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Review

Fighting fire with fire: Poisonous Chinese herbal medicine for cancer therapy

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ABSTRACT

Ethnopharmacological relevance: Following the known principle of "fighting fire with fire", poisonous Chinese herbal medicine (PCHM) has been historically used in cancer therapies by skilled Chinese practitioners for thousands of years. In fact, most of the marketed natural anti-cancer compounds (e.g., camptothecin derivatives, vinca alkaloids, etc.) are often known in traditional Chinese medicine (TCM) and recorded as poisonous herbs as well. Inspired by the encouraging precedents, significant researches into the potential of novel anticancer drugs from other PCHM-derived natural products have been ongoing for several years and PCHM is increasingly being recognized as a gathering place for promising anti-cancer drugs. The present review aimed at giving a rational understanding of the toxicity of PCHM and, especially, providing the most recent developments on PCHM-derived anti-cancer compounds.
Materials and methods: Information on the toxicity and safety control of PCHM, as well as PCHM-derived anti-cancer compounds, was gathered from the articles, books and monographs published in the past 20 years.
Results: Based on an objective introduction to the CHM toxicity, we clarified the general misconceptions about the safety of CHM and summarized the traditional experiences in dealing with the toxicity. Several PCHM-derived compounds, namely gambogic acid, triptolide, arsenic trioxide, and cantharidin, were selected as representatives, and their traditional usage and mechanism of anti-cancer actions were discussed.
Conclusions: Natural products derived from PCHM are of extreme importance in devising new drugs and providing unique ideas for the war against cancer. To fully exploit the potential of PCHM in cancer therapy, more attentions are advocated to be focused on their safety evaluation and mechanism exploration.

Contents

Abbreviations: APL, acute promyelocytic leukemia; CDKs, cyclin-dependent kinases; CHM, Chinese herbal medicine; DDS, drug delivery systems; FcεRI, Fc epsilon receptor I; HUVEC, human umbilical vascular endothelial cells; MAPKs, mitogen-activated protein kinases; MMP-2/9, matrix metalloproteinase-2/9; NF-κB, nuclear factor-κB; PCHM, poisonous Chinese herbal medicine; PKC, protein kinase C; PP1/PP2A, protein phosphatases 1 or 2A; ROS, reactive oxygen species; SRC-3, steroid receptor coactivator-3; STATs, signal transducers and activators of transcription; TCM, traditional Chinese medicine; TfR, transferrin receptor; VEGF, vascular endothelial growth factor; VEGFR2, vascular endothelial growth factor receptor 2.

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1. Introduction

As the essence of Chinese traditional culture, traditional Chinese medicine (TCM) has its own philosophy, diagnosis and treatment systems. TCM believes in the oneness of man and nature, and as such, Chinese herbal medicine (CHM) derived from botanicals, minerals and animals reflect the art of utilizing natural products in fighting diseases. It is a comprehensive summation of the experiences of TCM practitioners and its development has evolved into a holistic health care system, which shows great advantages in early intervention, personalized treatment and combination therapies as well. Traditionally, 12 870 kinds of TCM resources were prescribed, among which a number of potentially poisonous CHM (PCHM) are recognized to be restrictively applied for serious diseases. Even in the Pharmacopoeia of the People's Republic of China, many poisonous herbs are routinely recorded and described as slightly toxic, toxic and highly toxic (Table 1). This arises from the fact that poisonous herbs always possess stronger activity, and TCM physicians skilled in using poisonous medicines are highly admired in history. The application of these toxicants just provides a magic power to deal with severe diseases, this process might be described as "fighting fire with fire".

Cancer is one of the main causes of death all over the world. The World Health Organization (WHO) estimates that 84 million people would die of cancer between 2005 and 2015 (Danhier et al., 2010). Conventional cancer therapies, including surgery, chemotherapy and radiotherapy, are showing more and more limitations because of poor prognosis and serious side effects. There has been a consequent wave of complementary and alternative medicine among cancer patients in western countries, with a prevalence as high as 80% (Xu et al., 2006). Medical herbs do represent a huge and noteworthy reservoir for novel anti-cancer drug discovery. Statistics indicated that a half part of anti-cancer drugs approved internationally between the 1940s and 2006 was either natural products or their derivatives (Newman and Cragg, 2007). Moreover, although the potential use of natural products is increasingly recognized in cancer therapy, it has been estimated that only 1/5–1/6 of plant species have been properly studied for their medical applications so far (Abelson, 1990). What is more notable is that most of these marketed natural compounds (e.g., camptothecin derivatives, epipodophyllotoxin derivatives, vinca alkaloids, etc.) in cancer treatment are concentrated on the poisonous part of CHM. Following the known principle of "fighting fire with fire", PCHM, as a special group, have been ingeniously utilized by traditional Chinese practitioners for thousands of years. Their strong therapeutic actions are utilized to deal with many serious diseases, and many inspiring experiences were accumulated in this long process. It is well known that genotoxicity remains a challenge in the extensive application of PCHM. In cancer therapy, however, genotoxicity is what precisely desired to kill cancer cells. Through a proper approach, cytotoxic and genotoxic potential of anti-cancer drugs from PCHM can produce wonderful effects in future.

With researches progress, more and more active compounds from PCHM are identified and the mechanisms are gradually elucidated. A further improvement and application of PCHM with good prospects should be brought to light, which may help to bring PCHM to frontline of the war against cancer. Herewith, we gave a comprehensive introduction on the toxicity of CHM, aiming at providing a rational understanding of toxicity of CHM and a good controlling in clinical usage. Furthermore, through illustrating several novel PCHM-derived products in our paper, more researches are drawing praise for the sake of fully exploiting the potential of PCHM in valuable cancer therapy.

2. The boundary between toxic and non-toxic

TCM follows the concept of holism, where Chinese practitioners focus on the inherent balance of body. The human body is considered as a complexly and highly interconnected system, which is in accordance with the law of nature and dynamically regulated to maintain homeostasis (Wang et al., 2009b). The occurrence of diseases was attributed to a disturbance of the inner balance, thus drugs with special nature are used to mobilize and activate the body's natural resources to recover from the imbalanced state. Being different from the development of modern medicine, CHM safety evaluation was established based on long-term human

Table 1
Examples of PCHM in the Pharmacopoeia of the People Republic of China (Commission, 2010).

Categories of toxicity	Herb	Chinese name	Traditional indications	Safe dosage
Slightly toxic	*Evodia rutaecarpa* (Juss.) Benth.	Wuzhuyu	Epigastric and abdominal pain, headache, diarrhea, Beri-beri, vomiting with acid regurgitation, aphthous sores, etc.	2–5 g
	Prunus armeniaca L. var. ansu Maxim.	Kuxingren	Any kind of cough and asthma, constipation due to dehydrated intestines, etc.	5–10 g
	Melia toosendan Sieb. et Zucc.	Chuanlianzi	Flank, epigastric and abdominal pain, parasite infection, etc.	5–10 g
Toxic	*Pinellia ternata* (Thunb.) Breit.	Banxia	Cough with much sputum, dyspnea, nausea, vomiting, chest and epigastric tightness, globus hystericus, goiter, subcutaneous nodules, etc.	3–9 g
	Realgar (As_2S_2)	Xionghuang	Abscess, swollen sore, deep-rooted boil, ulcers, acariasis, etc.	0.05–0.1 g
	Xanthium sibiricum Patr.	Cangerzi	Headache, sinusitis and nasal congestion caused by exogenous wind-cold, urticaria, arthritis, etc.	3–10 g
Highly toxic	*Bufo bufo gargarizans* Cantor	Chansu	Abscess, carbuncle, furuncle, sore throat, toothache and blockage syndrome of coma, etc.	0.015–0.03 g
	Strychnos nux-vomica L.	Maqianzi	Swelling and pain due to carbuncles, falls, contusion and pain in bisyndromes caused by wind-damp, etc.	0.3–0.6 g
	Mylabris phalerata Pallas	Banmao	Warts, molluscum, abortifacient, and aphrodisiac, etc.	0.03–0.06 g

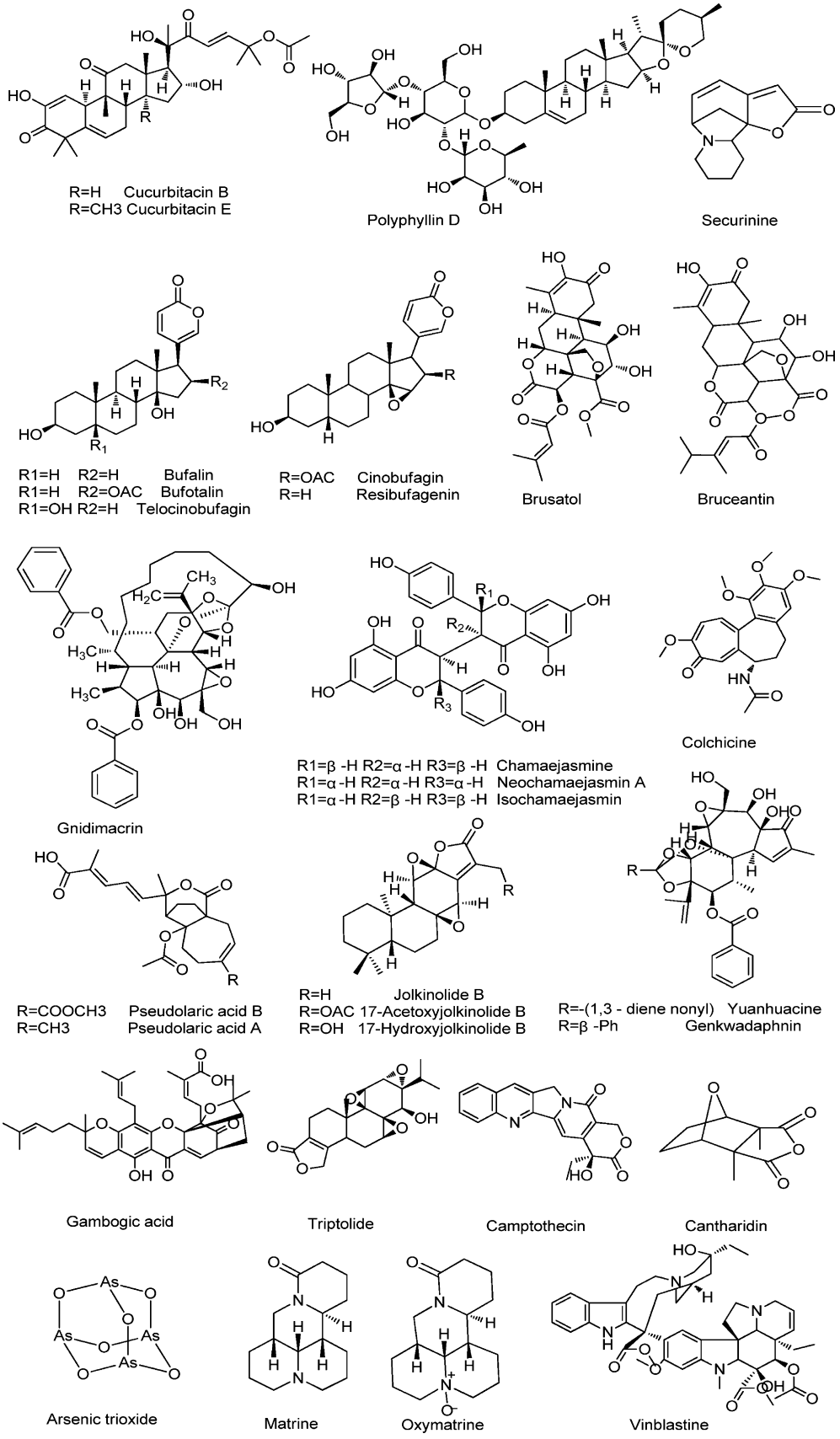

Fig. 1. Chemical structures of the active components displayed in Table 2 and Table 3.

toxicity data. Toxicity was considered as one of the most crucial natures of CHM, whose meaning has gone through two distinct stages, one broader and the other narrower.

Since early times, toxicity has been recognized as an intrinsic property of drugs. From another point of view, drugs can cure illnesses because they are to some extent noxious. *Shennong's Herbal Classic*, the earliest existing Chinese pharmacopoeia, asserted that drugs can attack illness because they are toxic, whereas those that restore deficiencies and aim at promoting longevity use are nontoxic (Zhang et al., 2008). In this book, drugs are divided into three classes, namely superior, average, and inferior. Drugs (e.g., *Mylabris phalerata* Pallas, *Strychnos nux-vomica* L.) classified under the inferior group are supposed to possess greatest toxic potential and are exclusively used for treating diseased conditions (Leung, 2006). In other words, toxic drugs seem to have stronger therapeutic actions actually. This definition relates to a broader understanding of toxicity.

In the narrower sense, toxicity refers to the undesirable effect, which is in accordance with the understanding of modern medicine. When drugs are misused or abused, adverse reactions can and do occur. Therefore, the annotation of individual herb toxicity can be dated back to its first application. From this point of view, toxicity has a much more specific meaning. Applying the theory of TCM, there are contradiction and identity between the meaning of toxicity and non-toxicity, which is a dialectic relationship. Herbs generally considered as nontoxic may be potential to cause adverse events, while those toxic herbs also can be used to fight diseases without triggering any undesired effects. Ginseng, a safe tonic herb, has been one of the most important herbal supplements in US for a long time. However, insomnia, gastrointestinal upset, diarrhea, vomit, headache, anxiety, hot flashes, and even hypertension, are associated with ginseng ingestion (Coon and Ernst, 2002; Seely et al., 2008). In contrast, though well known as a toxic agent, arsenic trioxide showed unnoticeable side-effects in acute promyelocytic leukemia (APL) patients, and the As_2O_3 levels in plasma and urine dropped after termination of As_2O_3 treatment were within recommended US safety limits (Shen et al., 2004). Actually, many CHM are a combination of active ingredients and toxic ingredients, and even the active ingredients are also the cause of toxicity in itself. A good understanding of the boundary between toxic and non-toxic is crucial, where the harmful can be transformed into the beneficial.

3. General misconceptions about the toxicity of CHM

Generally, natural products were regarded as "gentle medicines" for their inconspicuous side effects. All over the world, there are approximately 1.5 billion people trusting in the efficacy and safety of Chinese medicine (Hosbach et al., 2003). In this sense, excessive or improper use is quite common, especially through self-administration for health care purposes. In fact, there is a big misunderstanding. Most of the active constitutes are derived from the secondary metabolites of plants, which serve to protect organisms from foreign invasions. It makes sense that these constitutes would fulfill a protective function after administration. As previously mentioned, even Ginseng may also cause adverse effects inevitably. Moreover, among scientists and healthcare professionals, there is a general belief that there was no toxicity or efficacy data of any kind of CHM. Actually the information on the toxicities of poisonous herbs has been recorded as long as 2000 years, and the documentation of CHM toxicity is a dynamic process that always keeps updating and revising whenever new data were reported. For example, in the Pharmacopoeia of the People's Republic of China, *Mylabris* (Chinese cantharides) was changed from "toxic" in the 1963 edition to "highly toxic" in later editions (1977–2010) (Leung, 2006). The proper use of PCHM and methods to reduce the toxicity were also systematically summarized in a long time. In *Shennong's Herbal Classic*, these poisonous herbs were recommended to be used specially for serious diseases, and the dosage should be increased gradually to avoid unpleasant side effects (Wang et al., 2009b).

In recent years, this misconception seems to convert from one extreme to another. Since several serious adverse events happened in the last few years (aristolochic acid nephropathy as a well-known example), the public began to focus on adverse reactions of CHM and its preparations, even ignoring their considerable therapeutic potential. These events posed a negative impression on public and hereafter an excessive pharmacovigilance of CHM was aroused across the medical circles. Unfortunately, in most cases it is misuse that made the misconceptions. CHM injections represent a revolutionary breakthrough for the CHM administration. At present, 136 kinds of CHM injections have obtained licenses in China and their application has played an important role in clinic, especially for serious and emergency diseases (Bian et al., 2010). However, several adverse drug reactions/events were frequently reported, which let the public down and made the situation of CHM injections worrisome. Gets to the bottom of a matter, inappropriate compatibility with other injections, unreasonable menstruum, extra fast dripping rate and overdose were unquestionably the main causes (Cornelius et al., 2009; Bian et al., 2010). Take Shuanghuanglian injection as an example, its combination with penicillins accounts for 13.38% of the total adverse cases, which ranked the first in the past allergic history (Wang et al., 2010). Similarly, the reason for intoxication by aristolochic acid was that the original plant (*Stephania tetrandra* S. Moore) was replaced by a false one, *Aristolochia manshuriensis* Kom.

Duality is a nature for most of drugs, it must be noted that all pharmacologically active substances produce both wanted and unwanted effects at the same time, CHM is no exception. A herb cannot be abandoned just because it contains poisonous ingredients, if properly used, tragedies can be absolutely avoided. The ancient Greek scholar Paracelsus still gives our enlightenment: "The dose makes the poison" (Efferth et al., 2007), neither ignorance nor hyper-vigilance of CHM toxicity should never be advocated.

4. Artful application of PCHM-based on the aspects of control measures

With remarkable activities, poisonous herbs have long been used in traditional treatment for a host of diseases, especially some difficult miscellaneous diseases such as cancer. It is primarily due to the rich experiences accumulated by skilled TCM practitioners that toxic herbs were artfully utilized to achieve the goal of fighting fire with fire. In China, even some highly toxic herbs, such as *Tripterygium wilfordii* (Thunder god vine or Lei gong teng), Chansu (toad venom), and minerals containing arsenic (e.g., realgar or xiong huang), mercury (e.g., mercuric sulfide or Zhusha) and lead (e.g., lead tetroxide or Qiandan) are still routinely prescribed by TCM practitioners (Youns et al., 2010). To use these special drugs safely and efficiently, four primary factors need to be considered. These factors include processing of crude materials, dosage, drug compatibility and proper application in clinical instances.

Most toxic herbs (e.g., the Aconitum species, blister beetle, and mercuric sulfide, etc.) must be meticulously processed prior to their final manufacture for administration. Proper processing is of great importance to reduce the chance of poisoning or adverse effects. The various methods of processing (including soaking, dry stir-frying, stir-frying in liquid, steaming, calcining, baking) help to modify or control the nature and activities of the herbs, thus adapting them to the exigencies of medical practice which means a lot than ever (Chan, 2003). For example, the toxicity of Aconitum is

mainly caused by the diester diterpene alkaloids including aconitine, mesaconitine and hypaconitine. They can be decomposed into less or non-toxic derivatives through Chinese traditional processing methods, the so-called detoxification (Singhuber et al., 2009).

As is well known, dose is a secret being able to not speak. The safety and efficacy of toxic herbs with a narrow treatment index and high toxicity can be enhanced by strictly controlling their dosage. In the Chinese Pharmacopoeia and the classical literature, the most appropriate dosage parameters have been addressed based on clinical experiences of a hundred or more generation of practitioners. For instance, Chansu (the dried toad venom), which is applied to treat heart failure, pains and cancers in TCM, was found to cause cardiac arrhythmia, breathlessness, seizure and coma at high dosages (Dasgupta et al., 2000). Due to the clinical experience and its known toxicity, the Chinese Pharmacopoeia suggests that the safe dose of Chansu is only 0.015–0.03 g (Commission, 2010). As long as one stays within these standard acceptable parameters, the chance of toxicity is greatly reduced.

Based on the wholistic concept and individual therapy originated from principles of TCM, herbs are generally used in combination as formulas rather than as single herbs (Yin et al., 2008b). Ingenious drug compatibility can enhance the benefits and simultaneously decrease the side effects. With proper diagnosis and full understanding of the constituent herbs, TCM practitioners can adjust or customize the formulas to suit individual patients (Hsiao and Liu, 2010). More specifically, the foundation [Qi, blood, Yin, Yang, and the five elements (metal, wood, water, fire and earth)] for the development of one certain disease is quite different for each patient, and age, sex, psychology, race/ethnicity, living environment, etc., should be taken into consideration. Thus, treatment strategies against the same disease always vary with different patients.

However, though several aspects of control measures are implemented in clinical application, safety of PCHM is still a tough task. Quality of CHM may be significantly affected by species variation, geographical sources, harvesting, processing and storage, which has made quality control the most crucial issue in the process of modernization (Liang et al., 2009). Qualitative and quantitative analysis of active compounds are the most direct way to control CHM quality. Though a lot of modern techniques and methods of separation and characterization have been applied, the active constitutes of many CHM are scarcely known based on the existing knowledge (Wang et al., 2009b). Besides, as for PCHM, evaluation of the toxic components is also a must. Therefore, a large scale of basic elucidation of the corresponding toxic compounds is urgently in need, which will benefit not only the quality control of PCHM but also facilitates the exploration of new anticancer drugs from promising PCHM.

5. Novel PCHM-derived, anti-cancer natural products

At present, there are mainly four groups of plant-derived anti-cancer drugs in clinical use. They are vinca alkaloids (e.g., vinblastine and vincristine), epipodophyllotoxin derivatives (e.g., etoposide and teniposide), camptothecin derivatives (e.g., topotecan and irinotecan) and taxanes (e.g., paclitaxel) (Da Rocha et al., 2001; Efferth et al., 2007). All of these natural products are also traditionally used and recorded as poisonous herbs in TCM. Besides, there are still many other PCHM-derived compounds (arsenic trioxide, cantharidin derivatives, etc.) are also being applied in clinical trials. These drugs show strong therapeutic action in different types of cancers although their toxicities or side effects simultaneously exist and cannot be ignored (Table 2). In spite of their distinct toxicity, PCHM do represent a rich source for small-molecule inhibitors identification against novel anti-cancer targets (see Table 3). This fact speaks impressively for the power and the potential of PCHM. Specifically, we take a few compounds, namely gambogic acid, triptolide, arsenic trioxide, and cantharidin derived from PCHM as examples.

5.1. Gambogic acid

Gamboge resin, secreted by various *Garcinia* species including *Garcinia hanburyi* Hook. f. in Southeast Asia, is reported in traditional Chinese documents to possess diverse biological activities (Panthong et al., 2007). Gamboge resin also made its reputation as a poison, and was traditionally used in treating abscess, carbuncle and furuncle through transdermal administration. Gambogic acid (GA), the major active component of gamboge, has been demonstrated to be an important anti-cancer drug candidate for its excellent cytotoxic potential against various malignant tumors (Zhao et al., 2010b). What is more valuable is that the toxicity of GA was proved to be quite acceptable (Qi et al., 2008b), which is quite different from its parent plant. Currently, clinic trials of GA as a single agent are underway in China and phase II trial was recently finished (Wang et al., 2011a).

GA has been demonstrated to be a potent anti-cancer agent with diverse molecular targets through different mechanisms. GA presents potent effects on growth inhibition and G0/G1 cell cycle arrest in chronic myeloid leukemia cells via interruption of steroid receptor coactivator-3 (SRC-3) (Li et al., 2009). Thus far, although the apoptotic induction of GA is widely acknowledged, the precise mechanisms are still under debate. The binding to the transferrin receptor (TfR) (Kasibhatla et al., 2005), inhibition of Bcl-2 family proteins (Zhai et al., 2008) and topoisomerase II α (Qin et al., 2007) all explained the proapoptotic activity of GA. It also should be noted that a differential apoptotic induction of GA is observed in cancer cells and normal cells, suggesting the superiority of GA in clinical treatment (Yang et al., 2007). Meanwhile, it has been reported that GA significantly inhibits the proliferation, migration, invasion, tube formation and microvessel growth of human umbilical vascular endothelial cells (HUVEC) via inhibiting the activations of the vascular endothelial growth factor receptor 2 (VEGFR2) and its downstream protein kinases (Yi et al., 2008). GA also caused a dose-dependent suppression of cell invasion and obviously inhibited lung metastases of MDA-MB-435 cells in vivo via protein kinase C (PKC)-mediated matrix metalloproteinase-2 (MMP-2) and MMP-9 inhibition (Qi et al., 2008a).

Besides, conventional therapies combined with GA also exerted enhanced antitumor activity through synergistic or additive properties. Wang et al. reported that when combined with 5-fluorouracil (5-FU), GA induced considerably higher apoptosis rates in BGC-823 human gastric cells and remarkably inhibited tumor growth in human xenografts (Wang et al., 2009a). Celastrol, another natural product extracted from the traditional Chinese medicine "Thunder of God Vine", has seen to have a synergistic effect on the GA-induced apoptosis in oral cancer cells with little toxicity or side effects (He et al., 2009a). Further, low concentrations of GA are able to reverse docetaxel resistance though down-regulation of survivin in docetaxel-resistant BGC-823/Doc cells (Wang et al., 2008b). These findings suggest that GA may serve as a potent chemosensitizer in the treatment of human cancers.

5.2. Triptolide and tripterine

Tripterygium wilfordii Hook F. (TwHF), a famous poisonous plant, also known as "Thunder God Vine", is traditionally used to dispel wind, remove dampness, and relieve arthritis and pain in China. TwHF was historically recognized as a toxic herb for its frequently occurred side effects, including diarrhea, skin pigmentation, and

Table 2
PCHM-derived compounds used for cancer chemotherapy and their associated toxicity (Da Rocha et al., 2001; Xian-dao and Cun-ying, 2003; Hartmann and Lipp, 2006; Jilan et al., 2007; Jiangang and Hansheng, 2008; Liu et al., 2009; Song, 2010).

Active compound[a]	Organism name	Cancer type	Toxicity
Podophyllotoxin	*Sinopodophyllum hexandrum* (Royle) T.S. Ying or *Dysosma versipellis* (Hance.) M. Cheng	Lung, testicular cancer, lymphoma, leukemia, etc.	Myelosuppression, hypersensitivity reaction, nausea, vomiting, reproductive toxicity
Camptothecin	*Camptotheca acuminata* Decne	Ovarian, cervical, lung, colon, rectum, liver, stomach, leukemia, etc.	Diarrhea, nausea, vomiting, dyspnea, pneumonia, ancemia, myelosuppression, etc.
Arsenic trioxide	*Mineral*	Leukemia, myeloma, etc.	Cardiac disorders, hypokalemia, respiratory failure, cerebral infarction, etc.
Cantharidin	*Mylabris phalerata* Pallas or *Mylabris cichorii* Linnaeus	Liver, stomach, cardiac, lung, esophageal cancer, etc.	Nausea, vomiting, urinary system toxicity

[a] Chemical structures of the active compounds are shown in Fig. 1.

malfunction of the male and female reproductive system (Bao and Dai, 2011). However, due to its valuable anti-inflammation, immune modulation and anti-tumor activity (Brinker et al., 2007), the birth defect made no barrier to its application. Instead, TwHF has gained great momentum in the last few decades, and phase II clinical trials have been conducted to confirm the efficacy of its extracts in rheumatoid arthritis (Liu et al., 2011). TwHf is documented to contain more than 100 components such as diterpenes, triterpenes, sesquiterpenoids, and alkaloids. Triptolide and tripterine, two of the most widely studied and principal terpenoids that have been isolated from Thunder God Vine, have both been found to modulate diverse molecular targets involved in tumorigenesis, promising to turn traditional medicines into modern anti-cancer drugs.

Since the antileukemic effects firstly reported in 1972 (Kupchan et al., 1972), the anti-tumor activity of triptolide has been demonstrated in various tumor models, including promyelocytic leukemia, human hepatocellular carcinoma, cervical adenocarcinoma, pancreatic carcinoma, multiple myeloma (MM), cholangiocarcinoma, and oral cancer cells (Liu, 2011). Although discrepant conclusions have been obtained from the previous studies, triptolide seem to induce apoptosis via different pathways in various cell lines. For instance, triptolide induces apoptosis by the overexpression of the cytomembrane death receptor in cholangiocarcinoma cells (Clawson et al., 2010), while it also promotes apoptosis in leukemic by mediating mitochondrial mediated pathway (Carter et al., 2006). The potent inhibiting ability of triptolide in tumor angiogenesis has been verified in zebrafish embryo model, xenograft model and in vitro studies, where the down-regulation of nuclear factor-κB (NF-κB) signaling and the inhibition of vascular endothelial growth factor (VEGF) expression may contribute to the anti-angiogenesis action (Chang et al., 2007; He et al., 2009b; Zhu et al., 2010b). Further, triptolide is able to inhibit tumor metastasis against a broad spectrum of tumors (Yang et al., 2003; Zhang et al., 2006).

Tripterine, also known as celastrol, has different chemical structures from triptolide but shares several common properties (Salminen et al., 2010). Celastrol possesses anti-tumor activity against a broad spectrum of tumors, both in vitro and in vivo (Kannaiyan et al., 2011), which attributes to its multiple effects on apoptosis, cell cycle arrest, angiogenesis, and metastasis. Many signaling molecules are involved in the biological activity of celastrol, including the NF-κB (Sethi et al., 2007), activation of caspase family proteins (Yang et al., 2011a), VEGF receptors (Pang et al., 2010), heat shock proteins (Peng et al., 2010), potassium and calcium channels (Bai et al., 2003; Sun et al., 2006) and the immunoglobulin Fc epsilon receptor I (FcεRI) (Kim et al., 2009). In addition, celastrol also shows a synergistic effect when combined with chemotherapeutic agents, including radiation induced suppression of the proliferation of melanoma, ovarian cancer and lung cancer (Chen et al., 2009a; Zhu et al., 2010a; Lee et al., 2011). These results may open new opportunities for enhancing the effectiveness of future treatment regimens with celastrol.

5.3. Arsenic trioxide

In nature, arsenic is a commonly occurring substance that mainly exists as red arsenic (As_2S_2, referred to as realgar), yellow arsenic (As_2S_3, referred to as arsenikon), white arsenic (As_2O_3, or arsenic trioxide), phenylarsine oxide (C_6H_5AsO) and also as sodium, potassium, and calcium salts (Waxman and Anderson, 2001). For more than 2400 years, arsenic has been widely used as a powerful TCM for a variety of diseases, including ulcers, plague, and malaria (Emadi and Gore, 2010). The history of arsenic application is just a history of coping with its toxicity, for its potent toxicity and the resulting name “King of Poisons”. Arsenic is considered one of the most significant hazards in the environment, affecting millions of people around the world (Tapio and Grosche, 2006). The International Agency for Research on Cancer (IARC) designated arsenic and arsenic compounds as group I carcinogens (Huff et al., 2000). The past 100 years has seen a distinct decline in arsenic use for safety reasons, however, in 1992, Chinese researchers published the results of a trial that intravenous administration of arsenic trioxide produced a complete response (66%) in 21 of 32 patients with APL (Sun et al., 1992), rekindling once again more attention to arsenic.

To date, although the precise mechanism of arsenic trioxide action is incompletely understood, what is certain is that administration of arsenic trioxide by intravenous infusion is remarkably safe. In 2000, the FDA approved arsenic trioxide injection, Trisenox™, as a first-line chemotherapeutic agent for the treatment of APL. By affecting multiple pathways, arsenic trioxide spurs profound cellular alterations, including induction of apoptosis, stimulation of differentiation, inhibition of proliferation, and angiogenesis (Emadi and Gore, 2010). Interestingly, these functions execute in a dose-dependent manner. At low concentrations (0.1–0.5 μM), arsenic trioxide induces differentiation of APL cells through inactivation of the PML-RARα fusion protein (Zhang et al., 2000), while causing apoptosis via a number of mechanisms at high concentrations (0.5–2.0 μM) (Chen et al., 1997b). The activation of caspase cascade, the decrease of mitochondrial membrane potential $\Delta\Psi_m$, the production of reactive oxygen species (ROS) (Rojewski et al., 2004), down-regulation of Bcl-2 expression (Qin et al., 2008), and perturbation of the mitochondrial permeability transition pore (Larochette et al., 1999) all play roles in the induction of As_2O_3-induced apoptosis. Exposing a number of cancer cell lines to arsenic trioxide could induce G1 and/or G2–M phase arrest, which may attributed to the down-regulation of cyclin-dependent kinase2 (CDK2), CDK6, cyclin D1, etc. (Dilda and Hogg, 2007). Meanwhile, angiogenesis as a critical influence of the growth of solid tumors may also contribute to its antileukemic efficacy (Roboz et al., 2000).

Although possessing a selective toxicity for APL cells, arsenic trioxide also shows promising activity in various solid tumors, such as liver cancer (Oketani et al., 2002), pancreatic cancer (Li et al., 2002), breast cancer (Chow et al., 2004), gastric cancer (Wu et al., 2010), etc., and additional thorough research work is being conducted in

Table 3
Examples of compounds derived from PCHM with anticancer property.

Active compound[a]	Parental CHM and plants	Biological activity of corresponding CHM	Evidence of anticancer activity	Chemical analogues with anticancer activity[a]	Ref.
Gambogic acid	Tenghuang (Gamboge) *Garcinia hamburgy* Hook. f.	Anti-microbial, anticancer, analgesic, anti-pyretic	*Preclinical*: disturbs the cell cycle; induces apoptosis; suppresses cell invasion and inhibits metastases.	Gambogenic acid	Kasibhatla et al. (2005), Li et al. (2009), Qi et al. (2008a), Qin et al. (2007), Yi et al. (2008), Zhai et al. (2008)
Triptolide	Leigongteng (Common Threewingnut Root) *Tripterygium wilfordii* Hook. f.	Anti-inflammatory, anti-cancer, immunosuppression, analgesic, anti-fertility, anti-microbial	*Preclinical*: induces apoptosis; inhibits angiogenesis; inhibits tumor metastasis.	Tripterine	Carter et al. (2006), Chang et al. (2007), Clawson et al. (2010), He et al. (2009b), Yang et al. (2003), Zhang et al. (2006), Zhu et al. (2010b)
Arsenic trioxide	Pishuang (Arsenic)	Anticancer	*Preclinical*: induces apoptosis; disrupts the cell cycle; induces differentiation. *Clinical*: potentiates the activity of chemotherapeutic agents, induce remission and prolongs stable disease.	Realgar	Berenson et al. (2007), Chen et al. (1997a,b), Dilda and Hogg (2007), Larochette et al. (1999), Munshi et al. (2002), Qin et al. (2008), Roboz et al. (2000), Rousselot et al. (2004), Zhang et al. (2000), Zhao et al. (2001)
Cantharidin	Banmao (Mylabris) *Mylabris phalerata* Pallas or *Mylabris cichorii* Linnaeus	Anticancer, anti-virus, elevate leukocyte	*Preclinical*: induces apoptosis. *Clinical*: potentiates the activity of chemotherapeutic agents, improves immunity, relieves pain, prolongs survival.		Bonness et al. (2006), Cui and Yao (2008), Knapp et al. (1998), Liu and Chen (2009), Quan and Jian (2000)
Cucurbitacin B	Guadi (Muskmelon Base) *Cucumis melo* L.	Liver-protection, anti-cancer, increase capillary permeability, immunomodulatory	*Preclinical*: selectively inhibits the activation of the JAK2/STAT3 signal transduction pathway; causes considerable changes in the organization of the actin cytoskeleton in cells; affects cell adhesion	Cucurbitacin E	Duncan et al. (1996), Escandell et al. (2008), Haritunians et al. (2008), Musza et al. (1994), Thoennissen et al. (2009), Wakimoto et al. (2008), Yin et al. (2008a)
Bruceantin	Yadanzi (Brucea Frutus) *Brucea javanica* (L.) Merr.	Anti-cancer, anti-malarial, anti-amoeba, immunomodulatory	*Preclinical*: induces cell differentiation and down-regulate c-MYC; induces apoptosis involving the caspase and mitochondrial pathways. *Clinical*: phase I and II clinical trials were initiated without observing objective tumor (e.g., metastatic breast cancer, malignant melanoma, etc.) regressions and then clinical development was terminated. But recently there are voices that bruceantin should be reinvestigated for clinical efficacy against hematological malignancies.	Brusatol	Bedikian et al. (1979), Cuendet et al. (2004a,b), Cuendet and Pezzuto (2004), Elgebaly et al. (1979), Lia et al. (1976)
Bufalin	Chansu (Toad venom) *Bufo bufo gargarizans* Cantor or *Bufo melanostictus* Schneider	Cardiotonic, anaesthetic, blood pressure stimulation, excited respiration, anticancer, anti-inflammatory, anti-microbial, analgesic, anti-tussive, immunomodulatory	*Preclinical*: induces differentiation correlated with Na^+-K^+-ATPases inhibition, ERK cascade and PKC isozymes; induces apoptosis regulated by a range of cell signals (e.g., p53- and Fas-mediated pathways, PI3K/Akt pathway, Rac-1-PAK-JNK pathway, MAPK pathway, JNK pathway, mitochondrial pathway, etc.); disrupts the cell cycle associated with cyclin A, cyclin D3, $p21^{WAF1}$; inhibits angiogenesis	Cinobufagin, bufotalin, resibufogenin, telocinobufagin	Kurosawa et al. (2001), Lee et al. (1996), Qi et al. (2010), Takai et al. (2008), Yamada et al. (1998), Zhang et al. (1992)

Table 3 (*Continued*)

Active compound[a]	Parental CHM and plants	Biological activity of corresponding CHM	Evidence of anticancer activity	Chemical analogues with anticancer activity[a]	Ref.
Gnidimacrin	Ruixiang Langdu (Stellerae Chemaejasmes Radix) *Stellera chamaejasme* L.	Anti-cancer, anti-microbial, pesticide	*Preclinical*: regulates the cell cycle through p21(WAF1/Cip1) induction and cdc2 repression		Yoshida et al. (2001), Yoshida et al. (2003), Yoshida et al. (2009)
Chamaejasmine			*Preclinical*: inhibits β-tubulin depolymerization; Induces Apoptosis through a Ros-mediated. Mitochondrial pathway and Akt inactivation.	Neochamaejasmin A, isochamae-jasmin	Fang et al. (2011), Liu et al. (2008a), Tian et al. (2005), Wang et al. (2011c), Yu et al. (2011)
Pseudolaric acid B	Tujingpi (Pseudolaricis Cortex) *Pseudolarix kaempferi* Gord.	Anti-fungal, anti-cancer, anti-fertility	*Preclinical*: inhibits angiogenesis by Interacting with a novel binding site on tubulin and abrogating paracrine stimulation of VEGF; induces apoptosis via p53 and Bax/Bcl-2 pathways, activation of c-Jun N-terminal kinase and caspase-3; disrupt the cell cycle via the ATM signaling pathway; reverse multi-drug resistance.	Pseudolaric acid A	Gong et al. (2006), Gong et al. (2004, 2005), Li et al. (2004), Meng and Jiang (2009), Tong et al. (2006), Wong et al. (2005)
Jolkinolide B	Langdu (Euphorbiae Fischerianae Radix) *Euphorbia fischeriana* Steud.	Analgesic, sedative, anti-cancer	*Preclinical*: induces differentiation of LNCaP cells, apoptosis and arrests the cell cycle of K562 cells, LNCaP cells	17-Hydroxy-jolkinolide B, 17-acetoxy-jolkinolide B	Liu et al. (2002), Luo and Wang (2006), Wang et al. (2009c)
Polyphyllin D	Chonglou (Paridis Rhizoma) *Paris polyphylla* Smith. Var. *Chinensis* (Franch.) Hara. or *Paris polyphylla* Smith. Var. *Yuannanensis* (Franch.) Hand. Maxx.	Preventing cough, anti-tussive, anti-microbial, anti-cancer	*Preclinical*: reverse multi-drug resistance; induces endoplasmic reticulum stress followed by mitochondrial apoptotic pathway; inhibits expression of HIF-1α and VEGF mRNAs.		Lee and Chan (2005), Lee et al. (2009), Ma et al. (2009), Ong et al. (2004), Siu et al. (2008), Xiao et al. (2009)
Yuanhuacine	Yuanhua (Genkwa Flos) *Daphne genkwa* Sieb. et Zucc.	Diuretic, anti-tussive, analgesic, sedative, anti-microbial, anti-fertility, anti-leukemia	*Preclinical*: induces apoptosis involving many tumor-related genes and proteins (e.g., procaspase-3, PARP, Bax, Bcl-2, Bcl-X_L); inhibits DNA topoisomerase I.	Genkwadaphnin	Park et al. (2007), Zhang et al. (2009)
Colchicine	Lijiang Shancigu (Cormus Iphigeniae) *Iphigenia indica* A. Gray	Anti-gout, anti-cancer, liver-protection, anti-inflammatory	*Preclinical*: anti-mitotic agent interacting with tubulin and perturbs the assembly dynamics of microtubules.		Bhattacharyya et al. (2008)
Securinine	Yiyeqiu (Suffrutescent Securinega Twig) *Securinega suffruticosa* (Pal1.) Rehd.	Central stimulant, anti-cancer	*Preclinical*: induces differentiation through the activation of DNA damage signaling; induces autophagic by increasing Beclin-1 level; disrupts the cell cycle.		Subramanian (2011), Xia et al. (2011)
Matrine	Shandougen (Sophorae Tonkinensis Radix et Rhizoma) *Sophora tonkinensis* Gagnep.	Liver-protection, anti-microbial, anti-cancer, anti-ulcer, anti-inflammatory, anti-arrhythmic, immunomodula-tory	*Preclinical*: induces differentiation by decreasing c-myc mRNA expression level; induces apoptosis via mitochondrial pathway, MAPK Pathways and involving Fas, FasL, caspase-3, Bcl-2, Bax, cytochrome C, etc.; inhibits the invasiveness and metastasis of A375 cell.	Oxymatrine	Jiang et al. (2007), Li et al. (2006, 2007), Liu et al. (2006, 2008b), Zhang et al. (2001)

[a] Chemical structures of the active compounds are shown in Fig. 1.

this area. Of particular note, a promising application prospect has been demonstrated when arsenic trioxide is combined with other agents (Lin et al., 2005; Guo et al., 2006), indicating that greater benefit and lower toxicity in the application of arsenic trioxide is highly possible.

5.4. Cantharidin and cantharidin derivatives

Plenty of defensive secretions are produced by insects against foreign invasions and these molecules represent an attractive reservior of small molecules with potential as anti-cancer drugs

(Ratcliffe et al., 2011). Possessing both significant medicinal and toxic effects, the use of blister beetle (or *Mylabris phalerata*) as a traditional medicine in China dates back to more than 2000 years. These dried insect bodies are traditionally used to treat warts and molluscum through topical administration (Wang, 1989; Rauh et al., 2007). Meanwhile, the toxicity of blister beetle was also observed early which in contact with the skin causes blistering and also with the risk of aborticide. Cantharidin, the major bioactive compound in *Mylabris*, has been long acknowledged for its anti-tumor activity (Wang, 1989). However, in 1962 the status of cantharidin was changed, owing to the failure of its manufacturers to submit efficacy data to the Food and Drug Administration (FDA) (Moed et al., 2001). Half a century later, the potential of cantharidin has been further deeply elucidated, and its anti-tumor activity is considered primarily due to its potent and selective inhibitive ability on serine/threonine protein phosphatases 1 and 2A (PP1 and PP2A) (Knapp et al., 1998). Inhibition of protein phosphatases has been shown to regulate multiple cellular processes, through which cantharidin trigger G2/M arrest and apoptosis mediated by the mitochondrial caspase cascade (Liu and Chen, 2009). Moreover, cantharidin has been shown to increase the level of Bax, inhibit the level of Bcl-2 and survivin expression (Zhang et al., 2005), subsequently inducing apoptotic cell death (Bonness et al., 2006). Remarkably, inspired by the structure of cantharidin, there has been more/recent intense interest in developing potent and selective inhibitors of PP1 and PP2A on tumor cells (Liu and Chen, 2009). The successful experience provides very good example for excavating novel anti-tumor targets enlightened by PCHM.

The toxicity of cantharidin, particularly for the urinary system of mammals, remains a challenge for its development in the clinical application. Scientists have persisted in the search to maximize its potential and many cantharidin derivatives with significantly enhanced effect of cancer chemotherapy and simultaneously a remarkable improvement in toxicity have been synthesized (Thaqi et al., 2010; Yeh et al., 2010; Zhang et al., 2010). Norcantharidin, the demethylated cantharidin, possesses the advantage of easy synthesis and reduced intrinsic toxicity while still retaining a comparable anti-tumor property for cantharidin. In China, norcantharidin as an anti-cancer drug is currently used to treat breast cancer, hepatoma, leukemia, colon cancer, etc. The well-studied mechanisms for the anti-cancer activity of norcantharidin are its activity of inducing apoptosis via regulation of Bcl-2 superfamily member proteins and caspase activities (Chang et al., 2010), interruption of cell cycle arrest at G2/M phase (Liao et al., 2011), and inhibition of cell metastasis by down-regulates MMP-9 expression (Chen et al., 2009b). It was recently reported that mitogen-activated protein kinases (MAPKs) and signal transducers and activators of transcription (STATs) pathways are also involved in norcantharidin-induced apoptogenesis (Yang et al., 2011b).

6. Conclusions and prospects

TCM has played, and still plays, an important role in primary health care in China due to its magical and unique effects. "Fighting fire with fire" represents a distinctive thinking style of Chinese practitioners and this idea has set its proper position in cancer therapy. The impact of PCHM on anticancer drug discovery was enormous in the past years, it was certainly that the influence will continue since PCHM is a huge community and from which more and more promising candidates are being explored. Recently, phytochemistry and molecular biological approaches have further helped to elucidate the material foundation and pharmacological mechanisms of PCHM. Certainly, several crucial issues in the research and application need to be emphasized.

Demands for quality and safety control of CHM have urgently increased since TCM are getting more and more popular around the world. In 2005, the Commission of the European Pharmacopoeia decided to establish the monographs of approximately 100 Chinese herbal drugs, and till now 9 Chinese herbs have been accepted by the European Pharmacopoeia (Bauer and Franz, 2010). This is a well beginning, however, at present most PCHM still lack persuasive toxicological experimental data, and the precise mechanisms of most adverse reactions are not yet clear, which remains a main obstacle for the further development. For PCHM, their toxic constitutes, in most cases, simultaneously posses therapeutic effects. Studies on poisonous constitutes, including their pharmacology, toxicology, as well as the mechanism of detoxification of traditional measures, are of great importance for the safety of PCHM (Normile, 2003; Li et al., 2008). Take aconite as example, since the mechanisms of its toxic/active constitutes and the detoxification process were well conducted, the Chinese Pharmacopoeia (Commission, 2010) stipulates that the total content of the high-toxic diester diterpene alkaloids including aconitine, mesaconitine and hypaconitine in Chuanwu (Aconiti Radix) should be ranged from 0.05% to 0.17%. While the quality of Fuzi (Aconiti lateralis radix praeparata) is controlled by detecting the diester diterpene alkaloids (no more than 0.02%), the total alkaloids (no less than 1.0%) and three low-toxic alkaloids including benzoylmesaconine, benzoylaconine and benzoylhypacoitine (total content no less than 0.01%). Unlike aconite, there are still many poor-studied PCHM [e.g., Banxia (Pinelliae Rhizoma), Leigongteng (Common Threewingnut Root), Mengchong (Gadfly), Badou (Crotonis Fructus), etc.] that lack of enough scientific data on their toxic components, and thus results in the incompletion of quality control (Commission, 2010).

Another reason for such a bottleneck is the irrationality of toxicity evaluation methodology, which is unable to capture the special features of PCHM, such as the interactions among various biological constitutes. Therefore, more reasonable pharmacological evaluation systems are recommended to fully understand and evaluate the safety of PCHM. Fingerprint technique may be an effective method to evaluate the CHM quality because it presents the entire composition of the chemical components and their relative concentration (Liang et al., 2004; Liu et al., 2007). Besides, by analyzing the metabolite differences in holistic context, metabolomics is increasingly becoming a research hotspot and will provide an effective technology in safety evaluation (Wang et al., 2011b). The modernization of PCHM should be started from providing sufficient scientific toxicity data, and advanced technologies like fingerprint and metabolomics will play an indispensable role.

TCM is a complex system, herbal formulations are always used to prevent and treat diseases by an integration of multi-level, multi-target and coordinated intervention effects based on the mass bioactive constituents. However, researches on PCHM at present are mainly focused on the single active ingredient, few researches are involved in the herbal formulations of PCHM. There are evidences suggesting that the combination of multiple herbs could hit multiple targets and reduce the adverse effects (Zhao et al., 2010a). For instance, it is reported that Realgar-*Indigo naturalis*, a herbal formulation containing Realgar, *Indigo naturalis*, *Salviae miltiorrhizae* and Radix Pseudostellariae, had exerted a synergic effect in treating APL (Wang et al., 2008a). There are numerous herbal formulations containing PCHM with better curative efficacies and fewer side effects that have been used in China for many years, their potential and underlying mechanisms should be paid more attention to.

The combination use of chemotherapeutic agents and PCHM with distinct molecular mechanisms is considered to be a promising therapeutic strategy with a higher clinical efficacy and a better patient survival. Clinically, many chemotherapeutic agents are, in

Fig. 2. The research framework of PCHM is built up from many aspects, more sophisticated technologies and more suitable research methodologies are needed.

fact, used together in combinations, not only to enhance the efficacy of the treatment, but also to avoid the build-up of resistance in cancer cells. Moreover, combination treatment may also decrease the systemic toxicity caused by chemotherapies or radiotherapies, and efficacy can then be achieved with lower doses. Encouragingly, a series of sensitizers to conventional chemotherapy and radiotherapy from PCHM has been reported, and these results may help develop new orientations for the more rational utilization of PCHM.

Conventional chemotherapeutic agents are distributed non-specifically in the body, which has made tissue selectivity one of the most watched issues in pharmaceutical research. The basic purpose of chemotherapy is to increase survival time and the quality of life in patients, but the effective dose within the solid tumor is always unfeasible due to the severe side effects that occur on normal tissues. By the same token, application of PCHM for cancer therapy is limited by the non-selective virulence that affects both normal and tumoral tissues. Against this backdrop, the idea of exploiting novel drug delivery systems (DDS) for tumor targeting therapeutics becomes particularly noticeable and pressing. Nanotechnologies bring a real innovation for cracking many medical hard nuts. So far, nanomedicine has become an emerging field that holds great potential for dealing with cancer at the molecular scale and improving the resolution of tumor imaging to act on specific cancer cells (Jain and Stylianopoulos, 2010; Wang and Thanou, 2010). For example, norcantharidin has been successfully entrapped in PLGA nanoparticles by using an interfacial deposition method. Both in vitro and in vivo anti-tumor activity studies suggested that norcantharidin-loaded PLGA nanocarriers have not only low system toxicity, but also high efficacy for anti-tumor growth (Zeng and Sun, 2009). Target DDS of PCHM, using various carriers, is shedding new light on the application of the effective parts or monomers extracted from PCHM. Though voluminous studies have focused on this area, the development potential still deserves further research (Fig. 2).

Currently, cancer therapy has become a multidisciplinary challenge that requires close cooperation among clinicians, materials scientists, and biomedical engineers. Despite the excellent anticancer activities, the clinical use of PCHM still has challenges to overcome. A large number of sophisticated technologies and more suitable research methodologies should thus be applied in tight conjunction, which will facilitate the development of PCHM and its derived products for rational cancer therapy. We believe that the full potential for PCHM will be displayed in the years to come, and the natural products derived from PCHM can potentially be of extreme importance in devising new drugs and providing unique ideas for the war against cancer.

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