

# ADVERSE EVENTS INVOLVING CERTAIN CHINESE HERBAL MEDICINES AND THE RESPONSE OF THE PROFESSION

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## *Introduction*

As Chinese herbal medicine becomes increasingly widely practised in the West, reports of occasional adverse effects are appearing in the literature and questions are being asked about safety. If we are to retain the confidence and support of the public we must address these issues in a spirit of openness and with a willingness to learn the relevant lessons.

In this article I present a wide-ranging, though not exhaustive, review of reports in the English-language literature of adverse events involving Chinese herbs. In particular, I have devoted attention to a series of cases of liver damage, including two fatalities, which have occurred in the UK in patients taking Chinese herbs for skin disease. This is the first time all this information has been gathered together in one place.

It is important to remember that these adverse events are extremely unusual. Chinese herbal medicine is generally both safe and effective, and there are many patients who have experienced dramatic benefits to their health from treatment. All medicines are assessed in terms of their risk-benefit ratio and it should not be surprising that Chinese herbal medicines may also occasion rare but significant adverse events. The aim of this article is to assist a process of debate and development within the profession as we work to minimise what risks there are.

## *Kidney Damage from Slimming Treatment in Belgium*

One of the most serious recent occurrences of toxicity involving Chinese herbs came to light between 1991 and 1992 in Belgium, where a series of young women were admitted to hospitals suffering from renal failure<sup>1</sup>. Investigations initially discovered nine cases and revealed that they had all been taking medication for slimming from the same clinic, which was run by doctors not herbalists. The clinic had been giving slimming treatments for fifteen years without such problems, but in 1990 the composition of the slimming capsules was changed and two Chinese herbs were included.

The slimming clinic claimed that the new formula contained:

Cascara powder 20-150 mg

Acetazolamide 25-45 mg

Belladonna extract 1-2 mg

*Hou Po* (Cortex *Magnolia officinalis*) 100-200 mg

*Han Fang Ji* (Radix *Stephania tetrandra*) 100-200 mg<sup>1</sup>

However, as discussed below, it is now certain that the second Chinese herb was not in fact *Han Fang Ji* but rather was either *Guang Fang Ji* (Radix *Aristolochia Fangchi*) or an unknown adulterant.

In addition to the above formulation, most patients at the clinic were also prescribed a capsule containing the amphetamines fenfluramine and diethylpropion and the tranquilliser meprobamate, and were given intradermal injections of artichoke extract and euphyllin<sup>1</sup>. Many will consider such a regimen to constitute extremely dubious practice, and indeed the Faculties and Medical Board in Belgium have warned doctors not to prescribe slimming products composed of appetite inhibitors and diuretics<sup>2</sup>. Also, it will be immediately apparent to practitioners of Chinese herbal medicine that neither *Hou Po* nor *Han Fang Ji* are traditionally indicated for weight loss, and it is also obvious that they were not being prescribed on an individualised basis following a diagnosis according to the principles of Chinese medicine.

It is worth noting that these patients were also put on a low calorie diet, which might have enhanced the effect of the medicines they were given.

Since the first published report from Belgium, a total of 53 cases of renal failure have now been reported<sup>2</sup>. The patients affected require kidney dialysis with a view to eventual transplantation. This is clearly an extremely serious situation and it is important to try to understand what went wrong. The cases of kidney damage did only occur once the Chinese herbs were added to the formula, so the toxic reaction must have involved them in some way.

The first problem concerns the identity of the herbs involved. Chromatographic studies confirmed the presence of *Hou Po* in the capsules<sup>1</sup>. However, the same studies

showed that the capsules did not contain tetrandrine, which is a major constituent of *Han Fang Ji*. These studies also isolated an unknown alkaloid which was not present in samples of *Han Fang Ji*. Finally, microscopic examination showed the presence of calcium oxalate in both the capsules and the importer's sample of *Han Fang Ji*. Such crystals are not found in *Han Fang Ji* according to the Pharmacopoeia of the PRC<sup>3</sup> but they are present in *Guang Fang Ji* (Radix Aristolochia Fangchi). The Chinese Medicinal Material Research Centre (CMMRC) in Hong Kong also studied samples of the herb supplied as *Han Fang Ji* by the exporter in Hong Kong and found aristolochic acid to be present<sup>4</sup>. The CMMRC later studied samples of the slimming capsules themselves and found them to contain aristolochic acids A and B<sup>5</sup>.

One very definite possibility therefore is that the herb actually used in these capsules was not *Han Fang Ji* (Radix Stephania Tetrandra) but was in fact *Guang Fang Ji* (Radix Aristolochia Fangchi). This herb contains aristolochic acid, and this chemical in isolation can produce nephrotoxic reactions<sup>6</sup>. However, although the potential toxicity of *Guang Fang Ji* is known in Chinese medicine<sup>2</sup> the whole herb is used in China without producing such toxicity. It has also been pointed out that 185 kg of the supposed *Han Fang Ji* was distributed to practitioners throughout Belgium, but only in this one slimming clinic did problems occur. We have already mentioned that at this clinic the herbs were not prescribed by properly trained practitioners of Chinese herbal medicine, nor in accordance with Chinese medical theories. Furthermore, instead of being combined with other herbs which may serve to minimise any potential for toxicity, in this case the herbs were instead combined with an extraordinary mixture of pharmaceutical drugs.

It is certain then that the herb supposed to be *Han Fang Ji* was misidentified by the exporters in Hong Kong, by the importers in Belgium and by the doctors in the slimming clinic. It is very likely that the herb used was in fact *Guang Fang Ji* and that this herb's potential for toxicity was massively amplified by its use in combination with other drugs, in patients for whom it was not indicated, and by practitioners untrained in its use.

However, there is definitely some confusion here. The initial report of studies done in Belgium clearly states that the slimming capsules did not contain aristolochic acid<sup>1</sup>, and instead speaks of the presence of an unknown alkaloid. Only in the later report from the CMMRC is it claimed that the capsules did contain aristolochic acid<sup>2</sup>. There remains therefore a second distinct possibility, that the capsules contained neither *Han Fang Ji* nor *Guang Fang Ji*, but some unknown and severely nephrotoxic adulterant.

There are several lessons to be drawn from this tragic series of cases of kidney damage:

- Chinese herbs should only ever be prescribed by fully trained practitioners of Chinese herbal medicine, in accordance with a traditional individualised diagnosis.
- When herbs with some potential for toxicity are mixed

with modern drugs there may be previously unknown consequences, as a result of the potentiation of the toxicity of the herb by the metabolic and physiological effects of the drugs. This is clearly an important issue which requires further discussion and elaboration. Some important work has already been done on producing lists of herbs which are known to have some potential for toxicity<sup>7</sup>.

- Proper identification and quality control of herbs by suppliers is a key ingredient in the safe practice of Chinese herbal medicine.

### *Toxicity from Patent Medicines- Jin Bu Huan & Others*

Traditionally, patent medicines are based on traditional herbal formulas and are prescribed according to a traditional diagnosis. However, modern patents have moved away from the traditional formulations, and we have begun to see problems as a result. Reports from the USA in 1993 and 1994 drew attention to toxicity problems with the patent medicine *Jin Bu Huan Anodyne Tablets*, made by Kwangsi Pai Se Pharmaceutical/Bose Drug Manufactory, Kwangsi, China<sup>8,9</sup>. Seven adults developed symptoms of hepatitis after taking *Jin Bu Huan* for between 7 and 52 weeks. Symptoms and signs included fever, fatigue, nausea, pruritus, abdominal pain, jaundice and hepatomegaly. Liver function tests and liver biopsy results confirmed acute hepatitis and were consistent with a drug reaction. Two patients later recommenced the use of *Jin Bu Huan* and both experienced a rapid return of the symptoms of hepatitis. All seven patients made gradual but complete recoveries on ceasing the use of the patent medicine.

The precise mechanism of the hepatitis is not entirely certain. The abrupt reappearance of symptoms in the patients who recommenced taking the tablets suggests a hypersensitivity reaction, and the liver biopsy showed eosinophilia in two cases, which also suggests an allergic mechanism. An immunoallergic mechanism therefore seems most likely<sup>9</sup>. However, there are also some suggestions of a direct hepatotoxic effect<sup>9</sup>.

The package insert for these tablets recommended their use for pain relief or insomnia and claimed that the ingredients were 70% starch and 30% levo-alkaloid from *Polygala chinensis* (presumably this refers to *Yuan Zhi* - Radix *Polygalae Tenuifoliae*). However, analysis of the tablets showed that they contained 36% of levo-tetrahydropalmatine. This alkaloid is not found in plants of the genus *Polygala*, but it is found in the genera *Stephania* and *Corydalis*<sup>9</sup>. Almost certainly, the alkaloid in these tablets was actually extracted from *Yan Hu Suo* (*Rhizoma Corydalis Yanhusuo*). This herb is traditionally known to alleviate pain and we know there have been studies on the hypnotic and sedative effects of tetrahydropalmatine extracted from it<sup>22</sup>. This herb is also known as *Yuan Hu*, hence presumably the confusion with *Yuan Zhi* (although the Chinese characters are different).

Several points are evident here:

- The labelling of this product in English was inaccurate. In addition, the incorrect weight of the active ingredient suggests poor quality control by the manufacturers.
- Traditionally, Chinese herbs are always used in combination with other herbs and prescribed in order to treat the underlying disharmony causing the symptoms. This tablet was based on only a single herb and indicated purely for symptomatic relief.
- What is more, these tablets did not even contain the whole single herb, but a single chemical extracted from a herb. This is not the practice of traditional medicine, rather it represents a modern pharmaceutical approach. It is debatable whether this product could really be described as "herbal" at all - it is more akin to a novel and unlicensed drug! The chemistry of whole herbs involves complex interactions among their constituents which are poorly understood<sup>10</sup>, and there is evidence that whole herbs are significantly less toxic than single "active ingredients" isolated from them<sup>11,12</sup>. Certainly, there are no reports in the literature of any problems with the whole herb *Yan Hu Suo*.

Also in the USA, in three separate incidents, children aged two and a half years and 13- and 23- months took unintentional overdoses of *Jin Bu Huan*, amounting to 17, 60 and 7 tablets respectively. Each of these children became seriously ill, with rapid onset of life-threatening bradycardia and central nervous system and respiratory depression<sup>13</sup>. Fortunately each child made a full recovery. These cases underline the additional dangers from concentrated single chemical extracts from herbs.

There have also been reports from Hong Kong and the USA of patent medicines containing paracetamol, aspirin, antihistamines, theophylline, bromhexine and synthetic corticosteroids, and from Hong Kong, the USA and Australia of other patent medicines containing cadmium, lead and arsenic<sup>1</sup>. In Malaysia, a woman developed kidney damage after taking a patent medicine which was found to contain phenylbutazone<sup>14</sup>. In the UK, skin creams for eczema have been found to contain corticosteroids and a potent antibiotic<sup>15,16,17</sup>.

What is evident in these cases is that most of these problems are not being caused by traditional patent medicines but by modern formulations containing a single chemical only or combining Chinese herbs with Western drugs. The advice given to its members by the Register of Chinese Herbal Medicine (RCHM) in the UK is relevant here:

Never prescribe a patent medicine unless you know all its ingredients. Avoid all patents containing Western medicines (it is in any case illegal to prescribe many of these unless you are a registered medical practitioner). Patents with added Western drugs can often be identified by the words *Fu Fang* or *Qiang Li* before the name. Avoid all patents containing heavy metals (they are toxic and illegal). Use reputable suppliers. Suppliers must be encouraged to adopt careful quality control measures<sup>15</sup>.

### *Toxic Effects from Adulterants or Erroneous Substitutes*

In 1991 a case was reported from Hong Kong of encephalopathy and neuropathy following ingestion of a decoction supposedly prepared from *Long Dan Cao* (Radix Gentiana longdancao). Investigation showed that the toxicity was in fact due to adulteration of the herb by the supplier in mainland China with the roots of *Podophyllum emodi*, which contained podophyllotoxin<sup>18</sup>. Similarly, the Chinese Medicinal Material Research Centre (CMMRC) in Hong Kong investigated a case of serious vomiting and abdominal pain in Kuala Lumpur and a case of serious vomiting and headache from Taipei. Both people had taken decoctions supposedly containing *Wei Ling Xian* (Radix Clematis). Investigation revealed that the importers in Kuala Lumpur and Taipei had been persuaded to accept a new source of *Wei Ling Xian* and had not realised that the herb supplied was actually a toxic adulterant, which again proved to be *Podophyllum emodi*<sup>5</sup>.

The CMMRC also investigated four cases of drowsiness and confusion affecting four women in Hong Kong, all of whom had obtained their prescriptions from the same herb shop. In each case the prescription included *Ling Xiao Hua* (Flos Campis grandiflora or *C. radicans*). In Hong Kong and southern China this herb is commonly replaced with *Pao Tung Hua* (Flos Paulownia fortunei or *P. tomentosa*). However, in these cases the retailer at the herb shop had mistakenly used *Yang Jin Hua* (*Datura metel*), which contains atropine and scopolamine and is known to cause symptoms such as confusion at the doses used<sup>5</sup>.

In the USA, a man took a traditional herbal prescription containing 36 ingredients. He became ill with abdominal colic, muscle pain and fatigue, was hospitalised for 3 weeks, and was eventually diagnosed as suffering from acute intermittent porphyria. The cause was traced to lead poisoning due to contamination of the *Hai Ge Fen* (*Concha Cyclinae Sinensis*, clam shell) in his prescription<sup>19</sup>.

Expensive herbs such as *Ren Shen* (*Panax ginseng*) may particularly tempt fraudulent substitution. In the 1970s, Ginseng preparations bought in the USA were found to contain *Mandragora officinarum* (toxic component scopolamine), *Rauwolfia serpentina* (toxic component reserpine) and *Cola* species<sup>41</sup>. There have also been other reports of substitution of *Ren Shen*<sup>20</sup>, including a famous case involving Linford Christie at the Seoul Olympics where what was supposed to be *Ren Shen* was found to contain ephedrine. All these cases again point to the crucial need for good identification checks and quality control by suppliers. A minimum requirement would probably be the examination by microscopy and chromatography of each batch of herbs by trained pharmacognocists.

### *Problems with Herbs of Known Toxicity*

A handful of the hundreds of herbs commonly used in Chinese herbal medicine have always been known to be potentially toxic, but they have continued to be used with

care because of their therapeutic value. The most important examples are the aconites.

A review of reports of toxicity in Hong Kong<sup>21</sup> showed that most of the cases of serious poisoning were due to the use of *Cao Wu* (*Radix Aconitum kusnezoffi*) and *Chuan Wu* (*Radix Aconitum carmichaeli* - the main root). These herbs contain highly toxic alkaloids, including aconitine, which activate sodium channels and over-stimulate cell membranes. Side effects are neurological, cardiovascular and/or gastro-intestinal and death can occur due to cardiovascular collapse or ventricular arrhythmia.

Both of these herbs are traditionally known to be very toxic, and Chinese herbal pharmacopoeias warn of this. Nonetheless, in some of the Hong Kong cases quite high doses of 7-11g had been prescribed. This suggests a lack of appropriate caution to say the least and raises concerns over the training and competence of practitioners, particularly since herbal medicine is unregulated in Hong Kong. Even when the indications and dosage are correct, problems can arise. The roots may contain variable amounts of toxic components and patients' sensitivity may also vary<sup>22</sup>. Furthermore, patients are relied upon to boil these herbs for a long time to reduce their toxicity, and these instructions may not always be followed correctly. More complex is the situation relating to *Fu Zi* (*Radix Lateralis Aconiti Carmichaeli Praeparata* - the processed accessory roots). This herb is less toxic than the main root and is pre-processed to further reduce its toxicity (the unprocessed form is called *Sheng Fu Zi* and is rarely used). Herbalists find this herb extremely useful - it is warming and drying and it tonifies yang. However, there have been some reports of problems with *Fu Zi* in Hong Kong<sup>23</sup>.

In the UK, although the legal situation is somewhat ambiguous, it appears that all forms of aconite are effectively banned for internal use. It can certainly be argued that herbs with such clear and established toxicity as *Cao Wu* and *Chuan Wu* should be restricted to use only when patients are under close medical supervision, probably as in-patients. This would permit the rapid detection of adverse reactions, which can then be successfully treated with atropine. In the case of *Fu Zi*, one could argue for its use being allowed at low doses by qualified and regulated practitioners, and with clear advice to patients about the need to pre-boil *Fu Zi* to reduce its toxicity even further.

### **Toxic Effects from Rare Herbs - Hong Kong**

The herbs *Yang Jin Hua* (*Datura metel*) and *Nao Yang Hua* (*Flos Rhododendri mollis*) contain scopolamine, hyosamine and atropine and they have been reported as the cause of cases of anticholinergic poisoning in Hong Kong<sup>21</sup>. These herbs are rarely used by practitioners of Chinese herbal medicine in Europe, although the former can be obtained from some suppliers<sup>7</sup>. The related herb *Datura stremonium* is used by Western herbalists and in the UK this is allowed by the 1968 Medicines Act within a restricted dosage range. It would seem sensible for *Yang Jin Hua* (*Datura metel*) and

*Nao Yang Hua* (*Flos Rhododendri mollis*) to also be restricted to use at low doses by qualified and regulated practitioners.

### **Cases of Liver Damage in Skin Disease Patients**

In the UK there has been a great surge in the popularity of Chinese herbal treatment for skin conditions. This followed considerable media interest, stimulated by two clinical trials which showed the value of Chinese herbs in the treatment of eczema<sup>24,25</sup>.

There have now been several cases in the UK where patients have become clinically ill with liver problems after taking Chinese herbs for the treatment of skin conditions, and a similar case has been reported from New Zealand. Two of these patients have died.

The details of a number of these cases have now been published separately. It has often proved difficult to obtain much information about the herbs prescribed and details of the Chinese diagnosis have never been obtained, but there are a number of cases where details are now available of the prescriptions given. Unfortunately it is very difficult to identify the species, given a dried specimen of only one part of the plant, and to compound the difficulty the identification of the herbs in some of these cases was done by botanists, not by specialists in Chinese herbs. As a result some of these prescriptions may contain errors in identification. Nonetheless, there is enough information here to allow us to draw some clear conclusions. These are presented in the discussion section after the individual cases.

#### **Case 1**

This is the first fatality to have occurred in the UK which was linked to Chinese herbs. A letter from the National Poisons Unit reporting this case was published in the *Lancet* in 1992<sup>26</sup>.

The patient, a 28 year old woman, developed jaundice after taking Chinese herbs for several months and was admitted to hospital with hepatitis. The symptoms resolved satisfactorily. Six months later the patient began taking Chinese herbs again. Two or three weeks after this she was again admitted with jaundice, and tragically died of acute liver failure. A post-mortem revealed total necrosis of the liver.

The hospital was able to exclude the more common infectious causes, e.g. hepatitis A and B. There was no history of exposure to hepatotoxic chemicals, and the only Western drugs being taken prior to the jaundice were antacids. There were no traces of hepatotoxic drugs in the urine, nor of heavy metals in the blood or urine.

The *Lancet* letter also gave details of the herbal prescription which this patient supposedly was taking. However, after further investigations by Dr. David Atherton it has been discovered that the prescription given to the NPU was in fact for a different patient of the same name<sup>27</sup>! The NPU analysed their sample for aflatoxins (toxins from mould on

the herbs) and for pyrrolizidine alkaloids, and found none, but clearly this particular result is meaningless since the wrong sample was tested. The possibility of contamination or adulteration of the herbs therefore remains in this case. Dr. Atherton has now provided us with details of the prescription which was actually taken by this woman throughout her treatment<sup>27</sup>:

Pinyin name	Pharmaceutical name	Botanical name	Dosage
Bai Ji Li	Fructus Tribuli Terrestris	Tribulus terrestris	3 chien (9g)
Jing Jie	Herba seu Flos Schizonepetae Tenuifoliae	Schizonepeta tenuifolia	1 chien (3g)
Yin Chen Hao	Herba Artemisia Yinchenhao	Artemisia scoparia <sup>a</sup>	3 chien (9g)
Sheng Di Huang	Radix Rehmanniae Glutinosae (not pre-cooked)	Rehmannia glutinosa	3 chien (9g)
Mu Dan Pi	Cortex Moutan Radicis	Paeonia suffruticosa	3 chien (9g)
Bai Xian Pi	Cortex Dictamni Dasycarpi Radicis	Dictamnus dasycarpus	3 chien (9g)
Gan Cao	Radix Glycyrrhizae Uralensis	Glycyrrhiza uralensis	1.5 chien (4.5g)
Dan Zhu Ye	Herba Lophatheri Gracilis	Lophatherum gracile	2 chien (6g)
Mu Tong	Caulis Akebiae <sup>b</sup>	Clematis armandii <sup>b</sup>	2 chien (6g)

<sup>a</sup> This is the species I was given for this herb. However, both *Artemisia scoparia* and *Artemisia capillaris* are used and it is not entirely clear which was present here.

<sup>b</sup> The pharmaceutical name now used is *Caulis Mutong*. Old pharmacopoeias most often list *Akebia trifoliata* and *Akebia quinata* as this herb. However, in modern China either *Clematis armandi*, *Clematis montana*, or *Aristolochia manshuriensis* may be used<sup>22</sup>.

The above is based on the practitioner's written prescription, which gave the herb names in Chinese.

In response to this fatality, and a number of other early reports of high blood levels of liver enzymes in patients taking herbs for eczema and psoriasis<sup>28,29</sup>, the RCHM made the following recommendations to its members in 1992 and 1993<sup>15,16</sup>:

- that all patients with a history of liver or kidney disease in the last five years should not be treated without regular blood-testing to monitor liver and kidney function.
- that practitioners should carefully monitor their patients and be vigilant for any early indications of liver damage.
- that practitioners should take care with dosage in patients with skin diseases. A total prescription weight of 35 g/day (or 0.5 g/kg of body weight) was recommended.
- that practitioners should consider regular blood-testing of all patients with skin diseases. This last recommendation was only taken up by a handful of practitioners. Many practitioners were reluctant to import such a non-traditional measure into the practice of Chinese medicine, and there were also obstacles of cost and practicality.

### Case 2

This case came to the attention of the RCHM Council in May 1994, when we were approached by a woman whose sister had been admitted to hospital with jaundice whilst taking a course of Chinese herbs. The hospital had investigated other possible causes for the jaundice and concluded that the herbs were probably responsible. The woman approached the RCHM because the practitioner claimed to be "a registered practitioner". However, the practitioner turned out not to be a member of the RCHM. The practitioner was initially reluctant to give any details of the prescription, but after the patient's sister threatened legal action she divulged the following details. The dosages are not known.

Pinyin name	Pharmaceutical name	Botanical name
Jing Jie	Herba seu Flos Schizonepetae Tenuifoliae	Schizonepeta tenuifolia
Fang Feng	Radix Ledebouriellae Divaricatae	Ledebouriella divaricata <sup>a</sup>
Huang Qin	Radix Scutellariae Baicalensis	Scutellaria baicalensis
Ban Lan Gen	Radix Isatidis seu Baphicacanthi	Baphicacanthus cusia, Isatidis tinctoria or <i>I. indigotica</i>
Mu Dan Pi	Cortex Moutan Radicis	Paeonia suffruticosa
Zi Su Ye	Folium Perillae Frutescentis	Perilla frutescens
Mai Men Dong	Tuber Ophiopogonis Japonici	Ophiopogon japonicus
Gou Qi Zi	Fructus Lycii	Lycium barbarum or <i>L. chinense</i>
Bai Shao	Radix Paeoniae Lactiflorae	Paeonia lactiflora
Shan Yao	Radix Dioscoreae Oppositae	Dioscorea opposita
Mu Tong	Caulis Mutong	<i>Aristolochia manshuriensis</i> , <i>Clematis armandi</i> , or <i>C. montana</i> <sup>b</sup>
Fu Ling	Sclerotium Poriae Cocos	Poria cocos
Chen Pi	Pericarpium Citri Reticulatae	Citrus reticulata
Bai Xian Pi	Cortex Dictamni Dasycarpi Radicis	Dictamnus dasycarpus
Gan Cao	Radix Glycyrrhizae Uralensis	Glycyrrhiza uralensis
Bai Jiang Can	Bombyx Batryticatus	<i>Bombyx mori</i> infected with <i>Beauveria bassiana</i>

<sup>a</sup> Also known as *Ledebouriella seseloides* or *Saposhnikovia divaricata*.

<sup>b</sup> Old pharmacopoeias most often list *Akebia trifoliata* and *Akebia quinata* as this herb. However, in modern China either *Clematis armandi*, *Clematis montana*, or *Aristolochia manshuriensis* may be used<sup>22</sup>.

The above is based on the practitioner's written prescription, which gave the herb names in Chinese.

The information available on this case is rather limited, but it is included here to make the information available to practitioners, who may particularly wish to study all the prescriptions which may have been involved in adverse events.

**Case 3**

This case, reported by Kane et al.<sup>30</sup>, was of a 31 year old white woman who presented to her general practitioner in September 1991 complaining of loss of appetite, nausea and fatigue. She had had dark urine and yellow sclerae for the previous 24 hours. Examination revealed jaundice and an enlarged liver. Blood tests revealed raised levels of alanine transaminase, alkaline phosphatase and bilirubin, confirming liver damage.

The patient was not taking regular prescribed drugs, drank hardly any alcohol, and had had no recent injections or blood transfusions. The provisional diagnosis was viral hepatitis, but blood tests for hepatitis A were negative. Three months later she was tested for hepatitis B and C and for auto-antibodies and these tests were also negative.

The patient's liver function returned to normal over the next eight weeks, but after another six weeks she again complained of malaise, itching and dark urine. She had mild jaundice, and blood levels of alanine transaminase and alkaline phosphatase were again raised.

This time the patient was carefully questioned and she revealed that before the first episode she had taken Chinese herbs for her psoriasis. The herbs were taken daily for two months as a decoction. She had begun taking the herbs again just three days before the second episode of jaundice. She stopped the herbs again and her liver function returned to normal after eight weeks. She remained well during 18 months follow up.

In this case, the recurrence of both symptoms and biochemical evidence of liver damage shortly after resuming the herbs strongly incriminates the herbs as the cause of the liver damage.

The herbs showed no evidence of contamination by heavy metals or fungi. The prescription was examined and analysed at the Dept. of Pharmacognosy in the School of Pharmacy of the University of London. They identified the herbs by their Latin botanical names as:

Pinyin name	Pharmaceutical name	Botanical name
Bai Xian Pi	Cortex Dictamni Dasycarpi Radicis	Dictamnus dasycarpus
Mu Dan Pi	Cortex Moutan Radicis	Paeonia suffruticosa
Sheng Di Huang	Radix Rehmanniae Glutinosae (not pre-cooked)	Rehmannia glutinosa
Bai Hua She She Cao	Herba Hedyotidis Diffusae	Hedyotis diffusa <sup>a</sup>
Shan Dou Gen	Radix Sophorae Subprostatae	Sophora subprostata <sup>b</sup>
Long Dan Cao	Radix Gentianae Longdancao	Gentiana scabra
Tu Fu Ling	Rhizoma Smilacis Glabrae	Smilax glabra
Zao Xiu <sup>c</sup>	Paris polyphylla	Paris polyphylla

<sup>a</sup> Also known as Oldenlandia diffusa.

<sup>b</sup> There are two types of this herb: the southern type is known as *Guang Dou Gen* (*Sophora subprostata*, also known as *S. tonkinensis*) and is

considered to be toxic, the northern type is known as *Bei Dou Gen* (*Menispermum dahuricum*) and is mostly recommended for use since it is without adverse effects<sup>31</sup>.

<sup>c</sup> Also known as *Qi Ye Yi Zhi Hua*. This herb is traditionally considered to be slightly toxic<sup>31</sup>.

In this case it is clear that two herbs in the prescription had some known potential for toxicity.

**Case 4**

This case was also reported by Kane et al.<sup>30</sup> A 61 year old Chinese woman living in the UK presented with nausea, malaise, weight loss, dark urine and jaundice. Blood tests showed raised levels of aspartate transaminase, alkaline phosphatase and bilirubin, confirming liver damage. She had no known history of exposure to hepatitis viruses or other toxins, she drank very little alcohol, and her only prescribed drugs had been a short course of terfenadine. Blood tests for hepatitis A, B and C were negative. She had been taking Chinese herbs for her eczema for 11 months.

This patient was advised to stop the herbal treatment and her symptoms disappeared within days. Her liver function returned to normal within three months.

The herbs were identified by the Dept. of Pharmacognosy in the School of Pharmacy

Pinyin name	Pharmaceutical name	Botanical name
Bai Xian Pi	Cortex Dictamni Dasycarpi Radicis	Dictamnus dasycarpus
Mu Dan Pi	Cortex Moutan Radicis	Paeonia suffruticosa
Wu Wei Zi	Fructus Schisandrae Chinensis	Schisandra chinensis
Dang Gui	Radix Angelicae Sinensis	Angelica sinensis
Chai Hu	Radix Bupleuri	Bupleurum chinense
Huang Bai	Cortex Phellodendri	Phellodendron chinense
Bai Ji Li	Fructus Tribuli Terrestris	Tribulus terrestris
Jing Jie	Herba seu Flos Schizonepetae Tenuifoliae	Schizonepeta tenuifolia
Chan Tui	Periostracum Cicadae	Cryptotympana pustulata <sup>a</sup>
Fang Feng	Radix Ledebouriiellae Divaricatae	Saposhnikovia divaricata <sup>b</sup>

<sup>a</sup> Also known as *Cryptotympana atrata*.

<sup>b</sup> Also known as *Ledebouriiella divaricata* or *L. seseloides*.

In this case it seems extraordinary that this woman had been taking Chinese herbs for 11 months without any apparent problems for most of this time. This raises several important questions:

- was the prescription changed in the last few weeks? We only have information about the prescription she was taking when she became ill. If we knew that a herb had recently been added, then that herb would be strongly suspect.
- had there recently been a delivery of a new batch of one of the herbs? If so, there may have been problems with the correct identification and preparation of the herbs in the new batch. This would support the suggestion that good quality control is a key issue.

• had some other factor intervened? We do not know whether there had been changes in the patient's diet, or whether she had been stressed or over-tired etc.

**Case 5**

Another case of severe hepatitis was reported in 1994 in the New Zealand Medical Journal<sup>32</sup>. A 37 year old woman presented to her doctor with general malaise. Blood tests showed raised levels of alkaline phosphatase, GGT, ALT and AST, all consistent with liver damage. Over the next two weeks her liver function deteriorated and she was admitted to hospital. The blood levels of liver enzymes rose to very high levels before beginning to gradually decline. Her liver function finally returned to normal seven weeks after the initial presentation. Tests for hepatitis A, B and C were all negative. She had antibodies to Epstein-Barr virus showing that she had been exposed to the virus in the past and was now immune. Tests for other infective agents were negative. Liver biopsy revealed features most consistent with toxic or drug induced liver damage.

Thirteen days before presenting to her doctor, this patient had begun treatment with Chinese herbs for her psoriasis. She drank alcohol rarely and had no history of intravenous injection, blood transfusion or recent overseas travel. Interestingly, she had had a routine blood test three months previously and at this time the liver function tests were normal.

The herbs which were prescribed by the herbal practitioner were as follows. With the exception of *Jianqu* they are given by their Latin pharmaceutical or botanical names in the published report.

Pinyin name	Pharmaceutical name	Botanical name
Qing Dai	Indigo Pulverata Levisa	Processed from: <i>Isatis tinctoria</i> , <i>I. indigota</i> , <i>Baphicacanthus cusia</i> , <i>Polygonum tinctorium</i> or <i>Clerodendron cyrtophyllum</i> <sup>a</sup>
Dan Shen	Radix Salviae Miltiorrhizae	<i>Salvia miltiorrhiza</i>
Wu Wei Zi	Fructus Schisandrae Chinensis	<i>Schisandra chinensis</i>
Bai Zhi	Radix Angelicae Dahuricae	<i>Angelica dahurica</i>
Pu Gong Ying	Herba Taraxaci Mongolici cum Radice	<i>Taraxacum mongolicum</i>
Tu Fu Ling	Rhizoma Smilacis Glabrae	<i>Smilax glabra</i>
Bai Xian Pi	Cortex Dictamni Dasycarpi Radicis	<i>Dictamnus dasycarpus</i>
Wu Mei	Fructus Pruni Mume	<i>Prunus mume</i>
Jian Qu <sup>b</sup>	Massa Fermentata	<sup>b</sup>

<sup>a</sup> The published report names this herb as *Indigo naturalis*. It is not entirely clear whether this was *Da Qing Ye* (*Folium Daqingye*), i.e. the unprocessed leaf, or *Qing Dai*, which is woad - a powder made from the leaf.

<sup>b</sup> More commonly known as *Shen Qu*, this is a non-standardised fermented leaven including various herbs such as *Qing Hao* (*Herba Atermissiae Annuae*), *Xing Ren* (*Semen Pruni Armeniacae*), *Cang Er Zi*

(*Fructus Xanthii Sibirici*) and *Chi Xiao Dao* (*Semen Phaseoli Calcarati*)<sup>22,23</sup>.

**Case 6**

This case is the second fatality to have occurred in the UK. It was reported in a letter to the British Medical Journal in 1995<sup>33</sup>. A 32 year old man was admitted to hospital with fulminant liver failure, otherwise known as massive hepatic necrosis. Within a week of presentation he was deeply jaundiced and went into coma. Liver transplantation was attempted but did not succeed in saving the patient's life. Tests were unable to identify any viral, immunological or metabolic cause of liver failure. Four weeks before presentation the patient had begun treatment with Chinese herbs for lipomas.

The practitioner's notes reveal that the patient was born in India and had a history of jaundice as a child. Apparently he had also had jaundice in his early twenties. He had been prescribed ten packets of herbs and he had taken one packet of herbs a day as instructed. Throughout these ten days he had felt ill and had diarrhoea but he had persisted with taking the herbs. After three weeks he was still unwell and began to become jaundiced. At this point he went to his doctor and was hospitalised.

One of the tragic features of this case is that had this patient stopped the herbs as soon as the diarrhoea began, he would probably still be alive. His death could almost certainly have been prevented if he had been given written and verbal instructions to stop taking the herbs and contact the practitioner if he should develop any symptoms like those of a cold or flu, or any digestive disturbance such as nausea or diarrhoea.

The following is the herbal prescription as taken from the practitioner's notes, with the herbs given by their Chinese names. However, it should be said that the notes are scanty and not completely clear so we can not be entirely sure of the prescription given.

Pinyin name	Pharmaceutical name	Botanical name	Dosage
Bai Xian Pi	Cortex Dictamni Dasycarpi Radicis	<i>Dictamnus dasycarpus</i>	9g
Shan Zha	Fructus Crataegi	<i>Crataegus pinnatifida</i> or <i>C. cuneata</i>	9g
Zhi Ke	Fructus Citri Aurantii	<i>Citrus aurantium</i>	4.5g
Tian Hua Fen	Radix Trichosanthis Kirilowii	<i>Trichosanthes kirilowii</i>	9g
Chen Pi	Pericarpium Citri Reticulatae	<i>Citrus reticulata</i>	3g
Chi Shao Yao	Radix Paeoniae Rubrae	<i>Paeonia veitchii</i> or <i>P. lactiflora</i>	6g
Dang Gui Wei	Radix Angelicae Sinensis	<i>Angelica sinensis</i>	9g
Fang Feng	Radix Ledebouriellae Divaricatae	<i>Ledebouriella divaricata</i> <sup>a</sup>	9g
Bai Zhi	Radix Angelicae Dahuricae	<i>Angelica dahurica</i>	6g
Fu Ling	Sclerotium Poriae Cocos	<i>Poria cocos</i>	12g

Bai Zhu	Rhizoma Atractylodis Macrocephalae	Atractylodes macrocephala	9g
Gan Cao	Radix Glycyrrhizae Uralensis	Glycyrrhiza uralensis	6g

<sup>a</sup> Also known as *Ledebouriella seseloides* or *Saposhnikovia divaricata*.

The School of Pharmacy in the University of London is reported to have consulted a Chinese expert in pharmacognosy about the herbs in this prescription and they concluded that none of the herbs appears to be directly hepatotoxic, which probably points to an immunological mechanism. Further clarification of this report is required.

### Discussion of cases

In many of these cases all the other obvious possible causes of liver damage can be confidently excluded, and it is clear that something about the herbal treatment is the cause of the adverse reactions. Adulteration or misidentification of herbs seems an unlikely explanation since the cases are spread over several years and involved different practitioners, and the herbs have been examined and identified in several cases. The fact that the majority of these cases occurred in the UK may be due to the large number of patients with skin diseases being treated in this country. If we conclude then that something about the herbal treatment is the cause of the adverse reactions, this raises two important questions:

1. are these adverse reactions being caused by a single herb or by several?
2. is the herb or herbs directly toxic to liver cells, or is this an immunological or idiosyncratic reaction?

A careful examination of these prescriptions shows that one herb is common to them all, namely *Bai Xian Pi* (*Cortex Dictamni Dasycarpi Radicis*), and it has been suggested that this herb may be the cause of the hepatitis<sup>33</sup>. Since this herb is mostly used to treat skin disease, this would explain why these cases of liver damage have been confined to patients being treated for skin disease.

However, there are no reports in the literature of *Bai Xian Pi* being directly hepatotoxic, and this includes a recently published Chinese language pharmacopoeia which gives details of animal research and clinical studies on this herb<sup>34</sup>. So if *Bai Xian Pi* is involved, the mechanism would appear most likely to be a rare allergic hypersensitivity and not direct toxicity.

We should note that in two of the above cases (Cases 1 and 3), patients experienced a much more rapid adverse reaction when they re-started the herbs a second time. This is also strongly suggestive of an allergic mechanism.

In two controlled clinical trials examining the benefits of Chinese herbs in the treatment of eczema<sup>24,25</sup>, all participants were given liver function tests and there were no reports of problems. *Bai Xian Pi* is one of the ten herbs contained in the standardised herbal remedy *Zemaphyte* which was used in these studies. However, the relatively small numbers involved in these trials make it difficult to

draw firm conclusions, and further clinical research is clearly needed.

It has been pointed out by practitioners that probably as many as 70-80% of prescriptions for skin disease contain *Bai Xian Pi*. It is possible that this is the reason why this herb occurs in each of the above prescriptions, and that the causes of the hypersensitivity reaction are more complex. Certainly, it has been suggested that several herbs can be involved in immunological reactions<sup>35</sup>, and patients with atopic conditions such as eczema or with a history of liver disease might be particularly vulnerable to such reactions. In case 3 in particular, it is clear that other herbs in the prescription could have been involved in the toxic effect. We should therefore be cautious about attributing all these cases of hepatitis to a single herb when there are so many other variables.

In conclusion, it appears almost certain that the hepatotoxic effect which occurred in these cases was of an immunological type and was not due to a herb which is directly hepatotoxic. This has two major implications: firstly, that the toxic effect is probably not dose-related, and secondly that these sorts of herbal prescriptions are only potentially toxic to certain individuals who have an allergy-like sensitivity to them, and do not do any harm at all to the vast majority of people. The problem is to devise strategies to protect those individuals who do have this immunological sensitivity.

Chinese herbs are widely used in the UK for the treatment of eczema and psoriasis, so it is clear that the incidence of adverse events is quite low, probably affecting one person in tens of thousands. Most individuals definitely appear to tolerate the herbs without apparent harm, and the clinical trial results support this conclusion. The problem is that when the adverse reaction does occur it can clearly be life-threatening. No-one fully understands the mechanisms of such idiosyncratic reactions, which are also known to occur with some drugs. It is generally suspected that there can be a genetic susceptibility which makes some individuals vulnerable.

It is noteworthy that both of the fatalities involved people of Indian origin. This may indicate a genetic susceptibility, or it may be that both these individuals already had compromised liver function, perhaps as a result of infectious hepatitis earlier in life. In any case, it is clear that people with poor liver function will be particularly at risk.

However, great caution is undoubtedly needed with all patients. In Case 5 above the woman is known to have had perfectly fine liver function three months previously, but she nonetheless developed severe hepatitis and was hospitalised after taking the herbs for only 13 days.

In the light of the above, the RCHM has taken the view that whatever the precise mechanisms and whether or not a single herb is the cause, the first priority is to protect future patients. The second fatality in particular (Case 6) could almost certainly have been prevented by good practice, and the RCHM has emphasised this by issuing the following



updated guidelines<sup>36</sup>:

- A detailed case history is essential to determine whether there is any history of jaundice or hepatitis. Where there is such a history, patients must be closely monitored and this must include liver function tests.
- Although hypersensitivity reactions are not directly dose-dependent, continuing caution with dosage is advised for the time being.
- Patients should be carefully monitored, and in particular practitioners should be alert to any early signs of liver damage<sup>37</sup>.
- All patients should be given written guidelines warning them to stop taking their herbal medicine and immediately contact their practitioner if they experience symptoms such as nausea, vomiting, diarrhoea, flu-like symptoms, and hypochondriac tenderness.

The practitioners involved in the six cases reported above appear to have been fully trained, but five of the six were not members of the RCHM. In the one case where the practitioner was a member of the RCHM, the Register's guidelines had not been followed. Although the numbers are too small to allow firm conclusions, this may reflect the fact that a good level of training is not in itself enough to ensure safe practice, but must be complemented with membership of a professional body with Codes of Ethics and Practice, complaints procedures, and channels of regular communication to keep members informed.

A possible addition to the RCHM's guidelines would be for practitioners to take care to closely monitor patients who consume a lot of alcohol, and this should probably include liver function tests. Practitioners should also be aware that immunoallergic effects are often much worse on re-exposure to the medicine. A patient who has experienced suspicious symptoms and stopped taking their herbs may experience a much more rapid and more severe reaction if they begin to take the herbs again at a later date. Cases 1 and 3 are good examples of this.

It is important to stress to practitioners, most of whom have not experienced any problems with their own patients being adversely affected, that this does not mean that there is not a problem. Since it is probable that only one person in every few thousand is vulnerable to liver damage from the herbs, this would mean that one would have to treat five or ten thousand people before one would expect (statistically) to have one patient become ill with liver damage.

It has been suggested by some agencies that all patients being treated with Chinese herbs should receive routine blood tests for liver damage<sup>38</sup>. However, most practitioners are resistant to this idea, on grounds of cost and inconvenience to patients and because many patients dislike giving blood samples. It is also true that several prescription drugs carry small risks of liver damage but continue to be used without resort by doctors to liver function testing of all their patients. This illustrates the point that adequate training and good practice are the keys to patient safety.

It is unfortunate that we do not have enough details on

these cases to enable us to analyse them in terms of a Chinese medicine approach to the individual's patterns of disharmony. It is possible that factors in patients' diet or lifestyle or constitution may make them more vulnerable to hypersensitivity reactions to some herbs.

It has also been suggested that the overall balance of the prescriptions may be inappropriate in some way, and in particular that they may be focused too much on clearing pathogenic factors and may not do enough to support the Spleen or the Liver. However, many experts on herbal dermatology in China feel that focusing on the pathogenic factors is the correct strategy. Certainly it is true that some of the prescriptions given in these six cases are quite strongly draining, but the prescription used in Case 6 contained a number of herbs to support the Spleen, and the prescription used in Case 2 contained a number of herbs to support blood and yin. Another possible factor is that a high overall dosage of herbs may put additional stress on the Spleen in particular. In addition, it has been suggested that herbs which modern research has shown to have hepato-protective effects should be added to our prescriptions for skin diseases. There is a need for further discussion and debate of all these questions within the profession.

Another question arising from these cases is the absence of reports of liver damage in patients receiving treatment for skin diseases in modern China. It is striking that Case 4 above is of a Chinese woman, so there does not appear to be anything in the way of genetics or diet protecting Chinese patients. The most likely explanation is that hepatitis A and B are endemic in China anyway. It is entirely possible that if there are occasional cases of herb-induced hepatitis in China these are assumed to be infectious in origin and the true cause is missed.

A clear lesson from these tragedies is that the profession must urgently organise national and international reporting mechanisms in order to detect adverse effects from Chinese herbs quickly and effectively. Accurate information is most important. In the UK we are now seeing good levels of co-operation between the profession and bodies such as the National Poisons Unit and Schools of Pharmacy, which will help to improve the flow of information in both directions.

The second lesson is that good patient management is essential. In particular we can identify the following:

- good communication with patients. Patients must be warned both verbally and in writing of potential adverse effects and of the importance of stopping the herbs and contacting their practitioner should these occur.
- regular monitoring of patients. Patients should be seen every week or two at first and generally never less than every four weeks. Appointments should last for at least 15 minutes to allow time to fully review each case.

Finally, it is important to remember that Chinese herbal treatment has been shown to be remarkably effective for stubborn and unpleasant skin diseases such as eczema, which cause a great deal of suffering and distress<sup>24,25</sup>. Our

aim must be to continue to offer this beneficial treatment while protecting potentially vulnerable individuals from unnecessary and avoidable harm.

### Conclusion

In conclusion, we can see that the vast majority of adverse events involving Chinese herbs which have been reported in the literature can be avoided by the following measures:

- Chinese herbs should only ever be prescribed by fully trained practitioners of Chinese herbal medicine, in accordance with a traditional individualised diagnosis. Training of practitioners should include the ability to monitor for and recognise adverse effects. The RCHM has begun the task of establishing agreed educational standards in the UK and this is clearly a matter of some urgency. Professional bodies will increasingly need to be able to guarantee minimum standards of practice and to enforce codes of ethics and practice, and legal protection of title and self-regulation will be necessary to achieve this.
- Chinese herbs should be prescribed in the traditional manner, according to an individualised diagnosis based on the theory and practice of Oriental medicine. The herbs should be used according to their traditional indications and in established combinations.
- There should be compulsory Codes of Practice for practitioners which include many of the recommendations made in this paper, including requirements to monitor patients regularly, to arrange regular blood tests before treating patients with a history of liver diseases, to fully inform patients, etc. In the case of the RCHM such a Code already exists, but membership is entirely voluntary and as a result disciplinary procedures are weakened and some practitioners do not join at all.
- Whenever it is proposed to use herbs in novel ways, for example in the form of chemical extracts, or for symptomatic treatment, then careful and thorough clinical research and monitoring must be undertaken. A similar caution should be applied to the prescribing of obscure or unusual herbs.
- A handful of herbs traditionally known to be seriously toxic, such as *Cao Wu* and *Wu Tao*, should probably be restricted to use in hospital settings only.
- A number of herbs with some potential for toxicity, such as *Fu Zi*, should probably be restricted to use at specified doses by fully trained practitioners only. Herbs with some potential for toxicity should not be prescribed for patients who are also taking modern drugs.
- Proper identification and quality control of herbs by manufacturers and suppliers is a key ingredient in enabling the safe practice of Chinese herbal medicine. A minimum requirement would probably be the examination by microscopy and chromatography of each batch of herbs by trained pharmacognosts.
- Suppliers should not make available patent medicines whose ingredients are not certain, and practitioners should not prescribe them.

It is interesting to note that these suggestions are similar to the recommendations of the Report of the Working Party on Chinese Medicine appointed by the Secretary for Health and Welfare in the Hong Kong administration. The recommendations include: the registration of herbal practitioners; the creation of a list of "potent herbs" which should only be available with a prescription from a herbal practitioner; licensing of the processing, manufacture, import and distribution of raw herbs and patent medicines; and improvements to the training of both practitioners and dispensers<sup>39</sup>.

We should remember that adverse effects from Chinese herbs are rare. In Hong Kong, where the use of Chinese herbs is both widespread and unregulated, it has been shown that only 0.2% of the general medical admissions to the Prince of Wales Hospital were due to adverse reactions to Chinese medicine, as compared to 4.4% of admissions caused by Western pharmaceuticals<sup>40</sup>. As we have seen, improvements in quality control and in the training and regulation of practitioners would substantially reduce the already low incidence of problems involving Chinese medicine. These improvements will assist greatly in establishing Chinese herbal medicine in the West as a safe and effective form of treatment.

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### **Biography**

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