



Approximately 25 percent of Americans who consult their physician about a serious health problem are employing unconventional therapy, but only 70 percent of these patients inform their physician of such use.

Unlike conventional drugs, herbal products are not regulated for purity and potency. Thus, some of the adverse effects and drug interactions reported for herbal products could be caused by impurities (e.g., allergens, pollen and spores) or batch-to-batch variability. In addition, the potency of an herbal product may increase the possibility of adverse effects.

### Select Herbal Products & Side Effects

**Product:** Ginkgo biloba

**Side effects:** bleeding

**Drug interactions:** aspirin, warfarin (Coumadin), ticlopidine (Ticlid), clopidogrel (Plavix), dipyridamole (Persantine)

**Product:** St. John's wort

**Side effects:** gastrointestinal disturbances, allergic reactions, fatigue, dizziness, confusion, dry mouth, photosensitivity

**Drug interactions:** antidepressants

**Product:** Ephedra (ma huang)

**Side effects:** hypertension, insomnia, arrhythmia, nervousness, tremor, headache, seizure, cerebrovascular event, myocardial infarction, kidney stones

**Drug interactions:** caffeine, decongestants, stimulants

**Product:** Kava

**Side effects:** oral and lingual dyskinesia, torticollis, oculogyric crisis, exacerbation of Parkinson's disease, painful twisting movements of the trunk, rash

**Drug interactions:** sleeping pills, antipsychotics, alcohol

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### Ginkgo Biloba

The active ingredients in Ginkgo biloba extract account for its antioxidant properties and its ability to inhibit platelet aggregation.

Consequently, this herbal product is promoted for use in improving cognitive function and blood flow. To date, however, at least four reports of spontaneous bleeding in association with use of Ginkgo biloba have been published.

One report described a 70-year-old man who presented with bleeding from the iris into the anterior chamber of the eye one week after beginning a self-prescribed regimen consisting of a Ginkgo biloba concentrated extract (Ginkoba), in a dosage of 40 mg twice daily.

His medical history included coronary artery bypass surgery performed three years previously. His only medication was aspirin, in a dosage of 325 mg per day, which he had taken since his bypass surgery. After the spontaneous bleeding episode, he continued to take aspirin but discontinued the

ginkgo product. Over a three-month follow-up period, he had no further bleeding episodes. Interaction of the ginkgo product and aspirin was considered the cause of his ocular hemorrhage.

Ginkgo biloba may also interact with warfarin (Coumadin). A 78-year-old woman who had been taking warfarin for five years after coronary bypass surgery suffered a left parietal hemorrhage after using a ginkgo product for two months. No change was noted in her prothrombin time. The intracerebral bleeding was attributed to the antiplatelet effects of ginkgo.

In another reported case, a 33-year-old woman was diagnosed with bilateral subdural hematomas after almost two years of ingesting Ginkgo biloba, in a dosage of 60 mg twice daily. Her other medications were acetaminophen and an ergotamine-caffeine preparation, which she used briefly. While she was taking Ginkgo biloba, her bleeding times were 15 and 9.5 minutes. Within 35 days after she stopped taking the ginkgo product, her bleeding times were normal (three to nine minutes).

An additional case of spontaneous intracerebral hemorrhage was reported in a 72-year-old woman who had been taking Ginkgo biloba, in a dosage of 50 mg three times daily, for approximately six months. No history of head trauma could be elicited.

Until further information is available, patients who are taking garlic, vitamin E, warfarin, aspirin, or other drugs with antiplatelet or anticoagulant effects should be cautioned about potential interactions with ginkgo products. Patients who are taking ginkgo products should be counseled to inform their physician about unusual bleeding or bruising, new-onset headaches or vision changes.

## St. John's Wort

St. John's wort (*Hypericum perforatum*) is an herb widely promoted as a "natural" antidepressant. In Germany, this herb is commonly prescribed for various psychopathologic conditions involving depression and anxiety. Herbal products are permitted to be marketed in Germany if they fit general criteria in published monographs. However, the safety and efficacy of St. John's wort are not evaluated in the appropriately designed studies that the FDA requires for antidepressant drugs.

The German monograph for St. John's wort identifies hypericin, a purported monoamine oxidase (MAO) inhibitor, as the active ingredient in the herb. The hypericin content of St. John's wort is used as the basis for dosing. However, one U.S. study showed that pure hypericin does not bind to MAO. In this study, a crude St. John's wort extract exhibited significant receptor affinity for MAO, but the investigators stated that concentrations of the crude extract required for this activity are unlikely to be achieved after oral administration.

No instances of an interaction between tyramine-containing foods and St. John's wort have been reported, but drug interactions may be of concern. One report described a 50-year-old woman who had taken St. John's wort powder, in a dosage of 600 mg per day for 10 days, and then took one 20-mg dose of paroxetine (Paxil). She became incoherent and lethargic and also complained of nausea, weakness and fatigue.

Interestingly, the woman had been taking paroxetine, in a dosage of 40 mg per day, for eight months; she discontinued the paroxetine when she started taking St. John's wort.

Studies have shown that St. John's wort extract inhibits serotonin, dopamine and norepinephrine reuptake in vitro.<sup>14</sup> Consequently, it would be prudent to avoid the concomitant use of St. John's wort and antidepressants until further information is available. Given that the half-life of hypericin is 24 to 48 hours, a conservative recommendation would be to wait until two weeks after a patient has stopped taking St. John's wort and then prescribe an antidepressant.

However, if a patient needs to be started on an antidepressant expeditiously, a relatively long "washout period" may not be practical.

Despite the paucity of evidence for food and drug interactions with St. John's wort, patients who use this herb and then begin taking antidepressants or other serotonergic drugs should be observed carefully for adverse effects.

Side effects of St. John's wort include dry mouth, dizziness and confusion. In one open study 16 of more than 3,000 patients, gastrointestinal symptoms, allergic reactions and fatigue were reported by 0.6 percent, 0.5 percent, and 0.4 percent of patients, respectively.

Phototoxicity manifested as elevated, itching, erythematous lesions has also been reported in association with the use of St. John's wort. Neuropathy associated with sun exposure is another manifestation of phototoxicity.

In one case report, a 35-year-old woman developed stinging pain on sun-exposed areas after four weeks of self-treatment with ground St. John's wort. Her pain was worsened by cold, minimal mechanical stimuli and sun exposure. After she stopped taking St. John's wort, her symptoms resolved gradually over two months. The patient's symptoms were attributed to demyelination of cutaneous axons caused by photoactivated hypericins.

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## Ephedra

Ephedrine and related alkaloids are the pharmacologically active moieties of the extract of Ephedra (a genus of shrubs). Ephedrine constitutes 30 to 90 percent of the alkaloids of Ephedra species. The extract of some species also contains pseudoephedrine. Ephedra (ma huang) is commonly found in herbal weight-loss products referred to as "herbal fenphen." Some weight loss clinics and retail outlets promote herbal products as an alternative to the

use of fenfluramine (Pondimin) and dexfenfluramine (Redux), the prescription anorexiant recently removed from the U.S. market. Herbal fen-phen products that also contain St. John's wort are sometimes referred to as "herbal Prozac."

Ephedrine-containing products are also marketed as decongestants, bronchodilators and stimulants. Other promoted uses include enhancement of athletic performance and body-building efforts. Marketed uses of ephedrine-containing products such as "herbal ecstasy" include induction of a euphoric state and heightening of awareness and sexual sensations. The FDA has advised consumers not to use ephedrine-containing products marketed as alternatives to street drugs.

In the past few years, the FDA has investigated more than 800 reports of adverse reactions associated with more than 100 different products that contained or were thought to contain Ephedra alkaloids. Reported adverse reactions have included insomnia, nervousness, tremor, headaches, hypertension, seizures, arrhythmias, heart attack, stroke and death. Approximately 56 percent of the reported adverse effects occurred in persons younger than 40 years old; about another 25 percent occurred in persons 40 to 49 years of age. The relatively young age group in which serious cardiovascular events have occurred is of concern.

In response to the reports of cardiovascular effects, the FDA has proposed a dosage limit of 8 mg every six hours (24 mg per day) for ephedra alkaloids. The proposed rule also calls for a label advising consumers not to use an ephedrine-containing product for more than seven days and warning that exceeding the recommended dosage may result in heart attack, stroke, seizure or death. The Association of Food and Drug Officials (AFDO), which represents state food and health department officials, believes that serious adverse effects to ephedrine-containing products may occur even at a dosage of 24 mg per day.<sup>24</sup> In fact, life-threatening adverse reactions have been reported to occur with doses of 1 to 5 mg (dosages of 4 to 20 mg per day).

AFDO is also concerned that setting a dosage limit may imply that a safe dose exists. Ephedra-containing products have also been associated with the development of kidney stones. Ephedrine, pseudoephedrine and metabolites comprised almost 100 percent of a radiolucent stone removed from a 27-year-old male body builder who took up to 12 Pro-Lift tablets daily. Each tablet was found to contain approximately 10 mg of ephedrine. Information from a large kidney stone database shows that this is not an isolated incident; over 100 ephedrine-containing kidney stones were identified from January 1996 to June 1997. It is not known how many of these stones were associated with the use of herbal ephedrine-containing products.

The risks of using ephedrine-containing supplements appear to outweigh the benefits. Consequently, patients should be advised not to use these products if they are sensitive to the effects of sympathomimetic agents. Such patients include those with hypertension, hyperthyroidism, diabetes mellitus, psychiatric conditions, glaucoma, prostate enlargement, seizure disorders and cardiovascular disease. Concomitant use of ephedrine-containing products and caffeine or other stimulants should also be discouraged.

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## Ginseng

Little scientific evidence shows that ginseng is effective for any purpose. Nonetheless, this herb has been purported to strengthen normal body functions, increase resistance to stress and improve sexual function. Ginseng is generally well tolerated, but a probable interaction between the herb and warfarin has been reported.

A 47-year-old man with a mechanical heart valve who was taking warfarin to prevent thromboembolic events experienced a decline in International Normalized Ratio (INR) from 3.1 to 1.5 (target INR: 2.5 to 3.5) two weeks after he began taking a ginseng product (Ginsana) three times daily to improve his "energy level. For the nine months before he started taking the ginseng product, his INR had ranged from 3 to 4. His other medications included diltiazem (Cardizem), nitroglycerin and salsalate (Disalcid); he had been taking all three drugs for at least three years. The patient denied changes in drug therapy or diet, and he stated that he was not taking dietary supplements other than the ginseng product. Two weeks after he discontinued use of the ginseng product, his INR was 3.3. Because of the risks associated with a decreased INR, the patient was not rechallenged with ginseng.

Until studies or additional case reports can verify the interaction between ginseng and warfarin, it would be prudent to closely monitor patients on warfarin who begin taking dietary supplements that contain this herb. A possible mechanism for this interaction is not yet known.

## Kava

Kava is an herbal sedative with purported antianxiety or calming effects. In one case series involving four patients, kava was associated with extrapyramidal effects at dosages of 100 to 450 mg per day. Symptoms occurred 90 minutes after one patient took a single 100-mg dose, four hours after one patient took a single 100-mg dose, four days after one patient began taking 150 mg three times daily, and 10 days after one patient began taking 150 mg twice daily. The extrapyramidal side effects included oral and lingual dyskinesia, torticollis, painful twisting movements of the trunk, oculogyric crisis and exacerbation of Parkinson's disease.

Kava has also been shown to have additive effects with central nervous system depressants. A patient who was taking alprazolam (Xanax), cimetidine (Tagamet) and terazosin (Hytrin) became lethargic and disoriented after ingesting kava. Kava should not be used with benzodiazepines, barbiturates, antipsychotics and alcohol. In addition, patients with Parkinson's disease should be discouraged from using kava products. Kava dermatopathy has been reported with the use of kava as a traditional South Pacific beverage. Recently, two cases associated with use of commercially available kava preparations were reported. A 70-year-old man who had been taking kava extract for anxiety for two to three weeks experienced itching several hours after sun exposure. Erythematous, infiltrated plaques then developed on his face, chest and back. A similar case involved a 52-year-old woman who presented with papules and plaques on her face, arms, back and chest after taking a kava extract for three weeks. In both cases, biopsy revealed lymphocytic infiltration of the dermis with destruction of the sebaceous glands. Because kava is lipophilic, it was hypothesized that kava can concentrate in sebaceous oils and trigger an immune response, resulting in a drug reaction.

## Final Comment

Because dietary supplements are becoming increasingly popular, physicians need to ask questions about the use of herbal products as part of the medication history (Table 3). Even though herbal products are available without a prescription, medical guidance is necessary because of the adverse effects of these products and the potential for drug interactions. Consequently, physicians need to stay abreast of trends in dietary supplement use, with the realization that for most supplements the adverse effects and potential for drug interactions are not well characterized.

Objective information about herbal products can be obtained in publications such as *Alternative Medicine Alert* (800-688-2421) and *Review of Natural Products* (314-216-2100). Physicians can help broaden knowledge in this area by reporting adverse events to the FDA's MedWatch Program (800-FDA-1088).

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The IETF funds research to find the cause of essential tremor (ET) that leads to treatments and a cure, increases awareness, and provides educational materials, tools, and support for healthcare providers, the public, and those affected by ET.