



The Safety of Chinese Herbal Medicine and How it is Reported – Serious Safety Concerns or Mere Chinese Whispers?

Aims, Objectives and Rationale

It is our perception that the safety of Chinese herbal medicine is often unfairly reported in the media and medical journals. This led us to investigate one event concerning an adverse reaction to a Chinese herbal formula in 2010. We set out to:

- Look at how one high profile event concerning the safety of Chinese herbal medicine was conveyed, and identify any significant reporting bias.
- Determine whether this event gives cause for concern about the safety of Chinese herbal medicine in day-to-day practice in the United Kingdom.
- Develop a more thorough understanding of the complexity of the pathogenesis of aristolochic acid nephropathy (AAN) in order to acquire a balanced and less biased assessment of the contrasting evaluations in the scientific, medical and Chinese medicine journals and literature.
- We postulate that in developing and presenting this understanding, practitioners of Chinese medicine (prospective and practicing) might be better informed about adverse drug reactions (ADRs) and in turn, more equipped to respond to any subsequent issues concerning toxicity, regulation and the legislative process in the future.

“Spot Treatment Gave Woman Cancer, Court Told”¹

Introduction and Context

Patricia Booth took Long Dan Xie Gan Wan for 5 ½ years and developed renal failure and urothelial carcinoma. The case went to court in 2010. The herbal formula contained Mu Tong *Aristolochia manshuriensis*, which contains aristolochic acids (AAs), a known nephrotoxic and carcinogenic substance¹. Plants and herbs containing AAs were banned in 1999².

The following events took place...

1997	Between 1997 and 2002 Patricia Booth took Long Dan Xie Gan Wan for her acne
2002	November. she stopped taking the remedy because she felt ill
2003	February. Tests showed she had chronic long-term kidney failure and she went on dialysis
2006	She developed cancer of the urinary tract and had major surgery to remove it
2008	She had a heart attack and survived
2010	She was on dialysis 3 times a week and waiting for a kidney transplant. ¹ The verdict: Ying Wu was given a 2 year conditional discharge. ³ The judge stated that the case demonstrated the need for regulation of the profession ⁴

The Formula

The pills were analysed and found to contain aristolochic acid³ which has been a banned substance since 1999 and a prescription only medicine since 1997².

Long Dan Xie Gan Wan (<i>Gentiana Longdancao</i> Decoction to Drain the Liver)	
Long Dan Cao	<i>Radix Gentianae Longdancao</i>
Huang Qin	<i>Radix Scutellariae Baicalensis</i>
Zhi Zi	<i>Fructus Gardeniae Jasminoidis</i>
Chai Hu	<i>Radix Bupleuri</i>
Mu Tong – contains AA	<i>Aristolochia manshuriensis</i>*
Che Qian Zi	<i>Semen Plantaginis</i>
Ze Xie	<i>Rhizoma Alismatis Orientalis</i>
Sheng Di Huang	<i>Radix Rehmanniae Glutinosae</i>
Dang Gui	<i>Radix Angelicae Sinensis</i>
Gan Cao	<i>Radix Glycyrrhizae Uralensis</i> ⁵

* Please see later discussion, ‘What Other Relevant Issues Does This Case Give Rise To?’

“Traditional Chinese Practitioner Breaches Medicine Act”³

History of Aristolochic Acids:

1960s	Tested for antitumor effects and shown to be nephrotoxic ⁷
1980s	Shown to have carcinogenic and mutagenic properties ⁷
1993	Over 100 cases of irreversible nephropathy in Belgium slimming clinic that used Chinese herbs mixed with pharmaceutical preparations ⁸
1997	Became a prescription only medicine ⁴
1999	Became a banned substance ⁴
2002	Herbal remedies containing aristolochia shown to be carcinogenic ⁹
2012	The International Agency for Research on Cancer ^{10 (p13)} concluded that, ‘Plants containing aristolochic acid cause cancer of the renal, pelvis, and of the ureter.’

“Chinese Herbal Pills Gave Woman Cancer Court Hears”⁴

Should Aristolochic Acids Carry All the Blame?

- Dharmananda¹¹ argues that, ‘Ultimately, all herbs are toxic at some dosage level, and that all herbs contain ingredients that can be shown to be carcinogenic or mutagenic in a laboratory test.’ However in email correspondence with Dr. Debbie Shaw (government adviser on toxicity and herbal medicines), this argument was refuted; she argued that there is now sufficient clinical evidence regarding the toxicity of AAs.
- Blackwell¹² and Maciocia¹³ argue that in the 1993 Belgium incident, the potential drug-herb interactions were never investigated. Dr. Shaw has subsequently contested this argument, stating that possible ADR’s of the associated pharmaceuticals was tested and no association was found, ruling out therefore, the possibility of ‘inhibition’. Nevertheless, the assignment of the term of “Chinese Herbs Nephropathy” appears somewhat spurious.

“Chinese Medicine Has Caused Kidney Failure and Even Cancer. So How Safe are These Popular ‘Cures’.”⁶

How Does this Affect the Practice of Chinese Herbal Medicine?

The following have been banned^{14 (p 2)}:

‘...any medicinal product consisting of or containing a plant (a)-

(a) belonging to a species of the genus *Aristolochia*; or

(b) belonging to any of the species-

- Akebia quinata*
- Akebia trifoliata*
- Clematis armandii*
- Clematis montana*
- Cocculus laurifolius*
- Cocculus orbiculatus*
- Cocculus trilobus*
- Stephania tetrandra*.



Aristolochia Species – Those plants belonging to family *Aristolochiaceae*. Frequently found in CHM to include:-

Table with 4 columns: Aristolochia Species, Part Used, Pin Yin, Classical Categorisation and action. Rows include Aristolochia fangchi, Aristolochia manshuriensis, Aristolochia contorta, and Aristolochia debilis.

It is clear that exponents of Chinese herbal medicine assign different members of the Aristolochia species to same pinyin nomenclature. This reflects a practice of substituting one herb from within a given species with another. For example, the fruit of A. contorta and A. debilis may be substituted for one another and ascribed the name Ma Dou Ling, whilst the herb part of A. contorta and A. debilis is traded as Tian Xian Teng²¹⁻²⁵.

Aristolochic Acids and Aristolactams:

Aristolochic acids are the toxic components of *Aristolochic Species*. In terms of CHM the two most commonly discussed variants are Aristolochic Acid I (AA-I) and Aristolochic Acid II, (AA-2) but it is the former (AA-I) that appears to be associated with the development of AAN²⁷.

Aristolactams can be found occurring naturally in Aristolochia species but their presence within humans is generally the product of the detoxification of AA. Aristolactam I is metabolite of Aristolochic Acid I, which subsequently and upon activation, forms DNA-adducts. These in turn induce mutation and can lead the evolution of urothelial carcinoma^{21 & 28}.

Table with 4 columns: Botanical Name, Part Used, Pin Yin, Classical Categorisation and action. Rows include Asarum heterotropoides, Asarum sieboldii, and Asarum sieboldii.



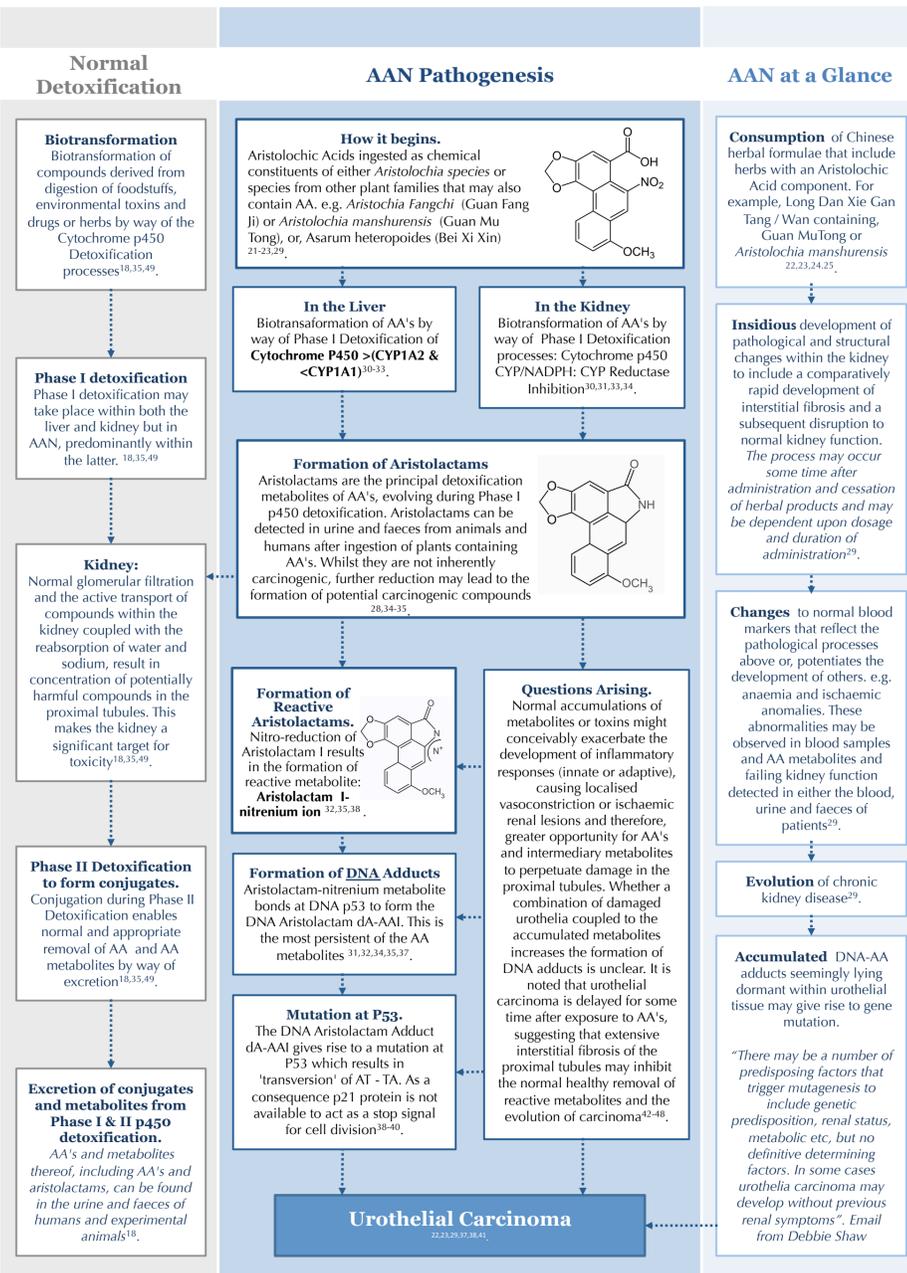
Other Chinese Herbs purported to contain AA's

A comparative study on the AAI content of Xi Xin root and aerial portion demonstrated that levels of AAI in the root of Xi Xin was negligible whilst levels in the aerial portion were higher. (0.3270.021microg/g (aerial) to 0.0870.06 microg/g (root))²⁶. The study also demonstrated that alcoholic (methanolic) extracts contained more AA1 than water extracts. The authors recommended that the herb be administered by way of water decoction. An earlier study undertaken by Jong, T. et al²⁷, reported that AA I content of nine *Asarium species* varied from 3.3ng/mg – 3376.9 ng/mg in alcoholic extracts^{26 & 27}.

RCHM VOLUNTARY RESTRICTIONS AND CAUTIONS:

Due the presence of Aristolochic Acid in Asarum species the RCHM has issued a voluntary ban on the use of: XI XIN (Asarum species)

The Scientific Evidence



Epidemiological Evidence

Aristolochic Acid Nephropathy and Balkan Endemic Nephropathy

Independent research undertaken to determine the underlying aetiological causes Aristolochic Acid Nephropathy (ANN) and the Balkan Endemic Nephropathy (BEN) yielded some profound similarities. Epidemiological evidence, including the clinical presentation of patients and histological findings, strongly support the view that ANN and BEN share the same aetiological factor, namely AA. This proposition has been substantiated by clear evidence that patients suffering from both conditions, and who in addition have developed urothelial carcinoma, also present with dA-AAI adducts in kidney tissue. It has been postulated that patients from the Balkan cohort may have been subjected to AA ingestion by way consumption of bread, produced from locally grown wheat that had grown and comingled in fields with *Aristolochia clematis*. This strongly supports the hypothesis that herbs or plants containing AA are the aetiological factors in the development of gross anatomical, histological and genetic renal abnormalities^{50,51}.

A comparison of the characteristics of Balkan Endemic Nephropathy and Aristolochic Acid Nephropathy.

Comparison table between BEN and AAN or CHN. Columns include Epidemiological characteristics, Geographic distribution, Family history, Sex distribution, Clinical characteristics, Progression to end-stage renal disease, Associated urothelial malignancies, and Histopathological characteristics.

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China and Taiwan.

A retrospective follow-up study undertaken by Chinese researchers in Taiwan of a random sample of nearly 200,000 people, concluded that a prescription of more than 30g of Mutong and 60g of Fangchi was associated with an increased risk of developing chronic kidney disease (CKD). Ruling out other confounding factors such as age, sex, hypertension and diabetes, and the use of non-steroidal anti-inflammatory drugs and paracetamol, the researchers demonstrated a dose dependent relationship between consumption of these herbs and the incidence of CKD⁵².

In a separate paper the same researchers demonstrated that a dose response relationship between the ingestion of more than 60g of Mutong (equivalent to 150mg of Aristolochic Acid) and the development of urinary tract carcinoma⁵³.

A longitudinal study undertaken in China between 1997 and 2006 (involving 300 patients with a AAN diagnosis), demonstrated that taking a high dose of AA-containing medication (AACM) frequently induced irreversible non-oliguric acute tubular necrosis and subsequent progressive renal failure. Long-term ingestion of AACM, either intermittently or continuously, resulted in insidious chronic interstitial tubular nephropathy whilst short-term consumption of a low dose resulted in abrupt tubular dysfunction. Interestingly, the researchers also suggested that the accumulation and high concentration of AAs in the kidney is one of the main deciders for the rapid progression of renal dysfunction in AAN patients and this may in part, be due to mechanisms that prevent the repair of tubular epithelial cells and therefore tissue⁵⁴.

What Other Relevant Issues Does This Case Give Rise To?

- **Nomenclature** - Mu Tong can have a number of herbal substitutions that will still be assigned and prescribed with the same Pin Yin nomenclature. One of these herbs is a species of Aristolochia, which is toxic; some of the other substitutions are harmless. There have been cases where pin yin names are very similar and have been confused with one another, with disastrous consequences¹⁵. A simple resolution for this is to use the binomial Latin naming system¹⁶.

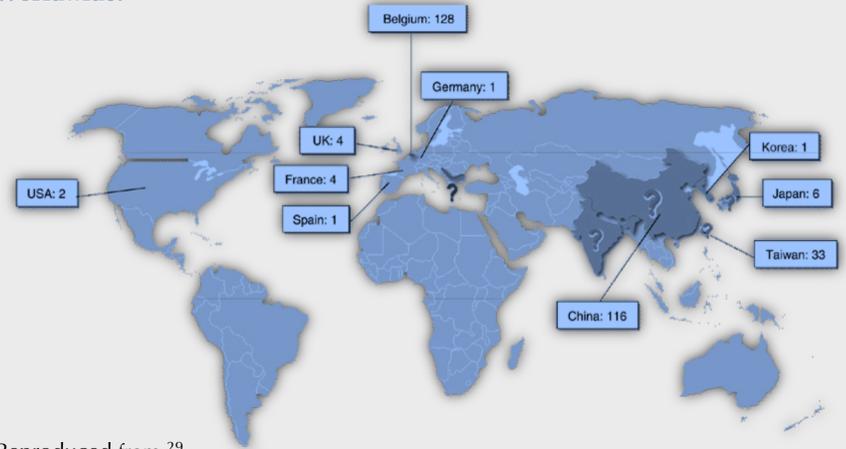
Botanical Name	Part Used	Pin Yin	Classical Categorisation
<i>Aristolochia manshuriensis</i>	Stem	Guan Mu Tong	
<i>Clematis armandii</i>	Stem	Chuan Mu Tong	Promotes Urination, directs fire and heat downward and out through urine, facilitates lactation and unblocks blood stasis ²⁴ .
<i>Clematis Montana</i>	Stem	Chuan Mu Tong	
<i>Akebia quinata</i>	Stem	Bai Mu Tong	
<i>Akebia trifoliata</i>	Stem	Bai Mu Tong	

- **Product Quality** – Although not directly related to this case, this is a common cause for safety concerns. Herbs can be contaminated with heavy or toxic metals, or can be adulterated for economic reasons¹⁷. However, according to a letter that the Register of Chinese Herbal Medicine (RCHM) sent out to its’ members in 2012 (personal communication with Emma Farrant), there have been no reported cases of contamination of Chinese herbs with heavy or toxic metals in the last 10 years.
- **Regulation = Safety.** After interviews with Michael McIntyre (Chair of the European Herbal and Traditional Medicine Practitioners Association) and Emma Farrant (Chief Executive Officer of the Register of Chinese Herbal Medicine RCHM) it became apparent that without regulation, a similar occurrence to the Patricia Booth incident might easily happen again. The judge who ruled on the case suggested that regulation of the profession was needed³.
- **A better-informed profession.** The education (first entry or continuing professional development) of practitioners of Chinese herbal medicine needs to instil a comprehensive understanding of adverse drug reactions (ADR’s) and the implication of a ‘Delayed’ or ‘End-of-use’ ADR and in turn, the need to monitor patient progress or by contrast, deterioration.

This will lead to safer practice, as clarified by Bibi^{18 (p 3)} ‘Thus, understanding the mechanism underlying drug interactions is useful, not only in preventing drug toxicity or adverse effects, but also in devising safer therapies for disease.’ In email correspondence to Dr. Shaw she explains the need for the profession to be better educated in these issues:

‘With the current/future legislation, as health professionals, knowing the risks and having risk management plans in place is a key to dealing with the authorities. Few herbs are banned or restricted and it is up to you professionals to keep it that way - and that will be a challenge.’

Worldwide:



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Due to the insidious nature of ANN, poor reporting and equally the delayed diagnosis and association of CKD with AAN, these statistics are likely to be conservative; Yang’s study for example, reported the evaluation of 300 patients with AAN. However, Zhang, L. et al (2012) suggests there is an estimated 119.4 million people with CKD in China. In spite of the multifactorial and aetiology of CKD, Gokmen, M and Lord, G (2012), appear to suggest that AAN maybe responsible for the increased prevalence of CKD in China^{55,56}.

Has This Been Fairly Reported?

Whilst reporting may appear biased and misrepresentative of Chinese herbal medicine per se, it is clear that AA is nephrotoxic and carcinogenic, so in this case it was fairly reported. However it is worthwhile comparing herb related ADR’s with drug related events. Lazarou et al¹⁹ found that adverse reactions to pharmaceutical drugs are the fourth most common cause of death in the USA, and that this has been the case for the last 30 years. According to the World Health Organisation monitoring centre (cited in Maciocia¹³), the total number of adverse reactions to herbs in the last 20 years, worldwide is 8984. Whereas, according to Lazarou et al¹⁹ the total number of fatal adverse reactions to pharmaceutical drugs in one year, in the USA was 106,000. According to McCarthy^{20 (p 4)}:

“Adverse reactions to herbs attract a disproportionate amount of attention in the media when compared to the scale of adverse reactions to orthodox drugs”.

Conclusion

The actual case of Patricia Booth was fairly reported; all relevant information was presented clearly and the claims that were made regarding toxicity appeared to have some factual basis. However it would seem that it is common practice for both the general press and medical literature to indiscriminately assign the attributes of a one Chinese herb to the collective practice of Chinese medicine; rather than naming the specific nephrotoxic herb, the headlines use generic terms such as, Chinese (herbal) medicine. This raises questions about racial bias or possible agendas that seek to undermine an alternative tradition. The high profile that this story received in the media, compared to what we actually know about the adverse reactions to pharmaceutical medications in general, appeared somewhat unfair. By contrast, according to McCarthy²⁰, there were 26,000 times more fatalities from medical misadventure and pharmaceutical drugs, than from herbal medicine. This is obviously not proportionally reported in the press. There are definite safety issues when using Chinese herbal medicine, but with more stringent regulation these concerns would be greatly reduced, and certainly in this case, Patricia Booth would not have suffered kidney failure and cancer.

The evidence accrued from the vast array of research that has been undertaken to determine the underlying pathological process behind nephropathy, (including interstitial fibrosis, chronic kidney disease and urothelial carcinoma), strongly confer that the most consistent culprit in this event is Aristolochic Acid. Epidemiological evidence and an ever-increasing prevalence of AAN events worldwide, that are independent of other concomitant ADR’s, environmental sources or biological predisposition, currently provide incontrovertible evidence for a justified removal of herbal medicines containing the substance.

Whilst far too many people have suffered as a result of inadvertent consumption of this nephrotoxic and carcinogenic substance, practitioners of Chinese herbal medicine might learn from the accrued evidence in the hope that comparable events are avoided in the future.

“Thus, understanding the mechanism underlying drug interactions is useful, not only in preventing drug toxicity or adverse effects, but also in devising safer therapies for disease”.¹⁸

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