Herbal Medicinals

Selected Clinical Considerations Focusing on Known or Potential Drug-Herb Interactions

Lucinda G. Miller, PharmD, BCPS

Herbal medicinals are being used by an increasing number of patients who typically do not advise their clinicians of concomitant use. Known or potential drug-herb interactions exist and should be screened for. If used beyond 8 weeks, *Echinacea* could cause hepatotoxicity and therefore should not be used with other known hepatoxic drugs, such as anabolic steroids, amiodarone, methotrexate, and ketoconazole. However, *Echinacea* lacks the 1,2 saturated necrine ring associated with hepatoxicity of pyrrolizidine alkaloids. Nonsteroidal anti-inflammatory drugs may negate the usefulness of feverfew in the treatment of migraine headaches. Feverfew, garlic, *Ginkgo*, ginger, and ginseng may alter bleeding time and should not be used concomitantly with warfarin sodium. Additionally, ginseng may cause headache, tremulousness, and manic episodes in patients treated with phenelzine sulfate. Ginseng should also not be used with estrogens or corticosteroids because of possible additive effects. Since the mechanism of action of St John wort is uncertain, concomitant use with monoamine oxidase inhibitors and selective serotonin reuptake inhibitors is ill advised. Valerian should not be used concomitantly with barbiturates because excessive sedation may occur. Kyushin, licorice, plantain, uzara root, hawthorn, and ginseng may interfere with either digoxin pharmacodynamically or with digoxin monitoring. Evening primrose oil and borage should not be used with anticonvulsants because they may lower the seizure threshold. Shankapulshpi, an Ayurvedic preparation, may decrease phenytoin levels as well as diminish drug efficacy. Kava when used with alprazolam has resulted in coma. Immunostimulants (eg, *Echinacea* and zinc) should not be given with immunosuppressants (eg, corticosteroids and cyclosporine). Tannic acids present in some herbs (eg, St John wort and saw palmetto) may inhibit the absorption of iron. Kelp as a source of iodine may interfere with thyroid replacement therapies. Licorice can offset the pharmacological effect of spironolactone. Numerous herbs (eg, karela and ginseng) may affect blood glucose levels and should not be used in patients with diabetes mellitus.

Arch Intern Med. 1998;158:2200-2211

The herbal market in the United States is experiencing unprecedented growth. Herbal medicinal sales increased nearly 59% in 1997.[1] In 1997, 60 million Americans stated that they had used herbs in the previous year, accounting for $3.24 billion in sales.[2] It has been noted that 70% of patients do not reveal their herbal use to their allopathic practitioners (ie, physicians and pharmacists).[3] Hence, not only is the potential for drug-herb interactions unmonitored but the concomitant use may not even be acknowledged. This phenomenon is fraught with peril and is the subject of this article.

It is paramount for clinicians to be aware of known or potential drug-herb interactions to adequately treat their patients. The selection criteria for this article were (1) relatively commonly used herbs and (2) herbs with known or potential drug-herb interactions. Frequently used herbs will be presented first, and their use with known efficacy studies with associated drug-herb interactions will be outlined. Second, drugs with narrow therapeutic margins and drugs with the known or potential drug-herb in-

From the Department of Pharmacy Practice, Texas Tech University Health Sciences Center, Amarillo.

teractions with commonly used herbal medicinals will be reviewed in the context of concomitant use. With both of these approaches, most of the known or potential important drug-herb interactions will be addressed.

COMMONLY USED HERBAL MEDICINALS AND ASSOCIATED DRUG-HERB INTERACTIONS

Chamomile

Chamomile is used for its mild sedative effects but has also been noted to have antispasmodic and antiseptic activity.[4] In a study of its sedative effects, chamomile was effective in inducing a deep sleep in 10 (83%) of 12 recipients who were about to undergo cardiac catheterization.[5] Unfortunately, allergic reactions seem to commonly occur with symptoms that include abdominal cramps, tongue thickness, tight sensation in throat, angioedema of lips and eyes, diffuse pruritus, generalized urticaria, upper airway obstruction, and pharyngeal edema.[6,7] Many of these patients were also allergic to ragweed, which serves as an IgE marker for cross-allerginicity. Chamomile contains coumarin, which is reported to exert an antispasmodic effect.[8] However, this effect has not yet translated into any coagulation disorders despite its widespread human use. Because chamomile's effect on the coagulation system has not yet been studied, it is unknown if a clinically significant drug-herb interaction exists with known anticoagulants such as warfarin. If used concomitantly, close monitoring is advised.

Echinacea

Three kinds of *Echinacea* exist: *Echinacea angustifolia*, *Echinacea pallida,* and *Echinacea purpurea*. The Germans recommend using the above-ground parts of *E purpurea* (not the roots) or the roots of *E angustifolia*. In vitro stimulation of phagocytosis has been reported with *E purpurea* attributed to immunologically active polysaccharides; therefore, it is touted as an anti-infective via immunostimulation.[9-12] Symptoms of immunostimulation (eg, shivering, fever, and muscle weakness) ensue after parenteral administration but generally are not observed following oral administration in which the most common adverse effect is an unpleasant taste.[13] Purportedly, tachyphylaxis ensues if *Echinacea* mechanisms are used for more than 8 weeks although the mechanism of this phenomenon has not been determined.[14] Since hepatotoxic effects may be associated with persistent use, it should not be taken with other known hepatotoxic drugs (eg, anabolic steroids, amiodarone, methotrexate, or ketoconazole). However, the magnitude of this hepatoxicity has been questioned since *Echinacea* lacks the 1, 2 unsaturated necrine ring system associated with hepatoxicity of pyrrolizidine alkaloids.

Feverfew

Feverfew's most common use is for migraines. Seventeen patients who used feverfew daily as migraine prophylaxis enrolled in a double-blind, placebo-controlled trial in which 8 patients continued to receive feverfew while 9 received placebo.[15] Those who received placebo (ie, untreated patients) had a significant increase in the frequency and severity of headache (mean ± SEM, 3.13 ± 0.77 headaches every 6 months when taking placebo vs 1.69 ± 0.57 headache every 6 months when taking feverfew), nausea, and vomiting, whereas there was no change in the group receiving feverfew. In a larger study of 72 patients preceded by a 1-month single-blind, placebo run-in, feverfew was associated with a 24% reduction in the mean number and severity of attacks (3.6 attacks with feverfew vs 4.7 attacks with placebo over a 2-month period; $P<.005$) although the duration of the individual attacks was unaltered.[16] Feverfew has been shown to suppress 86% to 88% of prostaglandin production but does not inhibit cyclooxygenase.[17] Nonsteroidal anti-inflammatory drugs (NSAIDs) may reduce the effectiveness of feverfew perhaps mediated by its prostaglandin inhibition effects.[18] Feverfew is contraindicated to those allergic to other members of the family Compositae (Asteraceae) such as chamomile, ragweed, or yarrow.[17] Not all products contain an adequate amount (0.2%) of parthenolide, a possible component for activity, therefore this bears validation.[19] Postfeverfew syndrome involves nervousness, tension, headaches, insomnia, stiffness, joint pain, and tiredness.[20] Feverfew has been shown to inhibit platelet activity.[21,22] Hence, it is advised to avoid use of feverfew in patients receiving warfarin or other anticoagulants.

Garlic

Although touted by the herbal industry to possess various properties (including but not limited to antispasmodic, antiseptic, bacteriostatic, antiviral activities, as well as a promoter of leukocytosis), the most recent use of garlic (*Allium sativum*) has targeted its hypotensive and hypocholesterolemic activity.[23] Numerous animal studies have documented garlic's hypotensive effects, with a usual onset of action of 30 minutes.[24-26] However, this was not sustained for more than 2 hours in the rat model.[24-26] In a review of human experiments, Kleijnen et al[27] observed that studies were not well designed and suffered from small enrollments with no treatment groups including more than 25 patients. They noted that blinding of the studies was nearly impossible because of garlic's characteristic odor, which correlated with the sulfide component. Furthermore, the dosages needed were unacceptably high (at least 7 garlic cloves daily) and often were associated with adverse effects, such as gastrointestinal upset, allergic reactions, and dermatitis.[27,28] In a meta-analysis of 8 trials evaluating 415 subjects, 3 trials demonstrated a significant reduction in systolic blood pressure and 4 studies found a decrease in diastolic blood pressure.[29] While garlic may have some benefit in patients with mild hypertension, there is still insufficient evidence to recommend its routine use in clinical practice.

Garlic has also been studied for its possible use in hypercholesterolemia. In a study of 47 ambulatory patients, garlic powder administered for 12 weeks was found to decrease diastolic blood pressure from 102 to 91 mm Hg after 8 weeks ($P<.05$) and to 89 mm Hg after 12 weeks ($P<.01$) with concomitant decreases in serum cholesterol (14%; 6.93-6.18 mmol/L [268-239 mg/dL] at 8 weeks;

$P<.05$) and triglyceride levels (18%; 1.93-0.45 mmol/L [171-40 mg/dL]; $P<.05$) (SDs not provided).[30] In a controlled trial and a meta-analysis of garlic use for patients with moderate hyperlipidemia, garlic's effects were modest at 300 mg, 3 times daily.[31] Garlic was associated with a mean reduction in total cholesterol concentration of 0.65 mmol/L. Hence, garlic's effectiveness for hypercholesterolemia can be expected to be even less than that associated with hypertension.

Nonetheless, adverse effects present a concern with the use of garlic. Its use is associated with inhibition of spermatogenesis in rats.[32] This inhibition is thought to be secondary to the reduction in cholesterol and trigcycleride levels, seemingly conflicting notions when considering the supposed lack of effectiveness of garlic for hyperlipidemia.[32] When used for hyperlipidemia in 308 patients, garlic was also associated with decreased platelet aggregation.[33] In a study of 6 healthy adults, decreased platelet aggregation was noted within 5 days of oral administration, theorized to be secondary to inhibition of epinephrine-induced in vitro platelet aggregation.[34] While these authors did not feel that the effect was of clinical significance, dysfunctional platelets have resulted in spontaneous spinal epidural hematoma in an 87-year-old man.[35] Furthermore, several practitioners have noted elevated international normalized ratios (INRs) and prothrombin times in patients previously stabilized while taking warfarin; therefore, extreme caution is advised if these preparations must be used concomitantly.

Ginger

Ginger (*Zingiber officinale*) has been used as an antinauseant and antispasmodic agent. It has been subjected to placebo-controlled trials. In one such study, 8 volunteers received 1 g of powdered ginger root and then 1 hour later, were put in a dark room with their heads placed supinely 30° forward.[36] Their vestibular system was then stimulated by irrigating the left ear for 40 seconds with water that was at 44°C with recording of provoked nystagmus via electronystagmography. Ginger root was found to reduce induced vertigo significantly better than placebo with no subjects experiencing nausea, whereas 3 patients administered placebo did experience nausea. In a study of 36 patients, ginger was compared with 100 mg of dimenhydrinate while patients were subjected to a motor-driven revolving chair designed to produce motion sickness.[37] None of the subjects receiving placebo or dimenhydrinate could stay in the chair for 6 minutes, whereas half of the patients receiving ginger stayed for the full time. Further study concluded that ginger exerts a gastric mechanism unlike dimenhydrinate, which has a central nervous system mechanism.[38] Sixty women were enrolled in a study of ginger, metoclopramide hydrochloride, and placebo effectiveness to treat postoperative nausea and vomiting after they had undergone major gynecological surgery.[39] Ginger and metoclopramide treatment were similarly significantly more efficacious than placebo. Ginger therapy has also been found effective in a study of 80 naval cadets unaccustomed to sailing in heavy seas who were subjected to voyages in high seas.[40] The cadets maintained symptom reports relating to kinetosis (ie, seasickness).[40] In keeping hourly scores for 4 consecutive hours following ingestion of either 1 g of ginger or placebo, use of ginger was found to be significantly ($P<.05$) better than placebo in reducing vomiting and cold sweating, as well as in reducing nausea and vertigo.[40] The onset of action was 25 minutes and the duration of action was 4 hours.[37] These successes have led some to investigate ginger's effectiveness in hyperemesis gravidarum. Powdered ginger root given to patients in daily 1-g doses was found to be significantly ($P = .035$) better than placebo treatment in diminishing or eliminating symptoms of hyperemesis gravidarum (relief score of 4.1 with ginger vs 0.9 for those receiving placebo).[41] However, enthusiasm for this indication has been tempered by the finding of possible mutagenesis in *Escherichia coli*.[42,43] Furthermore, ginger has been found to be a potent inhibitor of thromboxane synthetase, which prolongs bleeding time.[44] Obviously, this result has adverse implications for pregnant patients but also provides the basis for the recommendation to avoid concomitant use with warfarin if at all possible.

Ginkgo

Ginkgo biloba is one of the most popular plant extracts in Europe and has recently received approval in Germany for treatment of dementia.[45] *Ginkgo* is composed of several flavonoids, terpenoids (eg, ginkgolides), and organic acids believed to synergistically act as free radical scavengers.[46] Since excessive peroxidation and cell damage have been observed in Alzheimer disease, it is hoped that *Ginkgo* will prove effective.[47] In an intent-to-treat analysis of 2020 patients, *Ginkgo* was found to decrease the Alzheimer's Disease Assessment Scale-Cognitive subscale score 1.4 points better than the placebo group ($P = .04$) with a Geriatric Evaluation by Relative's Rating Instrument score of 0.14 points better as well ($P = .004$).[48] No significant difference in adverse effects was noted leading the investigators to conclude that *Gingko* was safe and capable of stabilizing and perhaps improving cognitive performance in patients with dementia and was of sufficient magnitude to be recognized by caregivers.

Ginkgo is considered relatively safe with few documented adverse effects, which seem to be limited to mild gastrointestinal upset and headache. However, spontaneous hyphema in a 70-year-old man taking a 40-mg tablet of concentrated *G biloba* extract has been reported.[49] Furthermore, spontaneous bilateral subdural hematomas have also occurred secondary to *Ginkgo* ingestion.[50] This condition has been attributed to ginkgolide B, a potent inhibitor of platelet-activating factor that is needed to induce arachidonate-independent platelet aggregation.[51] Hence, concomitant use with aspirin or any of the NSAIDs, as well as anticoagulants, such as warfarin and heparin, is ill advised. Of additional concern is the presence of *Ginkgo* toxin in both the *Ginkgo* leaf and seed, which is a known neurotoxin.[52] While the investigators concluded that the amount of toxin was too low to exert a detrimental effect, it would be prudent to avoid use in known epileptic patients because it may diminish the effectiveness of administered anticonvulsants (eg, carbamazepine, phenytoin, and phenobarbital). Additionally, concomitant

use with medications known to decrease the seizure threshold, such as tricyclic antidepressants, would also be ill advised. It is encouraging that *Ginkgo* did not interact or adversely affect concomitant therapy with cardiac glycosides or hypoglycemic drugs in a study of 112 outpatients with cerebral insufficiency.[53]

Ginseng

Wide variation exists among ginseng products. Ginsenoside extraction methods have found *Panax quinquefolius* in American ginseng, *Panax ginseng* in Oriental ginseng, and *Panax pseudoginseng* var *notoginseng* in Sanchi ginseng.[54] Panax-type ginsenosides were not detected in Siberian ginseng that instead contains *Eleutherococcus senticosus*. This distinction is important since properties vary according to the specific product. For example, the eleutherosides have been associated with falsely elevated digoxin levels in the absence of digoxin toxic effects presumably because of an interaction with the digoxin assay.[55] The ginseng identity issue is further compounded by the finding of tremendous content variation in products labeled as containing ginseng.[56] Using a spectrodensitometer and thin-layer chromatographic assay to quantify the panoxide and saponin content, only 25% of the commercially available products actually contained ginseng.[56] Nevertheless, ginseng enjoys widespread popularity and has been touted as an adaptogen, perhaps augmenting adrenal steroidogenesis via the pituitary gland.[57] In contradiction to this hypothesis is the finding of immunomodulatory effects of ginseng in mice (as measured by IgG and IgM responses to either a primary or secondary challenge with sheep red blood cells) with stimulation of interferon production in vitro.[58] The immunomodulatory effect of ginseng was confirmed in a sheep erythrocyte study in mice in which cell-mediated immunity and natural killer cell activity were increased following administration of 10 mg/d per mouse for 4 days.[59] Additionally, ginseng has had favorable results in a double-blind, placebo-controlled study of 36 newly diagnosed patients with type 2 diabetes.[60] A 200-mg dose improved the subjective ratings of mood, vigor, and well-being, which was associated with increased physical activity and reduced weight. A lower fasting blood glucose level was also associated with ginseng treatment but not with placebo (mean ± SEM, 7.4 mmol/L ± 1.1 and 8.3 mmol/L ± 1.3, respectively). The hypoglycemic effects have been attributed to ginsenoside Rb2 and more specifically to panaxans I, J, K, and L.[61-65] Certainly more studies are warranted regarding ginseng's use in the population with diabetes.

Ginseng's adverse effect profile includes hypertension, insomnia, vomiting, headache, and epistaxis.[66,67] Stevens-Johnson syndrome was noted in a 27-year-old law student from China following use of 2 tablets (unspecified milligram amount) of ginseng for 3 days, resulting in moderate infiltration of the dermis by mononuclear cells.[68] Oral administration of 200 mg of ginseng for an unspecified time to a 72-year-old woman resulted in vaginal bleeding attributed to a moderate estrogen effect.[69] Vaginal bleeding has also been reported following use of ginseng face cream for 1 month when an endometrial biopsy specimen demonstrated a disordered proliferative pattern.[70] Mastalgia with diffuse breast nodularity has been reported in a 70-year-old woman after 3 weeks of use of a ginseng powder; her condition resolved after she discontinued using ginseng.[71] Neonatal androgenization secondary to ginseng has been debated in the literature in cases in which maternal use of ginseng was identified as the cause of androgenization of the child.[72,73] However, others contend the entity in question was in fact a botanically distinct species, Siberian ginseng, that when studied in rats at equivalent doses is not associated with androgenicity.[74] Given the wide variety of ginseng products available, it would be prudent to avoid the use of ginseng during pregnancy until the issue is adequately resolved.

Drug interactions have been noted with the use of ginseng. A 47-year-old man with a St Jude–type mechanical heart valve in the aortic position had been stabilized while receiving warfarin for 5 years but became destabilized following administration of ginseng.[75] The patient's INR decreased to 1.5 after 2 weeks of ginseng, which had been preceded by an INR of 3.1. Following the discontinuation of ginseng therapy, the INR returned to 3.3 within 2 weeks. The mechanism underlying this drug-herb interaction is unknown but may be related to the antiplatelet components in *P ginseng*.[76] Concomitant use with warfarin, heparin, aspirin, and NSAIDs should be avoided. Several case reports have documented headache, tremulousness, and manic episodes in patients treated with phenelzine when they started a regimen of ginseng.[77,78] Central nervous system stimulant activity has been observed in a 2-year study of 133 ginseng users in which nervousness and sleeplessness were noted.[79] The author of that study likens this ginseng effect to that of corticosteroid toxic effects, suggesting a steroid mechanism of action for ginseng. As a consequence, it would be wise to avoid use of ginseng in patients with manic-depressive disorders and psychosis. Additionally, ginseng may augment corticosteroid toxic effects in predisposed patients. However, ginseng's effect on blood glucose levels may not be congruent with that expected of corticosteroids (ie, hyperglycemia).

Saw Palmetto

While touted for its use as a diuretic, urinary antiseptic, and for its anabolic properties, the most common use for saw palmetto is for benign prostatic hypertrophy. The hexane extract of saw palmetto has been identified as the active ingredient with predominantly antiandrogenic activity and in vivo estrogenic activity demonstrated in rats.[80] Saw palmetto has also been shown to inhibit both dihydrotestosterone binding at the androgen receptors and 5-α-reductase activity on testosterone, both being mechanisms thought to be influential in the management of benign prostatic hypertrophy.[81] In 2 double-blind trials both objective (eg, frequency of nocturia and urine flow rate) and subjective (eg, dysuria intensity and patient's self-rating) data indicated significant ($P<.01$) improvement when saw palmetto (320 mg/d) was

compared with placebo.[82,83] For example, the flow rate was mean ± SEM, 5.35 ± 1.51 mL/s before treatment and was 8.05 ± 2.47 mL/s after treatment (50.5% improvement; $P<.001$).[82] In a 3-year trial of 309 patients, saw palmetto increased urinary flow rate to 6.1 mL/s with a 50% decrease in residual urine volume vs finasteride that demonstrated a 30% decrease in symptom scores over 3 years, with only a slight improvement in urine flow and no change in residual volume.[84] A comparative study evaluating saw palmetto, doxazosin or terazosin (α_1-adrenergic blocking agent), finasteride (a 5-α-reductase inhibitor), and flutamide (an antiandrogen) in the treatment of benign prostatic hypertrophy is needed.

Adverse effects appear minimal and are characterized mostly by gastrointestinal upset.[83] While no drug-herb interactions have been documented to date, it would be prudent to avoid concomitant use with other hormonal therapies (eg, estrogen replacement therapy and oral contraceptives), which may provide an additive effect.

St John Wort

Hypericum perforatum is commonly referred to as St John wort. It is licensed in Germany for the treatment of anxiety, depression, and sleep disorders, with more than 2.7 million prescriptions written for it in 1993 (the seventh most popular preparation in Germany).[85] St John wort contains at least 10 constituents or groups of components that may contribute to its pharmacological effects, including naphthodianthroms, flavonoids, xanthose, and bioflavonoids.[86] Therefore, standardizing the product according to its *Hypericum* content confers no guarantee of the pharmacological equivalence of products. Hence, the usual dose has been touted as being 2 to 4 g of herb, equating this measurement with 0.2 to 1.0 mg of total hypericin, which is a questionable conversion. The mechanism of action is uncertain and has been purportedly characterized as a monoamine oxidase inhibitor (MAOI) (quercitrin content) or a selective serotonin reuptake inhibitor.[87] However, MAOI properties of *Hypericum* extracts have not been confirmed and may not be of a magnitude to be clinically significant; therefore, it may not be necessary to avoid concomitant use with tyramine-containing foods (eg, Swiss cheese, Chianti, or sauerkraut).[88] The Office of Alternative Medicine of the National Institutes of Health is now undertaking a study to define its characteristics and effectiveness. However, in a meta-analysis of randomized clinical trials enrolling 1757 patients, *Hypericum* extracts were found to be significantly superior to placebo (22.3% responded to placebo, compared with 55.1% to St John wort) and were similarly effective as standard antidepressants with fewer adverse effects (20% vs 53%, with standard antidepressants such as amitriptyline, or imipramine hydrochloride).[89]

The most prominent adverse effect associated with St John wort is photosensitivity attributed to its hypericin component.[90] Hence, fair-skinned individuals should be particularly cautious. Concomitant use with other known photosensitizers, such as piroxicam or tetracycline hydrochloride, should be avoided. Until the MAOI status of St John wort has been defined, it would also be prudent to avoid concomitant use with known MAOIs, such as phenelzine or with beta-sympathomimetic amines (eg, ma huang or pseudoephedrine hydrochloride). Similarly, symptoms of serotonism (eg, headache, sweating, dizziness, and agitation) may be encountered if used concomitantly with selective serotonin reuptake inhibitors (eg, fluoxetine and paroxetine) if St John wort is found to have selective serotonin reuptake inhibitor effects as well.

Valerian

In a study of 8 volunteers with mild insomnia, an aqueous extract of 450 or 900 mg of valerian was compared with placebo in a double-blind, repeated-measures, random study.[91] A significant decrease in sleep latency was noted with 450 mg of valerian compared with placebo (mean ± SEM, 15.8 ± 2.2 minutes vs 9.0 ± 1.5 minutes; $P<.01$).[91] The higher dose of valerian (900 mg) was not associated with any further improvement in sleep latency.[91] These findings concur with another study of 128 patients that notes not only significantly decreased sleep latency but also that patients felt sleepier waking in the morning.[92] Valerian has not been noted to change sleep stages or electroencephalographic spectra and has been characterized as a mild hypnotic substance.[93] Purportedly, valerian does not interact with alcohol but this finding has been disputed, leading some to warn against its use with alcohol.[94] Furthermore, valerian has been shown to prolong thiopental- and pentobarbital-induced sleep.[55,95,96] Hence, valerian should not be used with barbiturates.

ALLOPATHIC MEDICATIONS AND ASSOCIATED DRUG-HERB INTERACTIONS

The first drugs to be addressed will be those with a narrow therapeutic window. Given their toxicities and the potential adverse sequelae if blood levels fall outside the therapeutic range, those drugs can be quickly and acutely affected by concomitant herbal therapies. A summary of herb-drug interactions affecting commonly used drugs is provided in the **Table**.

DRUGS WITH A NARROW THERAPEUTIC WINDOW

Digoxin

Numerous herbs containing cardiac glycosides have been identified as containing digoxinlike substances. These include *Adonis vernalis* (adonis, false hellebore, pheasant's eye), *Apocynum androsaemifolium* (dogbane, milkweed, and wild ipecac), *Apocynum cannabinum* (dogbane, milkweed, and wild ipecac), *Asclepias tuberosa* (pleurisy root), *Convallaria majalis* (lily of the valley), *Cystisus scoparius* (broom), *Digitalis lanata* (yellow foxglove), and *Digitalis purpurea* (purple foxglove). Other herbal medicinals include *Eleutherococcus senticosus* (Siberian ginseng), kyushin (Chinese medicine), *Leonurus cardiaca* (motherwort), *Scilla maritima* (white squill), *Scrophularia nodosa* (fig-

Summary of Drug-Herb Interactions of Commonly Used Drugs

Drug	Interaction
Alprazolam	Excessive sedation may result if used concomitantly with kava
Corticosteroids	The immunostimulating effects of *Echinacea, Astragalus*, licorice, alfalfa sprouts, vitamin E, and zinc may offset the immunosuppressive effects of corticosteroids
Cyclosporine	The immunostimulating effects of *Echinacea, Astragalus*, licorice, alfalfa sprouts, vitamin E, and zinc may offset the immunosuppressive effects of cyclosporine
Digoxin	Additive effects possible with herbs containing cardiac glycosides; hawthorn purportedly potentiates digoxin; licorice may cause hypokalemia, hence predisposing the patient to digoxin's toxic effects; plantain may be adulterated with foxglove, hence elevating digoxin blood levels; Siberian ginseng and kyushin may interfere with digoxin assays; uzara root may exert additive digoxin-type cardiac effects
Diuretics	Sodium-sparing herbal aquaretics (eg, dandelion, uva-ursi) may offset antihypertensive effects of diuretics (eg, hydrochlorothiazide and furosemide); gossypol may exacerbate hypokalemia secondary to diuretics (eg, hydrochlorothiazide and furosemide)
Hypoglycemics (eg, sulfonylureas)	Chromium may decrease insulin requirements; karela has been shown to decrease dosage requirements for chlorpropamide
Iron	Tannin-containing herbs (eg, chamomile, feverfew, St John wort) may interact with iron, hence inhibiting iron absorption
Levothyroxine	Horseradish and kelp may suppress thyroid function, complicating thyroid function
Nonsteroidal anti-inflammatory drugs	Additive gastrointestinal irritation may be encountered with herbs known to irritate the gastrointestinal tract (eg, gossypol and uva-ursi)
Phenelzine (and other MAO* inhibitors)	Concomitant use with ginseng, yohimbine, and *Ephedra* may result in insomnia, headache, and tremulousness; St John wort and licorice may have MAO inhibitor activity and should not be used concomitantly with known MAO inhibitors
Phenobarbital	Thujone-containing herbs (eg, wormwood and sage) may lower seizure threshold, hence increasing anticonvulsant dosage requirements; gamolenic acid–containing herbs (eg, evening primrose oil and borage) lower seizure thresholds and may increase anticonvulsant dosage requirements.
Phenytoin	Same as for phenobarbital plus Shankhapulshpi may shorten the half-life and diminish effectiveness of phenytoin
Spironolactone	Licorice may offset the effects of spironolactone
Warfarin	Garlic, ginger, *Ginkgo*, and feverfew may augment the anticoagulant effect of warfarin; ginseng may decrease the effectiveness of warfarin

**MAO indicates monoamine oxidase.*

wort), *Strophantus kombe* (strophanthus), and *Uzarae radix* (uzara root). Reports have documented the various problems encountered with these entities. Various lots of plantain (used as an herbal laxative) have been adulterated with potentially toxic woolly foxglove resulting in a Food and Drug Administration advisory.[97,98] Foxglove was included in a product called Chomper, of the Cleanse Thyself line, Aris and Shine Company, Mount Shasta, Calif. While the company voluntarily recalled suspected batches, the Food and Drug Administration did report that 1 young woman had an abnormal heart rate with heart-block. Similarly, patients who present with ventricular tachycardia, unifocal and multiform premature ventricular contractions, and atrioventricular dissociation suggestive of digoxin toxic effects but who have not ingested digoxin should be asked if they have taken plantain. This incident speaks to the lack of good manufacturing practices of some herbal medicinal companies.

Licorice has been advocated for gastrointestinal complaints, particularly peptic ulcer disease.[99] However, in 1 case it was associated with pseudoaldosteronism that resulted in hypertension but both the pseudoaldosteronism and the hypertension resolved 2 weeks after the patient stopped using licorice.[100,101] Its active component has been identified as glycyrrhizic acid, known to inhibit 11-β-hydroxysteroid dehydrogenase and should be included in a differential diagnosis of factitious mineralocorticoid excess.[102-104] Licorice's mineralocorticoid effects can be offset with the use of spironolactone.[105] Potassium loss has been associated with the use of licorice with chronic ingestion resulting in acute flaccid tetraparesis and hypokalemia.[106] In this case, a 35-year-old man ingested 20 to 40 g/d of licorice tablets for 2 years, developing acute myopathy and complete paralysis of the proximal muscles of his arms and shoulder girdles, weakness of the muscles of his forearms and hands, weakness of his proximal leg muscles, and moderate weakness of his posterior and anterior neck muscles along with a serum potassium level of 2.1 mmol/L. With potassium repletion and discontinuation of the licorice regimen, the paralysis completely resolved within 3 days. However, an accelerated loss of potassium may result in increased sensitivity to digoxin treatment.

A Chinese medicine containing kyushin has been documented to cross-react with digoxin assays. A patient taking digoxin, 0.25 mg/d, for congestive heart failure had a serum digoxin level of 2.5 mmol/L with no symptoms of digoxin intoxication.[107] Kyushin contains chan su, the dried venom of the Chinese toad *Bufo bufo gargarizans cantor,* which purportedly has digoxinlike actions.[108] It was determined that 1 tablet of kyushin had digoxinlike immunoreactivity equivalent to 1.9 µg (TDX analyzer, Abbott Laboratories, North Chicago, Ill) and 72 µg of digoxin (Enymun-Test, Boehringer, Mannheim, Germany). Thus, patients with spuriously elevated digoxin levels without associated signs and symptoms of digoxin toxicity should be approached cautiously and questioned regarding herbal therapies.

Additional entities may also interfere with digoxin activity and monitoring. *Uzarae radix* (uzara root) in large doses has been found to have digoxin-type cardiac effects so that additive effects may be encoun-

tered.[109] Ginseng may falsely elevate digoxin levels.[9] (Hawthorn berries purportedly potentiate the action of digoxin.[110] No clinical studies have validated this assertion. Animal studies suggest hawthorn may possess β-blocking activities; however, others contend that hawthorn's cardiac effects may be secondary to angiotensin-converting enzyme inhibitor properties.[111]

Phenobarbital

Several herbal medicinals may lower the seizure threshold, thus offsetting beneficial effects from known anticonvulsants such as phenobarbital. Such herbs may contain thujone. Thujones are apparently present in wormwood (used as an appetite stimulant and for intestinal spasmodic disorders) and sage (used to treat flatulent dyspepsia, gingivitis, stomatitis, and galactorrhea).[112] The mechanism of this proconvulsant effect is unknown. However, it would be prudent to avoid concomitant use with anticonvulsants and with drugs known to lower the seizure threshold (eg, tricyclic antidepressants).

Evening primrose oil contains gamolenic acid (GLA) that lowers the seizure threshold.[113] Recently, evening primrose oil has gained popularity as a remedy for premenstrual syndrome, which purportedly has been associated with low GLA levels.[113] Evening primrose oil is touted as a good source of GLA. Evening primrose oil has also been used for diabetic neuropathy (with a purported reduced ability to desaturate essential fatty acids with resulting deficits in neuronal membrane structure), multiple sclerosis (although results have been contradictory), Sjögren syndrome (a feature of essential fatty acid deficiency is exocrine gland atrophy typical of Sjögren) and attention deficit/hyperactivity disorder.[113] Hyperactive children supposedly have abnormal levels of essential fatty acid; however, no improvements in behavioral patterns were noted in one trial with evening primrose oil.[114] Similarly, starflower (borage) has also been touted as a source of GLA. Borage is used herbally as a diaphoretic, expectorant, anti-inflammatory, and galactogogue.[115] It has been used for fevers, coughs, and depression and is reputed to act as a restorative agent on the adrenal cortex.[116] Borage oil is used as an alternative source to evening primrose oil for GLA. In human studies, it was found to attenuate cardiovascular reactivity to stress induced by a reduction in systolic blood pressure and heart rate and increased task performance although the underlying mechanism of action is unknown.[117] However, borage does contain low concentrations of unsaturated pyrrolizidine alkaloids known to cause hepatotoxic effects (eg, comfrey).[118] Therefore, do not use borage with other hepatotoxic drugs, such as anabolic steroids, phenothiazines, or ketoconazole. Neither evening primrose oil nor borage should be used concomitantly with other drugs known to lower the seizure threshold (eg, tricyclic antidepressants and phenothaizines).

Phenytoin

The effectiveness of phenytoin has been adversely affected by Shankapulshpi, an Ayurvedic preparation for epilepsy that contains[119] *Convolvulus pluricaulis* (chois), the leaves, *Centella asiatica* (urban), the whole plant, *Nardostachys jatamansi* (DC), rhizome, *Nepeta hinostana* (haines), the whole plant, *Nepeta elliptica* (Royle), the whole plant, and *Onosma bracteatum* (wall), the leaves and flowers.

After observing 2 patients experience loss of seizure control, investigators evaluated the effect of Shankhapulshpi on phenytoin.[120] They found with multidose administration of Shankhapulshpi (1 teaspoonful 3 times per day), the antiepileptic activity of phenytoin as well as the plasma levels were decreased. Phenytoin levels decreased from 9.62 ± 2.93 μmol/L when administered alone to 5.10 ± 0.67 μmol/L when coadministered with Shankhapulshpi ($P<.01$). Additionally, coadministration of Shankhapulshpi resulted in diminution of phenytoin's antiepileptic effectiveness measured using maximal electroshock seizure induced by administering a 150-mA current for 0.2 seconds to animals (abolition of tonic hind limb extension was interpreted as protection from maximal electroshock seizure, reflecting antiepileptic activity).[120] Thus, loss of seizure control with no changes in phenytoin dosing or pharmacokinetics should compel the clinician to explore the possibility of the patient self-administering this Ayurvedic preparation. Additionally, as with phenobarbital, thujone, evening primrose oil, and starflower may exert similar deleterious effects as outlined earlier with phenobarbital.

Warfarin

Warfarin is an anticoagulant with a narrow therapeutic window with potentially fatal consequences if either bleeding complications arise or if subtherapeutic levels occur, thus not protecting the patient from thromboembolic events. Several herbs may interact with warfarin. As previously discussed, ginseng may decrease the effectiveness of warfarin. A 47-year-old man with a St Jude–type mechanical heart valve had received warfarin therapy for 5 years with a therapeutic INR 4 weeks before he started taking ginseng. Within 2 weeks, his INR declined to 1.5 but returned to 3.3 within 2 weeks of discontinuing the ginseng regimen.[75] Fortunately, no thrombotic events occurred during this subtherapeutic period, but this result certainly highlights the potential lethality of this drug-herb interaction. Conversely, dan-shen (*Salvia miltiorrhiza*), a Chinese folk medicine remedy, has been noted to significantly increase maximum concentration (C_{max}) (mean ± SD, 5500 ± 1636 ng/mL to 10 976 ± 3.975; $P = .01$) and time as maximum concentration (T_{max}) (mean ± SD, 3.6 ± 0.8 hours to 7.2 ± 1.7 hours; $P = .001$) and decrease the volume of distribution (142.5 ± 75.20 to 54.5 ± 18.9 mL; $P<.005$) and elimination half-life (31.8 ± 6.4 to 16 ± 2.6 hours; $P = .001$) of warfarin.[121] Because of its coumarin constituents, excessive use is not recommended with known anticoagulants such as warfarin.[122] Herbs that may interfere with warfarin treatment include arnica, celery, chamomile, dan-shen, dong quai, fenugreek, feverfew, garlic, ginger, *Ginkgo*, and ginseng.

When used for hyperlipidemia for 308 patients, garlic was also as-

sociated with decreased platelet aggregation.[33] In a study of 6 healthy adults, decreased platelet aggregation was noted within 5 days of oral administration theorized to be secondary to inhibition of epinephrine-induced in vitro platelet activity.[34] While these authors did not feel the effect was of clinical significance, dysfunctional platelets have been implicated in spontaneous spinal epidural hematoma in an 87-year-old man who ingested 4 cloves of garlic daily (approximately 2000 mg) for an unspecified time.[35] Caution is advised if these preparations must be used concomitantly.

Ginger has been found to be a potent inhibitor of thromboxane synthetase with potential effects on bleeding time.[44] While not quantified and fully characterized, it is an effect that could become clinically significant if used long-term. This mechanism theoretically could cause excess bleeding if used concomitantly with warfarin. Caution is advised.

Feverfew may also inhibit platelet activity via neutralization of sulfydryl groups that may cause an increase in bleeding time and an associated increase in bleeding tendencies.[21] A dose-dependent and irreversible inhibition of eiconsanoid generation has been demonstrated when levels range from 5 to 50 µg/mL.[123,124] However, others contend that this platelet effect is of no clinical consequence and that platelets of all patients whether presently taking feverfew or having discontinued its use for 6 months have normal characteristic responses to adenosine diphosphate.[125] Therefore, until this potential drug-herb interaction is further defined, concomitant use with warfarin should be avoided.

Concomitant use of warfarin and *Ginkgo* is not recommended. Spontaneous bilateral subdural hematomas have occurred secondary to *Ginkgo* ingestion.[50] These hematomas have been attributed to ginkgolide B, a potent inhibitor of platelet-activating factor that is needed to induce arachidonate-independent platelet aggregation.[51] Hence, concomitant use with aspirin or any of the NSAIDs as well as anticoagulants such as warfarin and heparin are ill advised.

ADDITIONAL DRUGS WITH KNOWN OR POTENTIAL DRUG-HERB INTERACTIONS WITH COMMONLY USED HERBAL MEDICINALS

Alprazolam

Kava is used as a sedative to enhance sleep. Long-term use is not advised because tolerance has been shown to develop rapidly in animals.[126] Additionally, long-term use has led to *kawaism,* which is characterized by dry, flaking, discolored skin and reddened eyes.[127,128] The toxicity of kava is increased if taken with alcohol.[129]

α-Pyrone, the active component of kava, has been found to have weak effects on γ-aminobutyric acid and benzodiazepine receptors in vitro, although this has been disputed.[130-132] Synergism between α-pyrones and other actve sedatives with γ-aminobutyric acid was verified in 1994 by a German study group.[133] However, concomitant use with benzodiazepines is ill advised based on a case of coma following concomitant use. A 54-year-old man was hospitalized in a lethargic and disoriented state.[134] His medications included alprazolam, cimetidine, and terazosin hydrochloride; his alcohol levels were negative and his drug screen was positive for benzodiazepines. He became more alert after several hours and stated that he had been taking kava for 3 days; he denied overdosing on kava or alprazolam.[134] The kava–alprazolam drug interaction was identified as the cause.

Corticosteroids and Cyclosporine

The theoretical concern underlying this drug-herb interaction is that immunostimulating herbs will offset or minimize the immunosuppressive effects of corticosteroids and cyclosporine. *Echinacea* is classified as an *immunotonic* agent because of its ability to augment basophils, mast cells, and white blood cell counts.[134,135] *Astragalus* stimulates T-cell activity and ginseng is thought to nourish major immune system glands but in an unspecified manner.[136] Licorice root supposedly stimulates interferon production and pau d'arco with its antioxidant and anti-inflammatory activity has been recommended for use by herbalists for immunodeficiencies.[137,138] Alfalfa sprouts and some vitamin E products contain toxic amino acid L-canavanine that has been implicated in cases of systemic lupus erythematosus and other autoimmune diseases.[139]

Zinc

Zinc gluconate lozenges have been found useful in treating the common cold. In a randomized, double-blind, placebo-controlled study, time to complete resolution of symptoms was significantly shorter in the patients treated with zinc than the placebo group (median, 4.4 days compared with 7.6 days; $P<.001$). Patients treated with zinc had significantly fewer days with coughing (median, 2.0 days compared with 4.5 days; $P=.04$) and headache, (2.0 days compared with 3.0 days; $P=.02$) but were not significantly different in resolution of fever, muscle ache, scratchy throat, or sneezing.[140] Twenty percent of patients experienced nausea and 80% had a bad-taste reaction.[140] Mechanisms of action have yet to be determined but in vitro studies suggest that zinc may induce interferon production.[141] Other proposed zinc mechanisms include the ability of zinc to prevent formation of viral capsid protein thereby inhibiting in vitro replication of several viruses including rhinovirus.[142,143] This immunostimulating effect may be in opposition to immunosuppressive effects desired with the use of corticosteroids and/or cyclosporine. Therefore, zinc and other immunostimulating herbs should be avoided in autoimmune disorders (eg, rheumatoid arthritis and systemic lupus erythematosus) and in cases in which patients are using immunosuppressive therapies (eg, corticosteroids and cyclosporine) to avoid competing effects on the immune system.

Diuretics

Goldenseal is an aquaretic, but is referred to by most herbalists as a diuretic.[144] Other herbal diuretics include agrimony, artichoke, boldus, broom, buchu, burdock, celery seed, zea,

coughgrass, dandelion, elder, guaiacum, juniper, pokeroot, shepherd's purse, squill, uva-ursi, and yarrow.[145] The differentiation between a diuretic and an aquaretic is of clinical significance because with diuretics, sodium is excreted with the water whereas with aquaretics, sodium is not excreted. Therefore, aquaretics are not well suited for the treatment of edema and hypertension and may in fact worsen it. If taken with a diuretic (eg, hydrochlorothiazide) or any allopathic antihypertensive drug, it is conceivable that the antihypertensive effects will be diminished or offset as sodium is retained.

Gossypol

Gossypol inhibits lactate dehydrogenase X found in sperm and male gonadal cells, hence exerting contraceptive activity.[146] It has also been found to inhibit implantation and maintenance of a healthy pregnancy by adversely affecting lutenizing hormone levels and so has been studied in female fertility control.[147] However, it has been associated with renal loss of potassium resulting in hypokalemia.[146] Furthermore, this potassium loss cannot be reversed with potassium supplementation or with the use of the potassium blocker triamterene.[148] Hence, concomitant use with allopathic drugs known to promote potassium loss (eg, hydrochlorothiazide and furosemide) should be avoided. Additionally, use with digoxin whose effects are potentiated in hypokalemia should be avoided as well.

Iron/Tannin Complex With Iron-Inhibiting Iron Absorption

Tannin-containing herbs include chamomile, plantain, black cohosh, saw palmetto, feverfew, St John wort, hawthorn, valerian, nettle, and gossypol.[149]

The tannins complex has iron-inhibiting absorption.[149] While the interaction between iron and tannins has not yet been clinically observed, it is of sufficient concern to merit caution when the 2 components are used together. If a patient is not responding adequately to iron therapy, the clinician should inquire regarding concomitant use of herbal medicinals as described earlier.

Levothyroxine

Horseradish is used herbally as an antiseptic with circulatory and digestive stimulation effects and as a diuretic.[150] Traditionally, it has been used for pulmonary and urinary tract infections, urinary stones, and edematous conditions; it has been used externally for application to inflamed joints or tissues.[150] However, it may depress thyroid function and should not be used with levothyroxine or other thyroid replacements.[150] Patients with aberrant thyroid function tests should be questioned regarding herbal use of horseradish.

Kelp

Kelp diets promoted for weight loss have caused myxedema in patients sensitive to iodide and, unfortunately, neither baseline serum triidothyronine and thyroxine concentrations nor the degree of serum iodide elevations were of prognostic value in predicting which patients would develop myxedema.[151] Kelp contains 0.7 mg of iodine per tablet and may result in hyperthyroidism after 6 months of use as demonstrated in a 72-year-old woman who ingested a commercially available kelp product.[152] Her hyperthyroidism resolved 6 months after she discontinued using the product. Therefore, concomitant use of kelp with levothyroxine or other thyroid replacements may result in hyperthyroidism. Additionally, concomitant use with known stimulants (eg, amphetamines, methylphenidate, or ma huang) could be dangerous.

Nonsteroidal Anti-inflammatory Drugs

The NSAIDS should not be used with herbal medicinals that are known to cause gastrointestinal damage. Gossypol has been associated with tissue congestion, mucosal sloughing, mucosal necrosis, and ileus and intestinal wall hemorrhage.[153] Other gastric irritants include *Arctostaphylos uva-ursi*, *Ruta graveolens, Cetraria islandica, Sanguinaria canadensis, Chamaelirium luteum, Schinus terebinthifolia, Coffea arabica, Schinus molle, Cola acuminata, Symplocarpus foetidus, Cola nitida, Trillium erectum*, and *Quillaja saponaria*.[154,155]

Hence, a patient complaining of unexpected gastrointestinal upset should be questioned regarding herbal medicinal use and concomitant use with known gastrointestinal irritants, such as NSAIDs, should be avoided.

Phenelzine and Other MAOIs

The effect of phenelzine and other MAOIs may be potentiated by numerous herbal medicinals. *Panax ginseng* is one such agent. A 64-year-old woman treated with phenelzine developed insomnia, headache, and tremulousness following the addition of ginseng (Natrol High ginseng tea).[156] In the second case, a 42-year-old woman whose major depressive illness was being treated with phenelzine experienced headaches, irritability, and vague visual hallucinations with concomitant use of ginseng.[157] Yohimbine and ma huang (*Ephedra*) may be implicated as well. St John wort was once purported to have MAOI activity and thus should not be used with other MAOIs, but more recent data call into question the clinical significance of its MAOI activity.[88,158] Licorice (*Glycyrrhiza glabra*) may also adversely interact with MAOIs. Glycyrrhizin is 10 times more active as an MAOI as hypericin and has been identified as containing isoliquiritigenin, glycoumarin, licochalcone A, licochalcone B, and (-)-medicarpin (MAOIs).[159] So, while it is relatively common to advise patients of dietary precautions when taking MAOIs, counseling regarding herbal medicinals should be included as well.

Spironolactone

Licorice may offset spironolactone's effects. Licorice is advocated as an antispasmodic and anti-inflammatory herb for use in gastritis and peptic ulcer disease. The hemisuccinate derivative of glycyrrhetainic acid, a component of licorice, is carbenoxolone, which is used allopathically for duodenal and gastric ulcers.[160] Licorice renders the patient unable to convert 11-deoxy-

cortisol or deoxycorticosterone into the active glucocorticoids, cortisol, and corticosterone, respectively.[161] This acquired 11-β-hydroxylase deficiency results in sodium retention, hypertension, and hypokalemia.[161] Within 10 days to 3 weeks of the discontinuation of the licorice regimen, the blood pressure will return to baseline.[100,162,163] Given the underlying mechanism of licorice's effect on hypertension, spironolactone's antihypertensive effects may be diminished by licorice. Conversely, hypertension caused by licorice may be effectively treated with spironolactone.

Hypoglycemics

Numerous herbal medicinals have been shown to affect blood glucose levels including chromium, fenugreek, garlic, ginger, ginseng, *Gymnema sylvestre*, nettle, and sage for patients with hypoglycemia and devil's claw, ginseng, licorice, and ma huang for patients with hyperglycemia. Karela (*Momordica charantia*) has been shown to improve glucose tolerance.[164,165] When taken in conjunction with chlorpropamide, the dose of the latter needed to be reduced, although this report specified neither the starting or adjusted final dose.[166] Some claim chromium increases insulin activity and reduces the amount of insulin required to control blood glucose.[167] However, in a prospective, double-blind, placebo-controlled, cross-over study of 28 patients receiving chromium picolinate, 200 mg/d, or placebo for 2 months, no statistically significant difference ($P>.05$) was noted in blood glucose control.[168] Ginseng, whose activity has been attributed to 2% to 3% ginsenosides has been associated with hyperglycemic properties as well.[63] There have been no reports of ginseng-induced hypoglycemic or hyperglycemic incidents in humans to date reported in the literature. The use of these herbal medicinals in patients with diabetes, especially those with brittle diabetes should be avoided.

Estrogen Replacement Therapy

Theoretically, concomitant use of phytoestrogens with estrogen replacement may result in symptoms of estrogen excess such as nausea, bloating, hypotension, breast fullness or tenderness, migraine headache, and edema. Phytoestrogens are naturally occurring plant or food substances that are functionally similar to estradiol.[169] While more than 500 plant species contain phytoestrogens, the more common herbs include dong quai, red clover, alfalfa, licorice, black cohosh, and soybeans.[170,171] To date, no incidents of estrogen excess have been reported following concomitant use, but prudence would dictate avoiding simultaneous use if at all possible.

COMMENT

Standardization and monitoring for adulteration is needed to limit the present problem of wide interproduct and intraproduct (lot-to-lot) variation in composition of active constituents. Clearly, more scientifically based studies evaluating efficacy and safety issues on the use of herbal medicinals are needed. Such studies will no doubt prove to be a double-edged sword in which some herbal medicinals will fall into disfavor while others will provide the basis for new and effective drugs. Additionally, studies directed at drug-herb interactions would serve public safety. Perhaps a request for proposals from the Office of Alternative Medicine funded by the National Institutes of Health would be appropriate to promote such an agenda. However, since such studies are lacking, it is hoped that this overview of known and potential drug-herb interactions in the context of known efficacy studies of selected herbal medicinals will serve to alert the clinician to their possibility in his or her practice. Because 33% of American patients are taking herbal medicinals, clinicians should include them in their routine drug histories.[2]

Accepted for publication June 10, 1998.

Reprints: Lucinda G. Miller, PharmD, BCPS, Department of Pharmacy Practice, Texas Tech University Health Sciences Center, 1300 Coulter, Amarillo 79121.

REFERENCES

1. Richman A, Witkowski J. Herbs by the numbers. *Whole Foods Magazine.* 1997:20, 22, 24, 26, 28.
2. Johnston BA. One-third of nation's adults use herbal remedies. *Herbalgram.* 1997;40:49.
3. Eisenberg DM, Kessler RC, Foster C, Norlock FE, Calkins DR, Delbanco TL. Unconventional medicine in the United States: prevalence, costs, and patterns of use. *N Engl J Med.* 1993;328:246-252.
4. Newall CA, Anderson LA, Phillipson JD. Chamomile monograph. In: Newall CA, Anderson LA, Phillipson JD, eds. *Herbal Medicinals: A Guide for Health-Care Professionals.* London, England: Pharmaceutical Press; 1996:69-73.
5. Mann C, Staba EJ. The chemistry, pharmacology and commercial formulations of chamomile. In: Craker LE, Simon JE, eds. *Herbs, Spices and Medicinal Plants: Recent Advances in Botany, Horticulture and Pharmacology.* Vol 1. Binghamton, NY: Hayworth Press Inc; 1986:235-280.
6. Casterline CL. Allergy to chamomile tea. *JAMA.* 1980;4:330-331.
7. Benner MH, Lee HJ. Anaphylactic reaction to chamomile tea. *J Allergy Clin Immunol.* 1973;52:307-308.
8. Robbers JE, Speedie MK, Tyler VE. Terpinoids. In: Robbers JE, Speedie MK, Tyler VE, eds. *Pharmacognosy and Pharmacobiotechnology.* Baltimore, Md: Williams & Wilkins; 1996:80-107.
9. Bauer R, Khan IA, Wray V, Wagner H. Structure and stereochemistry of new sesquiterpene esters from *Echinacea purpurea. Helv Chim Acta.* 1985;68:2355-2358.
10. Wagner H, Suppner H, Schafer W, Zenk M. Immunologically active polysaccharides of *Echinacea purpurea* cell cultures. *Phytochemistry.* 1988;27:119-126.
11. Tubaro A, Tragni E, DelNegro P, Galli CL, Loggia RD. Anti-inflammatory activity of a polysaccharidic fraction of *Echinacea angustifolia. J Pharm Pharmacol.* 1987;39:567-569.
12. Stimpel M, Proksch A, Wagner H, Lohmann-Matthes ML. Macrophage activation and induction of macrophage cytotoxicity b purified polysaccharide fractions from the plant *Echinacea purpurea. Infect Immun.* 1984;46:845-849.
13. Parnham MJ. Benefit-risk assessment of the squeezed sap of the purple coneflower (*Echinacea purpurea*) for long-term oral immunostimulation. *Phytomedicine.* 1996;3:95-102.
14. Blumenthal M, Gruenwald J, Hall T, Riggins R, Rister R, eds. *German Commission E Monographs: Therapeutic Monographs on Medicinal Plants.* Austin, Tex: American Botanical Council; 1998.
15. Johnson ES, Kadam NP, Hylands DM, Hylands PJ. Efficacy of feverfew as prophylactic treatment of migraine. *BMJ.* 1985;291:569-573.
16. Murphy JJ, Heptinstall S, Mitchell JRA. Randomized, double-blind, placebo-controlled trial of feverfew in migraine prevention. *Lancet.* 1988;2:189-192.
17. Collier JOH, Butt NM, McDonald-Gibson WJ, Saeed SA. Extract of feverfew inhibits prostaglandin biosynthesis. *Lancet.* 1980;2:922-923.
18. Newall CA, Anderson LA, Phillipson JD. Feverfew monograph. In: Newall CA, Anderson IA, Phillipson JD, eds. *Herbal Medicinals: A Guide for Health-Care Professionals.* London, England: Pharmaceutical Press; 1996:119-121.
19. Hepinstall S, Awang DV, Dawson BA, Kindach K, Knight DW, May J. Parthenolide content and bioactivity of feverfew: estimates of commercial and authenicated feverfew products. *J Pharm Pharmacol.* 1992;44:391-395.
20. Baldwin CA, Anderson LA, Phillipson JD. What pharmacists should know about feverfew. *J Pharm Pharmacol.* 1987;239:237-238.
21. Heptinstall S, Groenewegen WA, Spangenberg P, Loesche W. Extracts of feverfew may inhibit platelet behavior via neutralization of sulphydryl groups. *J Pharm Pharmacol.* 1987;39:459-465.
22. Makheja AN, Bailey J. The active principle in feverfew [letter]. *Lancet.* 1981;2:1054.
23. Reuter HD. *Allium sativum* and *Allium ursinum,* part 2: pharmacology and medicinal applications. *Phytomedicine.* 1995;2:73-91.
24. Foushee DB, Ruffin J, Banerjee U. Garlic as a natural agent for the treatment of hypertension: a preliminary report. *Cytobios.* 1982;34:145-152.
25. Malik ZA, Siddiqui S. Hypotensive effect of freeze-

dried garlic sap in dog. *J Pak Med Assoc.* 1981; 31:12-13.
26. Ruffin J, Hunter SA. An evaluation of the side effects of garlic as an antihypertensive agent. *Cytobios.* 1983;37:85-89.
27. Kleijnen J, Knipschild P, Riet GT. Garlic, onions and cardiovascular risk factors: a review of the evidence from human experiments with emphasis on commercially available prepartions. *Br J Clin Pharmacol.* 1989;28:535-544.
28. Bleumink E, Doeglas HMG, Klokke AH, Nater JP. Allergic contact dermatitis to garlic. *Br J Dermatol.* 1972;87:6-9.
29. Silagy CA, Neil AW. A meta-analysis of the effect of garlic on blood pressure. *J Hypertens.* 1994;12:463-468.
30. Aue W, Eiber W, Hertkorn E, et al. Hypertension and hyperlipidemia: garlic helps in mild cases. *Br J Clin Pract.* 1990;69(suppl): 3-6.
31. Neil HAW, Silagy CA, Lancaster T, et al. Garlic powder in the treatment of moderate hyperlipidemia: a controlled trial and meta-analysis. *J R Coll Physician.* 1996;30:329-334.
32. Dixit VP, Joshi S. Effects of chronic administration of garlic (*Allium sativum* Linn) on testicular function. *Indian J Exp Biol.* 1982;20:534-536.
33. Cooperative Group for Essential Oil of Garlic. The effect of essential oil of garlic on hyperlipidemia and platelet aggregation: an analysis of 308 cases. *J Tradit Chin Med.* 1986;6:117-120.
34. Bordia A. Effect of garlic on human platelet aggregation in vitro. *Atherosclerosis.* 1978;30: 355-360.
35. Rose KD, Croissant PD, Parliament CF, Levin MP. Spontaneous spinal epidural hematoma with associated platelet dysfunction from excessive garlic ingestion: a case report. *Neurosurgery.* 1990; 26:880-882.
36. Grontved A, Hentzer E. Vertigo-reducing effect of ginger root. *J Otolaryngol.* 1986;48:282-286.
37. Mowrey DB, Clayson DE. Motion sickness, ginger and psychophysics. *Lancet.* 1982;1:655-657.
38. Holtmann S, Clarke AH, Scherer H, Hohn M. The anti-motion sickness mechanism of ginger. *Acta Otolaryngol (Stockh).* 1989;108:168-174.
39. Bone ME, Wilkinson DJ, Young JR, et al. Ginger root: a new antiemetic: the effect of ginger root on postoperative nausea and vomiting after major gynecological surgery. *Anesthesia.* 1990;45:669-671.
40. Grontved A, Brask T, Kambskard J, Hentzer E. Ginger root against seasickness: a controlled trial on the open sea. *Acta Otolaryngol (Stockh).* 1988; 105:45-49.
41. Fischer-Rasmussen W, Kjaer SK, Dahl C, Asping U. Ginger treatment of hyperemesis gravidarum. *Eur J Obstet Gynecol Reprod Biol.* 1990;38:19-24.
42. Nakamura H, Yamamoto T. Mutagen and antimutagen in ginger: *Zingiber officinale. Mutat Res.* 1982;109:119-126.
43. Nakamura H, Yamamoto T. The active part of the (6)-gingerol in mutagenesis. *Mutat Res.* 1983; 122:87-94.
44. Backon J. Ginger: inhibition of thromboxane synthetase and stimulation of prostacyclin: relevance for medicine and psychiatry. *Med Hypothesis.* 1986;20:271-278.
45. Cott J. Natural product formulations available in Europe for psychotropic indication. *Psychopharmacol Bull.* 1995;31:745-751.
46. Sastre J, Millan A, de la Asuncion G, et al. A *Ginkgo biloba* extract (Egb 761) prevents mitochondrial aging by protecting against oxidative stress. *Free Radic Bio Med.* 1998;24:298-304.
47. Benzi G, Moretti A. Are reactive oxygen species involved in Alzheimer's disease? *Neurobiol Aging.* 1995;16:661-674.
48. LeBars PL, Katz MM, Berman N, et al. A placebo-controlled, double-blind, randomized trial of an extract of *Ginkgo biloba* for dementia. *JAMA.* 1997;278:1327-1332.
49. Rosenblatt M, Mindel J. Spontaneous hyphema associated with ingestion of *Ginkgo biloba* extract [letter]. *N Engl J Med.* 1997;336:1108.
50. Rowin J, Lewis SL. Spontaneous bilateral subdural hematomas associated with chronic *Ginkgo biloba* ingestion have also occurred. *Neurology.* 1996;46:1775-1776.
51. Chung KF, McCusker M, Page CP, Dent G, Guinoit P, Barnes PJ. Effect of ginkgolide mixture in antagonizing skin and platelet responses to platelet activating factor in man. *Lancet.* 1987;1:248-251.
52. Arenz A, Klein M, Fiehe K, et al. Occurrence of neurotoxic 4′-o-methylpyridoxine in *Ginkgo biloba* leaves, *Ginkgo* medications and Japanese *Ginkgo* food. *Planta Med.* 1996;62:548-551.
53. Vorberg G. *Ginkgo biloba* extract: a long-term study of chronic cerebral insufficiency in geriatric patients. *Clin Trials J.* 1985;22:149-157.
54. Lui J, Staba EJ. The ginsenosides of various ginseng plants and selected products. *J Nat Prod.* 1989; 43:34-36.
55. McRae S. Elevated serum digoxin levels in a patient taking digoxin and Siberian ginseng. *CMAJ.* 1996;155:293-295.
56. Liberti LE, Marderosian AD. Evaluation of commercial ginseng products. *J Pharm Sci.* 1978; 10:1487-1489.
57. Ng TB, Li WW, Yeung HW. Effects of ginsenosides, lectins and *Momordica charantia* insulin-like peptide on corticosterone production by isolated rat adrenal cells. *J Ethnopharmacol.* 1987; 21:21-29.
58. Jie YH, Cammisuli S, Baggiolini M. Immunomodulatory effects of *Panax ginseng:* CA Meyer in the mouse. *Agents Actions Suppl.* 1984;15:386-391.
59. Singh VK, Agarwal SS, Gupta BM. Immunomodulatory activity of *Panax ginseng* extract. *Planta Med.* 1984;50:462-465.
60. Sotaniemi EA, Haapakkoski E, Rautio A. Ginseng therapy in non-insulin-dependent diabetic patients. *Diabetes Care.* 1995;18:1373-1375.
61. Yokozawa T, Kobayashi T, Oura H, Kawashima Y. Studies on the mechanism of the hypoglycemic activity of ginsenoside-Rb2 in streptozotocin-diabetic rats. *Chem Pharm Bull.* 1985;33:869-872.
62. Oshima Y, Konno C, Hikino H. Isolation and hypoglycemic activity of panaxans I, J, K and L, glycans of *Panax ginseng* roots. *J Ethnopharmacol.* 1985;14:255-259.
63. Konno C, Murakami M, Oshima Y, Hikino H. Isolation and hypoglycemic activity of panaxans Q,R,S,R and U: glycans of *Panax* ginseng roots. *J Ethnopharmacol.* 1985;14:69-74.
64. Konno C, Sugiyama K, Kano M, Takahashi M, Hikino H. Isolation and hypoglycemic activity of panaxans A, B, C, D and E: glycans of *Panax ginseng* roots. *Planta Med.* 1984;50:436-438.
65. Tokmoda M, Shimada K, Konno C, Sugiyama K, Hikino H. Partial structure of panaxan A: a hypoglycemic glycan of *Panax ginseng* roots. *Planta Med.* 1984;50:436-438.
66. Baldwin CA. What pharmacists should know about ginseng. *Pharm J.* 1986;237:583-586.
67. Hammond TG, Whitworth JA. Adverse reactions to ginseng [letter]. *Med J Aust.* 1981;1:492.
68. Dega H, Laporte J, Frances C, Herson S, Choisidow O. Ginseng as a cause for Stevens-Johnson syndrome [letter]? *Lancet.* 1996;347:1344.
69. Greenspan EM. Ginseng and vaginal bleeding [letter]. *JAMA.* 1983;249:2018.
70. Hopkins MP, Androff L, Benninghoff AS. Ginseng face cream and unexplained vaginal bleeding. *Am J Obstet Gynecol.* 1988;159:1121-1122.
71. Palmer BV, Montgomery ACV, Monteriro JCMP. Ginseng and mastalgia. *BMJ.* 1978;1:1284.
72. Koren G. Maternal use of ginseng and neonatal androgenization [letter]. *JAMA.* 1991;265:1828.
73. Awang DVS. Maternal use of ginseng and neonatal androgenization [letter]. *JAMA.* 1991;265;1828.
74. Waller DP, Martin AM, Farnswort NR, Awang DVC. Lack of androgenicity of Siberian ginseng [letter]. *JAMA.* 1992;267:2329.
75. Janetzky K, Morreale AP. Probable interactions between warfarin and ginseng. *Am J Health Syst Pharm.* 1997;54:692-693.
76. Kuo SC, Teng CM, Lee JG, Ko FN, Chen SC, Wu TS. Antiplatelet components in *Panax ginseng. Planta Med.* 1990;56:164-167.
77. Shader RI, Greenblatt DJ. Phenelzine and the dream machine-ramblings and reflections [editorial]. *J Clin Psychopharmacol.* 1985;5:65.
78. Jones BD, Runikis AM. Interactions of ginseng with phenelzine. *J Clin Psychopharmacol.* 1987;7:201-202.
79. Siegel RK. Ginseng abuse syndrome. *JAMA.* 1979;241:1614-1615.
80. Elghamry MI, Hansel R. Activity and isolated phytoestrogen of shrub palmetto fruits *(Serenoa repens* Small): an estrogenic plant. *Experientia.* 1969;24:828-829.
81. Sultan C. Inhibition of androgen metabolism and binding by a liposterolic extract of *Serenoa repens* B in human foreskin fibroblasts. *J Steroid Biochem Mol Biol.*1984;20:515-519.
82. Champault G, Patel JC, Bonnard AM. A double-blind trial of an extract of the plant *Serenoa rerpens* in benign prostatic hyperplasia. *Br J Clin Pharmacol.* 1984;18:461-462.
83. Tasca A. Treatment of obstruction in prostatic adenoma using an extract of *Serenoa repens:* double-blind clinical test vs placebo. *Minerva Urol Nefrol.* 1985;37:887-891.
84. Bach D, Schmitt M, Ebeling L. Phytopharmaceutical and synthetic agents in the treatment of benign prostatic hyperplasia (BPH). *Phytomedicine.* 1997;3-4:209-213.
85. Lohse MJ, Muller-Oerlinghausen B. Psychopharmaka. In: Schwabe U, Pffrath D, eds. *Arzeiverordnungreport '94.* Stuttgart, Germany: Gustav Fischer; 1994:354-370.
86. Wagner H, Bladt S. Pharmaceutical quality of *Hypericum* extracts. *J Geriatr Psychiatry Neurol.* 1994;7(suppl 1):65-68.
87. Sparenberg B, Demisch L, Holzl J. Investigations of the antidepressive effects of St. John's wort. *Pharm Ztg Wiss.* 1993:6P50-54.
88. Bladt S, Wagner H. Inhibition of MAO by fractions and constituents of *Hypericum* extract. *J Geriatr Psychiatry Neurol.* 1994;(suppl 1):S57-S59.
89. Linde K, Ramirez G, Mulrow CD, Pauls A, Weidenhammer W, Melchart D. St John's wort for depression: an overview and meta-analysis of randomized clinical trials. *BMJ.* 1993;313:253-258.
90. McGuffin M, Hobbs C, Upton R, Goldberg A, eds. *Botanical Safety Handbook.* New York, NY: CRC Press Inc; 1997:62-63.
91. Leathwood PD, Chauffard F. Aqueous extract of valerian reduces latency to fall asleep in man. *Planta Med.* 1985;51:144-148.
92. Leathwood PD, Chauffard F, Heck E, Munoz-Box R. Aqueous extract of valerian root improves sleep quality in man. *Pharmacol Biochem Behav.* 1982;17:65-71.
93. Balderer G, Borbely AA. Effect of valerian on human sleep. *Psychopharmacology (Berl).* 1985; 87:406-409.
94. Brown D. Valerian: clinical overview. *Townsend Lett Doctors.* 1995:150-51.
95. Hiller KO, Zetler G. Neuropharmacological studies on ethanol extracts of *Valeriana officinalis* L: behavioural and anticonvulsant activities. *Physiother Res Int.* 1996;10:145-151.
96. Capasso A, DeFeo V, DeSimon F, Sorrentino L. Pharmacological effects of aqueous extracts from *Valeriana adscendens. Physiother Res Int.* 1996; 10:309-312.
97. Food and Drug Administration. *FDA warns consumers against dietary supplement products that may contain digitalis mislabeled as plantain.* June 12, 1997.
98. Blumenthal M. Industry alert: plantain adulterated with digitalis. *HerbalGram.* 1997;40:28-29.
99. Evans WC. Saponins, cardioactive drugs and other steroids. In: Evans WC, ed. *Pharmacognosy.* 14th ed. Philadelphia, Pa: WB Saunders Co; 1996:293-321.
100. Wash LK, Bernard JD. Licorice-induced pseudoaldosteronism. *Am J Hosp Pharm.* 1975;32:73-74.
101. Walker BR, Edwards CRW. Licorice-induced hypertension and syndromes of apparent mineralocorticoid excess. *Endocrinol Metab Clin North Am.* 1994;23:359-377.
102. Stewart PM, Wallace AM, Valentino R, Burt D, Shackleton CHL, Edwards CRW. Mineralocorti-

coid activity of liquorice: 11-beta-hydroxysteroid dehydrogenase deficiency comes of age. *Lancet.* 1987;2:821-824.
103. Gomez-Sanchez EP, Gomez-Sanchez CE. Central hypertensivnogenic effects of glycyrrhizic acid and carbenoxolone. *Am J Physiol.* 1992;236:1125-1130.
104. Farese RV, Biglieri EG, Shackleton CHL, Rony I, Gomez-Fontes R. Licorice-induced hypermineralocorticoidism. *N Engl J Med.* 1991;325:1223-1227.
105. Salassa RM, Mattox VR, Rosevear JW. Inhibition of the mineralocorticoid activity of licorice by spironolactone. *J Clin Endocrinol Metab.* 1962;22:1156-1159.
106. Corse FM, Galgani S, Gasparini C, Piazza G. Acute hypokalemic myopathy due to chronic licorice ingestion: report of a case. *J Neurol Sci.* 1983;4:493-497.
107. Fushimi R, Tachi J, Amino N, Myiai K. Chinese medicine interfering with digoxin immunoassays [letter]. *Lancet.* 1989;1:339.
108. Suga T. Chemistry and pharmacology of Chansu, Taisha. *Chin Med J (Engl).* 1973;suppl 10:762-773.
109. Schliche H, ed. *Phytotherapy in Paediatrics: Handbook for Physicians and Pharmacists.* Stuttgart, Germany: Medpharm GmbH Scientific Publishers; 1997:143.
110. Hobbs C, Foster S. Hawthorn: a literature review. *HerbalGram* 1990;22:19-33.
111. Racz-Kotilla E. Hypotensive and beta-blocking effect of procyanidins of *Crataegus monogyna*. *Planta Med.* 1980;39:239-241.
112. Bisset NG, ed. *Herbal Drugs and Phytopharmaceuticals: A Handbook for Practice on a Scientific Basis.* Stuttgart, Germany: Medpharm GmbH Scientific Publishers; 1994:46,441.
113. Newall CA, Anderson LA, Phillipson JD. Evening primrose monograph. In: JD Newall CA, Anderson LA, Phillipson JD, eds. *Herbal Medicines: A Guide for Health-Care Professionals.* London, England: Pharmaceutical Press; 1997:110-113.
114. Barber JH. Evening primrose oil: a panacea? *Pharm J.* 1988;240:723-725.
115. Newall CA, Anderson LA, Phillipson JD. Borage monograph. In: Newall CA, Anderson LA, Phillipson JD, eds. *Herbal Medicines: A Guide for Health-Care Professionals.* London, England: Pharmaceutical Press; 1997:49.
116. Hoffman D. *The Herb Users Guide: The Basic Skills of Medical Herbalism*. Wellingborough, England: Thorsons; 1987.
117. Mills DE. Dietary fatty acid supplementation alters stress reactivity and performance in man. *J Hum Hypertens.* 1989;3:111-116.
118. Larsen L. Unsaturated pyrrolizidines from *Borage (Borage officinalis*) a common garden herb. *J Nat Prod.* 1984;45:747-748.
119. Dandekar UP, Chandra RS, Dalvi SS, et al. Analysis of a clinically important interaction betwween phenytoin and Shankhapulshpi, an Ayurvedic preparation. *J Ethnopharmacol.* 1992;35:285-288.
120. Swinyard EA. Woodhead JH. Experimental detection quantification and evaluation of anticonvulsants. In: Woodbury DM, Penry JK Pippenger CE, eds. *Antiepileptic Drugs.* New York, NY: Raven Press; 1982:111-126.
121. Lo ACT, Chan K, Yeung JHK, Woo KS. The effects of danshen on pharmacokinetics and pharmacodynamics of warfarin rats. *Eur J Drug Metab Pharmacokinet.* 1992;17:257-262.
122. Newall CA, Anderson LA, Phillipson JD. German chamomile monograph. In: Newall CA, Anderson LA, Phillipson JD, eds. *Herbal Medicines: A Guide for Health-Care Professionals.* London, England: Pharmaceutical Press; 1997:69-71.
123. Sumner H, Salan U, Knight DW, Hoult JR. Inhibition of 5-lipoxygenase and cyclo-oxygenase in leukocytes by feverfew: involvement of sesquiterpene lactones and other components. *Biochem Pharmacol.* 1992;43:2313-2320.
124. Gorenewegen WA, Heptininstall S. A comparison of the effects of an extract of feverfew and parthenolide, a component of feverfew, on platelet activity in-vitro. *J Pharm Pharmacol.* 1990;42:553-557.
125. Biggs MJ, Johnson EW, Persaud NP, Ratcliffe DM. Platelet aggregation in patients using feverfew for migraine [letter]. *Lancet.* 1982;2;776.
126. Duffield PH, Jamieson D. Development of tolerance to kava in mice. *Clin Exp Pharmacol Physiol.* 1991;18:571-578.
127. Ruzo P. Kava-induced dermatopathy: a niacin deficiency? *Lancet.* 1990;335:1442-1445.
128. Norton SA, Ruze P. Kava dermopathy. *J Am Acad Dermatol.* 1994;31:89-97.
129. Jamieson DD, Duffield PH. Positive interaction of ethanol and kava resin in mice. *Clin Exp Pharmacol Physiol.* 1990;17:509-514.
130. Davies LP, Drew CA, Duffield P, Johnston GA, Jamieson DD. Kava pyrones and resin: studies on GABAA, GABAB and benzodiazepine binding sites in rodent brain. *Pharmacol Toxicol.* 1992;71:120-126.
131. Davies LP, Drew CA, Duffield P. Kava pyrones and resin: studies on GABAA, GABAB and benzodiazepine binding sites in rodent brain. *Pharmacol Toxicol.* 1992;71:120-126.
132. Jussofie A, Schmiz A, Hiemke C. Kavapyrone-enriched extract from Piper methysticum as modulator of GABA binding sites in different regions of rat brain. *Psychopharmacology (Berl).* 1994;116:469-474.
133. Almeida JC, Grimsley EW. Coma from the health food store: interaction between kava and alprazolam. *Ann Intern Med.* 1996;125:940-941.
134. Stimpel M, Proksch A, Wagner H, Lohmann-Matthes ML. Macrophage activation and induction of macrophage cytotoxicity by purified polysaccharide fractions from the plant *Echinacea purpurea*. *Infection Immun.* 1984;46:845-849.
135. See DM, Broumand N, Sahl T, Tilles J. In vitro effects of echinacea and ginseng on natural killer and antibody dependent cell cytotoxicity in healthy subjects and chronic fatigue syndrome or acquired immunodeficiency syndrome patients. *Immunopharmacology.* 1997;35:229-235.
136. Jin R, Wan LL, Mitsuishi T. Effects of shi-ka-ma and Chinese herbs in mice treated with antitumor agent mitocycin C. *Chung Kuo Chung Hsi I Chieh Ho Tsa Chih.* 1995;15:101-103.
137. Utsunomiya T, Kobayashi M, Pollard RB, Suzuki F. Glycyrrhizin, an active component of licorice roots, reduces morbidity and mortality in mice infected with lethal doses of influenza virus. *Antimicrob Agents Chemother.* 1997;41:551-556.
138. Dinnen RD, Ibibuzaki K. The search for novel anticancer agents: a differentiation-based assay and analysis of a folklore product. *Anticancer Res.* 1997;17:1027-1033.
139. Herbert V, Kasdan TS. Alfalfa, vitamin E, and autoimmune disorders. *Am J Clin Nutr.* 1994;60:639-640.
140. Mossad SB, Macknin ML, Medendorp SV, Mason P. Zinc gluconate lozenges for treating the common cold. *Ann Intern Med.* 1996;125:81-88.
141. Salas M, Kirchner H. Induction of interferon-gamma in human leukocyte cultures stimulated by Zn2±. *Clin Immunol Immunopathol.* 1987;45:139-142.
142. Korant BD, Butterworth BE. Inhibition by zinc of rhinovirus protein cleavage: interaction of zinc with capsid polypeptides. *J Virol.* 1976;18:298-306.
143. Gesits FC, Bateman JA, Hayden FG. In vitro activity of zinc salts against human rhinoviruses. *Antimicrob Agents Chemother.* 1987;31:622-624.
144. Tyler V. Kidney, urinary tract and prostate problems. In: Tyler V, ed. *Herbs of Choice.* Binghamton, NY: Pharmaceutical Products Press Inc; 1994:73-86.
145. Newall CA, Anderson LA, Phillipson JD. Diuretic herbal ingredients. In: Newall CA, Anderson LA, Phillipson JD, eds. *Herbal Medicines: A Guide for Health-Care Professionals.* London, England: Pharmaceutical Press; 1997:281.
146. Olin BF, ed. Gossypol monograph. *Lawrence Review of Natural Products.* St Louis, Mo: Facts and Comparisons Inc; 1998.
147. Lin YC, Fukaya T, Rikihisa Y, Walton A. Gossypol in female fertility control: ovum implantation and early pregnancy inhibited in rats. *Life Sci.* 1985;37;39-47.
148. Liu Z, Hinton E, Cao J, Zhu C, Li B. Effects of potassium salt or a potassium blocker on gossypol-related hypokalemia. *Contraception.* 1988;37:111-117.
149. Pizarro F, Olivares M, Hertrampf E, Walter T. Factors which modify the nutritional state of iron: tannin content of herbal teas. *Arch Latinoam Nutr.* 1994;44:277-280.
150. Newall CA, Anderson LA, Phillipson JD. Horseradish monograph. In: Newall CA, Anderson LA, Phillipson JD, eds. *Herbal Medicines: A Guide for Health-Care Professionals.* London, England: Pharmaceutical Press; 1997:168.
151. Anonymous. Kelp diets can produce myxedema in iodide-sensitive individuals. *JAMA.* 1975;233:9-10.
152. Shilo S, Hirsch HJ. Iodine-induced hyperthyroidism in a patient with a normal thyroid gland. *Postgrad Med J.* 1986;62:661-662.
153. Waller DP, Zaveveld LJD, Farnsworth NR. Gossypol: pharmacology and current status as a male contraceptive. In: Wagner H, Hikino H, Farnsworth NR, eds. *Economic and Medicinal Plant Research.* London, England: Academic Press Inc; 1985:87-112.
154. De Smet PAGM. *Adverse Reactions of Herbal Drugs.* Vol 2. New York, NY: Springer-Verlag NY Inc; 1993.
155. De Smet PAGM. *Adverse Reactions of Herbal Drugs.* Vol 3. New York, NY: Springer-Verlag NY Inc; 1997.
156. De Smet PAGM. *Adverse Reactions of Herbal Drugs.* Vol 1. New York, NY: Springer-Verlag NY Inc; 1992.
157. d'Arcy PF. Adverse reactions and interactions with herbal medicines: part 2. *ADR Toxicol Rev.* 1992;12:147-162.
158. De Smet PAGM, Nolen WA. St John's wort as an antidepressant. *BMJ.* 1996;313:241-242.
159. Duke JA. Commentary-novel psychotherapeutic drugs: a role for ethnobotany. *Psychopharmacol Bull.* 1995;31:177-182.
160. Reynolds JEF, ed. *Martindale: The Extra Pharmacopoeia.* 29th ed. London, England: Pharmaceutical Press; 1989.
161. Gomez-Sanchez CE, Gomez-Sanchez EP, Yamakita N. Endocrine causes of hypertension. *Semin Nephrol.* 1995;15:1-15.
162. Blachley JD, Knochel JP. Tobacco chewer's hypokalemia: licorice revisited. *N Engl J Med.* 1980;302:74-75.
163. Beretta-Piccoli C, Salvade G, Crivelli PL, Weidmann P. Body sodium and blood volume in a patient with licorice-induced hypertension. *J Hypertens.* 1985;3:19-23.
164. Leatherdale BA, Panesar RK, Singh G, Atkins TW, Bailery CJ, Bignell AHC. Improvement in glucose tolerance due to *Momordica charantia* (karela). *BMJ.* 1981;282:1823-1824.
165. Gupta SS, Seth CB. Effect of *Momordica charantia* linn (karela) on glucose tolerance in albino rats. *J Indian Med Assoc.* 1962;39:581-584.
166. Aslam M, Stockley IH. Interaction between curry ingredient (karela) and drug (chlorpropamide) [letter]. *Lancet.* 1979;1:7607.
167. Anderson RA. Chromium, glucose tolerance and diabetes. *Biol Trace Elem Res.* 1992;32:19-24.
168. Lee NA, Reasner CA. Beneficial effect of chromium supplementation on serum triglyceride levels in NIDDM. *Diabetes Care.* 1994;17:1449-1452.
169. Kincheloe L. Gynecological and obstetric concerns regarding herbal medicinal use. In: Miller LG, Murray WJ, eds. *Herbal Medicinals: A Clinician's Guide.* Binghamton, NY: Pharmaceutical Products Press; 1998:285-314.
170. Costello C. Estrogenic substances from plants. *J Am Pharm Assoc (Wash).* 1950;39:177-180.
171. Holt S. Phytoestrogens for a healthier menopause. *Altern Ther Health Med.* 1997;1:187-193.