Journal of Ethnopharmacology 140 (2012) 33–45

Contents lists available at SciVerse ScienceDirect

Journal of Ethnopharmacology

journal homepage: www.elsevier.com/locate/jethpharm

Review

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

Shengpeng Wang[a,1], Xu Wu[b,1], Miao Tan[a], Jian Gong[a], Wen Tan[a], Baolin Bian[b], Meiwan Chen[a,*], Yitao Wang[a,*]

[a] State Key Laboratory of Quality Research in Chinese Medicine, Institute of Chinese Medical Sciences, University of Macau, Macau 999078, China
[b] Institute of Chinese Materia Medica, China Academy of Chinese Medical Sciences, Beijing 100700, China

ARTICLE INFO

Article history:
Received 23 September 2011
Received in revised form
22 December 2011
Accepted 23 December 2011
Available online 14 January 2012

Keywords:
Poisonous CHM
Cancer therapy
Toxicity
Safety
Novel PCHM-derived compounds

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.

* Corresponding authors at: Institute of Chinese Medical Sciences, University of Macau, Av. Padre Tomas Pereira S.J., Taipa, Macau, China.
E-mail addresses: mwchen@umac.mo, chenmeiwan81@163.com (M. Chen), ytwang@umac.mo (Y. Wang).
[1] These authors contributed equally to this work.

0378-8741/$ – see front matter.
doi:10.1016/j.jep.2011.12.041

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