

**PAPER****PATHOLOGY AND BIOLOGY**

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## A Review of the Potential Forensic Significance of Traditional Herbal Medicines

**ABSTRACT:** Traditional herbal substances may contain highly toxic chemicals and heavy metals, in addition to naturally occurring organic toxins. These substances may cause illness, exacerbate pre-existing ill health or result in death, particularly if taken in excess or in an unusual manner (e.g., injected rather than ingested). Lack of regulation of the content and quality of herbal medicines may result in contamination and adulteration with prescription medications. As there may be no history of the specific use of these products their contribution to death may not be fully appreciated during a standard autopsy. Even when their existence is known or suspected, it may be difficult to identify these substances on standard toxicologic screening. Herbal medicines may also be responsible for a range of symptoms and signs that may confuse the clinical presentation of cases. Given these issues the role of herbal medicines in forensic practice needs to be more clearly defined as deaths may be occurring where herbal medicines have made a significant, but as-yet unrecognized, contribution.

**KEYWORDS:** forensic science, death, herbal medicine, herbs, traditional Chinese medicine, heavy metal, toxins

Nonconventional medicine covers a range of practices including naturopathy, osteopathy, chiropractic and herbal therapies and is utilized by an estimated 70–80% of the world's population at all ages (1,2). Herbal medicines have been gaining considerable popularity in western countries in recent years with Chan citing an estimated budget in Europe of £300 million and a steady 10% increase in spending on botanical remedies in the United States alone (1). Access to such products is largely unrestricted, without the need for prescriptions. Unfortunately, problems exist with some herbal remedies in terms of composition, effects, and interaction with prescription medications. As these factors may impact on causes and mechanisms of death in forensic practice, the following review was undertaken to illustrate the range of problems that may be encountered with such products.

### Use of Herbal Medicines

There are at least 7000 species of medicinal plants utilized in China. Traditional Indian medical systems such as Ayurveda and Unani also rely heavily on plant products. In the United States it has been estimated that 30% of patients now use herbal remedies and this is often without the knowledge of their treating doctor (3–5). A desire to control personal therapy or a fear of ridicule or disapproval by their doctor may be behind this lack of communication (6).

There exists a popular perception that herbal remedies are safer than manufactured medicines as they are more “natural.” Only 0.2% of acute medical hospital admissions in Hong Kong were attributed to their use in one study (7) and they have been prescribed for many centuries in countries such as China. However, herbal remedies may contain toxic substances that can result in serious illness and even death (Table 1). Despite the possibility of containing such

pharmacologically active substances, herbal products are not subject to strict regulation or control, often because they are marketed as dietary supplements and not drugs (8). While it has been argued that the absence of side-effects of herbal medicines in traditional societies in the past demonstrates how safe natural products are, this does not take into account the potential for serious interaction with prescription medications that are now widely available, and the high mortality rates that were found in these communities.

### Toxic Ingredients

Heavy metals such as mercury, lead, thallium, cadmium, copper, iron, manganese, nickel, zinc, and arsenic have all been found as essential ingredients in certain remedies. An analysis of 251 Asian herbal products from stores in California, USA, identified arsenic in 36, mercury in 35, and lead in 24 (9). Unfortunately due to the unregulated nature of the manufacture of herbal medicines quite high and potentially lethal concentrations of these substances may occur (1). Lead encephalopathy and acute lead and mercury poisoning have been reported (3). One such case of lead poisoning involved a 5-year-old boy who had been treated with “Tibetan Herbal vitamins” and had ingested a total of approximately 63 g of lead over 4 years (10). Another case involved a 5-year-old boy with bilateral retinoblastomas whose parents resorted to a traditional Indian remedy that caused arsenic poisoning (11). Ernst summarized issues that occur in these cases as “nonmedically qualified healers, lack of product standards, undeclared ingredients, nondisclosure of usage and long-term medication” (12).

Organic toxins derived from animals or plants may also be added to herbal medicines including highly toxic substances such as aconite root (3). Traditionally, poisonous substances are blended with nontoxic herbs to reduce their toxicity.

Anticholinergic side effects of traditional medications have been deemed “common” and are most often due to derivatives of the *Datura* plant, but poisoning has also occurred from substituting

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TABLE 1—Reasons for dangerous ingredients being found in traditional herbal medicines.

|                              |  |
|------------------------------|--|
| Addition of toxic substances |  |
| Deliberate                   |  |
| Heavy metals                 |  |
| Organic toxins               |  |
| Inadvertent                  |  |
| Pesticides/herbicides        |  |
| Chemicals                    |  |
| Heavy metals                 |  |
| Microorganisms/insects       |  |
| Mycotoxins                   |  |
| Drug adulteration            |  |
| Deliberate                   |  |
| Prescription drugs           |  |
| Substituted herbs            |  |
| Inadvertent                  |  |
| Mistaken identification      |  |
| Deliberate                   |  |
| Cost cutting                 |  |
| Inadequate processing        |  |

herbs containing atropine, or atropine-like substances. Liquorice may be found in some medications and has been known to alter steroid metabolism causing hypokalemia and hypertension (3). *Ginkgo biloba* has been associated with spontaneous intracerebral hemorrhage, seizures, and intraocular hemorrhage.

*Chan su*, a traditional medicine used to treat sore throats, boils, and palpitations contains the venomous secretions of the auricular and skin glands of Chinese toads (*Bufo melanostictus Schneider* or *Bufo bufo gargarzinus Gantor*). These include substances known as bufadienolides that have a digoxin-like effect and stimulate the cardiovascular system with potentially lethal side effects of cardiac arrhythmias, seizures, or coma (5,13).

Infants are at greater risk than adults of suffering poisoning from herbal medicines due to their low body weight and less effective hepatic detoxification. The widespread use of the preparation *chuenlin* in neonates to “remove toxic products of pregnancy” may increase the risk of kernicterus-induced brain damage as the active alkaloid berberine increases free bilirubin concentrations by displacing bilirubin from plasma proteins (3).

Adverse effects on the liver have ranged from transiently high liver enzyme levels to fatal hepatic failure. It is believed that most

of these cases are caused by hepatotoxins integral to the preparations, although interactions with prescription medications may also be responsible for side effects (14). Toxic hepatitis has been caused by a variety of herbs including those of the *Aristolochia* species and germander (*Teucrium chamaedrys*). Fulminant liver failure requiring transplant, or resulting in death, have been caused by kava (*Piper methysticum*), pennyroyal (*Mentha pulegium*), *Jin bu huan*, *Syo saiko to*, *Ma huang*, and a Chinese herbal medicine called “eternal life” (15,16). Hepatic veno-occlusive disease has been due to comfrey (*Symphytum officinale*) and skullcap (*Scutellaria lateriflora*) ingestion. Other hepatotoxic events due to herbal products have been described in reviews by Pittler and Ernst, and by Stickel et al. (6,14).

Serious cardiovascular side effects of herbal medicines have included arrhythmias, myocardial infarction, congestive cardiac failure, hypotension, hypertension, arteritis, and pericarditis (17) (Table 2). Neurological side effects include stroke, movement disorders, muscle weakness, and seizures (18).

Substituted Ingredients

Certain herbs may be replaced during the preparation of traditional medicines. This may be intentional because of the scarcity or expense of the original ingredient resulting in the use of low quality herbs or substitutes (19). Unfortunately, cheaper herbs may not be as safe as more expensive ones, as was shown in Belgium when the herb *Stephania tetrandia* was replaced by *Aristolochia fangchi* in a medicine designed to help with weight loss. Unfortunately the substitute herb contained a nephrotoxin, aristolochic acid, that resulted in rapidly progressive interstitial nephritis with terminal renal failure. Urinary tract neoplasia in the form of carcinoma *in situ* has also been found in 40% of cases of so-called Chinese-herb nephropathy (20–22). Ginseng has been adulterated with cheaper *Mandragora officinarum* (scopolamine) and *Rauwolfia serpentina* (reserpine) (3). Substitution of one drug for another less safe drug is something that occurs in the illicit drug trade that may also be driven by availability and cost (23).

Accidental substitution may occur if a herb has been incorrectly identified, or if the name or formula has been misinterpreted from original texts. Confusion may arise when traditional herbal preparations have multiple names, different preparations have the same name, or where there are several vernacular names that differ from region to region (24). For example, the mistaken dispensing of *Podophyllum emodi* instead of *Gentiana species* has been responsible for causing podophyllin poisoning with renal, hepatic, and gastrointestinal disturbances and permanent neurological damage (3). Neonatal androgenization has resulted from the ingestion of Chinese silk vine rather than Siberian ginseng (25).

Incomplete Processing

Processing of fresh herbs is designed to clean and preserve the material and also to remove or reduce any unwanted toxic components that may be otherwise fatal. Failure to adequately process herbs may lead to residual toxins (1,26). This has been noted with the use of aconite root that is dispensed in a dry form and which must be soaked in water and boiled to reduce toxicity. Failure to do this has resulted in aconite poisoning that may cause death from cardiac failure and/or arrhythmia. Aconite toxicity has been responsible for most cases of serious poisoning by Chinese herbal medications (3).

TABLE 2—Significant illnesses and adverse effects that may be caused by traditional herbal medicines.

|                             |                                                                                                                                             |
|-----------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|
| Heavy metal poisoning       | Acute toxicity, encephalopathy                                                                                                              |
| Hepatic disease             | Fulminant liver failure                                                                                                                     |
| Cardiovascular disease      | Cardiac arrhythmias, hypotension, hypertension, cardiac failure, acute transplant rejection, myocardial infarction, arteritis, pericarditis |
| Respiratory disease         | Asthma                                                                                                                                      |
| Gastrointestinal disease    | Nausea, vomiting, diarrhea                                                                                                                  |
| Renal/Genitourinary disease | Urinary retention, interstitial nephritis, fulminant renal failure, acute transplant rejection.                                             |
| Endocrine/metabolic disease | Hyperthyroidism, hypoglycemia, hyperglycemia, pseudohypoadosteronism                                                                        |
| Neurological disease        | Confusion, coma, kernicterus, seizures, intracerebral hemorrhage/stroke, subdural- subarachnoid- extradural hemorrhage, encephalitis        |
| Hematologic disease         | Agranulocytosis, anemia                                                                                                                     |
| Miscellaneous               | Anaphylaxis, carcinogenesis, postoperative hemorrhage                                                                                       |
| Drug interactions           |                                                                                                                                             |

### Accidental Contamination

Herbal remedies may also be inadvertently contaminated by a variety of dangerous substances ranging from organochlorine pesticides to heavy metals. Herbal substances are either grown in the wild or are specifically cultivated for use and in the latter group in particular there may be contamination with pesticides that may have been used in excessive amounts and include banned substances such as DDT (27).

Inadvertent heavy metal contamination has been reported in a number of studies resulting from growth of herbs in contaminated environments or from faulty storage (1). Contamination may also occur with microorganisms, mycotoxins, insects, or herbicides from incorrect or erroneous treatments during storage (28).

### Adulteration

Herbal medicines are frequently adulterated with standard drugs presumably to increase their efficacy. For example, phenytoin poisoning with coma occurred in an epileptic patient (who had not been prescribed this drug) who had ingested a Chinese herbal preparation that was promoted as containing pure Chinese medicines that were effective in controlling seizures. No mention had been made of the presence of any prescription drugs on the packaging (29). Standard drugs have been found in as many as 24% of preparations in a study from Taiwan, a surprisingly high figure given that this is an illegal activity in that country (30). Unfortunately the nature and dosage of the added drugs is not always revealed to the consumer, who may have specific medical reasons, e.g., allergy, for needing to know the exact composition of what is being ingested. Aplastic anemia due to phenylbutazone has been reported following the use of an adulterated herbal medicine that also did not have this drug listed in the package insert, and significant hypoglycemia has occurred due to occult glyburide (5). Cushing syndrome may be caused by the ingestion of steroids that have been used to augment traditional herbal cures.

Added drugs have ranged from analgesics to steroids, including: aspirin, paracetamol, antihistamines, theophylline, bromhexine, diazepam, chlorthalidone, diclofenac, glibenclamide, hydrochlorothiazide, mefenamic acid, aminopyrine, phenylbutazone, phenytoin, phenacetin, indomethacin, and steroids (3,31).

### Interaction with Orthodox Drugs

Herbal medicines may also have a variety of effects on standard drugs. The actions of prescribed drugs may be enhanced, or reduced (thus causing treatment failure), or the herbal material and drug may combine actions and produce an idiosyncratic effect (4). Herbal preparations may increase drug levels by enhancing absorption and decreasing clearance (32). St. John's Wort (*Hypericum perforatum*) induces several cytochrome P450 enzymes and the transporter protein P-glycoprotein and has significant effects on a range of drugs causing reduced anticoagulation by warfarin, decreased action of cyclosporin with acute organ transplant rejections, and intermenstrual bleeding in women taking the oral contraceptive pill (8). It has also significantly reduced the bioavailability of many drugs including serum digoxin, theophylline, amitriptyline, indinavir (an HIV-1 protease inhibitor), and methadone levels, the latter resulting in the re-emergence of withdrawal symptoms (33–35).

Ginkgo (*Ginkgo biloba*) and garlic (*Allium sativum*) have increased the risk of bleeding with anticoagulants, while garlic has increased the hepatotoxicity of paracetamol and enhanced the effect of oral hypoglycemic agents (34).

Asian ginseng (*Panax ginseng*) has potentiated the adverse effects of the monoamine oxidase inhibitors, enhanced the effect of oral hypoglycemic agents, decreased the effects of immunosuppressants, and had an additive effect with benzodiazepines (36). Certain herbal remedies such as Borage oil and Evening primrose oil contain gamma-linolenic acid that lowers the seizure threshold in epileptics, thus counteracting drugs such as phenobarbitone and phenytoin. Other preparations may potentiate the action of warfarin thus increasing the risk of hemorrhage; these include *Dan shen*, *Dong quai*, Devils claw, ginseng, and Siberian ginseng (33). An enhanced bleeding tendency either involves the actions of natural vitamin K antagonists or antiplatelet actions (32). A review of the literature on herb-drug interactions has been provided by Hu et al. (37).

### Issues with Surgery

The American Society of Anesthesiologists has recommended the discontinuance of herbal medicines at least 2 weeks prior to surgery because of the potential for herb-drug interaction (33). Although only eight herbs were identified as being potentially dangerous in the perioperative period in a review by Ang-Lee et al., they accounted for 50% of all single herb preparations of the 1500–1800 herbal medicines sold in the United States (38). The authors reported the following specific problems:

Garlic: increased risk of hemorrhage due to inhibition of platelet aggregation and increased fibrinolysis.

Ginkgo: increased risk of hemorrhage due to inhibition of platelet activating factor.

The side effects of both of the above may be worsened if drugs that inhibit platelet aggregation are also being used.

Ephedra: increased risk of myocardial and cerebral ischemic events; potentially lethal interaction with monoamine oxidase inhibitors; intra-operative hemodynamic instability due to reduction of endogenous catecholamines; ventricular arrhythmias with halothane.

Ginseng: hypoglycemia; reduction of anticoagulation properties of warfarin; increased risk of hemorrhage due to inhibition of platelet aggregation.

Echinacea: allergic reactions, immunosuppression, reduced efficacy of immunosuppressants.

Kava: possible exacerbation of sedative effects of anesthetic agents.

Valerian: possible exacerbation of sedative effects of anesthetic agents.

St John's Wort: effects on drugs through the cytochrome P450 system as noted above (38).

Herbal products may also produce abnormal laboratory results by directly interfering with immunoassays, by increasing or decreasing concentrations of prescribed drugs, or by direct hepatotoxicity. The amount of interference due to cross-reactivity between herbs and drugs is also dependent on the assay method used (33,39).

### Identification

The identification of organic toxins on routine post-mortem screening may be difficult, particularly if the nature of the substance is not known. Even when a specific substance is looked for, levels may be very low and near the limit for laboratory detection (40). Analytical techniques have included gas and high performance liquid chromatography, and ultra-violet, infra-red, nuclear magnetic resonance and mass spectroscopy, with X-ray diffraction and combined high performance liquid chromatography-mass spectroscopy



and gas chromatography-mass spectroscopy. Capillary electrophoresis has also been used (1).

Given that the active components of herbs that are being looked for with the above chemical means may be reduced by physiological conditions, storage conditions, and the harvesting period, and that related plant species may have a very similar chemical composition, cytogenetic, and karyotyping have also been used to identify particular plants in recent years (1).

### Forensic Implications

A range of issues arise with the use of herbal medicines, including problems in determining what might constitute lethal levels of the active ingredients, how a particular herb may have contributed to death, and whether a herb may actually have caused death. The lack of diagnostic pathological findings at autopsy may also create difficulties (40–42). Cases may also present complex medicolegal problems if herbal medicines have been favored over more conventional therapy. This may be a particular issue in children with malignancies if parents have elected to use herbs rather than standard chemo- or radiotherapy. Death from the uncontrolled manifestations of malignancy must raise questions about duty of care and the possibility of criminal charges being laid.

Given the increasing popularity of herbal medicines it is likely that they will be encountered more often in forensic practice, however little has been written in the forensic literature about their potential problems. Lists of drugs found at death scenes should include any herbal remedies and if an unusual drug response is detected at autopsy the possibility of an interaction with herbal medicine should be considered. There should be an awareness that herbal remedies may play a part in cases with unexpected surgical or medical outcomes. The extent of the role of herbal medicines in the types of cases presenting to forensic facilities is yet, however, to be determined.

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