An Overview of the Toxicology of Commonly Used Traditional Chinese Medicine

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ABSTRACT

Traditional Chinese medicine (TCM) plays an important role in health care systems in many parts of the world. Recently, interest in TCM has revived due to the rediscovery of the potential of TCM and natural products in new drug development. There is a general perception that TCM lacks systematic pharmacological, toxicological, and clinical studies. The deficiency in efficacy and safety has been a major hindrance to the progress of TCM, despite the success of herbal medicine in treatment of diseases for which the orthodox drugs in western medicine are ineffective. This brief review aims to serve as an introduction and a reference guide to TCM toxicology. The review summarizes the toxicity of some commonly used TCMs in terms of acute, systematic, genetic, analytic, and clinical toxicology. Acute toxicity study has shown that herbal medicines and their chemical constituents exhibit LD_{50} values ranging from the practically nontoxic to supertoxic categories. Target organs of TCM toxicity include liver, kidney, gastrointestinal tract, nervous, and cardiovascular systems. TCM shows mutagenicity in the Ames test and increases the incidence of unscheduled DNA synthesis, micronucleus formation, and chromosomal aberration in cytogenetic assays. Some TCM products are contaminated with pesticides and heavy metals and adulterated with drugs of western medicine. Improper dispensing and use of TCM and individual idiosyncracy may result in adverse effects and fatality. Future TCM research, new drug development, and safety evaluation require adequate toxicity testing and mechanistic toxicology studies.

Key words: traditional Chinese medicine, natural products, toxicity.

INTRODUCTION

Traditional Chinese medicine (TCM) has been successful in the treatment of many diseases and disorders for thousands of years. TCM principles and practice are in harmony with the cultural background of many oriental societies. The Chinese materia medica is of natural origin. These characteristics of TCM are part of the reason that herbal medicine plays an important role in the health care systems of many parts of the world. Recently, TCMs and natural products have attracted new attention for their potential in new drug development [1, 2]. For example, a TCM therapy

has been shown to benefit patients with severe atopic dermatitis which was resistant to the treatments with orthodox drugs in western medicine [3, 4]. Taxol analogues derived from *Taxus brevifolia* (Pacific yew) and *T. baccata* (European yew) have been used in the treatment of ovary cancer [5]. Vincristine isolated from *Catharanthus roseus* (L.) has been used in anticancer therapy of chronic lymphocytic leukemia and Hodgkin's disease [6].

In spite of these traditional and new avenues of interest in TCM, there has been a longstanding reservation of the Chinese materia medica [1]. The general perception is that these medicinal herbs do not have well-documented clinical trials, pharmacological actions, systematic toxicological testing, or safety evaluation. These deficiencies have often hampered the progress of TCM to a new level of clinical and scientific significance. Many TCMs remain as remedies in folk medicine and some of the natural products may even produce adverse effects on human health [7].

An increasing number of studies have revealed that some commonly used TCM products are toxic and potentially hazardous. The toxicity covers a wide spectrum including acute, systemic, genetic, and clinical. Although the pharmacological actions and therapeutic uses of TCM have been extensively reviewed [6, 8-14], relatively few reports are addressed to TCM toxicology. This brief review summarizes the toxicity information of commonly used TCMs and describes briefly the action and indication of the herbal medicine. This article aims to serve as an introduction of TCM toxicology to those who are engaged in biomedical research areas and a reference guide to those who are interested in TCM toxicity from the regulatory and safety viewpoints.

CLASSIFICATION OF TCM

TCM is used as a composite formula to increase therapeutic effect, modulate drug action, and decrease adverse effects. A proper prescription of this composite formula requires a comprehensive knowledge of the underlying principles and theories. The herbal medicines have been classified according to their origins (botanical, zoological and mineral), and are further subgrouped according to the parts used such as Cortices, Radices, Fructus, Fores, and Semina [11, 13]. TCMs and natural products are grouped based on their pharmacological properties such as cardiovascular, nervous, alimentary, respiratory, hematopoietic and other systems [6, 9, 14]. TCMs can be divided into Yin and Yang categories of which Dahuang (rhubarb) and Renshen (ginseng) are the respective prototypes [15].

A revised version of Shen Nung Ben Cao Jing in 450 AD, the first written history of Chinese materia medica, classified 335 TCM herbs into the upper, middle, and lower categories according to their pharmacological and toxicological properties [6, 8]. The upper category herbs are regarded as nontoxic. One hundred and twenty tonics which can promote health and comfort belong to this category. TCM natural products in the middle category are considered toxic or nontoxic. One hundred and twenty herbs are associated with the middle category which have the ability to sooth the mental state. The lower category medicines are thought to be toxic. One-hundred-and-twenty-five herbs in the lower category are used to treat and cure various diseases. In a composite formula, the herbs in the upper category can be used for a long period of time, the middle category drugs are to be used in moderation, while the lower category herbs should only be used for a short period of time. The prescription of TCM is based on the principles of four groups namely the emperor (principal), minister (associate), assistant (adjuvant) and guide (messenger) herbs, according to their pharmacological actions [16]. These traditional classifications show that TCM has incorporated toxicological and pharmacological concepts into the principles and methods of Chinese herbal medicine. A TCM practitioner is supposed to use the herbal medicines based on these principles and methods. Inadequate comprehension and improper use of TCMs often result in undesirable effects.

ACUTE TOXICITY OF TCM

Lethality is one of the many references points in defining acute toxicity. LD_{50}, the median lethal dose, is the dose of a substance that can be expected to cause death in 50% of the test animals [17]. In general, acute animal toxicity testing has standard protocols for preparation of test material, route of administration, species, sex, and number of the test animals. Table 1 summarizes the numeric values of LD_{50} of some commonly used TCMs [6, 11, 12, 14, 18]. The reader is referred to the original references for details of the test protocols of these toxicity studies.

As expected, the LD_{50} values of many Chinese medicinal herbs are greater than 15 g/kg, which are generally regarded as practically non-toxic (Table 1). For example, Agrimoniae Herba (Xianhecao or Langyaocao) showed LD_{50} values greater than 50 g/kg in mice following intraperitoneal (i.p.) and oral (p.o.) administrations of ethanolic extracts of the herb [18]. The LD_{50} values of some TCM herbs are between 5 and 15 g/kg, which fall into the slightly toxic category. The LD_{50} of Daphnis Genkwae Flos (Yuanhua) in rats was 9.3 g/kg i.p. [6]. Some TCMs show LD_{50} values in the range of 0.5-5 g/kg belonging to the moderately toxic category. Administration of ethanol extracts of Akebiae Caulis (Mutong) to mice i.p. produced an LD_{50} value of 2.3 g/kg [18].

Several TCM natural products are extremely and highly toxic showing LD_{50} in the range of 5-50 and 50-500 mg/kg, respectively (Table 1). Bufonis Venenum (Chansu, toad venom) showed LD_{50} of 41 and 36 mg/kg in mice by intravenous (i.v.) and i.p. administrations, respectively [6]. The seed of *Antiaris toxicaris* Lesch (Jianshui-fuan-hou) is a rare example that TCM can be supertoxic with an LD_{50} less than 5 mg/kg. The LD_{50} of Jianshuifuanhou was 0.8 mg/kg in frogs [6].

Herbal interaction may alter the acute toxicity of TCM. For example, the LD_{50} values of Daphnis Genkwae Flos (Yuanhua) and Glycyrrhizae Radix (Gancao, glycyrrhiza) in mice are 5.5 and 8.0 g/kg i.p., respectively (Table 1). Coadministration of Daphnis Genkwae Flos and Glycyrrhizae Radix to mice produced an LD_{50} of 1.8 g/kg [14]. This synergistic effect points out the need to analyze the potentially complex effects of herbal interaction in toxicological studies of TCM. In some instances, the acute toxicity of TCM is dependent upon the route of administration. LD_{50} values of Puerariae Radix (Gegen) are 1, 2 and 4 g/kg for i.v., i.p. and p.o. administrations to mice, respectively [12]. However, a pronounced difference in LD_{50} was observed with different routes of administrations of Bupleuri Radix (Chaihu). Crude saikosides from Blupleri Radix showed LD_{50} values of 0.07, 0.11, 1.9 and 4.7 g/kg following i.v., i.p., s.c. and p.o. administrations to mice, respectively [12]. These marked differences in LD_{50} values show the importance of pharmacokinetics data in the safety evaluation of the herbal medicine.

An important aspect of TCM research is to study the toxicity of the chemical constituents of the medicinal herbs. The constituent compounds provide excellent opportunities to define the toxicological properties of the bioactive components of TCMs in terms of structure-activity relationship, drug-drug interaction, and mechanistic toxicity studies. In general, these compounds have more clearly defined toxicological properties because studies of pure chemicals are more reproducible and the toxicities are more predictable than those of the herbal mixtures of chemicals.

Table 2 shows the LD_{50} values of constituent compounds isolated from some commonly used TCMs. Paeoniflorin, a glucoside isolated from Paeoniae Radix, shows i.p. and i.v. LD_{50} in mice in the slightly and moderately toxic categories, respectively [12]. The chemical constituents and their metabolites from a medicinal herb may differ in acute toxicity. Geniposide, crocin and crocetin are the major bioactive compounds isolated from Gardenia Fructus. Acute toxicity studies of crocetin and crocin showed that LD_{50} of these compounds in mice were 2 and 10 g/kg i.p., respectively [12]. In the intestine, geniposide yields the iridoid aglycon genipin during the biotransformation process. The aglycon causes a marked increase in acute toxicity. The LD_{50} of geniposide in mice were greater than 3 g/kg i.v., i.p., and p.o.. In contrast, LD_{50} of genipin in mice were 153 mg/kg i.v., 190 mg/kg i.p. and 237 mg/kg p.o. [12].

Table 1. Acute toxicity of traditional Chinese medicines

Toxicity rating (LD_{50})	Botanical name	Latin name	Chinese name	LD_{50}	Animal	Route of administration	Reference
Practically nontoxic (> 15 g/kg)	Achyranthes bidentata Blume (Amarantaceae)	Achyranthis Radix	Niuxi	>50 g/kg	mice	i.p., p.o.	18
	Agrimonia pilosa Ledeb.var. japonica (Miq.) Nakai (Rosaceae)	Agrimoniae Herba	Xianhecao	>50 g/kg	mice	i.p., p.o.	18
	Angelica sinensis (Oliv.) Diels (Umbelliferae)	Angelicae Radix	Danggui	>38 g/kg	mice	i.p., p.o.	18
	Angelica dahurica Benth. et Hook (Umbelliferae)	Angelicae Dahuriae Radix	Paichi	>50 g/kg	mice	i.p., p.o.	18
	Biota orientalis (L.) Endl.	Thujae Orientalis Folium et Ramulus	Cebaiye	15 g/kg	mice	i.p.	6
	Cimicifuga heracleifolia Komarov, C. dahurica (Turcz.) Maxim., or C foetida L. (Ranun culaceae)	Cimicifugae Rhizoma	Shengma	>43 g/kg	mice	i.p., p.o.	18
	Curcuma zedoaria Rosc., C. aromatica Salisk., or C. kwangsiensis A. Lee	Zedoriae Rhizoma	Ezhu	17 g/kg	mice	i.p.	6
	Eucommia ulmoides Oliv (Eucommiaceae)	Eucommiae Cortex	Duzhong	>42 g/kg	mice	i.p., p.o.	18
	Eugenia caryophyllata Thunb.	Caryophylli Flos	Dingxiang	19 g/kg	rats	p.o.	6
	Ilex chinesis Sims		Sijiqing	~110 g/kg	mice	p.o., i.v.	6
	Ledebouriella seseloides Woll. (Umbelliferae)	Saposhinkoviae Radix	Fangfeng	>32 g/kg	mice	i.p., p.o.	18
	Ligusticum chuanxiong Hort.	Cnidii rhizoma (Liqustici Rhizoma)	Chuanxiang	66 g/kg	mice	i.p., i.v.	6
	Ligusticum sinensis Oliv. (Umbelliferae)	Ligusticum Sinensis Rhizoma et Radix	Gaoben	>42 g/kg	mice	i.p., p.o.	18
	Lobelia chinensis Lour.	Lobeliae Chinensis Herba	Banbianlian	75 g/kg	rats	p.o.	6
	Magnolia officinalis Rehd. et Wils.	Magnoliae Cortex	Houpu	51 g/kg	mice	-- [a]	12
	Panax ginseng C. A. Meyer	Ginseng Radix	Ginseng	17 g/kg	mice	s.c.	6

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Table 1. Continued

Species	Pharmaceutical name	Common name	LD₅₀	Animal	Route	Ref.
Physochlaina infundibularis Kuang		Hoashanseng	43 g/kg	mice	i.p.	6
Pinellia ternata Breit.	Pinelliae Tuber	Banxia	206 g/kg	rats	--	12
Pinus tabulaeformis Carr. (Pinaceae)	Pini Nodi Lignum	Songjie	>50 g/kg	mice	i.p., p.o.	18
Radix aconiti praeparata	Aconiti Tuber	Fuzi or Wutou	17 g/kg	mice	p.o.	6
Saliva miltiorrhiza Bge. (Labiatae)	Salivae Miltiorrhizae Radix	Danshen	>17 g/kg	mice	i.p., p.o.	6,18
Sophora flavescens Ait.	Sophorae Radix	Kushen	43 g/kg	mice	s.c.	6
Sophora subprostrata Chun et Chen	Sophorae Subprostratae Radix	Shandougen	16 g/kg	mice	i.p.	12
Stephania tetrandra S. Moore (Menispermaceae)	Hanfangchi Radix	Hanfanji	21 g/kg	mice	i.p.	18
Tribulus terrestris L. (Zygophyllaceae)	Tribuli Fructus	Baijili	>50 g/kg	mice	i.p., p.o.	18
Slightly toxic (5-15 g/kg)						
Aconitum coreanum (Levl.) Rap. (Ranunculaceae)	Aconiti Coreani Tuber	Fuzi	6.6 g/kg	mice	i.p.	18
Arisaema consanguineum Shott., *A. heterophyllum* Blume, & *A. murense* Maxim	Arisaematis Rhizoma	Nanxing	14 g/kg	mice	i.p.	6
Cimicifuga dahurica (Turcz.) Maxim. *C. heracleifolia* Komarov *C. foetida* L.	Cimicifugae Rhizoma	Shengma	7.9 g/kg	rats	p.o.	12
Corydalis yanhusuo W.T. Wang (Papaveraceae)	Corydalidis Tuber	Yanhusuo	8.5 g/kg	mice	p.o.	18
Daphne genkwa Sieb. et Zucc.	Daphnis Genkwae Flos	Yuanhua	9.3 g/kg / 5.5 g/kg	rats / mice	i.p. / i.p.	6 / 14
Evodia rutaecarpa (Juss.) Benth.	Evodiae Fructus	Wuzhuyu	8.1 g/kg	mice	i.p.	18
Firmiana simplex (L.) W. F. Wright	Firmianae Semen	Wutongzi	8.3 g/kg	mice	i.v.	6
Glycyrrhiza uralensis Fisch.	Glycyrrhizae Radix	Gancao	8.0 g/kg	mice	i.p.	14
Loranthus parasiticus (L.) Merr.	Loranthi Ramulus	Songjishang	11.2 g/kg	mice	i.p.	6
Magnolia officinalis or *M. officinalis* var. *biloba* (Magnoliaceae)	Magnoliae Cortex	Houpo	6.1 g/kg	mice	i.p.	6
Millettia dielsiana Harms.	Millettiae Caulis	Jixueteng	9.5 g/kg	mice	i.p.	18

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Table 1. Continued

(Leguminosae)						
Paeonia suffruticosa Andr. (Ranunculaceae)	Moutan Radicis Cortex	Mudanpi	14 g/kg	mice	i.p.	18
Panax zingiberensis	Polygoni Cuspidati Rhizoma	Sanqi	6.3 g/kg	rats	i.p.	6
			8.8 g/kg	mice		
Rhododendron molle G. Don	Rhododendri Molles Folium	Balima or Naoyanghua	8.6 g/kg	mice	p.o.	6
Zizyphus spinosa (Rhamnaceae), or Z. jujuba Mill.	Zizyphi Fructus	Suanzaoren	13.3 g/kg	mice	i.p.	6
Moderately toxic (0.5-5 g/kg)						
Aconitum carmichaeli Debx. (Ranunculaceae)	Aconiti Carmichaeli Radix	Chuanwu	2.8 g/kg	mice	i.p.	18
Akebia quinata (Thunb.) Decne (Lardizabalaceae)	Akebiae Caulis	Mutong	2.3 g/kg	mice	i.p.	18
Arisaema consanguineum Schott. (Araceae)	Arisaematis Rhizoma	Tiannanxing	3.2 g/kg	mice	i.p.	18
Artemisia annua L. (Compositae)	Artemisiae Apiaceae Herba	Qinghao	4.5 g/kg	mice	i.p.	18
Cimicifuga dahurica (Turcz.) Maxim. C. heracleifolia Komarov C. foetida L.	Cimicifugae Rhizoma	Shenma	2.5~5 g/kg	mice	p.o.	12
Cinnamomum cassia Blume	Cinnamomi Cortex	Gueipi	5 g/kg	mice	i.p.	12
Corydalis yanhusuo W.T. Wang (Papaveraceae)	Corydalidis Tuber	Yanhusuo	3.8 g/kg	mice	i.p.	18
Croton tiglium L. (Euphorbiaceae)	Crotonis Semen	Badou	1.2 g/kg	mice	p.o.	18
Eugenia caryophyllata Thunb.	Caryophylli Flos	Dingxiang	1.6 g/kg	mice	p.o.	6
			5 g/kg	dogs	p.o.	
Magnolia officinalis or M. officinalis var. biloba (Magnoliaceae)	Magnoliae Cortex	Houpo	4.3 g/kg	cats	i.v.	6
Panax ginseng C. A. Meyer	Ginseng Radix	Ginsen	5 g/kg	mice	p.o.	6
Panax zingiberensis	Polygoni Cuspidati Rhizoma	Sanqi	2.5-3 g/kg	rabbits	i.v.	6
Prunus armeniaca L.	Armeniacae Semen	Xinren	3.7 g/kg	rats	--	11

Table 1. Continued

Botanical name	Latin name	Chinese name	LD_{50}	Animal	Route of administration	Reference
P. armeniaca L. var. ansu Maxim. Pueraria lobata (Willd.) Ohwi var. i chinensis (Benth) Owh P. pseudo-hirsuta Tang et Wang	Puerariae Radix	Gegen	1~4 g/kg	mice	i.v., i.p., p.o.	12
Radix aconiti praeparata	Aconiti Tuber	Fuzi or Wutou	3.5 g/kg	mice	i.v.	6
Sophora flavescens Ait.	Sophorae Radix	Kushen	2 g/kg	mice	i.v.	6
Bufo bufo gargarizans Cantor.	Bufonis Venenum	Chansu	97 mg/kg	mice	s.c.	6
Highly toxic (50-500 mg/kg)						
Humulus lupulus L.	--	Pijiuhua	175 mg/kg	mice	i.p.	6
Phellodendron amurense Rupr.	Phellodendri Cortex	Huangbai	500 mg/kg	mice	i.p.	12
Bufo bufo gargarizans Cantor	Bufonis Venenum	Chansu	~40 mg/kg	mice	i.v., i.p.	6
Extremely toxic (5-50 mg/kg)						
Croton tiglium L. (Euphorbiaceae)	Crotonis Semen	Badou	46 mg/kg	mice	i.p.	18
Lithospermum erythrorhizon Sieb. et Zucc.	Lithospermi Radix	Zigen	40 mg/kg	--	i.p.	12
Supertoxic (≤ 5 mg/kg)						
Antiaris toxicaris Lesch.	--	Jiansufuanhou	0.8 mg/kg	frogs	p.o.	6

For additional details, see reviews and studies cited in the references.

a -- : not available.

Table 2. Acute toxicity of constituent compounds isolated from traditional Chinese medicines

Toxicity rating (LD_{50})	Compound	Source			LD_{50}	Animal administration	Route of administration	Reference
		Botanical name	Latin name	Chinese name				
Slightly toxic (5-15 g/kg)	crocin	Gardenia jasminoides Ellis.	Gardeniae Fructus	Shanzhizi	10 g/kg	mice	s.c.	12
	isoferulic acid	Cinicifuga dahurica (Turcz.) Maxim C. heracleifolia Komarov C. foetida L.	Cinicifugae Rhizoma	Shengma	7.9 g/kg	mice	p.o.	11

Table 2. Continued

Moderately toxic (0.5-5 g/kg)	paeoniflorin	*Paeonia lactiflora* Pall.	Paeoniae Radix	Shaoyao	5.8 g/kg	mice	i.p.	12
	cinnamaldehyde	*Cinnamomum cassia* Blume	Cinnamomi Cortex	Gueipi	0.6~2.2 g/kg	mice	i.p.,p.o.	12
	crocetin	*Gardenia jasminoides* Ellis.	Gardeniae Fructus	Shanzhizi	2 g/kg	mice	s.c.	12
	ephedrine	*Ephedra sinica* Staph *E. equisetina* Bunge *E. intermedia* Schrenk et Meyer	Ephedrae Herba	Mahuang	1~1.4 g/kg	mice	s.c., p.o.	12
	methylephedrine	*Ephedra sinica* Staph *E. equisetina* Bunge *E. intermedia* Schrenk et Meyer	Ephedrae Herba	Mahuang	0.7 g/kg	mice	s.c.	12
	oxymatrine	*Sophora subprostrata* Chun et T. Chen	Sophorae Subprostratae Radix	Shangdougen	0.6~1 g/kg	mice	i.p., s.c.	6
	paeoniflorin	*Paeonia lactiflora* Pall.	Paeoniae Radix	Shaoyao	3.5 g/kg	mice	i.v.	12
	paeonol	*Paeonia moutan* Sims.	Moutan Radicis Cortex	Mudanpi	0.8~3.4 g/kg	mice	i.p, p.o.	12
	pseudoephedrine	*Ephedra sinica* Staph *E. equisetina* Bunge *E. intermedia* Schrenk et Meyer	Ephedrae Herba	Mahuang	1.6 g/kg	mice	s.c.	12
	saponin	*Loranthus parasiticus* (L.) Merr.	Loranthi Ramulus	Songjushang	1.2 g/kg	mice	i.p.	6
	schizandrin	*Schizandra chinensis* (Turcz.). Baill	Schizandrae Fructus	Wuweizi	5.2 g/kg	mice	i.p.	12
	sinomenine	*Sinomenium acutum* (Thunb.) Rehd. et Wils.	Sinomenii Acuti Rhizoma	Hanfangji	0.6 g/kg	mice	p.o.	6
Highly toxic (50-500 mg/kg)	camptothecine	*Camptotheca acuminata.* Decne	Camptothecae Fructus et Radix	Xizhu	68 mg/kg	mice	i.p.	6
	cinnamaldehyde	*Cinnamomum cassia* Blume	Cinnamomi Cortex	Gueipi	132 mg/kg	mice	i.v.	12

Table 2. Continued

	Species	Pharmaceutical name	Chinese name	Dose	Animal	Route	No.
ephedrine	*Ephedra sinica* Staph, *E. equisetina* Bunge, *E. intermedia* Schrenk et Meyer	Ephedrae Herba	Mahuang	300 mg/kg	mice	i.p.	12
genipin	*Gardenia jasminoides Ellis.*	Gardeniae Fructus	Shanzhizi	153~273 mg/kg	mice	i.v., i.p., p.o.	12
gentianine	*Gentiana macrophylla, G. staminea, G. crassiaulis, or G. dahurica*	Gentianae Macrophyllae Radix	Qinjiu	250~480 mg/kg	mice	i.v., i.p., p.o.	6
gomisin A	*Schizandra chinensis* (Turcz.) Baill.	Schizandrae Fructus	Wuweizi	390 mg/kg	mice	i.p.	12
matrine	*Sophora flavescens* Ait.	Sophorae Radix	Kushen	72 mg/kg	mice	i.v.	6
methoxy-camptothecine	*Camptotheca acuminata.* Decne	Camptothecae Fructus et Radix	Xizhu	104 mg/kg	mice	i.p.	6
monocrotaline	*Crotalaria sessiliflora* L. or *C. assamica* Benth.	Crotalariae Sessiliflorae Herba	Yebaihe or Nunggili	296 mg/kg; 134 mg/kg	rats; mice	i.p.	6
paeonol	*Paeonia moutan* Sims.	Moutan Radicis Cortex	Mudanpi	196 mg/kg	mice	i.v.	12
piperine	*Piper nigrum* L.	Piperis Nigri Fructus	Hujiao	349 mg/kg	rats	i.p.	6
protocatechuic aldehyde	*Ilex chinensis* Sims.	--[a]	Shijiqing	500 mg/kg	mice	i.m.	6
pseudoephedrine	*Ephedra sinica* Staph, *E. equisetina* Bunge, *E. intermedia* Schrenk et Meyer	Ephedrae Herba	Mahuang	245 mg/kg	mice	i.p.	12
reserpine	*Rauwolfia verticillata* (Lour.) Baill.	Rauwolfiae Vertricillatae Radix	Luofumu or Baihualiang	500 mg/kg	mice	p.o.	6
rhynchophylline	*Uncaria sinensis* (Oliv.) Havil. *U. rhynchophylla* (Miq.) Jackson	Uncariae Ramulus et Uncus	Diaotenggou	165 mg/kg	mice	s.c.	12
rubescensine B	*Rabdosia rubescens* Hora.	--	Donglingcao	56 mg/kg	mice	i.p.	6

Table 2. Continued

Category	Compound	Plant source	Pharmaceutical name	Common name	LD50	Animal	Route	Ref
	tetramethyl pyrazine	*Ligusticum chuanxiang* Hort.	Cnidii Rhizoma or Ligustici Rhizoma	Chuanxiang	239 mg/kg	mice	i.v.	6
	toosendanin	*Melia toosendan,* or *M. azedarach* L.	Meliae Toosendan Fructus	Kulianpi	480 mg/kg 120 mg/kg	mice rats	i. p. p.o.	6
Extremely toxic (5-50 mg/kg)	aristolochic acid	*Aristolochia debilis* Sieb et Zucc.	Saussureae Radix	Qinmuxiang	22~49mg/kg	mice	i.v., p.o.	6
	deoxy-nupha-ridine	*Nuphar japonicum* DC.	Nupharis Rhizoma	Chuangu	20 mg/kg	mice	s.c.	12
	ethoxy-chele rythrine	*Macleaya cordata* (Willd.) R. Br. (Papaveraceae)	--	Bolorhui	18 mg/kg 5 mg/kg	rabbits mice	i.p.	6
	peimine	*Fritillaria thunbergii* Miq.	Fritillaria Bulbus	Beimu	6-8 mg/kg	mice	i.v.	12
	peiminoside	*Fritillaria thunbergii* Miq.	Fritillaria Bulbus	Beimu	32-68 mg/kg	mice	i.v.	12
	reserpine	*Rauwolfia verticillata* (Lour.) . Bail	Rauwolfiae Vertricillatae Radix	Luofumu	16 mg/kg	mice	i.p.	6
	vinblastine	*Catharanthus roseus* (L.) G. Don (*Vinca rosea* L., *Lochnera rosa* Reichenb.)	Catharanthi Herba	Changchunghua	10 mg/kg	mice	i.v.	6
Supertoxic (≤5 mg/kg)	β-dichroine	*Dichroa febrifuga* Lour.	Dichroae Radix	Changshan	6.6 mg/kg	mice	p.o.	6
	aconitine	*Aconiti pareparata Radix*	Aconiti Tuber	Fuzi or Wutou	0.3 mg/kg	mice	p.o.	6
	cantharidin	*Mylabris phalerata* Pall.	Mylabris	Bansao	1.7 mg/kg	mice	--	6
	durisoline	*Sophora subprostrata* Chun et Chen	Sophorae Subprostratae Radix	Shandougen	1.3 mg/kg	rats	i.p.	11
	harringtonine	*Cephalotaxus fortunei* Hook., *C. qinensis* (Rehd. et Wils.) Li, *C. oliveri* Mast, or *C. haiuansis*	--	Sanjinshan	4.3 mg/kg	--	p.o.	6
	hayatine	*Cissampelos pareira* Linn.	--	Xishengteng	0.5 mg/kg	mice	i.p.	6
	magnoflorine	*Aristolochia debilis* Sieb et Zucc.	Saussureae Radix	Qinmuxiang	2 mg/kg	mice	i.v.	6

Table 2. Continued

Compound	Source (species)	Name	Dose	Animal	Route	Ref.
metetrandrine	Stephania tetrandra S.Moore (Menispermaceae)	Aristolochiae Fangchi Fangji or Hanfangji	1.3 mg/kg	mice	i.v.	6
oleandrin	Nerium indicum Mill	Jiazhutao Indicum	0.4 mg/kg	pigeon		6
rhomotoxin	Rhododendron molle G. Don	Rhododendri Molles Folium Balima	0.5 mg/kg	mice	i.p.	6
saponin	Loranthus parasiticus (L.) Merr.	Kiranthi Ramulus Songjishang	1.2 mg/kg	mice	i.v.	6
vincristine	Catharanthus roseus (L.) G. Don (Vinca rosea L., Lochnera rosa Reichenb.)	Catharanthi Herba Changchunghua	2.1 mg/kg	mice	i.v.	6

For additional details, see reviews cited in the references.

a — : not available.

These data show that it is necessary to consider the acute toxicity of the bioactive constituents and metabolites in order to properly assess the potential toxicity of a medicinal herb.

The alkaloid peimine and its glucoside peiminoside are isolated from Fritillariae Bulbs (Beimu). LD_{50} of peimine and peiminoside in mice are about 7 and 50 mg/kg i.v., respectively, placing them into the extremely toxic category (Table 2). The different LD_{50} values of these two compounds serve as another example to show that the glucoside is less toxic than its aglycon in many TCM natural products. Some chemical constituents from TCMs are supertoxic. Aconitine from Aconiti Tuber (Fuzi, aconite root) is regarded as supertoxic because its LD_{50} in mice is 0.3 mg/kg subcutaneously (s.c.) [6].

SYSTEMIC TOXICITY OF TCM

Many organs are susceptible to the adverse effects of long-term exposure to TCMs (Table 3). Subacute treatment of rats with ethanolic extracts of Bupleuri Radix (Chaihu) increased liver weight and serum alanine aminotransferase activity, a biochemical indicator of hepatic injury [19]. Trichosanthis Radix (Tienhuafen) serves as a rare example of an immunotoxic TCM which is a potent immunosuppressant and irritative agent [6]. The major constituents of Trichosanthis Radix are eliminated primarily by renal excretion. Hence overdosage of the herb may cause renal damage [6]. Crotonis Semen (Badou, croton seeds), containing croton resin, phorbol, and crotonic acids, is highly irritative to the intestinal mucosa [12]. Aconiti Tuber (Fuzi) is highly toxic to the heart muscle [12]. Treatment of rats with crude saikosides of Bupleuri Radix caused hemolysis in rats [12]. Overdosage intoxication of Corydalis Tuber (Yanhusuo) leads to central nervous system depression and muscle relaxation [6]. Overdosage of Magnoiae Cortex (Houpo) can cause respiratory paralysis [6].

Many TCMs and natural products have multiple target organs. Liver, blood, and gastrointestine are susceptible to the adverse effects of Bupleuri

Table 3. Systemic toxicity of traditional Chinese medicines

Target organ	Botanical name	Latin name	Chinese name	Reference
Liver	*Angelica sinensis* (Oliv.) Diels (Apiaceae)	Angelicae Sinensis Radix	Danggui	19
	Bupleurum chinense DC. or *B. scorzonerifolium* Willd (Apiaceae)	Bupleuri Radix	Chaihu	19
	Ligusticum chuaxiong Hort.	Ligustici Rhizoma	Chuanxiong	11
	Rheum palmatum L.	Rhei Rhizoma	Dahuang	6
	Trichosanthes kirilowii Maxim.	Trichosanthis Radix	Tienhuafen	6
Kidney	*Trichosanthes kirilowii* Maxim.	Trichosanthis Radix	Tienhuafen	6
Gastrointestinal tract	*Bufo bufo gargorizans* Cantor *Bufo melanosticus* Schneider	Bufonis Venenum	Chansu	6
	Bupleurum chinense DC. *B. scorzoneraefolium* Willd.	Bupleuri Radix	Chaihu	6
	Coptis chinesis Franch., *C. deltoidea, or C. teetoides* C.Y. Cheng	Coptidis Rhizoma	Huanglian	6
	Croton tiglium L.	Crotonis Semen	Badou	12
	Dryopteris crassirhizoma Nakai	– a	Guanzhong	6
	Eugenia caryophyllata Thunb.	Caryophylli Flos	Dingxiang	6
	Ipomoea hederacea Jacq., *I. nil* Roth. *I. purpurea* (L.) Lam.	Pharbitidis Semen	Qianniuzi	12
	Melia toosendan or *M. azedarach* L.	Meliae Cortex	Kulianpi	6
	Panax zingiberensis	–	Sanqi	6
	Punica granatum L.	Granati Pericarpium	Shiliupi	6
	Rabdosia rubescens Hora.	–	Donglingcao	6
	Rhodea japonica Roth	–	Wannianqing	6
Cardiovascular system	*Aconitum carmichaeli* Debx.	Aconiti Tuber	Fuzi or Wutou	12
	Macleaya cordata (Willd.), R. Br. (Papaveraceae)	–	Bolorhui	6
	Myrica rubra Sieb. et Zucc.	Myricae Cortex	Yangmeipi	12
	Paeonia lactiflora Pall.	Paeoniae Radix	Shaoyao	12
	Pulsatilla chinensis (Bunge) Regel	Pulsatiliae Radix	Baitouweng	12
Hematopoietic system	*Anemarrhena asphodeloides* Bunge	Anemarrhenae Rhizoma	Zhimu	12

Table 3. Continued

Category	Scientific name	Pharmaceutical name	Chinese name	Ref.
	Bupleurum chinense DC. / *B. scorzonerifolium* Willd.	Bupleuri Radix	Chaihu	12
	Camptotheca acuminata Decne.	--	Xizhu	6
	Cephalotaxus fortunei Hook., *C. qinensis* (Rehd. et Wils.) Li, *C. oliveri* Mast., or *C. haiuansis*	--	Sanjinshan	6
	Croton tiglium L.	Crotonis Semen	Badou	12
	Eugenia caryophyllata Thunb.	Caryophylli Flos	Dingxiang	6
	Gleditsia sinensis Lamarck	Gleditsiae Fructus	Zaojia	12
	Prunus persica (L.) Batsch / *P. persica* (L.) Batsch. var. *davidiana* Maxim	Persicae Semen	Taoren	12
Immune System	*Trichosanthes kirilowii* Maxim.	Trichosanthis Radix	Tienhuafen	6
Nervous system	*Angelica dahurica* Benth. et Hook. var. *pai-chi* Kimura Hata et Yen	Angelicae Dahuricae Radix	Baizhi	12
	Bufo bufo gargorizans Cantor / *Bufo melanosticus* Schneider	Bufonis Venenum	Chansu	12
	Corydalis turtschaninovii Bess. f. *yanhusuo* Y. H. Chou et C. C. Hsu	Corydalis Tuber	Yanhusuo	12
	Digenea simplex (Wulf.) C. Agardh	Digenea	Hairencao	12
	Ephedra sinica Stapf.	Ephedrae Herba	Mahuang	6
	Ligusticum sinense Oliv.	Ligustici Sinensis Rhizoma et Radix	Haoben	12
	Mentha arvensis L. var. *piperascens* Malinv.	Menthae Herba	Bohe	12
	Phytolacca esculenta Van Houtt.	Phytolaccae Radix	Shanglu	11
Respiratory system	*Coptis chinensis* Franch., *C. deltoidea*, or *C. teetoides* C.Y. Cheng	Coptidis Rhizoma	Huanglian	6
	Magnolia officinalis Rehd. et Wils.	Magnoliae Cortex	Houpo	6, 12
	Quisqualis indica L.	Quisqualis Fructus	Shijiunzi	12
	Stephania tetrandra S. Moore (Menispermaceae)	Sinomeni Caulis et Rhizoma	Fangji	6

For additional details, see reviews and studies cited in the references.

[a] -- : not available.

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Radix (Table 3). Crotonis Semen can cause damage to gastrointestinal and hematopoietic systems. Similarly, Bufonis Venenum is toxic to nervous and gastrointestinal systems. The list of toxicants in Table 3 is far from being complete. Chang [20] reported that more than thirty TCMs can cause adverse effects on the liver and respiratory system. TCM has the ability to cause behavioral toxicity. Subchronic administrations of Ziziphi Fructus (Dazao) and Polygalae Radix (Yuenzhi, polygala root) decreased locomotive activity in rats [21].

GENOTOXICITY OF TCM

Several recent studies have evaluated genotoxicity of Chinese herbal medicines *in vivo* and *in vitro* [22-28]. In these studies, the genotoxicities of several hundreds of commonly used TCM natural products were determined using the Ames bacterial mutation assay [29, 30], unscheduled DNA synthesis in human fibroblasts [31], and micronuclei formation in mouse bone marrow [32]. The ethanolic and water extracts of more than fifty medicinal herbs showed mutagenicity in the Ames assay using *Salmonella typhimurim* tester strains TA98 and TA100 (Table 4). The water extract of Ligustri Fructus (Nuzhenzi) showed mutagenicity in the TA98 and TA100 tester strains [26]. The water extract of Eucommiae Cortex (Duzhong) showed mutagenicity in the TA100 tester strain [23]. The water extracts of Astragali Radix (Huangqi) and Inulae Flos (Xuanfuhua) showed mutagenicity only in the presence of the S9 bioactivation system in the Ames test [23, 27], indicating that the herbal mutagens required metabolic activation.

Studies with the same herbal medicine conducted in different laboratories showed variable results in some instances. These variations may be a reflection of the differences in the growth and pretreatment conditions of the herbs, the extraction methods of the crude drugs, and possible contaminants in the crude extract. There has been a general concern regarding the histidine and mutagenic mycotoxins present in the crude extract which might give artificially positive results in the bacterial reversion assay. In this regard, some chemical analyses have demonstrated the absence of histidine and mutagenic mycotoxins in the herbal extracts [22, 23].

The unscheduled DNA synthesis assay is a short-term assay which measures the genotoxicity of a chemical by its ability to increase DNA synthesis in cells which do not enter the S cycle [31]. The genotoxicity assays of TCMs were carried out using human fibroblast cells CRL1508 [26-28]. The results of the genotoxicity assay of approximately 100 herbal medicines indicated that in the absence of the cell cycle inhibitor hydroxyurea, most of the medicines decreased DNA synthesis in the mammalian cells. In the presence of hydroxyurea, some TCMs increased incorporation of [^{3}H]-thymidine into DNA, suggesting that these herbal medicines caused DNA damage (Table 5). The aqueous extract of Lipidii Semen (Tinglizi) at 5 mg/ml was as potent as 1μ M 4-nitroquinoline N-oxide, a positive control for the genotoxicity assay, in its ability to increase unscheduled DNA synthesis [26].

The micronucleus test is a short-term cytogenetic assay which measures the formation of micronucleated polychromatic erythrocytes of bone marrow in mice following i.p. injection of mutagen [32]. Administration of ethanolic or water extracts of nineteen herbs increased micronuclei formation in mouse bone marrow cells (Table 6). Administration of water extract of Datura Flos (Yangjinhua) at 0.01 to 0.1 g/kg to mice caused 2- to 10-fold increases in the incidence of micronucleated polychromatic erythrocytes in bone marrow [23]. Some of these clastogenic herbs also increased the incidence of chromosomal aberrations in the bone marrow of mice [23, 33]. For example, Datura Flos induced chromosomal breakage in the cytogenetic assay. However, it should be pointed out here that the extract of the dried flower did not show apparent mutagenicity in the Ames bacterial mutagenicity assay. This serves as an example to illustrate that the bacterial and mammalian test systems may yield different results and it is necessary to carry out genotoxici-

Table 4. Traditional Chinese medicines with mutagenicity in the Ames test

Botanical name	Latin name	Chinese name	Reference
Aconitum carmichaeli Debx.	Aconiti Tuber	Fuzi or Wutou	22
Aconitum coreanum (Levl.) Rap.	Aconiti Coreani Tuber	Baifuzi	25
Agrimonia pilosa Ledeb. var. *japonica* (Miq.) Nakai	Agrimoniae Herba	Xianhecao	25
Akebia trifoliata (Thunb.) Koidz.	Akebia Caulis	Mutong	25
Alpinia oxyphylla Miq.	Alpiniae Oxyphyllae Fructus	Yizhiren	28
Angelica dahurica Benth. et Hook var. *pai-chi* Kimura, Hayata et Yen	Angelicae Dahuicae Radix	Baizhi	25
Arctium lappa L.	Arctii Fructus	Niubangzi	22
Aristolochia debilis Sieb. et Zucc.	Aristolochiae Fructus	Madouling	24
Aristolochia heterophylla Hemsl	Hanfangchi Radix	Hanfangji	25
Asiasarum sieboldi F. Maekawa	Asiasari Radix	Xixien	22
Astragalus mongholicus Bunge	Astragali Radix	Huanqi	23
Benincasa cerifera Savi	Benincasae Semen	Donguazi	22
Bupleurum falcatum L.	Bupleuri Radix	Chaihu	22
Carthamus tinctorius L.	Carthami Flos	Honghua	28
Cassia angustifolia Vahl	Sennae Folium	Fanxieye	22
Catalpa ovata G. Don	Catalpae Fructus	Xinshi	22
Chrysanthemum morifolium Ramat.	Chrysantheni Flos	Juhua	24
Corydalis bulbosa DC.or *Corydalis yanhusuo* W.T. Wang	Corydalis Tuber	Yanhusuo	22, 25
Coptis japonica Makino	Coptidis Rhizoma	Huanglian	22
Curcuma zedoaria (Berg.) Rosc.	Zedoariae Rhizoma	Ezhu	28
Cuscuta chinensis Lam.	Cuscutae Semen	Tusizi	26
Dioscorea japonica Thunb.	Dioscoreae Rhizoma	Shanyao	22
Elfvinga applanata Karst.	Elfvinga	– a	22
Eriocaulon buergerianum Koern.	Eriocauli Herba	Gufingcao	28
Eucommia ulmoides Oliv.	Eucommiae Cortex	Duzhong	23
Evodia rutaecarpa (Juss.) Benth.	Evodia Fructus	Wuzhuyu	24
Gentiana lutea L.	Gentianae Radix	Longdan	22
Gentiana scabra Bunge	Gentianae Scabrae Radix	Longdan	22

Table 4. Continued

Geranium thunbergii Sieb. et Zucc.	Geranii Herba	Laohecao	22
Gleditsia sinensis Lam.	Gledistiae Semen	Zaocizi	22
Inula britannica L. var. *chinensis* (Rupr.) Regel	Inulae Flos	Xuanfuhua	27
Kochia scoparia (L.) Schrad.	Kochiae Fructus	Difuzi	26
Lepidium apetalum Willd.	Lepidii Semen	Tinglizi	26
Ligustrum lucidum Ait.	Ligustri Fructus	Nuzhenzi	26
Lonicera japonica Thunb.	Lonicerae Caulis et Folium	Jinyinhua	22
Mallotus japonicus Muell-Arg.	Malloti Cortex	--	22
Nelumbo nucifera Gaertn.	Nelumbinis Semen	Lianzi	26
	Nelumbinis Folium	Heye	28
Paeonia albiflora Pall. var *trichocarpa* Bunge	Paeoniae Radix	Baishao	22
Phellodendron amurense Rupr.	Phellodendri Cortex	Huangbai	22, 28
Prinsepia uniflora Batal.	Prinsepiae Semen	Rueiren	26
Prunella vulgaris L.	Prunellae Spica	Xiakucao	24
Rheum palmatum L.	Rhei Rhizoma	Dahuang	22
Scutellaria baicalensis Georgi	Scutellariae Radix	Huangqin	22, 24
Sinomenium acutum (Thunb.) Rehd. et Wils.	Sinomeni Caulis et Rhizoma	Fangji	22
Smilax glabra Roxb.	Smilacis Rhizoma	Tufuling	22
Sophora japonica L.	Sophorae Flos	Huaihua	23
Sophora subprosarata Chun et Chen	Sophorae Subprostratae Radix or Menispermi Rhizoma	Shandougen	22, 28
Swertia japonica Makino	Swertiae Herba	Dangyao	22
Tetragoniz tetragonoides O. Kuntze	Tetragoniae Herba	Fanxing	22
Thuja orientalis L.	Thujae Orientalis Semen	Baiziren	26
Trapa bispinosa Roxb. var *iinumai* Nakano	Trapae Fructus	Lingjiao	22
Zingiber officinale Rosc.	Zingiberis Rhizoma	Shengjiang	22

For additional details, see studies cited in the references.

[a] -- : not available.

Table 5. Traditional Chinese medicines that cause unscheduled DNA synthesis in human fibroblast cells

Botanical name	Latin name	Chinese name	Reference
Fritillaria cirrhosa D. Don	Fritillariae Cirrhorsae Bulbus	Chuanbeimu	27
Hydnocarpus anthelmintica Pier.ex Laness.	Hydnocarpi Semen	Dafengzi	26
Lepidium apetalum Willd.	Lepidii Semen	Tinglizi	26
Lilium brownii F. E. Brown var. *colchesteri* Wils	Lilii Bulbus	Baihe	27
Lycium chinese Mill.	Lycii Radicis Cortex	Digupi	24, 25
Millettia dielsiana Harms	Millettiae Caulis	Jixueteng	25
Nelumbo nucifera Gaertn.	Nelumbinis Semen	Lianzi	26
Prinsepia uniflora Batal.	Prinsepiae Semen	Rueiren	26
Saliva miltiorrhiza Bunge	Salivae Miltiorrhizae Radix	Danshen	25

For additional details, see studies cited in the references.

ty assays using more than one system to properly determine the mutagenic potential of TCMs.

CONTAMINANTS OF TCM

Pesticides are commonly used to control pests, fungi and weeds in the intensive cultivation of TCM herbs. Improper use of pesticides during the production and storage of TCM has become a major source of contamination. The level of pesticide residue is a major concern in interms of quality and safety. A recent survey of eleven medicinal herbs in Taiwan showed the presence of organic chlorine insecticides in Dongyangshen and Fanxieye [34]. The total content of benzene hexachloride (BHC) isomers was in the range of 0.018~1.266 ppm in fourteen out of twenty samples of Dongyangshen. Similarly, BHC content in seventeen out of twenty specimens of Fanxieye was 0.008~0.050 ppm. The content of dichlorodiphenyltrichloroethane (DDT) in some Fanxieye samples exceeded 0.2 ppm.

Heavy metals constitute another source of chemical contamination in TCMs. In Taiwan, more than 100 ppm lead was detected in the TCM material Cordeceps (Dongchongxiacao), a proprietary medicine Xiaerjingfeng, and an over-the-counter composite formula Babaofen [34]. About 100 to 4000 ppm mercury was detected sporadically in samples of Xiaerjingfeng, Babaofen, and a composite formula, Qilisan. In the same studies, cadmium and copper were detected in some of the TCM samples.

To increase therapeutic efficacy, certain synthetic pharmaceuticals were added to TCM illegally. For example, chemical analysis of a herbal product Zhuifengtouguwan revealed the presence of drugs such as aminopyrine, phenacetin, diazepam, dexamethasone and heavy metals such as lead and cadmium [35]. Clobezorex and diazepam were detected in an anorexiant TCM [36]. A quantitative analysis of a TCM product for the treatment of heart disease and uricosuria showed that the medicinal pills were adulterated with caffeine, ethoxybenzamide, chlorzoxazone, diazepam, and indomethacin [37].

Table 6. Traditional Chinese medicines that increase formation of micronuclei in the bone marrow of mice

Botanical name	Latin name	Chinese name	Reference
Aristolochia debilis Sieb. et Zucc.	Aristolochiae Fructus	Madouling	25
Aristolochia heterophylla Hemsl	Hanfangji Radix	Hanfangji	26
Astragalus mongholicus Bunge	Astragali Radix.	Huangqi	28
Carthamus tinctorius L. [a]	Carthami Flos	Honghua	23
Cinnamomum mairei Levl. [a]	– [b]	–	23
Cuscuta chinesis Lam.	Cuscutae Semen	Tusizi	27
Datura metel L. [a]	Daturae Albrae Flos	Yangjinhua	23
Eriocaulon buergerianum Koren	Eriocauli Herba	Gujingcao	28
Forsythia suspensa Thunb. [a]	Forsythiae Fructus	Lianqiao	23
Nelumbo nucifera Gaertn.	Nelumbinis Semen	Lianzi	27
	Nelumbinis Folium	Heye	28
Notopterygium incisium Ting. [a]	Notopterygii Rhizoma	Qianghuo	23
Paeonia suffruticosa Andr. [a]	Moutan Radicis Cortex	Mudanpi	23
Phellodendron amurense Rupr.	Phellodenri Cortex	Huangbai	28
Platycodon grandiflorum Jacq. A.DC. [a]	Platycodi Radix	Jiegeng	23
Prinsepia uniflora Batal.	Prinsepiae Semen	Rueiren	27
Prunella vulgaris L.	Prunellae Spica	Xiakucao	25
Rehmannia glutinosa f. *hueichingenesis* (fermented) [a]	Rehmanniae Radix	Shoudihuang	23
Sophora flavescens Ait. [a]	Sophorae Radix	Kushen	23, 28
Thuja orientalis L.	Thujae Orientalis Semen	Baiziren	27

For additional details, see studies cited in the references.

[a] : Positive in chromosomal aberration assay (23).

[b] – : not available.

Very often, the exact compositions of proprietary TCMs and composite formulae are not known. This makes it more difficult to qualitatively and quantitatively analyze the chemical contaminants and study the effects of contaminants on the toxicity of the TCM products. Extensive effort in analytical chemistry is required to monitor proprietary TCMs and herbal remedies. To complement chemical analysis, the development of morphological, histological, and molecular biology techniques to document the authenticity of the herbal medicines becomes an urgent task [38, 39].

CLINICAL TOXICOLOGY OF TCM

It has become clear that some proprietary TCMs may be adulterated with undeclared and often more toxic drugs [7]. The complex interactions of the constituents of the herbs with these xenobiotics may produce antagonistic, synergistic, or potentiation effects on the toxicity associated with the drug or herbal medicine. Such complex drug interactions and idiosyncratic reactions may lead to severe intoxication in individuals with high susceptibility [40]. The adulterated TCM Zhuifengtouguwan from Asia has been described as a deadly Chinese roulette in Dutch newspapers [35]. Consumption of proprietary TCM containing synthetic corticosteroids led to episodes of Cushing's syndrome [41].

Various species of Aconitum are commonly used in TCM. These plants are known to contain highly potent cardiotoxins [42]. An accidental ingestion of a herbal liniment prepared from Aconitum caused near fatal results [43]. Podophylli Rhizoma (Bajiaolian) contains the toxic ingredient podophyllotoxin. Cases of podophyllotoxin intoxication were observed with patients given the herb prescribed for postpartum recovery and treatment of a neck mass, hepatoma, and other diseases [44].

Several TCM products have been used as non-regulated health foods world-wide. Clinical cases with adverse reactions and mortality have been reported due to the abuse of these medicinal herbs. For example, Ephedrae Herba (Mahuang) is used in weight control pills and energy-stimu-lating formulae. Overdose of this herbal material resulted in tachycardia and death [45]. The Food and Drug Administration of the United States has issued several warnings about this herb [46]. The glycosides in Aloe (Luhui) can cause severe diarrhea which may be hazardous to pregnant women and people with irritable bowel syndrome. Gingko Folium (Yinxingye) extract is the most prescribed medicine for enhancing brain blood circulation in elderly patients in Europe. The use of this over-the-counter herbal medication has been linked to a spontaneous subdural hemorrhage [47, 48]. In addition, spontaneous hyphema associated with ingestion of this herbal extract was reported recently [49].

Increasing evidence has shown that certain foods can aid, help prevent or cure some chronic diseases. However, the limited medical knowledge of the public and the exaggerated advertisements have made the use of health foods a controversial issue. Several countries, including America, Japan, England, Canada and China, have set or changed the law to better define health food and the principles for pharmacological and toxicological evaluation. The US congress passed the Dietary Supplement Health and Education Act of 1994 to define the term 'dietary supplement' and the principles for functional and toxicological evaluation. The act requires that labels must meet the standard format of "Health Claim" and "Supplemental Facts". Apart from the Health/ Functional/ Structural Claim, any claims of drug effect (Drug Claim) for health foods is prohibited in most countries. In addition, several countries have organized special research groups to provide function and safety information on health food to government agencies and educational and medical parties. The future development of TCM as health food will depend on how successful herbal medicine can provide adequate toxicity and safety information.

CONCLUSION

Research should address the evaluation of pharmacological and toxicological properties of

TCM herbs as mixtures of chemicals with the hope of finding new treatments for diseases [7]. Similar to the complex systems in bioactivity testing, TCM toxicity testing should be expanded to include TCMs in the upper and middle categories. Toxicity testing of these categories will help to clarify some of the myths associated with Chinese herbal medicines and establish a systematic knowledge of the toxicity of each TCM category.

Toxicological studies are to be carried out in the course of the development and standardization of TCM. *In vitro* toxicity screening involves bacteria and mammalian cell systems to study the potential biochemical and genetic toxicities of TCM. Animal toxicology studies are much needed to determine the potential health effects of TCM, in terms of systemic, behavioral, and physiological changes possibly associated with ingestion of TCM herbs and pure compounds. Long-term bioassays are required to determine the carcinogenic and teratogenic potentials of TCMs. These TCM toxicological studies require appropriate animal and cell model systems, some of which need to be developed and established. Clinical studies can be carried out upon completion of the *in vivo* and *in vitro* toxicity testing procedures. Only adequate animal toxicology and clinical trial information will increase the efficacy and safety of T.M.

TCM studies have made a significant contribution to modern pharmacology [50, 51]. Similarly, studies of the herbal medicines will contribute to basic research of toxicology. Mechanistic studies of TCM can lead to a better understanding of the underlying basis of toxicity resulting from interaction between a natural product and a biological system. The understanding of toxicity mechanisms will provide a basis for the development of detoxification methods and preventive measures, and provide useful information for the regulation and safety assessment of TCM.

ACKNOWLEDGMENTS

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常用傳統中藥之毒理概觀

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摘　　要

　　傳統中藥在許多國家的醫療保健系統中扮演很重要的角色。近幾年中藥及天然物在新藥研發的潛能又重新被重視，一般認為中藥研發缺乏有系統的藥理、毒理及臨床研究。最近研究顯示中藥能治療某些西藥無效的疾病，但是因為藥效及安全性評估資料之不足，使得中藥的發展仍然受限制。此短篇概論將綜合整理常用中藥的急性、器官、基因、分析及臨床毒理資料，希望能成為一份中藥毒理介紹及參考資料。急毒性試驗顯示中藥的半致死劑量分佈由無毒到超毒等級。中藥毒性標的器官包含肝、腎、腸胃道、神經系統及心臟等。部份中藥在安姆氏試驗中顯示有致突變性，在細胞基因毒性試驗中有能力增加不按計畫之DNA合成，微小核生成及染色體異變。化學分析結果顯示有些中藥被農藥、重金屬污染或被添加西藥。中藥不當的使用及特異體質反應可能造成中藥的不良副作用。因此，完備、有系統的毒性試驗及詳細的毒理機制研究，將非常有助於中藥藥效、安全性之評估及新藥研發。

關鍵詞：傳統中藥，天然物，毒性。