

Review of Abnormal Laboratory Test Results and Toxic Effects Due to Use of Herbal Medicines

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Abstract

Herbal medicines are used widely in the United States, and according to a recent survey, the majority of people who use herbal medicines do not inform their physicians about their use. Herbal medicines can cause abnormal test results and confusion in proper diagnosis. Herbal medicines can alter test results by direct interference with certain immunoassays. Drug-herb interactions can result in unexpected concentrations of therapeutic drugs. For example, low concentrations of several drugs (eg, cyclosporine, theophylline, digoxin) can be observed in patients who initiated self-medication with St John's wort. Herbal medicines can alter physiology, and these changes can be reflected in abnormal test results. For example, kava-kava can cause drug-induced hepatitis, leading to unexpected high concentrations of liver enzymes. Use of toxic herbal products such as ma huang (an ephedra-containing herbal product), Chan Su, and comfrey may cause death. Other toxic effects of herbal medicines include cardiovascular toxic effects, hematologic toxic effects, neurotoxic effects, nephrotoxic effects, carcinogenic effects, and allergic reactions.

Herbal medicines, including Chinese herbal products, are readily available in the United States from health food stores without prescriptions. Ayurvedic medicines are used widely in India, and some preparations are available in the United States. Ginseng, St John's wort, ma huang, kava, ginkgo biloba, Dan Shen, feverfew, garlic, ginger, saw palmetto, comfrey, pokeweed, hawthorn, dong quai, and cat's claw are used by the general population in the United States. Intended uses of common herbal medicines are given in **Table 1**. Gulla et al¹ published a survey of 369 patient-escort pairs and reported that 174 patients (47.2%) used herbs. The most common herbal product used was ginseng (20%) followed by echinacea (19%), ginkgo biloba (15%), and St John's wort (14%).¹

Several herbal products interfere with immunoassays used for monitoring the concentrations of therapeutic drugs. Herbal medicines also can cause toxic effects, leading to abnormal test results. Therefore, the common belief that anything natural is safe is not correct. This review summarizes abnormal test results associated with the use of herbal medicines, as well as interactions between Western medicines and herbal products. This review also summarizes the toxic effects of commonly used herbal products.

Regulatory Issues Affecting Herbal Medicines

The US Food and Drug administration (FDA) mandates that only medicines have to be proven to be safe before being released into the market. Herbal products do not fall

Table 1
Intended Uses of Common Herbal Medicines

Herbal Medicine	Intended Use
Ginseng	Tonic capable of invigorating users physically, mentally, and sexually; also used for dealing with stress; used in China for more than 5,000 y
Siberian ginseng	Similar to ginseng
St John's wort	Treatment of mood disorders, particularly depression
Ginkgo biloba	Mainly to sharpen mental focus in otherwise healthy adults and also in people with dementia; improvement of blood flow in the brain and peripheral circulation; treatment of diabetes mellitus–related circulatory disorders, impotence, and vertigo
Kava	Relief of anxiety and stress; sedative
Valerian	Treatment of insomnia
Echinacea	Immune stimulant that helps increase resistance to colds, influenza, and other infections; wound healing
Saw palmetto	Treatment of benign prostatic hypertrophy
Feverfew	Relief from migraine headache and arthritis
Garlic	To lower cholesterol levels and blood pressure; prevention of heart attack and stroke
Ginger	Prevention of motion sickness, morning sickness, and nausea
Cranberry	Treatment of urinary tract infection; decrease kidney stone formation
Aloe	To heal wounds, burns, skin ulcers; also used as a laxative
Senna	Laxative
Dong quai	To alleviate problems associated with menstruation and menopause
Cat's claw	Immunostimulant with antiviral activity; also used by people with AIDS; prevention of colds and influenza; treatment of chronic fatigue syndrome
Hawthorn	For heart failure, hypertension, and angina pectoris
Pokeweed	Antiviral and antineoplastic; eating uncooked berry or root may cause serious poisoning

under the category of drugs as long as they are not marketed for the prevention of any diseases, and, as such, FDA approval is not needed. Herbal products are classified as “dietary supplements” and are marketed pursuant to the Dietary Supplement Health and Education act of 1994. However, herbal products are regulated differently in other countries. In the United Kingdom, any product not granted a license as a medical product by the Medicines Control Agency is treated as a food, and no health claim or medical advice can be given on the label. Similarly, herbal products are sold as dietary supplements in the Netherlands. In Germany, herbal monographs are prepared by an interdisciplinary committee (German Commission E), using historic information; chemical, pharmacologic, clinical, and toxicologic studies; case reports; epidemiologic data; and unpublished manufacturers’ data. If an herb has an approved monograph, it can be marketed.

Effect of Herbal Medicines on Clinical Laboratory Testing

Abnormal laboratory test results due to the use of herbal medicines can be classified in 3 categories:

1. Abnormal test results due to direct interference of a component of the herbal medicine with the assay
2. Unexpected concentration of a therapeutic drug due to drug-herb interactions
3. Abnormal test results due to toxic effects of the herbal product

Interference of Chinese Medicines With Digoxin Immunoassays

The Chinese medicine Chan Su is prepared from the dried white secretion of the auricular glands and the skin glands of Chinese toads (*Bufo melanostictus Schneider* or *Bufo bufo gargarzinas Gantor*). Chan Su also is a major component of the traditional Chinese medicines Lu-Shen-Wan and kyushin.^{2,3} These medicines are used as remedies for tonsillitis, sore throat, furuncle, and palpitations. Chan Su also is used for stimulation of myocardial contraction and pain relief.⁴ The cardiotoxic effect of Chan Su is due to its major bufadienolides, such as bufalin, cinobufagin, and resibufogenin.⁵ Bufalin is known to block vasodilatation and increases vasoconstriction and vascular resistance and, thus, blood pressure by inhibiting Na⁺,K⁺-ATPase.⁶ At high dosages, Chan Su causes cardiac arrhythmia, breathlessness, seizure, and coma. The death of a Chinese woman after ingestion of Chinese herbal tea containing Chan Su has been reported.⁷

Structural similarity between bufadienolides and digoxin accounts for the toxic effects and serum digoxin-like immunoreactivity of Chan Su. Fushimi and Amino⁸ reported a serum concentration of 0.4 ng/mL (0.51 nmol/L) in a healthy volunteer after ingestion of kyushin tablets containing Chan Su as the major component. Panesar⁹ reported an apparent digoxin concentration of 0.88 ng/mL (1.1 nmol/L) in healthy volunteers who ingested Lu-Shen-Wan pills. The author used the fluorescence polarization immunoassay (FPIA) of digoxin for the study. An apparent digoxin concentration of 4.9 ng/mL (6.3 nmol/L) was

reported in 1 woman who died of ingestion of Chinese herbal tea containing Chan Su.⁷ Although Chan Su falsely elevates the serum digoxin concentration when the FPIA is used, negative interference of Chan Su in serum digoxin measurement has been reported with the microparticle enzyme immunoassay (MEIA, Abbott Laboratories, Chicago, IL). However, interfering components in Chan Su are bound very strongly to serum proteins, while digoxin is only 25% protein bound. Therefore, monitoring the free digoxin concentration eliminates this interference. Another way to eliminate this interference is to use the chemiluminescent assay (Bayer Diagnostics, Tarrytown, NY).¹⁰

Dan Shen is a Chinese medicine prepared from the root of the Chinese medicinal plant *Salvia miltiorrhiza*. This herb has been in use in China for many centuries for treating various cardiovascular diseases, including angina pectoris, and it now is available in the United States. More than 20 diterpene quinones known as “tanshinones” have been isolated from Dan Shen. These compounds have structural similarity with digoxin. Feeding Dan Shen to mice caused digoxin-like immunoreactivity in serum when measured by the FPIA. The presence of Dan Shen falsely elevated serum digoxin concentrations as measured by the FPIA and falsely lowered the digoxin concentrations when measured by the MEIA. However, no interference was observed when the chemiluminescent assay was used.^{11,12} Interference of Dan Shen in the FPIA and MEIA can be eliminated by measuring free digoxin because the digoxin-like immunoreactive components of Dan Shen have much higher serum protein binding than digoxin. The EMIT 2000 digoxin assay and a recently FDA-approved turbidimetric digoxin immunoassay (Bayer Diagnostics) also are free from interference from Dan Shen. Interestingly, the same Chinese medicine prepared by different manufacturers showed significantly different digoxin-like immunoreactivity, presumably because Chinese medicines are not prepared by following rigorous standardization processes as used in the preparation of Western medicines.¹³

McRae¹⁴ reported a case in which ingestion of Siberian ginseng was associated with elevated digoxin concentrations in a 74-year-old man. In this patient, the serum digoxin concentrations had been maintained between 0.9 and 2.2 ng/mL (1.2-2.8 nmol/L) for a period of 10 years. After ingestion of Siberian ginseng, his serum digoxin concentration increased to 5.2 ng/mL (6.7 nmol/L), although the patient did not experience any signs of digoxin toxicity. The patient stopped taking Siberian ginseng, and the serum digoxin concentration returned to a normal value.¹⁴

Our study indicates that Siberian ginseng produces only modest interference in the digoxin FPIA and MEIA. Asian ginseng also showed modest positive (FPIA) and modest negative (MEIA) interference.¹⁵ Interferences of herbal products in therapeutic drug monitoring of digoxin are given in

Table 2.

Abnormal Drug Concentrations Due to Use of Herbal Medicines

Several herbal medicines lower the seizure threshold maintained by phenobarbital, offsetting the beneficial anticonvulsant activity. Evening primrose oil is used as a remedy for premenstrual syndrome, diabetic neuropathy, and attention-deficit/hyperactivity disorder. Evening primrose oil contains gamolenic acid that lowers the seizure threshold maintained by several anticonvulsants.¹⁶ Borage oil (starflower) also contains gamolenic acid. Shankhapushpi, an ayurvedic medicine for epilepsy, has adversely affected the effectiveness of phenytoin. Dandekar et al¹⁷ observed 2 patients experience loss of seizure control after self-medication with shankhapushpi. The serum phenytoin concentration dropped from 9.6 µg/mL (38.0 µmol/L) to 5.1 µg/mL (20.2 µmol/L) after ingestion of this herbal product (1 teaspoon 3 times a day).¹⁷

Warfarin

Warfarin is an anticoagulant with a narrow therapeutic range. The drug has potentially serious consequences if bleeding complications develop or if a subtherapeutic level

Table 2
Interference of Herbal Products in Therapeutic Drug Monitoring of Digoxin*

Herbal Product	Level of Interference	Comments
Chan Su	High	Chan Su has active components such as bufalin, which cross-react with digoxin assays; only Bayer assay has no interference; monitoring free digoxin also eliminates interference
Dan Shen	Moderate	Falsely elevated (FPIA) or falsely low (MEIA) digoxin level; no interference with EMIT, Bayer, Randox, Roche, or Beckman assays; monitoring free digoxin eliminates interference
Uzara root (diuretic)		Additive effect with digoxin; also interferes with digoxin assay
Siberian ginseng	Moderate	Falsely elevated (FPIA) or falsely low (MEIA) digoxin level; no interference with EMIT, Bayer, Randox, Roche, or Beckman assays; monitoring free digoxin does not eliminate interference
Asian ginseng	Moderate	Falsely elevated (FPIA) or falsely low (MEIA) digoxin level; no interference with EMIT, Bayer, Randox, Roche, or Beckman assays; monitoring free digoxin does not eliminate interference

FPIA, fluorescence polarization immunoassay; MEIA, microparticle enzyme immunoassay.

* Bayer Diagnostics, Tarrytown, NY; Roche Diagnostics, Indianapolis, IN; Beckman Coulter, Fullerton, CA.

occurs, thus failing to protect the patient from thromboembolic events. Several herbs interact with warfarin. The herbs that may increase the risk of bleeding (potentiate effects of warfarin) include angelica root, arnica flower, ansine, bogbean, borage seed oil, capsicum, feverfew, garlic, ginger, ginkgo, horse chestnut, licorice root, and willow bark. The herbs with documented interaction with warfarin include Dan Shen, ginseng, Siberian ginseng, Devil's claw, and dong quai, among others.¹⁸

A 47-year-old man with a mechanical heart valve took warfarin for 5 years and had an average international normalized ratio (INR) of 4. Within 2 weeks of using ginseng, his INR dropped to 1.5, but 2 weeks after discontinuing ginseng use, it returned to 3.3. Fortunately, no adverse effects occurred during the 2 weeks with a subtherapeutic INR.¹⁹ A subtherapeutic INR due to the intake of soy protein in the form of soy milk also has been reported in a 70-year-old man. INR values returned to normal 2 weeks after discontinuation of soy milk.²⁰ Conversely Dan Shen caused inappropriately increased anticoagulation (INR values ranging from 5.5-8.4) in patients taking warfarin.^{21,22} Apart from inhibition of platelet aggregation, Dan Shen also promotes fibrinolysis due to antithrombin III-like activities. Dan Shen increases the concentration of warfarin owing to a decrease in clearance.²²

Dong quai is a Chinese medicine used for treatment of menstrual cramps, irregular menses, and menopausal symptoms. A 46-year-old woman with stabilized atrial fibrillation who was taking warfarin experienced a greater than 2-fold rise in prothrombin time (23.5 seconds; baseline, 16.2 seconds) and INR (4.05, baseline value, 1.89) after taking dong quai for 4 weeks. A month later, her INR was 4.9 and the prothrombin time was 27.0 seconds. At that time, the patient admitted taking dong quai. The patient was advised to discontinue dong quai, and her INR was 2.48 and the prothrombin time was 18.5 seconds 4 weeks after withdrawal of the herb.²³ Dong quai contains coumarins, which are natural vitamin K antagonists.²⁴ Boldo-fenugreek also increases INR and bleeding time in patients taking warfarin.²⁵

Licorice

Licorice may offset the ability of spironolactones to reduce blood pressure. Licorice is used as an anti-inflammatory herb and also as a remedy for gastric and peptic ulcers. Carbenoxolone, one of the components of licorice, can elevate blood pressure and cause hypokalemia. However, discontinuation of licorice results in the return of blood pressure to normal.²⁶

Significantly Lower Concentrations of Drugs Due to Concurrent Use of St John's Wort

St John's wort is prepared from *Hypericum*, a perennial aromatic shrub with bright yellow flowers that bloom from

June to September. The flowers are believed to be most abundant and brightest around June 24, the day traditionally believed to be the birthday of John the Baptist. Therefore, the name St John's wort became popular for this herbal product. Many chemicals have been isolated from St John's wort, including hypericin, pseudohypericin, quercetin, isoquercitrin, rutin, amentoflavone, hyperforin, other flavonoids, and xanthones. Interestingly melatonin, a human pineal gland hormone, is also found in St John's wort.²⁷ The mechanism of action of St John's wort is not well established.²⁸

Several reports describe unexpected low concentrations of certain therapeutic drugs due to concurrent use of St John's wort. John et al²⁹ reported that 10 days' use of St John's wort resulted in a decrease of trough serum digoxin concentrations by 33% and peak digoxin concentration by 26%. Durr et al³⁰ confirmed the lower digoxin concentrations in healthy volunteers who concurrently took St John's wort. The authors also demonstrated that St John's wort activates cytochrome P-450 mixed-function oxidase liver enzymes (CYP3A4) responsible for metabolism of digoxin and many other drugs.³⁰ Barone et al³¹ reported 2 cases in which renal transplant recipients started self-medication with St John's wort. Both patients experienced subtherapeutic concentrations of cyclosporine, and in 1 patient, acute graft rejection developed owing to the low cyclosporine concentration. In both patients, termination of the use of St John's wort returned the cyclosporine concentrations to therapeutic levels.³¹ St John's wort also reduced the area under the curve of the HIV-1 protease inhibitor indinavir by a mean of 57% and decreased the extrapolated trough by 81%. A reduction in indinavir concentration of this magnitude could lead to treatment failure.³² A case report describes an interaction between St John's wort and theophylline. After she began taking St John's wort, a patient who had been taking 300 mg of theophylline twice daily required a dosage increase to 800 mg twice daily to maintain a serum theophylline concentration of 9.2 µg/mL (51 µmol/L). Seven days after discontinuation of St John's wort, her theophylline concentration increased to 19.6 µg/mL (109 µmol/L).³³

Fugh-Berman³⁴ and later Fugh-Berman and Ernst³⁵ have written reviews on interactions between herbs and drugs. The most common interactions between herbs and drugs are summarized in **Table 3**.

Unexpected Presence of a Drug in a Patient Who Never Used That Drug: Herbal Medicines Adulterated With Western Medicines

The adulteration of Chinese herbal products with Western drugs is a serious problem. Of 2,069 samples of traditional Chinese medicines obtained from 8 hospitals in Taiwan, 23.7% contained pharmaceuticals, most commonly

Table 3
Common Drug-Herb Interactions

Herbal Product	Interacting Drug	Comments
Ginseng	Warfarin	Ginseng may decrease effectiveness of warfarin
St John's wort	Phenelzine	Toxic symptoms, eg, headache, insomnia, and irritability
	Paroxetine hydrochloride	Lethargy, incoherence, nausea
	Digoxin	Decreased AUC; peak and trough concentration of digoxin; may reduce effectiveness of digoxin
Ginkgo biloba	Cyclosporine	Lower cyclosporine concentration due to increased clearance may cause transplant rejection
	Theophylline	Lower concentration, thus decreases the efficacy of theophylline
	Indinavir	Lower concentration may cause treatment failure in patients with HIV
	Aspirin	Bleeding; ginkgo can inhibit PAF
Kava	Warfarin	Hemorrhage
	Thiazide	Hypertension
	Alprazolam	Additive effects with CNS depressants, alcohol
Garlic	Warfarin	Increased effectiveness of warfarin; bleeding
Ginger	Warfarin	Increased effectiveness of warfarin; bleeding
Feverfew	Warfarin	Increased effectiveness of warfarin; bleeding
Dong quai	Warfarin	Dong quai contains coumarin; dong quai increases INR for warfarin, causes bleeding
Dan Shen	Warfarin	Increased effectiveness of warfarin owing to reduced elimination of warfarin
Soy milk	Warfarin	Causes decline in INR
Comfrey	Phenobarbital	Increased metabolism of comfrey producing a lethal metabolite from pyrrolizidine; severe hepatotoxic effects
Borage oil	Phenobarbital	May lower seizure threshold, requiring dosage increase
Evening primrose oil	Phenobarbital	May lower seizure threshold, requiring dosage increase
Licorice	Spironolactone	May offset the effect of spironolactone
Shankhapushpi	Phenytoin	Lower phenytoin level and loss of seizure control

AUC, area under the curve; CNS, central nervous system; INR, international normalized ratio; PAF, platelet-activating factor.

caffeine, acetaminophen, indomethacin, hydrochlorothiazide, and prednisolone.³⁶ Nonsteroidal anti-inflammatory drugs and benzodiazepines have been found in many Chinese medicines sold outside Asia. These herbs include Miracle-Herb, tung shueh, and Cuifong Toukuwan.³⁷ Heavy metal contamination also was found in herbal products. Ko³⁸ reported that 24 of 254 Asian patented medicines obtained from herbal stores in California contained lead, 36 products contained arsenic, and 35 products contained mercury.

Nelson et al³⁹ reported a case of aplastic anemia associated with the use of herbal medication in a 12-year-old boy. The authors demonstrated the presence of phenylbutazone in the herbal preparation, but that medication was not listed as an ingredient in the package insert. The boy had a hemoglobin concentration of 8 g/dL (80 g/L), a neutrophil count of 200/mL, and a platelet count of 5,000/mL. These hematologic abnormalities are related to phenylbutazone toxicity.³⁹ Lau et al⁴⁰ reported a case in which a 33-year-old patient had a serum phenytoin concentration of 48.5 µg/mL (192 µmol/L). The patient had a history of a seizure disorder that was managed with 400 mg sodium valproate 3 times a day, 200 mg of carbamazepine twice a day, and 150 mg of phenobarbital every evening. No phenytoin was given. The patient consumed a proprietary Chinese medicine before admission to the hospital. The manufacturer's information leaflets stated that the capsules contained pure Chinese medicines and were effective for controlling epilepsy.⁴⁰ Goudie and Kaye⁴¹ reported a case of severe hypoglycemia in a patient

(fasting glucose level, 37.8 mg/dL [2.1 mmol/L]) due to use of a Chinese medicine, ZhenQi, for diabetes. Analysis of this herbal medicine showed the presence of glyburide, a sulfonylurea. A sulfonylurea overdose can lead to profound hypoglycemia.⁴¹

Abnormal Laboratory Test Results Due to Toxic Effects of Herbal Medicines

Kava-Kava and Abnormal Liver Function Test Results

Kava is an herbal sedative with a purported antianxiety or calming effect. Kava is prepared from a South Pacific plant (*Piper methysticum*). The main bioactive compounds include yangonin, desmethoxyyangonin, 11-methoxyyangonin, kavain, and dihydroxykavin. These components are present in the lipid-soluble kava extract or kava resin.⁴²

Kava can have additive effects with central nervous system depressants. A patient who was taking alprazolam (Xanax), cimetidine, and terazosin became lethargic and disoriented after ingesting kava.⁴³ Kava lactones can inhibit cytochrome P-450 activities and have a potential for interaction with drugs that are metabolized by the liver.⁴⁴ Heavy consumption of kava has been associated with increased concentrations of γ-glutamyltransferase. Escher et al⁴⁵ described a case in which severe hepatitis was associated with kava use. A 50-year-old man took 3 to 4 kava capsules daily for 2 months (maximum recommended dose, 3 capsules). Liver function tests showed 60- to 70-fold

increases in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) concentrations. Blood tests were negative for hepatitis, cytomegalovirus, and HIV. The patient eventually received a liver transplant.⁴⁵ Because of the potential for toxic effects on the liver, the FDA warned the public against the use of kava-kava.⁴⁶

Chaparral and Abnormal Liver Function Test Results

Chaparral can be found in health food stores as capsules and tablets and is used as an antioxidant and an anticancer herbal product. Leaves, stems, and bark also are available in bulk for brewing tea. Chaparral-associated hepatitis has been reported. A 45-year-old woman who took 160 mg/d of chaparral for 10 weeks sought care because of jaundice, anorexia, fatigue, nausea, and vomiting. The results of liver enzyme and other liver function tests were abnormally high (ALT, 1,611 U/L; AST, 957 U/L; alkaline phosphatase, 265 U/L; γ -glutamyltransferase, 993 U/L; and bilirubin, 11.6 mg/dL [198 μ mol/L]). Viral hepatitis, cytomegalovirus, and Epstein-Barr virus were ruled out. Liver biopsy showed acute inflammation with neutrophil and lymphoplasmacytic infiltration, hepatic disarray, and necrosis.⁴⁷ Gordon et al⁴⁸ reported a case in which hepatitis developed in a 60-year-old woman owing to the use of chaparral for 10 months. Despite aggressive therapy, the condition of the patient deteriorated, and she required orthotopic liver transplantation.⁴⁸ Other cases of toxic effects on the liver due to chaparral have been reported.⁴⁹ The FDA has warned the public about the dangers of consuming chaparral.

Mistletoe and Liver Damage

Mistletoe is a parasitic evergreen plant that lives on trees such as oaks, elms, firs, pines, and apple. Mistletoe was used in folk medicine as a digestive aid, heart tonic, and sedative. Mistletoe berries are poisonous. In a 49-year-old woman with nausea, general malaise, and dull abdominal pain, the results of liver function tests suggested hepatitis (ALT, 123 U/L; lactate dehydrogenase, 395 U/L; AST, 250 U/L). Liver biopsy also suggested hepatitis. However, all serologic tests for hepatitis were negative. The patient had drug-induced hepatitis probably due to mistletoe.⁵⁰

Germander and Elevated Liver Enzyme Levels

Germander has been used as a remedy for weight loss and as a general tonic. Germander tea is made from the aerial parts of the plant and has been in use for centuries. Capsules made from germander powder also are available in health food stores. Twenty-six cases of germander-induced hepatotoxicity have been reported in Europe. A 55-year-old woman taking 1,600 mg per day of germander became jaundiced after 6 months. Laboratory results were as follows: bilirubin concentration, 13.9 mg/dL (238 μ mol/L); AST,

1,180 U/L; ALT, 1,500 U/L; alkaline phosphatase, 164 U/L. Serologic tests for all types of hepatitis were negative. A liver biopsy suggested drug-induced hepatitis. Germander therapy was discontinued, and the hepatitis resolved in 2 months.⁵¹ Acute cholestatic hepatitis with the transient appearance of antimitochondrial antibody also has been reported due to germander.⁵²

Comfrey and Liver Damage

The regular use of comfrey is a potential health risk owing to the presence of pyrrolizidine alkaloids. These alkaloids have hepatotoxic effects in animals and humans and also induce tumors in animals.⁵³ Ridker et al⁵⁴ documented hepatic veno-occlusive disease associated with consumption of comfrey roots. Long-term studies in animals have confirmed the carcinogenicity of comfrey in animal models.⁵⁵ A study showed that phenobarbital induced the metabolism of pyrrolizidine alkaloids to a lethal metabolite.⁵⁶ Stickel and Seitz⁵⁷ commented on serious hazards associated with the use of comfrey.

Kelp and Abnormal Thyroid Profile

Kelp (seaweed) tablets are available in health food stores and are used as a thyroid tonic, an anti-inflammatory, and a metabolic tonic. Kelp tablets are rich in vitamins and minerals but also contain a substantial amount of iodine (each tablet contains approximately 0.7 mg of iodine). A 72-year-old woman with no history of thyroid disease had the typical symptoms of hyperthyroidism. She had been taking 4 to 6 kelp tablets a day for 1 year. Her thyrotropin concentration was low (1.3 μ IU/L); the total thyroxine level was 14.4 μ g/dL (185.3 nmol/L; reference range, up to 12.4 μ g/dL [160 nmol/L]); and the total triiodothyronine level was 284 ng/dL (4.38 nmol/L; reference range, 69-219 ng/dL [1.07-3.38 nmol/L]). After discontinuing the kelp tablets, her hyperthyroidism resolved, and thyroid function test results returned to normal (thyrotropin, 3.1 μ IU/L; total thyroxine, 8.4 μ g/dL [108.1 nmol/L]; total triiodothyronine, 140 ng/dL [2.15 nmol/L]).⁵⁸

Chromium and Hypoglycemic Herbs: Abnormally Low Glucose Concentrations

Athletes and body builders use chromium for improving performance. Chromium is a trace metal that has an effect on the glucose-insulin system. Bunner and McGinnis⁵⁹ described a case in which a 29-year-old man was referred to the outpatient neuropsychiatry clinic because of his unusual behavior at work. The patient had been diagnosed with diabetes mellitus at the age of 20 years and was taking 9 U of NPH insulin (Humulin N) per day. His blood glucose concentrations ranged between 90 and 120 mg/dL (5.0-6.7 mmol/L). During the episode, he was agitated, and on

admission to the hospital, his blood glucose concentration was 30 mg/dL (1.7 mmol/L). The patient was taking 200 to 300 µg of chromium 2 to 3 times per week for bodybuilding, and the hypoglycemic episode most likely was linked to chromium use.⁵⁹ Anderson⁶⁰ reviewed the effect of chromium on the glucose-insulin system in subjects with hypoglycemia, hyperglycemia, diabetes mellitus, and hyperlipidemia. Ginseng, whose activity has been attributed to 2% to 3% ginsenosides, has been associated with hypoglycemic properties. Fenugreek, ginger, nettle, sage, and devil's claw also can affect glucose levels. Karela has been shown to improve glucose tolerance.⁶¹

Zhang et al⁶² reported that male subjects showed a significant reduction in the glucose concentration after taking garlic oil, but female subjects showed an increase. However, a small adverse effect on the lipid profile was observed in male subjects, while females had beneficial effects on the lipid profile following the use of garlic oil for 11 weeks.⁶²

Licorice and Hypokalemia

Fifty-nine licorice-induced hypokalemic myopathy cases have been reported. Laboratory findings include a mean serum potassium concentration of 1.98 mEq/L (1.98 mmol/L), a mean total creatine kinase concentration of 5,383 U/L, plasma aldosterone activity of 2.92 ng/dL (0.08 nmol/L), and a mean plasma renin activity of 0.17 ng/mL/h ($0.13 \cdot L^{-1} \cdot h^{-1}$).⁶³ Licorice-induced pseudoaldosteronism also has been reported.⁶⁴ Licorice contains glycyrrhizic acid, which inhibits the enzyme 11-β-hydroxysteroid dehydrogenase (converts cortisol to cortisone). Therefore, concentrations of cortisol may increase. Renin activity and aldosterone concentrations in serum usually decrease.

Lead Poisoning Due to Herbs: Abnormal Laboratory Test Results

Unexpected lead poisoning may occur owing to the use of herbal medicines contaminated with lead.³⁸ Anderson et al⁶⁵ reported a case of lead poisoning in a 23-year-old man with a 5-day history of severe, diffuse abdominal pain, vomiting, and diarrhea followed by constipation. The laboratory investigation showed elevated bilirubin and alanine transaminase concentrations, but the alkaline phosphatase activity was normal. The urinary porphyrin screen was positive, indicating the possibility of acute porphyria. Further investigation showed elevated concentrations of zinc protoporphyrin (145 µmol/L; reference range, <70 µmol/L) and lead (77 µg/dL [3.7 µmol/L]). The patient was taking an herb purchased in India. After discontinuation of the herbal medicine, his blood concentrations of lead and zinc protoporphyrin were reduced significantly.⁶⁵ Wu et al⁶⁶ reported 2 cases of lead poisoning due to the Chinese herbal medicine Cordyceps. One patient had a blood lead

concentration of 130 µg/dL (6.3 µmol/L), and another patient had a lead concentration of 46 µg/dL (2.2 µmol/L). The lead content in the Chinese medicine was found to be as high as 20,000 ppm.⁶⁶

Herbal Medicine and Surgery

Ang-Lee et al⁶⁷ reported their recommendation for discontinuation of herbal products before surgery. The American Society of Anesthesiologists suggested that patients should discontinue their herbal medicines at least 2 weeks before surgery. Ang-Lee et al⁶⁷ recommended that garlic and ginseng should be discontinued at least 7 days before surgery because both herbs have been reported to aggravate bleeding. Ginkgo biloba should be discontinued 3 days before surgery because it inhibits platelet aggregation, causing bleeding. Kava should be discontinued at least 24 hours before surgery because kava can increase the sedative effect of anesthetics. Ma huang (ephedra) should be discontinued 24 hours before surgery because ma huang increases the blood pressure and the heart rate. St John's wort should be discontinued 5 days before surgery.

Misidentification and Adulteration of Herbal Products

Labeling of herbal products may not accurately reflect the content, and adverse events or interactions attributed to specific herbs may be related to misidentification of the plant.⁶⁸ For example, a case of neonatal androgenization with Siberian ginseng was due to an unrelated species of Chinese silk vine.⁶⁹ More than 48 cases of nephrotoxicity attributed to fang-ji in a weight-loss preparation were due to guang-fang-ji.⁷⁰

Toxic Effects of Herbal Medicines

Many commonly used herbal medicines are toxic. The toxic effects of common herbal products are given in **Table 4**. Toxic effects of herbal medicines range from allergic reaction to cardiovascular, hepatic, renal, neurologic, and dermatologic toxic effects. Although ginseng is considered safe, the toxicity of ginseng has been reported in the literature.

Ginseng

In 1979, the term *ginseng abuse syndrome* was coined as a result of a study of 133 people who took ginseng for 1 month. Most subjects experienced central nervous system

Table 4
Potentially Toxic Herbs

Herb	Toxic Effect or System Affected	Intended Use (Should Anyone Use?)
Comfrey	Hepatotoxic	Repairing of bone and muscle; prevention of kidney stones
Ephedra	Cardiovascular	Herbal weight loss
Chan Su	Cardiovascular	Tonic for heart
Borage oil	Hepatotoxic; hepatocarcinogenic	Source of essential fatty acids; rheumatoid arthritis; hypertension
Calamus	Carcinogenic	Psychoactive, not promoted in the United States
Chaparral	Hepatotoxic; nephrotoxic; carcinogenic	General cleansing tonic; blood thinner; arthritis remedy; weight loss product
Licorice	Pseudoaldosteronism (sodium and water retention, hypertension, heart failure)	Treatment of peptic ulcer; flavoring agent

stimulation. The effect of ginseng on mood seems to be dose-dependent. At a dose of less than 15 g/d, subjects experienced depersonalization and confusion. At a dose of more than 15 g/d, some subjects experienced depression. Fourteen patients experienced ginseng abuse syndrome, which is characterized by symptoms of hypertension, nervousness, sleeplessness, skin eruption, and morning diarrhea.⁷¹ An episode of Stevens-Johnson syndrome was reported in a 27-year-old man following ingestion of ginseng at a dose of 2 pills for 3 days. The patient recovered after 30 days.⁷² Vaginal bleeding has been reported in cases related to ginseng use. Interestingly, 1 patient had undergone a hysterectomy 14 years earlier.⁷³ There is a case report describing symptoms including insomnia, headache, irritability, and visual hallucinations when phenelzine was taken concurrently with ginseng.⁷⁴

Ginkgo Biloba

Ginkgo biloba is prepared from dried leaves of the ginkgo tree by organic extraction (acetone/water). It is used mainly to sharpen mental focus and to improve diabetes mellitus-related circulatory disorders. It also is used as a remedy for impotence and vertigo. The most common adverse effects of ginkgo are gastric disturbances, headache, and dizziness. Miwa et al⁷⁵ reported a case of a 36-year-old woman who had a generalized seizure 4 hours after the ingestion of 70 to 80 ginkgo nuts.

One commonly reported adverse effect of ginkgo biloba is bleeding. Spontaneous intracerebral hemorrhage occurred in a 72-year-old woman who took 50 mg of ginkgo 3 times a day for 6 months.⁷⁶ Fessenden et al⁷⁷ reported a case of post-operative bleeding after laparoscopic cholecystectomy. One report described a 70-year-old man with bleeding from the iris into the anterior chamber of the eye 1 week after beginning a self-prescribed regimen of a concentrated ginkgo biloba extract in a dosage of 40 mg twice a day.⁷⁸ His only medication was 325 mg of aspirin daily. After the spontaneous bleeding episode, he continued taking the aspirin but stopped taking the ginkgo product. During a 3-month follow-up period, he had no further bleeding episode.⁷⁸

Echinacea

The Australian Adverse Drug Reaction Advisory Committee received 11 reports of adverse reactions associated with echinacea between July 1996 and September 1997. There were 3 reports of hepatitis; 3 reports of asthma; 1 report each of rash, myalgia, and nausea; 1 report of urticaria; and 1 report of anaphylaxis. There are other published reports of echinacea use associated with contact dermatitis and anaphylaxis.⁷⁹

Garlic

Garlic is promoted for lowering cholesterol and blood pressure levels. Garlic contains various sulfur-containing compounds, which are derived from allicin. Chopped garlic-and-oil mixes left at room temperature can result in fatal botulism food poisoning according to the FDA. *Clostridium botulinum* bacteria are dispersed throughout the environment but are not dangerous in the presence of oxygen. The spores produce a deadly toxin in anaerobic, low-acid conditions. The garlic-and-oil mixture produces that environment.⁸⁰

Ma Huang (Ephedra-Containing Herbal Diet Pills)

Ma huang (ephedra) is commonly found in herbal weight-loss products that often are referred to as herbal fen-phen, an alternative to fenfluramine, a prescription drug that was withdrawn from the market owing to its toxic effects. Herbal fen-phen products sometimes contain St John's wort and are sold as "herbal Prozac." "Herbal ecstasy" another ephedrine-containing product, can induce a euphoric state. The FDA has strongly advised consumers not to use ephedrine-containing products marketed as alternatives to street drugs. The German Commission E contraindicated use of ephedra by patients with high blood pressure, glaucoma, or thyrotoxicosis. (–) Ephedrine is the predominant alkaloid of ephedra plants. Other phenylalanine-derived alkaloids found are (+) pseudoephedrine, (–) norephedrine, (+) norpseudoephedrine, (+) N-methylephedrine, and phenylpropranolamine. Haller and Benowitz⁸¹ evaluated 140 reports of ephedra-related toxic effects that were submitted to the FDA between June 1997 and March 31, 1999. The authors

concluded that 31% of cases were definitely related to ephedra and another 31% were possibly related. Of the reports, 47% involved cardiovascular problems and 18% involved problems with the central nervous system. Hypertension was the single most frequent adverse reaction, followed by palpitations, tachycardia, stroke, and seizure. Ten events resulted in death, and 13 events caused permanent disability. The authors concluded that use of a dietary supplement that contains ephedra may pose a serious health risk.⁸¹

Conclusion

Contrary to popular belief that natural is safe, herbal medicines can cause significant toxic effects and even death. St John's wort demonstrated significant and potentially dangerous drug interactions with several Western medicines. Several Chinese medicines such as Chan Su, Dan Shen, and ginseng can interfere with digoxin immunoassay results. Abnormal laboratory test results can be encountered in otherwise healthy patients who are taking herbal products. For example, elevated liver enzyme concentrations can be observed in people taking kava-kava. These abnormal laboratory tests in many cases are a reflection of the toxicity of herbs.

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