracts were found to inhibit cell proliferation of human breast adenocarcinoma (MCF-7), human urinary bladder carcinoma (T-24), and bovine brain capillary endothelial (BBCE). The dominant compound of the extracts was oleuropein; phenols and flavonoids were also identified. These phytochemicals demonstrated strong antioxidant potency and inhibited cancer and endothelial cell proliferation at low micromolar concentrations, which is significant considering their high abundance in fruits and vegetables [42–45].

Anticancer Properties of Pomegranate The anticancer properties of pomegranate are discussed in Chapter 14. In brief, pomegranate peel extracts have been shown to reduce proliferation of cells from different human cancer cell lines, for example, from human breast cancer cells, MCF-7, and MDA-MB-231 cells compared to immortalized normal breast epithelial cells MCF-10A. Furthermore, proliferation of cells from an androgen-independent PC-3 cell line was dose dependently inhibited after treatment with acetone extract from whole fruits. This corresponded to changes in the cyclin kinase inhibitor– cyclin–cdk network. In addition, an acetone extract of whole pomegranate fruit treatment for nude mice implanted with androgen-sensitive CWR22Rnu1 human prostate cancer cells resulted in suppression of growth and a significant decrease in serum prostate-specific antigen. Other studies indicate that whole, complex pomegranate products possess potential antiproliferative activity against cancer cells superior to that of their principal active compounds. Despite the aforementioned preclinical observations that indicate anticancer properties with limited toxicity, there still remains few well-designed clinical trials measuring the anticancer and other health benefits of the pomegranate [46].

Pomegranate seed oil increased the occurrence of apoptosis (programmed cell death) in many cancer cell lines. Both the hydrophobic and hydrophilic pomegranate fractions appear to possess selective apoptotic potential with respect to different hormone-independent cancer cell lines, suggesting chemotherapeutic potential for compounds originating from each of these pomegranate compartments.

Recent investigations have shown that pomegranate-derived components may be capable of suppressing metastasis. For instance, cold-pressed pomegranate seed oil inhibited the invasion of estrogen-sensitive MCF-7 human breast cancer cells *in vitro* across an artificial Matrigel^{TM} membrane. In addition, pomegranate seed oil, pomegranate peel extract, and fermented pomegranate juice each resulted in 60% suppression of invasion, in Matrigel^{TM}, of androgen-negative PC-3 human prostate cancer cells. Synergistic effects were seen when equal amounts of any two of the pomegranate seed oil, pomegranate peel extract, or fermented pomegranate juice were combined, such that the combination resulted in a 90% suppression of invasion.

Inhibition of angiogenesis (blood vessel formation), first suggested by Avicenna who noted that cancer "can be arrested with anything, it can be so by vigorous excision ... including all the blood vessels supplying the tumor so that nothing of these will be left.", is still a promising therapeutic approach for treating solid tumor afflicted patients. Recent studies indicate that *Punica granatum* possess

antiangiogenic properties. Thus, *in vivo* angiogenesis in chicken chorioallantoic membrane (CAM) was significantly suppressed by fermented pomegranate juice. Proangiogenic vascular endothelial growth factor (VEGF) was potently downregulated in MCF-7 estrogen-dependent breast cancer cells, less so in estrogen-negative MDA-MB-231 breast cancer cells, and most strongly in MCF-10A immortalized normal breast epithelial cells by fermented pomegranate juice and pomegranate seed oil. The antiangiogenic migration inhibitory factor (MIF) was potently upregulated in MDA-MB-231 cells by fermented pomegranate juice and pomegranate seed oil, which also moderately suppressed human umbilical vein endothelial cell proliferation and tubule formation [46].

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CHAPTER 13

Modern *In Vitro* Test Systems

13.1 INTRODUCTION

Herbal-derived compounds need a deep assessment of their pharmacological qualities and safety issues due to the widespread and growing use of herbal-derived medicines all over the world, which cannot rely only on traditional or supposed millenarian beliefs. *In vitro* and *in vivo* studies are useful and complementary in the acquisition of reliable data both for health caregiver and patients. Currently, the development of new drugs (e.g., herbal-derived drugs) is suffering from two major limitations. First, none of the animal species or *in vitro* test system can properly mimic the complexity of the human body. Treatment with new developed drugs can have unprecedented positive or negative effects involving systemic interactions specific to humans. This phenomenon was first described by Avicenna (980–1037). In his *Canon*, he laid out the following rules for testing the effectiveness of a new drug or medication [1]. These principles still form the basis of modern clinical drug trials.

1. The drug must be free from any extraneous accidental quality.
2. It must be used on a simple, not a composite, disease.
3. The drug must be tested with two contrary types of diseases, because sometimes a drug cures one disease by its essential qualities and another by its accidental ones.
4. The quality of the drug must correspond to the strength of the disease. For example, there are some drugs whose heat is less than the coldness of certain diseases, so that they would have no effect on them.
5. The time of action must be observed, so that essence and accident are not confused.
6. The effect of the drug must be seen to occur constantly or in many cases, for if this did not happen, it was an accidental effect.
7. The experimentation must be done with the human body, for testing a drug on a lion or a horse might not prove anything about its effect on man.

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The later role implies that only clinical studies in humans can provide the final proof of the efficacy and toxicity (e.g., possible side effects) in man.

Second, significant drawbacks, such as severe adverse effects, often occur after drugs have entered the market. There are increasing indications that specific genetic predisposition is one of the key reasons for these high-profile recalls.

At present, the assessment of side effects of a new drug can only be measured by using *in vitro* systems to a limited extent. Although many advanced *in vitro* systems are available that allow prediction of the local effects of test compounds, yet even the most sophisticated *in vitro* test cannot be used to measure systemic effects (e.g., blood pressure or fever). Culturing cells is the most widely used *in vitro* method in pharmacology, toxicology, and biomedical research. In general, *in vitro* test systems represent the first phase of the evaluation procedure. The *in vitro* cell culture methods have the advantage of relatively well-controlled variables and are generally accepted as a very effective method for safety testing. Advantages of these systems over classical methods, such as long-term studies on experimental animals, include relatively well-controlled variables, decreased costs, a reduced time to completion, and reduced numbers of animals necessary to complete the study. Given the well-known problems of using two-dimensional cell cultures pharmaceutical test systems, more realistic three-dimensional tissue constructs are required in order to create more "*in vivo*"-like cell culture conditions, where cells and tissues do not exist in isolation but communicate with and are interdependent of neighboring tissue. The breakthrough might be to develop human three-dimensional *in vitro* test systems and tissue equivalents that could serve as *in vitro* model systems during the initial stages of drug discovery [2]. This chapter will provide an overview of *in vitro* test methods used both for preclinical toxicity and efficacy studies.

13.2 CELL CULTURE

Cell culture is the maintenance of prokaryotic, eukaryotic, or plant cells under controlled conditions. In practice, the term "cell culture" has come to refer to the culturing of cells derived from multicellular eukaryotes, especially animal cells. Cells are cultured in a monolayer on treated polystyrene (tissue culture polystyrene, TCPS) in the presence of nutrient-rich basal media (e.g., DMEM, RPMI 1640) that has been supplemented with animal sera (e.g., fetal calf serum). The historical development and methods of cell culture are closely interrelated to those of tissue culture and organ culture. Animal cell culture became a common laboratory technique in the 1950s, but the concept of maintaining live cell lines separated from their original tissue source was discovered in the nineteenth century [3–5]. The main advances of such test systems over the *in vivo* test systems include the following:

- Study of cell behavior without the variations that occur in animals
- Control of the growth environment leads to uniformity of sample; cells from one cell line are homogenous and have same growth requirements

- Characteristics of cells can be maintained over several generations, leading to good reproducibility between experiments
- Cultures can be exposed to reagents, for example, radio-chemicals or drugs at defined concentrations
- Use of animals is reduced
- They avoids the legal, moral, and ethical problems of animal experimentation

However, removal of cells from their *in vivo* environment means removing the cell–cell interactions, cell–substrate interactions, hormones, growth factors, support structures, and various other chemicals that the cells interact with *in vivo*. This fact makes it nearly impossible to recreate the *in vivo* environment. The limitations of *in vitro* systems include the following:

- The artificial conditions could cause cells to dedifferentiate, which will cause them to behave differently and produce proteins other than it would *in vivo*
- Cells that are cultured directly from a subject are known as primary cells; with the exception of some derived from tumors, most primary cell cultures have limited life-span
- After a certain number of population doublings, cells undergo the process of senescence and stop dividing, while generally retaining viability
- Systemic effects and side effects cannot be measured
- Pharmacokinetic effects cannot be tested
- Interactions between tissues cannot be evaluated
- Chronic effects cannot be studied

Currently, *in vitro* systems serve as the basis for studying of drugs and other compounds. In general, they are used for screening purposes and in mechanistic studies, for example, studying the action mechanism of a drug in a specific tissue or cell type. Although animal tests are more time-consuming and associated with legal, moral, and ethical problems, until today only studies in animals can be used to measure systemic effects of test compounds. However, it is important to mention that only clinical studies in humans can provide the final proof of the efficacy and toxicity (e.g., possible side effects) in humans. This principle was first described by Avicenna, who established the following role in testing a new drug: "*The experimentation must be done with the human body, for testing a drug on a lion or a horse might not prove anything about its effect on man*."

At present, the assessment of side effects of a new drug can only be measured by using *in vitro* systems to a limited extent. Although some modern three-dimensional *in vitro* systems are available (e.g., skin three-dimensional cultures) that allow prediction of the local effects of test molecules, even the most sophisticated *in vitro* test cannot yet be used to measure systemic effects (e.g., blood pressure or fever). *In vitro* research of a new pharmaceutical can start with a simple model while the model can become more complex at later stages. The best sequence is to start with cell lines,

then primary isolated cells, cocultures, and finally three-dimensional cell culture systems.

The optimal *in vitro* test system in a given situation depends on a number of factors, such as *in vivo* resemblance, expense, availability of the model, and ethical considerations. *In vitro* data from human and animal models can be used to choose the best *in vivo* model (e.g., mouse, rat, dog) for further testing. In conclusion, it can be stated that an *in vitro* model is always a compromise between convenience and relevance. Current guidelines by the FDA and the European Union Drug Regulatory Authorities for human drug development allow *in vitro* systems to be used in supportive studies, and therefore *in vitro* data should be used mainly qualitatively. For example, when *in vitro* results show a lack of drug–drug interaction, no *in vivo* experiments have to be performed, but when a drug–drug interaction is demonstrated, then *in vivo* experiments have to be conducted. A complete replacement of animal experiments by *in vitro* models in the near future seems to be an unrealistic scenario, because a lack of validation prevents acceptance by regulatory authorities.

13.3 ISOLATION OF CELLS

Cells can be isolated from organs/tissues for *in vitro* culture in several ways. They can be easily purified from blood; however, only the white cells are capable of growth in culture. Most other cells can be isolated from intact tissues by enzymatic digestion with enzymes such as collagenase, trypsin, or pronase, which break down the extracellular matrix. Alternatively, pieces of tissue can be placed in growth media, and the cells that grow out are available for culture. This method is known as explants culture. There are two types of cultured cells: primary isolated cells and continuous cell lines. Figure 13.1 summarizes the major *in vitro* cell culture systems and cell isolation techniques used.

Primary cultures are derived directly from excised, normal animal tissue and cultured as adherent cell monolayer or as a single cell suspension. The preparation of primary cultures is labor intensive and they can be maintained *in vitro* only for a limited period of time. During their relatively limited life-span, primary cells usually maintain many of their differentiated characteristics of the intact tissue. A primary cell culture can be obtained either by allowing cells to grow out of fragments or by disaggregating the tissue mechanically or enzymatically to produce a single cell suspension. The first method is convenient for the isolation of various cell types, such as osteoblasts. We have used this method for the isolation of rat tibia osteoblasts and found that cells isolated by this method were nearly 100% pure when examined by microscopic analysis and by indirect immunofluorescence with antiosteocalcin antibodies reacting specifically to osteoblasts [4,5].

For the digestion of tissue, trypsin and collagenase are the most frequently used enzymes. Collagenase gives incomplete disaggregation but is less harmful than trypsin, which gives the most complete disaggregation but may damage the cells [3]. Collagenase digestion is a convenient method for the isolation of certain cell types, for example, chondrocytes, hepatocytes, and keratinocytes. For example, primary

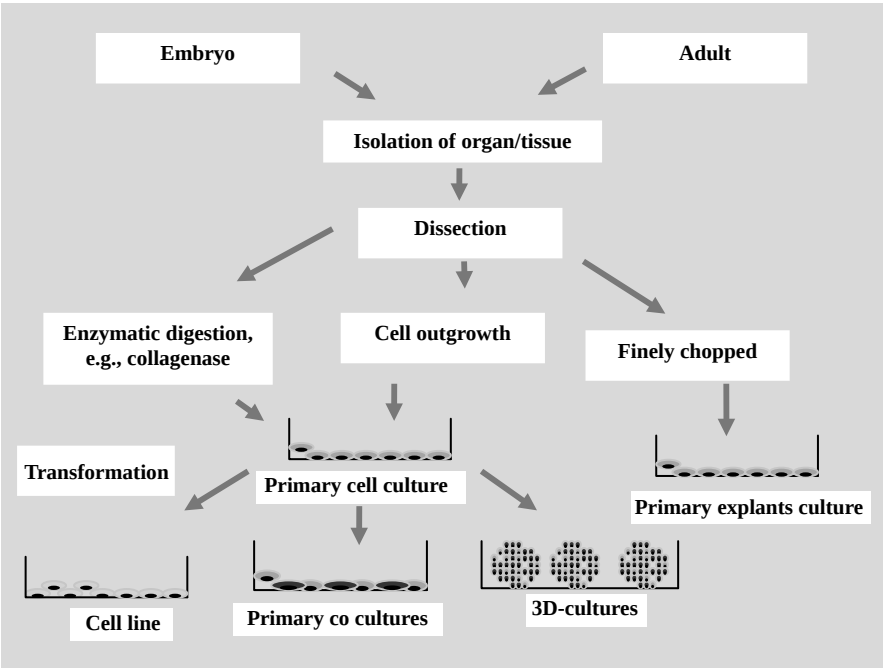

FIGURE 13.1 An overview of cell culture systems used in the development of drugs, for example, herbal-derived drugs. There are five types of cell cultures: primary cell culture, primary explants cultures, cell lines, cocultures, and three-dimensional cell cultures. Current *in vitro* cell culture technologies present some limitations as they cannot simulate or mimic *in vivo* situations.

xiphoid chondrocytes and primary hepatocytes are usually isolated in our laboratory from 4 to 6 months old male Sprague-Dawley rats by collagenase digestion. Cells isolated by this method exhibit a mean viability of more than 85% [4]. Primary isolated cells can be either maintained as monolayer of one cell type or as a coculture of two different cell types (e.g., hepatocytes and Kupffer cells for liver test; keratinocytes and fibroblasts for skin tests) (Figure 13.2).

Continuous cultures comprised of cells that can be propagated indefinitely generally have this ability because they have been transformed into tumor cells. Tumor cell lines are often derived from actual clinical tumors, but transformation may also be induced using viral oncogenes or by chemical treatments. Transformed cell lines present the advantage of almost limitless availability, but the disadvantage of having retained very little of the original *in vivo* characteristics. There are numerous well-established cell lines representative of particular cell types (Figure 13.1).

13.4 MAINTAINING CELLS IN CULTURE

Mammalian cells are usually grown and maintained at an appropriate temperature and gas mixture (typically, 37°C, 5% CO_2, and 100% humidity) in a cell incubator. Culture

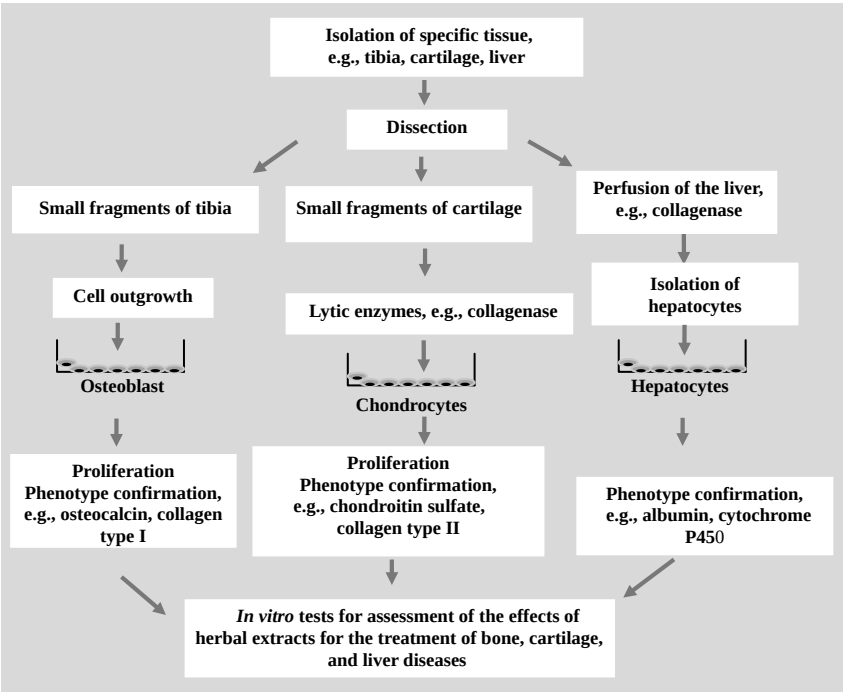

FIGURE 13.2 Isolation and cultivation of primary cell cultures. There are two main methods for isolation of primary cell cultures: cell outgrowth methods and enzymatic digestion methods. After isolation and proliferation the cell phenotype has to be confirmed prior to using the cultures in *in vitro* tests.

conditions vary widely for each cell type, and variation of conditions for a particular cell type can result in different phenotypes being expressed. Aside from temperature and gas mixture, the most commonly varied factor in culture systems is the growth medium. Recipes for growth media can vary in pH, glucose concentration, growth factors, hormones, vitamins, and the presence of other nutrients. The growth factors used to supplement media are often derived from animal blood, such as calf serum. Typically, media are supplemented with 10% (v/v) inactivated fetal calf serum, 1% nonessential amino acids, 1% glutamine, 100 U/mL penicillin, and 10 μg/mL streptomycin [3,4].

13.5 CULTURE MORPHOLOGY

Cells can be grown in suspension or adherent cultures. Some cells naturally live in suspension, without being attached to a surface, such as white blood cells. There are also cell lines that have been modified to be able to survive in suspension cultures so that they can be grown to a higher density than adherent conditions would allow.

Adherent cells require a surface, such as tissue culture plastic, which may be coated with extracellular matrix components to increase adhesion properties and provide other signals needed for growth and differentiation. Most cells derived from solid tissues (e.g., liver, kidney) are adherent. Another type of adherent culture is organotypic culture, which grows cells in a three-dimensional environment as opposed to two-dimensional culture dishes. This three-dimensional culture system biochemically and physiologically best resembles the intact tissue, but is technically challenging to maintain as a result of many factors such as diffusion, growth factors, and oxygen tension.

Attached cells can be classified as endothelial, epithelial, neuronal, or fibroblasts. Cell morphology is an essential function of a cell that has become adherent to a surface, and precedes cell proliferation to give a cell-covered surface. The final morphology of the cells, which involves complex cytoskeletal reorganization, depends on the chemical and physical properties of the substrate to which cells are attached. Conventionally, cells are cultured as monolayers on TCPS. In addition to substrate properties, the cell density influences the final morphology of the cells. For instance, subconfluent fibroblasts from hamster kidney or human lungs assume multipolar or bipolar shapes and are well spread on the culture surface, but at confluence they are bipolar and less well spread. Mouse fibroblasts from 3T3 cell line and human glial cells grow like multipolar fibroblasts at low cell density but become epithelial-like at confluence. Hence, comparative observations should always be made at the same stage of growth and cell density, and after growing on the same substrate [3]. The effect of the substrate on cell shape and function is well documented for cultured hepatocytes. It is well known that cell shape and maintenance of liver-specific functions in long-term cultures are drastically affected by the substratum to which they are attached. Hepatocytes cultured on collagen type I attach individually and spread rapidly, whereas cells seeded on crude membrane fractions or matrigel form irregular, more three-dimensional structures. Although, hepatocytes attach efficiently to collagen type I and remain viable on this substratum, they are unable to maintain the expression of many liver-specific functions, as demonstrated for other major components of basal membranes, including type IV collagen, laminin, or fibronectin. The appearance of the cells cultured on crude membrane fractions or matrigel indicates that cell–cell interactions are enhanced under these conditions. Observation of cell morphology is a simple and direct technique to identify cells. Cell morphology can be assessed, for example, by quantitative scanning electron. Another convenient method to analyze cell morphology is phase-contrast microscopy, which can be applied for transparent substrates [3,4].

13.6 CELL PURITY AND PHENOTYPE

Removal of cells from their microenvironment in the intact tissue means removing the cell–cell interactions, cell–substrate interactions, hormones, growth factors, support structures, and various other paracrine and autocrine factors that regulate cell functions, for example, proliferation, growth, and metabolic activities. After

TABLE 13.1 Phenotype Characterization

Cell Type	Phenotype Markers	Test Methods
Fibroblasts	Collagens, fibronectin	ELISA, hydroxyproline assay; ELISA
Hepatocytes	Albumin, macroglobulin	ELISA
	Cytochrome P450	HPLC, spectrophotometry
Endothelials	Collagen type IV, factor VIII antigen	ELISA, enzyme reaction
Chondrocytes	Collagen type II	ELISA, hydroxyproline assay
	Chondroitin sulfate	ELISA, Alcian blue
Osteoblasts	Collagen type I ELISA, hydroxyproline assay	
	Osteocalcin	ELISA, immunofluorescence
	Alkaline phosphates	Spectrophotometry, ELISA
Macrophages	Nitric oxide	Griess reaction
	TNF-α	Bioassay, ELISA
	Phagocytosis	TEM, confocal microscopy, phase contrast microscopy
Keratinocytes	Keratins (K10 and K14), involucrin, epidermal transglutaminase	ELISA
Myoblasts	Desmin	ELISA

isolations, cells are cultured under artificial cell culture conditions. These artificial conditions could cause cells to dedifferentiate which will cause them to behave differently and produce proteins other than it would *in vivo*. Since many cell types lose their differentiated phenotype after some serial passages *in vitro*, it is important to evaluate the purity and the specific phenotype of the cells prior to starting the *in vitro* testing. Table 13.1 lists phenotype markers of some commonly used cell types.

The cell phenotype can be confirmed by a number of tests. For example, in our laboratory we assess the chondrocyte phenotype by measuring the synthesis of collagen type II, the production of cartilage-related proteins such as chondroitin sulfate, and by measuring the morphological appearance of the cells. We used these mature chondrocytes, which were isolated from mature rats (4–6 months old) and had undergone four or five serial passages prior to seeding on a three-dimensional cell carrier (DegraPol-foam). The amount of collagen type II and chondroitin sulfate production per cell remained constant with time for chondrocytes cultured on the three-dimensional cell carrier, indicating that mature chondrocyte were also able to preserve their phenotype when maintained under appropriate culture conditions [6,7]. The osteoblast phenotype is checked by assessing the alkaline phosphates activity and the production of collagen type I and osteocalcin. Hepatocytes phenotype is assessed by measuring the levels of albumin and the cytochrome P450.

13.7 OXYGEN TENSION AND MEDIUM SUPPLEMENTS

The importance of the culture conditions including oxygen tension (i.e., concentration) and medium supplements for *in vitro* cell culture systems have been discussed in

detail by Freshney [3]. A brief synopsis of the importance of culture conditions on hepatocytes, as a model for studying hepatotoxicity and efficacy of liver active substances, is given here.

Investigations of the cellular and molecular mechanisms underlying the functional differences between periportal and pericentral hepatocytes would provide a better understanding of the regulation of processes involved in xenobiotic metabolism as well as of degenerative and regenerative changes. Since the phenotype preservation is crucial in hepatotoxicity and efficacy testing of liver active substances, it is important to maintain the cells in an "*in vivo*-like" culture conditions. The observed heterogeneous expression and induction of metabolism within the liver acinus, is most likely related to differences in the microenvironment of the hepatocytes, such as gradients in oxygen tension, hormones, extracellular matrix components, nonparenchymal cells, and effective exposure levels of xenobiotics from the periportal (pp) to the pericentral (pc) compartment. For instance, most of the cytochrome P450 isoenzymes are heterogeneously distributed within the liver lobules with the highest constitutive expression in the pericentral parenchymal cells. The major phenobarbital (PB) inducible cytochrome CYP2B1/2 protein is induced predominantly in the pericentral region after low-dose treatment, whereas this isoenzyme is also induced in the periportal area after rather high doses of PB. The individual factors responsible for this regio-specific expression are largely unknown. Investigations cannot be carried out *in vivo* because the physical and chemical factors determining liver zonation are experimentally difficult to distinguish. Furthermore, the sequential passage of drugs entering the liver lobule at the periportal area makes it difficult to estimate the actual concentration at the pericentral area, and in addition, metabolites formed at the periportal area subsequently migrate to the pericentral area. Therefore, the influence of physical and chemical factors, such as oxygen tension, insulin, and glucagon, on xenobiotic metabolisms can be best investigated in cell cultures where the exposure levels of the test compound and other factors responsible for the zone-specific enzyme induction can be controlled.

There are three major factors contributing to gradients from the pp toward the pc zone; oxygen tension, glucoregulatory hormone content, and exposure levels of the test compound [8,9]. In the portal area, cells receive their oxygen from mixed arterial and hepatic portal blood. Tissue oxygen tension is therefore higher than the pericentral area; gluconeogenesis, β-oxidation, and glycogenolysis are predominant and the oxidative xenobiotic metabolism is moderately developed. It has been postulated that during cellular aging or maturation, individual hepatocytes leave the portal area and enter the functional zone with low oxygen tension (4% O_2) so that metabolism shifts to liponeogenesis and glycogen synthesis. Similarly, tissue oxygen tension may also be a critical parameter for the observed zonation of xenobiotic metabolism within the liver lobule.

In efficacy testing, where long-term hepatocyte cultures are required, an approximation of periportal- or pericentral-equivalent oxygen tensions can be achieved by culturing hepatocytes in Teflon membrane dishes, in incubators with a 13% O_2 (pp) or a 4% O_2 (pc) atmosphere [8,9], respectively. It was shown that tissue oxygen tensions modulate the chemically induced mitogenic activity similarly to that expected from

periportally or pericentrally derived hepatocytes. Hepatocytes cultured in dishes coated with crude liver membrane preserved their liver-specific functions and xenobiotic metabolism in cultures with tissue oxygen tension for up to 9 days [10]. Using these culture conditions, it was further demonstrated that hepatocytes, in combination with the glucoregulatory hormones insulin and glucagon, adapt their glucose metabolism to that of the corresponding liver region. Glucagon stimulates gluconeogenesis predominantly in the periportal region and insulin supports glycolysis at higher capacity in the pericentral region. The pericentral zone is exposed to a higher insulin/glucagon ratio than the periportal zone [8–10].

13.8 SEEDING DENSITY

After reaching optimal cell density by serial passages and phenotype confirmation, *in vitro* cell tests can be performed. In general, seeding density is important for normal cell function, especially if cell–cell communications must be established, either by direct cell–cell contacts or via the paracrine secretion of trophic factors by the cells. It is well known that cells seeded at high cell density preserve their phenotype at higher levels than cells seeded at low cell density and the proliferation capacity is reduced at high cell density. Many cell types exhibit an inverse relationship between growth and differentiation *in vitro* [3]. Investigations of osteoblast developmental stages [4] indicate that, proliferating osteoblasts express decreased levels of their typical phenotypic activities during periods of rapid growth as well as cell replication slowed down, the cells began to produce more ALP and other markers of osteoblastic phenotype. Similar results were obtained in our group [4]. Osteoblasts cultured on TCPS demonstrated up to day 8 higher alkaline phosphatase (ALP) activity than on the three-dimensional DegraPol-foam. In contrast, after 12 days in culture, cells cultured in the three-dimensional DegraPol-foam showed higher ALP activity than on the two-dimensional TCPS. This observation is due to the fact that cells cultured on the polymer foam have lower cell density than on TCPS and, therefore, have a prolonged proliferation time. The optimal cell density depends on the biological endpoints to be measured. If one intends to measure effects of a drug on the metabolic activity of the cells, then it is important to use cells at high cell density (nearly 100% confluence). In contrast, nonconfluent cultures have to be used in case we intend to assess mitogenic/carcinogenic effects of a test pharmaceutical.

13.9 THREE-DIMENSIONAL CULTURE SYSTEMS

In order to obtain reliable results of toxicity and efficacy testing *in vitro*, it is crucial to perform the experiments under "*in vivo*-like" cell culture conditions. The expression of specific phenotype within the tissue in *in vivo* is regulated by autocrine, paracrine, and endocrine factors, and by cell–cell and cell–substrate interactions. Therefore, it is important to culture the cells under conditions where homogenous (monocultures) and heterogeneous (cocultures) cell–cell interactions are maintained at high levels.

Therefore, cell type, seeding density, and culture conditions are important factors in *in vitro* testing and, therefore, have to be taken into account prior to *in vitro* testing [2–4,11].

In vitro two-dimensional cell culture technologies, which lack a three-dimensional scaffold to support cell growth and proper tissue function, present some limitations, as they are not able to mimic *in vivo* cellular conditions. It is well known that the majority of vertebrate cells cultured *in vitro* have been grown as monolayer on artificial substrate. However, it has long been realized that while growth in two dimensions is a convenient way of preparing and observing a culture and allows a high rate of cell proliferation, it lacks the cell–cell and cell–substrate interaction characteristic of whole tissue *in vivo*. The cell-to-substrate interactions have been shown to influence the cell behavior. One impressive example demonstrating the significance of the environment is the finding that ectopic implantation of embryonic cells can transform them to malignancy and gives rise to cancer, whereas the same cells lead to normal embryogenesis in the uterus; conversely, teratocarcinoma cells may undergo normal development when implanted into an embryo. Many effects of the substrate on the cells, including cell shape, cell adhesion, cell proliferation, cell movement, and cell differentiation can be studied *in vitro* using appropriate cell culture system.

Currently, the available conventional TCPS are not suitable to form tissue-like aggregates *in vitro*, which require high cell density. Therefore, the engineering of a new generation of substrates that enables cultured cells to grow in three-dimensional conditions with higher cell density and *in vivo* like cell–cell interactions is one possible way to overcome the limitations of two-dimensional conditions.

At present, research on three-dimensional cell systems is more vital and productive than ever. The potential of three-dimensional cell cultures is currently being exploited in so many areas of biomedical research that it is impossible to review all aspects of these studies completely. Nevertheless, one reason for the recent progress in research on multicell systems may be the increasing interaction between researchers working in different fields of cell biology and biomedical science and using similar three-dimensional culture techniques. One major advantage of three-dimensional cell cultures is their well-defined geometry, which makes it possible to directly relate structure to function and which enables theoretical analyses, for example, of diffusion fields. Consequently, the most promising data on these cultures may be obtained with techniques allowing for spatial resolution. Combining such approaches with molecular analysis has clearly demonstrated that, in comparison with conventional cultures, cells in three-dimensional cultures more closely resemble the *in vivo* situation with regard to cell shape and cellular environment, and shape and environment can determine gene expression and the biological behavior of the cells. From a critical point of view, it should be kept in mind that the complexity of three-dimensional cell systems is not only an advantage but also a limitation. There will always be a number of questions that can only be answered by investigations using single cells or cell-free systems. At the same time, three-dimensional cultures cannot completely replace the testing of biological mechanisms for their relevance *in vivo*, for example, in knockout animals. Over the past two decades, with the help of tissue engineering techniques

many biomaterials have been introduced as carrier for three-dimensional cell constructs.

Tissue engineering products have huge potentials for regenerating medicine. Meanwhile, the technology developed in this field can also be utilized to create a highly *in vivo*-like microenvironment for *in vitro* applications, such as drug discovery and development, disease models, and personalized clinical drug testing in various cell-based platforms. For example, in drug discovery, cell-based assays are increasingly used for drug target validation and drug ADMET (absorption, distribution, metabolism, elimination, and toxicity) studies because cells can give more representative responses to drugs than simple molecular assays and are easier to use in a high-throughput format than animals. However, there are intrinsic drawbacks with conventional *in vitro* cellular tests using two-dimensional cultures, which lack a three-dimensional scaffold to support cell growth and proper tissue function, and thus are not able to mimic *in vivo* cellular conditions. There have been an increasing number of research studies addressing this difference. However, a big challenge in three-dimensional tissue culture is the mass transport barrier within the tissue construct, resulting in a limited nutrient supply and accumulated metabolic waste. Therefore, the authentic cellular response to the tested drug may be camouflaged by the limitations of a metabolic environment. This, however, could be alleviated via perfusion culture. For this purpose, the combination of tissue engineering and microfluidic techniques provides an effective strategy for such applications. Below, three-dimensional cultures on DegraPol will be discussed as a model for three-dimensional cultures (Figure 13.13).

DegraPol-Foam as Cell Carrier for Three-Dimensional Cell Cultures: DegraPol represents a versatile biodegradable class of multiblock copolymeric elastomers. This polymer has been developed for use as scaffolds for tissue engineering as well as for implantable medical devices. DegraPol-foam is a biodegradable, elastic, and open porous (pore size 200–400 μm) cell carrier (Figure 13.3) [4,6,7]. The compatibility of this structure as cell carrier for creation of three-dimensional cell cultures is evidenced by the following.

To examine the possible use of DegraPol-foams in the bone healing process, and as cell carrier for *in vitro* studies, primary isolated rat osteoblasts, osteoblast cell line MC3T3-E1, osteoblasts from the human cell line HF01, primary isolated bovine chondrocytes, primary isolated rat hepatocytes, peritoneal rat macrophages, keratinocytes from the human cell line HaCat, and primary isolated rat tenocytes were used. Cell adhesion, cell growth, and expression of specific phenotype were determined in cells seeded on DegraPol and compared to cells cultured on conventional TCPS. Figure 13.4 summarizes data obtained.

Cell Adhesion: The number of attached, viable cells 2 h after cell seeding was taken as an indicator for cell attachment. Compared to control cells cultured on TCPS, rat osteoblasts and osteoblast cell line MC3T3-E1 attached on the polyester urethane to about 140% and 200%, respectively (Figure 13.4).

Cell Growth: Rat osteoblasts proliferated with slightly lower doubling times (5 days) on DegraPol-foam than on TCPS (6.2 days). In contrast, osteoblast cell

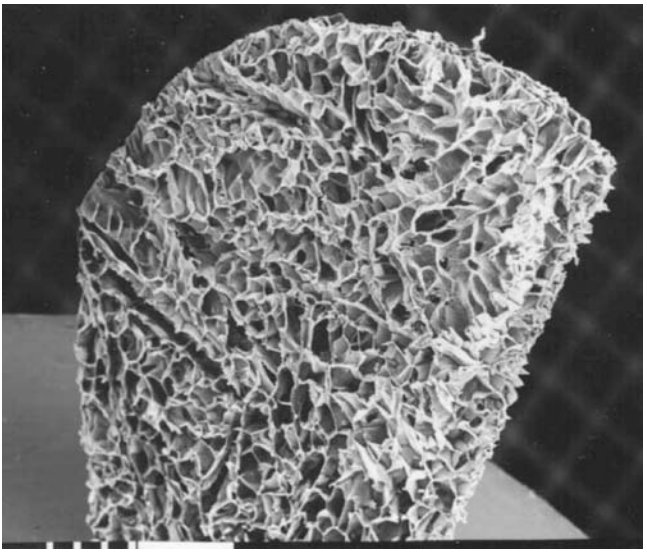

FIGURE 13.3 Scanning electron micrographs of DegraPol-foam, a biodegradable, elastic, and open porous (pore size 200–400 µm) cell-carrier.

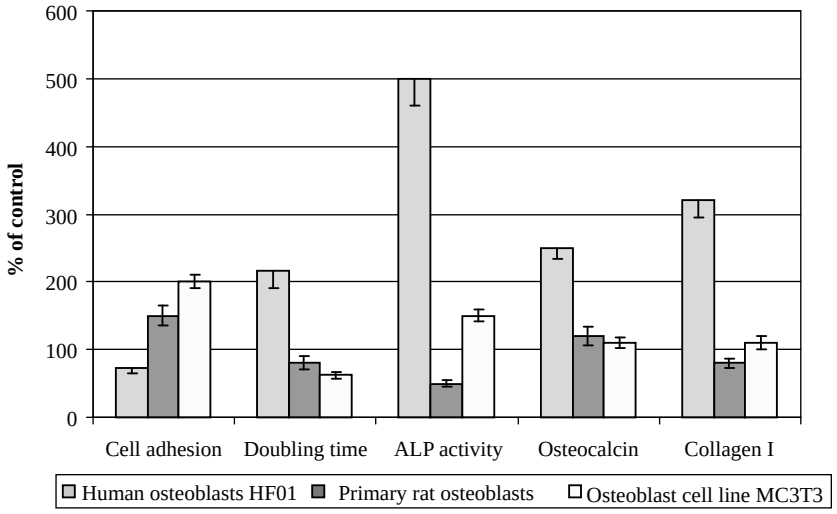

FIGURE 13.4 Cell adhesion, cell growth, and phenotype expression in three cell types of osteoblasts cultured on DegraPol-foam. Values given represent the mean (as % of TCPS); error bars indicate the estimated standard deviation.

lines proliferated at higher doubling rates on the polymer (5.4 days) than on TCPS (8.8 days) (Figure 13.4).

Phenotype Preservation: In addition to cell attachment and cell growth, it is important that the attached cells maintain their specific functions. Cells cultured on the DegraPol-foams expressed higher ALP activity compared with TCPS at day 12. Osteoblasts from the human cell line expressed fivefold higher ALP levels compared to cells cultured on TCPS. Similar data were obtained with osteocalcin and collagen type I determinations (Figure 13.4).

Cell Morphology: Figure 13.5 shows scanning electron micrographs of osteoblasts cultured on the DegraPol-foam. Eight days after cell seeding, osteoblasts exhibited a

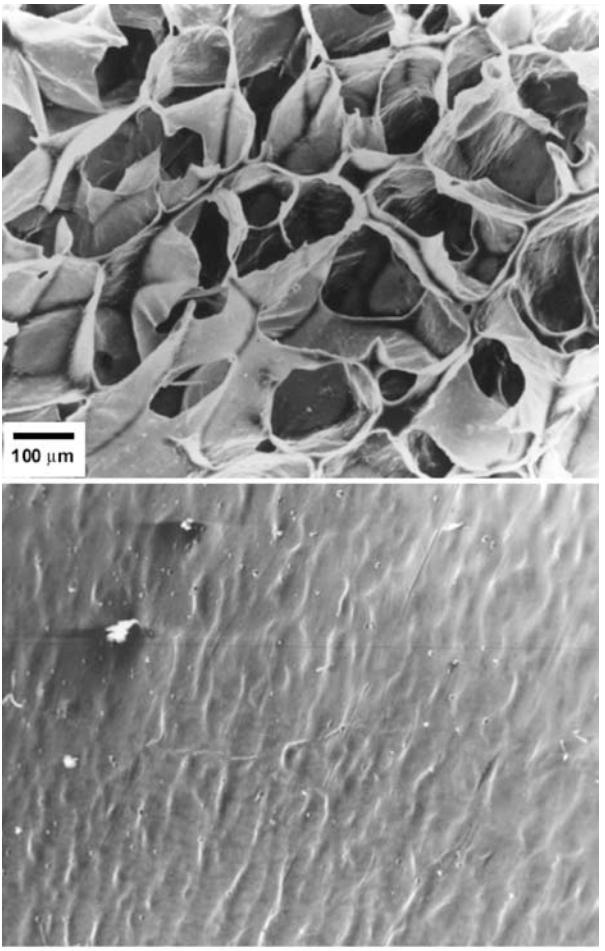

FIGURE 13.5 Scanning electron micrographs of osteoblasts (right) cultured on DegraPol-foam (lift) for 8 days.

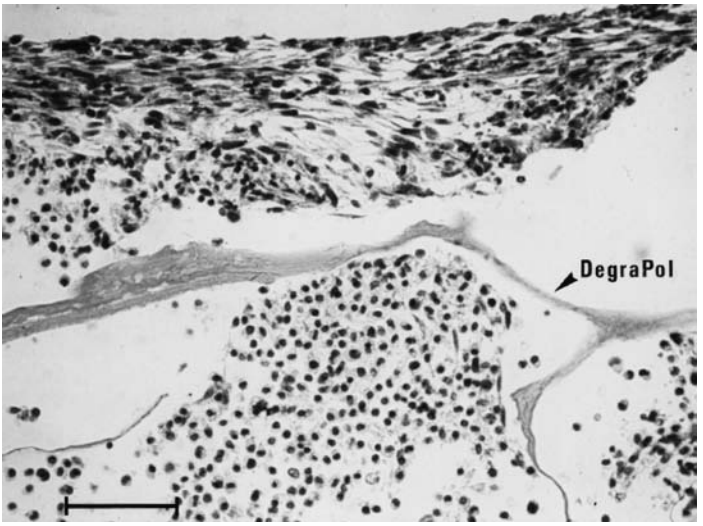

FIGURE 13.6 Histological cross-section of osteoblasts cultured for 8 days on DegraPol-foam. Original magnifications 200×.

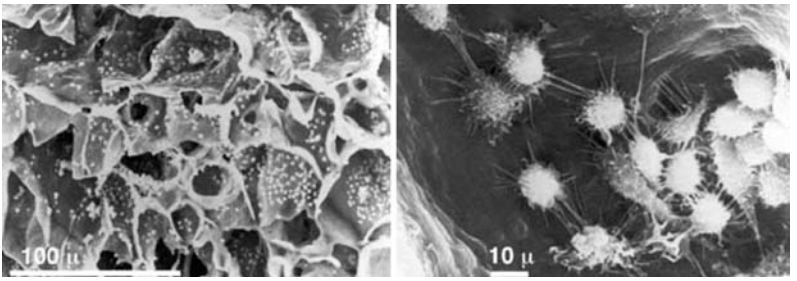

FIGURE 13.7 Scanning electron micrographs of macrophages cultured on DegraPol-foam for 4 days.

confluent cell multilayer on the surface and migrated into the pores of the DegraPol (Figure 13.6). Figure 13.7 shows electron micrographs of macrophages cultured on the DegraPol-foam.

13.10 CELL AND TISSUE CULTURE SYSTEMS USED IN PHARMACOLOGY AND TOXICOLOGY

The development of a new drug always involves a preclinical screening stage. During this stage, the main pharmacological and toxicological properties of the test drug are assessed. The preclinical investigation is based on both *in vitro* models and *in vivo* experiments in various animal species. Cell culture systems are the most widely used

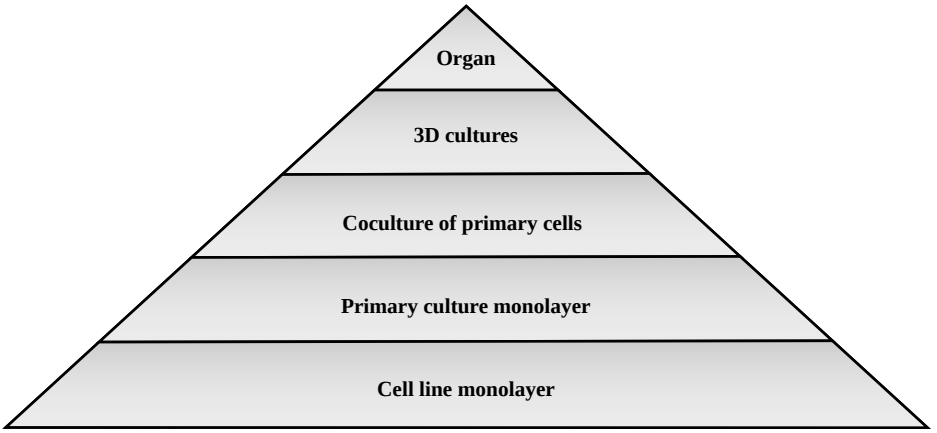

FIGURE 13.8 *In vitro* test systems used in biological and biomedical research. Cell line monocultures represent convenient test systems that are easy to handle and can be obtained from cell banks. Primary isolated cells preserve the tissue-specific phenotype. Tissue-specific functions are best preserved in coculture and three-dimensional culture systems.

in vitro method in pharmacology and toxicology, with cells being used either as continuous cell lines or as primary isolated cells. Cocultures of two or more cell types preserve tissue-specific phenotype at higher levels (Figure 13.2). Two examples of this are hepatocytes and Kupffer cells in *in vitro* liver model or keratinocytes and fibroblasts in skin models. Cell can be cultured under "*in vivo*-like" three-dimensional cell culture conditions in which the specific functions are highly preserved (Figure 13.8).

Other examples are the human skin models consisting of keratinocytes and fibroblasts cultured on three-dimensional cell carrier. These models are commercially available and have been used successfully to assess the efficacy and biosafety of new drugs. Usually, cell culture systems are used initially for screening purposes and in investigation of action mechanisms and cell and tissue specificity of drug. One of the major limitations of *in vitro* test systems is that these systems do not permit the assessment of systemic and side effects. Currently, the assessment of side effects and systemic effects can only be monitored in animals. Many biological endpoints can be measured *in vitro* using appropriate cell and tissue. Table 13.2 summarizes the main endpoint, which can be assessed *in vitro*.

13.11 *IN VITRO* LIVER MODELS IN TOXICITY TESTING

The liver is the predominant organ in which detoxification and biotransformation of xenobiotics (foreign substances) take place, although other organs may also be involved in pharmaceutical biotransformation. Most reports of toxic effects due to the use of herbal medicines and dietary supplements are associated with hepatotoxicity,

TABLE 13.2 Common Biological Tests Assessed by *In Vitro* Test Methods

Biological Endpoint	Measurement	*In Vitro* Test Methods
Cell adhesion	Attachment to cell carrier	Total DNA, total protein
	Detachment from carrier	MTT test
	Cell–cell adhesion	Counting the cell number
Cell proliferation	Cell counting	DNA (e.g., Hoechst 33342), protein (e.g., Biorad), MTT test
	Total protein content	
	Total DNA content	Counting the cell number
Cell morphology	Cell size and shape	SEM, TEM, phase contrast microscope
	Cell–cell contacts	
	Nuclear or cytoplasmic vacuolation	
Cell viability	Membrane integrity	MTT, neutral red, Amido black, Trypan blue dye exclusion
	Mitochondrial activity	
Membrane leakage	Membrane integrity	LDH, Trypan blue
Phagocytosis	Uptake of foreign bodies	TEM, confocal microscopy
Cell metabolism	Mitochondrial activity	MTT assay
	Cell specific functions, e.g., albumin production in the liver	ELISA test
Cytotoxicity	Cytotoxic effects of test molecules	DNA, protein, flow analysis, cell morphology, neutral red
Inflammation	Proinflammatory and anti-inflammatory cytokines	ELISA tests for cytokines, e.g., TNF-α, IL-6, IL-10
Apoptosis	DNA fragmentation	Gel-electrophoresis
	Bcl gene expression	PCR
Necrosis	Cell membrane integrity	LDH assay, Trypan blue assay
Antioxidant	Lipid peroxidation	Malondialdehyde (MDA) assay
	Glutathione	GSH levels

although reports of other toxic effects including kidney, nervous system, blood, cardiovascular, and dermatologic effects, mutagenicity, and carcinogenicity have also been published in medical literature. Hepatic impairment resulting from the use of conventional drugs is widely acknowledged, but there is less awareness of the potential hepatotoxicity of herbal preparations and other botanicals, many of which are believed to be harmless and are commonly used for self-medication without supervision. The reported toxicity of herbal formulations may be the result of several factors, including the contamination with pesticides, microbes, heavy metals, toxins, or adulteration with orthodox drugs. On the basis of various case reports, the liver injury from herbal remedies has ranged from mild elevations of liver enzymes to fulminated liver failure requiring liver transplantation. For example, Veno-occlusive disease may be caused by pyrrolizidine alkaloids, such as *Senecio* species, *Heliotropium* species, and Comfrey (*Symphytum officinale*). Chaparral (*Larrea divaricata*) leaf ingestion can lead to the development of either fulminant hepatic failure or

cirrhosis. Kava (*Piper methysticum*) has been identified as causing an acute hepatitis. Many traditional Chinese herbal preparations have also been described to cause hepatotoxicity and rarely liver failure [12–14].

A very sensitive method for testing the toxicology of new drugs and their degradation products is the assessment of *in vitro* toxicity. *In vitro* cell culture methods have the advantage of relatively well-controlled variables and are generally accepted as a very effective method for toxicology testing. Their sensitivity is equal to or greater than that of *in vivo* tests. Table 13.2 summarizes some of the common standardized test methods that are used. *In vitro* measurements of herbal-derived substances are bases on the extraction of the bioactive substances. The crude extracts or their fractions can be applied to the cells in different dilutions. After exposition of the cells to the extracts, cytotoxicity is assessed by various methods. The following systems have been used to evaluate cytotoxic effects of test molecules:

- Primary isolated hepatocytes from animals and humans
- Cocultures of hepatocytes with liver nonparenchymal cells, such as Kupffer cells or endothelial cells
- Hepatoma cell lines, such as HepG2
- Active liver microsomal fractions from the rat, for example, S9 fraction used in the Ames' test
- Liver slices

A wide array of morphologic and biochemical tests are available for obtaining information at the cellular and molecular levels to detect and measure chemical-induced cell and tissue damage. Several classifications can be proposed, for example, microscopic evaluation of cell morphology, parameters that estimate plasma membrane integrity, and parameters that estimate subcellular effects; parameters that assess irreversible cytotoxicity (necrosis and apoptosis); or nonspecific and liver-specific endpoints.

Ideally, an *in vitro* model for drug toxicity and biotransformation should accurately resemble biotransformation in the intact liver. Several *in vitro* human liver models have been developed in the past few decades, including freshly isolated hepatocytes cultured as monocultures or as cocultures with nonparenchymal cells, cell lines, liver slices, and perfused liver supersomes, microsomes, cytosol, and S9 fraction. A general advantage of these models is a reduced complexity of the study system. On the other hand, there are several more or less serious specific disadvantages for each model, which prevent their widespread use and acceptance by the regulatory authorities as an alternative for *in vivo* tests [2,3,12–14]. Here, we describe the practical aspects of selected *in vitro* human liver models with comparisons between the methods.

Nonspecific Endpoints: Nonspecific endpoints are usually used to estimate irreversible cellular damage. The choice of cytotoxicity indicator depends on a number of factors that include correspondence with the lesion being induced

in the liver, reliability, reproducibility and sensitivity, convenience, cost, and species specificity. Nonspecific criteria may monitor morphologic changes, membrane integrity, subcellular perturbations, and metabolic activities. Light microscopic examination is useful to support biochemical end points; cell rounding, cell detachment, blebbing indicative of cell membrane, and cytoskeleton disturbance, vacuolization, and accumulation of lipid droplets can be visualized, whereas transmission electron microscopy is required to detect subtle alterations of organelles. Endpoints for *in vitro* cytotoxicity evaluation include the following:

Morphologic Parameters: Light microscope is used for visualization of cell shape, nuclear and cytoplasmic alterations; accumulation of vacuoles, lipid droplets, formation of blebs, cell attachment and detachment (cell count), phase contrast microscope is used for monitoring of living cells *in vitro*, confocal microscope is used for monitoring intracellular alterations. Transmission electron microscope (TEM) is used for visualization of alterations of cell organelles; scanning electron microscope (SEM) is used for the assessment of alteration of cell shape.

Membrane Integrity: Trypan blue exclusion test, lactate dehydrogenase (LDH), neutral red uptake are the most commonly used *in vitro* tests for the assessment of membrane integrity. Lactate dehydrogenase, an enzyme located in the cytoplasm, catalyzes the conversion of lactate and pyruvate. When lactate dehydrogenase is found within the media on the cells, there are two possible causes. The first is cellular death and the second may be a "leak" in a cell membrane. When cells are disrupted, the lactate dehydrogenase activity is elevated. The lactate dehydrogenase activity can be measured by monitoring the amount of NADH spectrophotometrically at 340 nm. Since NAD^+, H^+, and lactate react to form NADH and pyruvate, higher absorbance at 340 nm indicates higher lactate concentrations. The rate of increase in absorbance is directly proportional to the lactate dehydrogenase activity in the sample. We used this assay in a recent study to evaluate medicinal plants hepatotoxicity in monocultures of hepatocytes and in cocultures of hepatocytes and monocytes. In this study, cells from the human hepatocyte cell line (HepG2) and in cocultures of cells from the HepG2 cell line and cells from the human monocyte cell line (THP1) were treated with various concentrations (1–500 μg/mL) of extracts of *Pistacia palaestina*, *Juglans regia*, and *Quercus ithaburensis* for 24 h. Then the LDH assay was carried out. Extracts from *Cleome droserifolia*, a known toxic plant, were taken as positive control. In the coculture system, toxic effects were seen after exposure to extracts of *P. palaestina* and *C. droserifolia*. These two extracts significantly reduced the cell viability as measured with the LDH assay (Figure 13.9). Whereas in the hepatocyte cultures, only extracts of *C. droserifolia* were found to affect the cell viability. It seems that the observed reduction in the cell viability after exposure to extracts of *P. palaestina* in the cocultures but not in monocultures is a result of monocyte-derived factors. The use of liver cell cocultures is therefore a useful

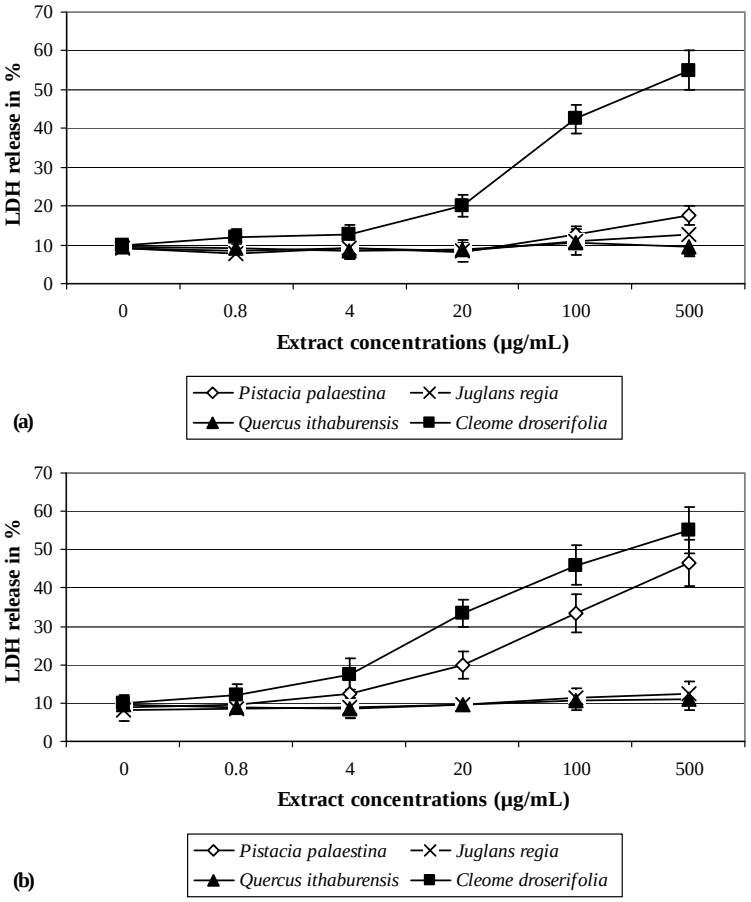

FIGURE 13.9 LDH leakage from HepG2 cells (a) and from cocultures of HepG2 and THP1 cells (b) after an overnight incubation with various concentrations of extracts from *P. palaestina*, *J. regia*, *Q. ithaburensis*, and *C. droserifolia* (positive control). The leakage of the cytoplasm located LDH into the extracellular medium is measured. LDH activity was measured in both the supernatants and the cell lysate fractions. Values given represent the mean ± standard deviations of three independent experiments carried out in triplicates.

approach to investigate the influence of intercellular communication on xenobiotic metabolism in liver [15].

The LDH assay was recently used to evaluate cytotoxicity of the following plant extracts and combinations used in the traditional Arabic and Islamic medicine [16–18]:

- Herbal combination for reduction of blood sugar: *J. regia*, *Olea europaea*, *Urtica dioica*, *Atriplex halimus.*
- Herbal extract for improvement of male sexual vitality: *Ferula foetida.*

- Herbal combination for weight loss*: Alchemilla vulgaris*, *O. europaea*, and *Mentha longifolia* L., *Cuminum cyminum* (Figure 13.9).
- Herbal extract for the treatment of inflammation: *Hypericum triquetrifolium*.
- Herbal combination for reducing raised blood cholesterol and fats*: Eriobotrya japonica* (Loquat) and *O. europaea.*

Metabolic Function: The metabolic activity can be evaluated by measuring the activity of a mitochondrial enzyme succinate dehydrogenase using MTT test. The MTT is designed to be used for the quantification of both cell proliferation and cell viability in cell population using 96-well plates with 25,000 cells/well. Dose–response curves are calculated from the results obtained, then the results are summarized as median inhibition concentration (IC_{50}) values; that is, the concentrations of test chemicals that modify the response of test wells by 50%. The IC_{50} value is usually considered the best indicator of *in vitro* cytotoxicity because it is taken from the middle of the dose–response curve. The MTT assay was recently used to evaluate cytotoxicity of plant extracts and combinations used in the traditional Arabic and Islamic medicine [15,17–19].

1. Antioxidant activity and cytotoxicity of eight plants used in traditional Arab medicine in Israel.
2. Evaluation of medicinal plant hepatotoxicity in co-cultures of hepatocytes and monocytes [15]. In this study, we used the MTT assay (Figure 13.10) in order to confirm results obtained with the LDH assay (Figure 13.9).
3. Antioxidant activity of *Crataegus aronia* aqueous extract used in traditional Arab medicine in Israel.
4. *H. triquetrifolium*—Derived factors downregulate the production levels of LPS-induced nitric oxide and tumor necrosis factor-alpha in THP-1 cells.

Glutathione Level: The tripeptide GSH is the most efficient protection of the cells against reactive metabolites and free radicals. GSH is an essential cofactor for GSH peroxidase and removes hydroperoxides; it is converted to its oxidized form (GSSG). GSH is also involved in the conjugation and inactivation by GST, of reactive metabolites formed by oxidation reactions. Intracellular GSH levels are usually measured by a spectrofluorimetric method. GSSG is converted back to GSH by the GSH reductase pathway. The most common pathway of GSH depletion in drug toxicity is excessive consumption of GST without recovery. One of the consequences of GSH depletion can be the modification of the sulfhydryl groups to arylating and oxidizing species. Several pharmaceuticals induce an oxidative stress that results in S-thiolation of proteins, presumably by thiol–disulfate exchange. Two mechanisms of dethiolation of proteins have been identified, both ultimately requiring GSH and enzymatic reduction by reduced NADPH: one involves GSH and GSH reductase and the other involves thioredoxin and thioredoxin reductase, a thiol reductant showing a broad specificity for reduction of disulfides (180). GSH is also present in mitochondria; it prevents the effects of oxidants generated during oxidative phosphorylation on sensitive thiol groups. Mitochondria rely on GSH

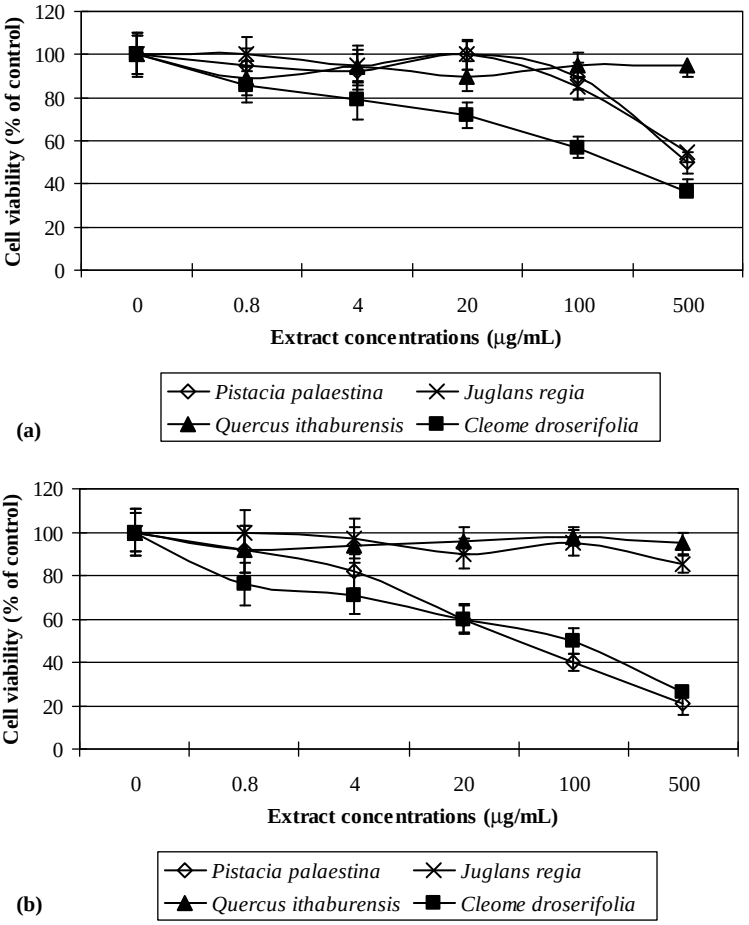

FIGURE 13.10 MTT assay in HepG2 cells (a) and in the coculture of HepG2 and THP1 cells (b) after an overnight incubation with various concentrations of extracts from *P. palaestina*, *J. regia*, *Q. ithaburensis*, and *C. droserifolia* (positive control). The absorbance of the MTT formazan was determined at 570 nm in an ELISA reader. Cell viability was defined as the ratio (expressed as a percentage) of absorbance of treated cells to untreated cells. Values given represent the mean ± standard deviations of three independent experiments carried out in triplicates.

peroxidase, and hence on GSH, to detoxify hydroperoxides. Intracellular GSH levels are usually measured by a fluorimetric method [13,14]. GSH levels have been recently used in the following studies to evaluate the effects of medicinal plants used in TAIM [20–22]:

- Antioxidant activity of *Crataegus aronia* aqueous extract used in traditional Arab medicine.

- Antioxidant action of extract of the traditional medicinal plant *Rhazya stricta* Decne.
- The protective effect of *Tribulus terrestris* in diabetes.

Lipid Peroxidation: Oxidative stress leads to generation of reactive oxygen species (ROS), which play an important pathogenetic role in different disease states. Lipid peroxidation has damaging effects on liver cell membrane. Lipid peroxidation results from interaction of unsaturated lipid components with oxygen-free radicals or excess H_2O_2 generated by toxic compounds during metabolism. Various analytical methods are used to measure the extent of lipid peroxidation *in vitro*; they are based on the detection of intermediates, reactants, and end products of lipid peroxidation. The methods include measurement of malondialdehyde formation using the thiobarbituric acid reaction, spectrophotometric detection of lipid-conjugated dienes, measurement of evolved gaseous hydrocarbons (ethane and pentane), quantification of fluorescent pigments, and chemiluminescence. Two widely used markers of lipid peroxidation are extracellular free malondialdehyde formation (although it appears to be related to only 10% of the total lipids oxidized estimated on the ultrafiltrate of culture medium by size-exclusion chromatography) and conjugated dienes evaluated by the second-derivative ultraviolet spectroscopy of the cell lipid extract. Recently, we measured the extent of lipid peroxidation in order to assess the antioxidative effects of a mixture of extracts of *A. vulgaris*, *O. europaea*, and *M. longifolia* L., and *C. cyminum.* This mixture is used in traditional Arabic and Islamic medicine as well as in European herbal medicine, in the treatment of overweight and obesity (Figure 13.11).

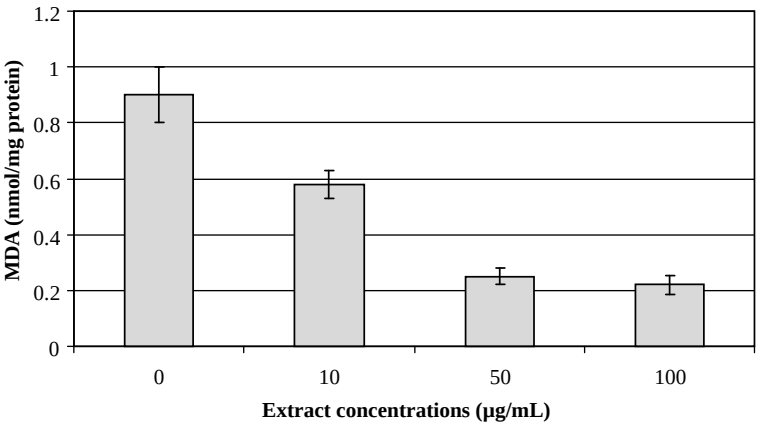

FIGURE 13.11 Effects of plant extracts on malondialdehyde (MDA) release from rat liver homogenates incubated with 100 μM ferrosulfate in the presence and absence of 0.01, 0.05, and 0.1 mg Weighlevel/mL. Values given represent the mean $\pm$ SEM of three independent experiments carried out in triplicates.

Plasma Proteins and Acute-Phase Proteins: A number of liver-specific functions serve as parameters of functional disturbances in isolated hepatocytes exposed to pharmaceuticals. The most widely tested markers include synthesis of plasma proteins such as albumin, α-macroglobulin, and transferrin and acute-phase proteins, glyconeogenesis, and glycogen synthesis; urea synthesis; lipoprotein synthesis; induction or inhibition of specific cytochrome P450 isoenzymes; and bile acid secretion. Albumin and acute phase proteins are commonly measured by ELISA (enzyme-linked immunosorbent assay) test. We used this assay to quantify albumin secretion in cultured hepatocytes treated with extracts of four medicinal plants used in TAIM in order to assess their hepatotoxic effects in cocultures of hepatocytes and monocytes. In brief, for the determination of albumin levels in culture supernatants, 1.5×10^4 HepG2 (human Hepatoma) cells and 5×10^3 THP1 (human monocytic cell line) cells were seeded in 96-microtiter plates. Twenty-four hours after cell seeding, cells were exposed to extracts of *P. palaestina*, *J. regia*, and *Q. ithaburensis* for 24 h. Extracts from *C. droserifolia*, a known toxic plant, were taken as positive control. After 24 h of treatment, the cell supernatants were collected from each well. The amount of albumin in the culture supernatant was measured using ELISA. Therefore, supernatants were incubated in 96-well microtiter plates for 1 h at 37°C or overnight at 4°C. After washing in PBS, nonspecific binding sites were blocked in PBS containing 0.5% bovine serum albumin (BSA) for 1 h at room temperature. After another washing step in PBS, peroxidase-conjugated goat antirat albumin antibody was added in PBS containing 1% BSA and incubated for 2 h at room temperature (this antibody cross reacts with human albumin). The microtiter plates were then washed, the substrate (0.5 mg 2,2-azino-di-3-ethylbenzothiazoline-6-sulfonic acid per mL 100 mM Na-acetate, 50 mM Na-phosphate, and 9×10^{-3}% H_2O_2) added and the absorption was measured at 405 nm in an ELISA reader (Figure 13.12). All washing steps were carried out with PBS at room temperature. Background values were measured in the absence of culture supernatant and subtracted from the experimental values. All ELISA determinations were carried out in duplicates. In the coculture system, toxic effects were seen after exposure to extracts of *P. palaestina* and *C. droserifolia.* These two extracts significantly reduced the cell viability as measured with the MTT test and the LDH assay. However, in the hepatocyte cultures (HepG2), only extracts of *C. droserifolia* were found to affect the cell viability. The production levels of albumin from hepatocyte were not affected by the treatment with plant extracts in both culture systems [15].

DNA Synthesis: The effects of a test chemical or its degradation products on cell proliferation can be assessed by measuring the DNA synthesis. ^{3}H-thymidine incorporation measures DNA synthesis and is often taken as a representation of cellular proliferation. Short pulse times, less than 24 h, can be used to avoid radiolysis of the nucleus (radiolysis is due to the short path length of β-emission (∼1 mm) within the nucleus, causing DNA strands to break). After pulsing the cells at 1 mCi/mL, the radioactive media can be removed and the cells washed

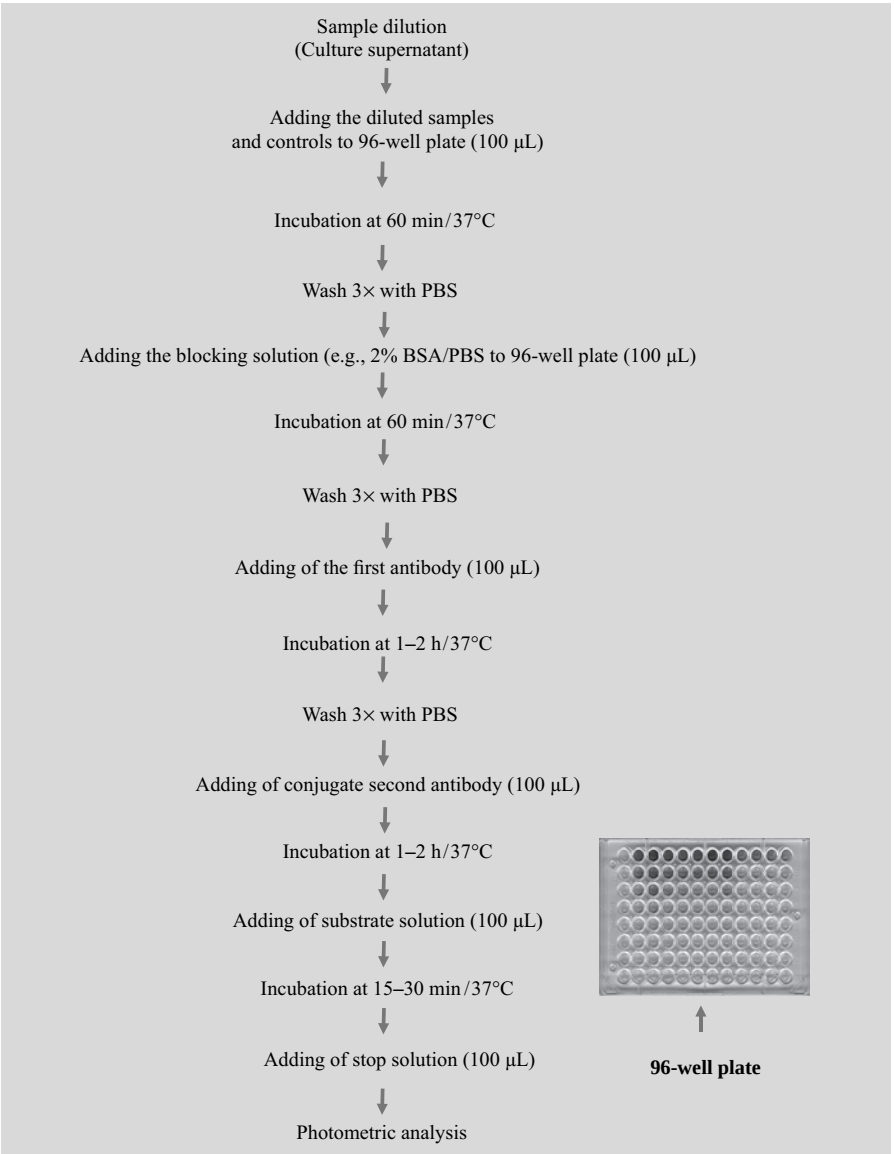

FIGURE 13.12 The enzyme-linked immunosorbent assay is one of the most used immunological tests.

with HBSS. One 10-min and two 5-min washes of ice-cold 10% TCA can be performed to remove any unincorporated precursor, after which the monolayer can be dissolved in 1% SDS in 0.3 N NaOH. The solution can be combined with scintillation fluid and the β-emission measured in a scintillation counter.

Alternatively, a nonradioactive precursor, bromodeoxyuridine (BrdU) can be used, which after uptake can be detected by a fluorescent dye-conjugated antibody reacting with BrdU.

Necrosis: This is the name given to unnatural death of cells and living tissue. It begins with cell swelling, chromatin digestion, and disruption of the plasma membrane and organelle membranes. Late necrosis is characterized by extensive DNA hydrolysis, vacuolation of the endoplasmic reticulum, organelle breakdown, and cell lysis. The release of intracellular content after plasma membrane rupture is the cause of inflammation in necrosis. The Trypan blue exclusion test is widely used to estimate the percentage of viable cells in isolated hepatocyte suspensions. Other indices of toxicity may reflect reversible injury. Thus increased permeability of plasma membranes to ions and small molecules precedes total loss of cell viability. A loss of intracellular K^+ and alteration of Ca^{2+} ion flux are usually observed.

Subcellular Changes: With the exception of direct action of a toxic compound on the cellular membrane, subcellular changes also occur prior to loss of plasma membrane integrity. Various specific alterations of organelles can also be observed in liver parenchymal cells by electron microscopic examination, for example, proliferation of smooth endoplasmic reticulum, increased number of peroxisomes associated with induction of the peroxisomal P-oxidation pathway, and characteristic accumulation of concentric membranes in lysosomes. These criteria are usually much more sensitive than end points of the plasma membrane integrity; they compare to criteria for metabolic competence. However, with a few compounds, major differences can be observed. Thus, cycloheximide inhibits protein synthesis but not urea synthesis, whereas norvaline does the opposite.

13.12 *IN VITRO* LIVER MODELS FOR BIOTRANSFORMATION

Drug biotransformation is one of the most important factors that can affect the overall therapeutic and toxic profile of a pharmaceutical. It can lead not only to detoxification and excretion of the drug, but also to bioactivation and transformation from a nontoxic chemical to a toxic chemical. For this reason, drug biotransformation is a pivotal factor in the early developmental stage of new drugs. Biotransformation occurs in many tissues, with the liver as the most important organ, but also the kidneys, skin, lungs, and intestine can be involved. Drug biotransformation is divided into two types of reactions, namely Phase I (hydrolysis, oxidation, and reduction) and Phase II reactions (conjugation). The biotransformation pathway of a drug is mediated by Phase I, Phase II, or a combination of both. The cytochrome P450 enzyme superfamily plays a dominating role in the Phase I biotransformation and is mainly present in the liver. Phase II enzymes (e.g., uridine diphosphoglucuronosyl transferase (UGT), *N*-acetyl transferase (NAT), glutathione S-transferase (GST), and sulfotransferase (ST) also have an important role in the detoxification and/or excretion rate of xenobiotics. The evaluation of biotransformation pathways in human, both Phase

I and Phase II biotransformation, is essential in the preclinical phase of the development of a candidate drug. It is becoming increasingly apparent that drug transporters (Phase III) influence not only the therapeutic efficacy but also the absorption, distribution, and elimination of a drug [14,23]. The drug transporters are located in epithelial and endothelial cells of the liver, gastrointestinal tract, kidney, blood– brain barrier, and other organs. They are responsible for the transport of most of the commonly prescribed drugs across cellular barriers and thus for the concentration at the target or biotransformation site. Thus, the elucidation of the influence of drug transporters on the absorption disposition metabolism elimination of a drug is essential in the early developmental stage of new drugs. A key question in human drug biotransformation research is how to make reliable extrapolations from the *in vitro* or *in vivo* model to clinical practice. Thus, the objective is to establish a useful model system with a strong predictive power for human biotransformation. Several models have been developed in the past, ranging from isolated enzymes to the intact perfused liver. They are used to obtain early information about biotransformation pathways and to predict drug–drug interactions at the metabolic level [24]. The quality of the human liver used in the preparations of the different *in vitro* methods described is a dominant factor in the outcome of the *in vitro* studies, especially in precision cut liver slices and isolated hepatocytes [25]. Livers that are not suitable for transplantation or liver sections from biopsies are used and, in order to ensure a viable cell yield as high as possible or, in the case of cell fractions, the highest enzyme activity, the liver or liver section needs to be processed as soon as possible after the resection. In the following, we will give an overview of different *in vitro* models for human biotransformation, with their advantages and disadvantages, is given (Figure 13.13).

Isolated Perfused Liver: Isolated perfused liver is considered to be the best representation of the *in vivo* situation. However, it has never been used with human liver and only on a small scale with animal livers. Many specific limitations make the animal perfused liver less attractive as a model for toxicity and biotransformation studies. The perfusion is carried out with Krebs–Henseleit buffer as perfusate. The test compound under investigation should be dissolved in the perfusate and the viability period of the liver is only 3 h. Although the isolated perfused liver gives an excellent representation of the *in vivo* situation, practical inconveniences, such as unavailability of human liver, poor reproducibility, and test limitation of 3 h prevents the method from being used on a large scale.

Cultures of Liver Slices: Cultures of tissue slices were developed in the 1920s by Otto Heinrich Wartburg. Currently, the maintaining of liver slices in culture media offers a powerful test system to study biotransformation *in vitro*. The thin slices obtained with the Krumdieck and the Brendel–Vitron slicers (about 250 μm thickness) strongly resemble the intact liver and have been used to study the biotransformation of many compounds. The resected tissue can be stored at 4°C in University of Wisconsin (UW) solution up to 48 h without loss of Phase I and Phase II enzyme activity. However, the long-term storage of liver slices in liquid nitrogen has been shown to be complicated and there is no optimal

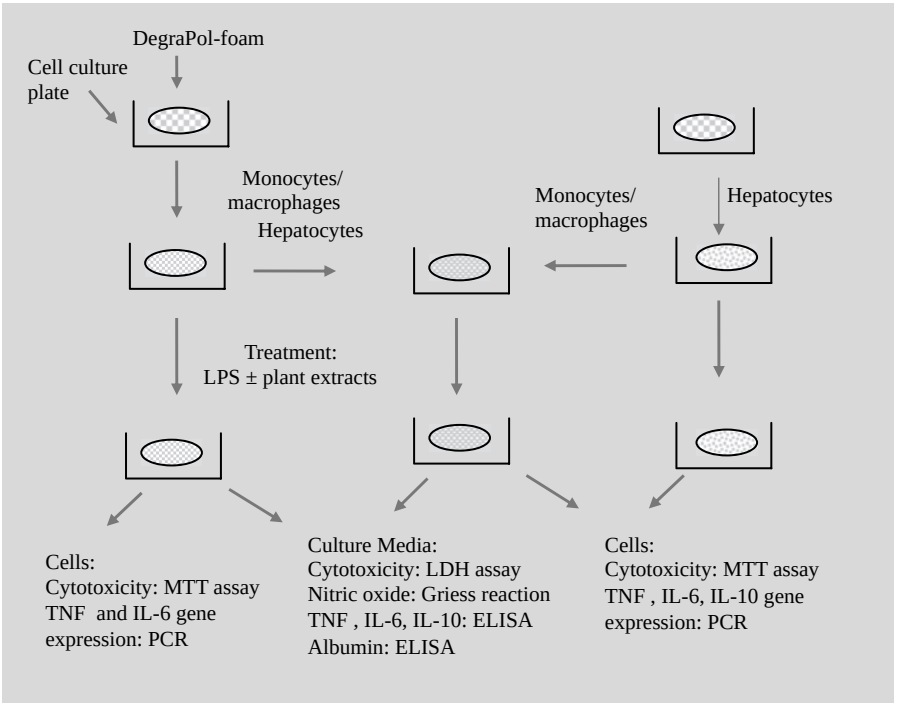

FIGURE 13.13 *In vitro* liver models in toxicity and efficacy using three-dimensional cell culture system with DegraPol as cell carrier.

cryopreservation protocol. The duration of the cytochrome P450 activity is short and this is probably due to impaired diffusion of nutrients and oxygen in the tissue slice; the amount of many cytochromes P450 drops below half of the initial value within 24 h [14,26].

Primary Hepatocyte Suspensions and in Culture: Primary hepatocytes are a popular *in vitro* system for both, toxicity testing and drug biotransformation due to their strong resemblance of *in vivo* human liver. Hepatocytes of various animal species can be isolated from the liver by the traditional collagenase perfusion operation developed by Howard and Pesch in 1967. This method requires the whole liver, which is not available in the case of human liver. Human liver is mainly obtained from patients that undergo partial liver resection, for example, because of liver metastasis. Therefore, a method for human liver parts has been developed by Puviani in 1998 and this is a modification of the traditional collagenase perfusion. Preferably, the perfusion takes place immediately after resection. When this is not possible, the tissue can be stored at 4°C for up to 48 h in University of Wisconsin (UW) solution, without relevant loss of viability. Once isolated, hepatocytes can be held in suspension, in which case they remain viable for only a few hours, or they

can be maintained in monolayer culture for a maximum of 4 weeks. Both cultured hepatocytes and suspensions of primary hepatocytes have repeatedly proven to be powerful tools to analyze the specific metabolic profile of a variety of drugs with good *in vitro–in vivo* correlations. However, it has been widely recognized that cultured hepatocytes are subject to a gradual loss of liver-specific functions, with special reference to a decreased cytochrome P450 (CYP) expression. This loss is different for the specific cytochrome P450 isoenzymes; for some isoenzymes it becomes evident after a few days of culture (CYP 2E1 and CYP 3A4), while others remain nearly unaffected by the isolation and culturing processes (CYP 1A2 and CYP). Various culturing methods have been explored in an effort to maintain the liver-specific characteristics of hepatocytes during prolonged culture. These include the application of culturing matrices (e.g., double-layer collagen gel sandwich; this culture method can be used to study not only biotransformation, but also transporter-mediated biliary excretion); the addition of specific nutrients, hormones, and inducers to the culture medium; and also the coculturing of hepatocytes with other cell types (e.g., the hepatic Kupffer cells) [2–4,8–10,13,14].

Cell Lines: Cell lines as an *in vitro* model are less popular compared to other described models. This is mainly due to their dedifferentiated cellular characteristics and incomplete expression of all families of metabolic enzymes. An important requirement of cell lines as a model is that they must resemble the normal physiology of human hepatocytes *in vivo*. The usefulness of hepatoma cell lines as *in vitro* model therefore falls or stands with their ability to express human Phase I and Phase II enzymes [2–4,8–10,13,14].

S9 Fractions: The liver S9 fraction contains both microsomal and cytosolic fractions. Human liver S9 fraction is mainly used in combination with the Ames test, which is a simple and rapid *in vitro* method for detecting the mutagenicity of chemicals. The test plays a critical role in development of new drugs and is used for predicting possible mutagenicity of a compound. However, many procarcinogens remain inactive until enzymatic transformation and thus a metabolic activation system, for example, human liver S9 fraction, is necessary for testing not only the genotoxicity of a drug, but also its metabolites in humans [27].

Toxicity and biotransformation research of a new drug can start with a simple model while the model can become more complex at later stages. The best sequence is to start with microsomes and cytosol, then CYP and UGT supersomes and NAT cytosol, the S9 fraction, followed by (transfected) cell lines and primary hepatocytes and cocultures, and finally liver slices.

13.13 *IN VITRO* MODELS FOR THE STUDYING OF ANTI-INFLAMMATORY EFFECTS

In response to tissue injury, a multifactorial network of chemical signals initiate and maintains a host response designed to "heal" the afflicted tissue. This involves activation and directed migration of leukocytes (neutrophils, monocytes, and eosi-

nophils) from the venous system to sites of damage. Inflammation is the first response of the immune system to infection or irritation. It is caused by cytokines such as TNF-α, IL-1, and IL-6, and by eicosanoid such as PGE2. Cytokines are regulators of host responses to infection, immune responses, inflammation, and trauma. There are two types of cytokines pro-inflammatory and anti-inflammatory. Thus, inhibitors of the pro-inflammatory cytokines have been considered as a candidate of anti-inflammatory drugs. Lipopolysaccharide (LPS)-activated macrophages are usually used for evaluating the anti-inflammatory effects of various materials. LPS is a principle component of the outer membrane of Gram-negative bacteria, is an endotoxin that induces septic shock syndrome and stimulates the production of inflammatory mediators such as nitric oxide (NO), tumor necrosis factor-alpha (TNF-α), interleukins, prostanoids, and leukotrienes. Therefore, LPS plays a key role in not only eliciting an inflammatory response but also in causing septic shock during a Gram-negative bacterial infection. Inflammatory responses are advantageous for eradicating bacteria, as long as they are under control. When out of control, however, deregulated inflammation leads to the massive production of pro-inflammatory cytokines such as TNF-α, interleukin-1 (IL-1), and interleukin-6 (IL-6) by macrophages, which can cause tissue injury and multiple organ failure. For example, the resident macrophages of the liver, the Kupffer cells, are among the first to respond to foreign antigens. Activated hepatic Kupffer cells play an essential role in LPS-induced liver injury (9). Following contact with the CD14 protein, the complex triggers a signal cascade involving the nuclear factor kappa B. This factor enhances the expression of inflammation-related genes. The acute-phase response is regulated by cytokines released by activated Kupffer cells, notably IL-1, IL-6, and TNF-α. Among these cytokines, IL-6, also known as hepatocyte-stimulating factor, is a major inducer of the acute phase response. In the liver, TNF-α production is not restricted to Kupffer cells. We have demonstrated that LPS affects the acute-phase response via hepatocyte-derived IL-6 and TNF-α in an autocrine loop and the NO production of parenchymal liver cells. TNF-α is also involved in inducing cell damage by promoting oxidative stress in mitochondria. TNF-α stimulates the production of ROS and reactive nitrogen species (RNS). ROS have been implicated in the pathogenesis of many forms of liver disease. When liver cells are exposed to excesses of ROS, oxidative stress occurs and affects many cellular functions. The inflammatory process is controlled by immunosuppression cytokines such as IL-10 and IL-4. Macrophage-derived IL-10 affects the growth and differentiation of various cell types of the immune system *in vitro*. It inhibits the production of inflammatory cytokines such as IL-1, IL-6, and TNF-α by LPS-activated macrophages. [18,28–33].

Based on knowledge from traditional Arab herbal medicine, we assessed in an *in vitro* study the anti-inflammatory mechanism of *H. triquetrifolium* through measuring the expression and release of pro-inflammatory cytokines TNF-α and IL-6, and the inducible nitric oxide synthase (iNOS) in human monocytic (THP-1) cells [18]. Herbal medicines containing *H. triquetrifolium* have been used in traditional Arab herbal medicine to treat various inflammatory diseases. The classic Arabic name for this plant species is *Dathi* or *Nabtat Yohanna*. Our previous studies show that *H. triquetrifolium* is not used any more within the practitioner communities in the

Galilee and in the West Bank. This fact reflects an extinction process of important elements of the Arab herbal medicine heritage. Utilizing the knowledge derived from traditional Arab herbal medicine and a recent *in vivo* report in which *H. triquetrifolium* extract exhibited anti-inflammatory activity in rats. In our *in vitro* study explored the anti-inflammatory mechanism of *H. triquetrifolium*. Therefore, the expression and release of pro-inflammatory cytokines TNF-α and IL-6, and the iNOS in human monocytic (THP-1) cells were measured as follows:

Cell Culture: The human monocytic cell line THP-1 was obtained from ATCC (American Type Culture Collection, Manassas, VA, USA). These cells express various receptors that are found in normal monocytes and have been used as a model system for macrophage biology and leukemia since 1980. Cells were grown in Dulbecco's modified Eagle's medium (DMEM) with a high glucose content (4.5 g/L), supplemented with 10% (v/v) inactivated fetal calf serum, 1% nonessential amino acids, 1% glutamine, 100 U/mL penicillin, and 10 μg/mL streptomycin. Cell lines were maintained in a humidified atmosphere of 95% O_2–5% CO_2 at 37°C. The culture medium was changed twice a week. Cells were seeded in 24-well plates at a density of 2×10^5 cell/mL. Cells were activated with PMA (100 ng/mL) and Vitamin D3 (0.1 μM). Twenty-four hours after cell activation, cells were exposed to various concentrations of the plant extracts in a fresh serum-free medium in both the absence, and presence, of LPS (5 μg/mL).

Nitrite Determination: The Griess reaction is a convenient method to measure the amount of nitrite in the culture supernatant of cultured cells. In this method, 50 μL aliquots of culture supernatant are mixed with 200 μL of the Griess reagent. The absorbance is read at 540 nm after 20 min of reaction and the NO_2^- concentrations are determined with reference to a standard curve using concentrations from 1 to 100 μM sodium nitrite in culture medium.

Quantification of TNF-: α *Production*: TNF-α levels were determined in TNF-α specific bioassay using WEHI cell line. WEHI 164 clone 13 fibrosarcoma cells at a concentration of 2×10^4 cells per 100 μL were incubated with serially diluted samples in 96-well flat bottom microtiter plate for 48 h at 37°C, 5% CO_2. Then 10 μL of a 5 mg/mL MTT tetrazolium solution in PBS was added in the plate, which was further incubated for 4 h. The dye was then removed and cells were lyzed by addition of 100 μL of isopropanol–5% formic acid. Plates were read at 620 nm on a multiscan bichromatic ELISA Reader (Flow Labs).

Immunoassay for Cytokines: Commercial ELISA kits (R&D Systems, Minneapolis, MN, USA) were used to quantify TNF-α and IL-6. The absorbance at 450 nm was read by a microplate reader (model 680; Bio-Rad Laboratories, Mississauga, ON, Canada) with the wavelength correction set at 550 nm. To calculate the concentration of TNF-α and IL-6, a standard curve was constructed using serial dilutions of cytokine standards provided with the kit.

RT-PCR Analysis: Samples were centrifuged at $1000 \times g$ for 10 min, and total RNA were prepared using Master pure RNA purification kit (EPICENTRE Biotechnologies). RT-PCR was performed using the Master pure RNA purification kit system (ABgene). Total RNA (0.1 μg) were used for a single reaction. Nucleotide sequences of oligonucleotide primers for the housekeeping glyceraldehyde-3-phosphate dehydrogenase (G3PDH) plus the TNF-α or iNOS primers pairs were used for RT-PCR which described elsewhere respectively. The reverse transcriptase reaction was performed at 55°C for 30 min. To amplify the G3PDH TNF-α, and iNOS cDNA, each sample was denatured at 95°C for 60 s, annealed at 55°C for 60 s, and extended at 72°C for 90 s. The RT-PCR products were subjected to agarose gel electrophoresis and stained by ethidium bromide.

Results obtained in this study indicate that *H. triquetrifolium* could modulate the regulatory mechanism of NO and pro-inflammatory cytokines (TNF-α and IL-6) in the LPS-activated THP-1 cells. *H. triquetrifolium* inhibited the production of NO and TNF-α, and the expression of iNOS and TNF-α, but not of IL-6.

13.14 *IN VITRO* MODELS FOR THE STUDYING OF ANTIAPOPTOSIS EFFECTS

In recent years, with the great progress on tumor cell biology and molecular biology, it has been recognized that the occurrence and development of tumor is not only the result of cell proliferation disorders and dedifferentiation, but also closely correlated with the abnormal apoptosis. Although abnormal apoptosis can promote the occurrence and development of tumor, we can also treat tumor by promoting apoptosis of cancer cell. Thus, it has become the new target in oncotherapy by way of inducing apoptosis of cancer cell. Apoptosis, or programmed cell death, is central to the development and homeostasis of multicellular organisms. Dysregulation of apoptosis leads to a variety of human pathologies including cancer, autoimmune diseases, and neurodegenerative disorders. Since the concept of apoptosis was established in 1972, research efforts have led to the identification of hundreds of genes that control the initiation, execution, and regulation of apoptosis in several species. Compelling evidence shows that the mechanism of apoptosis is evolutionarily conserved [34–36].

Apoptosis involves a series of biochemical events leading to a characteristic cell morphology and death, in more specific terms, a series of biochemical events that lead to a variety of morphological changes, including blebbing, changes to the cell membrane such as loss of membrane asymmetry and attachment, cell shrinkage, nuclear fragmentation, chromatin condensation, and chromosomal DNA fragmentation. Processes of disposal of cellular debris whose results do not damage the organism differentiate apoptosis from necrosis.

Although many pathways and signals lead to apoptosis, there is only one mechanism that actually causes the death of the cell in this process; after the appropriate stimulus has been received by the cell and the necessary controls exerted,

a cell will undergo the organized degradation of cellular organelles by activated proteolytic caspases. A cell undergoing apoptosis shows a characteristic morphology that can be observed with a microscope.

1. Decrease in cell volume and rounding due to the degradation of the cytoskeleton by caspases.
2. The cytoplasm appears dense, and the organelles appear tightly packed.
3. Condensation of the chromatin into compact patches against the nuclear envelope in a process known as pyknosis, a hallmark of apoptosis.
4. The nucleus breaks into several discrete *chromatin bodies* or *nucleosomal units* due to the degradation of DNA.
5. The plasma membrane shows irregular buds known as blebs.
6. The cell breaks apart into several vesicles called apoptotic bodies.
7. Apoptotic bodies undergo phagocytosis by macrophages.

The expression of several genes accompanies apoptosis. Some of the proteins encoded by these genes induce apoptosis, others are critical during apoptosis, and still others inhibit apoptosis. In the following, a brief description of main genes that regulate apoptosis is given.

p53 Gene: *p53* also known as tumor protein 53 is a transcription factor encoded by the TP53 gene. It has regulatory function in the normal cells circle. The tumor-suppressor protein p53 accumulates when DNA is damaged due to a chain of biochemical reactions. Part of this pathway includes alpha-interferon and beta-interferon, which induce transcription of the p53 gene and result in the increase of p53 protein level and enhancement of cancer cell-apoptosis. p53 prevents the cell from replicating by stopping the cell cycle at G1, or interphase, to give the cell time to repair, however, it will induce apoptosis if damage is extensive and repair efforts fail. Any disruption to the regulation of the p53 or interferon genes will result in impaired apoptosis and the possible formation of tumors.

Caspases: The mitochondria are essential to multicellular life. Without them, a cell ceases to respire aerobically and quickly dies—a fact exploited by some apoptotic pathways. Apoptotic proteins that target mitochondria affect them in different ways; they may cause mitochondrial swelling through the formation of membrane pores, or they may increase the permeability of the mitochondrial membrane and cause apoptotic effectors to leak out. Mitochondrial proteins known as SMACs (second mitochondria-derived activator of caspases) are released into the cytosol following an increase in permeability. SMAC binds to *inhibitor of apoptosis proteins* (IAPs) and deactivates them, preventing the IAPs from arresting the apoptotic process and therefore allowing apoptosis to proceed. IAP also normally suppresses the activity of a group of cysteine proteases called caspases (or *c*ysteine-*asp*artic acid prote*ases*), which carry out the degradation of the cell, therefore, the actual degradation enzymes can be

seen to be indirectly regulated by mitochondrial permeability. Caspases are a family of cysteine proteases, which play essential roles in apoptosis (programmed cell death), necrosis, and inflammation. Eleven caspases have so far been identified in humans. There are two types of apoptotic caspases: initiator (apical) caspases and effector (executioner) caspases.

Cytochrome c: Cytochrome release from the mitochondria precedes morphological change associated with apoptosis. It binds to *Apaf-1* (apoptotic protease activating factor 1 is a cytosolic protein involved in apoptosis) and ATP, which then bind to *pro-caspase-9* to create a protein complex known as an apoptosome. The apoptosome cleaves the pro-caspase to its active form of caspase-9, which in turn activates the effector *caspase-3*.

Two important examples of the direct initiation of apoptotic mechanisms in mammals include the *TNF-induced* (tumor necrosis factor) model and the *Fas-Fas ligand-mediated* model, both involving receptors of the *TNF receptor* (TNFR) family coupled to extrinsic signals.

TNF-Induced Model: TNF-α is a cytokine produced mainly by activated macrophages, and is the major extrinsic mediator of apoptosis. The binding of TNF-α to TNF-R1 (TNF-receptor 1) has been shown to initiate the pathway that leads to caspase activation via the intermediate membrane proteins TNF receptor-associated death domain (TRADD) and Fas-associated death domain (FADD) protein. Binding of this receptor can also indirectly lead to the activation of transcription factors involved in cell survival and inflammatory responses. The link between TNF-α and apoptosis shows why an abnormal production of TNF-α plays a fundamental role in several human diseases, especially in autoimmune diseases.

Fas-Fas Ligand-Mediated Model: Binding of the Fas receptor to the Fas ligand (FasL), a transmembrane protein that belongs to the TNF-α family, results in the formation of the *death-inducing signaling complex* (DISC), which contains the FADD, caspase-8, and caspase-10. In some types of cells (type I), processed caspase-8 directly activates other members of the caspase family, and triggers the execution of apoptosis. In other types of cells (type II), the *Fas*-DISC starts a feedback loop that spirals into increasing release of proapoptotic factors from mitochondria and the amplified activation of caspase-8. Following TNF-R1 and Fas activation in mammalian cells a balance between proapoptotic (BAX, BID, BAK, or BAD) and antiapoptotic (Bcl-Xl and Bcl-2) members of the Bcl-2 family is established.

Bcl-2 Family: Bcl-2 belongs to a growing family of proteins that regulate apoptosis. The Bcl-2 family of genes and proteins governs the mitochondrial outer membrane permeability and can thus exert potent pro- or antiapoptotic function. Bcl-2 family genes are discussed to play an important role in several cancers, including breast, prostate, lung, carcinomas, and melanomas. Importantly, they are involved in resistance to radiation and chemotherapeutic cancer

treatment. The Bcl-2 family includes both death antagonists such as Bcl-2 and Bcl-xL and death agonists such as Bax, Bak, Bid, and Bad. These related proteins share at least one of four homologous regions termed Bcl homology (BH) domains (BH1–BH4). As a prototypic member of this family, Bcl-2 can contribute to neoplastic cell expansion by preventing normal cell turnover caused by physiological cell death mechanisms. High levels of Bcl-2 gene expression are found in a wide variety of human cancers. In addition, Bcl-2 is implicated in chemoresistance as overexpression of Bcl-2 can inhibit the cell killing effect of many currently available anticancer drugs by blocking the apoptotic pathway. The expression levels of Bcl-2 proteins correlate with relative resistance to a wide spectrum of chemotherapeutic drugs and γ-irradiation. Therefore, the inhibition of the protective function of Bcl-2 protein overexpressed in tumor cells is an attractive strategy for either restoring the normal apoptotic process in these cells or making these cells more susceptible for conventional chemotherapy or radiotherapy. In this regard, cell-permeable, small molecule inhibitors of Bcl-2 may represent a new class of therapeutic agents for the treatment of cancer.

Apoptosis-directed therapies are promising therapeutic targets for new cancer therapies. It is hoped that agents that induce apoptosis can complement classical cancer therapies and the cancer from becoming resistant toward radiation and chemotherapy treatment. Therefore, there is increasing research activity in the field of medicine in order to identify herbal-derived factors that can stimulate apoptosis pathway in cancer tissues. There are more than 20 herbal remedies in the Mediterranean region, which are known to have anticancer activity. There several *in vitro* test systems commonly morphological, biochemical, and immunohistological methods used in the elucidation of apoptosis (Table 12.8). There are several commercially available *in vitro* Apoptosis Detection Kits (e.g., caspases detection kits, Bcl detection kits).

13.15 *IN VITRO* MODELS FOR THE STUDYING OF ANTIOXIDANT ACTIVITY OF HERBAL-DERIVED FACTORS

Oxidative stress, and the consequent accumulation of molecules damaged by oxidant by-products of respiratory metabolism, is considered a major cause of aging. In humans, oxidative stress is involved in many diseases, such as atherosclerosis, Parkinson's disease, and Alzheimer's disease. Reactive oxygen species can be beneficial, as they are used by the immune system as a way to attack and kill pathogens. Reactive oxygen species are also used in cell signaling (Figures 13.14 and 13.15).

The main sources of reactive species in all cells are mitochondria, cytochrome P450, and peroxisome. Under physiological conditions, there is a constant endogenous production of reactive intermediates of ROS and RNS that interact as "signaling" molecules for metabolism, cell cycle, and intercellular transduction

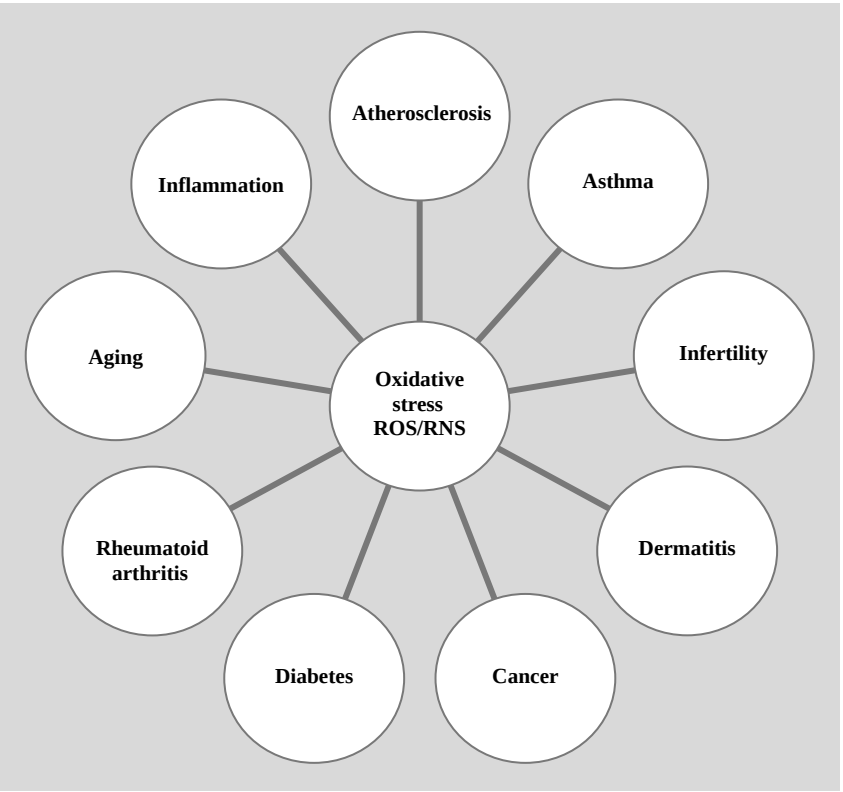

FIGURE 13.14 Oxidative stress effects.

pathways. The balance between beneficial and/or harmful effects of intermediate species is the crucial event in living organisms. In fact, the redox homeostasis is, *in vivo*, the main protective process from cell death. To control the balance between production and removal of ROS and RNS, there are a series of protective molecules and systems globally defined as "antioxidant defenses." These include enzymes such as superoxide dismutase, catalase, glutathione peroxidase, and glutathione-*S*-transferase, proteins that sequester transition metals, glutathione (GSH), cysteine, thioredoxin, and vitamins. Oxidative stress occurs when the generation of free radicals and active intermediates in a system exceeds the system's ability to neutralize and eliminate them. At the moment, the concept of oxidative stress originally confined to ROS—such as hydroxyl and superoxide radicals, and hydrogen peroxide and singlet oxygen—has been extended onto RNS as NO, peroxynitrite, and, recently, *S*-nitrosothiols. Therefore, the current concept of "oxidative stress" should also include the pathways related to the "nitrosative stress" and, for their implication in cellular and extracellular metabolic events, to the "metabolic stress." In these conditions, ROS and RNS act as "toxic" substances that may react with proteins, carbohydrates, and lipids, with consequent alteration both in the intracellular and intercellular homeostasis, leading to possible cell death and regeneration.

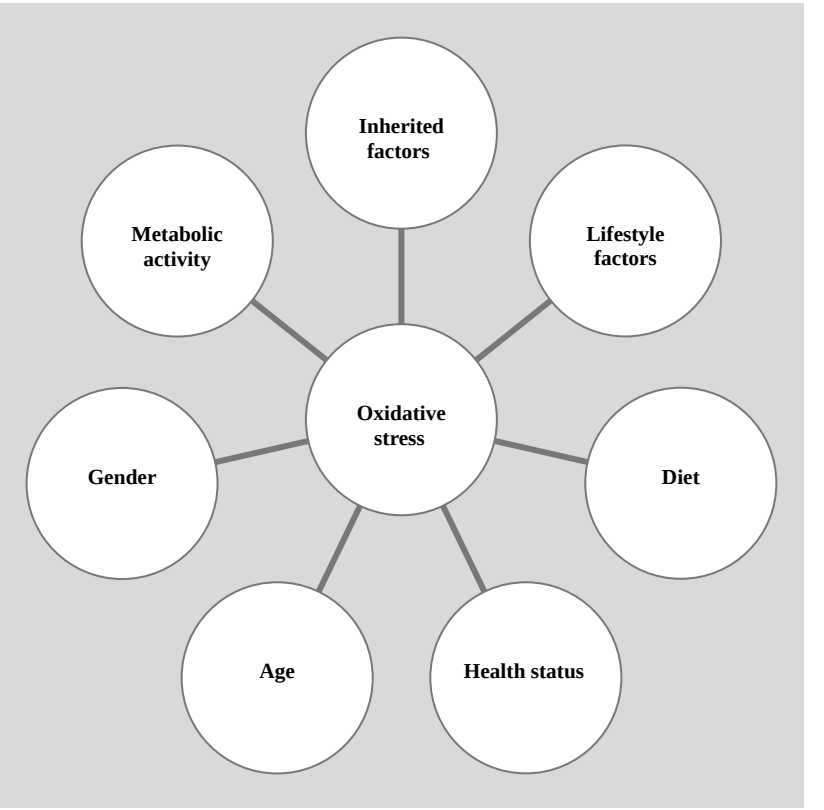

FIGURE 13.15 Causes of oxidative stress.

There is a growing interest in natural herbal-derived antioxidants because of the worldwide trend toward the use of natural additives in food and cosmetics. Herbs and spices are one of the most important targets to search for natural antioxidants from the point of view of safety. Three methods widely employed in the evaluation of antioxidant activity, namely 2,2′-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging method, static headspace-gas chromatography (HS-GC) and β-carotene bleaching test (BCBT).

Antioxidant Activity of Medicinal Plants Used in Arab–Islamic Medicine: Ethnopharmacological surveys conducted among herbal practitioners of traditional Arab medicine in Israel and the Palestinian area have revealed a large number of indigenous plant species that are used as sources of herbal therapies. Some of these herbal therapies are used to treat liver disease, jaundice or diabetes, conditions in which oxidative stress is prominent. In a recent *in vitro* study, the antioxidant activity of eight plants used in traditional Arab medicine in Israel has been evaluated. The antioxidant potential was assessed by measuring the plant's ability to suppress the extent of

iron-induced lipid peroxidation in rat liver homogenates. We found that all the extracts can suppress iron-induced lipid peroxidation. Of these extracts, those prepared from *Teucrium polium* and *Pistacia lentiscus* were the most effective in suppressing iron-induced lipid peroxidation.

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CHAPTER 14

Modern *In Vivo* Evaluations and Clinical Trials

14.1 INTRODUCTION

Greco-Arab and Islamic medicine, based on scientific and traditional knowledge, has shown remarkable success in treating acute as well as chronic diseases. As mentioned in previous chapters, Rhazes, Avicenna, Ibn Zuhr, among others, were the first to introduce scientific methods to medicine and pharmacy, particularly the introduction of animal tests, clinical trials, and quantification. Furthermore, hospitals in the Arab–Islamic world featured the first drug tests, drug purity regulations, and competency tests for physicians. The earliest known medical experiment was carried out by Rhazes (865–925). In order to locate the most hygienic place to build a hospital, he hung pieces of meat in places throughout Baghdad and built the hospital where the meat decomposition was the least. Rhazes described in his Comprehensive Book of Medicine clinical cases from his own experience and provided very useful recordings of various diseases. He also introduced urinalysis and stool tests. Avicenna (980–1037) introduced experimental medicine and systematic experimentation and quantification in physiology. He discovered the contagious nature of diseases, and described many medical treatments, including clinical trials, risk factor analysis, and the idea of a syndrome in the diagnosis of specific diseases. His *Canon of Medicine* was the first book dealing with evidence-based medicine, randomized controlled trials, and efficacy tests. He recommended the testing of a new drug on animals and humans prior to general use. Avicenna discussed the nature and quality of drugs (they were each assigned a pair of qualities, cold or warm, dry or moist), and how the way that mixing them influences their effectiveness. In this respect, he wrote the following statement:

> You can tell the potency of drugs in two ways, by analogy (qiyas) and by experiment (tajribah). We say experimenting leads to knowledge of the potency of a medicine with certainty after taking into consideration certain conditions.

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Furthermore, Avicenna was the first to describe the surgical procedure of intubation in order to facilitate breathing, and he also described the "soporific sponge," an anesthetic imbued with aromatics and narcotics, which was to be placed under a patient's nose during surgical operations. He also described the first known surgical treatment for cancer, stating that the excision should be radical and that all diseased tissue should be removed, including the use of amputation or the removal of veins running in the direction of the tumor. Avicenna laid down rules for the experimental use and testing of drugs and wrote a precise guide for practical experimentation in the process of discovering and proving the effectiveness of medical drugs and substances. His rules and principles for testing the effectiveness of new drugs and medications still form the basis of modern clinical trials. In his seventh rule, Avicenna stresses that only clinical studies in humans can provide the final proof of the efficacy and toxicity (e.g., possible side effects) in man "The experimentation must be done with the human body, for testing a drug on a lion or a horse might not prove anything about its effect on man" [1–13].

Other famous Arab and Muslim scientists also developed theoretical and practical knowledge on various preparation techniques and administrations forms of medicinal plants (see Chapters 3–5):

1. *Al-Kindi (Alkindus, 800–873)* was the first scholar in history who developed a scale to define the meaning of drug "degrees" in order to allow physicians to quantify the potency of their prescriptions.
2. *Ibn Zuhr (Avenzoar, 1093–1162)* was one of the earliest physicians known to have performed human dissection and postmortem autopsy in his medical experiments. He introduced the experimental method into surgery, for which he is considered the father of experimental surgery. Among many others, the following Arab and Muslim physicians introduced new techniques in the field of surgery and experimental medicine.
3. *Abu al-Qasim al-Zahrawi (Abulcasis, 930–1013)*, regarded as the father of modern surgery, contributed greatly to the discipline of surgery with his *Kitab al-Tasrif* (Book of Concessions or The Method of Medicine), a 30-volume medical encyclopedia, which was later translated to Latin and used in European medical schools for centuries. He introduced over 200 surgical instruments. Many of these instruments were never used before. These included the first instruments unique to gynecology as well as the surgical uses of catgut and forceps, the ligature, surgical needle, scalpel, curette, retractor, surgical spoon, sound, surgical hook, surgical rod, specula, bone saw, and plaster. His work also included anatomical descriptions and sections on orthopedic surgery and ophthalmology.
4. *Ibn al-Haitham (Alhacen, 965–1045)* made important advances in eye surgery, as he studied and correctly explained the process of sight and visual perception for the first time in his Book of Optics.
5. *Ibn al-Nafis (1210–1288)* dedicated a volume of The Comprehensive Book on Medicine to surgery. He described three stages of a surgical operation. The first

stage is the preoperation period that he calls the "time of presentation" when the surgeon carries out a diagnosis on the affected area of the patient's body. The second stage is the actual operation that he calls the "time of operative treatment" when the surgeon repairs the affected organs of the patient. The third stage is the postoperation period that he calls the "time of preservation" when the patient needs to take care of himself and be taken care of by nurses and doctors until he recovers. The Comprehensive Book on Medicine was also the earliest book dealing with the decubitus of a patient.

14.2 ANIMAL TESTS IN DRUG DEVELOPMENT

Animal tests performed at universities, private institutes, governmental laboratories, and industrial research play a crucial role in developing new knowledge that provides the basis for a new drug development. Scientists, regulators, patient groups, and members of the health care industry recognize that the appropriate use of animals in biomedical research, efficacy, and safety testing is an indispensable part of the process for acquiring the knowledge necessary to control or eliminate disease and injury in humans. In addition, regulatory bodies worldwide require efficacy and safety data for new medications based on animal experimentation before human clinical trials can be conducted. They mandate animal studies in order to reduce the risks for people and allow safer creation of new therapies. Thus, due to the lack of accepted, equivalent nonanimal alternatives, eliminating the use of laboratory animals in pharmaceutical research would significantly impede or altogether halt efforts by research-based health care companies to develop cures and/or more effective treatments for diseases such as cancer, AIDS, and heart disease. In general, there are eight major areas of medicine and biology where animals are used.

Basic Biological and Medical Research. This is necessary to unravel the secrets of nature. Knowing how different tissues and organs are regulated enables us to find out what goes wrong when disease strikes. Basic research in biology and medicine are foundations on which future discoveries are based. Indeed, animal tests are an integral part of understanding how basic systems of the body functions and what goes wrong with them to cause disease.

Developing New Drugs. Drug development is a complicated research process and is time-consuming, and costly. Thousands of chemical compounds must be made, purified (in the case of natural products) and tested in order to find a desirable therapeutic result. The Food and Drug Administration (FDA) in the United States estimates that it takes approximately 8.5 years to study and test a new drug before it can be approved for the general public. This estimate includes preclinical *in vitro* studies and animal testing, as well as clinical trials using human subjects. At present many serious diseases such as AIDS, Alzheimer's disease, Parkinson's disease, hepatitis, cancer, and cardiovascular diseases are still poorly understood and treated. Therefore, new and more effective therapies and diagnostics are desperately needed to improve the lives of patients affected with these diseases. The appropriate and

responsible use of animals is an indispensable part of biomedical research and pharmaceutical product safety testing.

The likelihood of adverse effects occurring during testing in humans can be significantly reduced if preceded by animal testing. The results of animal tests enable researchers to determine which experimental compounds in advanced development are unsuitable for use in humans either because the risk of potential toxicity is too great or because they do not have the desired pharmacokinetic profile, thus likely rendering them ineffective. Around 70% of serious adverse effects that occur in humans are identified at the animal testing stage. Therefore, animal testing is extremely beneficial in minimizing the risks to humans in clinical trials.

Preparations of Natural Products Used in Medical Research and Treatment. Animals can produce useful medical substances in their blood or milk, like antibodies, vaccines, and hormones that are important for diagnostic tests, medical treatments, and basic research.

Toxicity Testing. A wide range of chemicals and medicines used in day-to-day life, such as those in household products, in farming, and industry, need to be tested for their safe use in humans as well as in animals. Such preliminary testing is essential for avoiding pollution and associated health hazards, as well as for proper maintenance of the environment.

Study of Genetic Disorders. There are many diseases that are inherited and caused by basic faults in a person's genetic code. Certain animals have genetic faults similar to humans. There are mutant strains like dystrophic mice that have the same faulty gene as muscular dystrophic patients. The animal thus plays a vital role in the understanding and treatment of such genetic diseases. Some human pathologies are difficult to study because they do not occur naturally in animals. Therefore, to discover and develop new treatments and cures for many serious diseases, scientists need to involve genetically modified animals, that is, transgenic and gene-targeted mice. Such animal strains mimic human diseases, thus allowing the assessment of the efficacy of new medicines. Moreover, the use of genetically modified mice can potentially reduce the use of higher animals, such as nonhuman primates in drug development.

Development of New Diagnostic Tests for Diseases. If the treatment of a disease is to be effective, an accurate and quick diagnosis is essential. Animal experiments are vital in this area, which includes scanning of unborn babies to identify cancers, diagnosing heart diseases, and so on. Furthermore, animal tests have paved the way for many blood tests used infectious disease diagnosis.

In Biology and Medical Education. Animals are used in schools and colleges to contribute to the understanding of basic anatomy and physiology of man and other species. Medical research in the last 100 years has facilitated many ways to treat and prevent diseases in humans as well as in animals [14–16].

14.3 ANIMAL RIGHTS: AN ISLAMIC PERSPECTIVE

Islam not only has laid down the rights for humans regardless of race, color, language, and class or status, but has also laid down rights for animals. Animals, like humans are one of the creations of God. Prophet Mohammad (PBUH) was sent as a blessing to all creatures. The Holy Quran and *Hadith* by the Prophet provide broad guidelines concerning the spiritual and material aspects of life. While using animals for his service, man should not unnecessarily hurt or harm them. Although the plants and the animals are created for the benefit of mankind, the sacrifice of their lives is subjected to the condition laid down by the Holy Quran. The Prophet taught Muslims to be kind to animals and to be merciful toward all living things. Thus, there is reward for a human merely for feeding an animal. Islam gave animals rights at a time when animal rights were not recognized. Today the world acknowledges such rights, while Islam guaranteed them more than 1400 years ago. The most famous story about being kind to animals is seen when a cat came and slept on the robe of Prophet Mohammad (PBUH) while he was reading the Quran to the believers. When it was time for the Prophet to get up, instead of disturbing the cat, he cut that piece of the robe and stood up. The Prophet encouraged people to be good toward the animals and forbade acts that are cruel. Oppression is an evil whether the one being oppressed is human or an animal. Islam takes great care when laying down rules and regulation and it has made sure that men do not behave cruelly toward animals. Even in a state of war, Muslims are prohibited from killing animals within enemy lands and are also prohibited from burning or cutting down trees for no reason. Indeed, Islam is not only a religion but a complete way of life that additionally secures the rights of animals. Therefore, Muslim scientists must respect animals as created beings and not merely as laboratory tools. They have an ethical obligation to ensure that their research goals cannot be achieved without using animals. Whether a product is worth the animal suffering that it engenders, is a matter to be decided by society at large, but if substances are to be produced for human use, it is necessary that they be tested. As moral beings, man should not even countenance suffering on the part of animals except when it serves a clearly defined, higher purpose such as saving of precious life. Taken together, animal experimentation should take place when and where there are no real alternatives [14–17].

14.4 OVERVIEW OF THE CURRENT REGULATION OF HERBAL REMEDIES

All drugs, including "traditional" and "lifestyle" drugs, are regulated by the same provisions of health agencies, such as the Food and Drug Administration in the United States and the Food Drug and Cosmetic Act (FDCA). A drug is defined as a "new drug" and requires the submission of a new drug application (NDA) and premarket approval from the FDA, unless it "generally recognized as safe and effective" (GRAS/E) and has been used for a material extent and material time. The hurdle for a drug to be considered GRAS/E is substantial and generally requires the

types of scientific, well-controlled studies necessary to obtain premarket approval for a new drug. There are no specific provisions regulating traditional herbal medicines in the FDCA. Herbal remedies can theoretically be regulated under the same drug provisions as drugs. Indeed, the FDA has attempted address the application of drug regulations to herbal remedies. However, herbal remedies typically also qualify for regulation as dietary supplements under the Dietary Supplement Health and Education Act (DSHEA) of 1994. The regulatory regime applied to a given product is determined by the manufacturer or distributor's intended use. Intended use can be determined from any relevant source, including claims in the product's advertising and labeling. If the claims of the product include the cure, treatment, mitigation, or prevention of disease, the herbal remedy will be regulated as a drug. However, under DSHEA, dietary supplements can make "structure/function" claims, and still be excluded from regulation as a drug. In exchange for the prohibition on disease claims, dietary supplements are not subject to premarket approval. Despite the FDA's efforts to adapt drug regulations to herbal remedies, the availability of substantially less stringent regulatory regime of "dietary supplements" under DSHEA has effectively resulted in herbal remedies being regulated as dietary supplements (Figure 14.1).

Before a new drug, surgical procedure, or therapy becomes available to clinical uses, it must pass through a rigorous testing process and be evaluated by national and international regulatory health authorities, such as the FDA. These studies include information on the safety of using the drug in clinical investigations, through

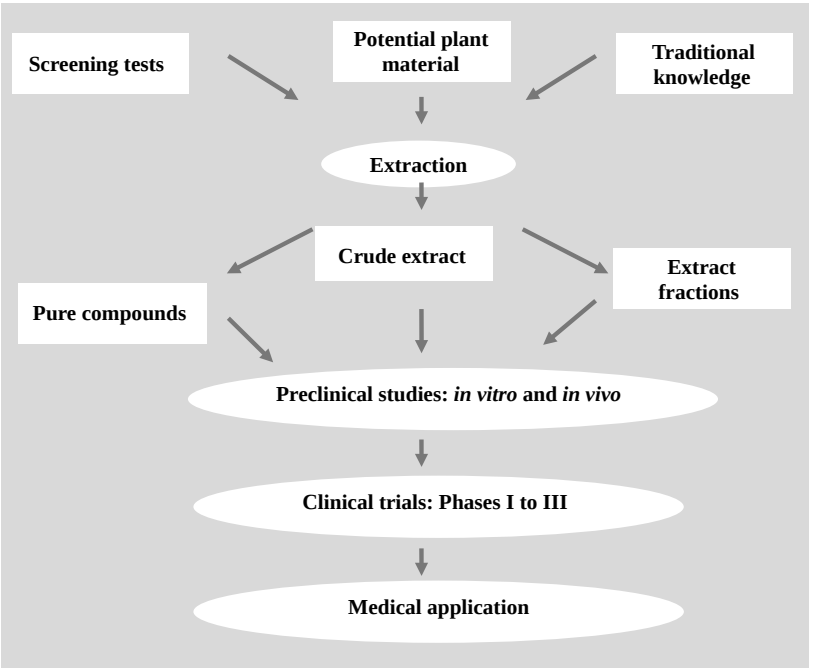

FIGURE 14.1 Overview of the current regulation of herbal-derived medicines.

preclinical pharmacological and toxicity studies in animals or *in vitro*, and a description of the chemical and manufacturing processes. Clinical investigations are generally conducted in three phases as described under Section . The vast majority of animals used in research are rats and mice (e.g., over 95% in the United States). Very few studies use dogs, rabbits, or nonhuman primates. A large majority of the animals used in research and development are specifically bred for research. Phase I studies typically consist of 20–80 people and are used to determine the metabolism and pharmacology of the drug in humans so that the design of Phase II can be optimized. Phase II studies are designed to evaluate the effectiveness of the drug and determine short-term side effects and risks; Phase II typically consist of several hundred people. Phase III studies are designed to assess safety and effectiveness, evaluate the overall risk and benefit of the drug, and determine the drug's labeling; Phase III usually require several hundred to several thousand people [17–21].

14.5 CURRENT TRENDS IN DRUG DEVELOPMENT AND ANIMAL TESTS

14.5.1 Preclinical Testing

Preclinical study represents a stage of research that begins before clinical testing in humans can begin. During this phase important toxicity, pharmacokinetics, and feasibility studies are performed. These studies involve exhaustively *in vivo* test systems. However, current trends are directed toward the use of sophisticated *in vitro* test systems (e.g., three-dimensional cell cultures) as alternative to animal tests as discussed in details in Chapters 11 and 13.

The main objectives of preclinical investigations are to determine a product's ultimate safety profile. Products may include new medical devices, drugs, gene therapy solutions, and so on. Each class of product may undergo different types of preclinical tests. For instance, drugs may undergo the following:

- *Pharmacodynamics*: The study of the physiological effects of drugs within/on the body, the mechanisms of drug action and the relationship between drug concentration and effect.
- *Pharmacokinetics*: The determination of the fate of substances administered to a living organism.
- *ADME*: Assessments of drug's absorption, distribution, metabolism, and excretion, and describe the disposition of a pharmaceutical compound within an organism.
- Toxicity testing through animal testing and *in vitro* studies. Data obtained allows researchers to estimate a safe starting dose of the drug for clinical trials in humans.

Most preclinical studies must adhere to Good Laboratory Practice or "GLP" guidelines of "The International Conference on Harmonization of Technical

Requirements for Registration of Pharmaceuticals for Human Use" (ICH) in order to be acceptable for submission to regulatory agencies. ICH is a project that brings together the regulatory authorities of Europe, Japan, and the United States and experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of pharmaceutical product registration.

As aforementioned, both *in vitro* (see also Chapters 11 and 13) and *in vivo* tests are performed during the preclinical phase. Toxicity studies include determination of site of activity (target organs) by that drug as well as long-term carcinogenic effects or toxic effects on mammalian reproduction. Results obtained from both *in vivo* (typically, animal testing involves two species) and *in vitro* studies are essential so that safe human testing can begin. The most commonly used models are murine and canine, although primate and porcine are also used. The choice of an appropriate animal model is based on which will give the best correlation to human trials. Differences in the anatomy (gut, circulatory system) and physiology make certain models more appropriate based on the dosage form, site of activity, or noxious metabolites. For instance, canines may not be appropriate models for solid oral dosage forms because the characteristic carnivore intestine is underdeveloped compared to the omnivores, and gastric emptying rates are higher. Also, rodents cannot be used as models for antibiotic drugs because the resulting alteration to their intestinal flora causes significant adverse effects. Depending on a drug's functional group, it may be metabolized or biotransformed in similar or different ways between species, which will affect both efficacy and toxicology. Furthermore, some species are used for similarity of specific organs or organ system physiology (swine for dermatological and coronary stent studies, goats for mammary implant studies, dogs for gastric studies, etc.).

Extrapolation of results from animal to man should be carried out with great caution. This issue was first noted by Avicenna who laid out the following principle for testing the toxicity and efficacy of a new medication: "The experimentation must be done with the human body, for testing a drug on a lion or a horse might not prove anything about its effect on man." Animal models only mimic the symptoms in man, but not the etiology or the overall clinical perspective. Thus, it is not possible to say that an extract that lowers blood pressure in rats rendered hypertensive by L-NAME, where the hypertension is due to endothelial dysfunction, would function beneficially in a patient whose hypertension is due to another cause. Streptozotocin induced diabetes in rats is not exactly diabetes in man. Not only is the condition different in etiology, but the human response may be quite different from that of the rat, particularly since diabetes in man is normally associated with a number of events that are not regularly seen in the rat. The metabolism and pharmacokinetic behavior of active constituents may differ from species to species, and accordingly the interpretation of animal findings may not necessarily be applicable to man. In general, therefore, animal models are artificially induced conditions said to be analogous to the human diseases they are intended to simulate, but they differ substantially from their human counterparts in both cause and clinical course. This also holds true for toxicological studies. Such studies should always be performed according to international guidelines and are a prerequisite for evaluating the safety of potentially useful therapeutic agents.

Based on preclinical trials, no observable effect levels (NOEL) on drugs are established, which are used to determine initial phase 1 clinical trial dosage levels on a mass API (active pharmaceutical ingredient) per mass patient basis.

14.5.1.1 In Vivo Test Systems The basic reason for animal trials is to determine two issues before any new compound is introduced into a human: safety and efficacy, whether a compound is safe for human ingestion and also whether or not a medication works for its intended purpose. Indeed, that process begins way before getting to animals. But at some point in the process it is critical to understand how a potential drug, for instance, an antihypertension medication, works in a whole living system. In addition to determining its effects on blood pressure or the heart, effects on all organs must be studied.

As aforementioned, safety and efficacy studies have to be carried out ultimately on laboratory animals and this has many ethical considerations regarding proper conduct and the relative cost versus the expected outcome. The use of laboratory animals is unavoidable but should be rationalized through careful planning. Preliminary *in vitro* testing should give some idea of the possible mechanisms of action and potential therapeutic usefulness of an herbal extract, but this obviously has its shortcomings. Such tests provide no information regarding biotransformation of the extract in the body, pharmacokinetic aspects of absorption and fate of the drug in the body. To determine potential therapeutic usefulness in a certain diseased state, however, appropriate animal models have been developed that mimic, to some extent, the human condition. Animal models have been developed for a multitude conditions, including hypertension, myocardial infarction, atherosclerosis, ischemia, bronchial asthma, arthritis, diabetes, parkinsonism, depression, epilepsy, gastric ulcers, reflux esophagitis, inflammatory bowel disease, and cancer among others.

Preclinical Toxicity Testing. In order to be certain that a new drug is safe, detailed *in vivo* and *in vitro* investigations are conducted including dose-dependent and time dependent studies. In the first series of experiments acute, subacute, and chronic studies are performed and data is collected. These include the following:

(a) *Acute Studies*: Short-term, acute studies are usually performed in one or more rodent species with the aim to assess the dose range for lethality of a test substance. Results gained in these studies (e.g., LD_{50}) are used to set doses for longer term, subchronic experiments. Acute studies can determine toxicity, time of onset of toxic signs, and recovery in the surviving animals. This data is crucial in an emergency situation where humans or animals are exposed to high concentrations of a toxic molecule. Occasionally, acute toxicity studies are used to establish antidotes to a given toxicant.

(b) *Subchronic Studies*: These studies are long term (generally 3–6 months) and are conducted using multiple doses. The purpose of subchronic studies is to determine target-organ toxicity, to determine the effects of prolonged dosing, and to help establish margins of safety for food additives and drugs. Subchronic studies are generally conducted in both sexes of two laboratory

animal species, one of which is a nonrodent species. At the end of a study all animals are autopsied and a complete gross and microscopic examination of tissues is performed. In addition, complete blood chemistries are evaluated and an overall clinical assessment is made on each animal.

(c) *Chronic Studies*: The next stage of toxicity study is the chronic testing. As for subchronic studies, this study is conducted in multiple species, in both sexes, and for a duration that approaches the life-span of the animal. These are very large and complex studies that necessitate a great deal of day-to-day management. There are multiple intermediate clinical evaluations, including daily observations, weekly food and water consumption, and body weight determinations. At the end of this period animals are killed, and their vital tissues, such as liver, heart, kidney, intestine, brain, and so on, are removed and studied grossly and microscopically by a pathologist. In addition to gross and microscopic pathology, biochemical, and physiological responses are measured as an indication of liver function, kidney function, endocrine function, and so on. Chronic toxicity studies provide a thorough examination of the dose effect of a given chemical on homeostasis, bodily function, induced diseases, and the effect on life-span. Chronic toxicity studies provide the bulk of the preclinical information used for assessing safety and risk.

LD_{50}. Is defined as the dose of a test substance estimated to be fatal to 50% of test animals under standard conditions of the test. These tests are frequently performed as a general indicator of a substance's acute toxicity. Data gained here have to be interpreted with necessary precaution since results may vary greatly between testing facilities due to factors such as the genetic characteristics of the sample population, environmental factors and mode of administration. For instance, many substances are less toxic when administered orally than when intravenously administered. For this reason, LD_{50} data are often qualified with the mode of administration, for example, "LD_{50} i.v." The substances are applied to the skin or eyes, injected intravenously, intramuscularly, or subcutaneously, administered orally, through a tube into the stomach, or by placing them in the animal's food. Doses may be given once, repeated regularly for many months, or for the life-span of the animal. The test is conducted without anesthesia, since drugs can change test results. The LD_{50} is usually expressed as the mass of substance administered per unit mass of test subject, such as grams of substance per kilogram of body mass. Stating it this way allows the relative toxicity of different substances to be compared, and normalizes for variation in the size of the animals exposed (although toxicity does not always scale simply with body mass). Typically, the LD_{50} of a substance is given in milligrams per kilogram of body weight (e.g., 11,900 mg vitamin C/kg, tested in rat after oral administration; the estimated LD_{50} for Botulinum toxin in humans is 1 ng/kg.).

Draize Test. The test involves applying 0.5 mL or 0.5 g of a substance to an animal's eye or skin (usually albino rabbits who are conscious and held immobilized in stocks) for 4 h. The animals are observed for up to 14 days for signs of erythema and edema on the skin, and redness, swelling, discharge, ulceration, hemorrhaging, cloudiness, or

blindness in the eye. The test is controversial and it is viewed as unnecessarily cruel by critics, as well as unscientific because of the differences between rabbit and human eyes. Despite two decades of research into alternatives to this test, no nonanimal alternatives have yet been successful, although the low-volume eye test is being investigated as an alternative that may reduce, but not eliminate, animal suffering. Because of its controversial nature, the use of the Draize test in the United States and Europe has declined in recent years and is sometimes modified so that anesthesia is administered and lower doses of the test substances used. Chemicals already shown to have adverse effects *in vitro* are not currently used in a Draize test, thereby reducing the number and severity of tests carried out.

Reproductive and Developmental Toxicity. Reproductive toxicity includes the toxic effects of a substance on the reproductive ability of an organism and the development of its offspring. It has been defined as any effect of chemicals that would interfere with reproductive ability or capacity, including effects on lactation that can be manifested at any point in the life-span of the organism. Animal tests are used to assess reproductive and developmental toxicity. These include evaluating the effects of prenatal exposure on pregnant animals and their offspring. This test is usually performed with female rats and rabbits. The test compound is administered orally, the pregnant animals are killed just prior to delivery, and the fetuses are examined for toxic effects. Reproductive and developmental toxicity tests can be conducted as follows:

- *One-Generation Reproduction Toxicity*: A one-generation reproductive toxicity study in rats or mice is used to evaluate toxic effects on male and female reproduction. Males and females are dosed orally before mating and again during pregnancy.
- *Two-Generation Reproduction Toxicity*: A two-generation reproductive toxicity study continues dosing with the test substance to the first-generation offspring. OECD TG 421 (Reproductive/Developmental Toxicity Screening Assay) uses male and female rats with the test substance administered orally for 4–9 weeks. Pathological effects are determined by daily observation, necropsy, and microscopic histopathology.

Developmental Neurotoxicity. Developmental Neurotoxicity Study involves the daily oral feeding of a test substance to female rats (preferred species) from the time of mating through lactation. The purpose is to determine *in utero* and early postnatal developmental neurological effects of the test substance. Offspring are evaluated for neurotoxic effects including gross neurologic and behavioral abnormalities, and the evaluation of brain weights and neuropathology during postnatal development and adulthood.

Chronic Toxicity Test. As mentioned above, these studies are generally conducted in both sexes of two laboratory animal species, one of which is a nonrodent species. These studies are of a longer duration, generally 3–6 months, and are conducted using

multiple doses. At the end of the test period, animals are killed and their vital tissues are removed and studied. Furthermore, biochemical and physiological responses are measured as an indication of liver function, kidney function, and endocrine function. These studies make up the bulk of the preclinical information used for assessing safety and risk.

Toxicokinetic Study. Toxicokinetic (TK) studies are conducted to characterize the absorption, distribution, metabolism, and elimination (ADME) of xenobiotic materials and to quantify the influence of exposure on those properties. Toxicokinetic studies help to interpret the results of toxicology and carcinogenicity studies with respect to the relationship between toxic effects and external exposure, and define the parameters of dose, distribution, metabolism, and elimination that can be used in human risk assessment and addresses the questions: Is the chemical absorbed? How is the chemical metabolized? Where are the chemical and/or metabolites distributed in the body? What are the elimination rate and route of the chemical? What is the effect of dose on absorption, distribution, metabolism, and elimination? Toxicokinetic studies also investigate the effects of sex, species, and age on ADME. Data collected during a toxicokinetic study focus on time profiles of parent chemical and metabolite concentrations in plasma and other tissues and can include rates of chemical absorption, metabolism, and excretion, chemical related changes in blood chemistry, bioavailability, protein binding, and depletion of cofactors.

Repeated Dose/Organ Toxicity. Repeated dose toxicity testing using oral administration of a test substance in rodents for 28 and 90 days is used to evaluate chronic toxic effects, primarily effects on various organ systems, and to establish a NOEL. Depending on the potential route of human exposure to the substance, similar testing using dermal and inhalation dosing may also be assessed. Doses are selected to be sublethal but still cause toxic effects. Long-term chronic toxicity studies with a minimum duration of 12 months are sometimes required.

Chronic toxicity testing consists of oral, dermal, and inhalation subacute repeated dose studies (28-day) and subchronic repeated dose studies (90-day) in rodents. Testing on both sexes is required. Some agencies may also require testing in a nonrodent species, typically dogs or nonhuman primates, and some agencies require longer testing periods (52 weeks). The most commonly performed studies are 28-day and 90-day oral toxicity tests in rodents. The end points for repeat dose testing consist of an evaluation of clinical observations, blood analysis, whole body gross necropsy, and microscopic examination of all organs and tissues (histopathology). The target organs/systems evaluated may include liver, kidney, lung, neural (central nervous system), reproductive organs, the hematopoietic system, the immune system, and the endocrine system.

Carcinogenicity Test. The term carcinogen denotes a substance or a mixture of substances that induces tumors (benign or malignant), increases their incidence or malignancy, or shortens the time of tumor occurrence when they are inhaled, injected, topically applied, or ingested. Carcinogens are classified according to their mode of

action as genotoxic or nongenotoxic carcinogens. Genotoxic carcinogens initiate carcinogenesis by direct interaction with DNA, resulting in DNA damage or chromosomal aberrations that can be detected by genotoxicity tests. Nongenotoxic carcinogens are agents that, at least initially, directly interact with DNA. These indirect modifications to DNA structure, amount, or function may result in altered gene expression or signal transduction.

Substances that induce tumors in animals are considered to be presumed or suspected human carcinogens until convincing evidence to the contrary is presented. The conventional test for carcinogenicity is the long-term rodent carcinogenicity bioassay. The objective of this test is to observe test animals for a major portion of their life-span for the development of neoplastic lesions during or after exposure to various doses of a test substance by an appropriate route of administration. The study is usually conducted using two species; rats and mice of both sexes are typically used. The animals are dosed by oral, dermal, or inhalation exposures, based upon the expected type of human exposure. Dosing typically lasts around 2 years. Certain animal health features are monitored throughout the study, but the key assessment resides in the full pathological analysis of the animal tissues and organs when the study is terminated.

There is no question that rodent tests are needed to definitively identify and characterize carcinogens, or to demonstrate noncarcinogenicity, despite the fact that the animal tests may not have 100% accuracy in identifying human carcinogens and noncarcinogens. However, because of the potential societal burdens of introducing new carcinogens into commerce, especially as food additives, drugs, and biocides, the animal test remains the most reliable indicator of human carcinogenicity, other than retrospective epidemiology studies. Carcinogenesis is discussed in details below under preclinical tests for identifying cancer chemopreventive compounds.

14.5.1.2 In Vitro Preclinical Studies *In vitro* toxicology, a multidisciplinary research field, applies isolated organs, isolated tissues, cell culture, biochemistry, and chemistry to evaluate toxic effects or adverse reactions to xenobiotics (e.g., herbal medicines). In general, these tests represent the first phase of the evaluation procedure. Various *in vitro* test systems are presently used to assess potential hepatotoxicity, carcinogenesis, mutagenesis, hormone action, immunotoxicity, eye irritation, and cellular and molecular. Advantages of these systems over animal tests, include relatively well-controlled variables, relative affordability, reduced completion time, ability to study specific mechanisms of action, and reduced numbers of animals necessary to complete the study. These tests are generally accepted as a very effective method for safety assessment in the preclinical stage. The disadvantage of these tests is that the homeostatic mechanisms and pathways found in animals are not present. For instance, *in vitro* assessment of adverse reactions to xenobiotics can only be measured to a limited extent. Although some advanced *in vitro* systems are available that allow prediction of the local effects of test pharmaceuticals, even the most sophisticated *in vitro* test cannot yet be used to measure systemic effects (e.g., blood pressure or fever). *In vitro* techniques and their applications in efficacy and safety assessment are discussed in depth in Chapters 11 and 13. Here we will focus on

the cell culture systems that are the most widely used *in vitro* method in safety assessment of new medicines [20–29].

In order to determine the effects of xenobiotics (e.g., herbal medicines, plant extracts or purified herbal-derived substances) cells cultured in monolayers on artificial substrate are applied. Three-dimensional culture models provide a well-defined environment for *in vitro* research in contrast to the complex host environment of an *in vivo* model. Due to their enormous potential 3D tumor cultures are currently being exploited by many branches of biomedical science with therapeutically orientated studies becoming the major focus of research. Recent advances in 3D culture and tissue engineering techniques have enabled the development of more complex heterologous 3D tumor models [25,27,29].

In vitro cytotoxicity studies are based on treatment of isolated cells with different concentrations of a test compounds. Cytotoxicity is assessed by various methods including microscopic evaluation of cell morphology, methyltetrazolium assay (MTT test), measurement of DNA and protein synthesis, lactate dehydrogenase (LDH) activity, neutral red uptake, and apoptosis tests [20–29].

14.5.2 Preclinical Efficacy Testing

Numerous preclinical *in vitro* and *in vivo* efficacy testing models are currently used to identify, assess, and prioritize synthetic chemicals and natural products with the aim of preventing and/or treating diseases. The first step of the preclinical tests is a sequential series of short-term *in vitro* screens of biological and biochemical assays. These assays provide quantitative data to help establish an early indication of therapeutic and/or chemopreventive potential and to assist in prioritizing agents for further investigation in longer term *in vitro* transformation bioassays and animal models. As for safety testing, the reliability of animal tests in pharmacodynamic and pharmacokinetic studies is questionable and the main question remains: what do animal trials really tell us about humans?

Here again, as aforementioned regarding toxicity testing, animals are surrogates for humans. The basic reason for animal trials is to determine two issues before any new compound is introduced into a human: safety and efficacy in its intended purpose. Over the past 70 years, scientists have figured out what works best in which models. The vast majority of animals used in efficacy testing are rodents, either rats or mice. Due to the relatively short life-span of rodents, the effects of a test compound can be assessed in young animals, and can also be assessed when such animals reach adulthood. Multigenerational studies are also possible, all within a reasonably short time frame. If the test compound is determined to be safe and effective in a rodent, its effects in another species are explored. For instance, for a neurological compound, oftentimes the cat is the preferred model because the neurological system of the cat more closely mimics that of a human. However, in cardiovascular studies, dogs or pigs serve as excellent models for cardiovascular experiments. Drug candidates with the desired *in vivo* efficacy profile may be further profiled *in vitro*, using assays such as metabolic stability, and cytochrome P450 inhibition and induction. Other important factors that can be studied *in vitro* are drug metabolism and biotransformation. The

usual effect of metabolism is to convert drugs into compounds that are less active, less toxic, and more readily excreted. However, there are examples in which metabolism sustains or increases the activity. In addition, it is known that only unbound drugs are pharmacologically active and therefore the assessment of a bound fraction by the estimation of plasma protein binding of a compound are other important parameters to be explored *in vitro*. Furthermore, an important part of pharmacology is the study of drug absorption, distribution, metabolism and excretion, that is, pharmacokinetics. The metabolism of drugs is an important topic in drug development and considerable effort is spent on detailed analysis of the bioconversions that a new drug undergoes. Modern analytical methods, such as mass spectrometry, permit the identification of minute amounts of metabolites.

Numerous preclinical *in vitro* and *in vivo* efficacy testing models are currently used to identify, assess, and prioritize synthetic chemicals and natural products. Discussing these efficacy tests will exceed the scope of the present chapter; therefore, in the following we will discuss preclinical tests used to identify cancer chemopreventive compounds using *in vivo* and *in vitro* test systems.

14.5.2.1 Preclinical Tests for Identifying Cancer Chemopreventive Compounds Cancer chemoprevention is the use of natural, synthetic or natural compounds to reverse, block, or prevent the development of tumors. Cancer begins when cells become abnormal and grow uncontrollably. The transition from a healthy cell to a cancerous one usually takes many years and occurs in a series of steps influenced by genetic, dietary, and environmental factors. The goal of chemoprevention is to delay the development of cancer, not to treat existing cancer.

The first step of the preclinical tests is a battery of short-term *in vitro* screens of biological and biochemical assays. These assays provide quantitative data to help establish an early indication of chemopreventive potential and to assist in prioritizing agents for further investigation in longer term *in vitro* transformation bioassays and animal models. Potential chemopreventive agents or combinations of agents that work through different inhibitory mechanisms are subsequently tested in well-established chemically induced or spontaneous animal cancer models, which typically include models of the colon, lung, bladder, mammary, prostate, and skin. Representative cancer models are listed in Table 14.1. These animal tests represent a strategic framework for evaluating chemopreventive agents according to defined criteria, and not only provide evidence of agent efficacy, but also serve to generate valuable dose-response, toxicity, and pharmacokinetic data required prior to Phase I clinical safety testing. Based on preclinical efficacy and toxicity screening studies, only the most successful agents considered to have potential as human chemopreventives will progress into clinical chemoprevention trials [30–41].

In Vivo Short-Term Screening Tests. Short-term assays identify compounds that might inhibit carcinogenesis in the early stages. Two test systems, which reflect major cancers in humans, are being used. They include the rat model of breast ductal carcinoma *in situ* (DCIS) model and the rat and mouse colorectal aberrant crypt foci (ACF) assay.

TABLE 14.1 Preclinical Animal Models for Studying Chemoprevention Efficacy

Induced Tumors	Carcinogens	Tissues and Species
Adenocarcinoma; adenoma; aberrant crypt foci	Azoxymethane; dimethylhydrazine; methylazoxymethanol acetate	Colon: mouse/rat
Squamous cell carcinoma; squamous cell papilloma	4-Nitroquinoline 1-oxide	Esophagus: mouse/rat
Squamous cell papilloma	Benzo[*a*]pyrene	Forestomach: mouse
Hepatocellular carcinoma; adenoma	2-Acetylaminofluorene; diethylnitrosamine; dimethylnitrosamine	Liver: mouse/rat
Squamous cell carcinoma; adenocarcinoma; adenoma	Benzo[*a*]pyrene; dimethylbenz[*a*] anthracene; urethane; 4-nitroquinoline 1-oxide	Lung: mouse
Adenocarcinoma; adenoma; fibroadenoma	Dimethylbenz[*a*]anthracene	Breast: mouse/rat
Adenocarcinoma; adenoma; acinar cell carcinoma	*N*-Bis(2-oxopropyl) nitrosamine; azaserine	Pancreas: hamster (duct cell); rat (acinar cell)
Squamous cell carcinoma; squamous cell papilloma	UV radiation; benzo[*a*] pyrene/12-*O*-tetradecanoylphorbol-acetate	Skin: mouse
Transitional cell carcinoma	*N*-Butyl-*N*-(4-hydroxybutyl) nitrosamine	Urinary bladder: mouse/rat
Transitional cell carcinoma	*N*-Methyl-*N*′-nitro-*N*-nitrosoguanidine; *N*-methyl-*N*-nitrosourea	Stomach: rat
Squamous cell carcinoma; squamous cell papilloma	4-Nitroquinoline 1-oxide	Tongue: mouse/rat

DUCTAL CARCINOMA IN SITU MODEL ASSAY. This assay is generally used for gaining toxicity as well as efficacy data of potential chemopreventive agents prior to testing in mammary cancer models. Therefore, the induction of mammary carcinogesis is initiated in weanling female rats by the intraperitoneal injection of the carcinogen *N*-methy1-*N*-nitrosourea. In general, test agents are administered in the diet, starting 1 week after the carcinogen administration, and thereafter are continued until the termination of the study (45–50 days later). Histopathological analyses of mammary tissue specimens are then performed. The efficacy is estimated as the percent reduction in the number of DCIS lesions in comparison to controls that receive a carcinogen alone.

ABERRANT CRYPT FOCI ASSAY. This is a short-term animal model that can identify effective compounds in preventing colorectal cancer (CRC). ACF are putative preneoplastic lesions consisting of aggregates of single and multiple crypt cells that

exhibit hyperplasia and/or dysplasia and are thought to be the earliest detectable lesions of CRC.

Two different protocols are available: The first protocol identifies compounds that inhibit initiation. Here, rats are given a test agent in the diet 1 week prior to the administration of a colonic carcinogen and continuing throughout the 5-week study period. The second protocol evaluates potential chemopreventive agents during the postinitiation phase of colorectal carcinogenesis. Therefore, rats are first treated with carcinogen, followed 4 weeks later by a test agent, which is given for additional weeks. Animals are killed and the ACF frequency is determined by microscopic evaluation.

Animal Efficacy Tests. Numerous animal models are used to study inhibition of chemical carcinogenesis in rodents. Representative carcinogenesis models are listed in Table 14.2. Typically, test agents are administered in the diet unless problems with stability are encountered. During the course of chemoprevention studies a maximum tolerated dose (MTD), defined as the highest dose level that does not cause $\geq$10% reduction or gain in body weight over a 6-week period, is determined. The treatment schedules include the administration of test agents either before, concurrently, or following exposure to the carcinogen. Effectiveness is based upon the percent inhibition of tumor incidence and/or multiplicity, or increased tumor latency in comparison to controls.

COLORECTAL CANCER MODELS. Potential inhibitors of colorectal carcinogenesis can be assessed utilizing rats and mice models. According to established protocols, 1,2-dimethylhydrazine or methylazoxymethanol acetate is administered intraperitoneally or subcutaneously, thus resulting in colorectal adenocarcinoma development within

TABLE 14.2 Proposed Mechanisms of Food and Medicinal Plants for Cancer Prevention

Plant	Compound	Antioxidant/ Anti-Inflammatory	Antimetastasis	Apoptosis Induction	Antiangiogenesis
Olive	Oleuropein	+	+	+	+
Milk thistle	Silymarin	+		+	+
Onion	Quercetin	+		+	+
Garlic	Diallyl sulfide	+		+	+
Tumeric	Curcumin	+		+	+
Black seeds	Thymoquinone	+	+	+	+
Pomegranate	Several polyphenols	+	+	+	+
Honey	Several active compounds	+	+		
Figs	Several flavonoids	+	+		

32–40 weeks in either species. The test agents can be orally administered either before, during, or following carcinogen treatment. In comparison to rats, mice should receive multiple exposures of a colonic carcinogen to induce colonic tumors and tumor development needs long-term period. A mouse model recently established for colorectal carcinogenesis, in which different colonic carcinogens are followed by a colitis-inducing agent, dextran sodium sulfate, is quite useful to identify potential chemopreventive agents within a short-term period.

HEAD AND NECK CANCER MODELS. Several well-established models of oral and respiratory tract cancer are applied. The buccal pouch squamous cell carcinoma is induced with topically applied 7,12-dimethylbenz[*a*]anthracene for a period of more than 12 weeks. Rats and mice develop tongue cancers when exposed to 4-nitroquinoline 1-oxide (4-NQO). Tongue squamous cell carcinomas and dysplasia can be induced in rats with 4-NQO in drinking water for 8 weeks. Tongue dysplasia occurs during 4-NQO treatment and the incidence of tongue squamous cell carcinoma is over 50% at 32 weeks after the exposure. In this model, test chemicals can be orally administered either before, during, or following 4-NQO exposure. Other tests models are listed in Table 14.1.

URINARY BLADDER CANCER MODELS. Urinary bladder neoplasms are typically induced by the carcinogen *N*-butyl-*N*-(4-hydroxybutyl)nitrosamine that can induce invasive transitional cell carcinomas morphologically similar to those found in humans. This carcinogen is given either intragastrically or in drinking water over an 8-week period to 50-day-old BDF mice or F344 rats, thus resulting in a 40–50% incidence of bladder tumor incidence at 180 days after treatment.

MAMMARY CANCER MODELS. Chemopreventive efficacy against mammary gland tumors routinely induced either with *N*-methyl-*N*-nitrosourea or 7,12-dimethylbenz[*a*] anthracene predominantly produce adenoma/fibroadenoma or invasive adenocarcinomas, respectively. Both protocols utilize female SD rats and require that the carcinogen is given as a single dose at 50 days of age. Tumor incidences at 120 days after carcinogen treatment are similar, ranging from 80 to 100% in the 7,12-dimethylbenz[*a*]anthracene protocol and 75–95% in the *N*-methyl-*N*-nitrosourea model. The chemopreventive activity of the test agents is determined by the percent reduction in tumor incidence or percent increase in tumor latency relative to controls treated with the carcinogen alone. These models produce hormonally responsive tumors. In addition to these mammary cancer models, several genetically engineered animals have been introduced to investigate breast carcinogenesis and evaluate the efficacy of potential chemopreventive compounds. They include a COX-2 overexpressing mouse model, a *Ras*-driven mouse mammary tumorigenesis model, and a HER-2/neu transgenic mouse model.

SKIN CANCER MODELS. Potential chemopreventive compounds in skin carcinogenesis can be assessed in a two-stage skin carcinogenesis model utilizing 7,12-dimethylbenz [*a*]anthracene and 12-*O*-tetradecanoylphorbol-13-acetate. These carcinogens are

applied topically to the back skin of mice. Skin papillomas appear as early as 6 weeks postcarcinogen treatment, eventually progressing to squamous cell carcinomas by 18 weeks. Test compounds are generally administered in the diet or in some experiments are topically applied according to several predefined treatment regimens.

Transgenic and Gene-Knockout Animal Models. Gene-knockout and transgenic and mice that carry defined genetic lesions predisposing them to carcinogenesis are appropriate models for chemoprevention testing. Some of the best developed models include the multiple intestinal neoplasia (Min) mouse and other strains possessing lesions in the Apc gene. These animals develop predominantly small intestinal adenomas, but a few in the large intestine. By manipulating two or more carcinogenesis-associated genes, such as modifier genes, in a single animal, closer approximations of human carcinogenesis may be possible. Numerous colonic tumors develop in the large bowel in Min mice at 3 weeks after 1-week-exposure of dextran sodium sulfate, thus suggesting the importance of gene–environmental interaction in cancer development. It might be feasible to knockout p53 in an animal that already carries another tumor suppressor defect such as Apc or p16. Recently, new transgenic animal models for mammary, tongue, pancreas, and gall bladder cancers have been reported. These models might be useful in identifying novel cancer chemopreventive agents.

14.6 PREVENTION AND TREATMENT OF CANCER IN THE GRECO-ARAB AND ISLAMIC MEDICINE

Worldwide at present, over 10 million new cases of cancer including over 6 million deaths, were estimated in the year 2000. Since 1990 there has been a 22% increase in cancer incidence and mortality with the four most frequent cancers being lung, breast, colorectal, and stomach and the four most deadly cancers being lung, stomach, liver, and colorectal. Cancer is the second leading cause of death in the United States, surpassed only by cardiovascular disease. Although these figures are disquieting, some progress has been made in cancer diagnosis and treatment as evident through the high incidence of breast, prostate, testicular, and uterine cancers as compared with their relatively low mortality.

Modern medicine describes cancer as a group of diseases characterized by uncontrolled cell proliferation that results in a tumor or a neoplasm. Carcinogenesis is a long and multistep process that includes three main stages; initiation (selection of a mutated cell), promotion (selective proliferation of the initiated cell) and progression as a consequence of an imbalance between cell proliferation and cell death (e.g., apoptosis). Additional genetic and epigenetic events are required for the progressive conversion of initiated normal cells into cancer cells. The establishment of a mutation is a prerequisite of cancer. Several factors can trigger carcinogenesis such as environmental agents or the activation of oncogenes. Most notable among proneoplastic mutations are those that result in increased expression of oncogenes (e.g., myc, ras, bcl-2) or decreased activity of tumor-suppressor genes (e.g., p53), conferring a

selective growth or survival advantage to the cell. Phenotypic changes representative of preneoplastic mutations include a decreased need for metabolites and growth factors, abnormal signal transduction, inappropriate expression of receptors for available growth factors (epidermal growth factor receptor, HER2/neu), dysregulation of cell-cycle checkpoints and resistance to apoptosis. At this point, any agent that causes increased cell proliferation increases the risk of neoplastic transformation. The damage to the DNA must survive the many DNA-repair processes and must be readable by DNA polymerase, which creates and locks in the mutation. If, by chance, this damage to the DNA results in a selective growth or survival advantage to the cell, it may become a precancerous lesion.

Avicenna (980–1037) described cancer as a tumor in the *Canon*. He noted that a "cancerous tumor progressively increases in size, is destructive and spreads roots which insinuate themselves among the tissue elements." Avicenna noted that cancers were caused by an excess of black bile, which caused excessive heat in the body. Like the ancient Greeks, he believed that if one of the body's humors was out of balance, then all four of them were unbalanced. As a result, Avicenna and his contemporaries understood cancer to be an extremely difficult disease to treat. He said a benign tumor could be differentiated from a cancerous one by certain symptoms such as pain, throbbing, and rapid growth. He also noted that cancerous tumors send out "crablike tracks" and occurred more often in "hollow" organs, which is why they were more common in women. Avicenna also stated that cancers often strike muscles, tendons, and the lymph nodes.

The Holy Quran and *Hadith* by the Prophet Mohammad (PBUH) have provided Moslems with a multitude of foods to contribute to the ideal diet. As outlined in Chapter 17, the Koran mentions many fruits and vegetables as well as meat, milk, and many spices among the foods that Muslims can enjoy for sound nutritional health. Among some of the fruits and vegetables mentioned in the Koran and *Hadith* are melons, grapes, citrus, squash, figs, and dates. Even dried fruits are beneficial according to the Koran and *Hadith*. The Prophet (PBUH) mentioned figs and then stated, "If I had to mention a fruit that descended from paradise I would say this is it because the paradisiacal fruits do not have pits . . . eat from these fruits for they prevent hemorrhoids, prevent piles and help gout." Figs are a top source of fiber, as well as potassium and vitamin B6. Fiber results in bulkier stools, which lessen the incidence of constipation, hemorrhoids and colon cancer. Fiber also lowers cholesterol and the risk of heart disease. Al-Bukhari (810–870) states that melon was among one of the fruits most often eaten by the Prophet. In fact, melon is one of the best recommendations for health that the Prophet has given us. It is one of the few fruits and vegetables rich in vitamin C, beta-carotene, and potassium. The favored foods by the Prophet were dates, honey, olive oil, and black seeds (*Nigella sativa*). Concerning olive oil, he said "Eat olive oil and massage it over your bodies since it is a holy (mubarak) tree." Black seeds were regarded as a medicine that cures all types of diseases. The Prophet once stated, "The black seed can heal every disease, except death." Dates are mentioned in 20 places in the Quran. Prophet (PUH) is reported to have said: "if anyone of you is fasting, let him break his fast with dates. In case he does not have them, then with water. Verily water is a purifier."

Avicenna realized that a cure is most likely if the cancer is identified at its earliest stage. The first goal of a treatment strategy should be to halt the cancerous growth. He suggested surgical removal if the tumor was small and accessible, and not close to major organs. He noted "it can be arrested with anything, it can be so by vigorous excision . . . including all the [blood] vessels supplying the tumor so that nothing of these will be left." Avicenna also recommended that surgery be preceded by purifying the body of excess black bile. This could be achieved by providing a nutritious and balanced diet to the patient to maintain purity and strengthen his or her organs and immune system. Avicenna most often treated cancer patients with drug remedies and also advised cancer patients to change their diets. One such remedy he discovered was the "Hindiba" (*Cichorium intybus*), an herbal compound drug that Ibn al-Baitar later identified as having "anticancer" properties, which could also treat other tumors and neoplastic disorders. Another method for treating cancer first described in Avicenna's Canon was surgical excision. It stated that the excision should be radical and that all affected tissue and veins running in the direction of the tumor must be removed. In advanced cases, however, he was against excision, saying the tumor most surely return [8,42].

To stay within the scope of this chapter we will discuss current preclinical studies that focus on three widely used herbal products, namely, black seeds, pomegranate, and olive leaf and fruits (Table 14.2). Other commonly used medicinal and wild edible plants are discussed in detail in Chapters 8 and 17.

14.6.1 Preclinical Anticancer Studies on Black Seeds

Numerous preclinical *in vitro* tests indicate that both the oil and the active ingredients of black seeds (*N. sativa*) possess anticancer properties. Volatile black seed oil demonstrated significant cytotoxic properties against various types of human cancer cell lines. As discussed in Chapter 12, exposure of cells from the MCF-7 breast cancer cell line with aqueous and alcohol extracts alone completely inhibited growth of these cells, suggesting that *N. sativa* is effective anticancer agent. *In vitro* investigations show that *N. sativa* extracts induced, in a concentration-dependent manner, inhibition of a number of tumor-derived metastasis-inducing factors, for example, collagenase type IV, metalloproteinase, and serineproteinase inhibitors, angiogenic protein-fibroblastic growth factor, tissue-type plasminogen activator, urokinase-type plasminogen activator, and plasminogen activator inhibitor type I. Therefore, it can be suggested that the anticancer properties of *N. sativa* oil might be mediated through antiangiogenic effects through inhibition of local tumor invasion and metastasis *in vivo*. In addition to the antitumor effects of the whole extract of *N. sativa*, thymoquinone, dithymquinone, thymohydroquinone, and thymol, are the main active compounds responsible for the therapeutic effects of *N. sativa* seeds. Both thymoquinone as well as dithymquinone were equally cytotoxic against cells from different human cancer cell lines, including the pancreatic adenocarcinoma, human uterine sarcoma and human leukemic. These effects seem to be the result of triggering apoptosis through arresting the growth of these cells in the G1 phase of the cell cycle, associated with increase in the gene and protein expression of p53 and inhibition of the

antiapoptotic Bcl-2 protein. Taken together, these preclinical *in vitro* studies indicate that the antineoplastic effect of thymoquinone is mediated by proapoptotic effects modulated by Bcl-2 protein and is linked to and dependent on p53 [43–45].

Much of the published *in vitro* anticancer properties of *N. sativa*-derived compounds have also been confirmed in different animal cancer models. For example, skin carcinogenesis induced in mice by 7,12-dimethylbenz[*a*]anthracene/croton oil in mice was inhibited by topical application of *N. sativa* oil. Furthermore, the onset of papilloma formation was delayed and the mean number of papillomas was reduced. The growth of Ehrlich ascites carcinoma and Dalton's lymphoma ascites cells were completely inhibited by the active principle fatty acids derived from *N. sativa*. Moreover, α-hederin, another active ingredient of *N. sativa* oil, was also found to show *in vivo* antitumor activity against leukemia and Lewis lung carcinoma, prolonging the life-span of the tumor bearing mice. In addition, orally feeding with *N. sativa* extract suppressed the growth of diethylnitrosamine-induced rat hepatic tumors. Furthermore, *N. sativa* oil suppressed methylnitrosourea or by 1,2-dimethylhydrazine-induced colon carcinogenesis. According to recent preclinical studies, the antitumor effects of *N. sativa* oil is mediated by thymoquinone. Administration of this molecule in drinking water significantly suppressed the benzo[*a*]pyrene-induced forestomach tumor. Thymoquinone significantly inhibited the tumor incidence and tumor formation of 2-methyclonathrene-induced soft tissue fibrosarcoma. In addition, treatment with *N. sativa* extract 30 days after subcutaneous administration of methyclonathrene reduced fibrosarcoma tumor incidence by about 67%, compared control tumor-bearing mice, indicating to therapeutic potentials of *N. sativa*. Other preclinical observations suggest that suppression of immune cell function associated with chemotherapy, radiotherapy, and late stages in tumor-bearing hosts is mediated, at least in part, by nitric oxide (NO) produced by immature granulocytes that are massively generated under these conditions. Therefore, it is possible that the antitumor effects reported for *N. sativa* oil and thymoquinone are mediated by their abilities to scavenge excess NO. The impact of *N. sativa* compounds, in particular thymoquinone on immature granulocytes in tumor-bearing hosts needs to be explored further. In addition, since chemotherapy induces massive expansion of the NO producing immature granulocytes, it might be feasible to follow chemotherapy with thymoquinone treatment that could potentially alleviate the suppressive effects of the immune responses from chemotherapy-induced NO. In addition to the possible antioxidant mediating antitumor effects of thymoquinone, it is also possible that it produces further antitumor effects if mediated by the ability to suppress PEG and LT. Higher levels of these inflammatory mediators have been reported to correlate with tumor progression *in vivo*, and several drugs that are able to block the eicosanoid signaling, both COX-1 and COX-2 pathways, are being tested in current clinical trials. However, the possibility that both the antioxidant and anti-inflammatory effects of thymoquinone mediate its antitumor effects needs to be directly tested by using mice that are knocked out for these mediators.

Taken together (Table 14.1), the findings of these studies indicate to the potential of the active ingredients of *N. sativa* oil, in particular thymoquinone, as a powerful chemopreventive agents against several experimental cancer, including forestomach,

fibrosarcoma, colon, skin, and hepatic tumors. It remains to be discovered whether the antitumor effects of *N. sativa* oil and thymoquinone are immune-mediated through modulation of antitumor immune responses [43–46].

14.6.2 Preclinical Anticancer Studies on *Punica granatum*

Selective inhibition of tumor cell proliferation but not normal cells is the most desired anticancer therapeutic effects. In this regard, pomegranate peel extracts have been shown to reduce proliferation of cells from different human cancer cell lines. For instance, significant antiproliferative effects of fermented pomegranate juice and pomegranate peel extract were observed in cells from human breast cancer cells, MCF-7 and MDA-MB-231 cells compared to immortalized normal breast epithelial cells MCF-10A. Furthermore, treatment of cells from an androgen-independent PC-3 cell line with acetone extract from whole pomegranate fruits, dose-dependently inhibited proliferation. This corresponded to changes in the cyclin kinase inhibitor-cyclin-cdk network. In addition, an acetone extract of whole pomegranate fruits treatment for nude mice implanted with androgen-sensitive CWR22Rnu1 human prostate cancer cells resulted in suppression of growth and a significant decrease in serum prostate-specific antigen. Other studies indicate that whole, complex pomegranate products possess potential antiproliferative activity against cancer cells superior to that of their principle active compounds, again suggesting therapeutic strategies that may depart from the traditional preference for a pure single compound.

Despite the aforementioned impressive preclinical work that indicates cancer chemopreventive and therapeutic efficacy with limited toxicity, there still remains few well-designed clinical trials measuring the anticancer and other health benefits of the pomegranate.

Apoptosis is an early marker for predicting anticancer effects of potential drugs. Aqueous pomegranate peel extract induced DNA fragmentation and suppression of growth of cells from two human Burkitt's lymphoma cell lines. Pomegranate seed oil increased the occurrence of apoptosis by 54% in MDA-MB-435 estrogen receptor negative, metastatic human breast cancer cells, compared to control cells treated with tocopherol, a known apoptotic-inducing compound. Fermented pomegranate juice and peel extract have also been shown to induce apoptosis in two androgen receptor negative human prostate cancer cell lines PC-3 (highly metastatic cell line) DU-145 (slower growing cell line). These effects were at least partially mediated by capsase enzyme, suggesting involvement of inflammatory processes in executing the apoptotic cascades. Capsase activation in PC-3 cells by acetone extract of whole pomegranate fruits correlates with down regulation of proapoptotic factors Bax and Bak, and downregulation of antiapoptotic factors Bcl-XL and Bcl-2. Similarly, acetone extract of whole pomegranate fruits reduced expression of cyclins D1, D2, and E and cyclin-dependent kinase (cdk) 2, cdk4, and cdk6. Taken together, both the hydrophobic and hydrophilic pomegranate fractions appear to possess selective apoptotic potential in respect to different hormone-independent cancer cell lines, suggesting chemotherapeutic potential for compounds originating from each of these pomegranate compartments.

The vast majority of cancer deaths arise from the metastasis of primary tumor cells. Local invasion and the formation of metastasis are most difficult to assess since they are the least understood. Nonetheless, recent studies have indicated that pomegranate-derived components may be capable of suppressing metastasis. For instance, cold-pressed pomegranate seed oil inhibited invasion of estrogen sensitive MCF-7 human breast cancer cells *in vitro* across an artificial Matrigel-TM membrane. In addition, pomegranate seed oil, pomegranate peel extract, and fermented pomegranate juice each resulted in 60% suppression of invasion, in Matrigel-TM, of human PC-3 androgen negative prostate cancer cells. Synergistic effects were seen when equal amounts of any two of pomegranate seed oil, pomegranate peel extract, or fermented pomegranate juice were combined, such that the combination resulted in a 90% suppression of invasion.

Angiogenesis, the initiation and development of new blood vessels, is essential to supply oxygen and nutrients for tumor growth and metastasis. Inhibition of tumor blood vessel formation, first suggested by Avicenna who noted that cancer "can be arrested with anything, it can be so by vigorous excision . . . including all the [blood] vessels supplying the tumor so that nothing of these will be left." is still a promising therapeutic approach for treating solid tumor afflicted patients. Interestingly, recent studies indicate that *Punica granatum* possess antiangiogenic properties. Thus, *in vivo* angiogenesis in chicken chorioallantoic membrane (CAM) was significantly suppressed by fermented pomegranate juice. Proangiogenic vascular endothelial growth factor (VEGF) was potently down regulated in MCF-7 estrogen dependent breast cancer cells, less so in estrogen negative MDA-MB-231 breast cancer cells, and most strongly in MCF-10A immortalized normal breast epithelial cells by fermented pomegranate juice and pomegranate seed oil. The antiangiogenic migration inhibitory factor (MIF) was potently upregulated in MDA-MB-231 cells by fermented pomegranate juice and pomegranate seed oil, which also moderately suppressed human umbilical vein endothelial cell proliferation and tubule formation. Conversely, pomegranate peel extract and fermented pomegranate juice potently inhibited human myometrial fibroblast proliferation suggesting selectivity toward the inhibition of cellular proliferation among cell types [47].

Cancer Chemopreventive Properties. Cold-pressed pomegranate seed oil reduced the tumor occurrence in 7,12-dimethyl-benz[*a*]anthracene-treated mouse mammary organ culture by about 87%. In addition, topical exposure to 5% pomegranate seed oil results in a significant decrease in both tumor incidence and multiplicity in female CD-1 mice with skin tumors induced by 7,12-dimethyl-benz[*a*]anthracene and subsequently promoted by 12-*O*-tetradecanoylphorbol-13-acetate. Similarly, topical pretreatment with acetone extract of whole pomegranate fruits prior to 12-*O*-tetradecanoylphorbol-13-acetate applications in 7,12-dimethyl-benz[*a*]anthracene-treated CD-1 mice decreased the tumor incidence by about 70% and increased latency of tumor development from week 9 to week 14. Pomegranate seed oil has also been shown to reduce both the incidence and multiplicity of colon tumors in rats treated with carcinogen azoxymethane. In addition, various preclinical *in vitro* studies reported that the anticancer effects of extracts and active compounds

may be mediated through modulation of cell cycle, cell differentiation, intracellular enzymes, and so on. For instance, cell cycle changes were observed following treatment of human Burkitt's lymphoma cells to pomegranate peel extract and human monocytic leukemia cells to pomegranate seed oil. Mechanisms for these effects likely involve modulation of cell signaling molecules in the cell cycle machinery (e.g., WAF1/p21). Other studies showed that differentiation of HL-60 promyelocytic human leukemia cells is potently promoted by pomegranate peel extract and fermented pomegranate juice, whereas the ethyl acetate extract of fresh, unfermented pomegranate juice has little effect. Differentiation may possibly figure into observed anticancer effects of pomegranate extracts in other cell lines, including breast and prostate [47].

14.6.3 Preclinical Anticancer Studies on Olive Oil and Olive Leaf

Herbal-derived factors as well as dietary factors influence carcinogenesis in a variety of tissues. A diet rich in fruits and vegetables has long been suggested to correlate with reduced risk of certain epithelial malignancies, including cancers in the lung, colon, prostate, oral cavity, and breast. In addition, there are interrelationships between diet, environmental factors, and genetics that can affect cancer risk. Potential chemopreventive agents against cancer development can be found among nutritive and/or nonnutritive compounds in inedible and edible plants. For instance, the incidence of cancer of the large bowel, breast, endometrium, and prostate is lower in the Mediterranean region, than in Scandinavian countries, the United Kingdom, and the United States. Increased forms of these cancers have been linked to dietary factors, particularly low consumption of vegetables and fruit, and to a certain extent, high consumption of meat. The traditional Mediterranean diet is characterized by high consumption of foods of edible plant origin, relatively low consumption of red meat, and high consumption of olive oil, which in several studies has been reported to be more beneficial against cancer than other forms of added lipids. Although only crude estimates are available, it can be calculated that up to 25% of the incidence of colorectal cancer; 15% of the incidence of breast cancer, and 10% of the incidence of prostate, pancreas, and endometrial cancer could be prevented if the populations of highly developed Western countries could shift to the traditional healthy Mediterranean diet. The major component of the leaves and unprocessed olive drupes of *Olea europaea* is oleuropein and the majority of polyphenols found in olive oil or table olives are derived from its hydrolysis. Oleuropein is a novel, naturally occurring antioxidant compound, which may be used to prevent cancer and cardiotoxicity induced by doxorubicin.

In the Islamic tradition, olive oil is mentioned in the Quranic verse: "God is the light of heavens (paradise) and earth. An example of His light is like a lantern inside which there is a torch, the torch is in a glass bulb, the glass bulb is like a bright planet lit by a blessed olive tree, neither Eastern nor Western, its oil almost glow, even without fire touching it, light upon light." The Quran also mentions olives as a sacred plant: "By the fig and the olive, and the Mount of Sinai, and this secure city." The Prophet said, "Eat olive oil and massage it over your bodies since it is a holy (mubarak) tree." He also stated that olive oil cures 70 diseases. In the Arab–Islamic world, olive oil has

been commonly used in cooking, cosmetics, pharmaceuticals, and soaps and as a fuel for traditional oil lamps.

As discussed in Chapter 13, oxidative stress has been found to increase cancer occurrence and consumption of antioxidants (found in olive oil, fruits, and vegetables) is believed to reduce the risk of carcinogenesis. Anticancer activity of olive oil is associated with its high content of antioxidants, such as hydroxytyrosol, tyrosol, secoiridoids, and lignans. In addition its anticancer effects are attributed to olive-derived compounds deemed to be anticancer agents (such as squalene and terpenoids).

In vitro investigations have found that olive oil phenols are potent antioxidants, which may provide potential chemoprotective properties. Hydroxytyrosol was found to induce apoptosis, to arrest cell cycle progression at the G1 phase, to protect cells from hydrogen peroxide-induced damage, and DNA from peroxynitrite-induced damage. In addition to antioxidant properties, oleuropein has been found to exhibit antiangiogenic effects and to inhibit cell growth, motility, and invasiveness. Furthermore, rapid tumor regression was observed when mice were given 1% oleuropein in drinking water. Saturated animal fats and polyunsaturated plant fats in the diet have been implicated in colon, breast, prostate, and ovarian cancers. The substitution of olive oil in the Mediterranean diet may explain its apparent cancer chemopreventive effects.

When olive oil was compared to other oils, it was found that fried olive oil has a protective effect against colon cancer. This agrees with data that unheated olive oil is beneficial in protecting against colon cancer. The heterocyclic amines (HCA) produced when protein-containing food is fried have been found to induce breast, colon, and pancreatic cancer in rats. When olive oil is used for frying, fewer HCAs are produced than when oils high in polyunsaturated fatty acids are used. Using specific cell lines, they investigated processes involved in cancer initiation, promotion, and metastasis, the three main stages in cancer development, and concluded olive oil phenols exert beneficial effects in all three stages. The oil extract was shown to reduce DNA damage (initiation), increase barrier function (promotion), and reduce cell invasion of surrounding tissue (metastasis) [48–51].

14.7 CLINICAL TRIALS

A clinical trial broadly refers to any testing done on human beings for the sake of determining the safety and efficacy values of a treatment for the sick or for preventing disease. The treatment can be anything considered to hold promise in caring for the sick, in the prevention of disease, or in the maintenance of health. There are several steps and stages of approval in the clinical trials process before a drug or device can be sold in the consumer market, if at all. After completing preclinical testing, involving extensive laboratory research that can involve years of experiments in animals and human cells, research continues and testing in humans can begin. Clinical trials are typically conducted in four phases. Each phase is considered a separate trial and, after completion of a phase, investigators are required to submit their data for approval from the health authorities before continuing to the next phase [52]. In respect to

herbal-derived compounds, 91 herbal-derived molecules are in clinical trials as of September 2007. These include anti-inflammatory, anticancer, cardiovascular, and neurological active compounds.

Phase I studies assess the safety of a drug or device. This initial phase of testing, which can take several months to complete, usually includes a small number of healthy volunteers (20–100), who are generally paid for participating in the study. The study is done to generate preliminary information on the chemical action and safety of the indicated drug and to find a safe dose, usually not randomized. This phase also investigates the side effects that occur as dosage levels are increased. Results obtained are used to determine drug doses to be used in later trials, how the drug is broken down in the body and excreted, and study short-term side effects (safety, pharmacokinetics, and pharmacodynamics of a drug). These trials are often conducted in an inpatient clinic, where the subject can be observed by full-time staff. The subject who receives the drug is usually observed until several half-lives of the drug have passed. In order to determine the appropriate dose for therapeutic uses, Phase I trials also normally include dose escalation studies (dose-ranging). The tested range of doses will usually be a fraction of the dose that causes harm in animal testing. Often healthy people are enrolled in Phase I trials rather than patients on the assumption that if the drug has unexpected side effects, healthy people have the best chance of escaping permanent harm. However, on other occasions, as with a drug treating involving a severe disease like cancer, Phase I subjects may be patients who have not improved from standard treatments. About 70% of experimental drugs pass this phase of testing. There are different kinds of Phase I trials:

Single ascending dose(SAD) studies involve a single dose of the drug that is given to small groups of volunteers while they are observed and tested for a predetermined period. In the absence of adverse side effects, a new group of volunteers receives a higher dose. This process continues until precalculated pharmacokinetic safety levels are reached, or intolerable side effects start showing up (at which point the drug is said to have reached the maximum tolerated dose.

Multiple ascending dose(MAD) studies are conducted to assess the pharmacokinetics and pharmacodynamics of multiple doses of the drug. Therefore, a group of volunteers receives multiple low doses of the drug, while blood and other fluids samples are collected at predetermined time points and analyzed to assess how the drug is processed within the body. The dose is subsequently escalated for further groups up to a predetermined level.

Food Effect: A short trial is conducted to study differences in absorption of the drug by the body, caused by eating before the drug is given. These studies are usually run as a crossover study, with volunteers being given two identical doses of the drug on different occasions; one while fasting, and one after being fed.

Phase II studies test the efficacy of a drug or device. This second phase of testing can last from several months to 2 years, and involves up to several hundred patients.

The goal of a Phase II trial is to learn more about safety and side effects, sharpen estimates of proper doses, and get an early appraisal of whether the drug is going to work. This trial is often the first time a drug is tested in actual patients. If the development process for a new drug fails, this usually occurs during Phase II trials when the drug is discovered not to work as planned, or to have toxic effects. Most Phase II studies are randomized trials where one group of patients receives the experimental drug, while a second "control" group receives a standard treatment or placebo. Often these studies are "blinded" which means that neither the patients nor the researchers know who has received the experimental drug. This allows investigators to provide the pharmaceutical company and the health authorities with comparative information about the relative safety and effectiveness of the new drug. About one-third of experimental drugs successfully complete both Phase I and Phase II studies.

Phase III studies are randomized controlled multicenter trials and consist of hundreds or thousands of people. This large-scale testing, which can last several years, provides a more thorough understanding of the effectiveness of the drug or device, the benefits and the range of possible adverse reactions. Many Phase III trials are randomized and double-blind trials. Randomized means people are assigned at random either to receive the new drug, the standard treatment for that disease, or a nonfunctional substitute (such as a sugar pill or placebo). This last group is often called the control group, or the placebo group. Because Phase III must answer definitively whether the drug works, it is important to compare people who receive it with others who do not.

While not required in all cases, it is typically expected that there be at least two successful Phase III trials, demonstrating a drug's safety and efficacy, in order to obtain approval from the appropriate regulatory agencies such as FDA (USA), EMEA (European Union), or TGA (Australia). Most drugs undergoing Phase III clinical trials can be marketed under FDA norms with proper recommendations and guidelines. If any adverse effects arise, the drugs can be immediately recalled from the market. *Phase IV* also called post marketing surveillance trials, is carried out after a drug or device has been approved for consumer sale. Pharmaceutical companies have several objectives at this stage: (1) to compare a drug with other drugs already in the market; (2) to monitor a drug's long-term effectiveness and impact on a patient's quality of life; and (3) to determine the cost-effectiveness of a drug therapy relative to other traditional and new therapies. Phase IV studies can result in a drug or device being taken off the market or, alternatively, restrictions on its use could be imposed depending on the new findings.

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CHAPTER 15

Medical Ethics in Arab and Islamic Medicine

15.1 INTRODUCTION

Ethics (derived from the Greek, meaning "moral" or "habit") deals with moral issues and judgments. It attempts to determine the propriety of human conduct, man's desires, and the consequences of his actions. While ethics deals with theory, morals (derived from the Latin *mos*, meaning "custom" or "usage") deal with concrete practical aspects of action. The terms "ethics" and "morals" are often used interchangeably. Medical ethics is a field of applied ethics, the study of moral values and judgments as they apply to medicine. It can be summarized as the code, which regulates the physician's behavior with colleagues, staff, and patients. As a scientific discipline, medical ethics deals with practical applications of morality in clinical settings as well as related work on philosophy, theology, and history. Medical ethic tends to be understood narrowly as an applied form of professional ethics, whereas bioethics appears to have broader concerns, touching upon the philosophy of science as well as biomedical and biotechnological research, for example, using animal tests and stem cell research. Still, the two branches often overlap and the distinction is more a matter of style than professional consensus. Medical ethics shares many principles with other fields of health care ethics, such as nursing ethics.

Moral problems relating to the practice of medicine have led to laws, edicts, guidelines, and oaths formulated for or by physicians. The Declaration of Helsinki is regarded as one of the most authoritative. The ethical problems confronting us today are not entirely new; many of them have been the subjects of debate for hundreds of years. Historically, such codes were written and implemented by physicians of all known medical systems, for example, the Code of Hammurabi, Egyptian papyri, Ayurvedic medicine, Chinese medicine, Greek, Roman, as well as the Greco-Arab and Islamic medical system.

The medical profession was highly respected in the Arab–Islamic world during the Golden Ages of the Islamic Empire and scholars retained this respect by laying down

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proper medical ethics. In this regard, when history mentions of "The Dark Ages," between the ancient civilizations and the Renaissance era in Europe, a fact that is often neglected is that this nomenclature only refers to Europe. In reality, while Europe was in "The Dark Ages," the flame of science, technology, knowledge, and discovery burned bright in the Arab–Islamic Empire. As this empire spread, Muslims brought with them Islamic teachings that amongst endless of other virtues, placed a great emphasis on the culture of learning and respect for knowledge. Such was the nature of Islam, that when vast territories were conquered by the Muslims, not only were the cultures of the conquered nations preserved, but they were also introduced to new concepts and ideals based on the teachings of Islam, which led to development and modernization. This in itself was of course a unique characteristic of the Arab–Islamic Empire, starkly different from other conquerors in history who were prone to eliminate any trace of those they have vanquished in favor of putting their own stamp on all that they have conquered. Instead, as the Muslims expanded their empire they laid the foundations for the formation of a well-organized society, with high regard for order, discipline, and respect for authority. They tolerated other religions, stressed the importance of knowledge, encouraged cleanliness, and forbade destruction. In short, in its Golden Age, the Arab–Islamic Empire gave rise to a fertile environment for the birth of a new civilization. It was in this period that medical science experienced its golden era of discovery and growth. Centers of medical knowledge bloomed in Syria, Egypt, and Persia. In these areas, physicians were encouraged to translate and study medical knowledge from ancient texts, and subsequently expand contemporary medical wisdom using research and experimentation. Baghdad, the center of the Arab–Islamic Empire, became a center of knowledge where vast amounts of scholarly works across different disciplines were pooled in great libraries. Great names in the history of science emerged in this era, namely Rhazes, Al-Zahrawi (Abulcasis or Alzahravius), Ibn Sina (Avicenna), and Ibn Rushd (Averroes), among others. Hospitals, as we know them today, were first conceptualized during this period. If previously the sick were given places to stay in temple annexes or places run by priests, the Arab–Islamic civilization introduced the concept of a hospital for all, a building run by physicians to aid the sick regardless of race, color, or creed. Separate wards for different ailments as well as separate wards for men and women were introduced in accordance with the teachings of Islam. Male and female nurses too were specially trained to care for the sick, and for the first time in history, proper medical records of patients were kept. In addition, it was during this period, specifically in 931 during the Abassid Caliphate, at which time Sinnan ibn Thabit was the Chief Court Physician, that for the first time, physicians were screened and only qualified physicians were allowed to practice. Ethics was one of the features that distinguished Arab–Islamic hospitals from their contemporaries. Hospitals in the Arab–Islamic Empire treated patients of all religions, ethnicities, and backgrounds, while the hospitals themselves often employed Jewish, Christian, and those of other minority backgrounds. Arab–Islamic physicians and staff were obligated to their patients, regardless of wealth or background. The ethical standards of physicians were first written in the ninth century by Ishaq bin Ali al-Rahawi, who wrote the *Adab al-Tabib* (*Conduct of a Physician*), the first treatise dedicated to medical ethics. He

regarded physicians as "guardians of souls and bodies," and wrote 20 chapters on various topics related to medical ethics, including personal characters of the physician as well as physician obligations toward patients, community, his colleagues, and toward his assistants [1–4].

Arabic–Islamic medicine and later Greco-Arab and Islamic medicine, attaches the highest importance to having a righteous attitude during sickness, and the religious obligations attached to being sick. The Holy Quran and *Hadith* indicate that those who become sick are not responsible for their situation. They are being examined and purified from sins and if they accept the will of God and bear their ordeal patiently, they shall be rewarded. Islamic law grants an ailing person exemption from certain religious obligations. Physicians are ordered to evaluate the capacity of patients to fast in holy month of Ramadan and the extent to which ritual impurity related to vomiting, diarrhea, hemorrhaging, or any such signs of illness should prevent them from performing prayers or fasting. Sick people are instructed to seek treatment; as one *Hadith* says, "To each disease there is a treatment,", and another says, "O servants of Allah seek the medical treatment."

Arab–Islamic ethics (*akhlaaq*), defined as "good character," was eventually shaped as a successful fusion of Quran teachings alongside the teachings of the Sunnah of the Prophet (PBUH), the precedents of Islamic jurists, the pre-Islamic tradition, as well as Persian and Greek ideas (Figure 15.1). Although a radical change was induced in moral values based upon the synergy of Islam and indigenous beliefs, the tribal practice of Arabs did not completely die out. Later Muslim scholars expanded the religious ethic of the Quran and *Hadith* in immense detail. The ethics of Arab–Islamic medicine do not differ from those of other medical systems, except for a few particularities. These include the obligation to invoke the name of God before any medical examination or treatment, as in any other significant act in Islam; the obligation to avoid cures that contain alcohol, and practices such as abortion and tattooing, which are prohibited by Islam.

15.2 ETHICS IN THE ARAB–ISLAMIC WORLD

The Islamic Empire was during its Golden Age one of the advanced and civilized nations in the world. This is because Islam stressed the importance and respect of learning, forbade destruction, and tolerance for other religions. Medicine flourished because it was promoted both by Islam (the Holy Quran and Prophet Mohammad's teaching) and the state (by the Caliph). Baghdad, Seville, Toledo, Granada, Kairouan, Fez and other cities were well known as centers for Arab–Islamic medical sciences. Within the general context of Islam's system of ethics, Arabs integrated Roman, Greek, Persian, and Indian theories and practices; they established and promoted then their own medical sciences in theory and practice. During the Arab–Islamic Golden Age, the medical sciences rose in esteem from that of a menial calling to the rank of a learned profession. Greco-Arab and Islamic medicine had advanced from ephemeral talismans and rituals to tangible hospital wards, mandatory testing for doctors, and the use of technical terminology. Hospitals

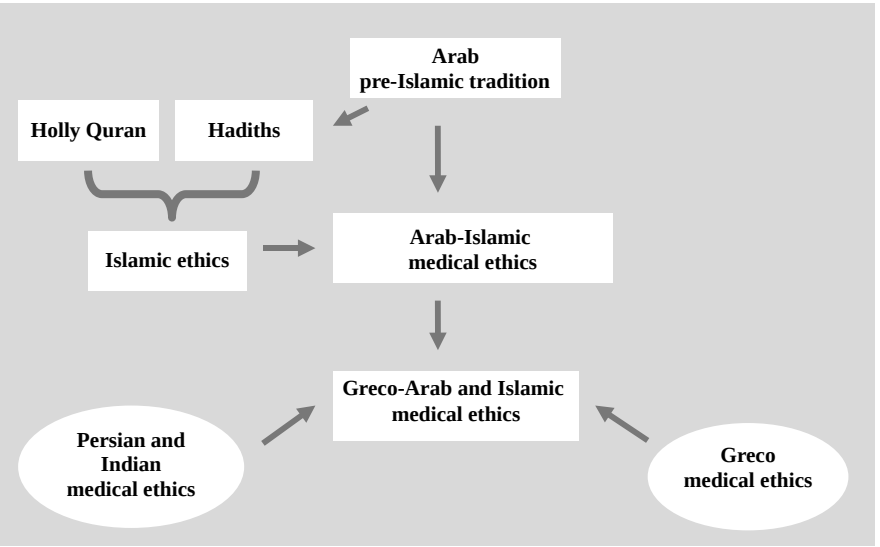

FIGURE 15.1 Development of Arab–Islamic ethics

became medical centers that contained libraries, pharmacies, intern systems, externs, and nurses. There were mobile clinics to reach the disabled, the disadvantaged, and those in remote areas. There were also regulations to maintain quality control of drugs. Pharmacists became licensed professionals and were pledged to follow the physician's prescriptions [1–6].

As mentioned in Chapter 10, the medical needs of the Islamic Empire over nine centuries and vast areas were not uniform. The everyday practices and the general health of the community were influenced by many factors. These included dietary and fasting laws, general rules for hygiene, the living conditions of nomadic, rural, and urban populations, agricultural successes or failures, the amount of travel undertaken for commerce, or as a pilgrimage, the maintenance of a slave class and slave trade. Therefore, there was a crucial need for ethics and hygiene regulations in all health care systems. Islamic philosophy played a central role in promoting the sciences and in the formulation of ethical and moral roles [4–6].

15.3 ISLAMIC PHILOSOPHY AND PROMOTION OF SCIENCES

Although Islamic philosophy has great diversity and richness, it is characterized by certain features that are of special significance for both understanding and for appraising its impact on other civilizations. Islamic philosophy was concerned with the basic issue of harmony between human reasoning and revelations in the Holy Quran. As a result, all sorts of sciences were studied in order to determine the relationship between humans and their universe on the one hand, and on the other hand

their relationship with their creator. One must remember that Islamic philosophy originated from a time when Islam had a great influence on everyday life. Thus it always leads to one main conclusion, that the power of God is supreme and that his words are the absolute truth. Islamic philosophy greatly encouraged all types of sciences, particularly mathematics and medicine. Without the constant encouragement of Islamic philosophy and science, the large number of discoveries made by Arab–Islamic scholars may never have taken place. Medical ethics can be seen as a branch of applied philosophy that seeks to answer what are the moral, honorable, and righteous sets of behaviors in a given circumstance.

15.3.1 Promotion of Science by Quran and *Hadith*

The promotion of science by Quran and *Hadith* as well as encouragement and support by the Caliphs, played a central role in creating a successful Arab–Islamic civilization that highly encouraged scientists to be leaders in many fields, especially in the medical sciences. As discussed in Chapter 10, Muslims challenged the civilized world at that time; they preserved the cultures of the conquered countries. A well-known example in this regard is the so-called Treaty of Omar. Accordingly, in 638, after a prolonged siege of Jerusalem, the Muslims finally entered the city peacefully following the signing of the treaty by the Patriarch of Jerusalem and the second Caliph Omar Ibn Alkhattab. Several years earlier, the Patriarch had announced that he would not sign a treaty with anyone other than the Caliph himself. For this reason, Omar personally came to Jerusalem after the Muslims had established control of all the surrounding territories. According to both Muslim and Christian accounts, Omar entered the city humbly, walking beside a camel upon which his servant was sitting; they alternated riding and upon entering the city it was Omar who walking alongside. He is said to have been given the keys to the city by the Patriarch of Jerusalem, Sophronius, after signing this treaty (see *The Treaty of Omar* below).

Unfortunately, toward the decline of the Islamic Empire, many Arab–Islamic contributions to the arts and sciences were destroyed. The Mongols, out of barbarism, burnt Baghdad (1258), and the Spaniards, out of hatred, demolished most of the Arabic heritage in Andalusia. The teachings of Islam made the difference between the Arab–Islamic civilization and other civilizations at that time. The main points in this respect are as follows:

1. Stressing the importance and respect of learning. For example, a captured enemy was freed if he paid a ransom or taught 10 Muslims writing and reading. The importance of learning is repeatedly stressed in the Holy Quran, as it says "Say (unto them, O Mohammad): Are those who know equal with those who do not know?" The Prophet stressed learning by saying, "One hour of teaching is better than a night of praying."
2. The general philosophy of Islamic medicine is that the healer is God and physicians are the instruments that God uses to heal people. The doctor–patient relationship is stronger in Islam than it is in modern medicine as the physician has responsibilities to God that he will account for on the Day of Judgment.

3. Islam provides laws that form a basis for the protection and the safeguarding of the human body as well as the spirit. Holy Quran says: "and whoever saves a life it would be as if he saved the life of all the people." Nowadays, this can be interpreted to encourage organ transplantation. In addition, the *Hadith* of the Prophet (PBUH) states that "Whoever helps a brother in difficulty, God will help him through his difficulties on the Day of Judgment." Islam provides rights and protection to all human beings at every stage and area of life. The Holy Quran states: "Do not kill your children on account of want or poverty, We provide them sustenance for you and for them."
4. Acts that have to be implemented during plague periods. For example, the Prophet (PBUH) decreed "No man may enter or leave a town in which plague broke out." And to make this law all the more binding and effective, he promised the blessing of heaven to those who die of plague by stating that if a man died of plague he would be considered a martyr.
5. There is no censorship in Islam on scientific research. Scholars have the duty to reveal the signs of God in His creation. However, freedom of scientific research shall not harm any human being or subject him to harm, including withholding therapy, defrauding him, or exploiting his material need. Additionally, freedom of scientific research shall not include cruelty to animals or torture.
6. Relationship with other religions. Islam recognizes Christianity and Judaism and considers its followers to be people with holy books like Muslims. Moreover, Muslim treated the Jews during an era when the latter were persecuted in Europe. Muslim rulers guaranteed security of both life and property for the Jewish people. Hence, there were many Christian and Jewish physicians who contributed to the Arab–Islamic civilization [1–8].

THE TREATY OF OMAR

In 638, after a prolonged siege of Jerusalem, the Muslims finally entered the city peacefully following the signing of a treaty by the Patriarch of Jerusalem and the second Caliph Omar Ibn Alkhattab himself. He is said to have been given the keys to the city by the Patriarch of Jerusalem, Sophronius, after conducting the peace treaty known as the Treaty of Omar.

> In the name of Allah, the Most Merciful, the Beneficent.
>
> This is what the slave of Allah, Umar b.Al-Khattab, the Amir of the believers, has offered the people of Illyaa' of security granting them Amaan (protection) for themselves, their money, their churches, their children, their lowly and their innocent, and the remainder of their people. Their churches are not to be taken, nor are they to be destroyed, nor are they to be degraded or belittled, neither are their crosses or their money, and they are not to be forced to change their religion, nor is any one of them to be harmed. No Jews are to live with them in Illyaa' and it is required of the people of Illyaa' to pay the Jizya, like the people of the cities. It is

> also required of them to remove the Romans from the land; and whoever amongst the people of Illyaa' that wishes to depart with their money together with the Romans, leaving their trading goods and children behind, then they, their trading goods and their children are secure until they reach their destination. Upon what is in this book is the word of Allah, the covenant of His Messenger, of the Khulafaa' and of the believers if they (the people of Illyaa') gave what was required of them of Jizya.
>
> The witnesses upon this were Khalid ibn al-Walid, 'Amr ibn al-'As, Abdur Rahman bin Awf, and Muawiyah ibn Abi Sufyan. Written and passed on the 15th year (after Hijrah)

15.3.2 Promotion of Sciences by the State

The Islamic Empire in the early eighth century was the beneficiary of scientific knowledge of late antiquity. Arab–Islamic scholars preserved it, elaborated upon it, and finally, passed it onto Europe. From their capital at Damascus, the Umayyad Caliphs ruled a vast empire, extending from Europe to India, until 750. From the beginnings they showed an interest in science. It was an era that for Europeans became the Dark Ages, and yet for Muslim scholars thrived as and era of philosophical prowess and scientific discovery and development. The Arabs and Muslims at the time not only assimilated the ancient wisdom of Persia, and the classical heritage of Greece, but adapted their own distinct ways of thinking. One of the early Umayyad princes, Khalid Ibn Yazid (end of the seventh century), gave up his treasure for the study of medicine and chemistry. He studied medicine under John, the Grammarian of Alexandria, and chemistry under Merrinos, the Greek. He also encouraged several Greek and Coptic medical books to be translated into Arabic. The Abbasi Caliphs during the eighth century encouraged the Persian physicians to translate into Arabic the medical knowledge therein, to build medical centers in Baghdad, the capital of their empire, and to run newly built hospitals. With further expansion East, the Arabs through contacts with India and China brought ideas and methods, not only in medicine, but also in mathematics, chemistry, and philosophy. Harun al-Rashid (786–809) and his son, al-Ma'mun (813–833) established House of Wisdom and sent emissaries to collect Greek scientific works in the Byzantine Empire. The most important of the translators was Hunayn ibn Ishaq al-Ibadi (809–873), who was reputed to have been paid for his manuscripts by an equal weight of gold. He and his team of translators rendered the entire body of Greek medical texts, including all the works of Galen, Oribasius, Paul of Aegina, Hippocrates, and the *Materia Medica* of Dioscorides, into Arabic by the end of the ninth century. These translations established the foundations of the Greco-Arab and Islamic medicine.

15.4 ARAB–ISLAM MEDICAL ETHICS

The medical profession was a highly respected specialty with a clearly defined code of ethics. Many specific works were written by Arab and Muslim physicians on the

subject of ethics and medicine. One of the well-known substantive works is *Adab al-Tabib* or *The Ethics of the Physician* written by Ishaq ibn "Ali al-Ruhani" (ninth century). Another impressive work was written by Al-Tabari, the chief physician in 970. He wrote the Islamic code of ethics in his book *Fardous Al Hikma* (*The Paradise of Wisdom*) stressing the personal qualities of the physician, the physician's obligations toward his patients, community, and colleagues. The main points of Al-Tabari's code of medical ethics are as follows:

Personal Characters of the Physician: The physician ought to be modest, virtuous, merciful, and to not use liquor. He should

1. wear clean clothes, be dignified, and have well-groomed hair and beard;
2. not join the ungodly and scoffers of truth, nor sit at their table;
3. select his company from among persons of good reputation;
4. be careful of what he says and should not hesitate to ask forgiveness if he makes an error;
5. be forgiving and never seek revenge;
6. be friendly person and a peacemaker;
7. not make jokes or laugh at the improper time or place.

Obligation Toward Patients: The physician should avoid predicting whether a patient will live or die; only God knows that. Furthermore, he should

1. not lose his temper when a patient keeps asking questions, but should answer them gently and compassionately;
2. be punctual and reliable;
3. not wrangle about his fees. If the patient is very ill or has an emergency, he should be thankful for what he is paid;
4. not give drugs to a pregnant woman to induce an abortion unless it is necessary for the mother's health. If the physician prescribes a drug orally, he should make sure that the patient knows the name of the drug in case he asks for the wrong drug and his condition worsens;
5. be decent toward women. He should not divulge the secrets of his patients. He should treat the rich and the poor, the master and the servant, the powerful and the powerless, the elite and the illiterate alike. God will reward him if he helps the needy;
6. not be late for his rounds or his house calls.

Obligation Toward The Community: The physician should speak no evil of reputable men of the community or be critical of any one's religious beliefs.

Obligations Toward His Colleagues: The physician should speak well of his colleagues. He should not honor himself by shaming others. If another physician has been called to treat his patient, he should not criticize his colleague even if the diagnosis and the recommendations of the latter differ from his own. However, he has the obligation of explaining the consequences of each method of treatment, since it is his duty to counsel the patient as best he can. He must warn him that combining different types of therapy may be dangerous because the actions of different drugs may be incompatible and injurious.

Obligations Toward His Assistants: If his subordinate makes a mistake, the physician should not rebuke him in front of others, but correct him privately and cordially.

ISLAMIC CODE OF ETHICS BY AL-TABARI IN 970

. . . The physician should be modest, virtuous, and merciful . . . He should wear clean clothes, be dignified, and have well-groomed hair and beard . . . He should select his company to be persons of good reputation . . . He should be careful of what he says and should not hesitate to ask forgiveness if he has made an error . . . He should be forgiving and never seek revenge . . . He should be friendly and peacemaker . . . He should avoid predicting whether a patient will live or die, only Allah knows . . . He ought not loose his temper when his patient keeps asking questions, but should answer gently and compassionately . . . He should treat alike the rich and the poor, the master and the servant . . . God will reward him if he helps the needy . . . He should be punctual and reliable . . . He should not wrangle about his fees. If the patient is very ill or in an emergency, he should be thankful, no matter how much he is paid . . . He should not give drugs to a pregnant woman for an abortion unless necessary for the mother's health. . . . He should be decent towards women and should not divulge the secrets of his patients . . . He should speak no evil of reputable men of the community or be critical of any one's religious belief . . . He should speak well of his colleagues . . . He should not honor himself by shaming others . . .

OATH OF MUSLIM

Published on the First International Conference on Islamic Medicine held in Kuwait in January 1981:

I swear by God . . . The Great. To regard God in carrying out my profession . . . To protect human life in all stages and under all circumstances, doing my utmost to rescue it from death, malady, pain and anxiety. To keep peoples' dignity, cover their privacies and lock up their secrets . . . To be, all the way, an instrument of God's mercy, extending my medical care to near and far, virtuous and sinner and friend and enemy . . . To strive in the pursuit of knowledge and. harnessing it for the benefit but not the harm of Mankind . . . To revere my teacher, teach my junior, and be brother to members of the Medical Profession . . . and to join in piety and charity . . . To live my Faith in private and in public, avoiding whatever blemishes me in the eyes of God, His apostle and my fellow Faithful . . . And may God be witness to this Oath.

15.5 CURRENT MEDICAL ETHICS AND MORAL ISSUES AND THEIR ISLAMIC PERSPECTIVE

It is difficult to define clearly the exact composition of Arab–Islamic medicine as promoted in modern times. From the practice point of view, the introduction of new technology in medicine in areas of sustaining life support systems, organ transplantation, stem transplantations, tissue engineered scaffolds, biotechnical parenting, and acquired immune deficiency syndrome (AIDS), has presented new questions, and affected the Arab–Islamic outlook regarding medical ethics. Although current bioethics was developed in the Western world, in the last four decades the Arab–Islamic world has felt the need to introduce courses in Islamic bioethics. The seek to understand what Islamic laws have to say about predominant bioethical issues, for example, informed consent, abortion, IVF, euthanasia, and organ transplantation, and many others [6–10].

In modern medicine, progress is based on research that ultimately must include studies involving human subjects. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases, and improve preventive, diagnostic, and therapeutic interventions (methods, procedures, and treatments). Even the most current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility, and quality. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. At present, the Helsinki Declaration represents the basis of medical and biomedical research activities in the Western world. It was published by the World Medical Association (WMA), which has developed the Declaration as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data. In research involving human subjects, the well-being of the individual research subject must take precedence over all other interests. The Helsinki Declaration indicates that it is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfillment of this duty. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence. Physicians should consider the ethical, legal, and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards.

The introduction of modern medical technology has posed perplexing new questions for Muslims, the answers to which they are still seeking. It is obvious that due to the current globalization movement all factors affecting non-Muslims sooner or later Muslims, directly or indirectly, will be affected as well. Muslims are split in two groups. One group is educated and modernized and accepts anything that serves science and humanity, irrespective of religious or moral laws that might be broken. The other group of so-called Islamic scholars has knowledge of Islam, but not of

medical sciences. They are quick to give their opinion on everything. In the followings we will try to summarize the Islamic view on various ethical and moral medical and biomedical issues.

The basic question in Islamic medical ethics is "Who is the giver of life and death?" Should man control his life and death and that of other humans? Man now "thinks" he can create life or take it away, prolong life (or misery). Are physicians to serve the creations of God, or act as God themselves?

The Right to Live and to Die. The care of the terminally ill is becoming very expensive. It is costing billions of dollars to keep patients alive in a vegetative state in intensive care units. The concept of euthanasia (mercy killing) is being revived. The question is who determines (the doctor, unconscious patient, or the family) that the "plug should be pulled" and the life support system should be stopped. What is the definition of death? Is the living will justifiable? Is stopping the life support system an act of mercy, a medical decision, murder, or merely a financial decision?

Muslims do not believe in prolonging the life as everyone has been born with predetermined life-span. Scientists are to assist but not replace God in the creation of death of human beings. Islamic morality governs the entire cycle of life. Islam places great emphasis on the sanctity of life and the reality of death. The Holy Quran says "If anyone killed a person, unless it is for murder or spreading mischief on earth, it would be as if he killed all of mankind. And if anyone saved a life it would be as if he saved the lives of all mankind." Thus, while Islam gives importance to saving lives (medical treatment or otherwise) it makes it clear that dying is a part of the contract (with God) and that the final decision is up to God. Preserving the health is equally or more important than the duration of living. Therefore, the physician and the family should realize their limitations and not attempt heroic actions for a terminally ill person or to prolong artificially the life (or misery). The heroic measures taken at the beginning of life (i.e., saving a premature embryo) may often be more justified than at the end of a life, though each case has to be analyzed individually. Islam is categorically opposed to mercy killing and regards it as an act of murder. Therefore, there is no difference between the gun used by a family member for his dying relatives and the syringe used by the physician for his dying patient. Both are weapons of death, no matter what the intentions of the killer were.

Organ Transplantation. Nowadays many diseased organs are being replaced by healthy organs from living donors, cadavers, and from animal sources. Successful bone marrow, kidney, liver, cornea, pancreas, heart, and nerve cell transplantations have taken place. Their incidence is limited only by cost and availability of the organs. The ethical questions concern the rights of the living donor, the dead body, and the recipient. To prolong a life, does the recipient have a right to take away the organs from the dead? Is the sale of organs justified? Is the taking of animal organs justified? Is accepting organs from aborted fetuses justified? Is the cost of transplantation worth the benefit derived from it? Will harvesting fetal tissues lead to more abortions?

According to the Holy Quran and *Hadith* interpretations by Muslim scholars, all three types of organ transplantations are permitted, namely animal to human, living to living (the sale is prohibited), and dead to living. However, transplantation can be performed after fulfilling strict conditions.

Abortion. Is abortion equal to killing? When is a fetus a living being? What are the rights of the fetus? Who guards those rights? Do both parents (even unwed) have the same rights over the life of the fetus? If life is a gift of God, who are we to take it away? Is killing an infant and the aged and terminally ill the same thing? What should be done with the pregnancy that results from rape? What is the role of the Muslim obstetrician? Is the sale of aborted fetus for transplantation of tissues and organs, or of their delicate skin to make expensive cosmetics justified?

Islam considers abortion of a viable fetus an infanticide except when to save the life of the mother. Even in this situation every attempt should be made to save both lives. The fetus is alive as a cell from the very beginning, with shaping starting at 4 weeks and movements at 4 months. According to *Hadith* at 120 days the angel visits the fetus and blows the spirit into it. This coincides with starting of the baby's first movement. The viability of the fetus medically has improved with the development of neonatalology. The Quran refers to abortion in many places: "Kill not your children for fear of want. We shall provide sustenance for them as well as for you. Verily the killing of them is a great sin."

In Vitro Fertilization. Infertility and the desire of a couple to have a child of their own is not a new problem. However, current and emerging techniques to solve this have added a new twist. Now we have successful technology to fertilize an egg outside the uterus (test tube babies) and inject sperm into the uterus from the husband or a surrogate male donor, take the ovum of a woman and fertilize it with the sperm of her husband and inject it into the uterus of another woman for incubation.

In Islam the marriage of a man and a woman is not just financial and physical arrangements of living together but a sacred contract, a gift of God, to enjoy each other physically and continue the lineage. "Among His signs is that He created consorts for you amongst yourselves, so that you may find tranquility with them, and He set love and compassion between you. Verily in this are signs for people who reflect." The Prophet (PBUH) has emphasized marriage by saying: "Marriage is my tradition. He who rejects my tradition is not of me." In fact, he described marriage as half of religion, the other half being God fearing. Therefore, violation of this sacred contract of marriage by a biotechnical technique is a violation of Islamic law. It is only allowed if it is the product of an intact marriage, that is, during the life-span of marriage. Artificial insemination using the husbands sperm, fertilized in the uterus of the wife, or the test tube is allowed.

Surrogate motherhood is not acceptable because of the main question: Who is the mother? "None can be their mother except those who gave birth." Recently a mother kept an embryo fertilized by her daughter and her son-in-law and gave birth to her son/or grandson.

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CHAPTER 16

Medicinal Herbs and Extracting Their Active Ingredients

16.1 INTRODUCTION

The plant kingdom has provided an endless source of medicinal plants with numerous biological properties and pharmacological potential. These herbs have been used for thousands of years either in their crude forms or as herbal teas, syrups, infusions, ointments, liniments, and powders. Owing to *Hadiths* of the Prophet (PBUH), "The one who sent down the disease sent down the remedy." and "For every disease, Allah has given a cure." every Muslim is encouraged to search for those remedies and use them with skill and compassion. In this respect, Arab and Muslim pharmacists introduced a large number of new drugs to clinical practice, including senna, camphor, sandalwood, musk, myrrh, cassia, tamarind, nutmeg, cloves, aconite, ambergris, and mercury. They also developed theoretical and practical knowledge on various preparation techniques and on the administration of medicinal plants, for example, syrups and juleps and pleasant solvents such as rose water and orange-blossom water as means of administering drugs. By using his mathematical and medical expertise, Al-Kindi (Alkindus) (800–873) was the first scholar in history who developed a scale to define the meaning of drug "degrees" in order to allow physicians to quantify the potency of their prescriptions. Jabir ibn Hayyan (ca. 776) wrote one of the first pharmacological treatises. This treatise was extensive and gave detailed descriptions of the physical properties and geographical origins of medicinal plants and methods of extraction and application that was known for the curing of diseases.

Nowadays, numerous herbal-derived substances remain the basis for a large proportion of the used commercial drugs for the treatment of all types of aliments, for example, heart disease, high blood pressure, inflammation, pain, asthma, and other illnesses. Approximately 25% of all drugs contain one or more herbal-derived ingredients from plants. With the development of chemistry, the active substances of a large number of medicinal plants have been purified, characterized, and duplicated

Greco-Arab and Islamic Herbal Medicine: Traditional System, Ethics, Safety, Efficacy, and Regulatory Issues By Bashar Saad and Omar Said

in the form of synthetic drugs. For instance, ephedrine, the active ingredient in ephedra, a medicinal herb, has been used in traditional Chinese medicine for more than 2000 years to treat asthma and other respiratory problems. Ephedrine is used in commercial pharmaceutical preparations to relieve asthma symptoms and other respiratory problems. Other classic examples of herbal-derived drugs are aspirin and taxol. Aspirin was initially discovered as salicylic acid in willow bark. Taxol was initially discovered in bark of yew trees and has been recently proven effective in treatment of breast and ovarian cancers [1–3].

This chapter will provide an overview of traditional Arab herbal medicine including criteria used to identify a potential medicinal plant, preparation techniques, and herbal-derived active compounds.

16.2 HISTORICAL BACKGROUND

Herbal remedies are used throughout the world and in the past herbs often represented the original source of most drugs. The medicinal use of herbal products precedes recorded human history probably by thousands of years (see Chapter 3 for more details). For instance, palaeoanthropological findings at the cave site of Shanidar, located in the Zagros Mountains of Kurdistan in have suggested that more than 60,000 years ago, Neanderthals might have been aware of the medicinal properties of various natural products, mainly plants, as evidenced by pollen deposits in one of the graves at the site. The oldest medical text, written on hundreds of clay tablets in cuneiform, comes from ancient Mesopotamia (about 2600 BC). It describes approximately 1000 plants and herbal-derived products, such as the oils of cedar, the resin of myrrh, and the juice of the poppy seed. Many of these herbs and formulations are still used today. The ancient Egyptian *Ebers Papyrus* (around 1550 BC) contains more than 700 natural products, such as *Aloe vera* (aloe), *Boswellia carteri* (frankincense), and the oil of *Ricinus communis* (castor). Hippocrates (460–377 BC), collected more than 400 natural agents and described their uses in his *Corpus Hippocraticum*. He mentioned using melon juice as a laxative, described the diuretic effect of the juice from *Ornithogalum caudatum* and detailed a description of the anesthetic properties of an extract from *Atropa belladonna*. He also advised using an extract of *Veratrum album* (white hellebore) as an emetic and how to use olive oil to improve wound healing. Dioscorides (40–80 AD) wrote *De Materia Medica*, which described the dosage and efficacy of about 600 herbal-derived drugs. Galen (129–200), described 540 plant-derived medicines and demonstrated that herbal extracts contain not only beneficial substances, but also harmful ingredients. *Charaka Samhita*, the first treatise devoted to the concepts and practice of Indian Ayurveda (around 900 BC) contains 341 plant-derived medicines.

Herbal medicine was a central part of medieval Islamic civilization. Responding to circumstances of time and place, Arab–Islamic physicians and scholars developed a large and complex medical literature exploring and synthesizing the theory and practice of medicine. They introduced many new ideas and upgraded the knowledge about herbs and their potential medical efficacy and safety. Numerous encyclopedias

on botany were written, with highly accurate precision and details of medicinal plants. For instance,

- Al-Dinawari (828–896) is considered as the founder of Arabic botany for his *Book of Plants*, in which he described about 640 plants and described the phases of plant growth and the production of flowers and fruit.
- Avicenna (980–1037) published several books such as *Alkanoon Fi Altib* (*Canon of Medicine*) in addition to Rhazes book *AlHawy* (*The Comprehensive*), which were translated into several different languages.
- Ibn Abil-Bayan in 1161 AC in Spain published *The Bimaristan Law in Pharmacopoeia*, *Materitenses*. This book contains 607 detailed medications.
- Ibn Zuhr (Avenzoar), who lived in Seville, Spain (1091–1161) wrote the *Al Kitab Al Jami* about liquids and creams. This book includes 230 medications that are mostly herbal and a few are of animal and mineral origin. This book gives a full description of the uses of herbs whether they are roots, seeds, or leaves.
- Rabbi Moses Ben Maimon, who lived in Spain (1135–1204) wrote the *Drugs Terminology*, which contains 405 chapters and gives synonyms of medications in Arabic, Greek, Persian, and Spanish languages.
- Abu al-Abbas al-Nabati published in the early thirteenth century several books and dictionaries on the use of medicinal plants describing each plant species, the plant parts used, the preparation procedure used for each remedy, and the treatment procedure of certain diseases.
- Ibn al-Baitar (Figure 16.1), who lived in Damascus, Syria (1197–1248) published *The Book on Drinks and Foods*, which is a collection of different drinks and foods. It is the most prestigious book in the Arabian pharmacopeia; it contains 260 references. The medications were classified in alphabetical order.
- Daoud al-Antaki used different herbs for treating patients and published a book on medicinal herbs summarizing the knowledge of his predecessors.

Al-Kindi developed a scale to define the meaning of drug "degrees" in order to allow doctors to quantify the potency of their medication, by using his mathematical and medical expertise. In the Golden Age of the Arab–Islamic civilization, pharmacology was a profession practiced by highly skilled specialists. Pharmacists were required to pass examinations and be licensed, and were then monitored by the state. At the start of the ninth century, the first private apothecary shops opened in Baghdad. Pharmaceutical preparations were manufactured and distributed commercially, then dispensed by physicians and pharmacists in a variety of forms—ointments, pills, elixirs, confections, tinctures, suppositories, and inhalants. Herbal medicines were classified according to their effects on the human body. For instance, stimulants (prescribed to increase blood flow and raise energy level), diuretics (promote urination and thus expel toxins), expectorants (remove mucous accumulation), topical antiseptic cleansers, tonics (general strength building and disease prevention), analgesics and anesthetics, digestive aids, and oral health [1–5].

FIGURE 16.1 Ibn al-Baitar (1197–1248) was one of the greatest botanist and pharmacist of the Middle Ages. Ibn Baitar's major contribution, "*Kitab al-Jami fi al-Adwiya al-Mufrada*," is one of the greatest botanical compilations dealing with medicinal plants written in Arabic, the lingua franca of the Arab–Islamic civilization. It enjoyed a high status among botanists up to the sixteenth century and is a systematic work that embodies earlier works, with due criticism, and adds a great part of original contribution. This book included some 1400 different items, largely herbs and vegetables, of which about 200 plants were not known earlier. It was translated into Latin in the eighteenth century. His second book "*Kitab al-Mlughni fi al-Adwiya al-Mufrada*" is an encyclopedia of medicine. The drugs are listed in accordance with their therapeutical value.

16.3 IDENTIFYING POTENTIAL MEDICINAL PLANTS

Arab–Islamic scholars used hundreds of medicinal plants. They also developed a large and complex medical literature exploring and synthesizing the theory and practice of medicine and botany with highly accurate precision and details. Like in other fields of science, Arab–Muslim physicians developed the first scientific methods for the field of medicine. This included the introduction of experimentation, quantification, experimental medicine, evidence-based medicine, clinical trials, dissection, animal testing, human experimentation, and postmortem autopsy by Muslim physicians, while hospitals in the Arab–Islamic world featured the first drug tests, drug purity regulations, and competency tests for doctors.

Arab–Muslim scholars were not guided by a long history of trial and error, but mainly by scientific methods, which led to the use of "evidence-based medication."

The correlation of particular herbs with the amelioration and/or complete curing of certain diseases was one of the factors led to the identification on new potential medicine. For instance, morphological features of the herb, including size, shape, color, texture, and taste were considered as important criteria in their selection for therapeutic purposes. For instance, seeds with kidney shape are used for treating kidney stones, for example, *Alhagi maurorum* and *Astragalus macrocarpus*. Roots shape similar to human body or fruits resemble human testis are used traditionally for stimulating sexual desire or treating sexual weakness, for example, *Mandragora autumnalis* and *A. macrocarpus*. The doctrine of signatures is reflected in some of the uses of certain herbs, for example, the yellow decoction obtained from leaves of *Rhamnus alaternus* and the yellow juice from the fruits of *Ecbalium elaterium* are used for treating jaundice and liver diseases. For several herbs, the plant's common name in Arabic refers to its use. This is the case for *Glaucium oxylobum*, *Hypericum lanuginosum*, *Mercurialis annua*, and *Ceterach officinarum*. All four plants are called "The wound's herbs," since they are used for treating external wounds. The exchange of people and culture between the Middle East, Europe, and the Far East has brought with it exchange of information, so that a given herb is used similarly in all these areas, for example, *Ammi visnaga* for kidney stones; *Matricaria aurea* for stomach aches; *Malva nicaensis* for wounds.

Plants either mentioned in the Holy Quran or in the *Hadith* by the Prophet (PBUH) were considered as highly potential medicinal plants (Chapters 8 and 17). For instance, the black seeds (*Nigella sativa*) as an example could be considered as either a meal for food consumption or as a preventive of high blood pressure and heart diseases. The oil as well as the fruits of olive (*Olea europaea*) is important source for food nutrition and antioxidants for preventing diabetes in many societies. Other plants include dates, figs, and pomegranates [1–7].

16.4 PREPARATION TECHNIQUES

Several techniques were developed by Arab and Muslim physicians, chemist, and pharmacists. Many of these methods are still practiced by traditional herbalists to obtain beneficial ingredients from selected plants (Table 16.1). The majority of herbal preparations are consumed orally in the form of tea or other drink containing either diluted or concentrated extracts. Teas are generally produced from the various parts of the herbs through infusion or as decoctions. Heating a raw plant in a solvent not only aids the extraction and concentration of curative substances, but also acts to eliminate poisons and impurities prior to consumption. The chemical composition of an herbal extract is largely influenced by the method of extraction. Hot water extracts of herbs will be rich in polar components because water is a polar solvent. Oil on the other hand is a nonpolar solvent and it will absorb nonpolar compounds. Alcohol lies somewhere in between. Other methods include the inhalation of aerosols (e.g., *Pimpinella anisum*), essential oils (e.g., *Jasminum fruticans*), and vaporized plant juices or teas.

Different techniques were also developed for drug preparation for external (topical) applications and are currently used by herbalists in the Arab–Islamic world.

TABLE 16.1 Preparations Methods Used for Oral Administrations

Form	Preparation Methods
Whole plant	Dried form (herbal powder), fresh juice, or fresh leaves and other plant parts
Tinctures	Preparations of herb extract using varying ratios of water and alcohol. Usually obtained by combining pure ethanol or 40–60% ethanol in water with the herb
Tisanes	Hot water extracts of herb, such as chamomile, sage, peppermint
Decoctions	A decoction is obtained by a long-term boiled extract of leaves, flowers, stems, roots, and bark
Macerates	Cold infusion of plants with high mucilage content as sage, thyme, and so on. Plants are chopped, added to cold water, and then left to stand for 7–12 h (depending on herb used). For most macerates 10 h is used
Vinegars	Vinegar extracts, prepared at the same way as tinctures
Syrups	Extracts of herbs made with syrup or honey. Sixty-five parts of sugar are mixed with 35 parts of water and herb. The whole is then boiled and macerated for 3 weeks
Extracts	Include liquid extracts, dry extracts, and nebulisates. Liquid extracts are liquids with a lower ethanol percentage than tinctures. They are usually made by vacuum distilling tinctures. Dry extracts are extracts of plant material that are evaporated into a dry mass. They can then be further refined to a capsule or tablet. A nebulisate is a dry extract created by freeze-drying
Inhalation	Can be used as a mood changing treatment to fight a sinus infection or cough, or to cleanse the skin on a deeper level

These include essential oils, salves, oils, balms, creams and lotions, or poultices and compresses (Table 16.2). In making a poultice, for example, plant parts are ground or crushed and combined with hot water or other liquids to create a medicinal paste or plaster. The resulting mixture is placed directly on wounds, bruises, aritric joints, burns, insect and animal bites, rashes, swellings, wrinkles, or dermatological irritations, for example, *Ceterach officinarum*; *Citrullus colocynthis*; *Eryngium creticum*.

A common extract preparation method of herbs for research purposes is alcohol/water extracts (Figure 16.2). In this method varying ratios of water and alcohol, usually ethanol and water, is mixed with the herb. For instance, we used the following methods for preparing crude extracts of antidiabetic, antihyperglycemic, anti-inflammatory, and antiobesity medicinal plants mixture as discussed in details in Chapter 12 [8–10]:

- *Water Extracts*: Fresh plants are collected, dried under shade, and powdered to a fine grade. Fifty grams of air-dried plants are added to 1 L of distilled water and boiled for 10 min. The boiled water extract are filtered through filter paper and are freeze-dried in a lyophilizer. The freeze-dried extracts are stored at $-70^{\circ}C$ for further evaluation. This method is used to extract hydrophilic substances.
- Fresh plants are collected, dried under shade, and powdered to a fine grade. Fifty grams of air-dried *plants* are added to 1 L of 50% ethanol in distilled water and

TABLE 16.2 Preparation Methods Used for Topical Applications

Form	Preparations
Essential oils	Application of essential oil extracts, usually diluted in carrier oil. Many essential oils can harm the skin. Diluting in olive oil or another food grade oil can allow these to be used safely as a topical
Salves, oils, balms, creams, and lotions	Most topical applications are oil extractions of herbs. Taking a food grade oil and soaking herbs in it for a long period (weeks to months) allows the extraction of certain ingredients into the oil. This oil can then be made into salves, creams, lotions, or simply used as oil for topical application. Any massage oils, antibacterial salves, and wound healing compounds are made this way
Poultices and compresses	One can also make a poultice or compress using whole herb (or the appropriate part of the plant) usually crushed or dried and rehydrated with a small amount of water and then applied directly in a bandage, cloth, or just as is

boiled for 10 min. The boiled water extract are then filtered through filter paper and are freeze-dried in a lyophilizer. The freeze-dried extracts are stored at $-70^{\circ}C$ for further evaluation. This method is used to extract both hydrophilic and hydrophobic substances.

16.5 HERBAL-DERIVED ACTIVE COMPOUNDS

The importance of natural products for medicine and health has been enormous since our earliest ancestors. In fact, it has only been during the past decades that natural products have taken a secondary role in drug discovery and drug development, after the advent of biochemistry, molecular biology and combinatorial chemistry made possible the rational design of chemical compounds to target specific biomolecules, for example, receptors, enzymes, and hormones. The extraction and characterization of active ingredients from medicinal herbs have resulted in the discovery of new drugs with high therapeutic value. A classic example is salicylic acid (aspirin) isolated from willow bark and leaves; another noted example is taxol, isolated form bark of yew trees, recently proven effective in treatment of breast and ovarian cancers. In four decades, there has been a revival of interest in natural or herbal-derived medicines worldwide, partly because of the realization that modern medicine is not capable of providing a "cure-all" solution against human diseases and that the presence of unwanted side effects is almost unavoidable (Figure 16.3).

Unlike modern drugs that consist of a single active compound, herb extracts and/or prescriptions contain multiple active ingredients. Several techniques have been used by traditional herbalists to obtain the beneficial herbal components from the

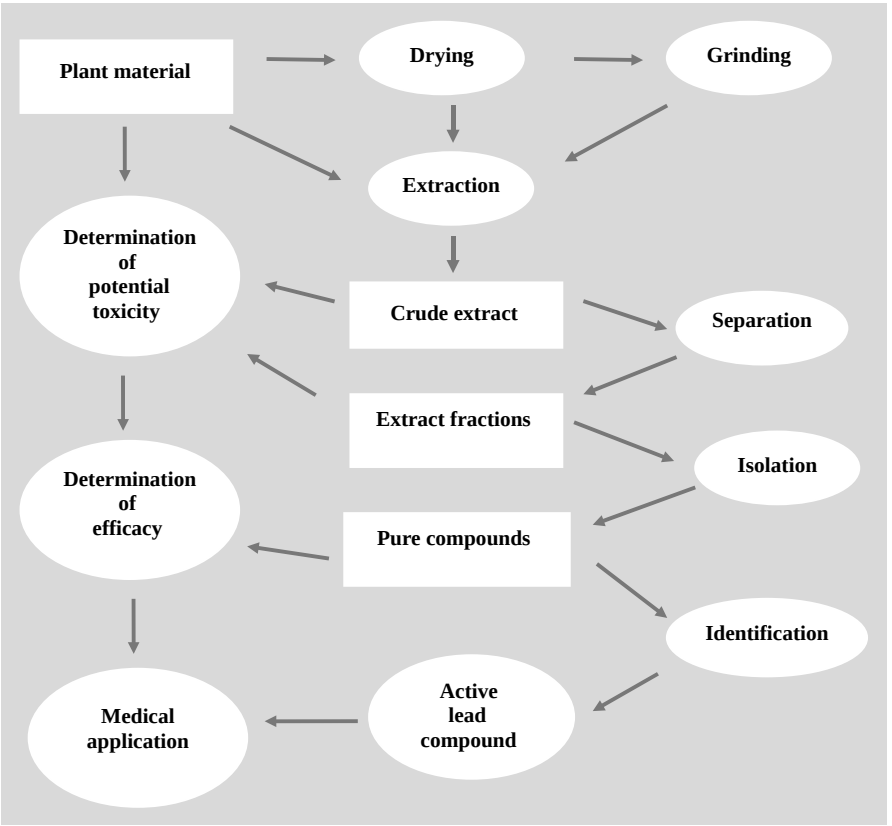

FIGURE 16.2 Commonly used preparation procedure.

selected species. The majority of herbal-based preparations have been taken orally in the form of tea or other drinks containing either diluted or concentrated active ingredients. Interestingly, compounds contained in these herbal mixtures can act in a synergistic manner within the human body, and can provide unique therapeutic effects with minimal or no undesirable side effects. A key factor in the widespread acceptance of natural therapies by the international community involves the "modernization" of herbal medicine. In other words, the standardization and quality control of herbal materials by use of modern science and technology is critical. Currently, however, quality-related issues (lack of consistency, safety, and efficacy) seem to be overshadowing the potential genuine health benefits of various herbal-derived products, and a major cause of these problems seems to be related to the lack of simple and reliable analytical techniques and methodologies for the chemical analysis of herbal products. The beneficial medicinal effects of plant materials typically result from the combinations of secondary products present in the plant [11–14].

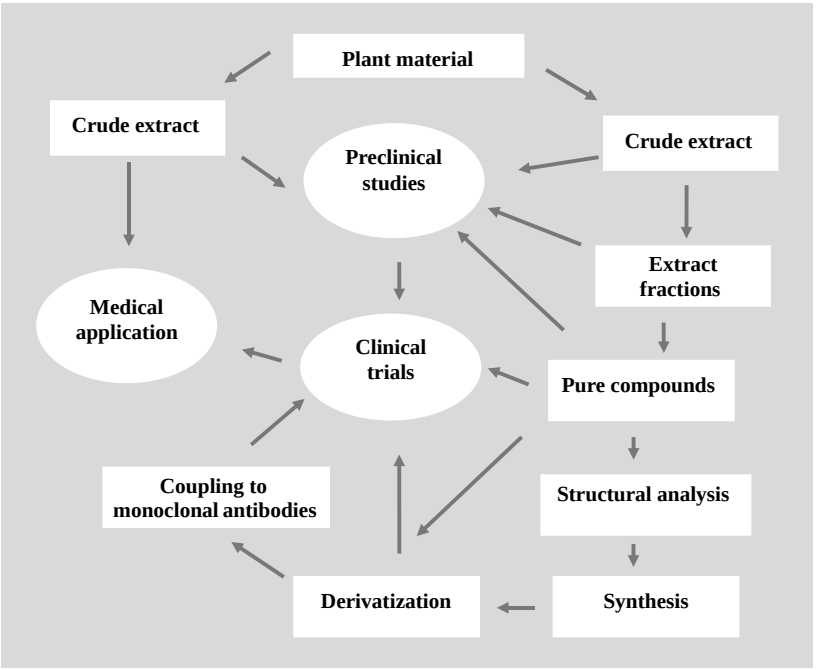

FIGURE 16.3 Isolation and modification of herbal-derived drugs: The structural analysis of herbal-derived compounds and the ability to synthesize them allowed chemists to modify them in order to suppress or enhance certain characteristics such as solubility, efficiency, or stability in the human body. It is estimated that about 60% of the drugs that are now available—including household names such as artemisinin, camptothecin, lovastatin, maytansine, paclitaxel, penicillin, reserpine, and silibinin—were either directly or indirectly derived from plants.

16.5.1 Secondary Products

Plant cells contain far more compounds than are produced by basic metabolism, namely polyphenols, terpenes, waxes, alkaloids, and pigments. Basic metabolism comprises all primary metabolites necessary for the survival of the cells, such as carbohydrates, lipids, proteins, heme, chlorophyll, and nucleic acids, which are common to all plants and are involved in the primary metabolic processes of building and maintaining plant cells and tissues (Table 16.3). In contrast, secondary plant products are produced usually only in special, differentiated cells and are not essential for the cells themselves but are useful for the plant as a whole. Examples are flower pigments and scents or stabilizing elements. Both metabolic processes overlap since it is often not understood why a certain compound is produced.

Although secondary plant products are very common, this does not mean that every plant can produce every product. Some compounds are restricted to single species, others to related groups. But they are usually found only in certain specific plant

TABLE 16.3 Primary and Secondary Products of Plants

Plant primary metabolites:

- Organic compounds produced in plants
- Essential for growth and development
- Produced in every plant
- Include carbohydrates, amino acids, nucleotides, fatty acids, steroids and lipids

Plant secondary metabolites:

- Organic compounds produced in plants
- Do not have apparent functions involved in growth and development
- Produced in different plant families, in specific groups of plant families or in specific tissues, cells or developmental stages throughout plant development
- Generally grouped into classes:
  1. Polyphenols (widely distributed in nature, responsible for the colors of many flowers, for example, delphinium, fuchsia, rose, and petunia, and of all red berried fruit. Others are present in bark, roots, and leaves of plants that are used for tanning hides and skins to give leather. Yet others are simpler compounds present in most fresh fruit and vegetables, onions, and tea)
  2. Terpenoids and steroids (over 35,000 known, derived biosynthetically from isopentenyl diphosphate)
  3. Fatty acid-derived substances and polyketides (more than 10,000 known, biosynthesized from simple acyl precursors such as acetyl CoA)
  4. Alkaloids (more than 12,000 known, derived biosynthetically from amino acids)
  5. Nonribosomal polypeptides (peptide-like compounds, biosynthesized from amino acids)
  6. Enzyme cofactors (coenzymes such as pyridoxal phosphate)

organs, often in just one type of cell. Also, they are often generated only during a specific developmental period of the plant. Hence, herbal-derived active compounds are unique to particular plant species or groups. Although plant secondary products have historically been defined as chemicals that do not appear to have a vital physiological role in the process of building and maintaining plant cells, recent studies have revealed an essential role of these compounds in the ecophysiology of plants. Accordingly, secondary metabolites have both a defensive function against pathogen attack, and interplant competition and an attractant role toward beneficial organisms such as symbionts or pollinators. In addition, plant secondary compounds have protective properties in relation to abiotic stresses such as those associated with changes in water status, mineral nutrients, temperature, and light levels. Recent studies have revealed the potential role of secondary compounds at the cellular level as plant growth regulators, modulators of gene expression, and in cell signal transduction. Although secondary products can have a variety of functions in plants, it is likely that their ecological function may have some bearing on beneficial pharmacological properties in humans. For example, they are involved in plant defense through cytotoxicity toward microbial pathogens could prove useful as antimicrobial medicines in humans. Likewise, secondary products involved in defence against herbivores through neurotoxin activity could have beneficial effects in humans (i.e., as antidepressants, sedatives, muscle relaxants, or anesthetics) through their action on the central nervous system.

Many scientists have attempted to explain the puzzle of why so many compounds in nature have biological effects in humans and other species. One explanation that has been widely accepted is that it is the result of long-term coevolution within biological communities. Such communities involve interacting organisms that evolved in close proximity to one another compounds developed that could influence the biological processes of neighboring species. As these compounds proved to be advantageous, they became a trait on which natural selection could act, and were retained and improved throughout the course of evolution. Given the similarities between aspects of human physiology and that of other animals, it is not surprising that such molecules can also exert biological effects in humans. In addition, to promote the ecological survival of plants, structures of secondary products have evolved to interact with molecular targets affecting the cells, tissues, and physiological functions in competing microorganisms, plants, and animals. In this respect, some plant secondary products may exert their action by resembling endogenous metabolites, ligands, hormones, signal transduction molecules, or neurotransmitters and thus have beneficial medicinal effects on humans due to similarities in their potential target sites (e.g., central nervous system, endocrine system, etc.). The development of structural similarity between plant secondary products and the endogenous substances of other organisms could be termed "evolutionary molecular modeling." Recent research has indicated that the benefits of phytomedicines often result from synergistic actions of multiple active compounds [11–14].

16.5.2 Synergistic Actions of Phytomedicines

In contrast to synthetic medicines based upon single molecule, many herbal-derived drugs exert their pharmacological effects through the additive or synergistic action of several active compounds acting at single or multiple target sites associated with a physiological pathway. This synergistic or additive therapeutic effect can be beneficial by eliminating or reducing unwanted side effects associated with the predominance of a single xenobiotic compound in the body. This theme of multiple chemicals acting in an additive or synergistic manner likely has its origin in the functional role of secondary products in promoting plant survival. For example, in the role of secondary products as defence chemicals, a mixture of chemicals having additive or synergistic effects at multiple target sites would not only ensure effectiveness against a wide range of herbivores or pathogens but would also decrease the chances of these organisms developing resistance or adaptive responses [11–14].

16.5.3 Examples of Herbal Compounds and Their Pharmacological Properties

Plants have an almost limitless ability to synthesize numerous substances that have been evaluated for their therapeutic potential. These include alkaloids, coumarins, saponins, and flavonoids. Flavonoids are probably the best known of these substances due to their antioxidant properties (Table 8.1). The therapeutic benefit of several plant species used by traditional herbalists, at least in part, was attributed to their effective

inhibition of oxidative processes. Several of these herbs are used traditionally in treating liver diseases, for example, *Pistacia lentiscus* was found effective in suppressing iron-induced lipid peroxidation in rat homogenates, and Trolox, the water soluble analogue of vitamin E, did not adversely affect cell membrane integrity or suppress mitochondrial respiration in cultured HepG2 and PC12 cells. A single dose of the aqueous boiled and nonboiled decoctions prepared from the leaves of *P. lentiscus* blunted the effects of single intoxicating dose of the known hepatotoxin, carbon tetrachloride. *Silybum marianum* is currently the most well researched plant used traditionally by Arab herbalists in the treatment of liver diseases. The active constituents of milk thistle are flavonolignas including silybin, silydianin, and silychristine, collectively known as silymarin. Silymarin is not water-soluble and so cannot be taken as a tea but as an encapsulated standardized extract [11–14].

Thymoquinone has been found to be the main compound responsible for the pharmacological properties of the volatile oil of black seed (*N. sativa*). As discussed in details in Chapters 8 and 16, Black seed has been used for hundreds of years in Arab–Islamic medicine for its magic healing properties, and for this reason, it is named "the blessed seed." According to a *Hadith* by the Prophet (PBUH), "the black seed can heal every disease, except death." Avicenna referred to *N. sativa* in his *Canon of Medicine*, as the seed that stimulates the body's energy and helps recovery from fatigue and dispiritedness. The therapeutic potential and toxicological properties of black seeds have been extensively studied. A MEDLINE search using *N. sativa* or "Black seed" reveals more than 700 citations that report antioxidant, anti-inflammatory, antimicrobial, hypotensive, antinociceptive, choleretic, uricosuric, choleretic, antidiabetic, and antihistaminic, immunomodulatory, anticancer, and antifertility effects.

Thymoquinone has been reported to have potent anticancer and superoxide anion scavenging abilities in animal models and cell culture systems. It directly interacted with glutathione and NADH to reduce the ferryl forms of methemoglobin and met-myoglobin to their oxidized forms, thus leading to the recovery of hemoglobin and myoglobin from oxidative stress. Other studies showed that thymoquinone acts as an antioxidant and inhibited iron-dependent microsomal lipid peroxidation, cardiotoxicity induced by doxorubin in rats, and ifosfamide-induced damage in kidney. It also prevented hepatic injury induced with carbon tetrachloride. In all mentioned test systems, thymoquinone lowered drug-induced toxicity and caused amelioration in the drug's anticancer activity. On the other hand, there are studies reporting that the anticancer potential of thymoquinone is related to its pro-oxidant activities. In human colon cancer cells and in isolated rat liver mitochondria, thymoquinone induced a significant release of reactive oxygen species (ROS) and inhibited the activity of aconitase, an enzyme sensitive to superoxide anion generation. One of the most promising effects of thymoquinone is that it exhibits high cancer specificity and low toxicity to normal cells. This has been observed in prostate cancer, colon cancer, canine osteosarcoma, and skin cancer. Many multidrug-resistant variants of human pancreatic adenocarcinoma, uterine sarcoma, and leukemia were found to be sensitive to thymoquinone. The mechanisms of thymoquinone anticancer action in cells range from the induction of G0/G1 phase arrest in colon, canine osteosarcoma and mouse papilloma cells, to G1/S phase arrest in prostate, and G2/M arrest in skin cells.

Thymoquinone-induced growth arrest is linked to the increased levels of the cyclin-dependent kinase (CDK) inhibitors, downregulation of androgen receptor, transcription factor E2F-1, and its positive regulator p-Rb. Thymoquinone and its synthetic derivatives have been shown to inhibit the function of the serine/threonine kinase Polo-like kinase 1 (Plk1 PBD) *in vitro*, and cause Plk1 mislocalization, chromosome congression defects, mitotic arrest, and apoptosis in HeLa cells. These results provide a great potential into the development of synthetic derivatives of thymoquinone as anticancer agents. Thymoquinone induces apoptosis through modulation of multiple targets and hence is a promising phytochemical that could be useful for the killing of many types of cancer cells. These results are also supported by reports in prostate and other cancer cells. Thymoquinone blocked angiogenesis *in vivo*, prevented tumor angiogenesis in a xenograft human prostate cancer (PC3) model in mouse and inhibited human prostate tumor growth with almost no side effects. In mouse, injection of the essential oil into the tumor site significantly inhibited solid tumor development and the incidence of liver metastasis, thus improving mouse survival. Thymoquinone induces apoptosis in cells by p53-dependent and p53-independent pathways, and drug-induced apoptosis is associated with the activation of caspases, increases in p53 expression, upregulation of proapoptotic Bax and downregulation of antiapoptotic Bcl-2, and decrease in cyclins B1 and D1. In SW-626 human colon cancer cells, thymoquinone induced major cellular damage and severely impaired the normal cellular metabolism, effects that were comparable to those triggered by 5-flourouracil, a colon cancer chemotherapeutic agent. Moreover, recent studies have shown that NF-κB is a legitimate target of thymoquinone, which was associated with cell growth inhibition and induction of apoptosis in cancer cells. *In vivo*, thymoquinone inhibited the growth of prostate and colon tumors implanted in nude mice with no noticeable side effects. In colon xenografts, growth inhibition by thymoquinone was not due to decreased proliferation but rather to the significant induction of apoptosis. However, in androgen-independent prostate tumor xenografts, the suppression of tumor growth was associated with a marked decrease in E2F-1 and induction of massive apoptosis. These results indicate that the antitumor activity or cell growth inhibition could in part be due to the effect of thymoquinone on cell cycle [6,12].

16.6 PURIFICATION AND CHARACTERIZATION OF ACTIVE INGREDIENTS

Despite the wide use of medicinal plants, their active ingredients remained all but unknown until the eighteenth and nineteenth centuries. However, early physicians, such as Galen, did understand that various natural products contained different compounds that would each affect the human body differently. Jaber Ibn Hayan extracted different anesthetic compounds from local herbs for local or general anesthetization. Furthermore, essential oils were first produced by Avicenna in the early eleventh century, using steam distillation, giving rise to aromatherapy. As a result, he is regarded as a pioneer in this field.

The past few decades, have seen a renewed interest in the use of herbal-derived compounds and, more importantly, their role as a basis for drug development. Modern developments in chemistry and biology have provided the tools to purify various herbal-derived, pharmacologically active compounds and to determine their structures. This, in turn, has given insights into their action on target tissue and organs of the human body, as well uncovering possible synergistic effects, which holds much promise for the development of new therapies against many devastating diseases, including dementia and cancer.

The use of purified herbal compounds started in the nineteenth century when the German pharmacist Friedrich Wilhelm Sertürner isolated in 1805; morphine from opium, and it became both the first pure naturally derived medicine and the first to be commercialized in 1826. Thereafter, pharmaceutical companies quickly began to prefer isolated compounds as ingredients to make drugs, rather than crude extracts. Furthermore, the determination of the molecular structures of many natural compounds enabled organic chemists to produce them, rather than purifying them from natural sources, which markedly lowered the cost of drug production. Thereafter, a large number of well-known herbal molecules were purified, identified, and synthesized. Many of these compounds are still widely used as drugs. For example, strychnine and brucine from *Strychnos nuxvomica*, quinine from *Cinchona ledgeriana*, caffeine from *Coffea arabica*, nicotine from *Nicotiana tabacum*, atropine from *A. belladonna*, and cocaine from *Erythroxylum coca*, salicin from *Salix alba*, colchicine from *Colchicum autumnale*, emetine from *Cephaelis ipecacuanha*. The isolation and identification of natural products continued and in the twentieth century the antibacterial properties of penicillin, derived from the mould *Penicillium notatum* were discovered. Later on various other antimicrobial compounds were identified that gave physicians an enormously powerful weapon in their battle against infectious diseases.

The structural analysis of natural compounds and the ability to synthesize them allowed organic chemists to modify them in order to suppress or enhance certain properties such as solubility, efficiency, or stability in the human body. These products have also been an invaluable source of inspiration for organic chemists to synthesize novel drug candidates. Some have even claimed that the switch away from natural products to combinatorial chemistry during the 1990s might have led to the current flaw of new drug candidates in the development pipeline. It is therefore a matter of great scientific, economic, and medical interest to analyze and understand why so many natural products are beneficial to human health [6,12].

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CHAPTER 17

Food Therapy

17.1 INTRODUCTION

Modern science is now rediscovering the power of food. Numerous scientific publications and books are filled with information on functional foods, dietary fiber, vitamins, how to detoxify the body by altering the diet, and books touting certain ways of eating such as macrobiotic or vegan as a "cure all" for any disease. Other books give specific recipes or lists of foods that cure various diseases. In reality, healing with food is one of the oldest methods of healing known to man and is not a "new" concept in any way. It is also one of the most economical and globally available methods of healing known to man.

Food was a substantial part of pre-Islamic medicine as well as in other traditional medicines, for example, Greek, Ayurvedic. Diet is a matter of faith in Islam, and plays an important role in maintaining a healthy body, soul, and spirit. Muslims are commanded follow a set of dietary laws outlined in the Holy Quran, were almost everything is permitted (halal), except what God specifically prohibited (haram). Later on, when the Islamic empire covered all of Arabia, half of Byzantine Asia, all of Persia, Egypt, the Maghreb (North Africa), and Spain, Arabs and Muslims became exposed to foreign and multinational culinary heritages. Great developments in scientific fields, the establishment of "modern" hospitals and growing socioeconomic conditions of Islamic empire, increased the awareness of the relationship between food and health. During this period, a type of Arab–Islamic food therapy developed that was a blend of Quranic teaching and pre-Islamic Arab medicine.

During the last half century, epidemiological studies have consistently shown that there are clear significant positive associations between intake of fruits and vegetables and reduced rate of heart diseases mortality, common cancers, and other degenerative diseases as well as ageing. This is attributed to the fact that these foods may provide an optimal mix of dietary fiber, natural antioxidants, and other biotic compounds. Various substances in the food can control the physiological functions of the body, and modulating immune responses. Immune functions are indispensable for defending the body against attack by pathogens or cancer cells, and thus play a pivotal role in the

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maintenance of health. However, the immune functions are disturbed by malnutrition, aging, physical and mental stress, or undesirable lifestyle. Therefore, the ingestion of foods with immune-modulating activities is considered an efficient way to prevent immune functions from declining and reduce the risk of infection or cancer. This chapter focuses on food therapy in the Greco-Arab and Islamic medicine and its role in preventing and curing diseases on the daily basis [1–11].

17.1.1 Healing with Food in Greco-Arab and Islamic Tradition

The Holy Quran and *Hadith* have provided Muslims with many ideas of foods that should be included in the ideal diet. The Quran mentions many fruits and vegetables as well as meat, milk, and many spices among the foods that Muslims can enjoy and benefit from in their nutritional and health values. These include melons, grapes, citrus, squash, figs, and dates. Even dried fruits are beneficial according to the Koran and *Hadith*. The Prophet (PBUH) mentioned figs and then stated, "If I had to mention a fruit that descended from paradise I would say this is it because the paradisiacal fruits do not have pits . . . eat from these fruits for they prevent hemorrhoids, prevent piles, and help gout." Figs are a top source of fiber, as well as potassium and vitamin B6. Fiber results in bulkier stools, which lessen the incidence of constipation, hemorrhoids, and colon cancer. Fiber also lowers cholesterol and the risk of heart disease. Al-Bukhari (810–870) states that melon was among one of the fruits most often eaten by the Prophet (PBUH). In fact, melon is one of the best recommendations for health the Prophet (PBUH) has given us. Melon is one of the few fruits and vegetables rich in vitamin C, beta-carotene, and potassium. Concerning olive oil, he said "Eat olive oil and massage it over your bodies since it is a holy (mubarak) tree." Black seeds were regarded as a medicine for that cures all types of diseases. The Prophet once stated, "The black seed can heal every disease, except death." Dates are mentioned in 20 places in the Quran. The Prophet is reported to have said: "if anyone of you is fasting, let him break his fast with dates. In case he does not have them, then with water. Verily water is a purifier."

According to a *Hadith* of the Prophet (PBUH) "The stomach is the central basin of the body, and the veins are connected to it. When the stomach is healthy, it passes on its condition to veins, and in turn the veins will circulate the same and when the stomach is putrescence, the veins will absorb such putrescence and issue the same." Indeed, the Prophet used to recommend food for ailments even more than he prescribed herbs or medicines. The Prophet used everything from barley soup to honey to camel milk to heal his followers and advised them to eat certain foods to prevent or cure other diseases. In fact, diet is one of the oldest and most respected healing agents available to man. Even the first fruits of paradise—the apple and/or the pomegranate—have numerous of curative properties. Later on, Rhazes said, "As long as you can heal with food, do not heal with medication." Therefore, in the Greco-Arab medical system, the patients were treated through a scheme starting with physiotherapy and diet; if this failed, drugs were used, and at last, surgery would be used. The physiotherapy included exercises and water baths. The Arabs had an elaborate system of dieting and were aware of food deficiencies. Proper nutrition was an important item of treatment [1–11].

17.1.2 Mediterranean Diet

Populations living in Mediterranean countries benefit from a longer life expectancy and a lower incidence rate of chronic diseases than Northern Europeans or North Americans. In fact, traditional Mediterranean diet is undoubtly healthier than many North European and American diets. It includes a significantly large amount and variety of plant foods, for example, fruits, vegetables, wild edible plants, breads, seeds, nuts, and olive oil (Table 17.1). Therefore, it guarantees an adequate intake of carotenoids, vitamins, tocopherols, α-linolenic acid, various important minerals, and several possibly beneficial nonnutrient substances such as polyphenols and anthocyanins, and dietary fiber.

Dietary fiber is a complex group of substances, commonly divided into soluble and insoluble fibers. Soluble fiber prolongs gastric emptying and macromolecule absorption, which results in delayed hunger feelings and decreased energy intake. For instance, soluble fibers improve glucose homeostasis and lipid profile. They have also been associated with short-term reduced energy intake in obese adults. Water-insoluble dietary fibers increase the rate of glucose disappearance and improve carbohydrate handling. It is suggested that the effects of dietary fiber consumption on body weight

TABLE 17.1 Commonly Used Fruits in the Mediterranean Region

Common Arabic Name	Common English Name	Latin Name
Ajas	Pear	*Pyrus communis*
Ajas soore	Syrian pear	*Pyrus syriaca Boiss*
Askadenia	Medlar tree/loquat	*Eriobotrya japonica*
Portokal	Orange	*Citrus aurantium/citrus sinensis*
Bromiaa'	Plum/gage	*Prunus section Prunus*
Pondok	Common hazel	*Corylus avellana*
Pomaly	Pomelo	*Citrus maxima*
Toffah	Apple	*Pyrus malus/Malus sylvestris*
Toffah sdom	Sodom apple	*Calotropis procera*
Tamr	Date palm	*Phoenix dactylifera*
Tot	Mulberry	*Morus nigra*
Ten	Common fig tree	*Ficus carica*
Joz	Walnut	*Juglans regia*
Kharrob	Carob/locust tree	*Ceratonia siliqua*
Khokh	Peach	*Prunus persica*
Romman	Pomegranate	*Punica granatum*
Zaiton	Olive tree	*Olea europaea*
Safarjal	Quince tree	*Cydonia vulgaris*
Karaz	Cherry/St Lucie cherry	*Prunus (cerasus) avium/Prunus mahaleb*
Karme	Common grape vine	*Vitis vinifera*
Loz	Almond	*Amygdalus communis*
Laimon aljanneh	Grapefruit	*Citrus paradisi*
Laimon alhamed	Lemon	*Citrus limon*
Moz	Banana	*Musa paradisiaca* L.

management may be related to gut hormones, which regulate satiety and energy intake. Ghrelin is a peptide hormone produced and excreted mainly in the stomach in two forms, acylated ghrelin and desacyl ghrelin. Acylated ghrelin acts as an orexigenic signal to the central nervous system, with increased levels during fasting, and suppressed levels postprandially. Ghrelin induced body weight gain in rodents by promoting food intake and decreasing fat utilization. In rodents, ghrelin increased the respiratory quotient, suggesting decreased fatty acid oxidation and increased glycolysis.

Migrant studies say the Mediterranean diet and lifestyle are behind the low incidence rate of chronic diseases in Mediterranean, rather than any genetic or racial factors. For instance, a comparative study between indogenous people (Arab and Jews) and new immigrants in Israel reveals that the striking differences between the prevalence of cancer are, in fact, the result of different dietary patterns, which may include nutritional factors that serve as cancer-inducing or cancer-protective mechanisms. Olive oil is the predominant oil used in Arab culture. For instance, the diet of Bedouin tribes in the desert consists of olive oil, milk, wild edible plants, and bread flour of wheat and little fat—a diet characterized by a very high percentage of carbohydrate calories, a low percentage of fat calories, and an adequate amount of linolenic and linoleic acid [1,2,9,10].

17.2 HONEY

Honey is a viscous, carbohydrate-rich solution derived from nectar gathered and modified by the honeybee. The honeybee makes honey from countless varieties of plant flowers and it is logical to assume that honey contain many substances of food and medicinal value that modern medicine has yet to discover. The composition of honey depends greatly on the botanical origin. Honey contains approximately 75% sugars (30% glucose, 40% fructose, 5% sucrose) and 20% water. It contains also many vitamins, minerals, amino acids, enzymes, and aroma compounds. The rapid absorption of honey's monosaccharide makes it as a desirable source of quick energy, a practical food and, at the same time, an effective heart stimulant.

Sidr honey is said to be the single most expensive honey in the world. It comes from the Hadramaut Mountains of Yemen in the Southwestern Arabian Peninsula, where it is harvested only twice per year. The honey is from bees who feast only on the pollen of the Sidr tree, considered by many to be a holy tree and is one of the most resilient, ancient tree varieties in the area. Sidr honey is reputed to have many medicinal benefits and has an unusually high level of antioxidants [12–14].

17.2.1 Historical Background

Honey has been known since thousands of years for its food and therapeutic values. In the most ancient scripts we already find references to honey as a glorified food, an ingredient of favored drinks, a popular medicine and the principal agent of liniments and plasters. The use of honey as an internal and external remedial agent must be much older than the history of medicine itself; it is, beyond doubt, the oldest therapeutic

agent. Honey has been used in wound care since ancient times and is frequently mentioned in early pharmacopeia, although more usually as an ingredient or carrier vehicle rather than a specific treatment. Dioscorides (40–80 AD) often mentioned honey as a vehicle for carrying therapeutic agents in *De Materia Medicis*. Hippocrates (460–377 BC), is often cited as advocating honey for wound care and listed it as one of many ingredients in a multitude of unguents. Galen recommended warming up the honey or cooking it, then using it to treat hemorrhoids and deep wounds. Honey's magic healing effects is praised in the Old and New Testaments, the Holy Quran, the sacred books of India, China, Persia, and Egypt [13–15].

17.2.2 Uses of Honey in Arab–Islamic Medical System

In Arab–Islamic medical system, as in other medical systems, including Ayurvedic, Chinese, and Roman traditions, honey is considered as healthy drink and prescribed in the treatment of wounds. The Holy Quran vividly describes the potential therapeutic value of honey: "And thy Lord has inspired the Bees, to build their hives in hills, on trees and in man's habitations, from within their bodies comes a drink of varying colors, wherein is healing for mankind, Verily in this is a Sign, for those who give thought."

One of the well-known *Hadiths*, in regard to the medical benefits of honey, that has been mentioned the book of medicine by Al-Bukhari (810–870). Accordingly, "A man came to the Prophet and said: 'My brother has some abdominal trouble' The Prophet (PBUH) replied to him 'let him drink honey.' The man came for the second time and the Prophet replied to him, 'let him drink honey.' He came for the third time and the Prophet replied, 'let him drink honey.' He returned and said, 'I have done that.' The Prophet (PBUH) then said, 'Allah has said the truth, but your brother's abdomen has told a lie. Let him drink honey.' So he made him drink honey and he was cured." There are two major remarks, which derive from this *hadith* that have to be put into consideration. First, the Prophet (PBUH) was aware of the disease and the cure that was suitable for the patient since he was surely belief of the benefit of honey for patient. It is the nature of honey to expel whatever is left of whatever has collected in the stomach and the intestines. In that time (early Islamic period), diarrhea was treated by making the patient vomit or by giving him laxative medicine to increase the flow by taking honey. Second, the Prophet (PBUH) instructed the patient to take honey for many times to make sure it may cure positively the disease. The patient should not lose patience for his suffering of illness because, sometime, certain diseases take many years to cure and in natural way can take at least months.

Al-Basri, a tenth century Arab philosopher, mentioned uncooked honey for swollen intestine whereas cooked honey was good for inducing vomiting when poisonous drug was ingested. For that purpose, he recommended mixing one pound of sesame oil with one-third pound of cooked honey. Rhazes (864–932.) claimed that honey ointment made of flour and honey vinegar was good for skin disease and sports nerve injuries and recommended the use of honey water for bladder wounds. His book, *Al-Hawi* (Encyclopedia of Medicine), a comprehensive medical textbook of medicine, which was translated from Arabic to Latin in the thirteenth century and

became a standard textbook of medicine up to the 1700s stated: "Honey is the best treatment for the gums. To keep the teeth healthy mix honey with vinegar and use as mouth wash daily. If you rub the teeth with such a preparation, it will whiten the teeth. Honey does not spoil and could also be used to preserve cadavers."

Likewise, Avicenna wrote in his Canon: "Honey is good for prolonging life, preserve activity in old age. If you want to keep your youth, take honey. If you are above the age of 45, eat honey regularly, especially mixed with chestnut powder. Honey and flour could be used as dressing for wounds. For lung disease, early stage of tuberculosis, use a combination of honey and shredded rose petals. Honey can be used for insomnia on occasions."

In conclusions, honey has to be recommended as part of an overall holistic approach to health and should be incorporated into one's everyday diet [6,13–15].

17.2.3 Composition of Honey

The carbohydrates are the main constituents, comprising about 95% of the honey dry weight. Beyond carbohydrates, honey contains numerous compounds such as organic acids, proteins, amino acids, minerals, polyphenols, vitamins, and aroma compounds. It should be noted that the composition of honey depends greatly on the botanical origin [12–18].

Carbohydrates. The main sugars are the monosaccharide fructose and glucose that are quickly transported into the blood and can be utilized for energy requirements by the human body. Additionally, about 25 different oligosaccharides have been detected. The principal disaccharides in honey are the sucrose, maltose, trehalose, and turanose, as well as some nutritionally relevant ones such as panose, 1-kestose, 6-kestose, and palatinose.

Proteins, Enzymes and Amino Acids. Honey contains about 0.5% proteins, mainly enzymes and free amino acids. The three main honey enzymes are amylase, decomposing starch or glycogen into smaller sugar units, invertase (sucrase, α-glucosidase), decomposing sucrose into fructose and glucose, as well as glucose oxidase, producing hydrogen peroxide and gluconic acid from glucose.

Minerals and Trace Compounds. It is known that different types of honey contain varying concentrations of minerals and trace elements. From the nutritional point of view chromium, manganese, and selenium are important, especially for children. Sulfur, boron, cobalt, fluoride, iodide, molybdenum, and silicon can be important in human nutrition too. Honey contains up to 25 mg/kg choline and up to 5 mg/kg acetylcholine. Choline is essential for cardiovascular and brain function as well as for cellular membrane composition and repair, while acetylcholine acts as a neurotransmitter.

Aroma Compounds. There is a wide variety of honeys with different tastes and colors, depending on their botanical origin. The sugars are the main taste-building

compounds. Generally, honey with a high fructose content (e.g., acacia) are sweeter compared to those with high glucose concentration (e.g., rape). The honey aroma depends also on the quantity and type of acids and amino acids present. In the past decades, extensive research on aroma compounds has been carried out and more than 500 different volatile compounds were identified in different types of honey. Indeed, most aroma compounds vary in the different types of honey depending on its botanical origin.

Polyphenols. Polyphenols are another important group of compounds with respect to the appearance and the functional properties of honey. Polyphenols in honey are mainly flavonoids (e.g., quercetin, luteolin, kaempferol, apigenin, chrysin, and galangin), phenolic acids, and phenolic acid derivatives. These are compounds known to have antioxidant properties. The main polyphenols are the flavonoids, their content can vary between 60 and 460 μg/100 g of honey and was higher in samples produced during a dry season with high temperatures [12–18].

17.2.4 Therapeutic Properties of Honey

Over the last four decades, scientific reports affirmed the effectiveness of honey in treating various wounds, burns, and serious infections. These reports and the emergence of drug resistant infections stimulated a number of scientists to conduct studies on honey, bringing about a resurgence of interest in the therapeutical uses of honey. Many studies have demonstrated that honey has microbial activities *in vitro*, and a small number of clinical case studies have shown that application of honey to severely infected cutaneous wounds is capable of clearing infection from the wound and enhancing tissue repair. The physicochemical properties (e.g., osmotic effects and pH) of honey also aid in its antibacterial actions. Various reports have indicated that honey may possess anti-inflammatory activity and stimulate immune responses within a wound. The overall effect is to reduce infection and to enhance wound healing in burns, ulcers, and other cutaneous wounds. Manuka honey, a monofloral honey derived from the leptospermum tree species in New Zealand and Australia, has been of particular interest as it has antibacterial activity independent of the effect of honey's peroxide activity and osmolarity. These honeys have been approved for marketing as therapeutic honeys (Medihoney and Active Manuka honey) [15–18].

Antimicrobial Properties. Honey works differently from antibiotics, which attack the bacteria's cell wall or inhibit intracellular metabolic pathways. Honey has been reported to have an inhibitory effect to around 60 species of bacteria including aerobes and anaerobes, Gram-positives and Gram-negatives. An antifungal action has also been reported for some yeasts and species of *Aspergillus* and *Penicillium* as well as all the common dermatophytes. Honey is hygroscopic, meaning it draws moisture out of the environment and thus dehydrates bacteria. Its high sugar content hinders the growth of microbes, but the sugar content alone is not the sole reason for honey's antibacterial properties. When honey is diluted with water, reducing its high sugar content, it still inhibits the growth of many different bacterial species that cause

wound infections. Over 100 substances are candidates for the particular antibacterial property of these honeys, but the active ingredient has not yet been identified. Recent research on honey has shed light on the mechanisms underlying its antimicrobial effects. In summary, the antibacterial effects are due to the following:

Osmotic Effect: Honey can be seen as a saturated carbohydrate solution of fructose and glucose. The interaction of these highly hydrophilic molecules dehydrates the microenvironment and leaves very little water available to support the growth of microorganisms.

Low pH: Honey is acidic, with a pH ranging from 3.2 to 4.5 that is low enough to inhibit the growth of many microorganisms.

Hydrogen Peroxide: Hydrogen peroxide is the major antibacterial compound in honey. Bees secrete the enzyme glucose oxidase from nectar. It converts glucose in the presence of water and oxygen to glucoronic acid and hydrogen peroxide. Both the acid and hydrogen peroxide preserves and sterilizes the honey during the ripening process.

Nonperoxide Molecules: There have been reports of isolation of various antibacterial chemical substances from honey that are not hydrogen peroxide but their concentration is reportedly too low to contribute much antibacterial activity.

Honey can vary as much as 100-fold in the potency of antibacterial activity (which is due to hydrogen peroxide). Honey is produced from many different floral sources and its antibacterial activity varies with origin and processing. This fact was known long ago, both Aristotle, Dioscorides, as well as Arab–Islamic physicians recommended that honey collected in specific regions and seasons and, presumably from different floral sources, be used for the treatment of particular disease. Scientific research has since shown that honey has certain organisms sensitive to it while others are resistant, and the sensitivity varies depending on the source of the honey. It is recommended that honey selected for clinical use should be evaluated on the basis of antibacterial activity levels determined by laboratory testing. *Staphylococcus aureus* is one of the species most sensitive to the antibacterial activity of honey [17–21].

Wound Healing: As aforementioned, honey has been used in Arab–Islamic medicine in the treatment of wounds. Recent research has tended to concentrate on the antibacterial activity of the many different types of honey rather than its effect on wound healing. Manuka honey, a monofloral honey derived from the leptospermum tree species in New Zealand and Australia, has been of particular interest as it has antibacterial activity independent of the effect of honey's peroxide activity and osmolarity. The substance responsible for this activity has not been definitively identified but has been termed Unique Manuka Factor (UMF). Manuka honey with a UMF rating has an antibacterial activity equivalent to a similar percentage of phenolic acid in solution. Recent research suggests methylglyoxal is the substance responsible for the nonperoxide activity. There is evidence from different animal models that honey may accelerate healing. Fifteen of the sixteen controlled trials in five different

animal models (mice, rat, rabbit, pig, buffalo calf) found honey-treated incisional and excisional wounds and standard burns healed faster than control wounds. In addition, a systematic review of honey as a wound dressing found seven randomized trials in humans, six in burns patients and one in infected postoperative wounds. Although the poor quality of the trial reports prevented any recommendations, the findings did suggest an effect in favor of honey.

Honey appears to draw fluid from the underlying circulation, providing both a moist environment and topical nutrition that may enhance tissue growth. Histologically, honey appears to stimulate tissue growth in animal and human controlled trials, with earlier tissue repair noted, fewer inflammatory changes, and improved epithelialization. Other reports have also noted the debriding action of honey. Taken collectively, wound healing beneficial effects of honey include the following:

- Stimulation of the healing process especially leg ulcers and diabetic ulcers.
- Speedy clearance of infection when used as dressing on infected wounds. Honey is reportedly extremely effective in the treatment of wounds infected with methicillin-resistant *Staphylococcus aureus* (MRSA) as well as wounds infected with multiresistant bacteria.
- *Cleansing Action on Wounds*: Honey has a debriding effect on wounds so that surgical debridement is unnecessary or only a minimum required.
- *Stimulation of Tissue Regeneration*: Honey promotes the formation of clean healthy tissue and growth of epithelium over the wound, thus helping skin regenerate.
- *Comfort Honey Dressings*: Honey is nonirritating and the pain or discomfort associated with changing dressings is significantly reduced.
- The current main therapeutical application of honey is in the treatment of infected wounds, chronic leg and skin ulcers, bedsores, especially in settings of drug-resistant infections.

Antioxidant Properties. The term "oxidative stress" describes the lack of equilibrium between the production of free radicals and the antioxidant protective activity in a given organism. Protection against oxidation is thought to prevent some chronic diseases (Figures 13.14 and 13.15). The oxidative modification of the lipoproteins is considered an important factor for the pathogenesis of arteriosclerosis. Honey has been found to contain significant antioxidant activity including glucose oxidase, catalase, ascorbic acid, flavonoids, phenolic acids, carotenoid derivatives, organic acids, and amino acids. The antioxidative activity of honey polyphenols can be measured *in vitro* by comparing the oxygen radical absorbance capacity (ORAC) with the total phenolics concentration. There is a significant correlation between the antioxidant activity, the phenolic content of honey and the inhibition of the *in vitro* lipoprotein oxidation of human serum.

Antimutagenic and Antitumor Properties. Mutagenic substances act directly or indirectly by promoting mutations of the genetic structure. During the roasting and

frying of food heterocyclic amines are formed, for example, Trp-p-1 (3-amino-1,4-dimethyl-5*H*-pyridol [4,3-β]indole). The antimutagenic activity of honeys from seven different floral sources (acacia, buckwheat, fireweed, soybean, tupelo, and Christmas berry) against Trp-p-1 was tested by the Ames assay and compared to a sugar analogue as well as to individually tested simple sugars. All honeys exhibited a significant inhibition of Trp-p-1 mutagenicity. Glucose and fructose were found to have a similar antimutagenic activity as honey. Nigerose, another sugar, present in honey has immunoprotective properties. The antimetastatic effect of honey and its possible mode of antitumor action were studied by the application of honey in spontaneous mammary carcinoma in methylcholanthrene-induced fibrosarcoma of CBA mice and in anaplastic colon adenocarcinoma of Y59 rats. A significant antimetastatic effect was achieved by oral application of honey. These findings indicate that honey activates the immune system and honey ingestion may be advantageous with respect to cancer and metastasis prevention. In addition, it is postulated that honey given orally before tumor cell inoculation may have a decreased effect on tumor spreading. A pronounced antimetastatic effect was observed when honey was applied before tumor-cell inoculation was seen in another study, which evaluated the effect of honey on tumor growth, metastasizing activity and induction of apoptosis and necrosis in murine tumor models (mammary and colon carcinoma). Furthermore, the antitumor effect of honey against bladder cancer was examined *in vitro* and *in vivo* in mice. Honey exhibited an effective inhibition of the growth of different bladder cancer cell lines (T24, RT4, 253J, and MBT-2) *in vitro*. It is also effective when administered intralesionally or orally in the MBT-2 bladder cancer implantation mice models.

Anti-Inflammatory Properties. Anti-inflammatory effects of honey in humans were studied in a recent study [22] after ingestion of 70 g honey. The mean plasma concentration of thromboxane B(2) was reduced by 7%, 34%, and 35%, that of PGE(2) by 14%, 10%, and 19% at 1, 2, and 3 h, respectively, after honey ingestion. The level of PGF(2α) was decreased by 31% at 2 h and by 14% at 3 h after honey ingestion. At day 15, plasma concentrations of thromboxane, PGE, and PGF decreased by 48%, 63%, and 50%, respectively. The ingestion of honey decreased inflammation in an experimental model of inflammatory bowel disease in rats. Honey administration is as effective as prednisolone treatment in an inflammatory model of colitis. The postulated mechanism of action is by preventing the formation of free radicals released from the inflamed tissues. The reduction of inflammation could be due to the antibacterial effect of honey or to a direct anti-inflammatory effect. The latter hypothesis was supported in animal studies, where anti-inflammatory effects of honey were observed in wounds with no bacterial infection [18–22].

17.2.5 Contaminants and Potential Toxicity

The same as any other natural food, honey can be contaminated by the environment, for example, by heavy metals, pesticides, and antibiotics. Generally,

the contamination levels found in Europe do not present a health hazard. The main problem in recent years was the contamination by antibiotics, used against the bee brood diseases, but at present, this problem seems to be under control. In the European Union, antibiotics are not allowed for that purpose, and thus a honey-containing antibiotic is not permitted to be traded on the market.

A few plants used by bees are known to produce nectar containing toxic substances. Diterpenoids and pyrrazolidine alkaloids are two main toxin groups relevant in nectar. Some plants of the Ericaceae family belonging to the subfamily Rhododendron, for example, *Rhododendron ponticum* contain toxic polyhydroxylated cyclic hydrocarbons or diterpenoids. The substances of the other toxin group, the pyrrazolidine alkaloids, found in different honey types. Cases of honey poisoning have been reported rarely in the literature and have concerned individuals from the following regions: Caucasus, Turkey, New Zealand, Australia, Japan, Nepal, South Africa, and some countries in North and South America. Observed symptoms of such honey poisoning are vomiting, headache, stomachache, unconsciousness, delirium, nausea, and sight weakness. In general, the poisonous plants are known to the local beekeepers and honey, which can possibly contain poisonous substances, is not marketed. To minimize risks of honey born poisoning in countries where plants with poisonous nectar are growing tourists are advised to buy honey in shops and not on the road and from individual beekeepers. Clostridium botulinum spores pervade our environment, existing in the soil, air, dust, and raw agricultural products. Due to the possibility of Clostridial contamination and many reports of infant botulism in the literature since the first description of this syndrome in 1976, it has been recommended by pediatricians, not to feed infants with honey and to place warning labels on packaging, as done in the United Kingdom and Norway [12–14].

17.3 OLIVE OIL

The olive tree, *Olea europaea*, is an evergreen tree of the family Oleaceae and is native to the Mediterranean basin. Its fruit, the olive, is of major agricultural importance in the Mediterranean as the source of olive oil and pickled olives. The oldest available data about olive trees has been obtained from the archeological excavations at Santorini, an Aegean Island. This data is a 39,000-year-old fossilized olive leaf. Another evidence dating back to 12,000 BC was found in archeological excavations in the Sahara Desert in Africa. Furthermore, a giant jars of two meters heights called “Pithoi” and tablets containing detailed information about olive oil trade were found on the island of Crete. In addition, there are thousands of ancient olive trees throughout the historic Palestine. Specifically, seven giant olive trees in the Galilee region have been determined to be over 3000 years old. All seven trees continue to produce olives. Traditional uses as well as pharmacological and toxicological properties of olive leaf are discussed in Chapter 8. Here we will concentrate on the food and therapeutic properties of olive oil.

17.3.1 Uses of Olive Oil in the Arab–Islamic Medical System

Olive oil and olive leaf are cited in the Bible as natural healing agents: "The fruit thereof shall be for meat and the leaf thereof for medicine." In Islam, olive oil is mentioned in the Quranic verse: "God is the light of heavens (paradise) and earth. An example of His light is like a lantern inside which there is a torch, the torch is in a glass bulb, the glass bulb is like a bright planet lit by a blessed olive tree, neither Eastern nor Western, its oil almost glow, even without fire touching it, light upon light." The Quran also mentions (tells) olives as a holy (mubarak) plant: "By the fig and the olive, and the Mount of Sinai, and this secure city (Mecca)." The Prophet said, "Eat olive oil and massage it over your bodies since it is a holy tree." He also stated that olive oil cures 70 diseases. In the Arab–Islamic world, olive oil has been commonly used in cooking, cosmetics, pharmaceuticals, and soaps and as a fuel for traditional oil lamps.

17.3.2 Composition

The composition of olive oil varies, depending on the cultivar, climate, ripeness of the olives at harvesting, and the processing system for the type of olive oil. Accordingly, olive oil is classified as virgin, common (ordinary), or pomace.

- *Virgin* means the oil was produced by the use of physical means and no chemical treatment.
- *Refined* means that the oil has been chemically treated to neutralize strong tastes (characterized as defects) and neutralize the free fatty acids content. Refined oil is commonly regarded as lower quality than virgin oil.
- *Pomace olive oil* means oil extracted from the pomace using chemical solvents, mostly hexane, and by heat.

Olive oil contains high amounts of monounsaturated fatty acid (MUFA). MUFAs are fatty acids that have a single double bond in the fatty acid chain, mainly of the mixed triglyceride esters of oleic acid and palmitic acid and of other fatty acids. It contains phenolic compounds and minor components found in the unsaponificable fraction (squalene, sitosterols, triterpenes, pigments, etc.). These compounds are extracted with solvents after the saponification of the oil. Olive oil phenolic compounds are the most well studied and characterized minor olive oil components. The major phenolic compounds in olive oil are simple phenols (i.e., hydroxytyrosol, tyrosol), polyphenols (oleuropein glucoside), secoiridoids, the dialdehydic form of oleuropein and ligstroside, and the aglycone form of oleuropein glucoside and ligstroside. Tyrosol, hydroxytyrosol and their secoiridoids derivatives represents around 30%, and other conjugated forms such as oleuropeine and ligstroside aglycone represents around 50% of the total phenolic content of a virgin olive oil. About 80% the phenolic compounds are lost in the refination process, thus, their content is higher in virgin olive oil (around 230 mg/kg, common range 130–350 mg/kg) than in other types of olive oil.

Quantitative analysis can determine the oil's acidity, defined as the percent of free oleic acid. This is a measure of the oil's chemical degradation; as the oil degrades, more fatty acids are freed from the glycerides, increasing the level of free acidity and thereby increasing rancidity. Another measure of the oil's chemical degradation is the organic peroxide level, which measures the degree to which the oil is oxidized, another cause of rancidity [23–25].

17.3.3 Pharmacological Properties

The Mediterranean diet, in which olive oil is the main source of fat has been associated with a low cardiovascular and cancer mortality. The beneficial effects of olive oil on coronary heart disease (CHD) risk factors are now attributed to the high MUFA content and other minor compounds found in the olive oil. Evidences from epidemiological studies suggest that a higher proportion of MUFA in the diet is linked with a low risk of coronary heart disease. There is a large body of clinical data that show that consumption of olive oil can provide heart health benefits, such as favorable effects on cholesterol regulation and inhibition of LDL oxidation. It exerts also anti-inflammatory, antithrombotic, antihypertensive as well as vasodilatory effects both in animals and in humans. The Federal Drug Administration (FDA) in the United States permitted, in 2004, a claim on olive oil labels stating "the benefits on the risk of coronary heart disease of eating about two tablespoons (23 g) of olive oil daily, due to the monounsaturated fat in olive oil" (Food and Drug Administration. Press release P04-100, 2004).

Olive oil, however, besides having a high MUFA level, contains oleic acid, which has multiple pharmacologically active components. Olive oil phenolics have shown to have antioxidant properties, higher than that of vitamin E, on lipids and DNA oxidation. They are prevent endothelial dysfunction by decreasing the expression of cell adhesion molecules, and increasing nitric oxide (NO) production and inducible NO synthesis by quenching vascular endothelium intracellular free radicals. In addition, olive oil phenolic compounds inhibited platelet-induced aggregation and have been reported to enhance the expression the gene of the antioxidant enzyme glutathione peroxidase. Other potential properties include anti-inflammatory and chemopreventive activity. In animal models, olive oil-derived phenolics retained their antioxidant properties *in vivo* and delayed the progression of the atherosclerosis. So far, most of the cardioprotective effect of olive oil in the context of the Mediterranean diet has been attributed to its high MUFA content. It must be noticed, however, that oleic acid is one of the predominant fatty acids in widely consumed animal foods in Western diets, such as poultry and pork. A direct association of meat intake with the plasma oleic acid concentration was observed in a Swedish female population. In this population, oleic acid plasma concentrations were higher than those of females of Granada in Spain, without differences in polyunsaturated (PUFA) levels. Thus, perhaps a high oleic acid intake is not the sole primary responsible agent for the healthy properties of olive oil. In spite of the promising results displayed in experimental studies, evidence concerning the consumption of phenolic compounds in olive oil is still under investigation. If the beneficial properties of olive oil in humans

can be attributed solely to its MUFA content, any type of olive oil, rapeseed/canola oil, or MUFA-enriched fat would provide the same health benefits. Thus, public health implications are involved in order to specifically recommend olive oil, and which type of olive oil (i.e., virgin olive oil rich in phenolic compounds), as individualized nutritional strategies for coronary heart disease prevention. Taken collectively, one key conclusion is that olive oil is more than a MUFA fat. The phenolic content of an olive oil can account for greater benefits on blood lipids and oxidative damage than those provided by the MUFA content of the olive oil. Therefore, it beneficial use of olive oil rich in phenolic compounds as a source of fat in order to achieve additional benefits against cardiovascular risk factors. In addition, olive oils with high phenolic content are in general more bitter and greener than those with low phenolic content, and for some individuals the taste could be too stronger. Olive oil must be taken as a part of a healthy and pleasant dietary pattern [23–25].

17.4 DATES

Date Palm, *Phoenix dactylifera*, is one of mankind's oldest cultivated plants. Due to its long history of cultivation for fruit, its exact native distribution is unknown. Date Palm is believed to have originated around the Persian Gulf, and has been cultivated since ancient times from Mesopotamia to prehistoric Egypt, possibly as early as 4000 BC. There is archaeological evidence of date cultivation in Eastern Arabia in 6000 BC. In later times, Arabs spread dates around South and South East Asia, Northern Africa, and Spain and Italy. The tree is 15–25 m tall and 20–40 cm in cross-sectional radius, often clumped with several trunks from a single root system, but often growing alone as well. The leaves are pinnate, 3–5 m long, with spines on the petiole and about 150 leaflets. The full span of the crown ranges from 6 to 10 m. Dates have been a staple food of the Middle East for thousands of years (Figure 17.1).

There are more than 2000 different varieties of dates (Tamr in Arabic). Depending on variety and growth conditions, date fruits vary in shape, size, and weight. Usually they are oblong in shape. Packed, dry dates keep well without the addition of preservatives for at least 8 months, the high sugar content acting as an effective preservative. Dates offer useful prospects for fighting hunger and diseases. The importance of the date in human nutrition comes from its rich composition of carbohydrates, salts and minerals, dietary fiber, vitamins, fatty acids, amino acids, and protein [26–29] (Table 17.2).

Dates pass through four stages of development known by their Arabic names; Kimri, Khalaal, Rutab, and Tamer.

Kimri: In this stage, the average fruit length is about 27 mm and its diameter is about 18 mm. The average weight of dates is 5.8 g. Dates in this stage contain an average of 5.6% protein, 0.5% fat, and 3.7% ash.

Khalal: The color of the date changes from green to somewhere between yellow and red depending on the cultivar (3–5 weeks), the average fruit length increases

FIGURE 17.1 *Phoenix dactylifera*, date palm and date fruits Rutab (left) and Tamer (right). (*See the color version of this figure in Color Plates section.*)

up to 32 mm and its diameter increases up to 21 mm. The percentages of protein, fat, and ash decrease to 2.7%, 0.3% and 2.8%, respectively.

Rutab: The date begins to soften and lose water (2–4 weeks). The protein, fat, and ash percentages in this stage decrease to 2.6%, 0.3%, and 2.6%, respectively.

Tamr: The date has now dried to a firm consistency with darker color but there are types of dates that do not develop to this stage. The average percentages of protein, fat, and ash in the Tamr stage are 2.3%, 0.2%, and 1.7%, respectively.

17.4.1 Traditional Medicinal Uses

Dates are an important traditional crop in Iraq, Eastern region of the Mediterranean, and Maghreb countries and are mentioned in 20 places in the Quran. Prophet Mohammad (PBUH) is reported to have said: "if anyone of you is fasting, let him break his fast with dates. In case he does not have them, then with water. Verily water is a purifier." Therefore, in Islamic countries, dates and yogurt or milk is a first meal

TABLE 17.2 Commonly Used Cultivated Edible Plants in the Mediterranean Region

Part Used	Common Arabic Name	Common English Name	Latin Name
Fruit	Bamiaa'	Lady's finger	*Abelmoschus esculentus*
Vegetable	Basal	Onion, garden onion	*Allium cepa*
Vegetable	Patata	Potato	*Solanum tuberosum*
Fruit	Batekh	Watermelon	*Citrullus vulgaris*
Vegetable	Bakdones	Parsley	*Petroselinum crispum*
Vegetable	Bandora	Tomato	*Lycopersicon esculentum*
Seed	Tormos	Lupines/wild lupin	*Lupinus albus/Lupinus pilosus*
Vegetable	Tot ardi	Strawberry	*Fragaria grandiflora*
Vegetable	Thom bostane	Garlic	*Allium sativum*
Vegetable	Jarjer	Garden rocket	*Eruca sativa*
Vegetable	Jazar bostane	Carrot	*Daucus carota*
Vegetable	Khas bostane	Lettuce	*Lactuca sativa*
Vegetable	Khiar	Cucumber	*Cucumis sativus*
Fruit	Zorah	Corn/maize	*Zea mays*
Vegetable	Sbanekh	Spinach	*Spinacia oleracea*
Leaf	Selk barre	Beet/red beet	*Beta vulgaris*
Seed	Simsim	Sesame	*Sesamum orientale*
Fruit	Shommam	Melon	*Cucumis melo*
Seed	Abad elshams	Sunflower	*Helianthus annuus*
Seed	Adas	Lentils	*Lens culinaris*
Fruit	Aenab	Grapevine	*Vitis vinifera*
Vegetable	Fasoliaa	Bean	*Phaseolus vulgaris*
Vegetable	Figl	Radish	*Raphnus sativus*
Seed	Filfil	Sweet pepper	*Capsicum annuum*
Seed	Fol	Broad bean	*Vicia faba*
Vegetable	Karnabet	Cauliflower	*Brassica oleracea*
Seed	Kizha	Black cumin	*Nigella sativa*
Stem	Kasab sokkar	Sugarcane	*Saccharum officinarum*
Seed	Kamh	Common wheat	*Triticum aestivum*
Leaf	Krafs	Wild celery	*Apium graveolens*
Vegetable	Lefet	Cabbage	*Brassica campestris*
Vegetable	Malfof	Wild cabbage	*Brassica oleracea*
Vegetable	Mlokheyeh	Jew's mallow	*Corchorus olitorius*

when the sun sets during Ramadan. Dry or soft dates are eaten out of hand, or may be pitted and stuffed with fillings such as almonds, walnuts, or marzipan. Dates can also be chopped and used in a range of sweet and savory dishes, from ka'ak (types of Arab cookies), tajines (tagines) in Morocco to puddings and other dessert items. Dates are also processed into cubes, paste called "Ajwa," spread, date syrup or "honey" called "dibs," or powder (date sugar). Dates were among the favored food of the Prophet who said, "Whoever takes seven 'Ajwa' dates in the morning will not be effected by magic or poison on that day." Dates have high tannin content and are used medicinally as a detersive (having cleansing power) and astringent in intestinal troubles. As an

infusion, decoction, syrup, or paste, dates may be administered for sore throat, colds, bronchial catarrh, and taken to relieve fever and number of other complaints. One traditional belief is that it can counteract alcohol intoxication. The seed powder is also used in some traditional medicines [26–30].

17.4.2 Composition

Dates contain a high percentage of carbohydrates (total sugars, 44–88%), mainly fructose and glucose. They are, therefore, a high source of immediate energy. One hundred grams of flesh can provide an average of 314 kcal. In addition, dates contain fats, minerals, proteins, vitamins, and a high percentage of dietary fiber (8.0 g/100 g), insoluble dietary fiber is the major fraction of dietary fiber in dates. The fatty acids occur in both flesh and seed as a range of saturated and unsaturated acids, the seeds contain 14 types of fatty acids, but only eight of these fatty acids occur in very low concentration in the flesh. Unsaturated fatty acids include palmitoleic, oleic, linoleic, and linolenic acids. Ten minerals were reported, the major being selenium, copper, potassium, and magnesium. The consumption of 100 g of dates can provide over 15% of the recommended daily allowance from these minerals. Additionally, the seeds contain aluminum, cadmium, chloride, lead, and sulfur. Dates contain fluorine that is useful in protecting teeth against decay. Dates contain vitamin C, and vitamins B1 thiamine, B2 riboflavin, nicotinic acid (niacin), and vitamin A. Vitamins B-complex and C are the major vitamins in dates. Dates are a good source of antioxidants, mainly carotenoids and phenolics [26–30].

17.4.3 Food and Medical Values

As aforementioned, dates contain dietary fibers, which are important for the health of the digestive tract. Dietary fibers consist of the edible plant material, which is not hydrolyzed by the human digestive tract. Many studies recommend the public to consume adequate amounts of dietary fiber from a variety of plant foods. Dates also contain useful quantities of antioxidants. Antioxidants are thought to play an essential role in the prevention of cardiovascular disease, cancers, and neurodegenerative diseases, such as Parkinson's and Alzheimer's diseases, as well as inflammation and continuous ageing. A dietary antioxidant is defined as a substance in foods that significantly decreases the adverse effects of reactive species, such as reactive oxygen (ROS) and nitrogen (RNS), on normal physiological function in humans. Antioxidants markedly delay or prevent oxidation of the substrate when they are present in foods or in the body at low concentrations. Natural antioxidants consist primarily of plant phenolics, vitamin C, carotenoids, and selenium. Examples of common plant phenolic antioxidants include flavonoid compounds (anthocyanins), cinnamic acid derivatives, coumarins, and tocopherols (vitamin E). The average contents of phenolics ranged from 193.7 mg/100 g for fresh dates to 239.5 mg/100 g for dried dates. In general, drying is regarded as unfavorable due to the possibility of inducing oxidative decomposition either enzymatically by polyphenol oxidase and glycosidase or by thermal degradation of phenolic compounds. The ORAC values (a measure for

total antioxidant content) are about 1656 μmol/100 g in fresh dates and reduced after drying to average 1025 μmol/100 g. The antioxidant content of other dried fruits ranged between 340 μmol/100 g for apricot and 3383 μmol/100 g for figs. Thus, in comparison with these fruits, dates are a good source of antioxidants. This finding is supported by other *in vitro* studies published on date antioxidants. For instance, a recent *in vitro* study measured antioxidant and antimutagenic properties of date extract. There was a dose-dependent inhibition of superoxide and hydroxyl radicals by an aqueous extract of date fruit. The amount of fresh extract required to scavenge 50% of superoxide radicals was equivalent to 0.8 mg/mL of date fruit in the riboflavin photoreduction method. An extract of 2.2 mg/mL of date fruit was needed for 50% hydroxyl radical scavenging activity in the deoxyribose degradation method. Concentrations of 1.5 and 4.0 mg/mL completely inhibited superoxide and hydroxyl radicals, respectively. Aqueous date extract was also found to inhibit significantly the lipid peroxidation and protein oxidation in a dose-dependent manner. In an Fe^{2+}/ascorbate system, an extract of 1.9 mg/mL of date fruit was needed for 50% inhibition of lipid peroxides. In a time course inhibition study of lipid peroxide, at a 2.0 mg/mL concentration of date extract, there was a complete inhibition of TBARS formation in the early stages of the incubation period that increased during later stages of the incubation. Similarly, in the high Fe^{2+}/ascorbate induction system a concentration of 2.3 mg/mL inhibited carbonyl formation measured by DNPH reaction by 50%. Moreover, a concentration of 4.0 mg/mL completely inhibited lipid peroxide and protein carbonyl formation.

Date fruit extract also produced a dose-dependent inhibition of benzo[*a*]pyrene-induced mutagenecity on *Salmonella* tester strains TA-98 and TA-100 with metabolic activation. Extract from 3.6 to 4.3 mg/plate was found required for 50% inhibition of His^+ revertant formation in TA-98 and TA-100, respectively. These results indicate that antioxidant and antimutagenic activity in date fruit is quite potent and implicates the presence of compounds with potent free radical scavenging activity [26–31].

17.5 CAROB

The carob tree, *Ceratonia siliqua*, is a species of flowering evergreen shrub or tree in the pea family, Fabaceae, and it is native to the Eastern Mediterranean region, where it is known as kharob. The tree reaches 6–8 m at maturity, bearing pea-like, black pods that are rich in protein and sugar. It is cultivated for its edible seedpods and grown in the region since hundreds of years. Carob seeds, whose mass was thought to be uniform, have given their name to the carat, and were used as units of weight to measure gold and diamonds. The tree's abundant and nutritious fruit explains its biblical name, St. John's Bread. Developing carob pods have the appearance of green broad beans but they turn a dark glossy brown with maturity. The pods contain four series of oval holes, each bearing a seed like a watermelon seed. Each pod can contain up to 15 seeds. Both, seeds and pods are edible. The ground seeds are used as a substitute for cocoa and as a food; the flesh is used to produce Debs (molasses), the remaining pith used as fodder and the seeds used in the gum extraction industries.

FIGURE 17.2 *Ceratonia siliqua*, the carob tree. (*See the color version of this figure in Color Plates section.*)

Carob powder is also used as a food stabilizer and as a darkening agent. Crushed pods are used in the Arab world to make a refreshing drink, which is a traditionally drunk during the holy month of Ramadan, and the flesh is used to produce molasses, which are used for preparing various kinds of sweets. Carob pods were an important source of sugar before sugarcane and sugar beets became widely available (Figure 17.2).

17.5.1 Food and Pharmacological Values

The main constituents of carob are large carbohydrates, which make carob gummy and able to act as a thickener to absorb water and help bind together watery stools. Carob contains up to 8% protein, vitamins A, B, B2, B3, and D. It is also high in calcium, phosphorus, potassium, and magnesium and contains iron, manganese, barium, copper, and nickel. It contains tannins and dietary fiber. The effects of dietary fiber consumption on body weight management may be related to gut hormones, which regulate satiety and energy intake. Ghrelin is a peptide hormone produced and excreted mainly in the stomach, and circulating in two major forms, acylated ghrelin and desacyl ghrelin. Acylated ghrelin acts as an orexigenic signal to the central nervous system, with increased levels during fasting, and suppressed levels postprandially. The administration of ghrelin induces body weight gain in rodents by promoting food intake and decreasing fat utilization. Carob pulp preparation (carob fiber), is rich in insoluble dietary fiber and polyphenols. In humans, consumption of carob fiber was shown to have a high antioxidant capacity and to lower serum cholesterol and serum triglycerides. Furthermore, other studies showed that polyphenols might increase fat oxidation and energy turnover in humans and in mice. Consumption of an insoluble dietary fiber rich in polyphenols obtained from carob pulp reduces postprandial free fatty acids and triglyceride concentrations and affects substrate utilization toward lipid oxidation. These observations are associated with a marked decrease in acylated ghrelin concentrations after consumption of the fiber-enriched liquid meal compared with the control meal.

Carob's tanins exhibit antimicrobial and antiviral activities. Furthermore, carob bean juice (CBJ) has been found to be a powerful adjunct to oral rehydration solution (ORS) treatment in diarrhea. In children, the treatment of acute diarrhea with standard oral rehydration solution provides effective rehydration but does not reduce the severity of diarrhea. As aforementioned, carob bean has been used in the Greco-Arab and Islamic medicine to treat diarrheal diseases. Clinical antidiarrheal effects of carob bean juice, were tested in 80 children who were admitted to Tepecik Teaching Hospital in Izmir, Turkey with acute diarrhea and mild or moderate dehydration. The children were randomly assigned to receive treatment with either standard WHO ORS alone or a combination of standard WHO ORS and CBJ. In the children receiving ORS + CBJ, the duration of diarrhea was shortened by 45%, stool output was reduced by 44%, and ORS requirement was decreased by 38% compared with children receiving ORS alone. Weight gain was similar in the two groups at 24 h after the initiation of the study. Hypernatraemia was detected in three patients in the ORS group but in none of those in the ORS + CBJ group. The use of CBJ in combination with ORS did not lead to any clinical metabolic problem [32–34].

17.6 BLACK SEED

Nigella sativa of the Ranunculaceae family is one of the most commonly used medicinal plants throughout the Middle East (Figure 8.1). Black seeds are known to have many medicinal properties and are widely used in Greco-Arab and Islamic medicine. *Nigella sativa* seeds have been used for centuries as a spice and food preservative, as well as a protective and curative remedy for numerous diseases. The seeds are the main source of the active compounds of the plant [2,4]. Pharmacological and safety properties of active compounds of black seeds are discussed in details in Chapter 8. Here, we discuss dietary and medicinal uses of black seeds in general.

Black seeds were used by ancient Egyptian and Greek physicians to treat nasal congestion, toothache, as a diuretic to promote menstruation, and to increase milk production. The seeds, known as black seeds, black cumin, or "Habatul-Barakah" in Arabic, have long been prescribed in Greco-Arab and Islamic medicine as well as in Indian and Chinese traditional medicine (Chapter 10) for prevention and treatment of a wide range of diseases, including bronchial asthma, headache, dysentery, infections, obesity, back pain, hypertension and gastrointestinal problems. The Prophet Mohammad (PBUH) stated in one of his *hadiths* that, "The black seed can heal every disease, except death." Avicenna referred to black seed in his *Canon of Medicine*, as the seed that stimulates the body's energy and helps recovery from fatigue and dispiritedness. In the Unani system of medicine (Chapter 10), seeds are regarded as a valuable remedy for a number of diseases. The seed's oil has been used to treat skin conditions such as eczema and boils and to treat cold symptoms. The aforementioned statement by the Prophet Mohammad describing black seed, as "having a remedy for all illnesses" may not as exaggerated as it appears. Recent research has provided

evidence, which indicates that black seed contains an ability to significantly boost the human immune system—if taken over time. In the words of the Prophet, "hold onto the use of the seed," this also emphasizes consistent usage of the seed. Therefore, one important point is that black seed should be regarded as part of an overall holistic approach to health and should be incorporated into one's everyday diet. In this way, nutritional values and therapeutic properties contained in the black seed can help in maintaining a healthy condition and supplying the immune system with the optimum resources it needs to help prevent and treat diseases. Therefore, in cognizance of black seed's substantial nutritional components, as well as its specific medicinal properties, the body's ability to maintain health and promote healing of a lasting nature is best increased through regular use of black seed.

The black seed is traditionally used in Eastern Mediterranean as an enhancer of milk production during breastfeeding. Black seed is an excellent form of added nutrition for both mother (black seeds mixed with toasted flour, toasted sesame, and honey and prepared as cakes) and the growing child while its immune system boosting properties serve as a natural, safe way to build resistance against illness. In addition, as studies have shown, black seed helps increase milk production during breastfeeding [35–37].

17.6.1 Composition

Black seeds are rich in nutritional values. Monosaccharide in the form of glucose, rhamnose, xylose, and arabinose are found in the black seed. They contain a nonstarch polysaccharide component, which is a useful source of dietary fiber. Black seeds are rich in fatty acids, particularly the unsaturated and essential fatty acids, for example, alpha linoleic acid (omega 3) and linoleic acid (omega 6). In addition, seeds contain eight of the nine essential amino acids. Both, essential fatty acids and essential amino acids cannot be synthesized within our body and are thus required from our diet. Black seeds contain carotene, which is converted by the liver into vitamin A, the vitamin known for its anticancer activity. The black seed is also a source of calcium, iron, sodium, and potassium. Required only in small amounts by the body, these elements' main function is to act as essential cofactors in various enzyme functions. Black seeds contain pharmacological active compounds, namely, thymoquinone, dithymoquinone, thymohydroquinone, and thymol. These compounds are the main active compounds responsible for the therapeutic effects of black seeds [35–37].

17.6.2 Pharmacological Activities

Therapeutic potential and toxicological properties of the seeds have been extensively studied A Medline and Google Scholar search using "*Nigella sativa*" and "medicine" reveals more than 1600 citations, including antioxidant, anti-inflammatory, antimicrobial, hypotensive, antinociceptive, choleretic, uricosuric, choleretic, antidiabetic, and antihistaminic, immunomodulatory, anticancer, and antifertility effects. For further details, see Chapter 8.

17.7 FIGS

The Common fig, *Ficus carica*, is a large, deciduous, shrub or small tree native to Southwest Asia and the Eastern Mediterranean basin. It grows to a height of 6.9–10 m tall, with smooth gray bark. The leaves are 12–25 cm long and 10–18 cm across, and deeply lobed with three or five lobes. The fruit is 3–5 cm long, with a green skin sometimes ripening toward purple. The sap of the tree's green parts is an irritant to human skin. As one of the oldest known human foods, figs as a fruit have a very high safety profile (Figure 17.3). The Common fig fruit of *F. carica* are used as food and for medicinal properties in Greco-Arab and Islamic medicine as well as in Ayurvedic and traditional Chinese medicine. There is a Sura (verse) in the Holy Quran named after the fig tree, and the fruit is mentioned in Quran in many places. As mentioned above, the Prophet (PBUH) mentioned figs and then stated, "If I had to mention a fruit that descended from paradise I would say this is it because the paradisiacal fruits do not have pits ... eat from these fruits for they prevent hemorrhoids, prevent piles and help gout." Figs are a top source of fiber, as well as potassium and vitamin B6. Fiber results in bulkier stools, which lessen the incidence of constipation, hemorrhoids, and colon cancer.

17.7.1 Food and Medicinal Uses

Some correlation between the ethnomedical employment and the pharmacological activities has been duly observed. Fig trees of several different species show multiple cancer preventive, cancer therapeutic and anti-inflammatory activities from their bark, roots, leaves, fruits, and latex. Evidence of such uses originated in ancient and medieval times, with classical writers of those periods claiming the efficacious use of these parts in carcinomas, inflammatory swellings, "hard swellings," and tumors in

FIGURE 17.3 *Ficus carica*, the Common fig. (*See the color version of this figure in Color Plates section.*)

general. Usually, fig tree products for cancer and other tumors and swellings were used externally, even when the tumor or swelling was internal, such as intestinal ailments, and often combined with other ingredients such as blue flag (*Iris versicolor*), barley and fenugreek. Both latex and fruits were, however, also employed orally.

Earlier Greek and Arabic texts include descriptions of the tree and later European texts have detailed drawings, which aid in their identification. Most concern *F. carica* and *Ficus sycomorus*, though close relatives of these may have been included under the common names "fig" and "sycomore." The parts of *F. carica* used for treatment of tumors and diseases associated or characterized by inflammation include the fruits in different stages of ripening, fresh or dry, tree bark, leaves, twigs and young shoots, and latex from the bark, fruit, and young branches. Additionally, ashes of the fig tree and fig stalks and lye made of the ashes of the branches and wood were used, as well as wine made from the fruits.

Although these historical records are frequently difficult to translate into modern diagnostic categories, both the frequency of these citations, and in some cases, their specificity, provides confidence that medicines deriving from *Ficus* trees were well known for treating both cancers and inflammatory processes, and that in many cases, amelioration of these conditions was subsequently observed. Pharmacological and chemical studies have demonstrated antineoplastic or anti-inflammatory activity of both the crude extract and pure compounds. Of particular promise, due to their potent cytotoxic activity against a number of cancer cell lines, are the phenanthroindolizidine alkaloids and the triterpenoids with a C-18 carboxylic acid functional groups. In fact, these alkaloids, which have also been found in a small number of other plant genera, are currently under active investigation as potential therapeutic leads. In addition to these cytotoxic compounds, several flavonoids, including anthocyanins, as well as other phenolic compounds, demonstrated antioxidant and anti-inflammatory activities. Furthermore, lectins in the seeds may function as immune modulators. The sterols found in figs may also help bolster immunity, as well as inhibit inflammation and invasion while promoting apoptosis and differentiation. Coumarins, in many cases, are selectively cytotoxic to cancer cells, and also have antioxidant activity and may interfere with formation of the lipoxygenase product 5-HETE to suppress inflammation.

In addition to the potential anticancer and antioxidant properties, fig fruit products exhibit pleasant taste and extremely benign safety profile. Because the antioxidant action is also means lowering chronic anti-inflammatory action and insulin resistance. Fig fruits hold potential in functional food approaches aimed at normalizing metabolic syndrome and boosting wellness beyond the widely accepted role of figs in the diet for improving bowel performance, and as a source of naturally sweet, readily available, quick energy [38–42].

17.8 THE POMEGRANATE

The pomegranate, *Punica granatum*, is a fruit-bearing deciduous shrub or small tree native to the region from Persia to northern India and has been cultivated and naturalized over the whole Mediterranean region as well as in other regions since

ancient times. The tree has very attractive flowers that are scarlet, white, or a mixture of the two. One of the primary benefits of the pomegranate is its use as a dye. Extracted from its scarlet flowers is a beautiful red dye, which has been used for centuries in Central Asia. The fruit, commonly known as Rumman in the Arab world, can be divided into three structural compartments: seed, juice, and peel. Pomegranate molasses (known as dibs al-Rumman in Arabic) is an essential Middle Eastern ingredient. The uses for this thick, tangy, piquant syrup are many.

The pomegranate has long been used in traditional Arab–Islamic medicine to treat a variety of ailments, including sort throat, inflammation, and rheumatism. These uses of the pomegranate are common throughout the Middle East, Iran, and India, where the fruit is common. Additional traditional uses include treatment of diarrhea and colic and to remove intestinal worms in children. The fruit is also used for treating bladder disturbances, strengthening gums, and soothing mouth ulcers. In India, the leaf of the pomegranate is used to treat cuts, as it contains a natural healing and soothing agent. Pomegranates feature prominently in all religions, Judaism, Christianity, Islam, Buddhism, and Zoroastrianism. According to the Quran, pomegranates grow in the gardens of paradise. Pomegranates, along with dates and olives, are also mentioned in the following verse from the Holy Quran, which speaks of the dues that have to be paid upon each harvest, as well as the evil of wastefulness.

> And it is He Who produces gardens trellised and untrellised, And date-palms, and crops of different shape and taste and olives, and pomegranates, similar (in kind) and different (in taste). Eat of their fruits when they ripen, but pay the due thereof on the day of its harvest, And waste not by extravagance. Verily, He likes not those who waste by extravagance.

In Ayurvedic medicine the pomegranate is considered "a pharmacy unto itself," the bark and roots believed to have antihelmintic and vermifuge properties, the peels a powerful astringent and cure for diarrhea and oral aphthae and the juice a "refrigerant" and "blood tonic." Dried pomegranate peels are decocted in water and employed both internally and externally for numerous problems demanding astringents and/or germicides, especially for aphthae, diarrhea, and ulcers. Mixtures of pomegranate seed, juice, and peel products paradoxically have been reported to not only prevent abortion but also conception.

The most abundant polyphenols in pomegranate juice are the hydrolyzable tannins called punicalagins, which are powerful antioxidants. Punicalagins are absorbed into the human body and may have dietary value as antioxidants; other phytochemicals include beta-carotene, and polyphenols catechins, gallocatechins, and anthocyanins such as prodelphinidins, delphinidin, cyanidin, and pelargonidin. The fruit contains also Vitamin C at 0.47 mg/100 g. The pharmacological uses of the pomegranate, as was seen with the two other plants of the Quran, dates and olives, are numerous. These include antioxidant, hormone replacement therapy, resolution of allergic symptoms, cardiovascular protection, oral hygiene, ophthalmic ointment, weight loss soap, and as an adjunct therapy to increase bioavailability of radioactive dyes during diagnostic imaging. Pomegranate-mediated antioxidant activity can be considered a means of

lowering the threshold for inflammation. Antioxidant activity, as well as suppression of inflammation, may contribute to chemotherapeutic and chemopreventive utility against cancer [1–3,43].

17.9 GARLIC

Garlic (*Allium sativum* L.) and onion (*Allium cepa* L.), which are among the oldest cultivated plants, are used both as a food and for medicinal applications. Garlic has been used for thousands of years for medicinal purposes. Sanskrit records mention its medicinal use about 5000 years ago, and it has been used for at least 3000 years in Chinese medicine. The Egyptians, Babylonians, Greeks, and Romans used garlic for healing purposes. In 1858, Pasteur noted garlic's antibacterial activity, and it was used as an antiseptic to prevent gangrene during World War I and World War II. Historically, garlic has been used around the world to treat many conditions, including hypertension, infections, and snakebites, and some cultures have used it to ward off evil spirits.

Garlic and onion are rich sources of several phytonutrients recognized as important elements of the Mediterranean diet, but are also used in the treatment and prevention of a number of diseases, including cancer, coronary heart disease, obesity, hypercholesterolemia, diabetes type 2, hypertension, cataract, and disturbances of the gastrointestinal tract (e.g., colic pain, flatulent colic, and dyspepsia). Garlic has a high concentration of sulfur-containing compounds. The thiosulfinates, including allicin, appear to be the active substances in garlic. Allicin is formed when alliin, a sulfur-containing amino acid, comes into contact with the enzyme alliinase when raw garlic is chopped, crushed, or chewed. Dried garlic preparations containing alliin and alliinase must be enteric coated to be effective because stomach acid inhibits alliinase. Because alliinase also is inactivated by heat, cooked garlic is less powerful medicinally. The antimicrobial, hypolipidemic, antioxidant, and antithrombotic effects that have been attributed to garlic are thought to be related to allicin and other breakdown products.

The pharmacological activities of garlic are related to the thiosulfinates, volatile sulfur compounds, which are also responsible for the pungent of garlic. Besides these low molecular weight compounds, onion and garlic are characterized by more polar compounds of phenolic and steroidal origin, often glycosilated, showing interesting pharmacological properties. These latter compounds, compared to the more studied thiosulfinates, present the advantages to be not pungent and more stable to cooking. Recently, there has been an increasing scientific attention on such compounds [1–3,44,45].

17.10 EDIBLE WILD PLANTS

Wild edible plants are commonly consumed of in the Eastern region of the Mediterranean (Palestine, Lebanon, Syria, Jordan). Wild plants are defined as

"those that grow spontaneously in self-maintaining populations in natural or seminatural ecosystems and can exist independently of direct human action." Wild edible herbs have always been a main part of traditional diets, and were appreciated for their health and medicinal qualities among local communities and indigenous people long before their nutritious, protective, and therapeutic effects were proved by science. A high percentage of individuals collects wild edible plants and consumes them as part of traditional food habits. Traditional food habits have been characterized by dietary diversity and have been associated with low health risks. Wild edible plants have been identified as main components of these diets and as important contributors to their health-protective properties. Many wild species are collected from the surrounding environment and consumed as part of local diets, especially in times of shortage. Various wild greens contain high nutritional values with relatively low energy. According to a recent survey by the group of Ali-Shtayeh of An-Najah University, Nablus, Palestine, recorded 103 edible plants. Sixty-four plants were cited to be used for food as well as for medicine. These are food plants that receive recognition as medicinal in the traditional Palestinian herbal medicine and represent a part of the Palestinian medicinal ethnoflora. The most significant species include *Majorana syriaca*, *Foeniculum vulgare*, *Malva sylvestris*, *Salvia fruticosa*, *Cyclamen persicum*, *Micromeria fruticosa*, *Arum palaestinum*, *Trigonella foenum-graecum*, *Gundelia tournefortii*, and *Matricaria aurea* [24].

Compared with commonly eaten vegetables, wild edible plants provide the diet with greater amounts of minerals. Additionally, several of these often called "famine foods" have proved to be important sources of high-quality protein and essential amino acids when compared with the WHO protein standard, as well as being rich in *n*-3 and *n*-6 essential fatty acids. Their antioxidant property, mainly from phytochemicals, was found to be two to three times higher than that of common vegetables. For these reasons, undomesticated greens are recognized as possessing a significant potential for widespread use and development, promoting global food security and nutrition.

Traditional knowledge and experience are a golden source for the exploration and collection of wild plants. Indigenous people are people who developed ways of living, practices and belief systems, which demonstrate their intimate relationship with the mountain environment and deep knowledge about the plants, wildlife, vegetation, and ecosystems that surround them. This set of beliefs forms the basis for participatory approaches, with the aim of reaching economic and sustainable development in local communities. Ethnobotany, the systematic study of traditional communities' botanical knowledge, permits the disclosure of various characteristics and benefits of wild plants that were revealed through the ancient interaction between man and nature. In the Mediterranean basin, there seems to be a wealth in ethnobotanical studies, mostly coming from Southern Europe and some Middle Eastern countries. During the last century, safety and efficacy of wild edible plants have gained the interest of the scientific community. Traditional uses, phytochemistry, and pharmacological properties of these wild plants are discussed in Chapter 8. Here we concentrate on their food values and their medical uses [1–3,46,47] (Table 17.2, Table 17.3).

TABLE 17.3 Commonly Used Wild Edible Plants in the Mediterranean Region

Part Used	Common Arabic Name	Common English Name	Latin Name
Fruit	Bamiaa'	Lady's finger/Little Lucy	*Abelmoschus esculentus*
Seed	Hab ala'ez	Chufa Sedge, Yellow Nutsedge, Earth almond	*Cyperus esculentus*
	Herf barre	Variegata	*Barbarea vulgaris*
Leaf	Hommed zgher	Cape sorrel	*Oxalis pes-caprae*
Leaf	Hommede	Pink sorrel	*Rumex cyprius*
Leaf	Ghobeze	Common mallow	*Malva micaemis*
Fruit	Khardal barre	Charlock	*Sinapis arvensis*
	Kharshof	Artichoke	*Cymara scolymu/Helianthus tuberosus*
	Khas barre	Wild lettuce/prickly lettuce	*Lactuca virosa/Lactuca serriola*
	Sdom	Christ-thorn jujube	*Ziziphus spina-christi*
Vegetable	Sannarye	Milk thistle/spotted golden thistle	*Silybum marianum/Scolymus maculatus*
Seed	Shaer	Barley/ancestral two-row barley	*Hordeum vulgare/Hordeum spontaneum*
	Shomar	Florence fennel	*Foeniculum vulgare*
Vegetable	Akkob	Tumble thistle/gundelia	*Gundelia tournefortii*
Vegetable	Alet	Dwarf chicory	*Cichorium pumilum*
Leaf	Farfahena	Garden purslane	*Portulaca oleracea*
Leaf	Korsaneye	Field eryngo	*Eryngium creticum*
Laef	Korres	Roman nettle	*Urtica pilulifera*
Leaf	Kozbarah	Coriander	*Coriandrum sativum*
Leaf	Lof falastene	Palestinian arum	*Arum palaestinum*
	Halion	Prickly asparagus	*Asparagus aphyllus*

17.10.1 Chicory

Chicory, *Cichorium intybus* (Hindibaa in Arabic), is a bushy perennial herb of the Asteraceae with a large taproot like that of dandelion and blue, lavender, or occasionally white flowers. Chicory is a well-known food and medicinal herb. The whole plant has been known for its curative benefits since the first century. It is used much like dandelion in European herbal medicine. That is, it is helpful in cleaning the body and supporting the liver and also in stimulating the eliminative processes via both the intestine and the kidneys. It is a warming and tonifying plant, and the fresh root is used traditionally in chest problems and cold conditions. The plant is classically used in cold countries as part of soup to ward off colds and flu. Professional herbalists also use the plant as part of mixtures for the treatment of dry coughs, chest pain, and bronchial problems. In the Mediterranean region, chicory is commonly known as "Hindbeh," and is renowned for its digestive properties as a laxative and its blood properties in terms of treating anemia. As for its effects on the blood, chicory is

mainly reported to "treat anemia" and to "strengthen blood," which we believe also implies "treating anemia."

Chicory flowers contain cichoriin, which is 6,7-glucohydroxycoumarin. The roots contain up to 8% inulin (a polysaccharide), a bitter principle consisting of one part protocatechuic aldehyde to three parts inulin, as well as lactucin and lactucopicrin. Constituents of the greens include chicoric acid (dicaffeoyl tartaric acid), flavonoids, catechol tannins, glycosides, carbohydrates, unsaturated sterols and triterpenoids, sesquiterpene lactones, and tartaric acid. Leaf proteins from chicory greens have also been reported. The root contains a large number of steam-distillable aromatic compounds. Acetophenone provides the characteristic chicory aroma. Upon roasting, inulin is converted to oxymethylfurfural, a compound with a coffee-like smell. Fructan:fructan 6G-fructosyltransferase (6G-FFT) was found to be an important enzyme in the formation of inulin. Chicory is the source of the taste-modifier maltol, which is known to intensify the flavor of sugar.

Chicory is cultivated widely throughout Europe for use in salads. Chicory, like many plants that support liver function and immunity, has strong antioxidant effects *in vitro*, but the clinical significance of this has not been tested. However, there have been several studies in humans on the therapeutic effects of the inulin and oligofructan polysaccharides. They have been shown to pass through the stomach and undergo fermentation in the colon. This leads to the selective stimulation of the healthy bifidobacteria population. The health consequences of this include the reduction of colonic diseases and diabetes, as well as support for the immune system. These polysaccharide components of chicory also have a significant effect on cholesterol levels, especially on reducing LDL cholesterol and increasing HDL cholesterol. In addition, other improvements in lipid metabolism, which may be signs of "blood purification" in the traditional herbal terminology, are caused by consuming chicory, along with a clearing out of body fat, bile and cholesterol through fecal excretion. These changes may support general health and disease prevention. There is very little scientific evidence on the general benefits to health of chicory. One study has demonstrated that elderly patients given chicory improve their hepatic function and rehabilitation. Traditional reports have described chicory as having antipyretic, anticolic, hypoglycemic and hepatic properties.

Concerning its nutritional value, chicory is a rich source of folate, containing 110 mg of folate per half cup of chopped raw chicory. Therefore, an increased consumption of chicory might explain its reported properties in cases of folate deficiency-related anemia in Greco-Arab and Islamic medicine. As for studies on its digestive properties, chicory is described to be bitter in taste and bitter plants have been used to treat digestive tract disturbances among various traditional systems, relieving gastrointestinal pains. Several sesquiterpene lactones found in chicory confer the bitter taste to the plant. The laxative effect of chicory can be explained by its high content of dietary fiber, having 3–6 g of dietary fiber per half cup of chopped raw chicory. Moreover, inulin, an indigestible carbohydrate, is found to some extent in the stalk of the plant. Inulin, like other dietary fibers, increases bowel movement and is thus responsible for the laxative and digestive-stimulant properties referred to by informants in the current study. Other reports of hepato-protective activity and hypoglycemic effects of chicory are well supported by previous scientific literature [1–3,46–48].

17.10.2 Palestinian Thyme

M. syriaca (Zaatar in Arabic) is a grayish shrub herb that belongs to the mint family Labiatae is native to the Eastern Mediterranean, Southern Europe and Western Asia, and is cultivated in many parts of the world and commonly called Syrian oreganum. It grows wild in the mountains of Eastern Mediterranean. Palestinian thyme, *M. syriaca*, is considered as one of the most popular herbs in the Arab world. The herb possesses distinctive aroma with a slight warm pungent taste. The green leaves of the herb are rich in essential oil, which is responsible for its characteristic flavor and fragrance.

When dining in the Middle East, it is customary to dip bread in olive oil and then in *za'tar* for a delicious taste. Although *za'tar* is the word for *thyme* in the Arabic language, it is also a term that describes a Middle Eastern spice blend of powdered dried thyme, sumac and sesame seeds. Each region makes za'tar a little differently.

It contains monoterpene hydrocarbons: α-pinene, myrcene, α-terpinene, *p*-cymene, and γ-terpinene. Oxygenated monoterpenes: linalool: terpinen-4-ol, α-terpineol, thymol methyl ether, carvacrol methyl ether, thymol, and carvacrol. The content of essential oil depends on soil, climate, and season.

Za'tar has served humans for thousands of years. Hippocrates prescribed it for bronchitis and pleurisy. Traditionally, *M. syriaca* has been used to remedy asthma, congestion, rheumatism, sore throats, wounds, ulcers, and tumors. A combination of ground dried thyme leaves, salt, sesame seeds, and the fruits of the tree *Rhus coriaria* (Sumac) are called "Za'tar" in Arabic, a very popular mixture that is used almost daily in the Middle East as food, additive in salads and spice for pastry, and meat. With its high content of volatile oils, the herb leaves are used in Greco-Arab and Islamic medicine as herbal tea to treat cold, flu, and cough. It has been reported that thyme in general comprises various medicinal benefits. For example, antibacterial and antifungal properties, hence, a solution of thyme most active ingredient, thymol, is used as over the counter antiseptic mouthwash product. Moreover, thyme extracts are frequently included in the popular cough syrups and prescribed to clear respiratory difficulties, including bronchial problems and coughs. The antimicrobial properties of thyme essential oils are mainly related to their high phenolic content. It is used as a powerful disinfectant in oral pharmaceutical preparations and flavoring agent of many food products [1–3,49,50–52].

17.10.3 Fennel

F. vulgare, fennel, known, as Shumar in the Eastern region of the Mediterranean, is a perennial herb. It is erect, glaucous green, and grows to heights of up to 2.5 m, with hollow stems. The fruit is a dry seed from 4 to 10 mm long, half as wide or less, and grooved. The main active constituents of fennel, which include the terpenoid anethole, are found in its volatile oil. Anethole and other terpenoids may have mild estrogen-like activity, which inhibit spasms in smooth muscles, such as those in the intestinal tract. In Greco-Arab and Islamic medicine as well as in other different medical systems, fennel is known for its laxative properties. It is also used as a muscle relaxant as well as to treat urinary disorders. In the Eastern Mediterranean countries fennel is used for its therapeutic effects on the gastrointestinal system as a pain

reliever as well as for its diuretic properties. Experimental as well as human studies demonstrated that fennel oil had antispasmodic and relaxing effects on smooth muscles. This activity is due to the similarity found between anethole, the major component in fennel oil, and the neurotransmitter dopamine. In animal studies, fennel was proved to have significant diuretic properties, which explains our informants' narratives [1–3,49].

17.10.4 *Eryngium creticum*

Eryngium creticum, "Qors Aanneh" in Arabic, has varied, less pronounced, health properties. The plant is known to contain acetylenes, flavonoids, coumarins, and triterpene saponins. In traditional Arab medicine *E. creticum* used for a wide range of ailments; particularly roots are used against various inflammatory disorders, oedema, sinusitis, urinary infections and inflammations, and snake or scorpion bites or goiter, roots and leaves for infertility and herbs for wound healing as well as food while fresh. Traditional reports stressed the use of *E. creticum* as an antidote for scorpion poison, as well as for its hypoglycemic effects. Accounts of its hypoglycemic effects are actually supported by animal studies. Extracts of the aerial parts of *E. creticum* confirmed their hypoglycemic effect in rat models. Similarly, reports regarding its antipoisonous property have been previously tested. In fact, the leaf extract from *E. creticum* possessed potent antidote activity. As for claims on its blood properties, further analysis of this plant might clarify this effect [1–3,49].

17.10.5 *Gundelia tournefortii* (Akkoub)

G. tournefortii L., commonly known, as Akkoub in the Arab world, from the Asteraceae family, is a medicinal plant and also used as a nutritious food (Figure 17.4). This plant is native to Mediterranean basin. Nutrient analysis of raw Akkoub highlighted its abundance in calcium (642 mg/100 g) and iron (279 mg/100 g). It is recorded that the flowers, leaves, seeds, and stems of Akkoub are used as food sources. In the Middle East, the young and still undeveloped flower buds are sold in the local markets just like artichoke hearts; it is a highly sought item. In Arab–Islamic traditional medicine, Akkoub is known for its hypoglycemic, laxative properties [1–3,49].

17.10.6 Purslane

Purslane, *Portulaca oleracea*, is an annual succulent in the family Portulacaceae and is commonly known as Farfahena in the Arab world. Purslane is used traditionally in the treatment of a variety of conditions that include headache, painful urination, stomachache, enteritis, mastitis, lack of milk flow in nursing mothers, and in postpartum bleeding. Externally it is used to treat burns, earache, ulcers, pruritis (itching skin), insect stings, inflammations, skin sores, eczema, and abscesses. These conditions are usually treated with the fresh herb used as a poultice or the expressed juice is used. *P. oleracea* is eaten as a salad and vegetable across the world.

FIGURE 17.4 *Gundelia Tournefortii* (*Akkoub*). (*See the color version of this figure in Color Plates section.*)

A water extract of purslane was shown to have skeletal muscle relaxant effects both *in vitro* and *in vivo*; it also relaxed guinea pig gastric fundus, taenia coli, and rabbit jejunum as well as contracted the rabbit aorta and raised blood pressure. Topical application of the aqueous extract onto the skin was effective in relieving muscle spasms. Other effects include antibacterial and antifungal, wound healing, anti-inflammatory, uterine stimulant, and diuretic in rabbits. Although norepinephrine may account for some pharmacologic activities, the active principle for most of the biological activities and medicinal properties of purslane are still unidentified.

Purslane contains large amounts of L-norepinephrine, a neurohormone that has vasopressor and antihypotensive activities and reduces hemorrhage at the tissue level. It also contains vitamins A, B1, B2, C, niacinamide, nicotinic acid, α-tocopherol, β-carotene, fatty acids, especially omega-3 acids whose concentration in purslane is the highest found in leafy vegetables, glutathione, glutamic acid, and aspartic acid. Other constituents include calcium oxalate, malic and citric acids, dopamine and dopa, coumarins, flavonoids, alkaloids. Recent research has shown that the plant also contains saponins [1–3,49,53].

17.10.7 High Mallow

Malva is a genus of about 25–30 species of herbaceous annual, biennial, and perennial plants in the family Malvaceae, one of several closely related genera in the family to bear the common English name mallow and Khebayzeh in Arabic (Figure 17.5). The genus is widespread throughout the temperate, subtropical, and tropical regions of Africa, Asia, and Europe. Khebayzeh been traditionally used as a laxative and an anti-inflammatory agent. An isolated polysaccharide from Khebayzeh leaves shows an

FIGURE 17.5 High mallow (*Khebayzeh*). (*See the color version of this figure in Color Plates section.*)

anticomplement activity, thus modulating the inflammatory response. Moreover, nutrient analysis of a different species of Khebayzeh eaten in the Arab world highlighted the plant as an important vegetable source of zinc, necessary for a healthy immune system. As previously recounted, the laxative effects of Khebayzeh could be attributed to its high mucilage content [1–3,49].

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CHAPTER 18

Drug Development from Herbal Sources

18.1 INTRODUCTION

The healing properties of various plants are recognized and utilized by humans and other primates, for example, gorillas, chimpanzees. Both, humans and primates select some of the same plants for the management of similar diseases, injuries, and other health problems. There is also a large body of archeological evidences indicating that medicinal plants were regularly employed by people in prehistoric times. Some of the earliest known written records also deal with the subject of healing with medicinal substances. The ancient Egyptians of 3000–6000 years ago are credited with developing an elaborate and effective pharmacological collection of numerous curing substances obtained from natural resources. The Egyptian doctors prescribed sedatives, analgesics, gastrointestinal disorder remedies, and medicines for urinary tract diseases and the common cold. Plant extracts were prepared and taken internally, applied topically, and administered by fumigation and vapor inhalation. Plant-based therapeutic treatments continued to be augmented later by health care practitioners in ancient Greece 3000 through 1500 years ago. Dioscorides, an authority on herbs who lived in the first century, is noted for assembling 24 detailed books on over 600 curative plants and their proper uses under the title *De Materia Medica*, the earliest known designation of that terminology. During the Golden Ages of the Arab–Islamic civilization (seventh to fifteenth centuries) Arab–Islamic scholars introduced hundreds of medicinal plants and developed a large and complex medical literature exploring the theory and practice of medicine and botany with highly accurate precision and details. They introduced many new ideas and upgraded the knowledge about herbs and their potential medical efficacy and safety. Al-Kindi (Alkindus) (800–873) was the first scholar in history who developed a scale to define the meaning of drug "degrees" in order to allow physicians to quantify the potency of their prescriptions.

Herbal-based drug discovery research is a multidisciplinary approach combining ethnopharmacology and traditional knowledge on the one hand and botanical, phytochemical, biological, toxicological, pharmacological, and molecular

Greco-Arab and Islamic Herbal Medicine: Traditional System, Ethics, Safety, Efficacy, and Regulatory Issues By Bashar Saad and Omar Said

techniques on the other hand. Several herbal-derived drugs have either recently been introduced to the market or are currently involved in late-phase clinical trials. Presently, medicinal plant-based drug discovery continues to provide new and important leads against various pathological conditions, for example, cancer, psoriasis, diabetes, malaria, and pain. With only 5–15% of the approximately 250,000 species of higher plants systematically investigated, and the potential of the marine environment barely tapped, these areas will remain a rich source of novel bioactive compounds. Although herbal-derived compounds continue to provide an important source of new drug leads, numerous challenges are encountered including the procurement of plant materials, for example, the selection and implementation of appropriate high-throughput screening bioassays, and the scale-up of active compounds.

It is generally believed that standardization and regulations of the plant material is not required when used by the rural communities for their primary health care. Nevertheless, regardless of whether the medicinal plant is to be used by local communities or by industry, a systematic approach is required for a traditionally used plant, as is done in modern medicine. It is necessary to standardize all stages of herbal-based drug discovery: from cultivation, ethnopharmacology, utilization, isolation and identification of active constituents to efficacy evaluation, pharmacology, safety, formulation, and clinical evaluation.

In general, many herbs are effective when consumed as whole or as extracts. Current trends, however, are directed toward the use of purified herbal-derived agents that can serve not only as new drugs themselves but also as drug leads suitable for optimization by medicinal and synthetic chemists. Even when new chemical structures are not found during drug discovery from medicinal plants, known compounds with new biological activity can provide important drug leads. In this respect, the sequencing of the human genome paths the ways for identification of thousands of new pharmacology active molecules. With the help of modern *in vitro* and *in vivo* screening assays directed toward these targets, known herbal-derived compounds may show promising and possibly selective activity. Several known herbal-derived compounds have already been shown to act on newly validated molecular targets (e.g., indirubin selectively blocks cyclin-dependent kinases). Other herbal-derived compounds have also been shown to act on novel molecular targets, thus reviving interest in members of these frequently isolated plant compound classes. In this chapter, we concentrate on important aspects of the herbal-based drug discovery: from collection of plant material, to efficacy and safety evaluation through preclinical studies and phytochemical standardization [1–5].

18.2 THE VALUE OF PLANTS USED IN TRADITIONAL MEDICINE FOR DRUG DISCOVERY

The currently observed rapid increase in the consumption of herbal remedies worldwide has been stimulated by several factors, including the notion that all herbal products are safe and effective. According to the World Health Organization (WHO)

(see Chapter 19 for more details), almost 65% of the world's population incorporates herbal-based medicines into their primary health care. Similar trends are observed in the Arab–Islamic world where there is a remarkable and increasing interest in Greco-Arab and Islamic herbal medicine. In addition, there is an increasing trend in research activities dealing with the safety and efficacy of medicinal plants in throughout the Mediterranean region. Greco-Arab and Islamic herbal medicine is the first choice for many in dealing with ailments, including simple diseases as well as intractable or chronic diseases such as infertility, epilepsy, psychosomatic troubles, and depression. It is a part of modern life in the Middle East, and it is acquiring worldwide respect, with growing interest among traditional herbalists and the scientific community. Medicinal plants are used in various forms as sources of therapeutic agents (see Chapter 9 for more details). These include the following:

Whole Plant: To use the whole plant or part of it as in herbal remedy is discussed in details in Chapters 8, 10, 16, and 17. For instance, black seeds, olive oil, dates, garlic, and many edible wild plants.

Crude Extracts: As described in Chapter 16, several techniques were developed in the Greco-Arab and Islamic medicine and are still practiced by traditional herbalists to obtain beneficial ingredients from selected plants (Table 16.1). The majority of herbal-based medicines are consumed orally in the form of tea or other drink containing either diluted or concentrated extracts. In this respect, the chemical composition of an herbal extract is largely affected by the extraction process. For instance, a hot water extracts of an herb will be rich in polar components. Oil on the other hand, is a nonpolar solvent and it will absorb nonpolar compounds. Alcohol lies somewhere in between. Other methods include the inhalation of aerosols (e.g., *Pimpinella anisum*, *Chamomilla recutita*), essential oils (e.g., *Jasminum fruticans*), and vaporized plant juices or teas. Different methods were also developed for drug preparation for external (topical) uses and are currently used by herbalists in the Arab–Islamic world. Herbal extracts with alcohol/water are commonly used for research purposes (Figure 16.2). In this method, a selected herb is boiled in varying ratios of water and alcohol. For instance, we used these methods for preparing crude extracts of antidiabetic, antihyperglycemic, anti-inflammatory, and antiobesity medicinal plants mixture (Table 12.2) as discussed in details in Chapter 12.

Isolated Bioactive Compounds: Numerous methods have been utilized to acquire compounds for drug discovery including isolation from plants and other natural sources. For instance, the following bioactive compounds have been discussed.

Ephedrine, first isolated in 1887 from *Ephedra sinica*, a plant long used in traditional medicine to treat asthma and other respiratory problems. Ephedrine is used as a basis for the synthesis of the antiasthma agents (beta agonists) and is used in the commercial pharmaceutical preparations for the relief of asthma symptoms and other respiratory problems.

Nitisinone, commercially available under the trade name Orfadin, is a recently released herbal-derived drug that treats tyrosinemia (a rare inherited disease)

through inhibition of the enzyme, 4-hydroxyphenylpyruvate dehydrogenase (HPPD), in both humans and maize. Nitisinone is a modification of mesotrione, an herbicide based on the leptospermone, an ingredient of *Callistemon citrinus* (Myrtaceae). Blocking of the HPPD enzyme in maize acts as an herbicide and results in reduction of plastoquinone and tocopherol anabolism, while in humans the HPPD enzyme inhibition blocks tyrosine catabolism and the accumulation of toxic by-products in the liver and kidneys.

Vinflunine is a modification of vinblastine from *Catharanthus roseus* developed for use as an anticancer compound with improved efficacy.

Tiotropium, commercially available under the trade name Spiriva, has recently been released to U.S. market for the treatment of chronic obstructive pulmonary disease (COPD). Tiotropium is an inhaled anticholinergic bronchodilator, based on ipratropium, a derivative of atropine that has been isolated from *Atropa belladonna* and other members of the Solanaceae family. Tiotropium shows higher efficacy and longer lasting effects when compared with other available COPD drugs.

Morphine, an analgesic, isolated in 1816 by the German pharmacist, Serturner, from the opium poppy, *Papaver somniferum*, used in ancient Mesopotamia, laid the basis for alkaloid chemistry and the development of a range of highly effective analgesic agents. For instance, morphine-6-glucuronide is a metabolite of morphine from *P. somniferum*, currently in Phase III clinical trials and will be used as an alternate pain drug with fewer side effects than morphine.

Calanolide A is a dipyranocoumarin isolated from *Calophyllum lanigerum*, a Malaysian rainforest tree. Calanolide A is an anti-HIV drug with a specific and unique mechanism of action as a nonnucleoside reverse transcriptase inhibitor of type-1 HIV and is effective against AZT-resistant strains of HIV.

Quinine, an antimalarial drug, from the bark of *Cinchona* species (e.g., *Cinchona officinalis*), was reported in 1820 by the French pharmacists, Caventou and Pelletier. The bark had long been used by indigenous groups in the Amazon region for the treatment of fevers, and was first introduced into Europe in the early 1600s for the treatment of malaria. Quinine formed the basis for the synthesis of the commonly used antimalarial drugs, chloroquine and mefloquine.

Other significant drugs developed from traditional medicinal plants include (Table 18.1): the antihypertensive agent, reserpine, isolated from *Rauvolfia serpentina* used in Ayurvedic medicine for the treatment of snakebite and other ailments; salbutamol and salmeterol; and the muscle relaxant, tubocurarine, isolated from *Chondrodendron* and *Curarea* species used by indigenous groups in the Amazon as the basis for the arrow poison, curare. Plants have a long history of use in the treatment of cancer, though many of the claims for the efficacy of such treatment should be viewed with some skepticism because cancer, as a specific disease entity, is likely to be poorly defined in terms of folklore and traditional medicine. Of the plant-derived anticancer drugs in clinical use, among the best known are the so-called vinca

alkaloids, vinblastine and vincristine, isolated from the Madagascar periwinkle, *C. roseus*. This plant was used by various cultures for the treatment of diabetes, and vinblastine and vincristine were first discovered during an investigation of the plant as a source of potential oral hypoglycemic agents. Their discovery, therefore, may be indirectly attributed to the observation of an unrelated medicinal use of the source plant. The two clinically active agents, etoposide and teniposide, which are semi-synthetic derivatives of the natural product, epipodophyllotoxin, may be considered being more closely linked to a plant originally used for the treatment of cancer. Epipodophyllotoxin is an isomer of podophyllotoxin, which was isolated as the active antitumor agent from the roots of various species of the genus *Podophyllum*. Taxol was initially discovered in bark of yew trees and has been recently proven effective in treatment of breast and ovarian cancers. Other examples are aspirin, morphine, digoxin, digitoxin, khellin, reserpine, vinblastine, vincristine (Table 18.1) [4–10].

TABLE 18.1 Herbal-Derived Drugs and their Plant Sources

Drug	Pharmacological uses	Plant source
Adoniside	Cardiotonic	*Adonis vernalis*
Aesculetin	Antidysentery	*Fraxinus rhynchophylla*
Ajmalicine	Circulatory disorders	*Rauvolfia serpentina*
Anisodamine	Anticholinergic	*Anisodus tanguticus*
Arecoline	Anthelmintic	*Areca catechu*
Atropine	Anticholinergic	*Atropa belladonna*
Bromelain	Anti-inflammatory	*Ananas comosus*
Caffeine	CNS stimulant	*Camellia sinensis*
(+)-Catechin	Haemostatic	*Potentilla fragarioides*
Cocaine	Local anesthetic	*Erythroxylum coca*
Codeine	Analgesic; antitussive	*Papaver somniferum*
Colchicine	Antitumor agent	*Colchicum autumnale*
Curcumin	Choleretic	*Curcuma longa*
Cynarin	Choleretic	*Cynara scolymus*
Danthron	Laxative	*Cassia* spp.
Digitalin	Cardiotonic	*Digitalis purpurea*
Digoxin	Cardiotonic	*Digitalis lanata*
Ephedrine	Sympathomimetic	*Ephedra sinica*
Etoposide	Antitumor agent	*Podophyllum peltatum*
Gitalin	Cardiotonic	*D. purpurea*
Hydrastine	Hemostatic; astringent	*Hydrastis canadensis*
Khellin	Bronchodilator	*Ammi visnaga*
Morphine	Analgesic	*P. somniferum*
Noscapine	Antitussive	*P. somniferum*
Papain	Proteolytic and mucolytic	*Carica papaya*
Picrotoxin	Analeptic	*Anamirta cocculus*
Protoveratrines A & B	Antihypertensive	*Veratrum album*
Quisqualic acid	Antihelmintic	*Quisqualis indica*
Reserpine	Antihypertensive	*R. serpentina*
Salicin	Analgesic	*Salix alba*

(*continued*)

TABLE 18.1 (*Continued*)

Drug	Pharmacological uses	Plant source
Scillarin A	Cardiotonic	*Urginea maritima*
Silymarin	Antihepatotoxic	*Silybum marianum*
Strychnine	CNS stimulant	*Strychnos nux-vomica*
Theobromine	Diuretic and bronchodilator	*Theobroma cacao*
Valepotriates	Sedative	*Valeriana officinalis*
Xanthotoxin	Leukoderma	*Ammi majus*
Yohimbine	Aphrodisiac	*Pausinystalia yohimbe*
Yuanhuacine	Abortifacient	*Daphne genkwa*

18.3 CHALLENGES IN DRUG DISCOVERY FROM MEDICINAL PLANTS

Basic research at universities, private institutes, governmental laboratories on the one hand and applied research in industry on the other hand, all play a highly important role in developing new knowledge, which provides the basis for a new drug development. Drug discovery is an outstanding example of collaboration between scientists of various disciplines with a common aim to develop new safe and effective therapeutic agents. There is no standard route through which drug development takes place. New drug research starts with an understanding of how the body functions, both normally and abnormally, at its most basic levels. The questions of this research help determine a concept of how a drug might be used to prevent, cure, or treat a pathological condition, and provide researchers with a target. It can take over 10 years from the time a drug is discovered to complete all the mandatory preclinical and clinical phases and obtain regulatory approval for the new medicine (see Chapter 14).

Despite the evident successes of drug discovery from traditionally used medicinal plants or from data obtained from ancient medical texts (e.g., by Avicenna, Rhazes, and Ibn al-Baitar), present and future efforts face many challenges. Pharmacognosists, phytochemists, chemists, and biologists will need to continuously improve the quality and quantity of agents that enter the drug development process to keep pace with other drug discovery efforts. The process of chemical drug discovery has been estimated by the Food and Drug Administration (FDA) in the United States to take approximately 8.5 years upwards and cost more than $800 million. This estimate includes preclinical *in vitro* studies and animal testing, as well as clinical trials using human subjects. Much of this time and money is spent on the numerous leads that are discarded during the drug discovery process. Thousands of chemical compounds must be made and tested in an effort to find one that can achieve a desirable result. In fact, it has been estimated that only one in 5000 lead compounds will successfully advance through clinical trials and be approved for medical uses.

Drug discovery from medicinal plants has traditionally been lengthier and more complicated than other drug discovery methods. Therefore, many pharmaceutical companies have eliminated or scaled down their medicinal plants research. Because drug discovery from medicinal plants has traditionally been so time-consuming,

faster and better methodologies for plant collection, bioassay screening, compound isolation, and compound development must be employed. Innovative strategies to improve the process of plant collection are needed, especially with the legal and political issues surrounding benefit-sharing agreements.

The design, determination, and implementation of appropriate, clinically relevant, high-throughput bioassays build a difficult process for all drug discovery programmes. Although the design of high-throughput screening assays can be challenging, after a screening assay is in place, compound and extract libraries can be tested for biological activity. Screening of extract libraries can be problematic, but new techniques, including prefractionation of crude extracts, can alleviate some of these issues. Challenges in specific efficacy bioassay remain a central issue in the future of herbal-derived drug development. Improving the speed of active compound isolation will necessitate the incorporation of new technologies. Although nuclear magnetic resonance (NMR) and mass spectrometry (MS) are currently in wide use for compound identification, new methods of using NMR and MS could be applied to medicinal plant drug discovery to facilitate compound isolation. Also, the use of high-throughput X-ray crystallography could be applied to medicinal plant lead discovery. Compound development of drugs discovered from medicinal plants also faces unique challenges. Natural products are typically isolated in small quantities that are insufficient for lead optimization, lead development, and clinical trials. Collaborating with synthetic and medicinal chemists is necessary to determine if synthesis or semisynthesis might be possible. Another technique to improve natural product compound development may involve the creation of natural product and natural-product-like libraries that combine the features of natural products with combinatorial chemistry. In conclusion, natural agents discovered from medicinal plants (and derivatives thereof) have provided numerous clinically used medicines. Even with all the challenges facing drug discovery from medicinal plants, herbal-derived compounds can be predicted to remain an essential component in modern drug discovery process [6–16].

18.4 FACTORS NEED TO BE CONSIDERED IN HERBAL-BASED DRUG DISCOVERY

With the tremendous worldwide increase in the use of herbal-based remedies, concerns regarding the efficacy and safety of these medicines have also been raised. Thus, it has become necessary to standardize the efficacy and safety measures so as to ensure supply of medicinal plant materials with good quality. After proper botanical identification, WHO guidelines should be followed for collecting plant material in terms of proper season and climatic conditions, correct plant part, practices that are nondestructive and would prevent contamination from soil, toxic weeds, or microbes. Post collection, appropriate processing and storage conditions are required to reduce drying time, detoxification to reduce side effects and to enhance therapeutic value of the plant material and to improve its shelf life. In the following, we will discuss the approaches that need to be considered while studying pharmacological properties of

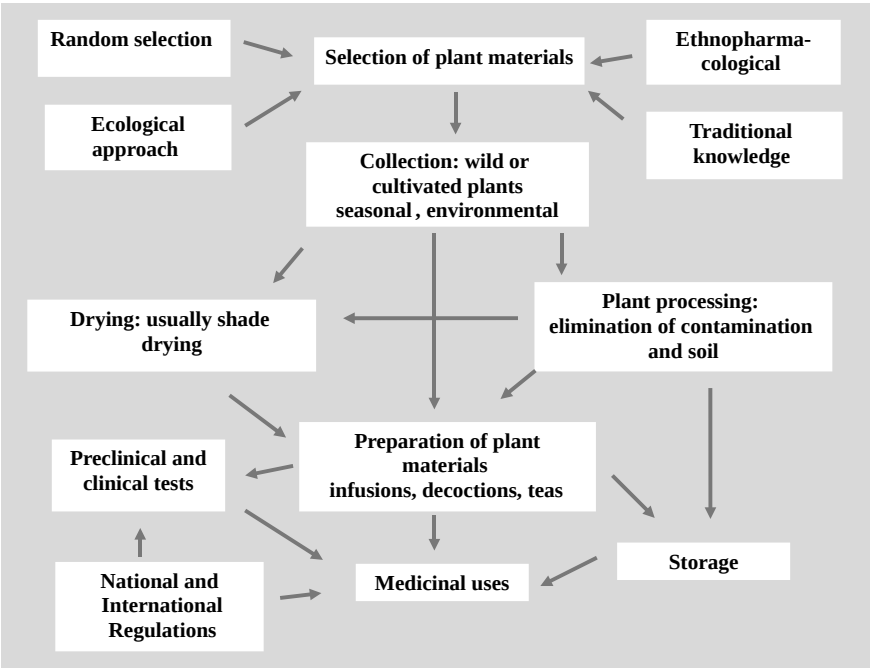

FIGURE 18.1 Important factors need to be considered in herbal-based drug discovery.

medicinal plants including source, selection, collection, processing and drying, preparation, storage, and phytochemical studies (Figure 18.1) [5–16].

18.4.1 Source of Plant Material

Wild harvesting is a prominent site of obtaining medicinal plants for both, community and pharmacological industry. Though many medicinal plants are commonly available in the wild and can be freely harvested, uncontrolled collection and sale of large quantities of edible wild plant material as well as medicinal plants can lead to destruction of many wild plants especially the endemic species that have a restricted geographical distribution. Furthermore, the increased demand for medicinal plants has created an ecological crisis for medicinal herbs growing in the wild raising alarm about their rate of extinction. As a result, conservation agencies and wild-protecting organizations are now recommending that wild species be brought into cultivation systems. In this regard, the present deteriorating condition of medicinal plants in the Mediterranean region needs immediate attention not only for conservation but also for propagation. Countries can protect their biodiversity in medicinal plants by working with industry toward monitoring and maintaining controlled nondestructive harvesting with habitat management. With the aim to preserve endangered indigenous Palestinian medicinal plants, we at the Galilee Society Research Center established the first botanical garden in eastern region of the Mediterranean. More than 120 plant

species are cultivated from which more than 35 medicinal species are rare or endangered. Local plant species are also preserved in the center and their traditional uses reintroduced to the community. A unique aspect of this project is that it offers a complete conceptual look of medicinal plants and their link to Arab–Islamic traditions and evaluation of their economic potential. In addition, this botanical garden not only focuses on the medicinal value of the plants, but also has established an educational mechanism to pass on the information to future generations.

Cultivation of Medicinal Plants: Cultivation of medicinal plants represents a commercially attractive option to companies because they have greater control over supply of the plant material and it is easier to control postharvest treatment. Furthermore, cultivation can reduce the dependence on collection of plants from wild and thus have the potential to save wild populations and conserve their genetic diversity. The feasibility of cultivating medicinal plants depends on several factors such as the ability of the species to thrive under monoculturing. The economic viability will depend on the demand and market prices. Furthermore, cultivation of medicinal plants requires intensive care and management and the conditions and duration required can vary depending on the quality of the medicinal plant material required. Risks of contamination from pollution by toxic agents should be avoided. Moreover, introduction of nonindigenous plant species into cultivation can lead to negative consequences on the ecological balance of the wild regions.

Pharmacological Quality of Cultivated Medicinal Plants: A point that needs specific consideration is that cultivated plants are sometimes considered qualitatively inferior to the wild collections. The pharmacological properties of herbal-based medicines are due to the combinations of secondary metabolites. Different plants have different combinations of these secondary metabolites that would often be taxonomically distinct in individual plants resulting in unique medicinal properties. Secondary metabolites that are generally produced for defense against pathogens or competitors or for protection/adaptation to environmental stress related to changes in soil conditions, temperature, water status, light levels, and mineral nutrients in their natural habitats. Therefore, secondary metabolites may not be expressed in optimum quantities when cultivated under optimum conditions to obtain better vegetative yields. For example, the therapeutic benefit of medicinal plants is often attributed to their antioxidant properties due to the presence of flavonoids, a class of natural polyphenols found in green plant cells. Wild plants tend to exhibit great variation in their content of aromatic compounds due to environmental and genetic differences. A recent study has showed that fertilization regimes may alter antioxidant activity of cultivated medicinal plants when compared with the antioxidant activity of wild medicinal plants. More specifically, increasing the amount of fertilizer increased the antioxidant activity of the powders prepared from cultivated *Teucrium polium*. In contrast, increasing the amount of fertilizer decreased the antioxidant activity of powders prepared from cultivated *Eryngium creticum*. Although, fertilization regimes influence

the antioxidant potential, this finding should not be interpreted to suggest that other therapeutically beneficial plant ingredients may not be affected in the same manner. These findings indicate that the indices of plant growth cannot be solely used as parameters of successful growth of cultivated plants.

18.4.2 Selection of Plants

According to WHO guidelines (WHO, 2003), the selected medicinal plant should be taxonomically same as described in the national pharmacopoeia or other related scientific documents. New introduced plant should be properly identified and documented before being selected and collected for medicinal applications. Here, the botanical identity, scientific name including genus, species, subspecies or variety, and family of the new plant should be documented. If available, the local name should also be verified. For instance, we have observed in our ethnobotanical surveys that the same plant may have many different names even in a small geographical region such as Palestine. In addition, complete taxonomical identification is an important factor during selection as taxonomy of the plant species can play an important role in their biological activity. Information regarding environmental conditions, such as soil, climate, and vegetation at the collection site, should be obtained. In addition, data regarding geographical distribution of the plant, its abundance, whether it is threatened or endangered, shrub/fast growing tree and other characteristics should also be documented. It is of immense importance that a voucher specimen be deposited in national or regional agencies for authentication and further consultation by other researchers.

It is important to mention that there are certain differences in approaches when selecting plants for an industrial or a rural application. The rural community requires medicinal plants for their primary health care and hence focuses more on selection of plants for treatment of common diseases such as diabetes, diarrhea, and wound infections. On the other hand, pharmaceutical industry requires medicinal plants for formulation of herbal drugs for commercial gain and hence focuses more on urban problems such as metabolic disorders, chronic diseases, and multidrug resistance among infectious pathogens. Whether for rural community or for industrial application the selection of plant should be based on its safety (acceptable side effects) and effectiveness in prevention and/or treatment of a given pathological condition. From the rural perspective, since the understanding of disease in terms of causative agents is not possible in the community, it is important that the plant formulation should address the common causative agents resulting in a given symptom, for example, diarrhea which is caused by various infectious microbes. The plants selected for uses by rural communities, should be able to control the respective diseases or else at least act as a stop gap until further medical aid becomes available. Moreover, these plants should be easily available so that the users of these medications can become self-reliant.

In general, the selection of medicinal plants can follow four main routes: random, ethnobotanical and ethnopharmacological, traditional knowledge obtained from ancient medical systems, and ecological search.

Random Selection Followed by Chemical Screening: These so-called phytochemical screening approaches have been used in the past and are currently pursued mainly

in the developing countries. The used test systems are simple to perform, but false-positive and false-negative tests often render results difficult to assess. More important, it is usually impossible to relate one class of herbal-derived agents to specific biological targets; for example, the alkaloids or flavonoids produce a vast array of biological effects that are usually not predictable in advance.

Activity-Based Random Selection: Safety and efficacy of plant extracts are evaluated both in experimental animals and *in vitro* using cultured cells. During the past four decades, thousands of plant species have been screened for their therapeutic effects, including antibacterial, antidiabetic, antifertility, antifungal, antihypercholesteremic, anti-inflammatory, antitumor, cardiovascular, central nervous system depressant, cytotoxicity, diuretic, and others.

Random search is extremely laborious and the success rate could be very low. Nevertheless, important drugs such as taxol, derivatives of camptothecin and homoharringtonine have been discovered by the National Cancer Institute (NCI) in collaborations with the United States Department of Agriculture (USDA) using this method.

Ethnobotanical and Ethnopharmacological Studies: Ethnobotanical and ethnopharmacological approach uses information obtained from ethnobotanical survey such as traditional medical uses, preparation techniques, geographical distribution of the plant, its abundance, whether it is threatened or endangered, shrub/fast growing tree, easily cultivable, easily identifiable (with minimum varieties), and so on. Information such as the season of collection, parts that are used and whether those parts are seasonal/replenishable and if there is any reported toxicity, are also required. The information can be obtained from traditional medical practitioners and other people such as village elders who are traditional users of medicinal plants. It is highly recommended to carry out the ethnobotanical surveys by a team of botanists, traditional healers, and medical practitioners. So that the traditional healers would identify medicinal plants for treatment of different diseases, the botanist can carry out appropriate taxonomical and botanical characterization of these medicinal plants, whereas the medical practitioners would help in proper identification of potential medical application and help in evaluating whether a herbal remedy is curative or is alleviating the symptoms only or whether it is a placebo effect. However, information obtained from the ethnobotanical surveys is not always reliable. It is possible that people may quote a particular plant more frequently since it is easily available, easily recognizable, or resembles a certain disease feature. People may also quote plants about which they have gained information from personal communication, books, from the media, or from the Internet. In addition, publications on medicinal plants are often compilations from other texts and seldom from personal experience, making evaluation difficult.

Knowledge Obtained from Ancient Medical Systems: A huge amount of medical information is available from ancient scripts of different systems of medicines such as the Greco-Arab and Islamic medicine, Chinese, and Ayurvedic medicine. Herbal preparations, based on these ancient systems, are still popular today because of their prolonged and apparently safe use usually is considered as an evidence of their safety and since they are multicomponent preparations. Arab–Islamic scholars introduced

hundreds of medicinal plants. They also developed a large and complex medical literature exploring and synthesizing the theory and practice of medicine and botany with highly accurate precision and details. They introduced many new ideas and upgraded the knowledge about herbs and their potential medical application and safety. As discussed in details in Chapter 16, this expertise was the result of the following factors:

1. Knowledge developed in the pre-Islamic period based on a long history of trial and error;
2. Islamic teachings. These include plants mentioned in the Holy Quran or in the *Hadith* of the Prophet Mohammad (PBUH) and are considered to have a high medicinal potential (Chapters 8 and 17). For instance, black seeds (*Nigella sativa*) can be considered effective for either food consumption or as a preventive of high blood pressure and heart diseases. The oil as well as the fruits of olive tree (*Olea europaea*) are important sources of food nutrition and for their use as an antioxidant or diabetes preventive in many societies. Other plants include dates, figs, and pomegranate;
3. Foreign sources, which became available to Arab–Islamic scholars after the translation of Greek and Persian scripts;
4. Arab–Islamic sources. Like in other fields of science, Arab–Muslim physicians developed the first scientific methods for the field of medicine. This included the introduction of experimentation, quantification, experimental medicine, evidence-based medicine, clinical trials, dissection, animal testing, human experimentation, and postmortem autopsy by Muslim physicians. Likewise, hospitals in the Arab–Islamic world featured the first drug tests, drug purity regulations, and competency tests for doctors. Therefore, Arab–Muslim scholars were not guided by a long history of trial and error, but mainly by scientific methods, which has led to production of "evidence-based medication."

The correlation of particular herbs with the amelioration and/or complete curing of certain diseases is one of the main factors that led to the identification on new potential medicine. For instance, morphological features of the herb, including size, shape, color, texture, and taste were considered as important criteria in their selection for therapeutic purposes. For instance, seeds with kidney shape are used for treating kidney stones, for example, *Alhagi maurorum* and *Astragalus macrocarpus*. Roots shape similar to human body or fruits resemble human testis are used traditionally for stimulating sexual desire or treating sexual weakness: *Mandragora autumnalis* and *A. macrocarpus*. The doctrine of signatures is reflected in some of the uses of certain herbs, for example, the yellow decoction obtained from leaves of *Rhamnus alaternus* and the yellow juice from the fruits of *Ecbalium elaterium* are used for treating jaundice and liver diseases. For several herbs, the plant's common name in Arabic refers to its use. This is the case for *Glaucium oxylobum*, *Hypericum lanuginosum*, *Mercurialis annua*, and *Ceterach officinarum*. All four plants are called "the wounds' herbs," since they are used for treating external wounds. The exchange of people and

culture between the Middle East, Europe, and the Far East has brought with it the exchange of information, so that a given herb is often used similarly in among these areas, for example, *Ammi visnaga* for kidney stones; *Matricaria aurea* for stomach aches; *Malva nicaensis* for wounds.

There is no doubt that Greco-Arab and Islamic medicine, Ayurveda, Kampo, and traditional Chinese medicine have flourished as systems of medicine in use for thousands of years. However, while using the ancient medical scripts, one must consider the fact that the plants may have evolved over a period of time resulting in changes in their phytochemical composition and hence their medicinal properties and therefore validation is required. Nevertheless, the success rates of the traditional-based approaches are substantially higher than those of random screening since the continued use of crude preparations are, in fact, comparable to small-scale clinical trials.

Zoopharmacognosy: pharmacologically active plants can also be identified using an ecological approach. The absence of predation in areas infested with herbivores, for example, can indicate the presence of toxic compounds. Selection can also be based on an approach called zoopharmacognosy, a variation from the ecological approach. This method proposes the selection of plant species regularly ingested by animals, which instinctively identifies plants with healing properties. The major antithrombotic drugs used today are all derived from veterinary practice in Canada in the 1920s when cattle were suffering from stomach hemorrhaging from eating moldy hay containing sweet clover (*Melilotus officinalis*). Freshly cut hay contains sweet smelling coumarins, many of which act as anticoagulants. Dicoumarol was the major drug synthesized as a result of these observations. It was first marketed by Abbot and Lilly in 1942. Furthermore, a number of species of monkeys and apes have been observed to repeatedly consume particular botanical species containing chemical components that act as analgesic, antimicrobial, anti-inflammatory, immunostimulant, antidiarrheals, digestive aids, and fertility regulators. Recent research on this intriguing subject reports that monkeys, gorillas, chimpanzees, and humans select some of the same plants for the management of similar diseases, injuries, and other health problems.

18.4.3 Collection of Medicinal Plants

Good collection practices of WHO guidelines (WHO, 2003) are necessary for the long-term survival of wild populations and their habitats. Medicinal plant materials should be collected in the proper season so as to ensure the best possible quality (optimal concentrations of active compounds) of both the starting material as well as the finished product. Medicinal plants may be collected from wild or cultivated plants and the task should be undertaken by skilled workers in a highly scientific manner (accurate identification). The season, time of the day at which each drug is collected is very important, since the concentration and sometimes the nature of the active constituents is variable throughout the year or even at different times during the day. Seasonal variations can affect the production levels of secondary metabolites (active compounds) by the plants and thus its medical activity and safety. In general,

maximum concentrations of chemical constituents occur at the time of flowering which then decline at the beginning of the fruiting stage. The time of collection also depends on the plant part to be used since it is well known that depending on the plant species the level of biologically active constituents can vary in different parts at different stages of the plant growth and development. Climatic and environmental conditions, for example, light, rainfall, and temperature (including daytime and nighttime temperature differences) also affect the physical, chemical, and biological qualities of medicinal plants. The water and temperature stress related increase in the content of active constituents such as the total phenolic compounds in *Hypericum brasiliense*. Hence, the best time of collection should be fixed according to the levels of the biologically active constituents rather than the vegetative yield. Information such as the correct plant parts that are used (roots, leaves, fruits, etc.) and optimal collection time point should be obtained. It is necessary that the collection practices employed should be nondestructive. For example, while collecting roots, the main root should not be cut or dug up and while collecting bark, the tree should not be girdled or completely stripped of its bark. Parts that are not required or are decomposed of and any foreign matter such as soil or toxic weeds should be removed during collection. Collection of medicinal plants should not be done from places that are contaminated or close to sources of environmental contamination such as areas where high levels of pesticides or other possible contaminants are used or found, for example, roadsides, drainages, mine tailings, garbage dumps, and industrial facilities which may produce toxic chemicals or active pastures that may lead to microbial contamination. Quality control ensures that the plant material is not contaminated with microbes, pesticides, heavy metals, or other toxic agents and that the final product is of consistent high standard. Handling of the plant material such as cleaning, drying, and storage should be carried out by trained personnel. Finally, rapid and safe transportation of the collected plant materials should be arranged in advance.

18.4.4 Processing and Drying of Plant Materials

Several steps need to be performed on the collected plant material before their medical application. These include sorting to eliminate undesirable materials, washing to remove soil and contaminants, and drying. In addition, the plant materials should be protected from conditions that may cause deterioration such as rain, moistures, and heat during or after collection till the processing begins. The plant material that needs to be used fresh should be delivered as quickly as possible to the processing facility to prevent microbial fermentation or thermal degradation. All processed materials should be protected from contamination and decomposition as well as from insects, rodents, birds, and other pests. Specific processing methods are often required, to reduce drying time, to detoxify the inherent toxic constituents, to reduce side effects, or to enhance pharmacological properties. For instance, drying conditions (temperatures and humidity) may affect the pharmacological properties of the resulting plant materials. Shade drying is the preferred method used in the Greco-Arab and Islamic medicine, since it can maintain or minimize loss of color of leaves and flowers and the lower temperatures can prevent the loss of volatile substances in the plant materials.

However, additional modern drying methods are used currently to dry the plant materials. These include drying in ovens/rooms and solar dryers, by indirect fire, baking, microwave, lyophilization, or by infrared. Depending on the plant part used additional processing steps have to performed, including peeling the skins of roots and rhizomes, boiling in water, steaming, soaking, pickling, distillation, fermentation, and roasting.

18.4.5 Preparation of Plant Materials

As described in Chapter 16, several techniques were developed by Arab–Muslim scholars that are still used currently by traditional herbalists to obtain the beneficial phytochemical components from the selected medicinal plant. Adherence to the original method of preparation as mentioned in the ancient texts is necessary depending on the form of preparation or the plant used as they may hold important information for obtaining an effective herbal preparation. The majority of herbal-based remedies are consumed orally in the form of tea or other drink containing either diluted or concentrated ingredients. The tea is generally produced from the various parts of the herbs through infusion or as decoctions. Heating a raw plant in a fluid medium not only aids the extraction and concentration of curative substances, it also acts to eliminate poisons and impurities prior to consumption. Since there is no sharp dividing line separating food and drugs, it is not surprising that various edible plant parts have been used as sources of both nutrition and medicine in different cultures. The seeds of *N. sativa*, as an example, could be considered as either a meal for food consumption or as a preventive of high blood pressure and heart diseases. The oil as well as the fruits of *O. europaea* are used for important food nutrition and as antioxidants or diabetes preventives in many societies. Some plant species are used for treating several types of pathological conditions, for example, *T. polium* (L.) is a perennial shrub commonly used in Greco-Arab and Islamic medicine as antidiabetic, anti-inflammatory, antiulcer, hypotensive, and liver diseases. Phytochemical assessments indicate that this herb contains various compounds such as flavonoids, iridoids, and crisiol. *T. polium* crude extract significantly decreased (64%) the blood glucose concentration in treated animals and enhanced insulin secretion (135%) after a single dose of plant extract. Other administration methods include the inhalation of aerosols (e.g., *P. anisum*), essential oils (e.g., *J. fruticans*), and vaporized plant juices or teas, as well as absorption to the skin (e.g., *Portulaca oleracea*). In making a poultice, for example, plant parts are grounded or crushed and combined with hot water or other liquids to create a medicinal paste or plaster. The resulting mixture is placed directly on wounds, bruises, arthritic joints, burns, insect and animal bites, rashes, swellings, wrinkles, or dermatological irritations (e.g., *Citrullus colocynthis*, *E. creticum*).

18.4.6 Storage of Plant Materials

Storage of the dried plant materials or the prepared plant extracts can also affect the pharmacological quality of plant materials and hence it is necessary to maintain appropriate storage conditions so as to increase their shelf-life. In general, it is

recommended to store the plant product in dried form since preparations such as decoctions/infusions can only be stored for a few days. Dried plant materials can be stored in whole, crushed, or powdered forms in conditions that include use of cloth bags, clear glass bottles and plastic. Plant materials that are used fresh should be stored under refrigeration, in jars or sandboxes, or using enzymatic or other appropriate conservation methods. However, they should be used as quickly as possible to avoid microbial contamination and deterioration caused by environmental factors (e.g., humidity). Shelf-life of plant material is usually ignored due to the general belief that the plant materials do not have an expiry date, however, dried plant materials usually retain their activity for about six months only. Different types of plastics can be used which prevent absorption of moisture and oxidation of the plant material by preventing the exchange of gases to increase the shelf-life of the plant material.

18.4.7 Phytochemical Studies

Phytochemical analysis is necessary for standardization, assessment of pharmacological significance, determination of optimal concentrations, and for preserving therapeutic activities. Identification and chemical analysis of active compounds can be conducted by obtaining a chemical fingerprint/profile or through bioactivity guided fractionation. Chemical fingerprints through chromatographic techniques, for example, thin layer chromatography (TLC) and high-performance liquid chromatography (HPLC) are the most commonly used methods for obtaining chemical fingerprints and identification of the crude plant extracts.

There are several possibilities that may arise while using these techniques for standardizing the crude extracts. It is possible that the plant material collected from the same plant in two different seasons can show different phytochemical fingerprints and therefore different pharmacological properties. Two plants with an identical taxonomy collected under same environmental conditions can show different phytochemical fingerprints but similar pharmacological effects. In such cases comparisons of the phytochemical profiles as an indicator of important ingredients can act as a shortcut for identifying the bioactive agent. Alternatively, DNA fingerprinting is another technique and seems to be of immense potential in identification of medicinal plants, particularly when profiling the genotypic differences. In addition to identifying these genetic variations, it can also aid in identification of germplasms of important or endangered plants for future cultivation or conservation. However, recent studies have also indicated at reduced biological activity with isolated active constituents compared to crude extracts. The efficacy of crude extracts may be due to the synergism between the different active constituents that may be present in the extract. In contrast to synthetic medicines, which are based upon single molecule, many herbal-derived drugs exert their pharmacological effects through the additive or synergistic action of several active compounds acting at single or multiple target sites associated with a physiological pathway. This synergistic or additive therapeutic effect can be beneficial by eliminating or reducing side effects associated with the predominance of a single active compound. This theme of multiple chemicals acting in an additive or synergistic manner likely has its origin in the functional role of

secondary products in promoting plant survival. For example, in the role of secondary products as defense chemicals, a mixture of chemicals having additive or synergistic effects at multiple target sites would not only ensure effectiveness against a wide range of herbivores or pathogens but would also decrease the chances of these organisms developing resistance or adaptive responses.

18.5 CURRENT TRENDS IN HERBAL-BASED DRUG DISCOVERY

Herbal-derived compounds can be used as new chemical entities (NCEs) to produce bioactive compounds of novel or known structures as lead compounds for semi-synthesis of patentable entities of higher efficacy and/or lower toxicity. Hence, herbal-derived compounds provide a starting point for new synthetic agents, with modified structures and often with multiple stereocenters that can be challenging synthetically. Many structural features common to plant secondary metabolites (e.g., aromatic rings, complex ring systems, degree of molecule saturation, and chiral centers) have been shown to be highly relevant to drug discovery efforts. For example, metformin, oxycodon, taxotere, teniposide, and amiodarone, which are based, respectively, on galegine, morphine, taxol, podophyllotoxin, and khellin (Figure 18.1). An analysis of the sources of new drugs over the period 1981–2002 indicates that about 40% of the 877 NCEs are synthetic, 33% are of natural origin, 16.4% correspond to synthetic molecules containing herbal-derived functional groups, and 12% are actually modeled on a natural product inhibitor of the molecular target of interest, or mimic (i.e., competitively inhibit) the endogenous substrate of the active site, such as ATP. In the area of antimicrobial and antiviral compounds, close to 70% are herbal-derived or modified, while in the cancer treatment area 67% are herbal-derived (e.g., taxol). The following modern techniques are applied on herbal-derived new chemical entities to produce bioactive compounds of higher efficacy and/or lower toxicity.

Combinatorial Biosynthesis: A process to prepare large sets of organic compounds by combining sets of building blocks. For instance, bacterial aromatic polyketides constitute a large number of structurally diverse natural products exhibiting a broad range of biological activities (e.g., tetracyclines, doxorubicin, and avermectin). Advances in the understanding of polyketide biosynthesis have led to the identification of multifunctional polyketide synthase enzymes (PKSs) responsible for the construction of polyketides of defined chain lengths. A recent example is an efficient method for scale-up production of epothilone D, currently undergoing clinical trials as a potential anticancer agent. Epothilone D is the most active of the epothilone series isolated from *Sorangium cellulosum* (a myxobacterium) and is the des-epoxy precursor of epothilone B.

Total Synthesis of Natural Products: The total synthesis of complex natural products has long challenged synthetic chemists worldwide, and has led to the discovery of many novel synthetic reactions and chiral catalytic reactions. Recent trends have focused on the synthesis and modification of agents that are difficult to purify in sufficient quantities for drug development. In the process of total synthesis, it is often possible to identify the pharmacophore (the essential features of the molecule

necessary for activity), and, in some instances, this has led to the synthesis of simpler analogues having similar or better activity. For instance, the cardiovascular activity in natural products led to the isolation of reserpine over five decades ago. Reserpine, obtained from the roots of the Indian plant *R. serpentina*, was brought to the attention of the modern Western world in 1949 by Vakil who described its use in hypertension. In rapid succession between 1952 and 1958, reserpine was isolated from *Rauvolfia*, its structure determined and its total synthesis achieved. A second discovery is the synthesis of the epothilones, which has permitted the preparation of a large number of designed analogues and detailed structure–activity studies. These studies have identified desirable modifications, which might eventually lead to more suitable candidates for drug development, but thus far none of the analogues has been reported to surpass epothilone B in its potency against cancer cells.

Combinatorial Chemistry and Natural Products: The analysis of the human genome as well as of the genomes of pathogenic microbes and parasites enables the determination of the structures of many of the proteins associated with pathological processes. With the development of these new molecular targets, there is an increasing demand for novel molecular diversity for screening. Combinatorial chemistry is a technique originally developed for the synthesis of large chemical libraries for high-throughput screening against such targets. This has led to the development of robotic systems and tools, such as solid-phase synthesis and new immobilization strategies involving novel resins, reagents, and linkers, which have permitted high-throughput parallel approaches to the synthesis of very large libraries of millions of compounds. Over the past few years, detailed analyses of active natural product skeletons have led to the identification of relatively simple key precursor molecules, which form the building blocks for use in combinatorial synthetic schemes that have produced numbers of potent agents. The combinatorial approach, using an active natural product as the central scaffold, can also be applied to the generation of large numbers of analogues for structure–activity studies, the so-called parallel synthetic approach.

Targeting Natural Products: A recurring liability of natural products, at least in the area of cancer chemotherapy, is that although many are generally very potent, they have limited solubility in aqueous solvents and exhibit narrow therapeutic indices. These factors have resulted in the demise of a number of pure natural products, such as bruceantin and maytansine, as promising leads. An alternative approach to utilizing such agents is to investigate their potential as warheads attached to monoclonal antibodies specifically targeted to epitopes on tumors of interest. The first FDA-approved, natural product-based example is Mylotarg®, using the microbial metabolite, calicheamicin, as the warhead. Another conjugate, huN901–DM1, produced by the coupling of DM1, a cytotoxic agent derived from maytansine, with a monoclonal antibody targeting small-cell lung cancer cells, is being developed for the treatment of small-cell lung cancer. The same maytansinoid derivative linked to a different antibody directed against the *muc*1 epitope in gastric cancers is currently in clinical trials in the United States.

Another novel strategy for delivery of anticancer drugs to the tumor site involves the coupling of cytotoxins to water-soluble copolymers. Coupling of doxorubicin to an *N*-(2-hydroxypropyl)-methacrylamide (HPMA) copolymer produces the construct

known as PK1, which is currently in clinical trials. Addition of a sugar to the polymer enables specific targeting for the hepatocyte, and this construct PK2 is currently in clinical trials. Another strategy of interest is the use of antibodies as vectors for enzymes capable of activating a nontoxic drug precursor (prodrug) to a potent cytotoxic moiety. After injection and localization of an antibody–enzyme conjugate at the tumor, a nontoxic prodrug is administered, and while remaining innocuous to the normal tissues, it is converted to the cytotoxin by the enzyme localized at the tumor site. This approach, called antibody-directed enzyme prodrug therapy, provides further potential for the application of potent natural products to cancer treatment [2–5].

18.6 BIOMEDICAL STUDIES

As described in Chapters 11, 12, 14, and 16, biological screening is necessary to provide a scientific basis for validating the traditional utilization of medicinal plants. Before a new drug, surgical procedure, or therapy becomes available to the public; it must pass through a rigorous testing process and be evaluated by national and international regulatory health authorities, such as the FDA. These studies include information on the safety of using the drug in clinical trials, through preclinical pharmacological and toxicity studies *in vivo* and *in vitro*, and a description of the chemical and manufacturing processes. A great number of screening programmes are ongoing worldwide for new plant-based drugs. Preclinical pharmacological studies and randomized clinical trials form an important part of the biological screening of medicinal plants. Preclinical studies usually serve to verify the data on mechanisms of action reported in animals or humans. However, a pharmacological effect observed *in vitro* or *in vivo* test systems, for both safety and efficacy needs to be reconfirmed by clinical studies and the information obtained from the preclinical studies can form the basis for further clinical trials. Clinical investigations are generally conducted in three phases as described under Section 14.7. Phase I studies typically consist of 20–80 people and are used to determine the metabolism and pharmacology of the drug in humans so that the design of Phase II can be optimized. Phase II studies are designed to evaluate the effectiveness of the drug and determine short-term side effects and risks; Phase II typically consist of several hundred people. Phase III studies are designed to assess safety and effectiveness, evaluate the overall risk and benefit of the drug, and determine the drug's labeling; Phase III studies usually require several hundred to several thousand people [17–25].

18.6.1 Preclinical Studies

Preclinical testing helps in collection of important efficacy and safety data before clinical trials can be carried out. Preclinical evaluation and authentication of medicinal plants involves documentation and testing of their pharmacological efficacy *in vitro* and *in vivo* systems and studies of toxicology, specificity, biopharmaceutical properties, drug interactions, as well as possible mechanism of action at cellular and molecular levels. The advantage of these studies is that one can easily

study and compare the efficacy of different plants in a cost effective manner and design rational drug combinations. This requires proper designing of bioassays that have significant impacts on the outcome of the overall drug discovery process. The selected bioassay should be able to mimic the *in vivo* situation as far as possible with high sensitivity and specificity. The basis for designing a screening bioassay is the identification of valid cellular and/or molecular target. An estimated 30–40% of experimental drugs fail due to an inappropriate target and hence it is important to develop new bioassays with newer and more specific targets. It is crucial to establish the role of the target in question in the cause or symptoms of a disease. Pharmacological manipulation of the target should consistently lead to desired phenotypic changes. The desired changes must also be reproducible in at least one relevant animal model. Emphasis must be placed on assessment of bioassay quality and validation of the parameters being used. Assay formats employed in screening can be either cell-based or molecular/biochemical. However, the logistics of cell-based assays are more challenging than with molecular/biochemical tests due to requirement of significant investments in cell culture technique (Chapters 11 and 13).

The current trend in drug discovery is clearly shifting toward cell-based assays. Cell-based screening has multiple advantages. It can provide biologically more relevant data on the nature of the activity. Furthermore, information regarding cellular membrane permeability and cytotoxicity can also be obtained. Unfortunately, when screening plants for infectious diseases the assay system is often limited to testing for antimicrobial activity. However, this approach is not always appropriate. Plants can exhibit their efficacy against infectious diseases by mechanisms other than antimicrobial activity.

Despite the great advantages and necessity of preclinical studies, they are accompanied with several shortcomings: (1) suitable pharmacological models have not yet been developed for many common diseases with unknown, or multi-factorial origins. In addition, extrapolation of *in vitro* and animal models to humans is difficult. In this regard, Avicenna stresses that only clinical studies in humans can provide the final proof of the efficacy and toxicity (e.g., possible side effects): "*The experimentation must be done with the human body, for testing a drug on a lion or a horse might not prove anything about its effect on man*" [1–13]. (2) Some phytochemicals that show good activity *in vitro* may be transformed *in vivo* into inactive metabolites. Alternatively, extracts may only show *in vivo* activity due to the metabolism of inactive compounds into active forms. (3) The pharmacological investigation of drug interactions in multicompound remedies is difficult due to the presence of constituents from several plants where some plants may show less specific activity and some plants may have been added to reduce the toxicity of the more therapeutically effective plants. (4) Some of the most common side effects are difficult to recognize in animal models, for example, nausea, nervousness, lethargy, heartburn, headache, depression, and stiffness.

18.6.2 Clinical Studies

As described in Chapter 14, clinical studies are necessary to confirm the pharmacological properties of herbal-based remedies before they can be integrated into

conventional medical practice. Well-established, randomized controlled clinical studies facilitate the national and international acceptance of herbal medicines. This would be especially true in case of some unrelated effects of therapy contributing to efficacy that may be difficult to measure preclinically. The general principles for the clinical studies that apply to conventional drugs should be followed when testing a new herbal-derived preparation, a new indication for an existing formulation, or a significantly different dosage form or route of administration (WHO, 2000). Well-recorded case reports can contribute toward useful information at such times and put forward new hypothesis and stimulate further study. However, double blind clinical trials may not be required when an extensive and detailed database of case studies is available. Such a database is especially important when a particular treatment is individualized. The methods and guidelines used for clinical trials of synthetic chemical drugs must be applied to herbal products even though the latter has a holistic approach to treatment. However, conventional concepts of clinical research design may be difficult to apply when using clinical research to evaluate various systems and practices of traditional medicine (WHO, 2000). This could be due to the fact that herbal remedies are individualized therapies and hence depend on the proficiency of medical practitioners. Clinical trials, in some cases, must be adapted to deal with the specifics of herbal medicines. Single-case studies, as per the theories and concepts of traditional medicine, for the evaluation of efficacy and randomization can allow for the individualization of treatments. Methods such as randomization and use of a placebo may not always be possible. The number of patients required for undertaking clinical trial of medicinal plants is large not only because the study design needs to be adequate and statistically appropriate, but also to cater to the control, confounders and placebo groups to provide sufficient evidence for judging efficacy of the test plant.

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CHAPTER 19

Herbal Remedies: Use and Demographic and Regulatory Issues

19.1 INTRODUCTION

Herbal-based preparations represented about 80% of all drugs in use by the middle of the nineteenth century. At the turn of the century, synthetic drugs dominated as a result of the rapid development in synthetic chemistry and pharmaceutical industry. This expansion of synthetic medicinal chemistry caused the proportion of new drugs based on natural products to drop to about 50%. Today, only about 25% of market drugs are plant based. Nevertheless, herbal-based medicines not only retained their importance, but their popularity has increased worldwide during the past three decades, probably stimulated by the belief that these remedies are safe (see Chapter 13), the sharp increases in prices of synthetic drugs, restricted access to physicians imposed by managed care, and media reports of certain adverse effects of prescription drugs. The revival of the interest in natural product-based medicines at a global level has been so dramatic that the sale of herbal products is now worth over $100 billion per year. In 2008, $4.8 billion was spent in the United States on herbal-based remedies. Germany is the leading country in Europe followed by France in the consumption of herbal medicines. Around 80% of German physicians prescribe herbs. St. John's wort, and *Ginkgo* are popular medicinal plants in Europe. The cost of about 40% of the herbal remedies prescribed by German physicians is covered by the health care system. In the United States, a large center of complimentary and alternate medicine has been established recently at the National Institutes of Health (NIH), with heavy funding and more recently, the NIH has started to sponsor research projects on large clinical trials of herbal-based medicines such as, *St. John's wort* and *Ginkgo*.

In addition, there is an increasing trend in the United States and Canada as well as in Europe to incorporate herbal-derived remedies as an essential component in the medical curriculum.

In line with the revival of interest in herbal-based remedies known from the ancient medical systems, such as Greco-Arab, Ayurvedic, and Chinese, there is also greater

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research activity on these medical systems particularly on the biological and molecular aspects of medicinal plants. Furthermore, conventional medicine is now beginning to accept the use of herbal remedies once their efficacy and safety are scientifically confirmed. Indeed, today many pharmacological classes of drugs include a natural product prototype. Antibiotics (e.g., penicillin, tetracycline, erythromycin), antiparasitics (e.g., avermectin), antimalarials (e.g., quinine, artemisinin), lipid control agents (e.g., lovastatin and analogues), immunosuppressants for organ transplants (e.g., cyclosporine, rapamycins) and anticancer drugs (e.g., taxol, doxorubicin) are a few examples of herbal-derived drugs that have revolutionized medicine. Most of these drugs were discovered through the study of accumulated traditional medical knowledge and some of these could not be substituted despite great progress in synthetic chemistry. Aspirin, an acetyl salt of salicylic acid isolated from Willow bark, is considered one of the most effective analgesic, antipyretic, and anti-inflammatory agents commonly used in conventional medicine. With the passage of time multiple therapeutic uses of aspirin have been emerged, with most prevalent use as the antiplatelet/anticoagulant observed at the low dose to prevent further problems in patients who have already suffered from one heart attack. Another example of herbal-derived medicine is morphine, which is isolated from the opium poppy (*Papaver somniferum*) is one of the early molecules entered into conventional medicine and is the most widespread and effective painkiller. Indeed, the isolation of morphine from crude opium by Serturner in 1806 stimulated much widespread research on herbal drugs that Megendie was able to publish a medical formulary in 1821, which contained only pure chemical agents, hence laid the foundation for the use of pure compounds instead of medicinal plants and their extracts.

Cardiovascular research is one of the important areas in which herbal-based substances have contributed successfully. For example, Digitalis and the cardiac glycoside derived from the foxglove (*Digitalis purpurea*) represent a widely used group of clinically effective compounds that produce positive inotropic effect on the failing heart as well as having value in the treatment of atrial fibrillation. As a group they are unrivalled to date by any synthetic or semisynthetic substitutes even though they are among the most toxic group of clinically useful drugs and have unique mode of action with selective cardiotonic activity, without accompanying tachycardia. Reserpine, isolated from the roots of the Indian plant *Rauwolfia serpentina*, was brought to the attention of the modern Western world in 1949 by Vakil who described its use in hypertension; in rapid succession between 1952 and 1958, its structure determined, and its total synthesis achieved. Later on, reserpine was found to be a potent agent in treating depression and Parkinson's disease. These findings stimulated further investigation and evidence was found that reserpine depleted not only brain serotonin but also norepinephrine and dopamine. This was a major stimulus for continued research on transmitter amine defects in depression and Parkinson's disease. This in part laid the foundation for the development of many of the modern psychoactive drugs and stimulated a significant interaction between researchers and drug industry.

Herbal-based medicines, also referred to as botanicals or phytomedicines, are classified in many European countries as drugs, in United States they are sold as

dietary supplements, whereas in the Arab–Islamic world as well as China and India they are mostly sold over the counter without clear regulations. As discussed in Chapter 11, safety assessment of herbal products has often been neglected since prolonged and apparently safe use usually is considered as an evidence of its safety. Nevertheless, evidence of the toxicity of such products has accumulated. This is not surprising, since herbal products are complex mixtures of secondary metabolites, many of which are potentially toxic (e.g., hepatotoxic and nepherotoxic). Therefore, the widespread use and popularity of phytomedicines brought some concerns and fears over professionalism of practitioners, safety, quality, and efficacy of these products. In regard to safety, biomedical journals have reported serious side effects, particularly hepatotoxicity. Other cases including kidney, nervous system, blood, cardiovascular, and dermatologic effects, mutagenicity, and carcinogenicity have also been published in the biomedical literature. In some cases, adulteration, inappropriate formulation, or lack of understanding of plant and drug interactions or uses has led to adverse reactions that are life-threatening or lethal to patients. For example, the herbal supplement ephedra. Ephedrine, first isolated in 1887 from *Ephedra sinica*, is a plant long used in traditional to treat asthma and other respiratory problems. Ephedrine is added to many supplements marketed to reduce weight and to boost energy. These preparations act as powerful stimulants to both the cardiovascular and the central nervous systems, and their application has been associated with strokes, cardiac arrhythmias, seizures, acute psychosis, myocardial infarction, and death. By 2000, more than 1200 serious reactions related to ephedra have been reported to the FDA, though the actual number of events is undoubtedly far greater. Under current regulations there is no penalty for withholding reports of adverse effects. However, the Justice Department, at the FDA's request, has initiated a criminal investigation because of false statements that claim an absence of adverse effects. Canadian, but not U.S., health authorities have requested the voluntary recall of health products containing ephedra, noting its enhanced toxicity when combined with caffeine [1–4].

19.2 FACTORS THAT CONTRIBUTE TO SAFETY AWARENESS

In addition to the above-mentioned points, the following factors contribute to the current safety awareness of herbal-based remedies [1–9]:

Lack of Standardization. Quality, consistency in composition of active compounds and pharmacological properties are essential prerequisites for the safe and effective use of therapeutic agents. However, as discussed in Chapter 18, herbal-derived remedies rarely meet this standard, as a result of problems in identifying plants, genetic variability, variable growing conditions, differences in harvesting procedures and processing of extracts, and above all, the lack of information about active therapeutic agents. The use of chromatographic techniques and marker compounds to standardize herbal preparations promotes batch-to-batch consistency but does not ensure consistent therapeutic properties or stability.

Adulteration of Botanical Preparations. The use of synthetic pesticides during the last five decades has often been careless and indiscriminate, and has led to a number of well-known pathologic conditions. In fact, synthetic pesticides caused environmental contaminations with toxic residues in many regions worldwide, as well as side effects on nontargeted insects and other organisms, an increase in the number of pest species resistant to pesticides, and pest resurgence. Many accidents have occurred due to unsuitable storage conditions and high temperatures during the summer season in the Mediterranean as well as the mishandling of highly toxic synthetic pesticides, causing deaths and injuries. Pesticides may be introduced to plants in different forms such as direct application, residue absorption from water and soil biochemical processes. In addition to chemical contamination, medicinal plants collected from contaminated soils may contain pathologic microorganisms. Ayurvedic medications have been known to cause lead poisoning in children because of their contamination with lead as well as other heavy metals, such as arsenic and mercury. Contamination of crop and medicinal plant samples with organic chemicals is a pressing problem in many countries of Arab–Islamic world. Low contamination levels were detected in cucumbers and tomatoes in Palestine, Jordan, and Egypt. Elevated levels of contamination were detected in vegetables from Pakistan, Egypt, and in grapes from Jordan. Several poisonous plant food contamination cases were reported in Morocco, Egypt, Iraq, Saudi Arabia, Sudan, Syria, Jordan, UAE, Pakistan, and Yemen in the past years. Popular Egyptian foods such as nuts and seeds, cereal grains were found to be contaminated with aflatoxins. Approximately, a third of used medicinal plants were found to be contaminated with aflatoxin B1.

Interactions Between Herbs and Drugs. Active compound of herbal remedies can act through a variety of mechanisms to alter the pharmacokinetic action of concomitantly taken conventional drugs. Herbal-based remedies are often mixtures of more than one active ingredient. The multitude of active compounds obviously increases the likelihood of herb–drug interactions, theoretically to a higher level than drug–drug interactions, if only because conventional drugs usually contain single chemical compound. Case reports and clinical studies have highlighted the existence of a number of clinically important interactions, although cause-and-effect relationships have not always been established.

The clinical importance of herb–drug interactions depends on many factors associated with the active compound of particular herb, drug, and patient. For example, systems such as the cytochrome P450 (CYP) may be particularly vulnerable to modulation by the multiple active constituents of herbs, as it is well known that the CYPs are subject to induction and inhibition by exposure to a wide variety of xenobiotics. Using *in vitro* and *in vivo* test systems, many herbs and their purified active compounds have been identified as substrates, inhibitors, and/or inducers of various CYP enzymes. St. John's wort, for example, induces the cytochrome P450 isozyme CYP3A4 and intestinal P-glycoprotein, accelerating the metabolic degradation of many drugs, including cyclosporine, antiretroviral agents, digoxin, and warfarin. Serious adverse effects have been reported when the addition of St. John's wort caused serum levels of cyclosporine and antiretroviral agents to fall to

subtherapeutic levels. St. John's wort also contains ingredients that inhibit CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Many other common medicinal herbs also exhibited inducing or inhibiting effects on the CYP system, with the latter being competitive, noncompetitive, or mechanism based. It appears that the regulation of CYPs by herbal products is complex, depending on the herb type, their administration dose and route, the target organ and species. Due to the difficulties in identifying the active compound responsible for the modulation of CYP enzymes, prediction of herb–drug metabolic interactions is difficult.

The extent of herb–drug interactions is unclear, but the potential magnitude of this problem is suggested by a recent survey of medication use in the United States indicate that 16% of persons taking prescription drugs also took an herbal-based medicines or supplement preparation. Thus, many people in the United States unknowingly risk therapeutic failure or adverse effects caused by herb–drug interactions; this is especially true of older people who take multiple medicines for chronic diseases.

Dosage of Phytochemicals. Herbal remedies, like synthetic drugs, can be therapeutic in one dose and toxic at another. Dose is defined as the amount of chemical that comes into contact with the body or gets inside the body, whereas exposure is defined as the amount of chemical that is directly available to the body. Exposure includes both the concentration of the chemical in the media and the length of time such chemical is available to the body (concentration $\times$ time). As aforementioned, the concentration of active ingredients and other chemicals in plants varies by the parts of the plant harvested and sold; the maturity of the plant at the time of harvest; the time of year during harvest; geography and soil conditions; soil composition and its contaminants; and year-to-year variations in soil acidity, water, weather conditions, and other growth factors. Therefore, the actual dose of active ingredients being consumed is often variable, unpredictable, or simply unknown. Dosage-variation has larger effects on children due to their smaller size and different capacity for detoxifying chemicals.

Lack of Reporting of Adverse Events. Although, the FDA maintains surveillance of drugs by requiring prompt reports from manufacturers of all adverse effects brought to their attention, it is estimated that only 10% of serious adverse effects associated with the use of prescription drugs are forwarded to the FDA. Neither preclinical studies nor premarketing safety testing are required for dietary supplements. Furthermore, there is no mandatory requirement for manufacturers of supplements to record, investigate, or forward to the FDA reports of adverse effects they might receive. Although some side effects to herbal remedies are acute and symptomatic, others, such as renal failure and cancer, have a delayed and gradual onset. Furthermore, the relation of the prior consumption of an herbal remedy to a medical problem with delayed onset may not be readily apparent. The limited reporting of adverse events to the FDA has generated concern at the level of the federal Office of the Inspector General. Furthermore, the FDA is often unable to investigate the reports it does receive, either because the consumer's identity and address cannot be obtained

or because the ingredients in the supplement and the identity and address of the manufacturer are unknown. The Inspector General's report estimates that less than 1% of side effects caused by dietary supplements, including herbs, are reported to FDA and only a fraction of these are adequately investigated.

Taken together, in order to regulate the production and sales of herbal products at both national and international levels the following points must be implemented. First, details of all producers should be registered. Health authorities are currently severely hampered in its efforts to investigate the adverse effects of dietary supplements by the lack of information about manufacturers and distributors. Second, the extension of good manufacturing practices (GMP) to manufacturers of herbal products can help preventing adulteration and improving the standardization of marketed herbal remedies. Third, the manufacturers of herbal remedies should bear full responsibility for ensuring the safety of their products. Fourth, the manufacturers of dietary supplements should be required to report all adverse effects promptly to the health authorities. This essential element of postmarketing surveillance is required for all prescription drugs and some over-the-counter drugs. Fifth, the labels of dietary supplements should contain a list of ingredients that identifies herbs by their botanical and common names. Information about possible adverse effects, including the potential for herb–drug interactions, should be included.

19.3 WHO GUIDELINES FOR THE ASSESSMENT OF HERBAL MEDICINES

At its 34th meeting in 1991 WHO published the "Guidelines for the Assessment of Herbal Medicines" in recognition of the worldwide increasing popularity in the use of herbal-based preparations in both allopathic and traditional medicine. These guidelines define criteria for the assessment of the safety, efficacy, and quality (levels of active compounds) of herbal-based medicines, and thereby assist national regulatory authorities, scientific organizations, and manufacturers in undertaking an assessment of the documentation/submissions/dossiers on such preparations. These guidelines also call for the recognition that long-term traditional use of herbal-based products as a presumption of safety unless contradicted by modern scientific research (Figure 19.1) [10–16].

Safety. According to WHO guidelines, a guiding principle should be that if the product has been traditionally used without demonstrated toxic effects, no specific regulatory action should be undertaken unless new evidence demands a revised risk-assessment. As a basic rule, documentation of a long-term of use should be taken into consideration when safety is being assessed. This means that, when there are no detailed toxicological studies, documented experience on long-term use without evidence of safety problems should form the basis of the risk assessment. However, even in cases of long-used drugs, chronic toxicological risks may have occurred, but may not have been recognized. If available, the period of use, the health disorders treated, the number of users, and the countries with experience should be specified. If a

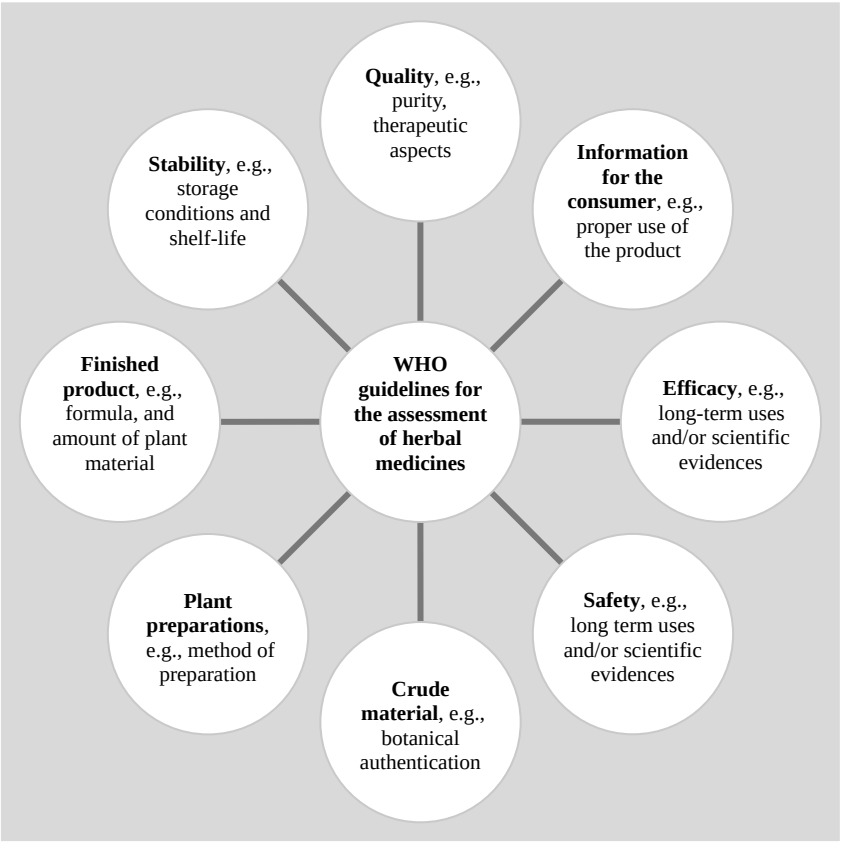

FIGURE 19.1 WHO guidelines for the assessment of herbal medicines. At its 34 meeting in 1991 World Health Organization (WHO) published the "Guidelines for the Assessment of Herbal Medicines" in recognition of the worldwide increasing popularity in the use of herbal-based preparations in both allopathic and traditional medicine. These guidelines represent criteria for the assessment of the safety, efficacy, and quality of herbal-based medicines. These guidelines also call for the recognition that long-term traditional use of herbal-based products as a presumption of safety unless contradicted by modern scientific research.

toxicological risk is known, toxicity data have to be submitted. Risk assessment, whether it is dose independent, or whether it is a function of dose, should be documented. In the second instance, the dosage specification must be an important part of the risk assessment. An explanation of the risks should be given, if possible. The potential for misuse, abuse, or dependence has to be documented. If long-term traditional use cannot be documented, or doubts on safety exist, toxicity data should be submitted [16].

Efficacy. Regarding establishing efficacy, WHO guidelines state: The indication(s) for the use of the medicine should be specified. In the case of traditional medicines, the

requirements for proof of efficacy shall depend on the kind of indication. For treatment of simpler diseases and for nonspecific indications, some relaxation is justified in the requirements for proof of efficacy, taking into account the extent of traditional use; the same considerations apply to prophylactic use. Experience with individual cases recorded in reports from physicians, traditional health practitioners, or treated patients should be taken into account. Where traditional use has not been established, appropriate clinical evidence should be taken into account (WHO, 1991).

Product Information for the Consumer. Product labels and package inserts should be understandable to the consumer or patient. The package information should include all necessary information on the proper use of the product.

Promotion. Advertisements and other promotional material directed to health personnel and the general public should be fully consistent with the approved package information.

Assessment of Quality. WHO guidelines also call for the establishment of monographs to determine the identity, quality, and therapeutic information on herbal medicines. WHO monographs contain standards for determining the identity and purity of herbal drugs as well as detailed information on the therapeutic aspects of the herbs.

Crude Plant Material. The botanical classification, including genus, species and authority, description of the part of the plant from which the medicine is made (e.g., leaf, flower, root) should be provided. In addition, the consuming form of the material whether fresh, dried, or traditionally processed should be indicated. The active and characteristic constituents should be specified and, if possible, content limits should be defined. Foreign matter, impurities, and microbial content should be defined or limited. Voucher specimens, representing each lot of plant material processed, should be authenticated by a qualified botanist and should be stored for at least a 10-year period. A lot number should be assigned and this should appear on the product label.

Plant Preparations. Plant preparations include green, dried, grinded, or powdered plant materials, extracts, tinctures, fatty or essential oils, expressed juices and preparations whose production involves fractionation, purification, or concentration. The manufacturing procedure should be described in detail. If preparations are supplemented with other substances during manufacture in order to adjust the plant-based drug to a certain level of active or characteristic constituents or for any other purpose, the added substances should be mentioned in the manufacturer label. A method for identification and, where possible, assay of the plant preparation should be added. If identification of an active principle is not possible, it should be sufficient to identify a characteristic substance or mixture of substances (e.g., "chromatographic fingerprint") to ensure consistent quality of the preparation.

Finished Product. The manufacturing procedure and formula, including the amount of plant material, should be described in detail. A finished product specification should be defined. A method of identification and, where possible, quantification of the plant material in the finished product should be defined. If the identification of an active principle is not possible, it should be sufficient to identify a characteristic substance or mixture of substances to ensure consistent quality of the product. The finished product should comply with general requirements for particular dosage forms.

For imported finished products, confirmation of the regulatory status in the country of origin should be required. The WHO certification scheme on the quality of pharmaceutical products moving in international commerce should be applied.

Stability. The physical and chemical stability of the product in the container in which it is to be marketed should be tested under defined storage conditions and the shelf life should be established.

In summary, the WHO guidelines for the assessment of herbal-based medicines are intended to facilitate the work of regulatory authorities, scientific bodies and industry in the development, assessment, and registration of such products. The assessment should reflect the scientific knowledge gathered in that field. Such assessment could be the basis for future classification of herbal medicines in different parts of the world. Other types of traditional medicines in addition to herbal products may be assessed in a similar way. The effective regulation and control of herbal medicines moving in international commerce also requires close liaison between national institutions that are able to keep under regular review all aspects of production and use of herbal medicines, as well as to conduct or sponsor evaluative studies of their efficacy, toxicity, safety, acceptability, cost and relative value compared with other drugs used in modern medicine.

19.4 REGULATION OF HERBAL MEDICINES IN THE UNITED STATES

In the United States, one of the leading countries in pharmaceutical industry, all drugs, including "traditional" and "lifestyle" drugs are regulated by the same provisions of health agencies, namely, the Food and Drug Administration (FDA) in the United States and the Food Drug and Cosmetic Act (FDCA). A new drug requires the submission of a New Drug Application (NDA) and premarket approval from the FDA, unless it "generally recognized as safe and effective" (GRAS/E) and has been used for a material extent and material time. The hurdle for a drug to be considered GRAS/E is substantial and generally requires the types of scientific, well-controlled studies necessary to obtain premarket approval for a new drug.

Herbal remedies typically also qualify for regulation as dietary supplements under the Dietary Supplement Health and Education Act (DSHEA) of 1994. DSHEA defines "dietary supplement" broadly, to include "an herb or other botanical" as well as "a concentrate, metabolite, constituent, extract, or combination" of the botanical or other dietary supplement.

Product Use Determines the Regulatory Regime. The regulatory regime applied to a given product is determined by intended use of the product. If the claims of the product include the cure, treatment, mitigation, or prevention of disease, the herbal remedy will be regulated as a conventional drug. A product that has been marketed, as a dietary supplement, does not lose its status as a dietary supplement even if it is later approved to as a new drug. However, a product that has been approved as a new drug prior to any marketing as a dietary supplement is excluded from the definition of dietary supplement.

Safety. A dietary supplement, regardless of whether it contains old or new dietary ingredients, is prohibited if it presents "a significant or unreasonable risk of illness or injury under (i) conditions of use recommended or suggested in labeling or (ii) if no conditions of use are suggested or recommended in the labeling, under ordinary conditions of use." The burden of proof for demonstrating the lack of safety of a dietary supplement is placed on the FDA.

Premarket Approval. Dietary supplements are excluded from the definition of food additives, thereby precluding the possibility of stricter regulation through classification of dietary supplements as food additives. Unlike drugs and food additives, dietary supplements are not subject to premarket approval. Unless the dietary supplement also meets the definition of a drug, a dietary supplement is considered a food. However, unlike for conventional foods, the manufacturer of a dietary supplements containing a "new dietary ingredient" is required to notify the FDA prior to marketing, and to include support for the safety of ingredient, unless the ingredient is chemically unaltered and is used in the food supply as food. A "new dietary ingredient" is one that is marketed prior to the passage of DSHEA (October 15, 1994).

Structure or Function Claims. Dietary supplements may make "structure or function" claims without being classified and regulated as a drug. To make structure/function claims, the manufacturer must have substantiation that claims are truthful and not misleading, notify the FDA within 30 days of making the claim, and include with the claim the boilerplate disclaimer: "This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease."

Labeling of Dietary Supplement. In addition to permitting structure/function claims on labels for dietary supplements, DSHEA narrowed the definition of "labeling." Labeling is a critical component of the FDA's regulatory powers, as labeling is used to determine the intended use of an article, and thus the regulatory scheme that applies to the article. Furthermore, the labeling is a key factor in determining whether an article is misbranded. Through a determination that an article is misbranded the FDA has to power to seize the article and criminally prosecute the manufacturers or distributors. DSHEA excludes accompanying publications from the definition of labeling, if certain conditions are met. The publication

cannot promote a specific manufacturer and must present a balanced view of available scientific information. However, the FDA has the burden of proving that the accompanying publications are not exempted from the definition of labeling. In summary, DSHEA eliminates the possibility of expansive FDA regulation of dietary supplements through the definition of labeling.

Taken together, public awareness of the safety concerns of dietary supplements has increased in recent years. There is a majority of the U.S. public that supports the idea of new rules that would require the FDA to review the safety of new dietary supplements before their sale; that would give increased authority to the FDA to remove unsafe products from the market; and that would regulate advertising claims about the health benefits of dietary supplements. In regard to the United States, most important was the enactment in 1994 of the Dietary Supplement Health and Education Act. By broadly defining herbs and other botanicals as "dietary supplements," the DSHEA substantially altered the definitions, standards, and mechanisms under which claims about the effectiveness and safety of these products are evaluated and enforced. This classification, as discussed in Chapter 19 is inappropriate, and has resulted in a serious and growing public health problem. Dietary supplements are now subject to lower safety standards than food additives. Consumers are provided with more information about the composition and nutritional value of general foods than about the active ingredients and potential hazards of herbal remedies.

19.5 REGULATION OF HERBAL MEDICINES IN THE ARAB–ISLAMIC WORLD

Arab and Islamic medicine is widely used in most Arab and Islamic countries, which form about one-fifth of the world's population (about 1.4–1.5 billion people) spread across many different nations and ethnic. As discussed in Chapter 10, the Arab and Muslim world refers in geopolitical sense to Muslim majority countries or countries in which Islam dominates politically (Tables 10.1 and 10.2). It includes 22 Arab states and 35 non-Arab Muslim states [5–14].

A very important factor that contributed to the current widespread use of Arab herbal remedies is the belief that these medicines are prepared according to the principles of Greco-Arab medicine, which builds the basis for the modern conventional medicine. Therefore, many producers and caregiver institutions of Arab–Islamic herbal medicines are named after the famous scholars Avicenna, Razes, Ibn al-baitar, or Al-Antaki. However, a history of traditional usage is not always a reliable guarantee of safety since it is difficult for traditional practitioners to detect or monitor delayed effects (e.g., mutagenicity), rare adverse effects, and adverse effects arising from long-term use. Based on recent surveys, the interest in Greco-Arab and Islamic herbal medicines by professionals and lay public is based the belief that these products are "natural" and therefore safe, that these medicines are prepared according to the principles of famous scholars such as, Avicenna and Razes and, therefore, they are effective in the treatment and prevention of diseases, that users have a feeling of better control of the disease and its management, the holistic philosophy behind herbal

medicines, and finally that most countries do not impose prescription regulations upon herbal preparations and, therefore, access to this kind of therapy is unrestricted and cheap.

Herbal remedies and other herbal products are sold in the Arab–Islamic world in small shops called Attarah. These natural and health food stores typically provide a large assortment of the herbal remedies and other nonherbal products. In addition, like in the Western world, herbal remedies and herbal dietary supplements are sold through other market channels, including health and natural food stores, warehouse and convenience stores, mail order, radio and television direct sales, Internet sales, network or multilevel marketing companies, health professionals in their offices and other channels. While market data companies are able to generate relatively accurate data of herbal dietary supplement sales for some market channels through cash register and computer scanning records, most Attarah and other channels do not have such tracking capabilities and are estimated with a lesser degree of accuracy.

According to the National Policy on Traditional Medicine and Regulation of Herbal Medicines—Report of a WHO Global Survey, the situation in the largest Arab–Islamic countries can be summarized in the following.

Egypt. Arab–Islamic traditional medicine is regulated in Egypt under the national drug policy issued in 2001. Herbal-based medicine regulation in Egypt began in 1955, and is achieved through the same laws that are used for conventional drugs. Regulatory requirements for manufacturing include adherence to information in pharmacopoeias and monographs, the same rules of good manufacturing practice as for conventional pharmaceuticals and special GMP rules. Regulatory requirements for safety assessment are limited to reference to documented scientific research on similar products. Control mechanisms exist in Egypt for both manufacturing and safety assessment requirements. Both registration and quality control of herbal drugs must be performed in the laboratories of National Organization for Drug Control and Research.

The majority of the Egyptians have great confidence in the effectiveness of herbal-based remedies in the treatment and prevention of diseases. They regularly frequent Attarah shops, which sell all types of natural products without any license, inspection or control by the official authorities. In addition, many preparations are either imported or manufactured by certain pharmaceutical factories and sold as dietary supplements. Usually, the manufacturers gave these preparations numerous medical claims, which in most cases lacking the scientific evidences for their safety or efficacy.

Jordan. Herbal regulations in Jordan were developed in 2001, and are partly the same as for conventional pharmaceuticals. Herbal medicines are regulated as prescription medicines, over-the-counter medicines and for self-medication. Claims may be made by law, medical, health, nutrient content, and structure/function. In place of a national pharmacopoeia, the U.S. Pharmacopoeia is used. The WHO monographs are used in place of national monographs, and they are legally binding. In

Jordan, the regulatory requirements for the manufacture of herbal medicines are the same GMP rules that apply to conventional pharmaceuticals; implementation is ensured by a control mechanism. Safety assessment requirements are the same as for conventional pharmaceuticals, but also include special requirements of traditional use without demonstrated harmful effects and reference to documented scientific research on similar products; a control mechanism also exists for these requirements, involving toxicological studies. As in most Arab countries, herbal remedies are sold in Attarah shops that sell all types of natural products without any license, inspection, or control of any of the official authorities. Usually, herbal preparations have a label with numerous medical claims, which in most cases lacking the scientific evidences for their safety or efficacy.

Saudi Arabia. No national pharmacopoeia exists, however, the German Pharmacopoeia, British Pharmacopoeia and WHO monographs are used instead. They are not legally binding. In place of national monographs the WHO monographs are used, although they are not legally binding. Regulatory requirements for manufacturing include some of the same GMP rules as for conventional pharmaceuticals, as well as special GMP rules. Implementation of these requirements is enforced through plant and factory inspections. Safety assessment requirements include some of the same requirements as for conventional pharmaceuticals, as well as reference to documented scientific research on similar products. Laboratory testing and analysis serve as the control mechanisms for these requirements. In Saudi Arabia, there are 450 registered herbal medicines, however, none are included on an essential drug list. In Saudi Arabia, herbal medicines are sold in pharmacies as prescription and over-the-counter medicines, and in special outlets without restriction.

Syria. Regulations of herbal medicines were introduced in Syria in 1998 as part of the same law that regulates conventional pharmaceuticals. Herbal medicines are regulated as prescription medicines, health foods, and as an independent regulatory category. Medical and herbal claims may be made by law. In place of a national pharmacopoeia, the U.S. Pharmacopoeia is used and is legally binding. No national monographs exist, but the Physician's Desk Reference is used and is also legally binding. The regulatory requirements for manufacture of herbal medicines include adherence to information in pharmacopoeias and monographs and the GMP guidelines for herbal medicines that were established in 2004. Implementation of these requirements is enforced by a control mechanism. Safety assessment requirements include clinical trials submitted during registration and product licenses. Clinical trials are required for preparations intended to be used for specific indications, and are assessed by the Ministry of Health's high-level technical committee. There are currently 44 herbal medicines registered in the Syria. There are no herbal medicines included on the national essential drug list. Herbal products are sold in Syria Attarah shops, which provide a large assortment of the herbal remedies and other nonherbal products. In addition, like in the Western world, herbal remedies are sold through mail order, radio and television direct sales, Internet sales, caregiver in their offices, and other channels.

Sudan. Regulations on herbal medicines were issued in Sudan in 1996 are separate from those for conventional pharmaceuticals. Herbal medicines are regulated as prescription medicines, self-medication and dietary supplements. Claims may be made about herbal medicines by law, medical, and nutrient content. In place of a national pharmacopoeia, the British Herbal Pharmacopoeia is used, and is considered to be legally binding. In place of national monographs, the WHO monographs are used. The regulatory requirements for manufacturing include adherence to information in the British Herbal Pharmacopoeia and the WHO monographs, as well as the GMP rules for conventional pharmaceuticals and special GMP rules for herbal medicines. The implementation of these requirements involves evaluation of quality control data submitted by the manufacturer, GMP inspection, and documentation of the raw material supply. Requirements for safety assessment include traditional use without demonstrated harmful effects and biosafety studies. To ensure adherence to these requirements, the biosafety study protocols are strictly followed. Herbal medicines in Sudan are sold in pharmacies as over-the-counter medicines and in special outlets.

Libya. There is no national law or regulation on herbal medicines; therefore, they have no status and are not sold with claims. Though no national pharmacopoeia or monograph currently exists or is being developed, the British Herbal Pharmacopoeia and the European Pharmacopoeia are used, although they are not legally binding. No regulatory requirements apply to the manufacturing or safety assessment of herbal medicines. There is no registration system for herbal medicines, and consequently no herbal medicines are included on the national essential drug list. Herbal medicines are either sold in pharmacies as over-the-counter drugs or sold without restriction.

Qatar. Herbal regulations in Qatar were issued in 1990 and updated in 2002; these laws are separate from those dealing with conventional pharmaceuticals. Herbal medicines are regulated as over-the-counter medicines, dietary supplements, complementary products, and as an independent regulatory category. Claims may be made about herbal medicines by law, medical, health, nutrient content, and structure/function. There is no national pharmacopoeia; instead, the German Herbal Pharmacopoeia and the British Herbal Pharmacopoeia are used, and are legally binding. Five national monographs exist; they were published by the University of Qatar. They are "Ecology and flora of Qatar (1981)," "Environment and plant life in Qatar (1986)," "Phytochemistry of the flora of Qatar (1986)," "Phytochemistry of the historical and cultural plants of Qatar (1989)," "and Medicinal and poisonous plants of Qatar (1995)." Regulatory requirements for the manufacture of herbal medicines are limited to adherence to information in pharmacopoeias and monographs; there is no mechanism for control of this requirement. Herbal medicines in Qatar are sold in pharmacies as over-the-counter medicines without restriction.

Bahrain. Bahrain regulates herbal medicines using the same, or partly the same, legal framework as is used for conventional pharmaceuticals. Herbal medicines are

regulated as dietary supplements, health foods, and health products. Manufacturing regulatory requirements include adherence to information in pharmacopoeias and monographs and the same rules of GMP as for conventional pharmaceuticals. No control mechanism exists. Safety assessment requirements are those used for conventional pharmaceuticals and reference to documented scientific research on similar products. Nevertheless, as in Arab–Islamic world, herbal medicine is sold in Bahrain in pharmacies as well as over-the-counter medicines and in Attarah shops.

United Arab Emirates. The national laws and regulations on herbal medicines were established in 1995, as separate laws and regulations that are partially the same as those for conventional medicines. Herbal medicines are regulated as prescription and over-the-counter medicines, and as a separate regulatory category. Claims may be made about herbal medicine by law, medical, health, nutrient content, and structure/function. While the national pharmacopoeia is in the process of being developed, others are used, but are not legally binding. No national monographs yet exist, but they are in development. In their place, a number of others, including the *WHO monographs*, are used, but are not legally binding. The regulatory requirements for the manufacture of herbal medicines include adherence to information in pharmacopoeias and monographs, as well as modified GMP rules. Compliance with these regulations is ensured through inspection and certification. The safety requirements for herbal medicines are special requirements, including demonstrated traditional use without harmful effects and reference to documented scientific research on similar products, in addition to the report of the Ministry of Health's quality control laboratory. The Zayed Complex for Herbal Research and Traditional Medicine was established in 1996 and serves as the national research institute for traditional and herbal medicine. A registration system exists, which includes about 70 herbal medicines and a number of single and combination homeopathic medicines, as well as a few proprietary traditional Chinese medicines, yet none are included on a national essential drug list. Many herbal and other products from natural sources are registered using a simpler criterion, namely registration of general sale pharmaceutical products. A postmarketing surveillance system has been established, and an adverse effect monitoring system is being developed. In the United Arab Emirates, herbal medicines are generally sold in pharmacies as prescription and over-the-counter medicines and in special outlets. However, many herbal products and food supplements are also imported under special permits from the municipalities and sold in health food outlets licensed by them.

Oman. Herbal regulation in Oman began in 2001; it is similar to legislation for conventional pharmaceuticals. Herbal medicines have no regulatory status. Medical claims may legally be made. No national pharmacopoeia or national monographs exist, nor are they in development. The same rules of GMP apply to herbal medicines as to conventional pharmaceuticals; no control mechanism ensures their implementation. Safety assessment requirements include the same requirements as for conventional pharmaceuticals, as well as special requirements consisting of use without demonstrated harmful effects and reference to documented scientific research on

similar products; again, no control mechanism exists. In Oman, herbal medicines are sold by licensed practitioners.

Kuwait. Kuwait began regulation of herbal medicine in 1989 with the introduction of a separate law on herbal medicines. Herbal medicines are regulated as over-the-counter medicines, self-medication, dietary supplements, health foods, and functional foods. Medical and health claims may legally be made. In place of a national pharmacopoeia and national monographs, the European Pharmacopoeia, British Pharmacopoeia, U.S. Pharmacopoeia, and International Pharmacopoeia are used and are legally binding. Regulatory requirements for the manufacture of herbal medicines include the same GMP rules as for conventional pharmaceuticals, as well as adherence to information in pharmacopoeias and monographs. Implementation of these requirements is enforced through quality control of raw materials, manufacturing and finished products. Safety assessment requirements include the same requirements as for conventional pharmaceuticals and traditional use without demonstrated harmful effects. The control mechanism is the same as for manufacturing requirements, in which random samples are tested for quality control purposes. In Kuwait, herbal medicines are sold in pharmacies as over-the-counter medicines without restriction.

Islamic Republic of Iran. Regulation of herbal medicines was revised in 1996. Herbal medicines are regulated as prescription, over-the-counter medicines and as dietary supplements. Special GMP rules apply to the manufacture of herbal medicines; the implementation of these requirements is ensured by GMP inspection and national laboratory testing. Safety assessment requirements are the traditional use without demonstrated harmful effects and reference to documented scientific research on similar products. Implementation of these requirements is ensured by the Adverse Drug Reaction Center. The registration system has registered 170 herbal medicines. No herbal medicines are included on an essential drug list. A postmarketing surveillance system that includes adverse effect monitoring exists. Herbal medicines are sold in pharmacies as over-the-counter and prescription medicines and in special outlets.

Pakistan. As discussed in Chapter 10, the Unani system of medicine came to the Indo-Pakistan subcontinent via Arab and Muslim physicians in twelfth century. In Pakistan, over half the population (66%) lives in the rural part of the country. Poverty, high rate of illiteracy, limited knowledge of health and disease, low status of women, and inadequate water and sanitation facilities, have a negative impact on health status. Pakistan has a very rich tradition in the use of medicinal plants for the treatment of various ailments, based predominantly on the Unani system of medicine. This traditional medicine sector has become an important source of health care, especially in rural and tribal areas of the country. Most Pakistanis rely on Unani medicine, finding it efficacious, safe, and cost-effective. Unani medicine is widely used throughout the country. About 70% of the populations, particularly in rural areas, use traditional and complementary/alternative medicine.

The type and duration of illness are major determinants of choice of care provider. In the case of a mild single symptom such as fever, home remedies or folk prescriptions are visited, whereas with multiple symptoms and a longer duration of disease, allopathic physicians are more likely to be consulted. Other reasons for consulting a Unani healer are the proximity, affordable fee, availability of the provider, family pressure, and the strong opinion of the community.

In addition to other traditional systems such as Ayurvedic and homeopathic, the Unani system has been accepted and integrated into the national health system. Pakistan is the only country in the Eastern Mediterranean region where formal Unani teaching institutions are recognized. According to WHO report, Pakistan's Unani teaching institutions (Tibbia colleges), are recognized by the Government and are under the direct control of the National Council for Tibb, Ministry of Health, which is responsible for maintaining standards of education in recognized teaching institutions, revising/modifying curricula and syllabuses, and holding annual examinations.

Herbal medicines are regulated as over-the-counter medicines and dietary supplements. No claims may legally be made about herbal medicines. The national pharmacopoeia is the Tibbi Pharmacopoeia (1967); the information is not legally binding. The Monographs of Unani medicines has been prepared and published. The Tibb el Unani, Ayurvedic, Homoeopathic, Herbal, and Any Other Non Allopathic Medicine Act has been prepared to regulate the manufacture, sale, storage, import, and export of medicines from these systems. Although this act has been approved by the Federal Cabinet and Prime Minister of Pakistan, there are currently no regulatory requirements for either manufacture or safety assessment of herbal medicines. There is no registration system. Herbal medicines are not included on an essential drug list. A postmarketing surveillance system is being developed.

Malaysia. The alternative and complementary medicine industry in Malaysia is growing at a rapid rate. It is currently estimated that the market is worth over one billion dollars, with more than 20% of that market being herbal medicine and related products. The rapid growth is largely due to a growing demand from the public, with reportedly more than 50% of Malaysians using herbal or complementary medicines. Although no statistics are available, traditional medicine is mainly practiced by providers of traditional medicine, whereas allopathic medical providers practice complementary/alternative medicine in addition to allopathic medicine. Traditional medical practices brought by Indian and Chinese traders and migrants complemented, but did not replace, the indigenous medical system in Malaysia. The introduction of Islam by Indians and Arabs, on the other hand, led to the introduction of Greco-Arab and Islamic medicine. The diversity in medical systems in Malaysia reflects the diverse population of Malay, Chinese, Indian, and indigenous heritage. In addition to allopathic medicine, the major systems of medicine practiced in Malaysia include Ayurveda, Siddha, Unani, traditional Chinese medicine, and traditional systems of medicine, such as that provided by traditional medicine practitioners, spiritualists, bonesetters, traditional birth attendants, and others who use home remedies. Medical options also include homeopathy, naturopathy, reflexology, aromatherapy, and chiropractic. Traditional Malay medical practices can be traced mainly to Indonesia.

These medical practices are especially popular among Malay in rural areas and rely on practical experience and observation handed down orally and in writing from generation to generation.

The Drug Control Authority is responsible for product registration, including quality and safety. Every manufacturer of traditional medicine is required to comply with good manufacturing practices, and importers are required to comply with good storage practices. All homeopathic medicines have to be registered with the National Pharmaceutical and Drug Control Board. The Ministry of Health has set up the Steering Committee on Complementary Medicine with a multisectoral membership to advise and assist the Minister in formulating policies and strategies for monitoring the practice of traditional Chinese medicine in the country. A national policy is being drafted on traditional Chinese medicine to encourage established practitioners to form their own self-regulatory bodies. These bodies will enable a system of official recognition of member practitioners. To ensure that the qualifications of practitioners are recognized and can be accredited for formal registration, the bodies are required to set formal standards, including training, for their own practices. They are also encouraged to update the skills and knowledge of their members. The Unit of Traditional Chinese Medicine has been established at the Primary Health Care Section, Family Health Development Division, Ministry of Health. It will be responsible for monitoring and facilitating the implementation of the Ministry's policies as well as strengthening national and international collaboration. There is no chiropractic law.

19.6 REGULATION OF HERBAL MEDICINES IN THE EUROPEAN COMMUNITY

In Western Europe, the professional use of herbs and phytomedicines enjoys relatively strong integration with conventional medicine. According to European Union (EU) definitions, herbal medicinal products (medicines) are "medicinal products containing as active ingredients exclusively plant material and/or vegetable drug preparations." Vegetable drugs are "plant material used for a medicinal purpose. An herbal drug or a preparation thereof is regarded as one active ingredient in its entirety whether or not the constituents with therapeutic activity are known." Herbal medicinal preparations are "comminuted or powdered vegetable drugs, extracts, tinctures, fatty or essential oils, expressed plant juices, and so on, prepared from herbal drugs, and preparations whose production involves a purification or concentration process. However, chemically defined isolated constituents or their mixtures are not considered herbal medicinal products. Other substances such as solvents, diluents, preservatives may form part of vegetable drug preparations. These substances must be indicated." Constituents with known therapeutic activity "are chemically defined substances or groups of substances which are known to contribute to the therapeutic activity of a herbal medicinal product or of a preparation."

In the countries of the European Union (formerly European Economic Community, EEC), herbal medicines are generally sold in pharmacies as licensed nonpre-

scription or prescription medicines. According to EU directive 65/65/EEC, all phytomedicines are treated as drugs. Registrations, based on quality, safety, and efficacy are required. Exceptions include the Netherlands and the United Kingdom, where botanicals are still sold as food supplements or dietary supplements.

One important initiative in the development of herbal monographs in Western Europe is European Scientific Cooperative on Phytotherapy (ESCOP), an affiliation of 15 national associations of phytotherapy, mostly from Western Europe, that formed in 1989 as a result of the European harmonization process. Since June 1997 ESCOP has produced a series of 50 herbal monographs to respond to the increasing integration of the European Union.

The ESCOP monographs were published in volumes ("fascicules") of 10 monographs each. They were published in the form of standardized drug dossiers of European drug licensing, known as specific product characteristics (SPCs). Unlike a pharmacopeial monograph that focuses on standards for identity and quality, ESCOP monographs, like those of German Commission E, deal with therapeutic aspects of each phytomedicine. Thus, ESCOP monographs include approved therapeutic uses and contain the format much like recent Commission E monographs, including recommended dosage, side effects and contraindications (if any), and other specific instructions for health professionals, industry, regulators, and patients.

ESCOP monographs do not deal directly with qualitative standards for herbal drugs; this area is covered in other pharmacopeial monographs. For example, the European Pharmacopoeia includes 60 monographs on herbal drugs. An additional 45 draft monographs have been published for comments. According to Keller, "This cooperative approach will greatly facilitate harmonization of herbal remedies." [10–15].

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APPENDIX A

Plant Naming

The plants kingdom, *Plantae*, includes trees, herbs, bushes, grasses, vines, ferns, mosses, and green algae. The scientific study of plants, known as botany, has identified about 350,000 extant species of plants. Over 80,000 plants are in use throughout the world for their therapeutic properties. The method of naming plants as well as other living things using "Latinized" names was introduced to end the confusions of common names, which can refer to different plants depending on the region where they grow. Although plants had Latin names from early times, a systematic system was first applied to plants in 1753 by a Swede, Carl von Linné, who adopted a Latin name for himself—Linnaeus. Plant names are usually descriptive, from the features of a plant (*parvifolia*—small-leaved, e.g., *Ulmus parvifolia*), who first discovered it (L.—Linnaeus), or its country of origin (*palaestinum*—Palestine, e.g., *Arum palaestinum*). Since the names are not always based in Latin, it is probably more accurate to describe it as the botanical, scientific, or approved name, although it is usually written in a Latin form. The "International Code of Botanical Nomenclature" is an agreement between botanists around the world to follow the Binomial System of naming which gives the Genera and Species of the plant. The International Congress of Nomenclature is the committee that meets every 4 years to decide on any additions or changes to the naming of organisms.

The plant is first classified according to some physical characteristics, usually leafs, flowers, and fruits. This arrangement and classification of organisms is called taxonomy.

- The name is in two parts (Binomial System), first the Genus starting with a capital letter followed by the Species, with the first letter in lower case, for example, *Nigella sativa*—common name Black seed.
- The Genus name is often shortened to a capital letter, if it has already been used and another Species in that Genus is referred to, for example, *S. aucuparia*—Mountain Ash.
- The Species may be further divided into Subspecies (subsp. or ssp.), for example, *Euphorbia characias* subsp. *wulfenii*.

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- Due to geographical and ecological differences, variations arise within a Species giving rise to a Variety name (var.). A Variety is usually Latinized, written in italics and the abbreviation var. is sometimes included, for example, *Geranium sanguinium* var. *striatum*.
- When this variation is due to selective breeding, it is called a Cultivar (cv.). A Cultivar name is not usually Latinized and is printed in standard type, but with a capital letter, and it is placed in single inverted commas, for example, *Geranium cinereum* 'Ballerina'. Often the Species name is left out and the Genus is followed by the Cultivar name, for example, *Cotoneaster* 'Autumn Fire'.
- Where the hybridization is between two Genera—a rare occurrence—the cross is placed at the beginning of the name, for example, ×*Fatshedera lizei*—between a false castor oil plant (Genus *Fatsia*) and an ivy (Genus *Hedera*).
- Despite all the care taken to give one name to each plant, some have more than one acceptable name. This usually occurs when a plant is reclassified due to more up-to-date methods of identification and the old name remains in use. In this case, the other name or synonym (syn.), is sometimes included on the label, for example, *Verbena bonariensis* syn. *V. patagonica*.

The lists below give some of the most commonly used names and their meanings. Knowing the origin of the name associates the meaning with the plant, so it is easier to remember those long names if you find out something about the plants. The Species in different Genera can have the same name so a culinary or medicinal herb can be called *officinale/is*, for example, *Fumaria officinalis* (Fumitory), *Melissa officinalis* (Lemon balm), *Rosmarinus officinalis* (Rosemary), *Salvia officinalis* (Sage), and *Zingiber officinale* (Ginger).

Species Names Describing Habitat: Names may end with (*um*), (*is*), or (*us*)

arvense	Fields or cultivated land, e.g., *Sinapis arvensis*
littorale	Of sea shores, e.g., *Griselinia littoralis*
montana	Of mountains, e.g., *Hosta montana*
palustre	Of swamps or marshes, e.g., *Ledum palustre*
rivulare	Of streams or rivers, e.g., *Ambystoma rivulare*
sylvatica	Of woods, e.g., *Geranium sylvaticum*

Species Names Describing Foliage: Names may end with (*um*) or (*us*)

arguta	Sharp, e.g., *Actinidia arguta*
coriacea	Leathery, e.g., *Holboellia coriacea*
cordata	Heart-shaped, e.g., *Alnus cordata*
crassifolia	Thick-leaved, e.g., *Ulmus crassifolia*
crenata	Shallow, rounded teeth, e.g., *Hyptis crenata*
decidua	Dropping its leaves, e.g., *Larix decidua*

dentata	Toothed, e.g., *Ligularia dentata*
glabra	Without hairs, e.g., *Glycyrrhiza glabra*
glutinosa	Sticky, e.g., *Alnus glutinosa*
heterophylla	Variable-leaved, e.g., *Tsuga heterophylla*
hirsuta	Hairy, e.g., *Cardamine hirsuta*
incana	Gray-downy, e.g., *Alnus incana*
integerrima	Without teeth, e.g., *Jatropha integerrima*
laevigata	Smooth and polished, e.g., *Rosa laevigata*
lanceolata	Lance-shaped, e.g., *Coreopsis lanceolata*
latifolia	Broad-leaved, e.g., *Dalbergia latifolia*
macrophylla	Large-leaved, e.g., *Flemingia macrophylla*
maculata	Spotted, blotched, e.g., *Neotinea maculata*
marginata	Margined, e.g., *Primula marginata*
microphylla	Small-leaved, e.g., *Salvia microphylla*
molle	Soft, e.g., *Alchemilla mollis*
nitida	Shining, e.g., *Lonicera nitida*
ovata	Egg-shaped, e.g., *Plantago ovata*
palmata	Hand-shaped, e.g., *Acer palmatum*
parvifolia	Small-leaved, e.g., *Ulmus parvifolia*
platyphylla	Broad-leaved, e.g., *Betula platyphylla*
reticulata	Net-veined, *Annona reticulata*
rotundifolia	Round-leaved, e.g., *Campanula rotundifolia*
sempervirens	Evergreen, e.g., *Cupressus sempervirens*
serrata	Saw-toothed, e.g., *Boswellia serrata*
tomentosa	Covered with short dense hairs, e.g., *Achillea tomentosa*
variegata	Variegated, two-colored, e.g., *Bauhinia variegata*

Species Names Describing Flowers: Names may end with (*um*) or (*us*)

grandiflora	Large-flowered, e.g., *Fragaria grandiflora*
macropetala	Many petalled, e.g., *Acmadenia macropetala*
paniculata	Panicle-shaped flower clusters, e.g., *Saxifraga paniculata*
parviflora	Small-flowered, e.g., *Aesculus parviflora*
pauciflora	Few flowers, e.g., *Eucalyptus pauciflora*
polyantha	Many flowered, e.g., *Allamanda polyantha*
spicata	Flowers in spikes, e.g., *Liatris spicata*
stellata	Starry flowers, e.g., *Magnolia stellata*
umbellata	Umbel-shaped flower clusters, e.g., *Chimaphila umbellata*
alba(um)(us)	For example, *Salix alba*, *Lawsonia alba*
argentea	Silvery, e.g., *Paronychia argentea*
aurantiaca	Orange, e.g., *Pilosella aurantiaca*
aurea	Golden, e.g., *Matricaria aurea*

bicolor	Two colored, e.g., *Fascicularia bicolor*
caerulea	Blue, e.g., *Passiflora caerulea*
cinerea	Ash gray, *Salix cinerea*
coccinea	Scarlet, e.g., *Schizostylis coccinea*
ferruginea	Rusty brown, e.g., *Prumnopitys ferruginea*
glauca	Sea-green, e.g., *Festuca glauca*
lactea	Milk white, e.g., *Euphorbia lactea*
lilacina	Lilac, e.g., *Pinguicula lilacina*
lutea	Yellow, e.g., *Asphodeline lutea*
nigra	Black, e.g., *Morus nigra*
purpurea	Purple, e.g., *Digitalis purpurea*
rosea	Rose pink, *Althaea rosea*
rubra	Red, e.g., *Filipendula rubra*
sanguinea	Blood red, e.g., *Geranium sanguineum*
variegata	Variegated, two-colored, e.g., *Bauhinia variegata*
violacea	Violet, e.g., *Ipomoea violacea*

Miscellaneous Species Names: Names may end with (*um*), (*us*), or (*is*)

amoena	Charming, pleasant, e.g., *Dieffenbachia amoena*
commune	Common, e.g., *Myrtus communis*
confusa	Confused identity, e.g., *Acacia confusa*
formosa	Beautiful, e.g., *Leycesteria formosa*
hybrida	Hybrid, e.g., *Vicia hybrida*
insigne	Outstanding, e.g., *Paphiopedilum insigne*
intermedia	Intermediate, e.g., *Leonotis intermedia*
macrorrhiza	With a large root, e.g., *Geranium macrorrhizum*
media	Midway between, e.g., *Stellaria media*
officinale	Used as a herb, e.g., *Rosmarinus officinalis*
praecox	Early, e.g., *Erophila praecox*
pulchella	Beautiful, e.g., *Gaillardia pulchella*
sativa	Cultivated, e.g., *Nigella sativa*
speciosa	Showy, e.g., *Tropaeolum speciosum*
squamata	Flaking, e.g., *Artedia squamata*
tinctoria	Used in dying, e.g., *Anthemis tinctoria*
tuberosa	Tuber rooted, e.g., *Turincia tuberosa*
vulgare(is)	Common, e.g., *Sorghum vulgare*

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FIGURE 8.1 *Nigella sativa*, black seed (Alhaba Alsawadaa or Habbatul-Barakah).

FIGURE 8.2 *Olea europaea*, the olive (*Alzaitun*).

FIGURE 8.3 *Hypericum triquetrifolium*, wavy leaf St John's wort (*Dathi*).

FIGURE 8.4 *Urtica dioica*, stinging nettle (*Querais*).

FIGURE 8.5 *Trigonella foenum-graecum*, fenugreek (*Hilbe*).

FIGURE 8.6 *Melissa officinalis*, lemon balm (*Melissa*).

FIGURE 8.7 *Salvia fruticosa*, common sage (*Mairamia*).

FIGURE 8.8 *Portulaca oleracea*, purslane (*Farfahena*).

FIGURE 8.9 *Ammi visnaga*, khella (*Khella*).

FIGURE 8.10 *Silybum marianum*, milk thistle (*Khurfaish*).

FIGURE 8.11 *Cuminum cyminum*, cumin (*Kamon*).

FIGURE 8.12 *Ruscus aculeatus*, butcher's broom (*Uhrf Aldeek*).

FIGURE 8.13 *Inula viscosa*, tayun (*Tayon*).

FIGURE 8.14 *Majorana syriaca*, Palestinian thyme (*Zaatar*).

FIGURE 8.15 *Eruca sativa*, rocket (*Jarjeer*).

FIGURE 8.16 *Cichorium intybus*, wild chicory (*Hindibaa*).

FIGURE 8.17 *Punica granatum*, the pomegranate (*Rumman*).

FIGURE 8.18 *Ruta chalepensis*, *Ruta* (*Faijan*).

FIGURE 8.19 *Conium maculatum*, poison hemlock (*Saykaran*).

FIGURE 8.20 *Capparis spinosa*, the caper (*Kabar*).

FIGURE 8.21 *Cyperus rotundus*, nut-grass (*Sueda*).

FIGURE 8.22 *Origanum majorana*, sweet marjoram (*Mardagoush*).

FIGURE 8.23 *Foeniculum vulgare*, fennel (*Jansoon*).

FIGURE 8.24 *Chamomilla recutita*, chamomile (*Babonej*).

FIGURE 8.25 *Zingiber officinale*, ginger (*Zanjabeel*).

FIGURE 8.26 *Rosmarinus officinalis*, rosemary (*Iklil Jabal*).

FIGURE 17.1 *Phoenix dactylifera*, date palm and date fruits Rutab (left) and Tamer (right).

FIGURE 17.2 *Ceratonia siliqua*, the carob tree.

FIGURE 17.3 *Ficus carica*, the Common fig.

FIGURE 17.4 *Gundelia Tournefortii* (*Akkoub*).

FIGURE 17.5 High mallow (*Khebayzeh*).