



## Review Article

# A U.S. Perspective on the Adverse Reactions from Traditional Chinese Medicines

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### Key Words

adverse reactions;  
herbs;  
traditional Chinese medicines

**Background.** Traditional Chinese medicines (TCM) are popular in the United States and Asian and non-Asian consumers are using the product for disease treatment and health prevention. As more people are using TCM products, there are increased reports on adverse reactions. **This review will focus on adverse reactions due to TCM as reported in the literature.**

**Methods.** The review is based on MedLine search of literatures using keywords including: herbs, herbal, traditional Chinese medicines with toxicity, adverse effects, death, drug interaction and pharmacokinetic. In addition, specific searches were performed using the above keywords with the common name and the scientific name of the plant product.

**Results.** **The causes of adverse reactions associated with TCM are diverse. They include variability in active/toxic ingredients due to growing conditions, use of inherent toxic herbs causing toxicity, overdose of herbs, drug-herb interactions especially with pharmaceuticals that have narrow therapeutic index, coexisting diseases, and idiosyncratic reactions like allergy, hepatitis and anaphylaxis.** Other adverse reactions can be due to manufacturing and quality problems causing adulteration, misidentification, substitution of one herb with another, variability in the amount of active ingredients, use of pharmaceuticals without identifying on the labels, improper processing and preparation, and contamination.

**Conclusions.** To minimize the adverse reactions from TCM and protect the public, there must be adequate laws and regulations to ensure that products are manufactured with the highest standards. Manufacturers should be licensed by regulatory agency and manufactured under good manufacturing practice. TCM products must be evaluated for their safety before marketing. Proper labeling and good surveillance systems shall ensure the protection of the consumers.

**C**alifornia is the largest state in the United States (U.S.) and has the fifth largest economy of the world. Geographically, it is considered part of the Pacific Rim and has the largest Asian population in the U.S. with most Asian products imported via California ports. **Many of the traditional Chinese medicines (TCM) are shipped into California before being distributed to the rest of the United States. As more consumers and patients use alternative medicines, especially TCM products, there will be more reports on adverse reactions. This review will focus on adverse reactions due to TCM as reported in the literature.**

The law that regulates TCM products in the U.S. is the Dietary Supplement Health and Education Act of 1994 (DSHEA).<sup>1</sup> It established dietary supplements as a new category of food and made provisions for specific areas of oversight by the U.S. Food and Drug Administration (FDA). **Dietary supplements include vitamins, minerals, amino acids, proteins, herbals and other botanicals.** The law requires that FDA develop good manufacturing practices (GMP) guidelines on dietary supplements, although there are currently no regulations published by the FDA on the GMP. In addition, in order for the FDA to take any action against dietary supplements,

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Received: April 2, 2003.  
Accepted: January 7, 2004.

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the government will have the burden of proof to show that the dietary supplement poses significant risks to the public. More recently, due to the terrorism against U.S., the Public Health Security and Bioterrorism Preparedness and Response Act of 2002 was enacted.<sup>2</sup> The law is intended to protect the food source in the U.S. The 2002 law requires that any manufacturers that engage in providing food for the U.S. must be registered with the FDA. Since dietary supplements and TCM herbs are considered food, it falls under the law. This applies to both foreign and domestic manufacturers and will affect all the TCM manufacturers.

The causes of adverse reactions associated with TCM are diverse. These include variability in active/toxic ingredients due to growing conditions, use of inherent toxic herbs causing toxicity, overdose of herbs, drug-herb interactions especially with pharmaceuticals that have narrow therapeutic index, and idiosyncratic reactions like allergy, hepatitis and anaphylaxis. Other adverse reactions can be due to manufacturing and quality problems causing adulteration, misidentification, substitution of one herb with another, variability in the amount of active ingredients, use of pharmaceuticals without identifying on the labels, improper processing and preparation, and contamination.

## METHODS

This review article is based on a literature search using MedLine as well as other reference source materials.<sup>3-5</sup> The MedLine computer database search for references published from 1966 to present (January 2003). The search used keywords including: herbs, herbal, traditional Chinese medicines with toxicity, adverse effects, death, drug interaction and pharmacokinetic. In addition, specific searches were performed using the above keywords with the common name and the scientific name of the plant product.

## RESULTS

A total of 186 papers are retrieved based on Medline search. Majority of the articles are in English except for 5 articles which are in Chinese and French. Approximately

50 percent of the articles are from authors located outside the U.S.

## DISCUSSION

Not all TCM herbs are safe. In China during 1993 to 1994, there were 1133 reports of adverse reactions in the Chinese literature. A total of 59 (9.1%) deaths were related to TCM raw herbs and 6 (1.2%) deaths attributed to Chinese patent medicines, the finished products.<sup>6</sup> From 1915 to 1990, there have been 2788 cases of adverse reactions associated with 460 different herbs reported in 408 Chinese medical journals. Prior to 1950, there were only 26 cases of adverse reactions reported, from 1950-1969, 147 cases, 1970-1979, 398 cases and in the eighties, 2217 cases.<sup>7</sup> Of the total adverse reaction cases reported in the Chinese literature, herbs constituted approximately 40% of all products (herbs and pharmaceuticals). The most common herb related adverse reactions are with Aconite roots (576 cases), followed by *Tripterygium wilfordii* Hook f. (90 cases) and *Isatis tinctoria* L. (38 cases). In 1990, there are 46 cases of aconite root related adverse reactions and 16 cases of *Isatis tinctoria* L.<sup>8</sup>

### Adulterated herbal products

It was reported that 23.7% (618 samples) of all 2609 TCM samples collected in Taiwan were contaminated by at least one adulterant. The most common adulterants include caffeine, acetaminophen, indomethacin, hydrochlorothiazide, prednisolone, chlorzoxazone, and ethoxybenzamide. Most common therapeutic claims are rheumatoid, analgesic and anti-inflammatory indications.<sup>9</sup> Similarly, in California, 260 TCM products were collected and analyzed. At least 83 (32%) of the samples contained undeclared pharmaceuticals or heavy metals, and 23 had more than one adulterant. The remaining products, which contained no detectable adulterants, cannot be assumed to be safe and free of toxic ingredients, in view of their batch-to-batch inconsistency, as well as limitations in our detection methods.<sup>10</sup> The types of pharmaceutical found in herbal products often depend on the label claims. For example, Tongyi Tang Diabetes Angel Pearl Hypoglycemic Capsules claimed to be made of all natural herbs were found to contain glyburide, a sulfonylurea used to lower blood glu-

cose.<sup>11</sup>

A more recent example of an adulterated herbal product is "Prostate Cancer Hope (PC SPES)". PC SPES claimed to be a herbal product that was manufactured using imported raw ingredients from China. It consisted of 8 different herbs and they were blended in the U.S. It had shown promising results for the treatment of prostate cancer. However, there were reports in the medical literature that PC SPES had estrogenic activity<sup>12</sup> and produced bleeding diathesis.<sup>13</sup> The California Department of Health Services tested PC SPES and found that it contained warfarin, indomethacin, diethylstilbestrol (DES) and ethinyl estradiol.<sup>14</sup> An analysis of the raw ingredient blends for PC SPES also detected these adulterants. The product was recalled and the manufacturer ceased operations as of June 2002. The manufacturer in the U.S. most likely did not have any performance criteria for raw ingredients or finished products, raw ingredient testing records, GMP procedures or adequate quality control procedures. Many patients were indirectly injured from PC SPES due to interactions of the pharmaceuticals with their prescribed medication and failure to seek proper treatment for their prostate cancer. Adulterated herbal products have been a widespread problem and they have caused numerous injuries and even death as a result of patients unknowingly using pharmaceuticals contained in the herbal products.<sup>14</sup> Though there are relatively few case reports in the literature on adulterated TCM products, the problem may be under-reported and it continues to be a clinical and regulatory concern. Reasons for adulteration can be due to competitive pressure to make promising claims on the herbal product and/or integration of TCM herbs with Western pharmaceuticals for optimal therapy of the patients. However, **if the pharmaceuticals are not declared on the label, it puts consumers and patients at risk and physicians cannot make the best decision on the treatment course.** The concern is further heightened by the wide availability of TCM products at the retail stores in most Western countries and patients' nondisclosure on the use of TCM products to their physician.

### **Substitution/Misidentification**

Substitution and misidentification of herbs have resulted in serious injury and death, especially in highly toxic herbs. Toad venom (Chan Su) from *Bufo bufo*

*gargarizans* or *B. Melanostictus* contains bufotoxins, which have similar molecular structure and pharmacology of digoxin, can cause arrhythmia and death. It was reported that Chan Su was mistaken for Ass Hide Glue (*Gelatinum Asini*), an innocuous herb, causing a death in a young pregnant female.<sup>15</sup> Chan Su is found in the Chinese patent medicine, Lu Shen Wan for treatment of respiratory symptoms<sup>16</sup> and Japanese pharmaceutical preparation, Kyushin for treatment of heart failure. Similarly, the **California Department of Health Services investigated a poisoning case in which a decoction supposedly contained Wei Ling Xian (*Clematis chinensis*) was contaminated with *Podophyllum emodi*, which contained podophyllotoxin.** The patient suffers permanent peripheral neuropathy. Symptoms of podophyllotoxin toxicity include nausea, vomiting, diarrhea, abdominal pain, neuropathy, encephalopathy, abnormal liver function tests, thrombocytopenia and leucopenia.<sup>17</sup> Ba jiao lian, the root of *Dysoma pleianthum*, is a herb that contains podophyllotoxin. **It is used in Taiwan for stomach pain and snake bite and excessive doses of this herb will also cause podophyllotoxin poisoning.**<sup>16,18</sup> *Stephania tetrandra* substituted with *Aristolochia fangchi* has been associated with interstitial nephritis due to aristolochic acid.<sup>19</sup> However, according to the Chinese literature, it is a common practice to interchange the 2 herbs without any reported adverse reactions. In addition, many patients in Germany who used aristolochic acid as an immunomodulatory agent did not develop nephritis.<sup>20</sup> It is possible that inappropriate use and inadequate processing of the herbs may contribute to the nephritis. Other possible explanations include variability of aristolochic acid in botanical products, individual or racial susceptibility to toxin, and other components in the remedies that contribute to the nephritis.<sup>21</sup>

### **Improper Processing**

**Processing herbs (pao chih) is an important component in the use of TCM products. Many herbs have very toxic ingredients when ingested without processing.** However, the same herbs can be relatively innocuous if it is properly treated. Treatment can involve soaking, heating, boiling, roasting, frying, and cooking with or without other ingredients. In addition to reduced toxicity, the processing can increase therapeutic effects or change the

pharmacological effects of the herbs or formula. The seed of *Strychnos nux-vomica* is used in TCM to promote blood circulation and relieve pain. However, it contains extremely poisonous alkaloids, strychnine and brucine which are strong convulsants. Traditionally, it must be heat treated to reduce the toxicity by converting strychnine and brucine to less toxic ingredients.<sup>22</sup>

The most common herb that causes toxicity in China and Hong Kong is the use of aconites from the dried root of *Aconitum carmichaeli* and *A. Kusnezoffii*. Poisoning from aconites can cause neurological and cardiac toxicity due to activation of sodium channels in the myocardium.<sup>23</sup> Initial symptoms include paresthesia in the oral cavity with progression to the extremities. Other adverse effects include nausea, vomiting, muscle weakness, and hypotension. Death can occur due to arrhythmias from bradycardia or tachyarrhythmias, including ventricular flutter or fibrillation.<sup>24-26</sup> The problem of aconite poisoning is usually due to incomplete processing of the herb or excessive doses being used. Traditionally, the dose for *A. Kusnezoffii* (caowu) is 1.5 to 3 gram and 3 to 15 gram for the lateral root of *A. carmichaeli* (fuzi).<sup>16</sup> Aconite is generally processed before it is sold. The processing involves soaking and boiling in water to reduce the toxicity by converting aconitine alkaloids to aconines and benzoylaconitines.<sup>27</sup> The patient is then instructed to prepare a decoction by boiling the herbs for a further period of time. Variability of the amount of alkaloids present in the plant may also contribute to increased adverse effects from aconite.<sup>16</sup>

### Idiosyncratic reactions

Idiosyncratic reactions due to TCM can be manifested as allergy, hepatitis and anaphylaxis. Other than life-threatening anaphylactic reaction, hepatitis caused by TCM can also lead to serious injury and death. Herbal related hepatitis can be caused by direct, dose-dependent hepatotoxicity (veno-occlusive disease or fibrosis) or in many cases are due to a hypersensitivity or idiosyncratic reactions. Unfortunately, diagnosis of herbal hepatotoxicity remains a challenging area. This is often due to lack of disclosure by patients on the use of herbs and risk factors are not well defined.<sup>28</sup> Levo-tetrahydropalmatine is the main active substance of *Corydalis decumbens* and has been used for its sedative and analgesic effects. It has

been found in the product, An Shu Ling<sup>29</sup> and Jin Bu Huan.<sup>30,31</sup> Both products are associated with hepatitis. The hepatitis is most likely due to hypersensitivity to the chemical. In the case of Jin Bu Huan, patients developed hepatitis upon re-challenge with the same product. The problem is further complicated when TCM formulas (which contains multiple herbs) are used and it is difficult to identify the responsible component within the formula. However, 1 genus of the plant, *Paeonia*, was present in at least 4 cases of severe or fulminant hepatitis.<sup>28</sup> Other TCM herbs that have been associated with hepatitis include *Ephedra* species (Ma Huang),<sup>32</sup> Shou-Wu-Pian (which contains *Polygonum multiflorum*),<sup>33,34</sup> *Dictamnus dasycarpus* (Bai Xian Pi),<sup>35</sup> Dai-saiko-to<sup>36</sup> (Chinese name is Da-Chai-Hu-Tang, consists of *Bupleurum chinensis* DC, *Scutellaria baicalensis*, *Citrus aurantium*, *Rheum officinale*, *Pinellia ternata*, *Paeonia lactiflora*, *Zingiber officinale*, *Ziziphus jujuba*) and Syo-saiko-to<sup>37</sup> (Chinese name is xiao-chai-hu-tang consists of *Bupleurum chinensis* DC, *Pinellia ternata*, *Scutellaria baicalensis*, *Ziziphus jujuba*, ginseng, *Glycyrrhiza uralensis* and *Zingiber officinale*).

### Coexisting Diseases

Coexisting disease is important not only that diseases can alter the metabolism of the herbs but also can affect its pharmacology. *Coptis chinensis/japonicum* and *Artemisia scoparia* are highly effective in displacing bilirubin from its serum protein binding and should not be used for patients with hyperbilirubinemia.<sup>38,39</sup> Kernicterus in preterm infants with neonatal jaundice caused by huanglian (*Coptis chinensis*) is probably due at least in part, if not all to its major and active ingredient, berberine, which acts as both a potent bilirubin displacer and an inhibitor of bilirubin metabolism.<sup>40</sup>

### Heavy Metals

Heavy metals have been a subject of attention in the U.S. as there are little uses of the metals in pharmaceutical preparation with a few exceptions. Arsenic, for example, has been used in the U.S. for treatment of syphilis up until antibiotics were discovered in the 1940's. However, heavy metals continue to play a role in TCM, but it must be used by qualified practitioners. A case was reported that a patient with a history of psoriasis was

smoking a herbal compound on the recommendation of an acupuncturist to treat the psoriasis. The patient developed a fever of 40 °C accompanied by malaise, weakness, dry cough, and shortness of breath four days after he began smoking the herbal compound. The herb was analyzed and found to contain 76% of mercury and trace amounts of lead and arsenic.<sup>41</sup>

In California, the Department of Health Services analyzed a total of 251 products for lead, arsenic, and mercury. Twenty-four products contained lead in a quantity of at least 10 parts per million (ppm) (range, 10 to 319; median, 29.8; mean, 54.9). Thirty-six products contained arsenic (range, 20.4 to 114,000 ppm; median, 180.5; mean, 14,553). Thirty-five products contained mercury (range, 22.4 to 5070 ppm; median, 329; mean, 1046); 2 of the 35 had labels that identified only pharmaceutical ingredients. The U.S. Pharmacopoeia limits total heavy metals in most oral dietary supplements to 20 ppm, with sometimes lower limits for lead, arsenic, and mercury.<sup>10</sup>

### Herb-Drug Interactions

Concurrent use of herbs with pharmaceuticals may magnify, mimic or oppose the pharmacological effects of the pharmaceutical. There is limited information in the literature on herbs-drug interactions. This may be due to a combination of under-reporting, difficulty to conduct clinical trials and benign nature of many herbs being used. The extent of herb-drug interaction is unknown, but may be substantial due to the increased use of TCM products by both Asian and non-Asian populations. In clinical practices, polypharmacy is common and in addition to the drugs physicians prescribe, patient add various over-the-counter medications, vitamins, herbs, and foods. All presented a potential of interactions. Most herb-drug interactions observed are similar to drug-drug interactions, i.e., mainly pharmacokinetic and pharmacological interaction. These include interference with the bioavailability of the pharmaceutical products by decreasing absorption or transit time (e.g. laxative decrease transit time), stimulation and inhibition of metabolic enzymes and kidney elimination, and synergistic and antagonistic pharmacological effects.

A number of articles have systemically reviewed herbs that potentially interact with pharmaceutical prod-

ucts.<sup>42-45</sup> However, there is only limited information on potential pharmaceutical drug interaction with TCM products, especially on herbal formulas. Danshen (*Salvia miltiorrhiza*) interacts with warfarin which results in increased international normalization ratio (INR) due to phytycoumarins.<sup>46,47</sup> Siberian ginseng (*Eleutherococcus senticosus*) may increase the effect of anticoagulant drugs and theoretically may cause additive effects with drugs that have sedative properties.<sup>48</sup> Korean ginseng (*Panax ginseng*) is commonly used in TCM. It has been reported to decrease the effectiveness of warfarin.<sup>49-51</sup> Theoretically, concomitant use of ginseng and antiplatelet agent might increase the risk of bleeding. However, this effect has not been reported in humans. *Panax ginseng* has also been reported to interact with monoamine oxidase inhibitor, phenelzine, causing headache and tremor.<sup>48</sup> Dong quai (*Angelica sinensis*) contains coumarins and estrogenic like ingredients. It will increase INR and is contraindicated for women with breast cancer.<sup>52,53</sup> Licorice (*Glycyrrhiza glabra*) has mineralcorticoid activity and has the potential to interact with antihypertensive drugs due to sodium and water retention.<sup>54,55</sup> Glycyrrhizin, an ingredient of licorice is an inhibitor of 11 beta-hydroxysteroid dehydrogenase and can change the pharmacokinetic activity of steroids.<sup>56,57</sup> Since licorice has mineralcorticoid and estrogenic and anti-estrogenic effects, patients who are using corticosteroids should be closely monitored for possible adverse effects. Ephedra (*Ephedra sinica*) which contains ephedrine and ephedrine alkaloids, is a stimulant and can interact with a number of pharmaceuticals.<sup>58</sup> Many herb-drug interactions affect the clotting ability of blood and the bleeding times should be monitored (some of the herbs interfere with platelet function, not the coagulation cascade, and thus will not affect prothrombin time, partial thromboplastin time, or INR). Other examples of TCM herb-drug interactions are Chinese rhubarb (*Rheum officinale*) which contains anthranoid, a laxative.<sup>44</sup>

### Toxic Herbs

There are a few herbs in TCM that are considered highly toxic and require additional control. *Mylabris phalerata* is also known as Ban Mao or Chinese beetle and it contains cantharidin. It can cause death with less than 60 mg.<sup>59</sup> *Tripterygium wilfordii* Hook f., which is

the second most frequent herb associated with poisoning in China, can cause hypovolemic shock and possible cardiac damage.<sup>60</sup> Others herbs that are toxic include heavy metals like cinnabar (mercuric sulfide), realgar (arsenic sulfide) or litharge (lead oxide) as part of the traditional formula, borneol (similar to camphor), aconite, bufo secreta (toad secretion), mylabris, scorpion, borax, and *Strychnos nux vomica* (strychnine). As certain herbs are highly potent, both Taiwan and China have required control for their sales.<sup>61</sup>

### Evaluation of TCM

Evaluation of herbal products must be based on risk versus benefits as many of the TCM products have a long history of use with positive empirical experience. There are very few clinical trials that are designed to evaluate the toxicity of TCM. Many TCM products failed randomized double-blind placebo-controlled trials because they are too short, too small, and poorly designed. Others failed to show efficacy under the rigorous evidence-based clinical trials. Yet, it has been argued that proper clinical trials of TCM should be based on TCM diagnostic criteria and indication. The prognostic end points must include not only Western clinical end points but also TCM end points.<sup>62</sup> If efficacy cannot be shown for the TCM product, then any potential risks associated with the product are not acceptable.

There are increased reports of adverse reactions related to TCM products. This does not mean that the incident rates of adverse reactions are increasing, but rather more people are using TCM products. There is also increased awareness by physician and consumers that not all herbs are safe and certain TCM can be highly toxic. The surveillance systems in the U.S. are sophisticated and many previously undetected adverse reactions are being reported by regulatory agencies and poison control centers. In addition, as more people are using TCM and pharmaceutical concurrently, herb-drug interactions are on the rise which contribute to increased adverse effects. Other potential for toxicity includes the use of TCM products in patients for whom it was not indicated and by practitioners untrained in its use.

Many of the adverse reactions from adulterated products, misidentified herbs, and inadequate processing can be avoided by having the manufacturers follow

proper GMP and good agriculture practices (GAP). China State Food and Drug Administration has recently required that all manufacturers of TCM must comply with GMP and GAP. Manufacturers that fail to be certified as GMP facilities will not be allowed to continue to manufacture TCM products. This will increase the quality of TCM products and reduce the number of adverse reactions.

To minimize the adverse reactions from TCM and protect the public, each country must have adequate laws and regulations to ensure that whole TCM industry, especially the importers, manufacturers, and practitioners are accountable for their actions. Manufacturers should be licensed by regulatory agency and manufactured under GMP. TCM products must be reviewed for their safety before marketing and surveillance systems developed to monitor for possible adverse reactions. It is essential that products have the proper labeling and there is a continual effort in reviewing the safety and efficacy of the TCM herbs.<sup>63</sup> By implementing the necessary control, the public will be protected. Thus, the modernization of TCM will enjoy the same status as Western pharmaceuticals and will be used as a primary treatment modality in many diseases.

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