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REVIEW

Analysis of the adverse reactions induced by natural product-derived drugs

Zhi-Ping Zeng and Jian-Guo Jiang

College of Food and Bioengineering, South China University of Technology, Guangzhou, China

Compared with the therapeutic effects of established medicinal drugs, it is often considered that natural product-derived drugs are of a more benign nature in side-effects, which has made natural medicines become a popular form of therapy. Traditional Chinese medicine (TCM) is generally considered as being natural and harmless. TCM has been paid much more attention than before and widely used for the treatment nowadays. However, with the increasing cases of adverse drug reactions (ADRs), the ADRs induced by TCM are becoming more widely recognized. Some ADRs are sometimes even life-threatening. This article reviews literatures on ADRs induced by TCM which was published in the past 10 years. A total of 3122 cases including complete data are selected for the present analysis. From the data of the 3122 cases, statistics is carried out to the distribution of administration routes and time of the occurrence of ADRs, the prognosis of ADRs, sex and age factors, types and clinical symptoms of ADRs, and drugs involved in ADRs. In addition, occurrence and influencing factors of TCM-induced diseases are also analysed, which includes spices confusion, processing drugs improperly, toxic components, long-term medication, improper concerted application, interaction of TCM and Western medicine. It is concluded that the efficacy and toxicity of TCM, often using the compound prescription involving various plants and animals, resulted from a variety of chemical constituents, which lead to a comprehensive response in the human body. The 'toxicity' of TCM should be correctly recognized and reasonably utilized.
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Introduction

Natural medicine is generally considered safe and with few adverse drug reactions (ADRs). As a representative natural medicine, traditional Chinese medicine (TCM) is more and more widely used nowadays. However, some of the ADRs are revealed eventually, with extended usage of certain types of TCM. Most common reactions are allergenic reaction and toxic reaction. Such reactions can cause unease and pain; furthermore, they can be life-threatening. Many consider that Chinese herbs are pure natural and with none ADRs. Excessive or improper use of drugs, especially through self-administration for nonmedical purposes will cause drug abuse (Legrand *et al.*, 1999). Extensive usage of tonics for nourishment, for example, is especially considered effective as 'curing when one is sick, and keeping fit when one is healthy'. In reality, it is far from true. Despite the fact that most of the Chinese herbs are natural, inappropriate usage may easily cause ADRs (Wang and Pan, 2000; Zhang and Li, 2005). Ginseng, for instance, can 'prolong life' and 'improving hearing and vision'. Excessive usage may not get such effects. In contrary, it may cause ADRs for nervous system and digestive system. Or, more seriously, it may be lethal.

There are 12 870 kinds of TCM resources (including taxon under species). Among those there are 11 146 species of medicinal plants belonging to 383 families and 2309 genera. There are 1581 species of medicinal animals belonging to 11 phyla, 33 classes, 141 orders, 415 families, 861 genera. There are 80 kinds of medicinal mineral substances, which are divided into 12 groups (Zhang *et al.*, 1995; Li *et al.*, 2008). Knowledge on the ADRs of TCM is not a new thing today. *Shen Nong's Herbal Classic* in the second century BC classified TCM into three kinds, top grade, medium grade and low grade, according to drug's efficacy and toxicity (Wu, 2007). Drug's toxicity is the degree to which a substance can do harm when acting on the human body with a certain dosage and time (Shaw *et al.*, 1997). After that, most of the TCM books in all ages specifically recorded the drug's toxicity and side-effects, and raised the methods for prevention and cure. A side-effect is usually considered as an undesirable secondary effect which occurs in addition to the desired therapeutic effect of a medication. It may vary for each individual

Correspondence: Jian-Guo Jiang, College of Food and Bioengineering, South China University of Technology, Guangzhou, 510640, China. E-mail: jgjiang@scut.edu.cn
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depending on the person's disease state, age, weight, gender, ethnicity and general health. (Arathi *et al*., 2005; Widakowich *et al*., 2007). In Qing Dynasty, *Herbal Lihai* written by Ling Huan expounded every species of drugs in order of three aspects, harm, benefit and therapy, and the harm (side-effects and its taboo) was listed at first, which indicated that the ancient physicians have long recognized the adverse effects of TCM.

Drugs have the duality, and there could be some side-effects in the process of curing disease. Western medicine and TCM are no exception (Zhang and Li, 2005). Every species of TCM includes a variety of ingredients. Some ingredients interact with each other, displaying pharmacological effect when they take effect in human body (Wang and Pan, 2000)). Take the total saponins of panax ginseng (TSPG) for example, the Rb and Rc in TSPG have definite haemolytic reaction, and Ra has anti-haemolysis but TSPG have not (Zhang *et al*., 2006a). Clinically, TCM is more often the combination of TCM prescriptions, and it has been partly confirmed by modern research that the compatibility brought about attenuation and synergistic action (Li, 2005a; Ma and Guo, 2005; Sun *et al*., 2005). The ingredients of TCM are very complicated, and the ADRs caused by them are diverse. In the present paper, the reports about ADRs of TCM which was published during the last 10 years are analysed. Meanwhile, the status, causation, pathology and other items of the ADRs caused by TCM are reviewed.

Currently, the world pays increasing attention to TCM. Meanwhile, the consciousness of ADRs is also gradually raised, but there has been no related report analysing this field comprehensively. Therefore, through systemic statistics and analysis of ADRs induced by TCM in this paper, more and more attention are expected to be paid to the study of adverse reactions in order to promote a more healthy and positive development and application of TCM.

Statistical analysis of ADRs induced by TCM in the past decade

According to WHO Collaborating Centre for International Drug Monitoring, 4960 ADRs cases were reported before 1994, and it reached to 8986 at the end of 1999 (Wang, 1999). Searching reports and relevant materials on ADRs of TCM in the past 10 years, author found there was a trend that the ADRs were increasing gradually in the past decade. A total of 3122 effective cases, all including data of sex, age, drug names, administration routes, the duration from initiation of drugs' intake to the occurrence of ADRs, types of ADRs, are selected for the present analysis. A database involved the 3122 cases was established by numeration and classification for the use of statistics.

Administration routes

It can be seen from the distribution of administration routes of ADRs, intravenous injection had the largest number, about 1661 cases accounting for 53% of all cases (Table 1). Other administration routes including oral, inhaling, external use, intramuscular injection, buccal administration had 1461 cases, 46.8% of the total, which indicates every administration route may cause the ADRs (Zhang and Li, 2005).

Table 1 Adverse drug reaction distribution of administration routes

Administration routes	*The number of cases*	*Percentage (%)*
Intravenous injection	1661	53.20
Oral administration	1015	32.51
External use	189	6.05
Inhaling	133	4.26
Intramuscular injection	77	2.47
Buccal administration	47	1.51

Table 2 Occurrence time of adverse drug reactions induced by traditional Chinese medicine

Time	*Cases*	*Percentage (%)*
<30 min	1004	32.16
30 min-1h	325	10.41
1–5h	337	10.79
5–24h	198	6.34
1–10d	983	31.49
>10d	275	8.81

Administration routes also have an extremely important impact on the occurrence of ADRs and its severity (Qiu, 2006; Wang *et al*., 2006b; Zhang, 2006b). The main traditional administration route of TCM is oral administration, which can be used for most drugs and most patients. However, the special administration routes of some drugs should come into notice to prevent ADRs caused by the change of administration routes (Wu *et al*., 2006). The oral preparation and external preparation of some Chinese herbal antibacterial drugs such as Honeysuckle Flower, *Radix Scutellariae* and *Fructus Forsythiae* are safe, but ADRs of Shuanghuanglian injection made from the three drugs are very common (Chen and Shao, 2002).

Occurrence time of ADRs

It can been seen from the occurrence time of ADRs (Table 2), there are 1004 cases whose ADRs occurred within 30 min, 32.16% of all the cases; and 1258 cases whose ADRs occurred after more than 24 h, 40.3% of all cases, which indicates that different drugs, different individuals, different uses and different dosages result in difference occurrence time of ADRs. In our database, one case using ahylysantinfarctase showed negative reaction to hypersensitive test, but suffered anaphylactic shock 1 min after medication. In another one case using mailuoning injection, 11 days after medication the patient got itchy skin all over the body (Wang *et al*., 1998). Therefore, we should keep eyes on patients during the medication, paying attention to a variety of drug reactions during the treatment.

Prognosis of ADRs

When the ADRs appeared, all patients stopped taking medicine and were given appropriate treatments, the ADRs may

Table 3 Prognosis of adverse drug reactions induced by traditional Chinese medicine

Results	*The number of cases*	*Percentage (%)*
Cure	1896	61.86
Improvement	1087	35.46
Extend	65	2.12
Worse	14	0.46
Dead	3	0.1
	3065	100

In 3122 cases, 57 cases didn't have prognosis reports.

Table 4 Distribution of sex and age

Age	*Male*	*Female*	*Numbers*	*Proportion (%)*
<10	374	242	616	19.73
11–20	157	131	288	9.22
21–30	132	147	279	8.94
31–40	265	222	487	15.60
41–50	245	209	454	14.54
51–60	207	198	405	12.97
>61	331	262	593	18.99
	1711	1411	3122	100

disappear (Table 3). Some patients didn't take any medicine, ADRs may also disappear naturally. In these cases who turned better, one case had acute non-lymphocytic leukaemia underwent bone marrow transplant. In the death cases, two cases were allergic shock caused by compound Danshen injection (Liu and Liang, 2001), one case was anaphylactoid purpura caused by *herba houttuyniae* injection.

Sex and age

Among 3122 ADRs cases, 1711 cases were male, 1411 cases were female. The youngest patient was 7 months old, the oldest was 82 years old. The sex and age distribution are presented in Table 4.

The incidence rate of ADRs is normally distributed in various age groups, which agrees with natural population distribution. The incidence rate of 21–60 years old is high, accounts for 52.01% of total, which is due to the large number of this group. The age distribution shows that there is no age selectivity in the 3122 cases. In these cases, male accounts for 54.80%, and female 45.20%, indicating the incidence rate among male and female are roughly equal.

Types of ADRs and clinical symptoms

A total of 3122 cases of ADRs involved 140 kinds of drugs in total. From the distribution of dosage form, the cases caused by injections were the highest, which was up to 1738 cases and account for 55.67% of the total (Table 5). *Herba houttuyniae* injection (Li, 1997a; Bai and Shao, 1998) and Shuanghuanglian injection were the two most common drugs involved in ADRs, which were 28 cases and 25 cases respectively. TCM may lead to ADRs in various tissues and systems, such as the digestive system, nervous system, blood system, cardiovascular system, urinary system (Table 5).

Most of ADRs were allergies, mainly presented as skin itch, drug eruption (Wu, 2001), dermatitis, high fever, oedema, anaphylactic shock (Zhao *et al.*, 1997; Ma *et al.*, 2000; Zhang and Li, 2000; Tang *et al.*, 2003). Among these symptoms, anaphylactic shock was the most harmful to the body, sometimes life-threatening (Zhu, 2006). Chills and fever may be related to pyrogen in drugs, and also be considered as a kind of reaction similar to pyrogen reaction which is caused by drug itself. There were 128 cases showing anaphylactic shock (Yang *et al.*, 2000; Zhou, 2002; Luo and Wang, 2006), accounting for 4.10% of the 3122 cases. Most of them were caused by intravenous injection (Wang *et al.*, 2005c; Chen, 2006), which was because when given intravenous injection, a large number of antibodies were produced, antigen–antibody binding extent was greater than the other administration routes (Yang *et al.*, 2000).

Apart from some inorganic substances in TCM, most are big molecular organic substances such as protein, polypeptide, polysaccharide, etc. They have both immunogenicity and reactionogenicity, and can induce the immune response through immune system, making the body produce antibodies or sensitized lymphocyte, which finally leads to allergies (Wei and Wu, 2001). The importance of allergy in the ADRs caused by TCM does not lie in how high its ratio is, but it's unpredictable like the allergies of antibiotics and other chemicals. Moreover, some of them are very harmful, and often lead to death (Lai *et al.*, 2002).

Drugs involved in ADRs

A total of 140 kinds of drugs involved in ADRs are observed (Table 6). According to the severity and the number of type of ADRs cause by them, the order is *Tripterygium wilfordii* tablets, Ganmaotong tablets, Shuanghuanglian injection, Danshen injection, Qinkailing injection, Niuhuang Jiedu Wan, Shenmai injection, polyporus polysaccharide, Yinzhihuang injection, Cantharis, Fufang Qingdai Wan (Ma and Sun, 1997), Huoxiangzhengqishui (He, 1997), Liushen Pill (Fang, 1997; Nie, 1998), Chuanhuning, essential balm and zhenghonghua oil (Dai and Hu, 1997; Liu *et al.*, 1997a; Sun and Xu, 1998).

From the analysis above: (i) the ADRs may lead to damage of multi-organs as well as multi-systems and can also have an influence on the treatment. Furthermore, it may be life-threatening; (ii) the allergic and suspected allergic, including anaphylactic shock, allergic reactions and drug eruption, accounted for 40.63% of the total (412/1014). This indicates that a lot of TCM could induce allergies (Luo, 2006; Zhang *et al.*, 2006b). As we can see from another analysis report of 111 ADR cases, the allergies including skin reaction, anaphylactic shock, drug fever and exfoliative dermatitis is up to as high as 66.67% (Liu, 2000). Although their report could not display real situation completely because of the small number of cases in the analysis, it showed the cases suffering from allergies were not uncommon. In the past, most allergic reactions caused by drugs for external use were considered as contact dermatitis, and relatively safe. However, there were reports that Java Brucea Fruit (Jin, 1997) and Essential balm could cause not only contact dermatitis, but also anaphylactic shock. In addition, Jieeryin lotion caused drug eruption and

Table 5 Case number and types of adverse drug reactions caused by forms of medication drugs and their main clinical symptoms

Types of adverse drug reactions	*Oral intake*	*Injection*	*External use*	*Total*	*Main clinical symptoms*
Anaphylactic shock	19	108	1	128	Sweating, palpitations, blood pressure dropping, heart rate increasing, loss of consciousness
Skin and other attachment	360	580	322	1262	Hemorrhagic erythematous eruption all over the body, urticaria pruritus, local skin rashes
Digestive system	96	351	12	459	Liver damage, anorexia, inappetence, bellyache, diarrhoea, vomiting, gastrointestinal tract damage, inflammatory gastrointestinal mucosa disease, oesophagitis, gastrointestinal ulcers and bleeding, disturbance of absorptive function, pancreatitis, etc.
Urinary system	135	166	0	301	As to the degeneration of renal tubule, the impairment of renal proximal convoluted tubules is obvious, showing necrotizing disease. The symptoms include lumbago, make water little or anuria, urinary incontinence, haematuria, proteinuria, cylindruria, azotemia, decrease in renal function, etc.
Respiratory system	15	30	1	46	Coughing, chest aches, obstruction of upper respiratory tract, choke, cyanosis, vocal cords oedema, bronchoscopy, dyspnoea, respiratory failure, etc.
Eye damage	11	7	13	31	Optic neuritis, blurred vision, conjunctival haemorrhage, eyelid oedema
Cardiovascular system	48	83	0	131	Chest distress, cyanosis, shortness of breath, chest panic, pale face, cold limbs, blood pressure decline or increase, muffled heart sounds, conduction block, ECG changes, etc.
Nervous system	22	54	0	76	Numbness of limbs, dizziness, headaches, somnolence, high fever, twitching, stupor, coma, confusion, respiratory failure, circulatory failure, incontinence, may cause death in extreme cases.
Fever	56	17	1	74	Chilling, fever, generalised malaise, upset.
Blood and endocrine system	105	37	0	142	Leucopenia, thrombocytopenia, gum bleeding, bone marrow depression, aplastic anaemia, DIC, milk secretion.
The others	148	305	19	472	Mental disorders, skin redness and necrosis, limb trembling, tinnitus, hallucination, facial palsies, hypokalaemia, hypoglycaemia
Total	1015	1738	369	3122	

zhenghonghua oil caused acute gastrointestinal by external use (Liang *et al*., 2006; Wu *et al*., 2006).

In the above information, although the species of the TCM and the number of cases are limited, it is not difficult to see that in the past 10 years, a large number of ADRs occurred, the proportion of allergies in ADRs reached to as much as 40.63% ~ 66.67%, and many of them were serious reactions. With the development of the pharmaceutical industry, the varieties of TCM preparations are increasing. At the same time, ADRs including allergic reactions caused by them will also increase, which is the reality we must face (Wu *et al*., 2006).

Occurrence and influencing factors of TCM-induced diseases

Species confusion

China is abundant in medicinal plant resources, reaching more than 8000 species. Homonym and synonyms is inevitable. Misusing drugs will lead to side-effects and drug-induced diseases (Yu and Zhang, 2006; Chen and Yuan, 2008). Active ingredients, side-effects, biological activity are totally different for different drugs which have different original sources.

The most typical example of mistaken species is the confusion of Akebiae (Mu Tong) and *Caulis Aristolochiae manshuriensis* (Guan Mu Tong). Mu Tong in Akebiae is a kind of plants recorded in Compendium of Materia Medica as genuine, whose diuretic effect is obvious, also with a better antibacterial activity and less side-effects. However, *Caulis Aristolochiae manshuriensis* contains aristolochic acid (AA), which has a strong renal toxicity (Ye and Cui, 1997; Li, 1997b; Li, 2005b; Yalýnbaþ *et al*., 2006). It proved that AA was a potential carcinogen, based on the analysis of DNA adduct of AA and its metabolite in some reports (Schmeiser *et al*., 1996; Cosyns *et al*., 1999).

There were many reports of mistaking *Radix Aristolchiae Fangchi* for *Stephania tetrandra* that led to degenerative nephritis, for the former has renal toxicity and carcinogenesis. A report said that two females in a clinic in Belgium suffered kidney failure after taking obesity attenuation capsule containing *Stephania tetrandra*, in fact it was *Radix Aristolchiae Fangchi* (Vanherweghem *et al*., 1993), which was named the 'Chinese herbs nephropathy' and shocked the world. In Hong Kong, podophyllum was mistaken for Chinese gentian, leading to degenerative encephalopathy (Wang *et al*., 2006b). The direct cause of these tragedies was the wrong identification of components.

Improper process of drugs

Standardized processing of drugs can reduce side-effect of drugs, improve therapeutic effects and reduce the incidence of ADRs. In particular, some drugs containing toxic components must go through a standardized processing before use (Liu, 2005). Take daphnarcphne genkwa for an example, it need to be boiled with vinegar or stir-baked with vinegar before use. Stir-baking with vinegar has little effect on flavonoids in

Table 6 Drugs involved in adverse drug reactions and their clinical symptoms

Drug names	*Main ingredients*	*Clinical symptoms*											*References*
		Anaphylactic shock	*Skin and other attachment*	*Digestive system*	*Urinary system*	*Respiratory system*	*Eye damage*	*Cardiovascular system*	*Nervous system*	*Fever*	*Blood and endocrine system*	*Others*	
External use													
Caowu ointment	Aconitine, mesaconitine and atisine							+					Chen *et al.* (1997); He and Duan (2001)
Clove oil	Eugenol, acetyl eugenol and caryophyllene							+					Yu and Duan (1998)
External preparations such as burn cream and so on	*Scutellaria baicalensis*, phellodendron and Coptis Root		+										Gao *et al.* (2006)
Huoxiangzhengqishui	*Wrinkled Gianthyssop Herb*, poria, shell of areca nut, perilla leaf, angelica dahurica, pericarpium citri reticulatae, *glycyrrhiza uralensis, rhizoma pinelliae, et al.*			+									He (1997)
Java Brucea Fruit (Yadanzi)	Nigakilactone, alkaloids and flavonoids	+			+	+		+					Jin (1997); Wang (2007)
Qizheng Xiaodu plaster	*Lamiophlomis rotata Kudo.*, Myricaria germanica, Herba Oxytropis Falcatae, Buffalo Horn, *et al.*		+										Zhang *et al.* (2006b)
Shexiang Gao	Musk, Angelica, Giant Typhonium Rhizome, Szechwan Lovage Rhizome, Dahurian Angelica Root, *Paeonia Lactiflora, et al.*			+									Pan (2006)
Shexiang Zhuanggu Gao	Musk		+										Zi (1999)
Tianhe Gutong plaster	*Caulis Erycibes*, Ephedra, Angelica, Dried Ginger, Dahurian Angelica Root, Frankincense, Notoginseng, Kadsura Pepper Stem, *et al.*							+					Wang *et al.* (2006a)
Yunnan Baiyao	Notoginseng				+						+		Ma and Guo (2005)); Liu and Yang (2005)
Zhenghonghua oil	Turpentine Oil and Methyl Salicylate	+											Dai and Hu (1997)); Sun and Xu (1998)
Oral administration													
999 Ganmaoling granule	Railway beggarticks herb, Wild Chrysanthemum Flower, Caffeine, Paracetamol, Chlorphenamine Maleate, *et al.*		+		+								Liu and Zhang (2002)
Aconitine	Aconitine							+					Ma and Guo (2005)
Airpotato yam	Steroidal saponin, diterpene lactone, flavonoid, polysaccharide and microelement			+									Zi (1999)
Akebiastem	Akebin				+								Zhang and Li (2000)); Huang and Yu (2006)

Angong Niuhuang Wan	*Calculus Bovis*, Turmeric Root Tuber, Rhino horn, Baical Skullcap Root, *Rhizoma Coptidis*, Realgar, Cape Jasmine Fruit, Cinnabar	+						Zhang *et al.* (2006a)
Banlangen granule	*Radix Isatidis*						+	Hu and Jia (1998)); Tong (1998)
Cantharis	cantharidin and its derivations		+	+				Chen *et al.* (2006)
Caoshan Hu Hanpian	Herba sarcandrae, Menthol and Oil of Peppermint	+			+			Luo (2006)
Centipede Powder	Fatty acid, protein, amino acid, ornitrol		+					Wang *et al.* (2006a)
Chanfukang	Motherwort Herb		+					Wei (1997
Chasu capsule	Extracts from green tea		+					Pan (2006)
Chinese Wolfberry Root-bark (Digupi)	Organic acid, alkaloids				+			Sun and Du (1997)); Chen *et al.* (2006); Liu and Yang (2005)
Chuanxinlian pill	Extracts from *Herba Andrographitis*	+						Wang *et al.* (2006a)
Cinnabar	Ethiopsite			+				Sun *et al.* (2005)
Compound Danshen tablet	Danshen Root, Notoginseng and Borneol	+				+		Huang and Yu (2006)
Cordyceps Concentrated Powder	Cordycepic acid, protein, amino acid, polysaccharoses, fatty acid and vitamin				+			Chen and Shao (2002)
Dahuoluodan	Ra*idix Saposhnikoviae*, *Rhizoma Gastrodiae*, kudzuvine root, Chinese Angelica, ginseng and bungarus minimus, *et al.*	+						Sun *et al.* (2005); Gao *et al.* (2006)
Dioscorea bulbifera L.	Diterpene lactones, steroid saponin and flavonoid		+					Wang *et al.* (2006a)
Duanlongmu	Drgon's bone and oyster shell				+			Chen *et al.* (2006)
Ershiwuwei Songshi Wan	Tophi, Coral, Cinnabar, Emblic Leafflower Fruit, Musk, Saussureae, Saffron, Tabasheer, Entire meconopsis herb, *et al.*			+				Wang *et al.* (2006a)
Fleeceflower Root (Heshouwu)	Stilbene glucoside, chrysophanol, rheum emodin, rhein, physcion, lecithin and glucoside		+					Ding and Ding (1997)); Fang (1997)
Fufang Jiegeng tablet	Meconium, Platycodon Root and Kalium slfuricum				+			Chen *et al.* (2006); Gao *et al.* (2006)
Fufang Qingdai Wan	Natural Indigo, Smoked Plum, Danshen root, Dahurian Angelica Root, Purslane Herb, Chinese Magnolivine Fruit, *et al.*		+					Zhang (1997b)
Fufang Wulongsan	Bungarus Parvus, Lightyellow Sophora Root, Danshen Root, Radix Notoginseng, *Rhizoma* and gecko, *et al.*						+	Zhang *et al.* (2006b)

Table 6 *Continued*

Drug names	*Main ingredients*	*Clinical symptoms*											*References*
		Anaphylactic shock	*Skin and other attachment*	*Digestive system*	*Urinary system*	*Respiratory system*	*Eye damage*	*Cardiovascular system*	*Nervous system*	*Fever*	*Blood and endocrine system*	*Others*	
Ganlu Xiaodu Wan	Grassleaf Sweetflag Rhizome, Baical Skullcap Root, Artemisiae capillaris, Round Cardamon Fruit, Tendrilleaf Fritillary Bulb, Blackberrylily Rhizome, *et al.*				+								Chen and Shao (2002)
Ganmao Qing	Baphicacanthus Root, *Folium Isatidis*, railway beggarticks herb, holly root, paracetamol, *Herba Andrographitis*, moroxydine hydrochloride and chlorphenamine maleate										+		Liu and Zhang (1998)); Tang *et al.* (2003)
Ganmaotong tablet	Diclofenac sodium, Calculus bovis factitious and Chlorphenamine Maleate		+	+	+	+					+		Zi (1999)
Gastrodiae capsule	*Rhizoma Gastrodiae*										+		Luo (2006)
Gejie Dingchuan Wan	Gecko, Snakegourd Seed, Tatarian Aster Root, Ephedra, Turtle Shell, Baical Skullcap Root, *Radix Glycytthizae, et al.*			+									Liu and Yang (2005)
Ginkgo leaf tablet	Total flavonoids from Ginkgo biloba, Ginkgolide and Bilobalide		+										Guo (1997)
Glycyrrhiza uralensis	glycyrrhizin, saponins and flavonoid			+									Gao *et al.* (2006); Zhang *et al.* (2006b)
Herba Centipedae	Triterpenes, sterols, flavonoid and organic acid							+					Sun *et al.* (2005)
Honghua	Safflor yellow, polysaccharides, flavonoid, sitosterol, fatty acid and amino acids	+											Liu and Jiang (2002)
Honghua tablet	Sow thistle tasselflower, *Herba Hedyotis Diffusae*, rose mallow root or herb, mallotus paniculatus, downy rosemyrtle root, Suberect Spatholobus, *et al.*		+										Liang *et al.* (2006)
Huisheng Diyidan tablet	Woodlouse, angelica, frankincense, pyrite, musk and cinnabar		+	+									Liang *et al.* (2006)
Huolisu oral liquid	Epimedium Herb, Prepared Fleeceflower Root, Solomonseal Rhizome, Barbary Wolfberry Fruit, Milkvetch Root, Danshen Root			+									Yin (1998)
Huoxiangzhengqi pill		+											Luo (2006)
Jidan oral liquid	Extracts from chicken gall		+										Liang *et al.* (2006)

Keke capsule	Ephedra, Poppy Capsule, *Radix Glycytthizae*, Bitter Apricot Seed, Radish Seed, Platycodon Root, Gypsum		+					Liu and Yang (2005)
Kusheng capsule	Oxymatrine			+				Luo and Wang (2006)
Leech	Hirudin, protein, amino acids, heparin, antithrombase			+				Cui *et al.* (1997); Wang *et al.* (2005a)
Liushen Wan	*Calculus Bovis*, Realgar, Musk, Borneol, Toad Venom			+			+	Wu and Zhang (1997)
Liuweidihuang Decoction	Prepared Rehmannia Root, *Fructus Corni*, Common Yan Rhizome, *Cortex Moutan*, Rhizoma *Alismatis*, Poria	+						Tai *et al.* (1997)
Longdan Xiegan Wan	Chinese Gentian, Chinese thorowax, Baical skullcap root, Cape Jasmine Fruit, Angelica, Plantain Seed, Prepared Liauorice Root, Rehmannia Root				+			Liu (2002)
Longdanxiegan decoction	Radix Gentianae, Angelica, Chinese thorowax, *Rhizoma Alismatis*, *Radix Glycytthizae*, Plantain Seed, Angelica, Caulis hocquartiae, Rehmannia dride rhizome, Cape Jasmine Fruit	+						Chen *et al.* (2006)
Longstamen Onion Bulb	Allicin, steroid saponin, sulphocompound and amino acids			+				Fu *et al.* (2002); Liu and Yang (2005)
Mugua Wan	Fructus Chaenomelis, Angelica, Szechwan Lovage Rhizome, Dahurian Angelica Root, Radix Clematidis, Cibot Rhizome, Ginseng, Radix Aconiti preparata, Prepared Kusnezoff Monkshood Root, Caulis Spatholobi, Kadsura Pepper Stem						+	Chen (1997b); Zhao and Zou (1998)
Niuhuang Jiedu Wan	*Calculus Bovis*, Baical Skullcap Root, *Rhizoma Coptidis*, Rhubarb, Bark of Chinese Corktree, *et al.*	+	+					Wu *et al.* (2006)
Niuhuang Ninggong Tablet	*Calculus bovis*, amber, pearls, *Flos Lonicerae*, rhubarb, Baical skullcap root, kudzuvine root, *et al.*					+		Chen *et al.* (2006)
Oriental Waterplantain Rhizome	Triterpenoids, essential oil, starch, protein and amino acids				+			Liang *et al.* (2006)
Pericarpium papaveris	Morphine, codein, narcotine and papaverine				+			Pan (2006)
Poria	β-pachyman, tumulosic acid, lecithin and sterol			+	+			Wang *et al.* (2006a)

Table 6 *Continued*

Drug names	*Main ingredients*	*Clinical symptoms*											*References*
		Anaphylactic shock	*Skin and other attachment*	*Digestive system*	*Urinary system*	*Respiratory system*	*Eye damage*	*Cardiovascular system*	*Nervous system*	*Fever*	*Blood and endocrine system*	*Others*	
Qiguanyan Kesou Tanchuan Wan	HogfenneL Root, Rhizoma *Cynanchi Stauntonii*, Bitter Apricot Seed, Ephedra, Perilla Fruit, Belamcandae, Dutohmanspipe Fruit, *et al.*		+										Chen *et al.* (2006)
Radix Notoginseng tablet	*Radix Notoginseng*	+											Liang *et al.* (2006)
Rupixiao oral preparation	Chinese thorowax, *Radix Paeoniae albiflora*, *Radix Paeoniae Rubra*, Nutgrass Galingale Rhizome, Szechwan hinaberry Fruit, *et al.*			+									Pan (2006)
Sanhuang tablet	Rhubarb, Berberine hydrochlorideand Baical Skullcap Root			+									Liang *et al.* (2006)
Sanjin Xiguashuang Runhou Pian	Mirabilitum praeparatum, Borneol, Dementholized peppermint oil, Menthol		+		+								Liu *et al.* (2005b)
Sapium sebiferum	Flavonoids and amino acids				+								Wang *et al.* (2006a)
Semen Sterculiae Lychnophorae	unsaturated fatty acid, polysaccharide				+								Peng (2006)
Senna	Senna Fructus, chrysophanol, aloe-emodin and rhein			+				+					Chen *et al.* (2006)
Shenbao capsule	Icariin, Radix Clematidis, Eucommia Bark, Dodder Seed, *Cordyceps*			+									Wu (2001)
Shenbao Heji	Epimedium Herb, Common Fenugreek Seed, Prepared Rehmannia Root, *Fructus Rosae Laevigatae*, Dodder Seed, Desertliving Cistanche, Prepared Fleeceflower Root, Barbary Wolfberry Fruit, Palmleaf Raspberry Pruit, Milkvetch Root, angelica, Poria, *et al.*							+					Wei (2003)
Shuanghuanglian	Honeysuckle, Baical skullcap root, *Fructus Forsythiae*	+	+			+		+	+				Luo and Wang (2006)
Shuanghuanglian oral liquid	Honeysuckle, Baical skullcap root, *Fructus Forsythiae*		+										Sun *et al.* (2005)
Shufeng Dingchuan Wan						+							Huang and Yu (2006)
Suxiao Jiuxin Wan	Szechwan Lovage Rhizome, Borneol		+										Wu *et al.* (2006)); Zi (1999)
Taurine granule	Taurine, sucrose and lemon yellow		+										Ma and Guo (2005)
Tongxiekang	*Rhizoma Paridis*, Kusnezoff Monkshood Root, tuniclike psammosilene root, Bleeding-Stopping Bolus, *et al.*		+										Gao *et al.* (2006)

Tripterygium hypoglaucum hutch	Triptolide, tripterolide, wilforine, saponin and lactone				+					Zhang (1997a)
Tripterygium wilfordii tablets	Triptolide				+	+		+	+	Huang and Yu (2006)
Xiaohuoluo Wan	Bile Arisaema, Radix Aconiti preparata, Prepared Kusnezoff Monkshood Root, earthworm, frankincense and myrrh							+		Chen *et al.* (2006); Gao *et al.* (2006)
Xiaojin Wan	Frankincense, myrrh, Prepared Kusnezoff Monkshood Root, Beautiful Sweetgum Resin, Cochinchina Momordica Seed, earthworm, faeces trogopterorum, musk, angelica			+	+					Liang *et al.* (2006)
Xiaoke pill	Kudzuvine root, Rehmannia Root, Milkvetch Root, Trichosanthes root, Stigmata maydis, Chinese Magnolivine Fruit, Common Yan Rhizome	+								Pan (2006)
Xiaokechuan tablet	Dahurian Rhododendron Leaf							+		Luo and Wang (2006)
Xinfufang Daqingye Pian	*Folium Isatidis*, *Rhizomza Seu Radix Notopterygii*, Bistort Rhizome, Honeysuckle, rhubarb, Paracetamol, caffeine, Amobarbital and Vitamin C						+			Chen (1997a); Kong and Li (1997)); Liu and Deng (1997)); Wang and Zhang (1997)); Xu (1998)
Yangshen granule	Extracts from Ginseng root					+				Sun *et al.* (2005)
Yangxue Shengfa capsule	Prepared Rehmannia Root, Angelica, Rhizomza Seu Radix Notopterygii, *Fructus Chaenomelis*, Szechwan Lovage Rhizome, Dodder Seed, *Rhizoma Gastrodiae*, Prepared Fleeceflower Root				+					Li *et al.* (2005)
Yinqiaojiedu Pills	Honeysuckle Flower, Fructus Forsythiae, Fermented soybean, Great Burdock Achene, *Radix Glycytthizae, et al.*	+								Liu and Yang (2005)
Yinxiedi capsule	Zaocys dhumnades, *Herba Schizonepetae*, Divaricate Saposhnikovia Root, *Periostracum Cicadae*, Frankincense,*Radix Glycytthiza, et al.*								+	Liu and Yang (2005)
Zhengtian pill	Angelica, Szechwan Lovage Rhizome, Gambir Plant, Manchurian Wildginger, Ephedra, Rehmannia, *et al.*			+						Luo (2006)
Zhuanggu Guanjie pill	Cibot Rhizome, Epimedium Herb, *Radix Angelicae Pubescentis*, *Rhizoma Drynariae*, Himalayan Teasel Root, Malaytea Scurfpea Fruit, Common Aucklandia Root, Frankincense, *et al.*				+	+				Zi (1999)

Table 6 *Continued*

Drug names	*Main ingredients*	*Clinical symptoms*											*References*
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Injection													
Aescine injection	Aescine		+										Liu *et al.* (2005b)
AiDi	Ginseng, *Radix Astragali*, *Acanthopanax senticosus*, Cantharis		+										Hu and Hua (1998)
Banlangen injection	Extracts from *Radix Isatidis*		+										Chen *et al.* (2006); Gao *et al.* (2006)
Buxuekang	Immunoglobulinand, albumin, various kinds of amino acids	+											Zhang *et al.* (2006a)
Chaihu injection	Extracts from Chinese thorowax	+	+										Han (1997); Wang (1997); Zhuang and Shan (1997)); Gong (2001); Shi *et al.* (2001)
Chuanhuning	*Potassium Dehydroandrographolide Succinate*	+	+	+		+					+		Wang *et al.* (2006a)
Compound Chinese lobelia injection	*Herba Lobeliae Chinensis* and Spreading Hedvotis Herb		+										Gong (2001); Liu and Liang (2001)
Compound Danshen injection	Extracts from Danshen root and Rosewood		+							+			Zhang *et al.* (2006a
Corydalis saxicola Bunting injection	Dehydrocavidine									+			Gao *et al.* (2006)
Danshen injection	Danshen Root, Sodium hydrosulphite	+	+	+		+							Ma and Guo (2005)
Daphne giraldii Nitsche injection	*Daphne giraldii Nitsch.*	+											Liu *et al.* (2005b)
Dextran	Dextran									+			Chen *et al.* (2006
Diemailing	Adenine riboside and flavonoid										+		Hou *et al.* (1998)); Wang and Li (2005)
Fleabane injection	Caffeotannic acid, Caffeic acid, Quininic acid, Scutellarin, *et al.*							+					Xu and Zhang (1997)); Li (1998)
gastrodine	gastrodine		+										Wu and Li (1997)); Zheng (1998); Liu and Liang (2001)); Chen *et al.* (2006)
Ginkgo leaf	Ginkgetin and bilobalide					+							Hu (1997); Wang and Wang (2000)); Gao *et al.* (2006)
Ginkgo Leaf Extract and Dipyridamole (Yinxing Damo)	Total ginkgo flavone-Glycoides, ginkgolide, bilobalide and dipyridamole	+											Zhang *et al.* (2006a)
Gu Ning	Polypeptide	+											Xu and Liu (1997)); Han (1998)
Herba houttuyniae	Decanoyl acetaldehyde, laurinaldehyde, methyl-n-nonylketone, total flavonoid and quercetin	+	+	+		+							Zi (1999)
Honghua injection	Safflor yellow, polysaccharides, flavonoid, sitosterol, fatty acid and amino acids					+							Chen and Shao (2002)

Kuhuang	Lightyellow Sophora Root, rhubarb, *Folium Isatidis*, *Virgate Wormwood Herb*, Chinese thorowax									+		Wei and Liu (1997)); Li *et al.* (2002); Tang *et al.* (2003); Zhang *et al.* (2006a)
Kushenin injection	Kushenin			+								Luo (2006)
Ligustrazine	Ligustrazine	+										Luo and Wang (2006)
Mahuang	Ephedrine and Pseudoephedrine							+				Chen and Shao (2002)
Mailuoning	*Raidix Scrophulariae*, *Herba Dendrobii*, achyranthes and honeysuckle		+					+				Liu and Yang (2005)
Maitong	inseng, rhizome of chuanxiong and Radix Notoginseng					+						Chen *et al.* (2006)
Methotrexate	Methotrexate										+	Luo and Wang (2006)); Zhang *et al.* (2006a)
Palmatine	Palmatine		+									Liu (1997); Li (1997a); Bai and Shao (1998) Chen *et al.* (2006)
Polyporus polysaccharide	Polyporus polysaccharide		+	+								Wang (1998)
Puerarin	Puerarin		+	+				+			+	Zhang *et al.* (2006a)
Qiangliling	Glycyrrhizic acid, cysteine and glycin			+								Liu and Liang (2001)
Qianglining injection	Glycyrrhizic acid, Cysteine hydrochloride and Glycine				+							Cai (1998); Wang *et al.* (1998)
Qingkailing	Cholic acid, baicalin, honeysuckle, cornu bubali, Isatis root, *et al.*	+	+			+						Luo (2006)
Qingkailing injection	*Calculus Bovis*, Buffalo Horn, Nacre, Baical Skullcap Root, Honeysuckle Flower, *Radix Isatidis*, *et al.*	+	+					+				Chen *et al.* (2006)
Radix Acanthopanacis Senticosl (Ciwujia injection)	Extracts from Radix *Acanthopanacis Senticosl*							+				Zhang *et al.* (2006b)
Radix Notoginseng	*Radix Notoginseng*			+								Zeng and Mei (2004)
Shengmai injection	Red Ginseng, Dwarf Lilyturf Tuber, Chinese Magnolivine Fruit, *et al.*	+	+	+				+	+			Chen *et al.* (2006); Xu (2006)
Shuanghuanglian injection	Honeysuckle, Baical skullcap root, *Fructus Forsythiae*	+	+	+	+		+	+		+		Luo (2006)
Sowthistle-leaf ixeris seedling (Kudiezi)	Adenosine and flavonoids								+			Tang *et al.* (2003); Wang *et al.* (2006a)
Xingding	Total flavonoids from Ginkgo biloba and dipyridamole		+									Liang *et al.* (2006)
Xinxuetong injection	Calcitonin-gene-related peptide(CGRP), Atrial natriuretic peptide(ANP), Inosine, *et al.*						+					Pan (2006)
Xuesaitong	Notoginseng leaf saponins			+								Chen and Shao (2002)
Yinzhihuang injection	Virgate Wormwood Herb, Cape Jasmine Fruit, Baicalin and Honeysuckle Flower	+	+									Zhang *et al.* (2006a)
Yujin	Honeysuckle and *Herba houttuyniae*	+										Wang and Wang (2004)
Zedoary oil	Zedoary oil	+										Lu (2006a)

Table 7 Chinese crude drugs containing toxic ingredients and their functions

Name of drug materials	*Main ingredients*	*Main function*
Baijiang Dan	Mercuric Chloride, mercurous chloride	Cure carbuncle, detoxification
Cantharis	Cantharidin, formic resin, pigment	Detoxification, relieving blood stasis, vesiculation, cold moxibustion
Toad Venom	Cinobufotoxin, Cinobufotalin, Cinobufotalidin, Arginine	Detoxification, detumescence, relieving pain
Hydrargyri Oxydum Rubrum	Mercuric Oxide	Detoxification, removing necrotic tissue, promoting tissue regeneration
Huechys Sanguinea	Cantharidin	Detoxification, dispersing blood stasis, breaking to accumulate
Yellow Azalea Flower	Andromedotoxin, ericolin	Expelling wind, removing dampness, relieving pain
Arsenic Sublimate (Arsenicum Sublimatum, Diarsenic Trioxide)	Arsenous oxide	expelling intestinal parasites
Cantharis Sinica	Cantharidin	Detoxification, dispersing blood stasis
Calomelas	Mercurous chloride	Detoxification, removing necrotic tissue
Unprocessed Croton Fruit	Croton oil, protein(including crotin), alkaloid crotonoside	Purgation, dispelling water, detoxification
Unprocessed Giant Typhonium Rhizome	Organic acid, saponin, b-sitosterol	Clearing wind phlegm, antispasmodic
Unprocessed Pinellia Tuber	Triterpene alcohol, b-sitosterol, alkaloid	Depriving the evil wetness, dissipating phlegm, antiemetic
Unprocessed Kusnezoff Monkshood Root (Caowu)	Aconitine, isoaconitine, mesaconitine, hypaconitine	Relieving beriberoid disease, relieving rheumatic, relieving pain
Unprocessed Common Monkshood Mother Root	Aconitine, mesaconitine	Relieving beriberoid disease, relieving rheumatic, relieving pain
Unprocessed AconiteRoot	Including 6 kinds of crystallinic alkaloids, many of which are hypaconitine	Reviving yang, relieving pain, dispelling cold
Unprocessed Gansui Root	Triterpenoid, euphorbon	Decreasing the retention of fluid in the body, reduce accumulation, facilitating bowel movement
Unprocessed Euphorbia Fishericana	Triterpenoid, euphorbon	Removing stasis, expelling intestinal parasites
Unprocessed nux vomica	Strychnine, brucine	Smoothing veins and arteries, relieving pain, detumescence
Unprocessed Rhizoma Arisaematis	Triterpenoid saponin, benzoic acid	Spasmolysis, detumescence
Unprocessed Caper Euphorbia Seed	Leptochloa chinensis sterol, Daphnetin	Detumescence through inducing diuresis, removing stasis
Unprocessed Gamboge	Morellin	detumescence, detoxification, stopping bleeding
Unprocessed Henbane Seed	Hyoscyamine, scopolamine, atropine	Anti-epilepsy, relieving pain, spasmolysis
Mercury	Mercury	Expelling intestinal parasites, detoxification
Realgar	Yellow arsenic	Detoxification, deprive the evil wetness, expelling intestinal parasites
Shortstalk monkshood root	Aconitine, isoaconitine	Relieving beriberoid disease, relieving pain
Datura Flower	Hyoscyamine, scopolamine	Smoothing asthma, relieving a cough, relieving pain

daphnarcphne genkwa. Furthermore, daphnarcphne genkwa stir-baked with Vinegar has more predominant effect on promoting enterokinesia than the unprocessed, and its LD_{50} doubled. This means that stir-baking daphnarcphne genkwa with vinegar improved its therapeutic effects and reduced toxicity (Yuan *et al*., 1999).

Decoction is the most commonly used dosage form of TCM. Decoction of Chinese herbs is particular in the selection of container, heating strength, decoction time, and the order of adding medical materials. The correct method of decocting can improve therapeutic effects, and reduce toxicity of drugs (Liu, 2005). For example, decoction of aconite root could not only promote hydrolysis of toxic components, but also promote separation of despin-demethyl coclaurine, methyldopamine chloride, salsolinol and other active components contained in aconite root, thereby enhance the efficacy (Wu, 2002). As for the medication, the frequency of medication, the time of medication, before meals or after meals, warmer or cooler condition, all of these must be based on the nature and function of drugs, the symptoms of the disease and the severity of the disease (Yu and Zhang, 2006).

Toxic components

Some drugs have acute toxicity, and their therapeutic dose is close to toxic dose. The improperly use of these drugs may cause toxicity or death. These drugs are called toxic substances. There are 27 kinds of raw TCM, not including preparations and processed products, belonging to toxic substances (Table 7). These toxic TCM contain toxic components which have an effect on physiological and biochemical function as well as cause damage to structure. Take nux vomica for instance, it is extremely toxic because it contains brucine namely strychnine which has small safety range and intense toxic reactions. For adults, taking in 5–10 mg nux vomica once may cause toxicity, and 30 mg may cause death (Liu, 1998). Excessive dosage of these TCM containing toxic components may easily produce toxicity.

Individual factors

Age and sex. Functions of organs have not yet been mature in children, and gradually decline in the elderly, thus the elderly and children are weaker in drug tolerance and metabolic

capacity than adult (Yang, 2000). In terms of sex, women have menstruation, leucorrhoea, conceiving, childbirth and other physiological characteristics. For example, women are sensitive to purgatives during menstrual and gestation periods, some potent purgatives such as rhubarb, mirabilite, Senna (Zhang, 1997a), Gansui, Euphorbia, Croton may lead to menorrhagia or abortion induced by pelvic organ congestion (Wei and Wu, 2001).

Pathological state. The drug tolerance and metabolic capacity of patients who have been ill for a long time decline. Purgatives used incorrectly to these patients may cause side-effects easily, moreover, tonic prescription may also have a negative effect on the body therefore it was said in TCM that 'Xu bu shou bu (too weak to excessive curing)' (Xu, 1995).

Individual differences. The individual differences are generally categorized as follow: the first is the high sensitivity. A few people particularly are sensitive to certain drugs, thus only smaller dose will have a strong pharmacological effect. For example, toxic dose of Aconite is more than 30 g generally (Wang *et al.*, 1997b; Wu, 2002). However, it was reported that only 3 g Aconite in the compound led to toxicity. The second is the tolerance. Opposite to high sensitivity, some people are particularly insensitive to certain drugs, the dose must be larger in order to have a proper pharmacological effects. For example, a report said even 120 g Aconite was still not up to toxic dose for some insensitive people. The third is the idiosyncrasy. For example, if a person has haemolytic reaction (Zhang, 1997c) after eating the therapeutic dose of Banlangen syrup, it may be related to the congenital absence of glucose-6-phosphate dehydrogenase.

Long-term medication

Long-term medication was also a very prominent issue in the clinical application of TCM (Jiang *et al.*, 2008). Long-term use of certain drugs, particularly drugs with slow rate of metabolism, could lead to drug accumulation in the body and cause toxicity (Yu and Zhang, 2006). It was reported that in Britain two female patients were taking TCM and TCM tea for the treatment of eczema for a long time, up to 2 and 6 years, respectively, were found to have renal failure, at the same time, AA was found in the TCM they had taken (Lord *et al.*, 1999). In addition to direct damage to kidney, the toxicity of AA is related to its accumulation in body caused by its long-term use. It was confirmed in experiments that AA had chronic toxicity to renal (Li, 2005b).

Improper compatibility

To our knowledge, drug–drug interaction is the effects which will occur when drug administered with other drugs together (Egger *et al.*, 2003; Yu *et al.*, 2008). The purpose of compatibility is to use the interaction between drugs, expand the scope of treatment, enhance the clinical efficacy and reduce or eliminate side-effects, based on the interaction between drugs (Wang, 2008). But the changes after compatibility are complicated, and the clinical results are diverse as well. 'Shen Nong's Herbal Classic' summed up the compatibility of the drugs as 'Seven Relations' (Seven Relations namely seven methods in prescription compatibility including drug used singly, mutual enhancement, mutual promotion, incompatibility, counteract toxicity of another drug, mutual inhibition and antagonism), in which the 'antagonism' (Xiang Fan) means that the combination of two drugs can cause or aggravate side-effects, or even lead to drug-induced diseases. At present, in addition to 'eighteen antagonisms' (Shi Ba Fan) and 'nineteen mutual inhibitions' (Shi Jiu Wei), the incompatibility of drugs in prescription include the commonly recognized '36 incompatible drugs' mentioned in 'Compendium of Materia Medica'. There are more than 70 kinds of incompatible drugs recorded in 'The Collection of TCM Nationwide'. At present, people still have not come to the identical conclusion as to the research on incompatibility of drugs in prescription. Further study on this aspect is still needed.

Joint use of TCM and Western medicine

Joint use of TCM and Western medicine can improve the clinical efficacy, expand the scope of treatment and have positive effects especially for the treatment of some incurable diseases (Gao, 2006; Hu *et al.*, 2006; Lu, 2006b). However, TCM and Western medicine, after all, belong to two different systems of medicine. Their guiding theory and source are so different that the combination of two types of drugs is a more complicated issue (Zhang, 2006a; Zheng *et al.*, 2006). Especially, the interaction between TCM and Western medicine sometimes leads to unexpected side-effects which are expressed as following: first, physical and chemical reactions occur in injections (Wang, 2006; Zhuang, 2006). For example, sediment will occur once the injections containing coptis and baicalin (Chinese medicine) are mixed with penicillin. Second, combination of TCM and Western medicine has an impact on drugs absorption, distribution, metabolism, excretion and other body processes. For example, when sulpha drugs and TCM with a high content of organic acids (fructus mume, hawthorn, Schisandra, cornel and fructus mume pills) are mixed, a large amount of organic acids can make urine more acidic, reducing the solubility of sulpha drugs as well as its acetylation products in the urine, so they precipitate more easily, which leads to obstruction and renal tubular injury (Zhang, 2006a). Third, combination of TCM and Western medicine has a negative impact on the pharmacodynamics, decreasing the effects of medicine or producing ADRs. For example, the combination of cardiac glycosides drugs and the Ca^{2+}-rich TCM-like gypsum, Long gu, oysters, Pumice can enhance the cardiotonic effects of cardiac glycosides, but it will easily induce the toxicity of cardiac glycosides (Zhang, 2006a). There were reports from Britain and Japan that the combination of western weight-reducing medicine (fenfluramine) and Chinese herbs caused valvular heart disease, these issues should not be simply linked to TCM (Wu *et al.*, 2006).

Discussion

The side-effects of TCM can be classified into two types, Type A and Type B (Wu *et al.*, 2006). A-type ADRs are caused by the

pharmacological effects of drugs, often with a change of the pharmacokinetics, such as the impact of drug absorption, integration, distribution, metabolism, excretion, the sensitivity of target organ, and other factors. A-type ADRs have a high clinical morbidity as well as low mortality rate, and it is usually predictable. B-type ADRs, also called allergy, are a kind of special reaction which has nothing to do with pharmacological effects of the drugs, it often results from physical abnormalities of patients, involving aspects such as genetic, immunization, carcinogenic, teratogenic and so on. Allergic reaction is the most common kind of B-type ADRs, it is hard to predict, with a low incidence rate but serious consequences. In addition to TCM themselves, their metabolic products in the body, pharmaceutical additives, excipient vehicles and solubilizer in the process of producing, can also cause B-type ADRs.

A drug cannot be banned just because it contains toxic ingredients, such as the commonly used Chinese herbs aconite, nux vomica and almond. Take almond for an example, it contains amygdalin, which can be decomposed into a highly toxic substance – hydrocyanic acid, but the almond is widely used in the clinical application. The ancient prescription Ma Huang Tang, Ma Xing Shi Gan Tang, and modern cold coryza antipyretic granules also contain almond, but no toxic reaction is found. At present, there are over 70 kinds of toxic TCM widely used in clinical, such as cantharis, Toad Venom, arsenic and leech. Recent research shows that Cantharidin contained in cantharis can inhibit synthesis of DNA and protein in cancer cells, and then kill cancer cells. Leech has good effect in treating cardiovascular, hyperlipidaemia, nephrotic syndrome and thrombotic disease (Ren and Yang, 2006). Although snakes and scorpion are toxic, they are effective drugs for treating apoplexy. Nowadays some people treat leukaemia and swollen ringworm with arsenic. Hence, the 'toxicity' of TCM should be correctly understood and developed.

Traditional Chinese medicine is a complex system, and often uses the compound prescription. It prevents and treats disease by the integration of multi-link, multi-level and multi-target, and the determination of treatment based in pathogenesis obtained through differentiation of symptoms and signs (Zhang, 2006a). Efficacy and toxicity of TCM resulted from a variety of chemical constituents, which lead to a comprehensive response in the human body. Owing to these characteristics, the toxic problems cannot be solved just by a model and an approach. An evaluation system of pharmacology and toxicology, which is in line with the characteristics of TCM, should be established. The research of the quality standard of TCM should be strengthened.

At present, most Chinese herbal medicine still lacks proper pharmacological and toxicological experimental data, even if some relevant pharmacological methods such as Chinese Serum Pharmacological research methods (Mei *et al.*, 2000; Lei and Hu, 2009) were developed, but still far from perfect, a lot of adverse reactions pharmacology mechanisms are not yet clear, and therefore we need to gather more toxicological data in the future, to promote and establish more complete pharmacological evaluation methods and standards. Proteomics and genomics bring hope to the modernization of TCM (Li and Liu, 2006; Li, 2007; Kang, 2008). Practice has proved that the rapid growth of proteomics field provides new tools for the integration of TCM with modem technology and system biology, meanwhile, genomics plays an important role in many aspects of TCM development, including the rapid identification of TCM, the elucidation of active ingredients of TCM, the discovery of effective parts and the mechanism of compound prescription, the individualized treatment, the development of new drugs of TCM, and the reduction of the adverse effects of TCM.

Because of the complexity of TCM, along with the modernization of TCM, metabolomics could be applied widely in the process of exploiting TCM. It involves research at different levels including cell, tissue, organ, organism and system level, fasting studying the effect of complex mixtures used in TCM (Wang *et al.*, 2005d). The material basis and mechanism of TCM could be studied effectively by using some metabolomics methods such as the application of different techniques (liquid chromatography-mass spectrometry, gas chromatography-mass spectrometry, nuclear magnetic resonance, etc.) (Wang *et al.*, 2005d; Kang *et al.*, 2008; Wei *et al.*, 2009). Furthermore, this approach is considered to have the potential to uncover a general mechanism of ADRs induced by TCM and to advance the development of Chinese herbal medicine.

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Conflict of Interest

The authors state no conflict of interest.

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