Toxicological Risks of Chinese Herbs

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Abstract

As traditional Chinese medicine (TCM) has become more popular there have been increasing concerns about safety and potential toxicity of the Chinese materia medica (CMM) comprising plants, animal parts and minerals. The potential toxicity of many CMM is well recognised in TCM and to reduce risks use of some herbs is restricted whilst specific processing methods have been developed to modify the activities/toxicity of others. However adverse reactions have been reported, many of these are due misuse or abuse of Chinese medicine. The main problem remains products adulterated with pharmaceuticals for weight loss or erectile dysfunction. But some herbs have narrow therapeutic ranges (e.g., *Aconitum* species) so toxic effects are frequently reported. Toxic effects from chronic or cumulative dosing are difficult to detect in the traditional setting and recent reports have demonstrated the health problems from *Aristolochia* species. Despite safety concerns, Chinese medicine appears to be relatively safe with comparatively few reports of adverse reactions compared with overall drug reports. The wealth of information in the Chinese literature needs to be more widely available. As TCM is widely used by patients, improved pharmacovigilance and pharmacoepidemiology can contribute valuable safety information, relevant to clinical use.

Introduction

Over the past 15 years use of traditional Chinese medicine (TCM) has spread beyond China and Asia and become increasingly popular in Australia, Europe and USA. In the UK it has been estimated that there are over 2000 shops/clinics providing TCM treatment including herbs, acupuncture, moxibustion, etc. Whilst acupuncture has been adopted by orthodox medical professionals for treatment of some conditions such as pain relief, Chinese herbal medicine (CHM) has remained the remit of specialist TCM practitioners. Although referred to as "herbal" medicine, this term is not really accurate as the Chinese materia medica (CMM) includes animal parts and minerals as well as plants. Outside of China, only around 500 herbs are commonly used which is a small fraction of the medicinal herbs available in China. In the Chinese Pharmacopoeia [1] 582 items of CMM are officially recognised and described, but if other widely used herbs or regional variations and folk medicine are included then the estimate increases to around 13 000 items of CMM in use in China [2].

For the majority of CMM, efficacy and toxicity assessments are based on traditional knowledge and clinical experience rather than evaluation in a laboratory. Safety (and efficacy) is usually based on the use of herbs combined into formulas of up to 20 herbs based on TCM principles; rarely are single herbs used in isolation. In contrast, most of the scientific investigation on the toxicology or efficacy of Chinese herbs has been carried out on extracts of single herbs in various *in vitro* or *in vivo* studies which may not accurately reflect the use of the herb in practice [3]. Isolated active ingredients extracted from herbs that have been developed as products (e.g., levo-tetrahydropalmitine) are listed as biomedicine in China as these are not based on TCM theory [4].

Herbs with pharmacological activity are likely to be clinically useful, but may also be toxic, especially if used incorrectly. A number of potentially toxic CMM are recognised in TCM (e.g., Chan Su) that should not be generally used. Even in the Chinese Pharmacopoeia herbs are described as

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mildly toxic to highly toxic, with 59 items of CMM in the latter category [1]. In traditional terminology these are called superior, average and inferior herbs; superior herbs have the least toxicity with inferior herbs having the greatest toxic potential [5]. In order to use these herbs safely the pharmacopoeia and classical literature describe the most appropriate method of processing, formulation and dose.

Whereas in orthodox medicine drug interactions are generally avoided because of concerns about adverse effects, within TCM interactions between herbs are deliberately used to modify therapeutic effects. Herb combinations can be classified as mutual reinforcement, mutual assistance, mutual restraint, mutual detoxification and mutual antagonism [6]. This is further illustrated by the hierarchy of herbs in a prescription that will also modify toxicity – Monarch, Minister, Assistant and Envoy. The function of the Assistant and Envoy herb(s) is to reduce toxicity (or increase potency) and mediate the effects of the other herbs in the formula, for example, Radix Glycyhyrriza (Gan Cao) is often regarded as a detoxifying herb so it is widely used with herbs thought to have even minor toxicity [7]. Some combinations which have been traditionally identified as increasing toxicity are contraindicated and 18 incompatible herbs in 3 groups are listed and should not be used together, e.g., Ban Xia (*Pinellia ternata*) should not be used with Chuan Wu, Cao Wu or other aconite-derived drugs [6, 8]. However, the toxicity of the interactions between most of these groups of incompatible herbs has not been verified by scientific investigation.

Despite this emphasis on toxicity, the majority of herbs in TCM appear to have a wide therapeutic index, demonstrated by the wide range of doses that are used in the clinical setting without apparent ill effects. Most herbs have a 3-fold dose range from minimum to maximum dosage; but herbs such as Radix Glycyrrhiza (Gan Cao) have a normal dose range of 1.5–9 g but up to 30 g can be used; Radix Codonopsis (Dang Shen) normal dose is 6–9 g but up to 30 g can be used [9]. However if used indiscriminately and inappropriately then even CMM with a very good safety profile may give rise to unexpected adverse effects.

Sources of Toxicity

There are a number of causes of toxic reactions to Chinese medicinal herbs, which can be divided into “direct” and “indirect” toxicity. Direct toxicity is the intrinsic toxicity of the CMM at normal therapeutic dosage or in overdose. Indirect toxicity includes all other factors that can contribute to toxicity, for example, lack of quality control of the CMM may lead to the supply of poor quality, poorly processed incorrect or substitute herbs. Use of the wrong herb can lead to unexpected side effects, for example, in Hong Kong *Tupistra chinensis* (root) was supplied instead of *Panax notoginseng* (root) and *Datura metel* (flower) instead of *Campsis grandiflora* (flower) resulting in cardiac toxicity and atropine poisoning, respectively [10]. The primary cause of safety alerts is the poor quality of some products and adulteration of Chinese patent medicines with pharmaceuticals.

Many factors affect even the direct toxicity and safety evaluation of CMM because of the intrinsic variability of the herbs and composition of patient prescriptions. There is considerable variation among batches of herbs as chemical composition is dependent on source, geographical/geological origin, genotype, part of plant, conditions during growth, time of harvest, use of pesticides, herbicides, storage conditions and processing [3].

The processing of herbs is very important in TCM. Basic processing includes washing, drying or slicing of the plant material to clean the herbs and improve storage properties. Additional processing such as stir-frying, boiling, or steaming is used to modify the therapeutic effects (detoxify, increase potency), alter bioavailability or preserve active ingredients [6]. The decocting of the complex herbal prescriptions can be considered as further processing as there are likely to be interactions between the herbs/constituents during the boiling process.

It is due to the complexity of TCM with use of multi-herb formulas and interactions of herbal constituents that investigating the toxicity and even efficacy of CMM can be more difficult than for pharmaceutical drugs [5]. For any clinically relevant health effects the toxic constituents have to be both bioavailable and present in physiologically active doses. Phytochemical investigations may identify potentially toxic constituents in a plant but these may not be present in clinically relevant amounts, in the part of the plant that is used, may be lost or modified by processing, may not be absorbed or may be destroyed/inactivated by metabolism.

Types of Toxicity

Identification of adverse drug reactions (ADR) and investigating the causes and mechanisms of these effects is well established in orthodox medicine. Types of reaction and mechanisms of toxicity have been classified and defined and are equally relevant to Chinese medicine and herbal medicine in general. Adverse reactions are classified as Type A (acute/augmented); Type B (bizarre/idiosyncratic); and Type C (chronic/cumulative and duration of use) [11].

The safety of herbs is mostly based on empirical experience and traditional use and is effective in identifying acute toxicity which has a rapid onset of symptoms within hours or days of using any herbal medicines. Acute toxicity (Type A) is usually dose-related and can be explained by the pharmacological properties of the herb [11]. The short time scale makes it easier to associate the use of the herbs and the adverse effect. However traditional experience is not effective at identifying herbs or herb combinations that cause cumulative, chronic or delayed toxicity (Type C). The first signs of adverse effects might not be recognised until months or years after starting or even stopping the use of the herbs/drugs and with such a delay the use of the herbs is likely to be forgotten. Aristolochic acid nephropathy (AAN) is a very good example of chronic toxicity as the effects are cumulative and renal symptoms can be delayed for 2 years after stopping the use of the herbs [12]. Various species of *Aristolochia* have been used in the traditional medicines of many countries [13] (*A. manshuriensis* and *A. fangchi* in Chinese medicine) but although aristolochic acids were known to have the potential to cause renal toxicity, the severity of damage to the tubules and DNA was not fully understood. It was only because of the cluster of cases in Belgium with detailed follow-up that the pattern of toxicity was characterised with full histological description and details of progression of the disease [12, 14].

Idiosyncratic reactions (Type B) can occur within days or weeks of starting the use of a medicine but are difficult to identify as these are not predictable, neither dose- nor time-dependent and are not necessarily related to pharmacological activities but can result from formation of reactive metabolites and immune-mediated reactions [11]. Such reactions occur rarely (> 1 : 10 000

and < 1 : 1000) but are significant as they may be serious or even fatal [15]. Drug-induced hepatotoxicity is often due to an idiosyncratic reaction. It is difficult to confirm single case reports of suspected herbal toxicity which may be due to idiosyncratic reactions as symptoms may be non-specific and there is no clearly identifiable toxic compound that can be measured in laboratory analysis.

ADR Reports from Around the World

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As Chinese herbs are so widely used clinically, spontaneous reporting systems or active pharmacovigilance can be effective in identifying therapeutically relevant safety issues. Whilst there is extensive literature on adverse effects of TCM in the Chinese, Japanese and Korean literature, very little is readily available in other languages [5].

Reports from China

One review of the Chinese literature found that 748 reports of adverse effects from CHM were published in Chinese journals in 1996 [16]. There was an increase of adverse reaction reports from 2217 in the 1980s to 2724 cases between 1990 and 1994 [17]. Song [18] identified 329 cases of adverse effects published in a single Chinese medical journal between 1990 and 1999. In 2004 the SFDA improved regulation of ADR monitoring, reports increased from 173 000 in 2005 to 547 000 by 2007. Herbal reports account for about 20%, the majority being reactions to injected herbal extracts [19]. Another review of ADR reports over a 10-year period identified 3122 case reports involving 140 drugs. Of these, oral use accounted for 32% of reports and 56% from injected extracts. Allergies (skin itch, dermatitis and anaphylactic shock) were the most common ADRs [20].

Reporting of adverse reactions has been encouraged in Hong Kong since the review of TCM and the publication of the Chinese Medicine Ordinance in 1999. Between January 2000 and June 2005, there were 77 adverse events reported to the Hong Kong Department of Health [21]. Causes included erroneous substitutions, quality defects (contamination and adulteration) and misuse as well as direct toxicity. The most common reports were 15 cases of cardiac toxicity from overdose or use of incorrectly prepared species of *Aconitum* and 9 cases of renal damage from aristolochic acid-containing medicines [22]. Hepatotoxicity was reported with various patent medicines, for example, Zhuang Gu Guan Jie Wan and herbs such as *Dioscorea bulbifera* (root) [21, 22].

Reports from Japan

In Japan, Kampo medicine uses similar herb combinations to CHM but only 210 medical prescriptions are registered. The association of various traditional herbal formulas such as "Sho-saiko-to" with liver damage is acknowledged [23]. Pharmacokinetic interactions of some formulas with orthodox medicines such as carbamazipine have also been reported [24, 25].

Other reports

The National Centres for ADR reporting in Europe, Australia and USA do not have systems specifically for TCM, but take reports on any herbal medicines. Concerns about liver toxicity first emerged in the early 1990s when cases of jaundice and liver failure from the use of a variety of Chinese prescriptions for skin and other conditions were published in the European literature [26–32]. Another cluster of hepatitis cases were focussed on the use of He Shou Wu (*Polygonum multiflorum*) [33–37]. However, the reports that attracted the most attention were the cases of AAN following misuse of *Aristolochia fangchi* by a Belgian slimming clinic [38]. The incidence of these adverse reactions to TCM cannot be estimated as there is no information on the extent of use of specific herbs/formulas by patients. However the main safety alerts from regulatory authorities around the world are warnings about adulterated and poor quality "herbal" products, mainly for slimming or erectile dysfunction, which have been shown to contain pharmaceuticals such as sibutramine or sildenafil and their analogues. In 2009 the regulatory authorities in Hong Kong, Singapore, Canada, USA and UK issued at least 30 warnings about adulterated products.

Toxic Herbs and Cases of Toxicity

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Although a number of herbs have been identified as potentially toxic, there is a focus on relatively few herbs, such as species of *Aconitum* or *Aristolochia* and *Polygonum multiflorum*. Most of the TCM reports in the Western medical literature refer to adverse events following the use of complex herbal formulae and specific "culprit" herbs are rarely identified.

Aconitum species (Chuan Wu, Fu Zi, Cao Wu)

The CMM derived from *Aconitum* species are useful for treating a diverse range of conditions from rheumatoid arthritis, collapse, gastroenteritis to bronchial asthma but the incorrect use of these herbs remains one of the main causes of toxicity reports from TCM [39]. The Chinese Pharmacopoeia specifies the lateral roots of *A. carmichaeli* (Chuan Wu, Fu Zi) and *A. kusnezoffii* (Cao Wu) as the official source of the drugs [1] but a number of other species are also used. All parts of the plant contain highly toxic cardiotoxins, the C_{19}-diterpenoid alkaloids such as aconitine, mesaconitine and hypaconitine. These alkaloids activate voltage sensitive sodium channels in the heart and other nervous tissues which then become refractory to further stimulation. Onset of symptoms such as numbness of the mouth and tingling of the hands and feet is rapid, usually within 10 minutes of ingestion. Other symptoms include nausea, vomiting, dizziness, hypotension, ventricular tachycardia, torsades de pointes and heart block which can lead to death. The lethal dose is estimated to be approximately 2 mg of aconitine [39].

The role of processing in the detoxification of *Aconitum* species has been well investigated with over 70 methods described in the literature [3, 40]. Boiling the roots hydrolyses the alkaloids reducing the aconitine content by around 90%; Chuan Wu contains approximately 0.137% aconitine which is reduced to between 0.0041 and 0.021% when boiled. Similarly Cao Wu contains around 0.199% aconitine which is reduced to 0.0084–0.034% after processing [39]. The products of hydrolysis, such as benzylaconine and aconine, are less toxic than aconitine [39]. Processing with *Glycyrrhiza* species (Gan Cao) or *Zingiber* species (Gan Jiang) has been shown to further reduce the aconitine alkaloids by enhancing hydrolysis [40, 41]. This detoxification is prevented when *Pinellia ternata* (Ban Xia) is added as the pH is decreased, inhibiting hydrolysis of the alkaloids [42].

Poisoning from *Aconitum* spp is mainly due to incorrect use – either use of poorly processed roots resulting in overdose of the alkaloids or due to poor directions for use, for example, ingestion of liniments prepared for topical use only [43]. In one example in the UK, a 22-year-old male erroneously drank about 10 mL (1–5 mg aconitine) of an alcoholic extract of aconite root (Wu Tao)

that had been prepared for topical use [44]. Onset of symptoms was within minutes including perioral parasthesia, nausea, vomiting and generalised weakness. After hospitalisation his cardiac function deteriorated with ventricular fibrillation and loss of cardiac output but he was resuscitated and made a full neurological recovery.

This clearly demonstrates the importance of correct processing for the safe use of potent, useful herbs such as aconite. Although the SFDA of China stipulates that only the processed detoxified roots of *Aconitum* species can be used in clinical decoctions or in pharmaceutical manufacturing [40] use of these herbs remains a constant source of poisoning and better methods for controlling processing to ensure that only detoxified roots are supplied for patient use are required.

Xanthium sibiricum (Cang Er Zhi)

Another herb, *Xanthium sibiricum* (Cang Er Zhi) is also reported to require processing to prevent poisoning. Cang Er Zhi is used for treating sinusitis, headache from sinus congestion, urticaria, and arthritis. If incorrectly used the adverse effects can be severe, including jaundice, hepatomegaly, oedema, oliguria, haematuria, tonic clonic seizures, coma, respiratory and circulatory failure [8]. The toxic constituent is thought to be a diterpenoid carboxyatractyloside that prevents oxidative phosphorylation by inhibiting ADP/ATP transport. The fruit is processed by stir-frying or charring to remove the spines. As the atractyloside is also present in the seeds, the loss of the spines may only be an indicator for adequate heating and processing. It has been shown that roasting reduces the content of atractyloside and other derivatives with formation of less toxic aglycones [45].

Aristolochia species (Guang Fang Ji, Guan Mu Tong)

Whereas the toxicity of *Aconitum* can be avoided by processing and limiting the dose, in contrast, the renal toxicity and carcinogenicity of the *Aristolochia* species, and aristolochic acids (AAs) cannot be controlled by such simple methods. Until the mid-1990s *Aristolochia* species were used in TCM as Guang Fang Ji or to treat skin conditions as Guan Mu Tong. The health implications of using these CMMs have only been extensively investigated since 1993 in response to the reports of serious renal toxicity following the erroneous use of *Aristolochia fangchi* in a formula along with other herbs and pharmaceuticals (including acetazolamide and fenfluramine) by a Belgian slimming clinic [38]. Over a period of about 5 years, approximately 112 patients who had attended this clinic were diagnosed with acute renal failure requiring dialysis, around half of whom required kidney transplantation [46]. The pattern of renal injury aristolochic acid nephropathy (AAN) has been described in the medical literature. The cases were characterised by a rapidly progressive interstitial nephropathy with patients developing end-stage renal disease within months of the first renal symptoms [14,47]. The 15-year follow-up study of patients who developed end-stage AAN confirmed the carcinogenic properties of the AAs. Despite chemotherapy, 3 patients died from metastatic cancer [48].

The occurrence of this large cluster of cases enabled the rapid characterisation of AAN, details of progression of the disease and development of urothelial carcinomas. Without this case series, it is unlikely that the association between the use of these medicinal herbs and the renal disease with subsequent carcinoma would have been identified as the onset of symptoms is delayed, often until many months or years after stopping use of herbs containing AAs.

Although attracting a considerable research effort, this is largely of scientific interest only as these herbs are unlikely to be used therapeutically. AAN has led to the ban on the medicinal use of all *Aristolochia* species in many countries [49]. *Aristolochia* species were defined as carcinogenic in 2002 by the International Agency for Research on Cancer [50] and the "Report on Carcinogens 12" has recommended that aristolochic acids should be listed as substances known to be a human carcinogen [51].

The contrast between *Aconitum* and *Aristolochia* species is a useful example of the differences in acute and chronic toxicity. The toxic effects of *Aconitum* are acute, occurring soon after ingestion so associating these with the adverse effects is relatively easy. The renal toxicity of *Aristolochia* is cumulative and delayed – identification of toxicity is difficult from traditional use only as the late onset of symptoms makes any association difficult. The carcinogenic properties require a long follow-up with complete medical history and specialist analytical techniques to identify the DNA damage which would not be available within historical traditional use.

In addition, the use of *Aconitum* and *Aristolochia* illustrate the key principles in using TCM (or any herbal medicine) – the need to understand the context of use of the plant, the names, the processing and the use of herbs in combination. With aconite root the difference in potency between processed and unprocessed forms of Cao Wu or Fu Zi may not be obvious to an untrained person who might consider that they are interchangeable as they are all derived from *Aconitum kusnezoffii*. Similar names, Fang Ji and Guang Fang Ji and a lack of understanding of the Chinese materia medica with use of interchangeable herbs, led to the inclusion of *Stephania tetandra* and/or *Aristolochia fangchi*, in the slimming formula [52]. Some potentially toxic herbs may be used safely within context, but even herbs that are normally considered safe may cause adverse effects if used inappropriately or by untrained personnel.

Ephedra sinica (Ma Huang)

Ma Huang contains ephedrine alkaloids which, although not as potent as a CNS stimulant as the pharmaceutical products, is a useful herb for treating asthma, cough and wheezing [53]. In TCM this herb requires careful prescription and monitoring as inappropriate doses or prolonged duration of use can lead to adverse effects. This is another herb that may undergo additional processing to modify its properties, in this case removing the foam after boiling for reducing irritability and diaphoresis [53]. Toxic effects include excitability, insomnia, nausea, poor appetite, increased blood pressure, cardiac arrhythmia and convulsions [3]. The misuse of this herb in dietary supplements as a stimulant or for weight loss resulted in thousands of reports of adverse effects in the USA, including gastrointestinal, psychiatric and autonomic adverse effects as well as sudden cardiac death [54]. The resulting major review of the use of *Ephedra* for either weight loss or athletic performance showed limited value and the herb was banned from dietary supplements in the USA in 2004 [55].

Liver Toxicity

Idiosyncratic drug-induced liver injury is the main cause of withdrawal of drugs from the market and is the main challenge to the pharmaceutical industry [56]. The best studied herbal liver toxins are the unsaturated pyrrolizidine alkaloids which occur in *Sene-*

cio and *Symphytum* species [57]. Chronic use results in a very specific liver injury, veno-occlusive disease, with occlusion of the central and sublobular hepatic veins which can progress to cirrhosis. Another herb which has been extensively studied is *Teuchrium chamaedrys* (not used in TCM) which provides a good example of liver damage caused by the formation of reactive compounds by metabolism [58, 59]. The furan ring of the neoclerodane diterpenoids is metabolised by CYP3A4 to electrophilic metabolites which deplete reduced glutathione leaving the liver vulnerable to injury. The Chinese herb, *Scutellaria baicalensis* (Huang Qin) also contains neoclerodane diterpenoids but these lack the furan ring needed for metabolic activation having instead a tetrahydrofuran ring. Although there is evidence that large doses of Huang Qin diterpenoids may cause damage to rat hepatocytes *in vitro* this may not be clinically relevant in man [60].

Polygonum multiflorum (He Shou Wu) is used for anaemia, dizziness, tinnitus and as a hair tonic. Since 1996 at least five cases of hepatotoxicity with products containing He Shou Wu have been reported in the international literature along with another 11 reports in the UK [33–37, 61]. A review of the Chinese literature published between 1978–2008 identified 24 cases of liver toxicity and 10 reports of allergy [62]. A number of causes of toxicity have been suggested, either that the herb was used incorrectly (overdose, extended use, incorrect herbal combinations) or that it was inadequately processed as it has been reported that hydrolysis reduces the toxicity of the anthraquinones [63]. Unfortunately the products/herbal material were not systematically analysed to support the claim about processing. The herb was self-prescribed in the majority of the reports so incorrect use may have been a contributory factor [63].

A series of case reports in the medical literature caused safety concerns about the potential hepatotoxicity of Chinese herbs resulting in a number of studies and reviews [26–32, 64–66]. One study in the UK evaluated 58 reports of suspected liver toxicity of Chinese herbs from the medical literature (UK, USA, New Zealand) and a hospital source in the UK [67]. Of these reports, association with liver toxicity was judged to be likely in 40 cases. In all cases patients received practitioner-prescribed individualised formulae for a range of conditions such as eczema, psoriasis, pain, hypertension and well-being. Patients developed hepatitis, jaundice or liver failure; 3 patients died following liver transplantation. No single herb or herb combination was common to all formulas. A case-control study of single herbs found no increase in the risk of hepatotoxicity with any of the most frequently used herbs (e.g., Gan Cao). These are considered idiosyncratic reactions as in all cases the toxicity was unpredictable and there is no suggestion of a herb or dose relationship [67].

Two other studies reviewed patients attending single clinics or hospitals. The Kotzing hospital in Germany carried out a review of 1507 patients using TCM and orthodox medicine for chronic pain [65]. Of these, only 14 patients showed minor elevation of liver enzymes which returned to normal even with continued TCM treatment after 8 weeks. This study is significant in that it found no clinically significant herb/drug interactions in these patients, and showed spontaneous resolution of elevated liver enzymes as has been reported with orthodox drugs.

The second study was carried out in the UK [66]. Of 1265 patients attending a TCM clinic, 124 had raised ALT levels before starting TCM treatment of which 71 returned to normal during treatment. A total of 107 patients developed raised ALT during treatment, 94 of which retuned to normal despite continued treatment and 1 patient developed idiosyncratic hepatitis.

A case-crossover study on 200 000 individuals in the Taiwanese National Health Insurance Research Database (1997–2002) compared medications taken in the 30- and 60-day period prior to hospitalisation. They found a 3.5-fold increase in frequency of hospitalisation for acute nonviral, nonalcoholic hepatitis in TCM users, but numbers were small, only 12 of 354 patients [68].

A retrospective study in Japan reviewed the 14 616 outpatients using Kampo medicine at a Toyama hospital from 1979 to 1999 [69]. Of 2496 patients with liver injury 15 cases were identified that were possibly related to the use of Kampo medicine. The incidence of liver injury associated with Kampo medicines was 0.6% of liver admissions and 0.1% of all admissions. There have also been reports from Japan about liver toxicity of some formulas, such as Sho-saiko-to. These are also complex formulas with more than one herb and the cause of toxicity has not been identified [70].

In the case reports in the medical literature, the reporting physician often links toxicity with single herbs, usually those that are mentioned in more than one published report [30, 64]. Herbs suggested as being hepatotoxic include *Dictamnus dasycarpus* (Bai Xian Pi), *Astragalus membranaceous* (Huang Qi), *Paeonia lactiflora* (Chi Shao, Bai Shao) although there is no scientific or clinical evidence linking these individual herbs with causing liver damage. Toxicity of individual chemical constituents is also frequently cited. For example, glycyrrhizin (from *Glycyrrhiza* species, Gan Cao) was reported to be hepatotoxic because of reports that intravenous administration of the extract caused 2 cases of hepatitis although this route does not reflect normal use in a decoction [71, 72]. There may be other misconceptions about activity; for example, Bai Xian Pi (*Dictamnus dasycarpus*) was labelled as hepatotoxic as it was reported to contain furanocoumarins [30]. Furthermore, it was suggested that dictamine, a quinoline alkaloid, undergoes similar hepatic metabolism to xanthotoxin as it also contains a furan ring, although these are quite distinct compounds [73].

Idiosyncratic liver injury is a serious adverse reaction and is potentially fatal (3 patients died from liver failure) [67]. However from the studies so far, no common profile of susceptible patients has been defined and no single herb or combination of herbs have been identified as culprit herbs. Because of the negative publicity in the UK some TCM practitioners have introduced regular liver function monitoring as a standard part of their treatment. Practitioners are aware of the symptoms of liver injury and specific advice is given to patients. As this is a serious complication, there needs to be greater awareness of this issue amongst TCM doctors and their patients. Improved reporting of these cases may contribute to recognition of susceptible patient profiles.

Conclusions

Chinese herbal medicine is a complex system – if used indiscriminately then problems may occur, as clearly shown by the errors that led to the cases of renal failure in Belgium [52]. In any search for new drug leads from the CMM, investigators need to be aware of the subtleties of the system of TCM – the naming systems, processing, substitutes, use of herbal combinations and types of extract used clinically. For any toxicity/efficacy tests, accurate botanical identification of the plant material is essential and voucher specimens should be retained for future use.

If CMMs are used in specialised extracts or as single compounds then the safety profile of that particular extract has to be reevaluated as the chemical profile will be different from that of the

traditional herbal drug. Unexpected toxicity may result from changing formulations – even safe herbs may cause adverse effects if used inappropriately.

Despite all the concerns, Chinese herbal medicine appears to be relatively safe. Even within China the number of adverse reactions reported to the National Centre following use of herbal decoctions is small compared with all drug reports [17, 18, 20]. Toxicity reports from TCM are mainly due to misuse or incorrect use of herbs, generally leading to acute or chronic overdose, clearly demonstrated by the misuse of Ma Huang [53]. But the potential toxicity of any herb has to be seen in context – this also reflects its pharmacological activities which may be therapeutically useful if used correctly (as in many orthodox medicines).

As the majority of herbs have had extensive use in patients, relatively few have been studied in detail in animal models to develop in-depth pharmacology or toxicology as would be expected in pharmaceutical medicine. But there is a considerable amount of valuable data in the Chinese literature; the classical literature includes over 300 texts with information on toxicity as well as properties of the herbs [5]. There are extensive publications on other aspects of herbs and formulations, for example, a recent review identified over 30 reports of surveys of TCM adverse reactions to hospitals/regions within China [20]. However, these are mainly in the Chinese or other Asian literature and not readily accessible outside of China. One project to address this gap has been started by the University of Western Sydney in Australia. They have developed a Chinese toxicology database which will translate and incorporate the body of the Asian literature producing individual herb monographs with toxicity gradings for therapeutic use and overdose [74].

As TCM is extensively used clinically, spontaneous ADR reporting schemes and active pharmacovigilance can be used to obtain invaluable safety/toxicity information on TCM. Some pharmacoepidemiological studies have been undertaken in China and Taiwan demonstrating the usefulness of such research methods [68, 74–77]. But improved pharmacovigilance schemes are needed in other countries using TCM to collect reports of adverse reactions and build up a fuller picture of safety concerns. Good guidelines on reporting, especially regarding correct naming and identification of the CMM and full ingredient lists (of patent medicines or individualised formulae) as well as accurate clinical details are critical to improve the case data for safety evaluations of herbs. TCM has many benefits to offer, but it is important that the balance between benefits and harms is evaluated. Unnecessary cases of toxicity from poor quality herbs or bad prescribing must be avoided to ensure that patients receive the most effective treatment with few adverse effects.

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