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REVIEWS

Integrated analysis on the "toxicity-efficacy" of toxic Chinese materia medica

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[Abstract] The Chinese materia medica (CMM) has been applied in the prevention and treatment of many diseases for thousands of years, including common diseases, frequently-occurring diseases, and rare diseases with remarkable curative effects. However, due to abuse or misuse, environmental pollution, and improper preparation methods in clinical application, some CMM present safety problems, such as cardiac toxicity, liver toxicity, neurotoxicity, renal toxicity, and even carcinogenic effects. Based on the coexistence characteristics of toxicity and efficacy of toxic CMM, integrated analysis is a powerful method to systematically study traditional Chinese medicine (TCM). In our review, scientific connotation of toxic CMM-induced toxicity and efficacy, including historic development and characteristics of toxic CMM, and challenges for evaluating the toxicity and efficacy of toxic CMM were summarized. Hereby, we put forward the integrated analysis thought and methods for "material basis of toxicity-efficacy, mechanisms of toxicity-efficacy, synergy and attenuation principles" of toxic CMM, as well as taking *Radix Aconiti Lateralis Preparata* (namely Fuzi) as the representative to elaborate the integrated analysis path on the "toxicity-efficacy" of toxic CMM, which provides scientific evaluation ideas and criterion of clinical application for CMM in the prevention and treatment of diseases in accordance with the characteristics of TCM.

[Key words] Toxic Chinese materia medica; Toxicity-efficacy; Integrated analysis; Traditional Chinese Medicine; *Radix aconiti lateralis preparata* (Fuzi)

1 Introduction

The effectiveness and safety of the Chinese materia medica (CMM) that has always received more and more attention is a solid foundation for inheritance, development, and utilization of traditional Chinese medicine (TCM). The fundamental prerequisite of TCM service for the global health is to guarantee the effectiveness and safety of CMM. The unclear definition and insufficient understanding of "toxic CMM" for a long time have seriously hindered the development of TCM. Kidney failure caused by CMM for weight loss in Belgium (containing aristolochic

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acid), interstitial pneumonia induced by Little Bupleurum Decoction in Japan, coptidis poisoning event in Singapore, American ephedra event, and Chinese patent medicine containing excessive heavy metal in Hong Kong have led to a misunderstanding of the toxicity of CMM[1-2]. Toxic CMM can induce toxicity or side effects on the body at a small dose due to overuse or misuse. At present, toxic CMM is divided into traditional and modern toxic CMM[3]. The former is usually recorded in traditional Chinese herbal medicine historical literature, and the latter is mainly found in modern toxicology research. These toxic CMM often have significant effects on some severe or incurable diseases, which have both toxicity and efficacy. Moreover, the toxicity of toxic CMM can be reduced by various traditional methods, such as processing by rules, medication by symptoms, reasonable compatibility, and dosage control, according to the guidance of TCM theory[4]. Thus, the "toxicity-efficacy" of toxic CMM should be systematically evaluated to promote the clinical safety of CMM and guide the public to objectively and truly understand the scientific connotation of toxic CMM.

In this review, based on the idea of "systemic CMM" and scientific connotation of toxic CMM-induced toxicity and efficacy, integrated research thought and methods for "material basis of toxicity-efficacy, mechanisms of toxicity-efficacy, synergy and attenuation principles" of toxic CMM was proposed. In addition, *Radix Aconiti Lateralis Preparata* (namely Fuzi) was chosen as the representative to elaborate the integrated analysis path on the "toxicity-efficacy" of toxic CMM, which provides research ideas and methods for scientific and systematic evaluation on the "toxicity-efficacy" of toxic CMM[3, 5].

2 Scientific connotation of toxic CMM-induced toxicity and efficacy

2.1 Historical development of toxic CMM

TCM has a long history of understanding the "toxicity-efficacy" of CMM, which is a knowledge and technology system gradually formed during the medical practice of long-term struggle against diseases and modern pharmacology and toxicology research. Records on the "toxicity-efficacy" of CMM in the existing herbal literature in China were first found in the "Shennong's Classic of Materia Medica", which labeled "toxic or non-toxic" to indicate the properties of drugs. 365 kinds of drugs contained in this literature were divided into three grades based on the toxic or non-toxic and life-span prolongation or diseases elimination. The lowest grade with high toxicity needs to be forbidden taking for a long time, such as euphorbia, *Flos Genkwa*, *Radix Kansui*, aconitum, Fuzi, and croton, which are highly toxic to the body. The literature labeled "toxicity" under the entry for specific drugs was found in "Wupu's Materia Medica". Subsequently, various "toxic or non-toxic" CMM were recorded, and their toxicity according to large, toxic, small or slightly toxic was recognized in Materia Medica. In addition, "Zhou Li · Tianguan" recorded that the physician was in charge of medicine and used poisons for medical treatment. "Classified Canon Volume XIV" pointed out that every drug that avoided evil could be called poisons. In the Eastern Han dynasty, the physician considered that poison was equal to medicine or side effects. However, if these toxic CMM are applied properly, the curative effect will be outstanding, which is used by famous medical masters in the past to treat diseases. Modern research on the "toxicity-efficacy" of CMM really began in the middle of the 19th century. After western medicine entered China, medical scientists began to apply modern toxicology theories, techniques, and methods to study the toxicity, mechanism and material basis of CMM. The 2015 edition of "Chinese Pharmacopoeia" contained a total of 83 kinds of poisonous Chinese herbal medicines and pieces, including 10 kinds of strong toxic CMM, 42 kinds of toxic CMM, and

31 kinds of mild toxic CMM. In recent years, more traditional and modern toxic CMM were widely studied, including *Radix Aconiti*, *Radix Aconiti Kusnezoffii*, *Monkshood*, *Tripterygium wilfordii*, S*emen strychni*, pinellia, euphorbia, *Flos Genkwa*, *Venenum bufonis*, arsenic, realgar, vermilion, Xanthium, *Airpotato Yam Rhizome*, *Polygonum multiflorum*, psoralen, aristolochic acid, Bupleurum total saponin, and pyrrolizidine alkaloids[6].

2.2 Characteristics of toxic CMM

2.2.1 Diverse material basis

The material basis of CMM is extremely abundant, containing a variety of toxic and effective ingredients. According to chemical structure of components in toxic CMM, the main risk substances reported in the literature include alkaloids, glycosides, terpenes and lactones, toxic proteins, and heavy metals. Alkaloids include aconitine derived from *Radix Aconiti, Radix Aconiti Kusnezoffii, Monkshood*, wilfordine extracted from *Tripterygium wilfordii and Tripterygium hypoglaucum*, brucine derived from *Semen strychni*, scopolamine and scopolamine containing in *Datura metel* L., and nicotine and coniine in *Rhizoma Pinellia, Rhizoma Arisaematis*. Glycosides mainly include cardiac glycosides derived from digitalis, evergreen, octagonal maple, and oleander, cyanogenic glycosides containing in almond and peach kernel, saponins extracted from *Radix Phytolaccae* and *Airpotato Yam Rhizome*, and flavonoid glycosides in *Flos Genkwa* and *Subprostrate Sophora Root*. Terpenes and lactones, such as absinthin and coriamyrtin, mainly present strong local irritant effects, including induction of liver cell damage and inhibition of the central nervous system. Toxic proteins are commonly found in plant or animal toxins, such as croton, cocklebur, and castor bean[4]. In addition, some mineral CMM contain excessive heavy metals, including arsenic, mercury, and lead.

Toxic material basis are closely related to active material basis. Active ingredients of some CMM may be their toxic components. CMM at the appropriate dose will exert efficacy, while overdose will produce toxicity. For example, brucine derived from *Semen strychni* is not only an effective ingredient for anti-inflammatory and analgesic, but also induces neurotoxicity and nephrotoxicity. Integrated research for "dose-time-toxicity/efficacy" can systematically analyze the dose, time, and state of toxic CMM-induced toxic and effective effects[3]. Moreover, the effective and toxic components of some CMM may be different. For instance, the main pharmacological substances of *Senecio scandens* are alkaloids and flavonoids, while pyrrolizidine alkaloids are the key ingredient of *Senecio scandens*-induced hepatotoxicity. Interestingly, the active substance basis and toxic substance basis of some CMM can be converted to each other under different pathological conditions. Diester alkaloids in Fuzi can cause cardiotoxicity for the treatment of heart failure, while diester alkaloids are converted into an active ingredient for relieving pain. Both overdose and long-term administration with diester alkaloids will produce cardiotoxicity, neurotoxicity, and embryotoxicity.

2.2.2 Multi-toxic manifestations

According to the effects of toxic CMM on different levels of the body, toxicity caused by toxic CMM show targeting and integrity characteristics, including cytotoxicity, target organ toxicity and overall toxicity.

Cells are the basic unit of vital activities. Different substance basis of toxic CMM can directly or indirectly induce changes in the structure and function of target cells, thereby triggering cytotoxicity, which may involve cell morphology and ultrastructure, cell membrane stability, cell energy metabolism, key enzymes and receptors damage,

and cell proliferation activity. Our study showed that morphological damage occurred after exposure to 3% aconitine for 30 s, which was manifested with reduced cellular connectivity, increased voids, cell shrinkage, and visible granular particles in cells. Results of HE staining indicated that the pseudopodia of cells were shortened or reduced. The above-mentioned damage progressively worsened with the prolonged administration time with aconitine[7]. Furthermore, Na^+ and Ca^{2+} contents in cardiomyocytes increased significantly, and K^+ and Mg^{2+} levels decreased significantly, so that the activities of Ca^{2+} ATPase, Na^+-K^+ ATPase, and Ca^{2+}-Mg^{2+} ATPase in cardiomyocytes all decreased after aconitine treatment[8].

Toxic manifestations of toxic CMM on the body often present targeting for organs. For example, *Semen strychni* mainly damages the nervous system, respiratory system, digestive system, cardiovascular system, and urinary system. The early neurotoxic symptoms of *Semen strychni* poisoning were manifested with headache, dizziness, restlessness, muscle twitching, and difficulty swallowing. Liver morphology and liver function were affected in rats administrated with asarum powder for 4 weeks, which were mainly manifested with increased serum alanine transaminase (ALT) and total bilirubin (TBIL), elevated hepatocyte permeability, and even necrosis, indicating that the intake, binding, and excretion of bilirubin were affected in liver. Pyrrolizidine alkaloids contained in *Senecio* scandens have strong hepatotoxicity, which can induce cross-linking of DNA, RNA, and proteins, or form adducts with other substances, and the combination with cytoskeletal proteins in liver cells, thereby resulting in apoptosis and necrosis[4].

Toxic CMM with high toxicity, such as *Radix Aconiti, Radix Aconiti Kusnezoffii*, and *Semen strychni*, enter the body in a short time to induce systemic toxic symptoms soon. After gavage or intraperitoneal injection of *Radix Aconiti* extract at a dose of 10 g/mL in mice, toxic reaction showed a marked decrease in activity, hypersecretion, heartbeat from rapid to slow, mental weakness, fluffy and damp hair, increased stool, and then limb convulsion, pupils shrink, difficult breathing or even stop. In addition, toxic CMM with general toxicity can cause systemic poisoning symptoms after long-term overdose administration. For example, *Fructus Xanthii* water extract at a dose of 21 g/kg was given to rats by gavage for 28 consecutive days. As a result, rats successively showed reduced coat glossiness, depilation, decreased activity quantity and food intake, and lags in response[4].

2.2.3 Controllable toxicity

During the long-term clinical application and practice, CMM has accumulated and formed a series of methods to reduce or control toxicity and increase efficacy, mainly including selection of high-quality CMM, processing by rules, medication by symptoms, reasonable compatibility, and dosage control, and mastering methods of decocting and taking.

The toxicity of toxic CMM varies greatly depending on the place of origin. A comparative study of the toxicity of Fuzi in Sichuan, Shaanxi, Hubei, Chongqing, Yunnan, and other places of origin found that the toxicity of Fuzi in Yunnan was 18 times that of Fuzi in Sichuan[9]. Selection of high-quality CMM can control the content and toxicity of Fuzi. Diester alkaloids extracted from Fuzi are hydrolyzed to the less toxic monoester alkaloids during processing, such as benzoyl aconitine, benzoyl mesaconine, and benzoyl hypacomne, which are further hydrolyzed to alcohols aconitine, mesaconine, and hypacomne, thus reducing the toxicity by 70% to 80%[4]. Studies showed that raw Fuzi and salt Fuzi were more toxic, while processed products white Fuzi and black Fuzi tablets were significantly less toxic[10]. Toxic CMM should be applied according to the

state of the body or pathological characteristics, and otherwise cause adverse reactions. Studies found that hypertensive rats were more prone to aconitine-induced arrhythmias than hypotension rats[11]. The combination of toxic CMM with its own components or other CMM can regulate the relationship between toxicity and efficacy. Research showed that a reasonable combination could not only decrease the content of toxic components ester alkaloids, but also reduce toxicity and increase efficacy by studying the synergistic detoxification mechanism of Fuzi with licorice, Fuzi with dried ginger, Fuzi with ginseng, Fuzi with rhubarb and screening the best mixing ratio between effective components, toxic components, and toxicity control components[12]. Efficacy can be enhanced following the increased decoction time and dosage, and toxicity can be increased as the decoction time decreases and the dosage increases[13]. We established acute heart failure and Yang deficiency model with propafenone hydrochloride in rats. Results showed that the above decoction could significantly increase heart rate, and optimum decoction time and dosage were 6 h and 12 g/kg, respectively[14]. Overdose is one of the key factors of toxic CMM poisoning. Aconitine, hypoaconitine, and neo-aconitine at different doses show cardiotoxicity or cardioprotective effects. Hence, the principle of "starting with a low dose and gradually increasing the dosage" should be followed during clinical medication.

2.3 Challenges for evaluating toxic CMM-induced toxicity and efficacy

Both toxicity and efficacy of CMM exist objectively. However, it does not mean that any TCM will injury the body or cause toxic reactions under any circumstances. The toxicity and efficacy of CMM are mainly related to several factors, such as drugs, body status, and clinical application, which make the evaluation for the "toxicity-efficacy" of toxic CMM more complex. Due to diverse variety of CMM and different medication habits in different regions, the source of the variety and the part of the medication may varied. For instance, *Cyrtomium Rhizome* is non-toxic, while *Rhizoma Dryopteris Crassirhizomae* is toxic. North *Cortex Acanthopanacis* contains cardiac glycosides with strong toxicity, while south *Cortex Acanthopanacis* produced in Sichuan is non-toxic[15]. CMM in different regions, different seasons, and different plant ages have different active ingredients with differences in toxicity. The contents of toxic substances of Fuzi in different regions differ by as much as 8 times[16]. Individuals with different medications have different sensitivities and tolerances to toxic CMM. It is generally believed that individuals with strong resistance and long-term exposure to toxic CMM are more resistant to toxicity. There is a habit of eating Fuzi in winter in areas where Fuzi is cultivated. No toxic reactions occur when taking more than the usual amount of Fuzi[17]. In addition, there are many causes for CMM-induced toxicity. Overdose or misuse is the main causes for toxicity events induced by CMM. Individual responses are different after receiving different doses of CMM. The dose size varies from person to person and from place to place. Drugs do not correspond to the symptoms. Although the processing or compatibility is improper, CMM is still applied directly. *Radix Aconiti* decoction for 2 h at doses of 13.8 g and 6.9 g crude drug/kg had no effects on the neurobehavior of mice, while the neurobehavioral activity could be inhibited at a dose of 27.6 g crude drug/kg[4].

The "toxicity-efficacy" of toxic CMM has various substance foundations with a close relationship. Multi-component, multi-target/pathway, multi-effect characteristics of toxic CMM make the mechanism extremely complicated. Therefore, the target organs, target molecules, target pathways, pharmacokinetic changes, and the relationship between "dose-time-toxicity/efficacy" should be studied to clarify the mechanism of toxic

CMM-induced toxicity and efficacy, especially the transformation mechanism between toxic material basis and active material basis of toxic CMM. In addition, a series of effective methods for reducing toxicity and enhancing efficacy of toxic CMM with definite curative effects has been gradually formed during the long-term clinical practice, which is the original thinking for studying toxic CMM. However, the principle of synergy and attenuation of toxic CMM has not been fully uncovered. Therefore, we should scientifically explain the relationship between toxicity and efficacy of toxic CMM, systematically summarize the application rules, and analyze the material basis, mechanism, and principle of synergy and attenuation to promote the modernization and internationalization of studies on the "toxicity-efficacy" of CMM.

3 Integrated analysis thought and methods on the "toxicity-efficacy" of toxic CMM

3.1 Multi-dimensional evaluation and integrated analysis

Based on the integrity and complexity of CMM, the "variety, quality, preparation, property, efficacy, and application" of CMM should be systematically studied to build a multi-dimensional evaluation system of "drug-organism-application"[6,18]. "Variety" refers to varieties of medicinal materials, varieties of processed products, and varieties of Chinese patent medicines. For example, Fuzi, a single-base original plant, includes 4 subtypes, more than 30 kinds of processed products, of which 5 are recorded in the pharmacopoeia, and more than 300 Chinese patent medicines containing Fuzi[19]. "Quality" refers to the quality of the overall characteristics of CMM, including external and internal quality. Salt Fuzi is preferably large, heavy, grayish-black, with salt frost on the surface. Black Fuzi tablets with dark brown skin, oily and shiny cut surface, and white Fuzi with large, yellow-white and oily are preferred. "Preparation" mainly includes origin processing of CMM, processing of decoction pieces, extraction process, preparation process, and automated production. Medicinal property refers to the basic properties and characteristics of CMM on the body, which is the core of the basic theory of CMM and a distinctive sign that CMM differs from plant medicines and natural medicines. "Efficacy", the core of systemic CMM, is an important feature of systemic CMM that distinguishes from traditional herbal medicine and modern pharmacology. The clinical application of CMM mainly includes processing, compatibility, usage, and dosage, etc.

Toxic CMM have the characteristics of diverse substance basis, multiple toxic manifestations, and controllable toxicity. The "material basis of toxicity-efficacy, mechanisms of toxicity-efficacy, synergy and attenuation principles" of toxic CMM should be integrated analyzed. Specifically, we should scientifically analyze the toxicity and efficacy substance basis, action links, and effects of toxic CMM on the body, the dynamic process of drug absorption, distribution, metabolism, and excretion (ADME) in the body, as well as the conditions, processes, and outcomes of the mutual conversion between toxicity substance basis and efficacy substance basis under different pathological conditions. In addition, according to different synergy and attenuation methods, such as processing by rules, medication by symptoms, and reasonable compatibility, integrated analysis on the methods, processes, and mechanisms of the transformation between toxic substances and effective components in different application states and the theory, technology and clinical practice of synergy and attenuation should be carried out to cope with challenges for the "toxicity-efficacy" research of CMM[3, 5].

3.2 Integrated analysis methods

The integrated research on the "toxicity-

efficacy" of CMM guided by the theory of TCM should be directed to toxic CMM with prominent safety issues at home and abroad by using systematic toxicology, chemical biology, omics, and network pharmacology to explain the synergistic rules of multiple ingredients, multiple targets, multiple pathways, and multiple levels.

Chemical biology can be used to explore and manipulate biological systems through the novel chemical methods at the molecular level. Some small molecule probes, such as the phytotoxic components or animal drug toxins, are applied to study chemical and biological mechanism of toxic CMM, thereby revealing the interaction between material basis and target molecule and process of information transmission. Chemical biology will lay a theoretical foundation for the discovery of new drugs and drug safety. Systematic toxicology refers to the integrated analysis on the changes of gene expression profile, protein profile, and metabolic profile at different doses and at different time points after exposure to exogenous materials by bioinformatics and computer toxicology technology to systematically study the interaction between exogenous substances and the body. High-throughput omics, including genomics, transcriptomics, proteomics, metabolomics, interaction omics, and phenotyping omics, constitutes a technical platform for systematic toxicology. CMM, as a complex system with multiple genes, pathways, and target cells, regulates the body's balance and homeostasis. Therefore, we should not only study chemical components of single medicine or compound, but also reveal the interaction and regularity of various components on the body. Systematic toxicology is beneficial to the integrated study of toxic CMM-induced toxicity and efficacy. At present, omics technology has been widely used in various aspects, such as material basis, molecule mechanism, biomarkers, and safety evaluation of toxic CMM. For example, multi-directional metabolic transformation of toxic CMM can be revealed by metabolomics[20–21]. High-throughput information at the molecular, cell, and tissue levels can be integrated to systematically study the interaction between toxic substances and the body and construct multi-level and multi-scale prediction models to quantitatively evaluate drug safety. Toxicology mechanisms and new biomarkers of toxic CMM can be predicted through establishing research models, such as static network analysis and prediction, dynamic network simulation and harmful outcome paths[22].

Network pharmacology is in accordance with the dialectical thinking and the holistic view of TCM, which is suitably used to predict the role of multi-component, multi-target, and multi-path of CMM. Therefore, some scholars have proposed the "network target" hypothesis due to that CMM involving disease-related biological networks is different from single-targeted chemical drugs. Network target analysis methods, such as drug target prediction, are created to study the interaction network of "drug-target-toxicity/efficacy" of CMM, thus providing new ideas and methods for integrated analysis on the mechanism of CMM-induced toxicity and efficacy (Fig. 1)[23]. A "target-pathway" network and topological analysis were constructed to reveal the mechanism of toxicity

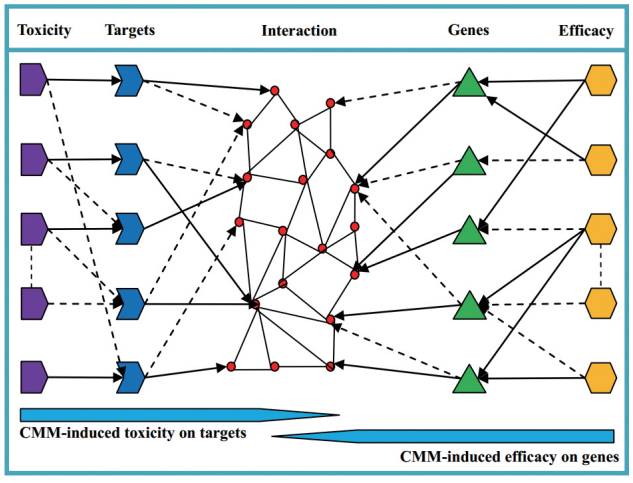

Fig. 1 Analysis on "drug-target-toxicity/efficacy" interaction network by network pharmacology

and efficacy effects of *Tripterygium wilfordii*. Results showed that *Tripterygium wilfordii* involved 65 targets mainly through the regulation of inflammation signaling and cancer signaling pathways for the treatment of immune disease and cancer, which might be related to apoptosis and drug metabolism enzymes[24]. The toxicity and efficacy division model of CMM based on the network target is expected to discover material basis, biomarkers, and mechanism of synergy and attenuation for CMM-induced toxicity and efficacy. Network pharmacology has become a new worthy path to study the relationship between the toxicity and efficacy of toxic CMM[25].

CMM are metabolized into prototype substance and various metabolites by means of several metabolic forms, which regulate the function of target cells. At present, the "multi-directional metabolism" modes of CMM include qualitative, quantitative, and internalized metabolism[20-21]. Qualitative metabolism refers to a series of phase I and II reactions that can occur in CMM under the action of various enzymes in the body, resulting in a change in chemical structure of drugs. Quantitative metabolism refers to the hydrolysis and degradation of the same components family of CMM through the intestinal flora, thus producing the prototype components of CMM with the changed proportion of each component. Internalized metabolism refers to that CMM can be metabolized into endogenous metabolic intermediates through multiple biological transformations, which are integrated into the human metabolic process or affect the endogenous small molecule metabolites in the body to present pharmaceutical effects. Studies have shown that active substances of many CMM, such as flavonoids, polyphenols, saponins, and alkaloids, are also the toxic substances when the dose is large, following some of the same targets, which is probably related to the alteration of drug metabolic process, form and products. Therefore, toxicokinetics and pharmacokinetic studies on toxic CMM are very important to reveal the relationship between the toxicity and efficacy of CMM[26-27]. Modern mass spectrometry (MS) technologies, including microdialysis-MS, ultra-high performance liquid chromatography-MS, atmospheric pressure ionization-MS and MS imaging technology, are widely applied for CMM metabolism and pharmacokinetics due to the advantage of high sensitivity and rapidity[28].

4 Integrated analysis path on the "toxicity-efficacy" of *Radix Aconiti Lateralis Preparata* (Fuzi)

In the past, we proposed and established a "multi-dimensional evaluation and integrated analysis" path for the diversity of Fuzi germplasm resources, the complexity of chemical components, the multi-direction of drug effects, and the extensiveness of clinical application guided by "systematic CMM", which basically clarified the dynamic change process between different spatial distribution, collection time, decoction time, chemical levels, and dynamic process between different dosages and effects of Fuzi, and basically revealed the material basis of "toxicity-efficacy", biological effects, and synergy and attenuation principles of Fuzi[3, 5, 29-31].

Fuzi, the lateral root of *Aconitum carmichaeli* Debx., has toxicity and efficacy on the body with a long history of application. As early as 140 BC, "Huai Nanzi" recorded that "Tianxiong and Wuhui are most virulent, but can be used to save lives by excellent doctors." The medical sage Zhang Zhongjing used 19 types of Fuzi prescriptions for reversing disease symptoms, dispelling cold and relieving pain, and warming the Yang and eliminating evil. Modern pharmacological research also showed that Fuzi had many pharmacological effects, such as cardiotonic, anti-inflammatory, sedative, and analgesic[32]. However, Fuzi with high toxicity is classified as the low grade. Fuzi induces poisoning symptoms

after orally taking with 0.2 mg, and leads to death after taking with 2 mg to 4 mg. Fuzi mainly acts on different target organs, including the heart, nervous system and embryos, which are manifested with heart rhythm abnormalities, limb numbness, convulsions, cerebral edema, and other symptoms[33]. Fuzi with a close "toxicity-efficacy" relationship has a rich material basis, mainly including C-19 and C-20 diterpene alkaloids, flavonoids, polysaccharides, sterols, and organic acids. C-19 diterpene alkaloids are the main "toxicity-efficacy" material basis of Fuzi with the highest content[34]. First of all, according to the toxicity and efficacy of Fuzi on different target organs, targeted research on different substance basis are carried out, including the correlation between substance basis and "toxicity-efficacy", the "dose-time-toxicity/efficacy" relationship, drug ADME process, and transformation mechanism of the "toxicity-efficacy" substance basis. Secondly, mechanisms of Fuzi-induced toxicity and efficacy on the molecules, cells, tissues, and organs levels is analyzed, which may involve ion homeostasis, oxidative stress, mitochondrial toxicity, apoptosis and autophagy, abnormal cell metabolism, or changes in signal transmission[35-37]. Systematic biology and network pharmacology provide an effective path for integrated analysis on the multi-dimensional relationship of "Fuzi-target-toxicity/efficacy". Finally, based on traditional synergy and attenuation methods, such as the selection of high-quality drugs, processing by rules, scientific preparation, medication by symptoms, reasonable compatibility, and dosage and duration control, the synergy and attenuation mechanism of Fuzi through systematic biology and network pharmacology are explored to clarify basic transformation methods, processes and mechanism of toxicity and efficacy substances in different application states. Therefore, the multi-dimensional relationship between "material basis (crude drugs-decoction pieces-components-ingredients)" - body (overall-organs-cells-molecules) - application (high quality materials-processed by rules-preparation methods-medication by symptoms-reasonable compatibility-dosage and duration control)" of toxic CMM is revealed to study "material basis of toxicity-efficacy, mechanisms of toxicity-efficacy, and synergy and attenuation principles" of Fuzi (Fig. 2).

During multi-dimensional evaluation and integrated analysis on the "toxicity-efficacy" of Fuzi, we found that a close correlation existed in the toxicity and efficacy of Fuzi. The main toxicity target organs of Fuzi are the heart, nerve system, and embryo. There are two types of substances with opposite effects in Fuzi, including toxic substances (diterpenoid alkaloids) and active substances (non-diterpenoid alkaloids). Toxic substance basis and active substance basis of Fuzi are able to be transformed in different states. For example, although diterpenoid alkaloids are the main toxic substance basis of Fuzi, they can be converted into active substances after hydrolysis when Fuzi presents anti-inflammatory and analgesic. Following different origins, processed products, preparation methods, and compatibility methods, the material basis and mechanism of Fuzi-induced toxicity and efficacy are different due to different disease states of the body. There is a complicated network relationship between "Fuzi-body-application".

5 Conclusion

We should correctly understand the scientific connotation of toxic CMM-induced toxicity and efficcy, grasp the characteristics of "multi-component, multi-effect, and controllable toxicity" of toxic CMM, and adopt chemical biology, systematic biology, network pharmacology and metabolic kinetics methods to integrally analysis the "material basis of toxicity-efficacy, mechanisms of toxicity-efficacy, synergy and attenuation

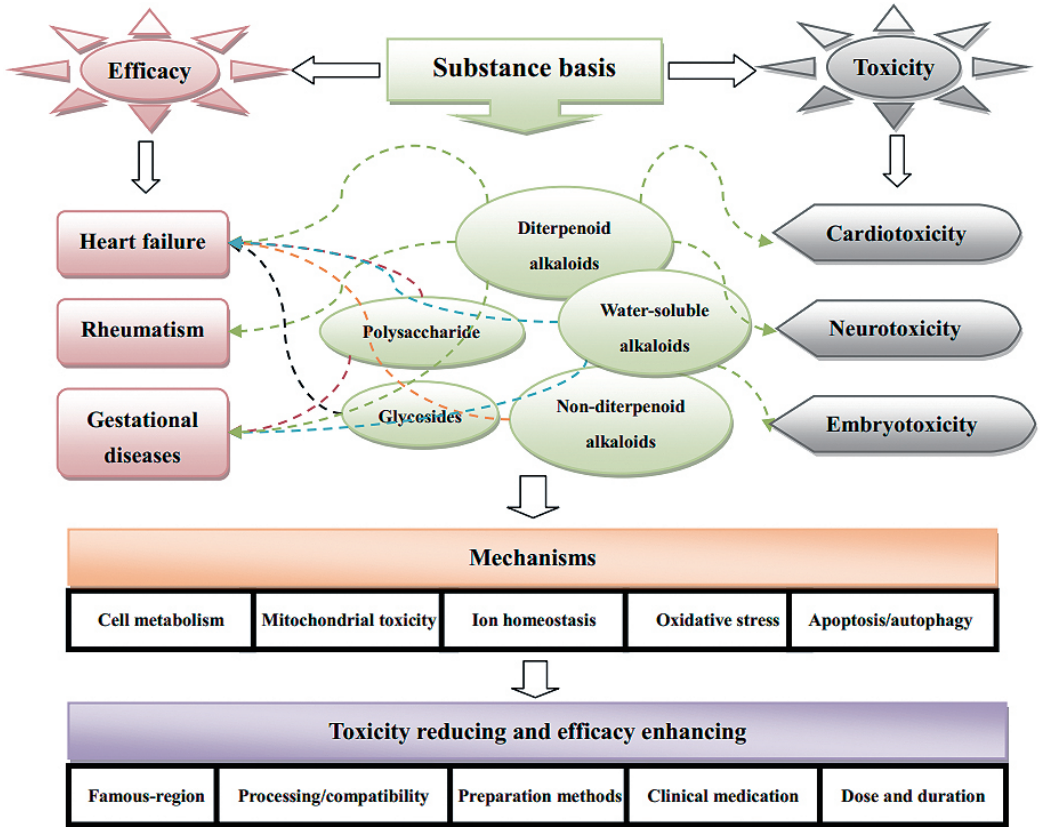

Fig. 2 Integrated analysis on the "toxicity-efficacy" of Fuzi

principles", which will provide important support for the modernization and internationalization of CMM. In the future, the safety and effectiveness evaluation of CMM should also follow "adhering to problem-oriented, highlighting the characteristics of CMM, facing the frontiers of science, and revealing scientific problems" to realize the integrated analysis of CMM.

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