

Did the Herb Cause This?

Myths and Facts about Chinese Herbs

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Introduction

Reflecting on my years of involvement as a clinician, clinical teacher and investigator in Traditional Chinese Medicine (TCM) studies and information service, I venture to address something fundamental but of great concern to all of us in this article.

The training of medical students and junior doctors has deeply indoctrinated in them the routine of asking “Do you take any traditional medicine?” during history-taking, which is a good practice. However, that would lead nowhere as most will not know what to do if the patient indeed produces a list of recently ingested herbs. The simplest reaction is then, “you better stop taking them”.

I would thus like to share here some facts and also dispel some myths in the safety of TCM herb consumption.

Does that stuff contain steroids?

In Singapore General Hospital (SGH), a Traditional Medicine Information Service (TMIS) was established in 2011 as an extension to the Drug Information Service of the Department of Pharmacy, ceasing operation in 2015 when funding ended. TMIS handled enquiries on traditional medicine from healthcare professionals and provided evidence-based information. One of the commonly asked questions was whether the herbal formulation or product contained steroids. We in the service conducted a comprehensive search of medical literature from PubMed, China National Knowledge Infrastructure and the Health Sciences Authority’s (HSA) websites for evidence of herbs or herbal products that have been studied for their potential glucocorticoid, mineralocorticoid, androgenic or oestrogenic activity.¹

Liquorice root (*Radix glycyrrhizae*, 甘草) is a commonly used herb in many TCM formulations. Pseudoaldosteronism has

been caused by liquorice consumed at high doses; unfortunately, a safe dose is elusive due to the highly variable glycyrrhizic acid content in the different preparations, and the wide interindividual susceptibility to its side effects.² Contrary to common belief, ginseng (*Radix Panax ginseng*, 人參) – which is widely used even in the west and hailed as the panacea by some, has not been reported to cause Cushing’s syndrome, even though some of the ginsenosides are ligands of glucocorticoid receptor.³ In fact, a comprehensive search of the literature failed to find good evidence of glucocorticoid activity in any commonly prescribed herbs used in TCM.¹

Deer musk (*Moschus*, 麝香) and deer antler (*Cornu cervi pantotrichum*, 鹿茸) contain naturally occurring androgens.^{4,5} Both ginseng and Chinese angelica (*Radix Angelicae sinensis*, 当归) have been implicated to cause gynaecomastia in case reports.^{6,7} However, when studied in placebo-controlled, double-blind clinical trials for post-menopausal symptoms, both did not demonstrate clinical estrogenic activity of inducing menstruation.^{8,9}

In contrast to the paucity of evidence of corticosteroidal effect in raw herbs, glucocorticoids have been reported time and again as one of the several adulterants added to herbal formulations and sold as Chinese proprietary medicine (CPM). In Singapore, the import and local sale of CPM is subjected to testing and pre-marketing approval by the HSA,¹⁰ but consumers may obtain products with various health claims from overseas and local black markets. A list of those investigated can be found in the HSA’s Illegal Health Products Database (<http://bit.ly/2Trjey9>), as well as press release archives. Besides glucocorticoids, nonsteroidal anti-inflammatory drugs, antihistamines, sedatives and sex-

enhancing drugs are commonly found adulterants in such products.¹¹

Did that herb cause the bleeding?

Another question frequently asked involves the potential antiplatelet or anticoagulant effects of herbs with “blood activating” activities by their traditional indications. While the antihaemostatic function of some herbs, such as red sage root (*Radix Salviae miltiorrhiza*, 丹参) and notoginseng (*Radix notoginseng*, 三七) were studied and proven,^{12,13} such knowledge on many other commonly used herbs, including the innocent herb Cordyceps (*Cordyceps sinensis*, 冬虫草) implicated for fatal post-operative bleeding not so long ago, is still seriously lacking, as most were based on in vitro or mice data which cannot be extrapolated to actual clinical effect. Between 2013 and 2014, we at SGH conducted a randomised, double-blind, placebo-controlled study on the antihaemostatic effects of three common health supplements: turmeric (*Curcuma longa*, 姜黄), ginseng and Chinese angelica. Based on in vitro studies, the reputable *Natural Medicines Comprehensive Database* assigned these herbs with a “moderate” and “high” severity risk of bleeding when used with anticoagulant or antiplatelet.

In the 25 healthy volunteers studied for each herb, there was no derangement in platelet count, coagulation and platelet function (with a few exceptions for the latter) with these herbal products used as single agent alone for three weeks, neither did they further aggravate the effect of aspirin when consumed together with aspirin. There was no bleeding observed in the 75 participants studied.¹⁴ This provided level 1 evidence on the lack of antihaemostatic effect of these commonly used herbs and more importantly, testified to the fact that in vitro observations cannot be extrapolated to clinical effect.

Can herbs cause haemolysis?

The topic of herb and haemolysis brings to memory the 30-year ban on two commonly used herbs, coptis root (*Rhizoma coptidis*, 黄连) and phellodendron bark (*Cortex phellodendri*, 黄柏), as the berberine content was implicated in neonatal jaundice (NNJ) based on circumstantial evidence.¹⁵ There is conflicting data on the potential of these berberine-containing herbs in causing haemolysis. G6PD-deficient red cells become susceptible to haemolysis when incubated with coptis root extract.¹⁶ Paradoxically, the prevalent Chinese folk tradition of feeding boiled coptis root to neonates for reducing NNJ enabled a retrospective analysis on 122 G6PD-deficient neonates admitted for NNJ. The 62 with history of post-natal consumption of coptis root had a significantly delayed onset of NNJ of 3.2 days (likely due to displacement of bilirubin from protein binding) compared to 2.07 days in the 60 without herbal exposure, with one and two cases of death due to kernicterus respectively.¹⁷ In a clinical study from Taiwan comprising 22 neonates in the study group and 23 in the control group, where three and four were G6PD deficient respectively, feeding with coptis root liquid as a single agent for three days from 20 hours of life for the study group did not result in acute haemolysis or any other adverse effects.¹⁸ In 2013, HSA concluded that there are no major safety concerns with appropriate use of both herbs and lifted the ban, but cautioned that it should still be avoided in infants, G6PD-deficient individuals, and pregnant and breastfeeding women (<http://bit.ly/2YJZC2J>).

As for other herbs, haemolysis has been reported with the intravenous administration but not oral ingestion of pueraria root (*Radix puerariae*, 葛根),¹⁹ a herb commonly used in cold remedies. Cases of haemolysis after ingestion of CPM containing lead and arsenic have also been reported. In this regard, the readers can be assured to know that heavy metal (arsenic, copper, lead and mercury) content of CPM is tightly regulated by HSA.¹⁰

Are herbs toxic to liver, kidneys or other organs?

Organ toxicity can be caused by the inherent toxicity of the herb, improper usage, idiosyncratic response, unintentional contamination, substitution or adulteration. "Chinese Herb Nephropathy" is the unfortunate term coined after the substitution of

aristolochia fruit (*Aristolochia fangchi*, 广防己) for tetrandra root (*Stephania tetrandra*, 汉防己) in slimming clinics in the Europe in the 1990s, which led to interstitial nephritis, renal failure and urothelial carcinoma.²⁰ There are other herbs that contain aristolochic acids,²¹ but we can be assured that these herbs are banned by HSA locally and in many other countries. One other well-recognised herb with renal toxicity is thunder god vine (*Tripterygium wilfordii*, 雷公藤), used for its anti-inflammatory activity to treat nephritis, lupus and rheumatoid arthritis.²² Heavy metals present in plants and minerals can potentially cause nephrotoxicity too.

Liver toxicity has been repeatedly reported for the commonly used herb fleecflower root (*Polygonum multiflorum*, 何首乌),²³ which is used for its purported anti-ageing effect. Dioscorea tuber (*Rhizoma Dioscoreae bulbiferae*, 黄药子), a herb used for inflammation, oncology and thyroid disease, is known to cause hepatitis.²⁴ Xanthium (*Fructus Xanthii*, 苍耳子) is a common herb used after processing for rhinitis and sinusitis, but its raw form in large quantity results in acute and chronic systemic toxicity, including hepatotoxicity.²⁵ Certain herbs contain pyrrolizidine alkaloids which can cause veno-occlusive disease.

Other well-studied toxicities include aconitine in unprocessed aconite root (*Aconitum carmichaelii*, 附子) used for its analgesic and cardiotoxic properties. Aconitine poisoning resulting from overdosing or inappropriate processing of herbs before consumption can cause cardiovascular, gastrointestinal and neurological toxicities.²⁶ Unprocessed bitter almond (*Semen armeniacae amarum*, 杏仁) can cause cyanide poisoning. Abuse of ephedra (*Herba Ephedrae*, 麻黄) for its thermogenic and stimulatory effect has been reported to cause sudden cardiac death.²⁷ As with any drugs, herbs may also cause allergic rash.

Therefore, most of the toxicities as illustrated above are avoidable when herbs are prescribed with correct identification and consumed in properly processed form, at recommended dosage and duration. Some are unavoidable due to idiosyncratic reaction. A busy clinician is understandably unable to spend additional effort going in depth into such issues. This is an area of unmet need where an information service such as TMIS could serve to provide valuable information and help solve clinical puzzles.

Similar to the case of steroids, in contrast to the infrequent toxicity attributable to the inherent pharmacological activity of herbs, of much higher prevalence is adverse reaction due to adulterant present in formulation, as mentioned above. A review by the HSA on adverse events associated with complementary and alternative products revealed serious events due to adulterants mostly consumed for sexual performance enhancement, pain relief and slimming purposes.¹¹ Strictly speaking, these should not come under adverse effect of TCM, but unfortunately in the local context, this has to be brought to the readers' attention and emphasised to rectify misconceptions.

Is it safe to take herbs together with drugs?

Drug-herb interaction is an area of great concern for doctors and patients alike. However, while drug-drug interaction is well studied, the knowledge in drug-herb interaction, especially TCM herbs (in contrast to herbs used in Western folk medicine), is seriously lacking. The usual advice of taking them "two hours apart" (or even four hours) instructed by most TCM practitioners addresses only interaction in the stomach. However, besides absorption, there are downstream processes of distribution, metabolism and excretion which are subjected to pharmacokinetic interaction with other drugs. In addition, pharmacodynamic interaction that may potentiate or antagonise the pharmacological activity needs to be considered too.

One common question on drug-herb interaction that TMIS received concerned warfarin. The lack of readily available references on its interaction with commonly used herbs and health supplements prompted the TMIS to embark on an ambitious project to compile a warfarin-herb interaction database. Not unexpectedly, high-level evidence is lacking for most herbs due to lack of well-conducted randomised controlled trials (RCT). Ginkgo leaf (*Ginkgo biloba*, 银杏叶)^{28,29} and ginseng,³⁰ despite anecdotal reports, were shown in RCT to not affect International Normalised Ratio (INR) in patients on warfarin. On the other hand, other similarly popular herbs such as Chinese angelica root, glossy privet fruit (*Ligustrum lucidum*, 女贞子), wolfberry fruit (*Fructus Lycii*, 枸杞子), red sage root or cordyceps are severely lacking in clinical studies on their interaction with warfarin, with only case reports or animal/in vitro

studies available. The simplest solution to address potential drug-herb interaction is to stop the herb, but a more scientific approach is close monitoring if there are measurable drug levels (eg, anti-epileptics and calcineurin inhibitors) or therapeutic effect (eg, INR in warfarinised patients). Regardless, a non-judgemental attitude to encourage honest declaration by patients on their use of herbal medicine is the first step towards safe combination of drug and herb.

Cytochrome P450 3A4 (CYP3A4), as an important metabolising enzyme, is responsible for many known drug-drug interaction and even food-drug interaction. Compounds within grapefruit with CYP3A4 inhibitory activity may increase the level of CYP substrates, such as calcineurin inhibitors and tyrosine kinase inhibitors. The commonly used fruit and ripe peel of

bitter orange (*Citrus × aurantium*, 枳实, 枳壳) have similar chemical composition as grapefruit and therefore potential for interaction with these drugs too.³¹

In our clinical trial on TCM herbs for cytopenic haematological conditions,³² we observed the aggravation of hyperkalemia in two patients with diabetic nephropathy on angiotensin receptor blocker after ingestion of customised TCM formulations which returned to baseline upon stopping TCM, likely due to the high content of potassium in some of the plant-derived components.

Conclusion

TCM herbs, in their raw forms or as finished products, are neither totally safe nor totally responsible for all unexplained clinical observations. A medical practitioner will gain more trust and respect from his/her

patients if he/she keeps an open mind and adopts an objective and scientific approach towards this matter. An information service to address herb-related enquiries will contribute greatly towards the safety and well-being of our patients. ♦

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