

Dietary supplements and herbal medicine toxicities—when to anticipate them and how to manage them

D. H. Phua · A. Zosel · K. Heard

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Abstract

Background Dietary supplements and herbal medicines are gaining popularity in many developed countries.

Aims Although most can be used without any problem, serious toxicities do occur.

Methods Problems can be anticipated when they are used for non-traditional indications, at excessive dose, for prolonged duration, or by patients who are also on multiple modern pharmaceuticals. Problems should also be anticipated when these products claim to be able to relieve symptoms rapidly or when herbs with pronounced pharmacological effects or toxic components are used.

Results Resuscitation, symptomatic and supportive care are the most important aspects of management of toxicities from these products.

Conclusion This article reviews when problems with these products can be anticipated and outlines a practical approach to management.

Keywords Dietary supplements · Herbals · Toxicity · Poisoning · Drug contamination · Herb-drug interaction

The views expressed in this paper are those of the author(s) and not those of the editors, editorial board or publisher.

D. H. Phua (✉)
Emergency Department, Tan Tock Seng Hospital,
11 Jalan,
Tan Tock Seng S(308433), Singapore
e-mail: dong_haur_phua@ttsh.com.sg

A. Zosel · K. Heard
Rocky Mountain Poison and Drug Center,
Denver, CO, USA

K. Heard
Emergency Medicine, University of Colorado,
Denver, CO, USA

Introduction

Dietary supplements and herbal medicines play important roles in health care. Vitamins and minerals are important, as they are necessary for enzymatic reactions and bodily functions; lack of these compounds can lead to deficiency-related diseases. Herbal medicine was the predominant form of health care for the world's population before the advent of modern medicine and still is the predominant form of health care in many underserved populations. Herbal medicine continues to infuse new ideas and treatments into modern medicine for the benefit of our patients.

According to the 2006 American Association of Poison Control Center (AAPCC) data, there were a total of 972,073 exposures to pharmaceutical products resulting in adverse events, of which there were 6,809 major outcomes and 507 deaths [1]. Of these exposures, 76,364 (7.9%) were due to dietary supplements and vitamins, with 42 major outcomes (0.6% of all major outcomes) and only 3 deaths (0.6% of all deaths). Hence, serious adverse effects and death from these products are relatively uncommon. A review of hospital admissions in Hong Kong found only 0.2% of the cases were due to adverse reactions from herbal products [2]. A London unit had 5,536 enquiries on traditional medicines and food supplement exposures from 1983 to 1991, and only 12% of the patients were symptomatic [3]. Despite the prevalent use of these products, adverse outcome and death only arise occasionally. It is safe to conclude that in most instances, dietary supplements and herbal medicines are relatively harmless when used appropriately.

Nevertheless, there are many reports in the literature that suggest that unnecessary or reckless use of these products can lead to problems. We see two major issues

that contribute to these problems: A public perception that these products are inherently safe, and the lack of knowledge about these products in the medical profession. This article reviews the toxicities described in the literature associated with their use and when to anticipate problems with them, and describes an approach that an emergency physician can adopt when he or she encounters patients with such toxicities.

Definitions

The World Health Organization (WHO) and the United States (US) Dietary Supplements Health and Education Act (DSHEA) of 1994 both define dietary supplements as a product (other than tobacco) that is meant to supplement the diet. Both organizations include vitamins, minerals, herbs, botanical products, amino acids, or dietary substances in their definitions [4].

The WHO also defines herbal medicines as plant-derived materials or preparations intended for human therapeutic use or for other health benefits in humans [4]. However, most indigenous herbal traditions not only have plant matters in their material medica, but also include animal matters and mineral compounds. Herbal products are usually ingested raw, as tea or as decoctions (concentrated extracts). Sometimes they are applied as a paste or powder on the skin. Some herbal traditions, such as traditional Chinese Mmdicine (TCM) and Ayurvedic medicine, have medicinal products that are packaged in the form of pills or liquids for ease of consumption and retailing [5]. These are sometimes called proprietary medicine, finished products, or patent medicine.

When to anticipate adverse effects and toxicities

Certain patterns of use or use of certain products tend to produce adverse effects and toxicities. Table 1 outlines when problems can be anticipated.

In most instances, problems arise due to inappropriate usage of these herbs and supplements. Herbs and supplements can be toxic when used for inappropriate indications, or prepared inappropriately, or used in large excessive dosages, or for a prolonged duration of time. When patients provide such a history of use, physicians should be on a look out for possible toxicities. For example, excessive doses of vitamin D due to overzealous fortification in milk resulted in hypercalcemia; similarly, excessive and prolonged intake of vitamin A can lead to osteoporosis and hepatotoxicity [6–9].

Many serious adverse effects have arisen because of using of traditional herbs for non-traditional indications. *Ephedra* is used in small dose in TCM for indications, such as wheezing and cough [10], but it was never used as a stimulant, a dieting agent, or recreational agent; however, such uses in excessive doses and durations have resulted in serious toxicities, including death, seizures, psychosis, myocardial infarction, cardiac arrhythmia, and stroke [11, 12]. Similarly, the use of *Datura* species for recreational purposes instead of therapeutic effects has resulted in anticholinergic poisoning and death [13].

In Belgium in the early 1990s, the TCM herb *Stephania tetrandra* was used for weight loss. *Aristolochia fangchi* was mistakenly used instead, and this resulted in more than 100 cases of renal failure and more than 20 cases of urothelial dysplasia [9]. Similar problems were later reported in the UK [14]. The culprit is thought to be the

Table 1 When adverse effects and toxicities may arise

Factors predisposing to adverse effects and toxicities	When to anticipate them
Inappropriate usage and inherent toxicity of herbs	Inappropriate indications (non-traditional indications)—weight loss, athletic performance, recreational use Inappropriate duration—use for prolonged periods of time, usually several weeks to months Inappropriate dosage—excessive dose in order to achieve some particular results Inadequate processing—herbs that are usually consumed in a certain way in a particular herbal tradition being processed in other non-recommended ways Herbs with pronounced pharmacological effects or toxic components Finished products claiming fast relief of symptoms or sexual enhancement
Adulteration with modern pharmaceuticals (NSAIDs, steroids, antihistamines, Sildenafil, sulfonylurea) Drug interaction	Patients on multiple modern pharmaceuticals, especially drugs with a narrow therapeutic index, such as warfarin, and taking dietary supplements and herbal products Patients taking multiple dietary supplements or herbal medicines
Heavy metal toxicities	Finished products from TCM, Ayurvedic traditions, or Mexican folk remedies

aristolochic acid found in *Aristolochia fangchi*. In TCM practice, *Stephania tetrandra* and *Aristolochia fangchi* were never meant to be used for weight loss [9, 15].

Inappropriate processing of herbs can also result in problems. In TCM practice, *Aristolochia fangchi* requires extensive boiling into a decoction before being applied in small amounts. In the Belgian slimming clinic, it was used as a powder. Aristolochic acid concentration is much lower in decoctions as it has low water solubility; hence, a decoction is a safer way to administer it [5, 10].

Herbal medicines do not usually produce immediate relief of symptoms as most of them are generally concerned with homeostasis. When products claim to provide immediate relieve of symptoms, physicians should watch out for possible intentional adulteration with pharmaceuticals. Such adulterations can cause problems and toxicities. These products are usually in the form of finished products meant for ingestion or occasionally for topical applications. A survey in Taiwan found that of 2,609 herbal samples analyzed, 23.7% were adulterated with pharmaceuticals [16]. A study of 243 proprietary products in California found that 7% contained undeclared pharmaceuticals [5]. In 1999, out of 3,320 TCM herbal products screened in Singapore, 1.2% were found to contain undeclared pharmaceuticals [17, 18]. Usually only one adulterant is found, although there are instances of multiple adulterants. Another form of adulteration is the substitution of one herb for another that may be cheaper or more readily available, but has a less desirable safety profile.

The most common adulterants are pharmaceuticals that are used to relieve uncomfortable symptoms, such as non-steroidal anti-inflammatory drugs (NSAIDs) and antihistamines [5, 9, 16]. Adulteration in steroids and sexual-enhancing drugs, such as Sildenafil, are also commonly reported [17, 18]. Serious adverse effects including death can result from such adulterations, especially since the drugs added can have serious toxic effects; for example, sulfonyleurea, phenylbutazone, phenytoin, and corticosteroids can have serious toxic effects [19]. Problems that can arise from adulterants in these products include allergic reactions, Addisonian crisis, and Cushing's syndrome from unsuspecting use of products with added steroids [20]. Hypotension can occur in patients on nitrates for cardiac ischemia and unsuspected use of products adulterated with Sildenafil, and severe or fatal hypoglycemia can result from unsuspected use of products with sulfonyleurea.

For patients taking multiple medications and dietary supplements or herbal medicines, physicians should look out for herb-drug interactions. Sixteen percent of adults in US who take prescription medicine also take herbal medicines [21]. Patients with chronic illnesses, who are most likely to be taking multiple medications, are also most likely to consume dietary supplements or herbal medica-

tions, putting them at risk of drug-herb interactions [22]. Patients may consume multiple dietary supplements or herbal medicines and take products that contain multiple components, putting themselves at risk of herb-herb interactions.

Patients most at risk of harmful drug-herbs interactions are those at extremes of age, on multiple prescriptions, with chronic illnesses or with impaired organ functions and those on prescription medications with a narrow therapeutic margin, such as warfarin [23]. Coagulative problems arising from drug-herb interactions with warfarin are commonly reported, sometimes with serious consequences, such as intracranial hematoma [24]. Garlic, ginkgo, ginger, and *Angelica sinensis* (Dong quai) are commonly implicated as they are commonly used, but any herb that may contain compounds related to salicylate or coumarin can augment anti-coagulative effects, resulting in bleeding [22].

Augmentation of sedative effects of modern pharmaceuticals is another problem, especially with popular herbs with sedative effects, such as *Piper methysticum* (kava) and *Valeriana officinalis* (valerian). Kava has been reported to increase the frequency and duration of "off-periods" in Parkinson's patients, and long-term use of this herb can also lead to hepatotoxicity and dermatopathy [24, 25]. Another form of interaction is with metabolic enzymes. For example, *Hypericum perforatum* (St John's wort), popularly used as an herbal anti-depressant, is a strong inducer of CYP3A, which metabolizes about 50% of all modern pharmaceuticals. This induction can lead to a sub-therapeutic effect in drugs that are inactivated or potential toxic effects in drugs that are activated by this family of enzymes [22].

Contamination of dietary supplements and herbal medicines with unwanted substances is another area of concern. Problems arising from contaminations are difficult to anticipate except that they appear to be more widely reported with products from some herbal traditions, such as TCM, Ayurvedic practices, and Mexican folk remedies. Physicians need to be aware of this problem when they encounter patients using products of these herbal traditions and presenting with non-specific symptoms. One form of contamination that is often reported is heavy metal contamination; it can lead to heavy metal poisoning and should be suspected in patients presenting with features suggestive of heavy metal toxicities after using dietary supplements and herbal medicines [26–28]. Heavy metal contamination arises due to defective manufacturing processes or because the herbs were grown in polluted soil [27]. However, in some instances, like in TCM and Ayurvedic medicine, heavy metals exist as part of their formulary and are deliberately added into preparations for therapeutic effects [5, 27]. Lead poisoning is frequently reported and presents with anemia, abdominal pain, and

encephalopathy. It is reported in children given Mexican folk remedies for gastrointestinal symptoms [29–31] and also in calcium supplements derived from animal sources [32–34]. Mercury, arsenic, and thallium use are reported in TCM [17, 18, 35]. Arsenic poisoning from herbal medicine is usually chronic and presents with features, such as skin changes, leucopenia, anemia, sensory neuropathy, and malignancies [18]. Other heavy metals reported to contaminate dietary supplements and herbal products include, cadmium, copper and molybdenum [27, 36, 37].

Other contaminants include micro-organisms, pesticides, industrial chemicals, and toxic herbs. These usually result in gastroenteritis, but more severe problems have been reported, such as eosinophilia-myalgia syndrome and death due to unknown chemical contamination of L-tryptophan supplements [9, 38–40]. Chinese herbal products have been reported to be contaminated with toxic herbs such as podophyllum and *Datura metel* [41]. These can produce features of toxicities due to the inherent toxicities of these herbal contaminants; for example, podophyllum poisoning can lead to agranulocytosis, and *Datura* ingestion can lead to anti-cholinergic toxicities [41].

Dietary supplements and herbs that possess pronounced pharmacological effects or toxic constituents can be inherently poisonous, and physicians should anticipate problems with such toxicities if they encounter patients using these products. The clinical features encountered will depend on the inherent compounds present in the products. Table 2 outlines some of the frequently reported herbs and their expected toxicities. Toxic herbs frequently encountered in reports are those with stimulant effects, such as *Ephedra* species, caffeine, ginseng, and ginkgo; those with

cardiac effects, such as herbs containing cardioactive glycosides or *Aconitum* species; those with autonomic effects, such as *Datura* species, *Lobelia* species, and yohimbine; those with hepatotoxic effects, such as herbs with pyrrolizidine alkaloids; those with nephrotoxic effects, such as herbs with aristolochic acid; and those that are used as abortifacients, such as pennyroyal oil [5, 9, 15, 36, 42–46].

The problem of the inherent toxicity is compounded by the variation in content of the active ingredients found in these products. The chemical constituents in a plant are dependent on the soil they are grown in, rainfall and sunshine, the season of harvesting, the stage of the plant growth during harvest, diseases afflicting it, and the parts that were harvested. Even in finished products, such as pills and liquids, there can be large batch-to-batch variations in content, and this can result in toxicity. For example, a survey of ginseng products found up to 200 times variation in content between different products. In another survey of *Ephedra* products, within the same product, up to ten times variation in active ingredients among batches was found [47, 48].

Allergic reactions to dietary supplements and herbal medicines appear to be common and under-reported [49]. These reactions may present as mild reactions, such as pruritus and urticaria, to more severe reactions, such as angioedema and anaphylaxis. Patients may react to compounds inherent in the dietary supplements and herbal medicines, such as proteins found in animal products. Patients may also develop allergic reactions to compounds that were added into these products as intentional adulterants or contaminants. It is difficult to anticipate allergic

Table 2 Organ toxicities and toxidromes, and common dietary supplements or herbal medicines that can cause them

Clinical features	Xenobiotics
Cardiac	Sodium channel effects— <i>Aconitum</i> species (widen QRS, shock) Digoxin-like effects— <i>Digitalis</i> species, bufo toads
Central nervous system	Seizures—strychnine, thujone, essential oils (camphor, eucalyptus) Sedation— <i>Valeriana</i> species, kava kava
Dermatological	Blistering—cantharidin (Chinese blister beetle)
Hematological	Coagulopathies—G-herbs (ginger, garlic, ginkgo) Agranulocytosis—anti-mitotic agents (colchicine, podophyllotoxin)
Hepatotoxic	Hepatitis—multiple agents, germander commonly reported Veno-occlusive disease—pyrrolizidine alkaloids (comfrey, <i>Senecio</i> species, <i>Heliotropium</i> species)
Nephrotoxic	Renal failure— <i>Aristolochia</i> species Hypertension, hyperkalemia—licorice
Anticholinergic	<i>Datura metel</i> commonly used in TCM Hexing herbs (<i>Atropa</i> species, <i>Hyoscyamus</i> species, <i>Mandrago officinarum</i>) common in Western herbal practice
Sympathomimetic	<i>Ephedra</i> species, <i>Citrus aurantium</i> (bitter orange)
Salicylate poisoning	Willow bark, checkerberry

reactions to these products unless previous allergies are known.

Management of patient with toxicities

Toxicities from dietary supplements and herbal medicines present unique management challenges. Patients may not inform their physicians about herbal supplement use because they do not perceive these products as medications. When toxicities arise, patients may not be aware that the dietary supplements or herbal products are causing the problems, so they continue to use the products. Such behaviors can hamper diagnosis or make the toxicities worse.

Information about product content and dose may also be difficult to obtain. Labeling of these products can be inaccurate or incomplete. The quantity of content can be different from the label given the lack of quality assurance and labeling consistency. Multiple components within a product make identification of the offending agent difficult. Unsuspected adulterants or contaminations may make the presentation more confusing. Raw herbs, dried herbs, or herbs processed into powders or liquids may prove difficult or impossible to identify. Even when labeling is accurate or herbs can be identified, scientific and toxicological information regarding them may not be readily available from conventional resources. A study in the US of adverse effects from dietary supplements found that less than half of the products or ingredients were listed in the poison information software that is used in most US poison centers [50].

Nevertheless, the spectrum of toxicities from dietary supplements and herbal medicines is similar to that of toxicities from pharmaceuticals in that similar organ system

effects or toxidromes can be expected. Furthermore, some herbs or formulations are well known to result in certain organ toxicities or toxidromes, and their presence should be suspected when these clinical features occur (see Table 2).

The approach to patients with toxicities from dietary supplements and herbal medicine is similar to the approach to patients with other forms of toxicities. Table 3 outlines steps generally recommended by authors for treating these patients [22, 51]. Patients who present with unstable medical conditions, such as cardiac dysrhythmias or seizures, require immediate stabilization. Once they are stabilized, extended history taking, physical examination, and laboratory investigation can be done. Once the problem is identified, the use of the product can be stopped or altered, and appropriate therapy can be initiated.

Good resuscitative, symptomatic, and supportive care is paramount in these patients, as in all patients with poisoning. In such circumstances, offending agents would most likely not be identified early, and even if identified, specific antidote treatment may not exist, making resuscitative, symptomatic, and supportive care more important. Some generalizations for management can be made. Patients who present early with toxic ingestion of dietary supplements or herbal products that can cause severe life-threatening effects, such as *Aconitium* species or colchicines, should undergo gastric lavage with adequate airway protection. Similarly, activated charcoal can be given in an acute overdose of toxic dietary supplements and herbal medicines if there is adequate airway protection. In patients with stimulant effects, agitation or seizures can be managed with benzodiazepines. In patients suffering from digoxin toxicity, digoxin antibody is expected to work, but a non-standard dose may be required. In patients with sodium

Table 3 Useful steps in managing patients with toxicities from dietary supplements or herbal medicines

1. Ask specifically regarding use of such products
2. Secure sample for identification
 - a. Actual herbs or product used
 - b. Prescription or packaging
3. Laboratory studies
 - a. Basic blood count, renal function, liver function, and electrocardiogram
 - b. Heavy metal screening if suspected or if symptoms are non-specific
 - c. Analysis methods exist for some herbal toxins only—colchicines (HPLC, GCMS), tropane alkaloids (GCMS, oxalate (GCMS), vinca alkaloids (HPLC), cardioactive steroids (immunoassay)—check with local laboratory
4. Good resuscitative, symptomatic, and supportive care
5. Use antidote if appropriate
6. Instruct patients and family to stop using the product
7. Consider outpatient monitoring of renal function, liver function, and blood counts
8. Report case to regulating authority
9. Report unusual cases in the medical literature

channel effects (wide QRS complexes, shock), sodium bicarbonate can be used, and class IB anti-arrhythmics such as lignocaine can be used if sodium bicarbonate fails. The local poison information centers can be good resources to assist with diagnostic or management issues.

When obtaining history from patients suspected of suffering from dietary supplement or herbal medicine toxicities, it is important to remember that patients often do not volunteer information regarding the use of these products to their physicians. When suspected, physicians need to ask patients specifically if they were or currently are consuming such products. And these products include specialty teas for weight loss or calming effects. Studies have shown that up to 70% of patients who use alternative therapies do not inform their physicians about it [52].

During physical examination, features suggestive of toxidromes should be looked for, such as pupils size, mucosa moisture, skin moisture, and bowel sounds. Features of organ toxicities should also be sought, especially signs of liver injuries or failure. These toxidromes and organ toxicities can often be related to certain commonly used dietary supplements and herbal medicines (see Table 2).

Whenever possible, a sample of the actual product used by the patient should be secured; otherwise, prescription or packaging should be secured. If this is not possible, samples from where the patient actually obtained the product may be useful. If raw herbs were involved, obtain information about the parts used and how they were processed. These can be used to identify offending agents. Although immediate identification or analysis is often not possible, efforts should still be made to identify them later as some herbs and products can have long-term effects, such as hepatotoxicity or nephrotoxicity.

Basic diagnostic studies, such as blood count, electrolytes and renal function, liver function, and electrocardiograms, should be performed, as well as other tests based on the patient's clinical presentation. If symptoms are non-specific or suggestive of heavy metal toxicities, a heavy metal screen may be useful. Analytical methods exist for herbal toxins, such as colchicines, tropane alkaloids (anti-cholinergic), vinca alkaloids, and cardioactive glycosides[53]; however, the availability of these tests depends on local laboratories. When such analyses are indicated, it is essential to check with the local laboratory if the tests are available. The salicylate level should be available in most laboratories.

For patients who can be discharged, they should be specifically instructed to stop using the dietary supplements or herbal medicines[22]. This discussion should involve family members as well, as they may be taking similar products or be supplying them to the patients. Consideration should also be given to referring patients for outpatient monitoring of liver function, renal function, and blood counts in a week or two, as toxicities in these organs

may be delayed and not clinically apparent. Some authors and herbal practitioners advocate that patients using TCM should have their liver function monitored regularly as many herbs can cause hepatotoxicity [36].

The relevant regulating authorities should be informed of such events so that offending products can be investigated and if necessary taken off the market to prevent more people from being affected. The range of dietary supplements and herbal products are expanding rapidly, and medical and scientific knowledge of these products is still growing. Unusual cases should be reported to the medical literature to inform the medical community of potential problems [22].

Discussing dietary supplements and herbal medicines with patients

Opportunities arise at times to discuss the use of dietary supplements and herbal medicines with patients or patients' family members. Physicians trained in modern medicine may find themselves inadequately prepared for this task; the simplest option practiced by most physicians would then be to denounce all such products. However, such practice may alienate patients and their family members, especially among ethnic groups where herbal traditions are important. This would also cause the patients to be less willing to approach their physicians for help when adverse effects arise.

Ko outlined some useful advice that can be used for patient education or discussion about dietary supplements and herbal medicines [54]. Some advice that can be easily committed to memory and applied in discussions is as follows:

1. Dietary supplements and herbal medicines should be considered as medicines. Hence, dosage recommendation should be followed, and long-term therapy should be avoided. If unsure whether a product is safe or useful, or if it will interact with one's prescription, always consult a physician or pharmacist first.
2. Obtain dietary supplements and herbal medicines from reputable sources. The most reliable sources are large manufacturers, especially if they are located in countries that regulate these products like pharmaceuticals. This would reduce the chance that products may contain contaminants or adulterants. If obtaining herbs, consult an experienced herbal practitioner. In countries where herbalists or traditional healers are licensed legally, licensed practitioners should be consulted.
3. If new symptoms developed during the use of these products, stop using the product and consult a physician.

- Vulnerable patients, such as women who are pregnant or nursing and young children, should avoid using herbal medicines or dietary supplements (except folate and iron supplements) if possible.

Conclusion

Dietary supplements and herbal medicines play an important role in the general health-care system of many developing countries worldwide and are gaining popularity rapidly in many developed countries. Most of these can be used safely if the public is given the right education and advice. Physicians need to be ready to discuss or advise patients with regards to their use.

Adverse effects, such as allergy, drug interactions, heavy metal poisonings, reactions to adulterants or contaminants, and toxicities, can arise from the product itself. When these problems manifest, a rational approach in management emphasizing good resuscitation, symptomatic, and supportive care can be helpful. Clinical features may give clues about the offending agents. Physicians should consider following up these patients for delayed organ-toxic effects.

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Dong-Haur Phua is an Emergency Physician and Clinical Toxicologist of the Emergency Medicine Department at Tan Tock Seng Hospital, Singapore. His research interest include elderly mistreatment, resuscitation, all aspect of clinical toxicology especially plants and herbal poisoning and decision making in clinical medicine.