

## Adverse reactions to watch for in patients using herbal remedies

Alternative medicine has increased in popularity in the United States. In 1997, an estimated \$27 billion was spent on alternative therapies; at that time, the use of herbal remedies had increased 380% compared with 1990.<sup>1</sup> The dietary supplement industry, which manufactures many herbal products, represents a \$13 billion market with \$3.24 billion in sales.<sup>2</sup> The passage of the Dietary Supplements Health and Educational Act (DSHEA) of 1994 allowed dietary supplement manufacturers to make certain functional claims on labels, shifting the burden of proof regarding toxicity from the seller to the regulator. Herbal remedies are considered food products under the DSHEA and hence are not subject to rigorous clinical testing, as are pharmaceutical products. No manufacturing standards regulate the quality and production of herbal remedies. All these factors have led to increased adverse reactions in patients choosing alternative therapies. It is imperative that physicians and healthcare providers inquire into their patients' use of herbal remedies and become knowledgeable about potentially adverse effects of herbs and possible drug-herb interactions.



St. John's Wort

A-Z Photos/K.D. Miller

Adverse reactions associated with dietary supplements, especially herbal remedies, can be caused by inherently toxic herbs, by herb overdoses, or by drug-herb interactions, especially with pharmaceuticals that have a narrow therapeutic index. They can also represent idiosyncratic reactions to herbs, such as allergic responses or anaphylaxis. Other adverse reactions can be due to adulteration caused by manufacturing and quality problems, misidentification, substitution of one herb for another, variability in the amount of active ingredients, inaccurate or incomplete label identification, improper processing and preparation, or contamination.

Table 1 lists some herbs commonly used by consumers, as well as indications, potential adverse reactions, and possible drug-herb interactions. Additional information can be obtained from recent review articles on herbs<sup>3-5</sup> and

potential drug-herb interactions.<sup>6-9</sup> It is important to realize that personal experience is not a reliable basis for the exclusion of uncommon reactions to herbal remedies.<sup>10</sup> A patient with generally stable reactions to an herbal remedy may still experience an adverse reaction, since there may be batch-to-batch variations and/or accumulation of toxic components. Physicians who are treating patients suspected of herb-related adverse reactions are encouraged to contact the US Food and Drug Administration's MED-WATCH program or the local poison control center, so that data can be collected and analyzed.

### Methods

This review article is based on a literature search using MEDLINE and other reference source material.<sup>7-11</sup> The MEDLINE search included the following keywords: herbs, herbal, traditional Chinese medicines, toxicity, adverse effects, death, drug interaction, and pharmacokinetic. Specific searches were performed combining these keywords with the common names and scientific names of plant products.

### Adverse reactions

The most common herbs used in alternative therapies are listed in Table 1. Other commonly used herbs can cause adverse reactions as well, including the following:

**Siberian ginseng** (*Eleutherococcus senticosus*) has been implicated in causing hypertension in a female who had been taking the product for 15 years. Rechallenge with the same product was repeated twice, causing a rise in blood pressure.<sup>12</sup>

**Dang gui** (*Angelica sinensis*) binds to estrogen receptors and promotes uterine growth. It could potentially stimulate estrogen receptor-positive cancer cells, a risk for women with breast cancer.<sup>13</sup>

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### Advice for patients who use herbal remedies

- Treat herbal remedies as medicinal products, not food products. "More" does not mean "better."
- Do not exceed recommended dosage and do not use herbal remedies for a prolonged period of time. A good rule of thumb is no more than four weeks unless under the supervision of a healthcare provider.
- Patients with serious diseases should consult a physician before using herbal remedies.
- Herbal remedies can interact with other pharmaceutical products. Consult a physician or a pharmacist when using herbal remedies in conjunction with pharmaceuticals.
- If side effects develop, stop taking the herbal remedies and consult a physician.
- Purchase herbal remedies only from reputable sources.
- Do not use herbal remedies during pregnancy and lactation unless directed to do so by your physician.
- Do not give herbal remedies to infants or young children.

Table 1

Common name (scientific name)	Conditions treated and other uses	Side effects/safety issues	Drug interactions, if any
Echinacea [ <i>Echinacea pallida</i> (Nutt.) and <i>Echinacea purpurea</i> (L.) Moench]	Common cold URT infection <sup>11,48,49 * §</sup> Lower UTI <sup>11 * §</sup> Immune stimulation <sup>50 *</sup>	Anaphylaxis <sup>51</sup> Contraindicated in multiple sclerosis, collagenosis, HIV infection, tuberculosis <sup>7,11</sup>	None known or substantiated
Feverfew ( <i>Tanacetum parthenium</i> )	Arthritis <sup>52 †</sup> Migraine <sup>53 *</sup>	Inhibits human blood platelet aggregation <sup>54</sup> Contact dermatitis <sup>55</sup>	Warfarin or other anticoagulants May reduce effectiveness of NSAIDs by inhibition of prostaglandin <sup>56</sup>
Garlic ( <i>Allium sativum</i> L.)	Hyperlipidemia (adjunct treatment) <sup>11 §</sup> Familial hyperlipidemia (pediatric) <sup>57 †</sup> Hepatopulmonary syndrome <sup>58 *</sup> Hypercholesterolemia <sup>59,60 †</sup> Platelet aggregation <sup>61,62 *</sup>	GI symptoms <sup>11</sup> Allergic reactions including contact dermatitis, asthma, rhinitis, urticaria <sup>63</sup>	Caution in patients stabilized with warfarin <sup>6</sup> and antiplatelet drugs May increase serum insulin levels <sup>7</sup>
Ginger ( <i>Zingiber officinale</i> Roscoe)	Dyspepsia and motion sickness <sup>11,64 * §</sup> Nausea and vomiting (prevention) <sup>45,65,66 *</sup> Thrombosis <sup>67,68 *</sup> Rheumatism and musculoskeletal disorders (pain relief) <sup>69 *</sup>	Contact dermatitis <sup>70</sup>	Caution in using antiplatelet drugs
Ginkgo biloba ( <i>Ginkgo biloba</i> L. leaf)	Erectile dysfunction <sup>41 *</sup> Antidepressant-induced sexual dysfunction (predominantly that caused by SSRIs) <sup>42 *</sup> Alzheimer's disease <sup>11,35,71 † §</sup> Asthma (reduces airway inflammation) <sup>72 *</sup> Chronic schizophrenia (additive effect with fewer side effects) <sup>73 *</sup> Cerebrovascular ischemia <sup>74 *</sup> Oxidative stress in cardiovascular surgery (adjuvant therapy) <sup>75 *</sup> Intermittent claudication <sup>11,37 * §</sup> Irradiation (anticlastogenic effect) <sup>76 *</sup> Vertigo, dizziness, tinnitus caused by vestibular disorders <sup>11,39,40 * §</sup> Symptoms of premenstrual syndrome <sup>77 *</sup>	Inhibits platelet-activating factor <sup>78</sup> Intracerebral hemorrhage <sup>79</sup>	May compete for MAO inhibitor <sup>80</sup> May cause bleeding when combined with NSAIDs, anticoagulants, and anti-platelet drugs <sup>81</sup> Interaction with thiazide diuretic, causing hypertension <sup>12</sup>
Ginseng ( <i>Panax ginseng</i> C.A. Meyer)	Fatigue, decline in capacity for work and concentration <sup>11,82,83 * §</sup> Common cold (prevention) <sup>86 *</sup> Cancer (prevention) <sup>88 *</sup> Also: Enhances exercise performance <sup>84,85 *</sup> Immunomodulatory effects <sup>87 *</sup>	Androgen effect <sup>89</sup>	Interacts with warfarin and other anticoagulants <sup>7,8</sup> May interact with phenelzine and other MAO inhibitors <sup>90</sup> Not advised with stimulants, antipsychotic drugs, or hormones <sup>7</sup>
Goldenseal ( <i>Hydrastis canadensis</i> L.)	Malaria <sup>91 *</sup> Diarrhea <sup>92,93 *</sup> Ventricular tachyarrhythmias <sup>94 *</sup>	Acute hemolysis in babies with G6PD deficiency <sup>95</sup>	Contraindicated in neonates with jaundice and pregnant women <sup>96</sup> May antagonize heparin <sup>7</sup>
Saw palmetto ( <i>Serenoa repens</i> [Bartram] Small)	Benign prostatic hypertrophy <sup>11,34,97 † §</sup>	GI symptoms <sup>98</sup>	Avoid with hormone therapy (e.g., estrogen and oral contraceptives) <sup>6</sup>
St. John's wort ( <i>Hypericum perforatum</i> L.)	Mild depression/anxiety <sup>11,36,99 † §</sup> Topical myalgia, burn <sup>11 * §</sup> Also: Wound-healing, anti-inflammatory, and analgesic activity <sup>100 *</sup>	GI symptoms, dizziness/confusion, tiredness/sedation, photosensitivity <sup>101,102</sup> Inhibition of sperm motility <sup>103</sup>	May potentiate MAO inhibitors and SSRIs <sup>7</sup> May interact with drugs binding to $\mu$ -opioid receptor (e.g., known photosensitizers such as piroxicam or tetracycline) <sup>6</sup>
Valerian ( <i>Valeriana officinalis</i> L.)	Restlessness, sleeping disorders <sup>11,105,106 * §</sup>	Cardiac complications and delirium associated with withdrawal <sup>107</sup>	Prolongs sedation from barbiturates <sup>6</sup> Additive effects with benzodiazepine <sup>108</sup>

\*More information needed; †probably not effective; ‡probably effective; §from German Commission E Monograph. In 1978, the German Ministry of Health established Commission E to review the safety and efficacy of phytotherapy and herbal substances; the Commission has published a total of 462 monographs<sup>11</sup>. G6PD: glucose-6-phosphate dehydrogenase; GI: gastrointestinal; MAO: monoamine oxidase; SSRI: selective serotonin reuptake inhibitors; NSAID: nonsteroidal anti-inflammatory drug; SSRI: selective serotonin reuptake inhibitor; URT: upper respiratory tract; UTI: urinary tract infection.

**Aconite** (*Aconitum carmichaeli*) poisoning is probably the most common cause of cardiac toxicity among people taking Chinese herbs. Clinical presentation typically includes numbness and paresthesia beginning in the mouth and spreading to the limbs, as well as dizziness, nausea, vomiting, weakness, sweating, and palpitations. The conscious state may be reduced. With severe poisoning, hypotensive sustained ventricular tachyarrhythmias may develop, often complicated by acidosis and hypokalemia. The poisoning is reversible with supportive therapy.<sup>14</sup>

**Chaparral** (*Larrea tridentata*),<sup>15</sup> **germander** (*Teucrium chamaedrys*),<sup>16</sup> **jin bu huan** (*Lycopodium serratum*, which contains levo-tetrahydro-palmatine),<sup>17,18</sup> **ephedra** species (**ma huang**),<sup>19</sup> and **syo-saikoto-to** (a mixture of seven herbs),<sup>20</sup> among other herbs, have been associated with toxic hepatitis.

Toxic hepatitis shows no specific pattern of symptoms and is difficult to diagnose. When considering herbs as a cause for toxic hepatitis, physicians will frequently rely on the elimination of other causes and a temporal relationship between ingestion of herbs and onset of hepatitis and between withdrawal of herbs and recovery. Autoimmune hepatitis triggered by an herbal formula, dai-saiko-to, has also been reported.<sup>21</sup> It was hypothesized that the immunostimulating effects of the formula may have modulated the latent autoimmunity of the patient.

**Pyrrrolizidine alkaloid**—which is found in *Crotalaria assamica* Benth and *C sessiliflora* of the Leguminaceae family, *Senecio chrysanthemoides* and *S scandens* Buch-Ham of the Compositae family, *Packera candidissima*,<sup>22</sup> and Eupatorium species—has been shown to induce hepatic veno-occlusive toxicity and can have similar effects on an unborn fetus.<sup>23</sup> Not all pyrrolizidine alkaloids are hepatotoxic, however, depending on the structure activity of the pyrrolizidine nucleus.<sup>24</sup> Symptoms of pyrrolizidine alkaloid poisoning in veno-occlusive disease include arterial hypertension and right ventricular hypertrophy,<sup>22</sup> abdominal pain, ascites, hepatomegaly, and raised serum transaminase levels.<sup>25</sup>

**Licorice root** (*Glycyrrhiza glabra* L.), which contains glycyrrhizin, has also been reported to be associated with Fanconi syndrome.<sup>26</sup> Other herbs related to renal toxicity may be secondary causes, with toxicity due instead to adulteration with pharmaceutical products (for example, mefenamic acid<sup>27</sup>) or contaminants.

**Ephedra** products have been associated with adverse events, including deaths related to myocardial infarction and cerebrovascular accident. Many products that contain ephedra also contain multiple stimulants such as caffeine and are marketed for weight loss, energy and performance enhancement, body building, and as substitutes for street drugs.<sup>28</sup> All the claims and ingredients connected with these products are clear deviations



Ginger

from the traditional Chinese medicinal usage of ephedra for asthma and pulmonary diseases.

**Chinese patent medicines**, imported herbal products formulated into pills and tablets, often cause adverse reactions. They may contain natural toxins, heavy metals, or pharmaceuticals.<sup>29</sup> Cinnabar (mercuric sulfide), realgar (arsenic sulfide), or litharge (lead oxide) may be present as part of the traditional formula. Other common toxic herbal ingredients found in these imported patent medicines include borneol (similar to camphor), aconite, bufo secreta (toad secretion or bufotoxin), mylabris, scorpion, borax, and *Strychnos nux vomica* (strychnine).

### Drug-herb interactions

Drug-herb interactions are an important consideration, especially regarding pharmaceutical products with narrow therapeutic indexes. Because herbs contain pharmacologically active compounds, potential drug interactions can occur when multiple herbs are used or when pharmaceuticals are administered to a patient using herbs.

**Papaya extract**, which contains papain, caused an increase in the International Normalized Ratio (INR) in a patient previously well-maintained on warfarin. After withdrawal of both warfarin and papaya extract, the patient's INR returned to normal. Papain is contraindicated with warfarin, since it may damage the mucous membranes of the gastrointestinal tract and result in increased bleeding.<sup>12</sup>

**Ginkgo biloba** and thiazide diuretic can interact to cause hypertension.<sup>12</sup>

**Feverfew, garlic, ginkgo, ginger, and ginseng** may alter bleeding time. When used concomitantly with warfarin, close monitoring is advised.<sup>6</sup>

**Kava-kava** (*Piper methysticum* F.) is used mainly for its euphoric effects. When combined with benzodiazepine, it may result in a semicomatose state.<sup>7</sup> It should not be used with barbiturates, antipsychotics, or alcohol.<sup>8</sup>

**Licorice** (*Glycyrrhiza glabra* L.) can potentiate the effect of cardiac glycoside. Close monitoring is required when the two are used concomitantly.<sup>7</sup>

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### Questions physicians should ask their patients

- Is the patient using any dietary supplements? Be specific with questions and be sure the answer includes use of vitamins, minerals, herbs or other botanicals, amino acids, concentrates, metabolites, extracts, or other dietary substances.
- If the patient is using dietary supplements, what is the dosage formulation and what are the directions for use?
- Is the patient seeing an herbalist, acupuncturist, naturopathic practitioner, or natural healer?
- What is the dietary supplement for? (Asking this question allows patients to express their knowledge as well as any untold symptoms or complaints.)
- If the herbal remedies require preparation on the part of the patient, ask for more details about the procedure and the patient's source of information about that procedure.
- Has the patient observed any serious side effects from the herbal remedies?
- Is the patient taking any other over-the-counter or prescription medications?

### Communication with patients

It is important for physicians and other healthcare providers to establish open communication with their patients regarding the use of dietary supplements. Many patients are unwilling to inform their physicians, fearing disapproval and perceiving a lack of knowledge and understanding in their physicians. Inquiring about the use of herbs, vitamins, and other remedies should be part of normal history taking, along with other questions about social habits and background. Physicians often talk with patients about controversial subjects, so discussing the merits and drawbacks of herbs does not require new skills.<sup>30</sup> When communicating with the patient, the physician should pose questions that are direct, neutral, and nonjudgmental.<sup>31</sup>

Patients often consider herbal remedies as natural products or food and not as medicine. They assume, therefore, that herbal remedies are free from side effects. Physicians need to emphasize that many pharmaceuticals were originally derived from plant products and that herbal remedies can be as potent as pharmaceuticals. Physicians need to ask specific questions regarding the use of vitamins, minerals, herbs or other botanicals, amino acids, concentrates, metabolites, extracts, and any other dietary substances being used by their patients. They should also obtain information about directions for use, methods of preparation, and dosage formulations.

It is especially important for physicians to inquire about method of preparation when raw botanicals are being used. In traditional Chinese medicine, prescriptions frequently consist of decoctions of a number of different herbs. Such an herb decoction is a concentrated extract, usually prepared by boiling the herbs in water until the mixture is reduced to a small volume. Knowing the method by which

an herbal remedy has been prepared is important, because many toxic herbs can become relatively safe for use if they have been processed properly. For example, aconiti tuber toxicity can be greatly reduced after the plant material is specially prepared through heat and water extraction.<sup>32</sup> There are five reported cases of podophyllotoxin toxicity due to ingestion of *Dysosma pleianthum* or bajaolian, a species of mayapple prescribed in traditional Chinese medicine. Toxicity responses ranged from nausea and vomiting to abnormal liver function tests and central nervous system disturbance. The inconsistent relationship between doses and clinical severity of symptoms might be due to different methods of preparation.<sup>33</sup>

Patients should be asked whether they have consulted with other healthcare providers, e.g., acupuncturists, herbalists, naturopathic practitioners, or natural healers. Asking this question directly will often reveal other complaints, other symptoms, or the choice of alternative treatments, including dietary supplements. All this information will assist physicians in making the proper diagnosis. Physicians should speak with patients about the efficacy and toxicity of herbal remedies, basing the discussion on firm knowledge and scientific fact, and about potential drug-herb interactions and side effects of herbal remedies. By the same token, patients and providers alike must acknowledge that as long as information on the efficacy and toxicity of alternative therapies remains inadequate, advice will remain imperfect and a matter of judgment rather than fact.<sup>31</sup>

### Herbal products as treatment options

An increasing number of scientifically based clinical trials are being conducted on the efficacy of herbal remedies and comparing herbs and pharmaceuticals for the treatment of different diseases. Although some of the herbal remedies have shown promise, no large clinical trials have yet demonstrated efficacy equal to that of pharmaceuticals for clearly defined disease states.<sup>34-36</sup>

The following herbs show some promise in treating various diseases, especially when current treatments are inadequate.

**Ginkgo biloba** has shown promise in the treatment of patients suffering from peripheral occlusive arterial disease. It causes a significant and therapeutically relevant prolongation of patients' walking distance.<sup>37</sup> It may be effective in the treatment of patients with circulatory encephalopathy<sup>38</sup> and can considerably improve oculomotor and visuovestibular function in patients complaining of vertigo or dizziness caused by vascular vestibular disorders.<sup>39,40</sup> Ginkgo may have beneficial effects in erectile dysfunction and sexual dysfunction caused by selective serotonin reuptake inhibitors.<sup>41,42</sup>

**Dang gui** (*Angelica sinensis*) may be useful in relieving menopausal symptoms, especially in women who

have ruled out prescription drugs and are not at risk of breast cancer.<sup>13</sup>

**Milk thistle** (*Silybum marianum gaertn*) contains silymarin, which acts as liver-protective agent. This herb shows promise in treating *Amanita phalloides* mushroom poisoning<sup>43</sup> and a variety of liver disorders, including hepatitis.<sup>44</sup>

**Ginger and pyridoxine** (vitamin B<sub>6</sub>) may be beneficial for nausea and vomiting resulting from pregnancy.<sup>45</sup>

**Asian ginseng** (*Panax ginseng* C.A. Meyer) may protect against radiation and liver toxicities.<sup>46</sup>

**Shi-Quan-Da-Bu-Tang** ("Ten Significant Tonic Decoction" or "SQT") consists of a mixture of ten medicinal herbs and may reduce the adverse effects caused by chemotherapeutic agents and radiation in cancer patients.<sup>47</sup>

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