

Toxicity Classification and Detoxification Strategies of Chinese Materia Medica

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ABSTRACT

In recent years, more and more poison incidents of Chinese Materia Medica (CMM) were reported by China and other countries, which made people to doubt about the safety of CMM, especially for the toxic CMM. In this review, the toxicity of CMM and the toxicity classification of CMM were introduced. And traditional TCM theory and methods particularly used for control and attenuation of CMM's toxicity were described in detail. The traditional processing technology and CMM drug combination were most important detoxifying measures used in CMM formulation and clinical practice. Finally, some factors that have influence on occurrence of CMM's toxicity were discussed such as different species, producing technology and so on.

Key words: Toxicity of Chinese Materia Medica, Drug Combination, Drug interaction, Detoxification, Toxicity-influencing factor, Toxicology
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INTRODUCTION

With the spreading use of Chinese Materia Medica (CMM), toxicity of CMM had become a major concern among doctors and patients. In recent years, more and more poison incidents related to CMM were reported by researchers from China and other countries, which arouses serious concerns for the safety of using CMM, especially the toxic CMMs^[1-4]. The toxicity of CMM not only damages the health of patients but also seriously affected the reputation and globalization process of traditional Chinese medicine (TCM). Since every medicine has its side effect, toxicity of TCM is an objective manifestation of a drug. Toxicity of CMM was recorded as early as in the very first Chinese herbal book named “Shen Nong Ben cao Jing” around 2000 years ago. In the long-term medical practice, TCM doctors not only noticed the toxicity of CMM, but also established corresponding theory and methods to detoxify the toxicity of CMM. The toxicity of CMM could be influenced by multiple factors and the goal of attenuation and synergism in CMM can be achieved. This review systematically discussed the recent progress in the understanding the concept and advance of CMM toxicity, toxicity grading system, and factors affecting the toxicity, which would enable us to further understand the toxicity of CMM and guide the clinical application.

Toxicity of Chinese Materia Medica (CMM)

In the long-term clinical practice, the toxicity of CMM was realized by TCM physicians in China^[5]. It is found that some CMMs appeared to be more toxic than others, and therefore, the former are called “toxic CMM” in TCM classic books. Furthermore, according to the degree of the toxicity, the toxic CMMs were empirically classified into 3 categories: severe, moderate, and minor toxicity. The traditional definition and

classification of the toxic CMM have been followed up to now in China, and actually, 83 CMMs are officially defined and recorded as the toxic CMM in the Pharmacopoeia of People's Republic of China in 2010 edition, in which 10 CMMs are ranked as the CMM with severe toxicity, 42 CMMs as moderate toxicity, and 31 as minor toxicity (Table. 1). It should be emphasized that the definition and the classification of aforementioned toxic CMMs are essentially based on traditional experience in clinic practice and its descriptions in TCM works written in ancient time, but not based on modern pharmacological and toxicological evidence. Standards and rationalization underlying the definition and the classification remained unclear. Therefore, it is strongly recommended that the toxic TCM drugs and their classification should be established and revised on the basis of modern toxicological and pharmacological evidence rather than TCM experience^[6-8]. However, not all the experimental data match with the traditional classification. It was emphasized that the classification system and criteria to differentiate the toxic CMMs should be established. The classification of CMM toxicity needs to be further investigated and greatly improved.

CMM toxicity can be generated not only by an individual CMM, but also by interaction between two or more CMMs. Because TCM therapy is characterized by a combination of CMMs, the toxicity induced by a CMM combination should be emphasized. Consequently, in order to avoid the possible toxicity by the CMM combination, the TCM combination taboo from toxicological point of view was gradually established in hundreds of years ago. The combination taboo is described as follows:

1. The 18 incompatible medicaments

The following 18 CMMs are believed to give rise to serious side effects when the combination between them is used, and

Table. 1 Three categories of the toxic CMM drugs in chinese pharmacopoeia

Severe toxic 10	Moderate toxic -42	Minor toxic -31
FRUCTUS CROTONIS RADIX ACONITI RADIX ACONITI KUSNEZOFFII MYLABRIS SEMEN STRYCHNI SEMEN HYOSCYAMI FLOS RHODODENDRI MOLLIS SEMEN STRYCHNI PULVERATUM SEMEN CROTONIS PULVERATUM HYDRARGYRI OXYDUM RUBRUM	FRUCTUS XANTHII RADIX SOPHORAE TONKINENSIS RADIX KANSUI RADIX EUPHORBIAE PEKINENSIS FLOS GENKWA RADIX PHYTOLACCAE SEMEN PHARBITIDIS SEMEN EUPHORBIAE SEMEN EUPHORBIAE PULVERATUM AGKISTRODON CORTEX PERIPLOCAE RADIX ACONITI LATERALIS PREPARATA CORTEX MELIAE RHIZOMA PINELLIAE RHIZOMA ARISAEMATIS PROCESSED RHIZOMA ARISAEMATIS SEMEN GINKGO CHELIDONII HERBA FLOS DATURAE RADIX PHYSOCHLAINAE CINNABARIS SCORPIO SCOLOPENDRA RHIZOMA CURCULIGINIS PERICARPIUM PAPAVERIS RADIX DICHROAE REALGAR VENENUM BUFONIS CORTEX PSEUDOLARICIS CALOMELAS RESINA TOXICODENDRI RADIX ACONITI KUSNEZOFFII PREPARATA RADIX ACONITI PREPARATA BUNGARUS PARVUS RHIZOMA ANEMONES RADDEANAE SEMEN RICINI PERICARPIUM PAPAVERIS SEMEN MOMORDICAE BERBERIDIS RADIX LAGGERAE HERBA SULFUR EUPHORBIAE EBRACTEOLATAE RADIX	RHIZOMA PARIDIS FRUCTUS BRUCEAE CAULIS ERYCIBES FRUCTUS EVODIAE FRUCTUS TOOSENDAN FOLIUM ARTEMISIAE ARGYI EUPOLYPHAGA SEU STELEOPHAGA HIRUDO SEMEN ARMENIACAE AMARUM FRUCTUS CARPESII FRUCTUS CNIDII FRUCTUS GLEDITSIAE ABNORMALIS FOLIUM ACONITI KUSNEZOFFII SEMEN IMPATIENTIS RADIX ZANTHOXYLI FRUCTUS PODOPHYLLI RHIZOMA MENISPERMI CORTEX ILLICII RADIX KNOXIAE RAMULUS ET FOLIUM PICRASMAE FOLIUM ET CACUMEN MURRAYAE FRUCTUS CAROTAE RHIZOMA DRYOPTERIS CRASSIRHIZOMATIS RHIZOMA DRYOPTERIS CRASSIRHIZOMATIS OSMUNDAE RHIZOMA FRUCTUS TRIBULI GLEDITSIAE SINENSIS FRUCTUS EUPHORBIAE HIRTAE HERBA PSAMMOSILENES RADIX PTEROCEPHALI HERBA

toxicologically, their combination therapy is generally not allowed in clinical practice, for example, Radix Glycyrrhizae (甘草) being incompatible with Radix Euphorbiae Pekinensis (大戟), or Flos Genkwa (芫花), Radix Gansui (甘遂) and Sargassum (海藻); Aconite (乌头) incompatible with Bulbus Fritillariae (贝母), or Fructus Trichosanthis (瓜蒌), Rhizoma Pinelliae (半夏), Radix Ampelopsis (白藜), Rhizoma Bletillae (白及); Falsehellebore Root and Rhizome (藜芦) incompatible with Radix Ginseng (人参), Radix Glehniae (沙参), Radix Salviae Miltiorrhizae (丹参), Radix Scrophulariae (玄参), Herba Asari (细辛) and Radix Paeoniae (芍药)^[9].

2. The 19 medicaments of mutual antagonism

The following 19 CMMs appear to be antagonized in their therapeutic efficacy when they are used in combination: Aconite (乌头) being antagonistic to Cornu Rhinocerotis

(犀角), Radix Ginseng (人参) to Faeces Troglodytorum (五灵脂), Cortex Cinnamomi (肉桂) to Halloysitum Rubrum (赤石脂), Flos Caryophylli (丁香) to Radix Curcumae (郁金), Fructus Crotonis (巴豆) to Semen Pharbitidis (牵牛), etc.^[10].

Due to the consideration that the combination between the 18 CMM drugs can probably cause side effects and the combination between the 19 CMM drugs can probably lead to less or no efficacy, traditionally and empirically, the use of their combination has been basically prohibited. In order to explore whether or not the above mentioned combination theory is scientifically justified, a great number of investigation should be conducted and accumulated data obtained from modern pharmacological experiments have shown that some of them are proven to be scientific. For example, the toxicity was increased to some extent in the combination between Aconite with Rhizoma Pinelliae, or with Fructus

Trichosanthis, or Bulb of Thunberg Fritillary, or Rhizoma Bletillae, or Radix Ampelopsis; Radix Glycyrrhizae with Euphorbia pekinensisrupr, or Flos Genkwa, or Radix Gansui, or Sargassum^[11]. While no additional toxicity was found among a number of the combination by the 18 or 19 mentioned herbs such as Aconite and Rhizoma Pinelliae, Sargassumu and Radix Glycyrrhizae, Radix Ginseng (Radix Codonopsis) and Faecstrogopterori^[12]. Toxicity can arise from multiple other causes^[13]. Up to now, it still remains controversial about the theory, but the theory has been followed in TCM clinical practice and new drug application evaluation for marketing by CFDA.

Theory and methodology of detoxification in TCM

Although the toxic CMM drugs are more likely to induce adverse drug reactions (ADR), better therapeutic effects from them can be manifested when their toxicity is properly contained. A lot of experience and knowledge have been accumulated in safe use of the toxic CMM drugs in clinical practice, and a quite number of methods have been developed in detoxifying CMM toxicity, among which traditionally processing of CMM raw materials and a drug combination are the most important and commonly-used detoxifying measures^[14]. Raw materials of CMM are generally processed by traditional technology before use, and one of the purposes of traditional processing is to eliminate the toxicity^[15]. Fructus Crotonis, one of the toxic CMMs, can induce severe diarrhea because it contains essential oil, which accounts for 40-60% chemical composition of Fructus Crotonis. The traditional processing method of Fructus Crotonis includes heating (to degenerate the toxic constituents), and depressing (to remove about 80% the toxic oil), which could lead to dramatic decrease of its toxicity^[16]. Traditionally, only processed Fructus Crotonis but not the raw material could be used in clinical practice, therefore the clinical use of Fructus Crotonis was safe and effective^[17-18]. Aconite, another very toxic CMM is traditionally processed into a "Prepared CMM Slices" (usually it was cut into a thin slices after traditionally processed) by "steam-heating" method in order to decrease its toxicity. Clinically, the raw material of aconite without processing could not used at all. It was found that, following the traditional processing, the content of Aconitine, which is the most toxic component contained in aconite, which is mainly responsible for aconite toxicity, is greatly decreased in the prepared aconite slices due to the hydrolysis of double ester alkaloids into single ester alkaloids.. Therefore, the processing method for aconite not only reduces the level of its alkaloids, but also alters the proportion between double ester and single ester alkaloids^[19]. Rhizome Pinelliae without the traditional processing appears to be strongly stimulating to skin and mucous membrane, while prepared Rhizome Pinelliae slices after traditional processing have no stimulating toxicity at all^[20] Raw Radix Aconiti Carmichaeli has obvious toxicity but its toxicity is greatly alleviated after processing^[21-23]. In summary, traditional processing technique is a useful measure to reduce or

eliminate CMM toxicity, and also a key technology in TCM pharmaceuticals.

TCM is characterized by herbal combination in TCM therapy and one of the motives for combination is to use one TCM drug to antagonize the toxicity of the other one in a TCM formula. Hence, the herbal combination is another detoxifying measure in TCM theory and its clinical practice. The detoxification by the combination is clearly described in "Huangdi Neijing", a classic TCM work written in about 2,000 years ago. As for the TCM combination, a total of the 7 interactional natures between CMMs have been summarized in TCM classic works, of which there are 2 interaction natures are directly correlated to toxicity: Mutual-detoxification and Mutual-restrain for each other's toxicity. Mutual-detoxification or mutual-restrain is defined as that one drug can remove or restrain (weaken) the toxicity of the other drug or ingredient. Many examples of mutual-detoxification or mutual-restrain between two drugs are listed in ancient TCM classic works. The typical examples are as the following: Radix Polygala, Radix Saposhnikoviae Divaricatae could attenuate the toxicity of Radix Aconiti Praeparata; the toxicity of Radix Aconiti Praeparata can be decreased by Radix Saposhnikoviae Divaricatae, Radix Glycyrrhizae and Radix Astragali. The interaction between Aconite and other TCM herbs was experimentally investigated in the author's laboratory. The experiments were designed to observe whether or not the toxicity of Radix Aconiti Praeparata would be antagonized by other TCM herbs. The results demonstrated that either acute toxicity (LD₅₀) or cardio-toxicity (arrhythmia) induced by Aconite extract was significantly decreased by its combination with Radix Glycyrrhizae or Radix Astragali^[24-25] (See Tables 2 and 32).

The toxicity of Realgar, which is found to be effective to leukemia, was greatly diminished when it is used in a combination with other CMM herbs in a multi-ingredient TCM preparation, which legally marketed in China^[26]. Therefore, a toxic CMM such as Radix Aconiti Praeparata and Rhizoma Pinelliae can be safely used clinically after it is treated with the traditionally-detoxifying measures as aforementioned. Experimental results have been reported to show a reasonable CMM combination being able to alleviate or eliminate the toxicity^[27-30].

TCM toxicity-influencing factors

Owing to the fact that CMM herbs are unique in many aspects, their toxicity is influenced by the following factors that are different from those of western medicine:

1. Misuse of TCM species

It is a common phenomenon that, under the same name, there are different species, genus, or even family herbs. Careful attention must be paid to the confusing fact that different herbs under the same name are easily misused, therefore leading to severe adverse reaction. Stephania tetrandra and Aristolochia fangchi share the same name "Fang-ji" in TCM,. However, Stephania tetrandra has no toxicity to kidney at all, while Aristolochia fangchi is

Table 2 Acute toxicity LD₅₀ of Aconiti Lateralis Radix Praeparata alone and its combinations with Glycyrrhizae Radix et Rhizoma at different ratios

Study Drug		LD ₅₀ g /kg	95% CI g /kg
Aconite alone		17.7	16.2–19.3
Aconite combination	Aconite: Licorice(3:1)	16.8	15.5–18.2
	Aconite: Licorice(1:1)	25.4	23.5–27.4
	Aconite: Licorice(1:3)	>22.8	Only 2 animals died out of 10 in the group with maximum dosage

potentially nephrotoxic due to its containing toxic compound-aristolochic acid [31]. The latter was misused instead of the former for slimming treatments in Belgium, leading to severe adverse drug reaction (ADR). *Aristolochia manshuriensis* vs *Clematis armandii* is another example for name confusion since both have the same name of “Mu-tong”. The latter is relatively safe, while the former is very toxic to kidney like *Aristolochia fangchi*. Also, the life-threatening ADRs were reported mainly owing to their misuse. It was reported that pyrrolizidine alkaloids (PAs), isolated from *Senecio vulgaris*, are the toxic components which can cause liver damage [32]. In China, only one species of *Senecio* Genus, *S. scandens* alone, can be used as the raw material of TCM drug, but not *S. vulgaris*. The experimental data showed that *S. scandens* contains pyrrolizidine alkaloids (PAs) 8 times less than *S. vulgaris*. This may be reasons that *S. scandens* has little toxicity to the liver, while *S. vulgaris* exhibits significant toxicity [33]. Therefore, it is very important to correctly characterize the identity of TCM herbs before use.

2. Production technology

A TCM raw material, especially a medicinal herb, usually contains hundreds of constituents, either water-soluble or lipophilic. Its chemical compositions would vary with different production technologies, such as water-extraction, ethanol-extraction, leading to possible differences in biological or toxicological activity. It is well known that pyrrolizidine alkaloids are difficult to be resolved in water, and hence, a TCM preparation named as Qian Bai Bi Yan Pian, which

Table 3 Heart toxicity TD₅₀ of Aconiti Lateralis Radix Praeparata alone and its combinations with Glycyrrhizae Radix et Rhizoma at different ratios

Study Drug		TD ₅₀ g /kg	95% CI g /kg
Aconite alone		8.6	7.5–9.9
Accountitum combination	Aconite: Licorice(3:1)	12.9	11.7–14.3
	Aconite: Licorice(1:1)	15	13.2–16.9
	Aconite: Licorice(1:3)	>11.4	No toxicity in the group with maximum dosage

contains *S. scandens*, contained little pyrrolizidine alkaloids partially because the traditional water extraction (TCM raw materials are soaked in water and then heated for about one hour) was used in its production. It was reported that water-extract of *S. scandens* was able to protect the liver from chemical-induced damage [34]. In addition, the length of the heating time of TCM raw materials in water also affects chemical compositions and toxicity of TCM. Aconitine alkaloids contained in Aconite could be hydrolyzed into less toxic compounds when heated in boiling water, and the longer heating time with more hydrolysis and less toxicity. And two or more hours heating duration would dramatically decrease the Aconite toxicity [35–36]. It can be expressed in a plausible equation that a compound toxicity doesn't equal to the toxicity of one TCM containing the compound, also doesn't equal to the toxicity of a multi-ingredient TCM preparation containing the TCM. Obviously, the equation has to be scientifically and experimentally proven before a convincing conclusion is drawn.

3. TCM treatment coinciding with TCM diagnosis

TCM therapy is a kind of individualized therapy. The use of TCM drugs or a TCM formula is dependent on the body conditions of patients such as symptoms. The individual physiological and pathological characters are emphasized during TCM clinical treatment. One of characteristic features in TCM clinical practice is to provide different treatments to different patients even though they suffer from the same disease. In general, the patient with “Hot” symptoms is treated with a TCM with “Cold” properties, and vice versa. If “Hot” symptoms were treated with a TCM with “Hot” properties, ADR would be more likely to occur. However, if TCM drugs perfectly coincide with the patient's symptoms and conditions according to TCM theory, the toxicity of a TCM drug would be significantly alleviated, even the TCM drug is well-known as a toxic one. There is a physician named “Yang-heping”, who is characterized by over-dosing of Aconite with “Hot” property, which can be suitable particularly for the patients with “Cold” condition. The officially-recommended therapeutic dose of Aconite ranges from 3–9 g per day, while its dose at 100g per day or more is commonly used for the patients with “Cold” or “Yin” symptoms without any side effects, where in addition, other detoxifying measures such as the drug combination, TCM traditionally processing and adequate heating preparation are simultaneously taken. Only if all of the TCM detoxifying methods mentioned above are used, the toxicity of Aconite can be essentially reduced with its overdose, and its therapeutic effects could be optimized. Therefore, it is recommended that the safe use of CMM should be directed under the prescription or advice of a qualified TCM physician [37].

In addition to the above-mentioned influencing factors, there are still some other ones, such as TCM raw material habitat, its harvesting time, combination with western medicines, etc.

In conclusion, in the long-term medical practice in clinics, TCM physicians have accumulated rich experience for the

control of CMM toxicity. The present paper systematically reviewed and summarized the various experiences accumulated during the long TCM practice. Furthermore, based on modern pharmacology and toxicology, it was tried to illustrate scientific connotation and draw the rule, which can provide scientific basis to better understand CMM toxicity (its toxicological characteristics) and rational use of the toxic CMMs in clinics.

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