

REVIEW ARTICLE

Traditional Chinese herbal medicine and anaesthesia

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Summary

An increasing number of people in the western world are using traditional Chinese herbal medicines. There are concerns that these Chinese medicines may contain potentially toxic ingredients and contaminants such as heavy metals. Undeclared conventional western drugs such as the non-steroidal anti-inflammatory and antihistamine drugs, steroids and oral hypoglycaemic agents are frequently added to Chinese herbal medicines. The constituents of the herbal products can cause adverse effects. The anaesthetist should be aware of the potential adverse effects of the herbal products, their contaminants and also of undeclared additives. The potential for drug interactions, coagulopathy and organ dysfunction caused by traditional Chinese herbal medicines has important anaesthetic implications.

Keywords *Medicine, herbal; Chinese. Drug toxicity. Drug interactions. Anaesthesia.*

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Traditional Chinese herbal medicines (TCHM) are increasingly used throughout the world, as they are considered to be effective and to have few side-effects. Contaminants of TCHM include heavy metals and undeclared drugs. The toxicity of these contaminants and additives, and the toxic effects of the herbal ingredients have important implications during the peri-operative period. The anaesthetist must consider the potential for drug interactions and systemic adverse effects of TCHM.

The aims of this review are to summarise the history and use of TCHM and to provide an account of their adverse effects and potential interactions, and a commentary on the potential anaesthetic implications TCHM.

Methods

Published articles for this review were sourced by using a Medline search for the years 1980–2001. Key words used included traditional Chinese medicine, drug interactions, herbal medicine, adverse effects, heavy metal contaminants and combinations of the above. In addition, the Internet site for the National Library of Medicine PubMed

(<http://www.asahq.org/PublicEducation>) was also searched using the above keywords. Bibliographies of included studies were also searched for additional references.

Prevalence

The use of TCHM is gaining popularity around the world. In China, the use of TCHM is ubiquitous and is often the only form of medicine available. In Singapore and Hong Kong, where western medicine is readily available, the use of TCHM is still popular. In Hong Kong, a study reported that 54% of pregnant women used TCHM [1]. A survey of Chinese mothers in Singapore reported that 89% of their children had been treated with TCHM within the first 30 months of life [2]. In Singapore, the trade in TCHM is worth > S\$ 80 million (US\$ 49 million) a year [3]. TCHMs are increasingly popular in western countries because they are considered to be safe, effective and free from side-effects. In the USA, annual retail sales approach US\$ 4 billion and are increasing at a rate of 18% per year [4]. An Australian survey in 1996 estimated that the use of TCHM doubled in the four years after 1996 [5]. Over 1 000 000 people in

the UK use TCHM every year with over 3000 clinics and shops selling TCHM [6].

Overview of traditional Chinese herbal medicine

TCHM originated thousands of years ago and was developed by trial and error. In Chinese mythology, the emperors Huangdi and Shennong wrote medical manuals ('*Huangdi neijing*' – *The Yellow Emperor's Manual on Corporeal Medicine* and '*Shennong ben cao jing*' – *Classical Pharmacopeia of the Heavenly Husbandman*) about 5000 years ago [7].

Traditional Chinese medicine is largely based on experience and is guided by a holistic concept. Theories such as the 'yin-yang' theory and 'five-element' theory embrace the view that treatment is targeted at correcting an underlying imbalance [8]. Yin-yang literally means 'opposites' and refers to opposing influences such as positive and negative forces. The five-element theory is named 'Wu Shing' in Chinese and expounds that everything is maintained in kinetic balance under the movement of five elements. Prescription of herbs based on these theories may comprise a single herb or more commonly a mixture of herbs in differing amounts. The prescribed herbs are classified according to four properties: 'Zhing', 'Chen', 'Zhou' and 'Shi'. Zhing is the major or 'chief' herb. Chen is an 'adjuvant' herb. Zhou is the 'assistant' or helper-like herb and Shi are 'guider' herbs [8].

There are different systems of classification that are based on the 'physical' properties of the herbs. The 'five-element' theory is based on taste (sour, bitter, sweet, pungent and salty). Another traditional classification involves four properties of herbs (cold, warm, heat and cool) so that 'hot' symptoms are treated with 'cold' herbs. Alternatively, herbs may be classified in terms of direction (ascending, descending, floating and sinking) or in relation to treatment of various organs, e.g. herbs for 'calming the liver and suppressing wind' [8].

Classification of the Chinese herbs according to their chemical composition can be a complicated process because of the large and diverse group of compounds present in each herb, and is further complicated by the mixtures of herbs used. Furthermore, there is no standardisation in the manufacture or preparation of Chinese medicines. TCHMs that claim to have the same contents, or even those from the same batch, contain varying components in different amounts. For example, ginseng (*Panax ginseng*) contains 2–3% ginsenosides (triterpene saponins), of which there are several types, the main ones being Rg1, Rc, Rd, Rb1, Rb2 and Rb0. It also contains essential oils and polyacetylenes. Different types of ginseng products have been reported to increase or

decrease blood pressure, depending on the content of various ginsenosides. Ginsenoside Rg1 increases blood pressure and Rb1 decreases it. As is evident, the contents of a single herb are complex, and most Chinese medicines are a mixture of a number of different herbs. For example, the formulation 'Danggui-Nian-Tong-Tang', which is used for the treatment of acute gouty arthritis, consists of 15 different herbs [9].

TCHMs have been used for a multitude of diseases ranging from skin rashes to ischaemic heart disease. However, there are few studies providing evidence of their efficacy in these conditions. One review of the efficacy of TCHM in the treatment of eczema reported that it could not be concluded that the TCHM products were efficacious, although the evidence was encouraging [10]. The number of randomised controlled trials is increasing in the Chinese literature. A review of some of these studies indicated that the quality of Chinese trials were poor and that many had serious methodological deficiencies [11].

Other studies of the efficacy of traditional Chinese medicine include comparative studies of TCHM and conventional western drugs [12, 13]. The formulation, 'Danggui-Nian-Tong-Tang' showed no efficacy in the treatment of gout when compared with indomethacin [12].

However, TCHM is a valuable foundation for modern drug development. In 1882, ephedrine was synthesised from *Ephedra sinica* ('Ma Huang'). More recently, there has been research and development in the areas of chemotherapeutic agents, drugs for the treatment of adult immunodeficiency virus infection, and antimalarial, antiviral, antifungal and anti-inflammatory drugs. Indirubin, which is used in the treatment of chronic myeloid leukaemia, was developed from a TCHM: 'Dang Gui Lu Hui' (*Indigo naturalis*) [14]. The antimalarial agent artemisinin and its synthetic derivatives were developed from 'Qing Hao' (*Artemisia annua*) [15, 16].

Contaminants in traditional Chinese herbal medicines

TCHMs often contain contaminants, although they are commonly thought to contain natural herbal ingredients. The contaminants are either heavy metals or undeclared conventional western drugs. Heavy metals such as lead, mercury, copper, cadmium, arsenic and thallium have been detected in TCHM [17]. In Singapore, there are regulations regarding the permissible concentration of toxic heavy metals in TCHM, and routine screening for the presence and amount of each metal is performed. Between 1990 and 1997, 2080 medicines were screened, and 42 TCHM were found to contain excessive

concentrations of the arsenic, copper, lead and mercury (legal concentrations of arsenic, copper, lead and mercury were 5, 150, 20 and 0.5 p.p.m., respectively). The most common toxic metal detected was mercury (66.7% of the 42 toxic medicines), followed by lead (19%), arsenic (16.7%) and copper (2.4%) [2].

The other common contaminants of TCHM are conventional western medications. In Singapore, screening of 2080 TCHM revealed that 32 had contaminants of 19 conventional drugs that included antihistamines, non-steroidal anti-inflammatory drugs (NSAIDs), analgesic antipyretics, corticosteroids, sympathomimetics, bronchodilators, diuretics and hypoglycaemic agents [2]. The most common drug encountered was berberine, followed by chlorpheniramine, diclofenac and paracetamol. A study of Chinese herbal creams prescribed for dermatological conditions found that 8 of the 11 analysed contained high concentrations of dexamethasone that were inappropriate for young children or the treatment of areas of thin skin [18].

Adverse effects of traditional Chinese herbal medicines

The adverse effects of TCHM include those related to the herbs themselves and the toxic effects due to the contaminants.

Adverse effects due to herbal ingredients

A number of toxic herbs are still commonly used in Chinese traditional medicine. The most common is the dried root of the *Aconitum* species, *A. carmichaeli* and *A. kusnezoffii*, which is used as an anti-inflammatory or analgesic agent. These herbs contain aconitine, diterpenoid esters and derivatives that activate sodium channels *in vivo*, causing dose-dependent cardiac and neurological toxicity. Initial symptoms include paresthesia of the mouth, tongue and extremities, nausea and vomiting, weakness and dizziness. Hypotension and arrhythmias such as atrial flutter or fibrillation can occur, with ventricular fibrillation and cardiovascular collapse occurring at higher doses [17]. The toxic effects may be decreased or removed by boiling the herbs in water, a process that converts the toxic aconitines into less toxic benzoylaconines [2].

Another common toxic herb is from the *Datura* species. Herbs such as *Datura metel* can lead to toxicity related to anticholinergic substances such as scopolamine, hyoscyamine and atropine. Typical features of toxicity include confusion, fever, tachycardia, flushed dry skin, dilated pupils, dry mouth and urinary retention [2, 17]. The flower of the *D. metel* plant ('Yangjinhua') is used in the treatment of chronic bronchitis and asthma.

Less common toxic components of TCHM include shandougen (the root of *Sophora tonkinensis*). Large doses of shandougen can cause vomiting, diarrhoea, headache and dizziness. Animal toxins may be present because animal products may be mixed with the TCHM. 'Chansu', prepared from the skin and venom glands of the toad (*Bufo bufo gargarizans* or *B. melanostictus*), contains bufotoxins that have a digoxin-like effect. It can cause potentially fatal cardiac arrhythmias [17].

The root of the herb *Podophyllum emodi* ('Guiji') is applied to the skin for the treatment of warts. Because it resembles *Gentiana rigestens* and *Clematis*, it may be mistakenly ingested, causing nausea and vomiting, and, in severe cases, neuropathy and encephalopathy [17].

Other toxic herbs include *Aristolochia fangchi* (nephrotoxicity), *Salvia miltiorrhiza* (inhibits platelet function and coagulation) and *Panax ginseng* (nervousness and anxiety) [2].

Toxicity caused by contaminants or undeclared additives

The toxicity of TCHM may be related to heavy metals or undeclared western drugs. Mercury is the most toxic metal contaminant, and is an undeclared constituent of some Chinese medicines (Table 1). Clinical symptoms of mercury poisoning include nausea, vomiting, abdominal pain and neurological symptoms such as memory loss, insomnia, and excitability, progressing to delirium in severe cases [19]. Lead poisoning causes abdominal pain, anaemia, renal disease, headache and peripheral neuropathy in adults. In children, lead poisoning causes ataxia, slurred speech and, in severe cases, convulsions, coma and death [19]. Cadmium toxicity is characterised by vomiting, abdominal pain and severe diarrhoea causing hypovolaemic shock. The symptoms of thallium toxicity are primarily gastrointestinal in nature, with peripheral neurological effects such as paraesthesia, myalgias, weakness, tremor and ataxia. Arsenic poisoning is caused by the binding of sulfhydryl groups in tissues and by the inhibition of enzymes in the tricarboxylic acid cycle, resulting in multiorgan failure [19]. A case report described fatal arsenic poisoning, caused by a TCHM used to treat gingivitis, in a 13-year-old girl who presented with fever, vomiting, diarrhoea and dyspnoea. She had pulmonary oedema, pericarditis and metabolic acidosis, and subsequently developed acute renal failure, liver failure and cerebral oedema [17].

The other contaminants of TCHM are conventional western drugs that can cause adverse effects. The NSAIDs added to TCHM cause side-effects such as peptic ulceration, renal impairment and bleeding. Phenylbutazone added to TCHM has been reported to cause agranulocytosis in a patient [20]. Steroids, usually dexamethasone, added to TCHM can cause osteoporosis,

Table 1 Heavy metal contaminants in Chinese herbal medicines.

Traditional Chinese medicine product	Uses	Heavy metals detected
Babaodan (Li Zhi)	Rheumatism, appendicitis, hepatitis	Lead
China Ling Zhi Capsules	Tonic	Mercury
Ching Fei Yi Huo Wan (Golden Lily)	Cough, sore throat	Mercury
Chunbaodai Tablet (Cang song)	Tonic	Arsenic
Danggui Yang Xue Pian (Da Ming Gong)	Anaemia	Mercury
Fargelin for Piles (Yang Cheng)	Piles	Arsenic
Gan Mao Ling (Snow Lotus)	Influenza	Mercury
Hindu Magic Pills	Insomnia and loss of appetite	Copper
Shi Hu Pian (China's Guiyang Chinese medicine factory)	Poor eyesight	Mercury
Su Shi Bai Feng Wan (Hua Ling)	General weakness	Mercury
Tienqi Dieda Wan (Xing Qun)	Tonic	Lead
Tien Wang Pu Xin Wan	Heart problems	Mercury
Wild Ling Chih Capsules (Mei Hua)	Tonic	Arsenic
Xiang Sha Yang Wei Wan	Stomach problems	Mercury
Zhong Guo Xiong Can Zhi Chuang Wan	Piles	Arsenic
Zhu Bei Dinchuanpian (Golden Sun)	Cough	Mercury, arsenic
Shanhaidan Capsules	Coronary disease	Lead

fractures, psychosis and immunosuppression. Severe hypoglycaemia has been documented in patients using TCHM contaminated with oral hypoglycaemic agents. A case study reported prolonged hypoglycaemia in a patient taking the herbal medication 'Zhen Qi' for diabetes despite large amounts of intravenous glucose being administered. Analysis of the capsules revealed the presence of glibenclamide [21].

Cardiovascular adverse effects

The ephedra alkaloids are commonly present in TCHM. These alkaloids commonly cause hypertension, tachycardia and palpitations, and adverse cardiovascular effects reported include myocardial ischaemia and infarction, arrhythmias and cardiac arrest [22]. Hypertension has also been reported to result from ingestion of the TCHM Dong quai (*Angelica sinensis*) [23]. Dong quai is used in the treatment of dysmenorrhoea, irregular menstruation and postpartum weakness. A case report described hypertension in a 33-year-old mother and her 3-week-old son after drinking a soup prepared from the herb [23].

Neurological adverse effects

Adverse neurological events such as subarachnoid haemorrhage, intrathalamic haemorrhage, seizures and transient ischaemic attacks have been documented with the dietary supplements containing ephedra alkaloids [22]. Acute confusional states can result from anticholinergic toxicity from herbs of the *Datura* or *Rhododendron* species. Other neurological symptoms such as nervousness and elevation of mood are associated with the 'ginseng abuse syndrome', thought to be caused by dammarenetriol glycosides present in ginseng [17]. Severe encephalopathy and neurotoxicity have been documented to result from

podophyllotoxin toxicity in cases when *Podophyllum emodi* was mistaken for *Gentiana rigescens*. Podophyllotoxin inhibits cellular protein synthesis, and therefore enzymes and neurotransmitters, and mitosis in the brain, liver, intestine and pancreas [17].

Gastrointestinal adverse effects

Acute hepatitis has been reported with the use of the Chinese herbal product 'Jin Bu Huan'. These tablets contain levo-terrohydroalmitine, which is thought to cause hepatitis after long-term use. Other potentially hepatotoxic herbal products contain germander, chaparral and pyrrolizidine alkaloids [17]. Gastrointestinal ulceration, bleeding and perforation can be caused by the undeclared NSAIDs added to TCHM used for rheumatism and arthritis [2, 17] (Table 2).

Haematological adverse effects

Traditional Chinese herbal medicines have been reported to cause serious haematological adverse effects. A case report described severe thrombocytopenia (platelet count = $16 \times 10^9 \cdot \text{dl}^{-1}$) in a 51-year-old Japanese woman using a TCHM called 'Jui' [24]. The platelet count recovered spontaneously to $305 \times 10^9 \cdot \text{dl}^{-1}$ without treatment, but on re-exposure to the herb, her platelet count decreased to $2 \times 10^9 \cdot \text{dl}^{-1}$ in one day. An idiosyncratic immune mechanism was suggested because the patient responded to steroid therapy [24]. *Ginkgo biloba*, used for treating cognitive disturbances, has been reported to produce an anticoagulant effect by inhibition of platelet activating factor [25]. Large doses of garlic cause anticoagulant effects mediated by platelet inhibition, and a spontaneous epidural haematoma has been reported in a 87-year-old man consuming excessive amounts of garlic [26].

Table 2 Conventional western medicines added to Chinese herbal products.

Traditional Chinese herbal product	Uses	Conventional drugs detected
Ba Bao Feng Shi Huo Luo Dan (Mei Hua) Black Pills	Rheumatism Weight gain	Diclofenac Cyproheptadine
Dahuo Luodan (Golden Sun)	Pain, rheumatism	Berberine
Dr Yap Condensed Honey, Chon Poui Pei Pa Lo	Bronchitis, cough	Chlorpheniramine
Fuchingsong Shaiodu Chie Yang Capsule	Anti-inflammatory, anti-itch	Chlorpheniramine, paracetamol
Ginseng Zaizaowan (Golden Sun)	Pain	Berberine
Gu Ben Wan	Multiple conditions	Caffeine, dexamethasone, diazepam, hydrochlorothiazide, indomethacin, prednisolone Berberine
Huang Lian Shang Qing Pian	Sore throat, fullness of head, tinnitus, etc.	
Jin Bu Juan Anodyne Tablets	Gastric or duodenal ulcer pain, nervousness, insomnia, spasmodic cough	Tetrahydropalmitine
Kuek Hum Siau Asthma Cure Powder Life Blood Medicine	Asthma, cough, whooping cough Boost body's immune system, enhance red blood cell production, etc.	Ephedrine Dexamethasone
Nasalin	Rhinitis, nose blockage, headache, influenza, runny nose	Chlorpheniramine
Shenchin herb (Sheng Chih Wei) S-Magon Morning	Pain in muscles or bones Chronic bronchial asthma, bronchitis, hay fever, hepatitis, skin scaling	Diazepam, ibuprofen, paracetamol. Promethazine, theophylline
She Xiang Zhui Feng Tou Gu Wan (Mei Hua) Tung Sheuh Wan Wonder pills	Rheumatism Rheumatism Diabetes mellitus	Diclofenac Caffeine, diazepam, indomethacin, prednisolone Phenformin
Unguentum Fluocinon-ide Zhong Gan Ling	Skin (itching, dermatitis, eczema) Cold	Fluocinon-ide Dipyron

Agranulocytosis has been documented as being caused by TCHM. Four cases of agranulocytosis related to ingestion of TCHM were reported in four Americans in the San Francisco Bay area. The agranulocytosis was caused by phenylbutazone and aminopyrine, undeclared contaminant drugs present in the Chinese herbs used. The patients suffered bacteraemia and life-threatening septic shock associated with the agranulocytosis, and one patient died [20].

Danshen (the root of *Salvia miltiorrhiza*) suppresses the formation of thromboxane and inhibits platelet aggregation as well as acting as a vasodilator. The interaction of Danshen and warfarin has the potential for causing excessive bleeding [27]. Ginseng, the most popular herb, has been reported to decrease the international normalised ratio (INR) in a patient who had been stabilised on warfarin [28].

Renal adverse effects

Cases of rapidly progressive renal failure and urothelial carcinoma have been reported in association with the herb *Aristolochia fangchi*. 'Chinese herb nephropathy' is a progressive form of renal fibrosis that was first identified in a group of patients taking weight-reducing pills containing *Aristolochia*. Further investigations of these

patients revealed a high prevalence of urothelial carcinoma (18/39 patients) [29].

Drug interactions

Both TCHMs and their undeclared contaminants have the potential for pharmacodynamic and pharmacokinetic interactions with other prescribed conventional western medicines. The interaction of TCHM with warfarin is widely reported. Both danshen and dong quai (*Angelica sinensis*) can potentiate the anticoagulant action of warfarin [30]. Danshen and dong quai potentiate warfarin by pharmacodynamic mechanisms in animal studies [31, 32]. NSAIDs are common undeclared additives in Chinese traditional medicines and can inhibit platelet function.

Ginseng has been reported to interact with monoamine oxidase inhibitors such as phenelzine, causing stimulation of the central nervous system. It has also been shown to decrease the anticoagulant effect of warfarin and to increase digoxin levels [17].

Anaesthetic considerations

Anaesthetists should be aware of the potential problems of TCHM because of the potential drug interactions, as well

as the toxic effects of the herbal constituents and the undeclared contaminants or additives. Danshen, dong quai, jui, ginkgo biloba and garlic have anticoagulant effects and therefore increase the risk of bleeding during surgery. The increased risk of epidural haematoma has to be considered when a neuraxial blockade is planned. Furthermore, Chinese herbal medications have the potential for interacting with conventional western drugs, causing increased anticoagulation effects [27]. Peri-operative cardiovascular instability may be caused by TCHM. Herbs containing ephedra alkaloids have the potential to deplete sympathetic neurotransmitters, predisposing to peri-operative hypotension. Traditional Chinese herbal medicines can cause renal and hepatic dysfunction and can therefore cause alterations in the pharmacokinetics of drugs used during anaesthesia.

Anaesthetists must be aware of the contaminants and undeclared conventional western drugs contained in TCHM because these can cause toxic effects and interactions. Peri-operative hypoglycaemia may be caused by oral hypoglycaemic drugs added to TCHM and can be fatal if not recognised. Steroids added to TCHM may cause adrenal suppression, resulting in peri-operative hypotension, electrolyte disturbances, impaired wound healing and immunosuppression.

It is important for anaesthetists to enquire about the use of complementary medications and TCHM during pre-operative assessment of the surgical patient. It may be prudent to advise patients to cease the use of TCHM at least two weeks before surgery.

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