

11-20-2015

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Recommended Citation

Sultan S, Viqar M, Ali R, Tajik AJ, Jahangir A. Essentials of herb-drug interactions in the elderly with cardiovascular disease. *J Patient Cent Res Rev*. 2015;2:174-191. doi: 10.17294/2330-0698.1212

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Essentials of Herb-Drug Interactions in the Elderly With Cardiovascular Disease

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Abstract

As the number of individuals, particularly the elderly, using herbal products with prescription drugs continues to grow, the risk for adverse interactions increases but remains poorly recognized. The true incidence and nature of adverse herb reactions or herb-drug interactions remains unknown since no postmarketing surveillance mechanism exists. Adverse events are greatly underreported, and information regarding safety mainly comes from case reports and suboptimally conducted studies in a limited number of healthy young volunteers or patients with limited comorbidities. Therefore, convincing evidence for the safety of herbal products in the elderly is lacking, and the true magnitude of problems that herb-drug interactions pose to public health, particularly in elderly patients with cardiovascular diseases, is not known. Since cardiovascular diseases themselves are life-threatening, necessitate use of multiple medications and occur in a population with extensive comorbidities, the risk of herb-drug and herb-disease interactions is not minor and cannot be ignored. This review addresses these concerns in an effort to raise awareness about the use of herbal medicine by the elderly and its potential adverse impact on the efficacy of prescription medications that can increase predisposition to catastrophic events such as major bleeding, inadequate anticoagulation leading to undesired clotting, transplant organ rejection and life-threatening cardiac arrhythmias. (*J Patient-Centered Res Rev.* 2015;2:174-191.)

Keywords

complementary therapy, herb, integrative medicine, cardiovascular agents, elderly, herb-drug interaction

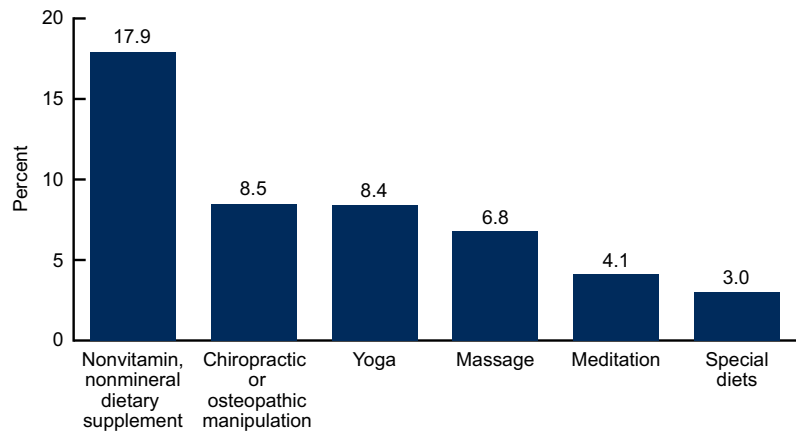
The use of herbal and dietary supplements continues to increase, rising from 2.5% in 1990 to 12.1% in 1997,¹⁻³ with a 2007 National Health Interview Survey showing that U.S. adults annually spend more than \$33.9 billion out of pocket on complementary health approaches.⁴ Nonvitamin, nonmineral dietary supplement use (17.9%) was greater than any other complementary health approach per another national survey from 2012 (Figure 1).⁵ Total sales of herbal and dietary supplements in 2013 was reported to be 7.9% higher than 2012, making the 10th year in a row in which herb sales increased over the previous year.⁶ Sales of the

top 10 herbal supplements in 2012 are summarized in Table 1,⁷ and the global herbal market for 2015 is projected to be greater than \$93 billion.⁸

Natural products — including vitamins, herbs, amino acids, minerals and probiotics — are often sold as dietary supplements and regulated as food products by the U.S. Food and Drug Administration (FDA). Unlike allopathic medicines, these supplements do not need FDA approval of their safety and efficacy. Since the use of herbal products is increasing, particularly by elderly patients who also use medicinal products, the likelihood of adverse interactions is rising.⁹ Nahin and colleagues,¹⁰ investigating the relationship between prescription medications and supplements in patients age 75 years or older, showed that 82.5% of patients used at least one supplement and 54.5% used three or more; the average number of prescription medications

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Figure 1. Percentage of U.S. adults who used complementary health approaches, by type, in the past 12 months (2012).⁵ Note: Not all complementary health approaches are presented in this figure. Source: www.cdc.gov/nchs/data/databriefs/db146.pdf.



used per patient was 3.5, which was similar to the average number of dietary supplements used by the same population.

Although drug-drug interactions are typically taken into account, the importance of herb-drug interactions is slowly being recognized as a potential factor affecting outcomes in the elderly, especially those with multiple comorbidities,¹¹⁻¹³ polypharmaceutical use¹⁴ and aging-associated physiological changes that alter pharmacokinetics and pharmacodynamics.¹⁵ Drugs with a narrow therapeutic index, such as anticoagulants, chemotherapeutics, organ antirejection agents and antiarrhythmic compounds, are particularly vulnerable to interaction.

The majority of patients taking herbal supplements do not disclose such to health care professionals.¹⁶ Thus, the risk for potential interactions between supplements and medications can go undetected; therefore, it is important for providers and patients to educate themselves.^{17,18} In this review we describe common herbal remedies used by the elderly and their potential interactions with cardiovascular drugs. We also highlight regulatory issues regarding herbal supplements and discuss possible ways to improve safety and minimize adverse effects.

Search Strategy and Selection Criteria

We searched Medline, the National Center for Complementary and Integrative Health (NCCIH) website, the Natural Standard Research Collaboration at Medline Plus¹⁹ and the Cochrane database from 1966 to February 2015 for information on herbal products using the key words herbs, herb-drug interactions,

complementary and alternative medicine, cardiovascular diseases, elderly and each of the individual herbs discussed in this review. We also manually searched references and articles written with a focus on the risk of herb-drug interactions, particularly those used in the care of patients with cardiovascular diseases.

Factors Affecting Herb-Drug Interactions in the Elderly

Factors contributing to drug-herb interactions include patient-related factors (age, body size/composition, metabolism and kidney function, genetics, lifestyle and comorbidities) as well as drug- and herb-related factors (amount, route and time of administration). This is particularly relevant to the elderly in whom the chances for adverse interactions are higher due to presence of aging-associated comorbidities,¹¹ use of polypharmacy¹⁴ and reduced functional reserves.²⁰ Poor nutritional status, impaired organ function and genetic variants in drug metabolism are other factors that increase predisposition to adverse interactions.²¹⁻²⁸ With aging, drug metabolism and elimination pathways also are affected by changes in the liver or intestinal membranes harbouring the cytochrome P450 enzyme superfamily or other enzymes that metabolize drug to a form that can then be eliminated through the kidney or the gut. This is especially true for interactions between herbs, such as St. John's wort or grapefruit juice, that have inhibitory effects on CYP3A4 enzymes or P-glycoprotein transporter protein.^{12,13,29,30}

Aging is associated with a reduction in kidney mass, renal blood flow and the number of functioning glomeruli that reduces kidneys' ability to eliminate drugs, resulting in prolongation of their elimination half-life and potential

Table 1. The 10 top-selling herbal dietary supplements in the food, drug and mass market channel in the United States for 2012⁷ (per SymphonyIRI Group*)

Herb (Latin Name)	Sales (in U.S. dollars)
1. Cranberry (<i>Vaccinium macrocarpon</i>)	\$65,483,940
2. Garlic (<i>Allium sativum</i>)	\$34,950,540
3. Saw palmetto (<i>Serenoa repens</i>)	\$31,775,810
4. Soy (<i>Glycine max</i>)	\$28,017,310
5. Ginkgo (<i>Ginkgo biloba</i>)	\$25,853,420
6. Milk thistle (<i>Silybum marianum</i>)	\$21,143,560
7. Black cohosh root (<i>Actae racemosa</i> [†])	\$16,925,990
8. Echinacea [‡] (<i>Echinacea</i> spp.)	\$15,898,880
9. St. John's wort (<i>Hypericum perforatum</i>)	\$12,193,790
10. Ginseng [§] (<i>Panax ginseng</i>)	\$11,136,960

*Source of data: SymphonyIRI Group Inc., a Chicago-based market research firm. "FDM market sales data for herbal supplements, 52 weeks ending December 23, 2012."

[†]Synonym: Cimicifuga racemosa.

[‡]Echinacea collectively refers to supplements made from roots and/or aerial parts of plants from three species in the genus *Echinacea*, including *E. angustifolia*, *E. pallida* and *E. purpurea*.

[§]It is not clear from the SymphonyIRI data whether this figure also includes the sales of American ginseng root products (made from *Panax quinquefolius*), the sales of which are not as high as sales of supplements made from Asian ginseng (*P. ginseng*).

for adverse effects. There is limited data on drug-herb interactions in the elderly, particularly those 80 years and older, who are at higher risk of adverse interactions with drugs that have a narrow therapeutic index, such as anticoagulants and sedatives.^{31,32}

Common herbal remedies and their potential interactions with drugs that produce adverse effects on the cardiovascular system are summarized in Online Supplemental Appendix 1. We have narrowed this review to the purported use, potential side effects and interactions of the top 10 selling plant products (per a SymphonyIRI Group report⁷) and grapefruit juice with drugs used in cardiovascular medicine in the elderly.

Cranberry

Cranberry (*Vaccinium macrocarpon*) fruits and extracts have been used in traditional medicine to treat urinary tract infections (UTI), diabetes, *H. pylori*-induced gastric ulcers, and blood and digestive disorders. The exact mechanism of action is not known, but the inhibitory effect of cranberry proanthocyanidins on growth, adhesion and virulence of *E. coli* bacteria has been suggested to prevent infections.¹⁸ Although a few small studies demonstrated benefit from cranberry use in women with recurrent UTIs, a 2012 Cochrane review showed no statistically significant differences when the results of a much larger study were included and recommended against the use of cranberry for UTI prevention.³³ This inconsistency in study results could be due to the variability in study designs, cranberry products used, study compliance or differences in pathogenesis of UTI in different groups such as young children, sexually active young adults or the elderly. Some case reports in the elderly^{34,35} reported raised international normalized ratio (INR) and life-threatening bleeding with coadministration of warfarin and cranberry. In 12 young healthy volunteers, a single dose of warfarin after 2 weeks of cranberry juice consumption caused a 30% elevation in INR,³⁶ suggesting the potential for adverse event may be higher in elderly patients who have multiple comorbidities. Therefore, cranberry juice should be avoided in patients on chronic anticoagulant therapy. Some studies have reported that cranberry juice inhibits CYP2C9 and CYP3A4,³⁷ however, others have not confirmed these findings.³⁸ Due to these inconsistent findings, additional research is warranted to clarify cranberry's efficacy and safety in the elderly with multiple comorbidities.³³

Garlic

Garlic (*Allium sativum*), a medicinal herb, has many potential benefits with its antimicrobial, immune-enhancing and anticholesterolemic effects, and is widely used for heart disease, high blood pressure, high cholesterol and prevention of stomach and colon cancers. Some clinical studies have shown aged garlic extract to be a safe adjunct treatment to conventional antihypertensives³⁹ and to improve glycemic control and lipid profile when used in combination with antidiabetics.⁴⁰ An enhanced antihyperglycemic response was described in a woman on chlorpropamide after eating a curry containing garlic and *Momordica charantia*

(bitter melon), another plant product used for medicinal purposes.⁴¹ Garlic is used as a dietary supplement by patients infected with human immunodeficiency virus (HIV) and can cause detrimental effects, including severe gastrointestinal toxicity, when coadministered with protease inhibitors like ritonavir.⁴² In a controlled trial of patients with coronary artery disease randomized to receive either garlic oil (4 g/day) or placebo taken with prescribed nitrates, garlic significantly decreased total serum cholesterol and increased serum high-density-lipoprotein cholesterol.⁴³ However, other trials have shown no significant effects on total cholesterol, low-density-lipoprotein cholesterol, blood pressure, platelet count or triglycerides in patients taking garlic supplements.^{36,44}

Garlic is believed to have antithrombotic activity⁴⁵ and decrease platelet aggregation,⁴⁶ which can increase clotting time and risk of bleeding when taken with anticoagulants such as warfarin.⁴⁷ However, in healthy volunteers, garlic in combination with warfarin was shown to have no effect on INR or bleeding risk over short-term follow-up.^{36,44} Garlic should be used with caution in those on oral anticoagulants, as garlic-associated postoperative bleeding⁴⁸ and spontaneous spinal epidural hematoma⁴⁹ have been reported. It is recommended that garlic supplements be discontinued about 10 days before elective surgical procedures, especially in patients on antiplatelet agents or anticoagulants.⁴⁸

Saw Palmetto

Saw palmetto (*Serenoa repens*), an extract of the ripe berries of the American dwarf palm, is the most widely used phytotherapeutic agent for benign prostatic hyperplasia. Other purported uses include treatment of genitourinary conditions, for augmentation of breast size, to increase libido and sperm production, and as a mild diuretic. While there is some ambiguity around its mechanism of action, saw palmetto has demonstrated inhibitory effect on prostatic estrogen receptors⁵⁰ and antiandrogen activity⁵¹ including inhibition of 5-alpha reductase,^{51,52} the enzyme responsible for conversion of testosterone to its active metabolite dihydrotestosterone. Earlier studies reported short-term efficacy of saw palmetto in ameliorating benign prostatic hyperplasia symptoms;⁵³ however, this claim has been refuted in subsequent studies. In a randomized, double-blind study

of saw palmetto using standard dose (320 mg/day) for a year, Bent and colleagues⁵⁴ failed to demonstrate benefits in improving symptoms or objective measures of benign prostatic hyperplasia over placebo. Tacklind et al.'s Cochrane review demonstrated similar negative results of saw palmetto, even at higher doses,⁵⁵ which was confirmed in a more recent trial (CAMUS) funded by the NCCIH that used up to 960 mg/day of saw palmetto extracts in men with moderate lower urinary tract symptoms.⁵⁶

Reported adverse reactions from saw palmetto include sexual dysfunction, fatigue, tachycardia, angina pectoris, extrasystole,⁵⁷ hypertension,⁵⁸ intraoperative hemorrhage,⁵⁹ bleeding susceptibility,⁶⁰ pancreatitis⁶¹ and cholestatic hepatitis.⁶² In vitro studies suggest that saw palmetto inhibits some cytochrome P450 isoenzymes, including CYP2D6, CYP2C9 and CYP3A4.⁶³ However, human studies indicated no clinically relevant effect on the majority of cytochrome P450 isoenzymes.⁶⁴ Published reports of elevated INR in a patient on warfarin after taking a saw palmetto-containing product (curbicin) that normalized after discontinuation of curbicin⁶⁵ and excessive bleeding in a middle-aged man undergoing a surgical procedure to remove a brain tumor raise concerns regarding the risk of bleeding.⁵⁹

Soy

Soy, obtained from *Glycine max* (fam. Fabaceae), a plant in the pea family, has been used in Japanese cuisine for thousands of years, with a recent boost in sales of soy phytoestrogens in American markets after publication of a study by the Women's Health Initiative showing harmful effect of estrogen-progestin combination and the belief that natural phytoestrogens may safely prevent bone loss and the consequences of estrogen deficiency without harmful effects.⁶⁶ It is sold as food (tofu, soy milk) or dietary supplements (tablets, capsules). Purported benefits of soy protein include alleviation of menopausal symptoms, osteoporosis and hyperlipidemia. Soy protein products contain bioactive phytoestrogens or isoflavones, which have partial estrogen agonist and antagonist properties.⁶⁷ Earlier studies demonstrating soy protein's beneficial effects on low-density-lipoprotein cholesterol and other cardiovascular risk factors or in reducing hot flashes in women^{68,69} were not confirmed by more recent studies.⁷⁰ Mixed estrogenic and antiestrogenic properties of

isoflavones make their effects on cancers complex, and it remains to be determined if isoflavone supplements increase the risk of endometrial hyperplasia.⁷¹

The long-term safety of soy isoflavones has not been established. Controversy exists regarding the beneficial effect of soy food versus isoflavone aglycones in promoting mammary and endometrial carcinogenesis in animal models,^{72,73} and its use should be avoided in women with breast cancers or other hormone-sensitive tumors. Soy isoflavones decrease the absorption of levothyroxine and should not be used in conjunction.⁷⁴ Soy can inhibit CYP3A4 and CYP2C in vitro.⁷⁵ Fermented soybean contains high level of vitamin K and may decrease the activity of warfarin or other anticoagulants.⁷⁶ Cases of botulism from home-fermented tofu have been reported.⁷⁷ Natto, a Japanese food made from fermented soybean containing high levels of vitamin K, strongly antagonized the effects of warfarin in experimental models,⁷⁸ markedly reduced the effects of acenocoumarol, a warfarin-derivative anticoagulant,⁷⁹ and decreased INR to subtherapeutic levels when coadministered with warfarin⁷⁶ (Table 2).

Table 2. Common herbs interacting with warfarin

Herbs that increase anticoagulant effect (potentiate risk of bleeding)	Herbs that decrease anticoagulant effect (potentiate risk of thromboembolism)
Alfalfa	Camellia sinensis
Angelica	Coenzyme Q
Bilberry	Ginseng
Cannabis	Licorice
Capsicum	Soya
Cat's claw	St. John's wort
Chamomile	
Clove	
Cranberry	
Danshen	
Devil's claw	
Fenugreek	
Fever few	
Garlic	
Ginger	
Ginkgo biloba	
Grapefruit juice	
Kava	
Kelp	
Lycium	
Motherwort	
Red clover	
Saw palmetto	
Yohimbine	

Ginkgo

Ginkgo derived from the *Ginkgo biloba* leaf is popular and one of the most widely used herbal medicines in the world. Its active constituents are terpenoids, flavonoids and ginkgolides A, B and C, which have purported beneficial effects for Alzheimer's dementia,⁸⁰ senile macular degeneration, tinnitus⁸¹ and peripheral arterial disease.⁸² Overall the evidence for ginkgo's beneficial effect in patients with dementia or cognitive impairment is inconsistent in the literature, and the majority of trials report no significant difference between ginkgo and placebo in improving dementia or cognitive impairment.⁸³ Ginkgo biloba extracts can inhibit thromboxane A2 synthesis⁸⁴ and have inhibitory effects on platelet aggregation through increase in cyclic adenosine monophosphate, cyclic guanine monophosphate production and matrix metalloproteinase-9 activation, or inhibition of platelet-activating factor.^{85,86} Therefore, there is concern regarding increased risk of bleeding with ginkgo when coadministered with anticoagulants (Table 2) or antiplatelet drugs such as ticlopidine.⁸⁷ Bleeding events attributed to ginkgo use in warfarin-associated intracerebral hemorrhage,⁸⁸ ibuprofen-associated intracerebral mass bleeding,⁸⁹ aspirin-associated spontaneous hyphema,⁹⁰ postoperative bleeding⁹¹ and subphrenic hematoma requiring laparoscopic evacuation⁹² have been reported.

Clinical studies in healthy volunteers over short-term follow-up are presented as evidence for ginkgo's safety and lack of significant effect on blood coagulation or platelet function.^{93,94} Ang-Lee et al. identified increased potential for bleeding with ginkgo extracts and recommended discontinuation 36 hours before surgery.⁹⁵ The American Society of Anesthesiologists recommends patients discontinue herbal medicines (including ginkgo) 2 weeks before elective surgery.⁹⁶ Ginkgo is also a potent peripheral vasodilator,⁹⁷ and long-term ingestion can potentiate the effect of antihypertensives with excessive reduction of blood pressure. Ginkgo is a weak inhibitor of CYP3A4 (Table 3) and should be used cautiously with drugs metabolized by this enzyme system. Other adverse ginkgo-drug interactions include risk of priapism when combined with antipsychotic drug risperidone,⁹⁸ seizure with anticonvulsants (valproic acid or phenytoin),⁹⁹ coma with antidepressant trazodone¹⁰⁰ and virological failure with efavirenz, a non-nucleoside reverse transcriptase inhibitor.¹⁰¹

Table 3. Drugs affecting CYP3A4 enzymes*

Strong inhibitors (≥ 5-fold ↑ in AUC or > 80% ↓ in CL)	Strong inducers (≥ 80% ↓ in AUC)
Boceprevir, clarithromycin, conivaptan, grapefruit juice, [†] indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole	Carbamazepine, phenytoin, rifampin, St. John's wort ^{‡§}
Moderate inhibitors (≥ 2-fold but < 5-fold ↑ in AUC or 50–80% ↓ in CL)	Moderate inducers (50–80% ↓ in AUC)
Amprenavir, aprepitant, atazanavir, ciprofloxacin, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice, [†] imatinib, verapamil	Bosentan, efavirenz, etravirine, modafinil, nafcillin
Weak inhibitors (≥ 1.25-fold but < 2-fold ↑ in AUC or 20–50% ↓ in CL)	Weak inducers (20–50% ↓ in AUC)
Alprazolam, amiodarone, amlodipine, atorvastatin, bicalutamide, cilostazol, cimetidine, cyclosporine, fluoxetine, fluvoxamine, ginkgo, [§] isoniazid, nilotinib, oral contraceptives, ranitidine, ranolazine, tipranavir/ritonavir, zileuton	Amprenavir, aprepitant, armodafinil, echinacea, [§] pioglitazone, prednisone, rufinamide

*Note that this is not an exhaustive list. Source: U.S. Food and Drug Administration (<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#cypEnzyme>).

[†]The effect of grapefruit juice varies widely among brands and is concentration-, dose- and preparation-dependent. Studies have shown that it can be classified as a “strong CYP3A inhibitor” when a certain preparation was used (e.g. high dose, double strength) or as a “moderate CYP3A inhibitor” when another preparation was used (e.g. low dose, single strength).

[‡]The effect of St. John's wort varies widely and is preparation-dependent.

[§]Herbal product.

AUC, area under curve; CL, clearance.

Milk Thistle

Milk thistle (*Silybum marianum*) extract is a popular herbal product used for mushroom poisoning (*Amanita phalloides*), chemoprevention and hepatoprotection in the setting of hepatitis or cirrhosis. Silymarin is a flavonoid complex, extracted from the seeds of milk thistle, with active constituents silibinin, isosilybinin, silydianin, silychristin and other phenol compounds. Silymarin has strong antioxidant activity¹⁰² and exhibits antiviral, cytoprotective,¹⁰³ anti-inflammatory, immunomodulatory, anticarcinogenic¹⁰⁴ and antiapoptotic effects. Silymarin inhibits both phase I and phase II liver enzymes, but has limited effect on in vivo pharmacokinetics of several drugs¹⁰⁵ despite inhibiting the activity of CYP and uridine 5'-diphosphoglucuronyltransferase enzymes and reducing P-glycoprotein transport. Metabolic interactions of milk thistle with substrates metabolized by CYP3A4 or CYP2C9 or transported by P-glycoprotein, especially drugs with a narrow therapeutic index such as anticoagulants or digoxin, cannot be excluded^{106,107} and should be monitored closely.

Black Cohosh

Black cohosh (*Cimicifuga racemosa*) is used as an herbal remedy for relief of symptoms of premenstrual tension, menopause and other gynecological disorders. The exact mechanism of action of black cohosh is unclear. Recent findings suggest some of the physiological effects of black cohosh may be due to compounds that bind and activate serotonin receptors.¹⁰⁸ It also contains complex biological molecules, such as triterpene glycosides, which block osteoclastogenesis in vivo and in vitro, thereby reducing cytokine-induced bone loss (osteoporosis).¹⁰⁹ A National Center of Complementary and Integrative Health (NCCIH)-funded study found black cohosh, whether used alone or with other botanicals, failed to relieve hot flashes and night sweats in postmenopausal women.¹¹⁰ In a Cochrane systematic review of 16 randomized controlled trials, recruiting a total of 2,027 perimenopausal or postmenopausal women, no significant difference between black cohosh and placebo in the frequency of hot flashes or in menopausal symptoms was found.¹¹¹

The current evidence on the safety of black cohosh is inconclusive due to poor reporting. Davis et al. showed no increase in the incidence of primary breast cancer in black cohosh-treated transgenic mice, but increased lung metastasis of preexisting breast cancer.¹¹² While uncommon, a few cases of black cohosh-related hepatotoxicity were reported.¹¹³ Although a 2011 meta-analysis refuted this concern,¹¹⁴ regulatory agencies in Australia, Canada and the European Union released statements regarding the “potential association” between black cohosh and hepatotoxicity. The United States Pharmacopeia advises that black cohosh products be labeled with a cautionary statement of hepatotoxicity. This is a change from its expert committee’s 2002 decision, which required no such statement.¹¹⁵

Echinacea

Echinacea (*Echinacea purpurea*, *Echinacea pallida* and *Echinacea angustifolia*) is known mainly for its immunostimulant properties used for the prevention and treatment of common cold and influenza, but efficacy studies have yielded inconsistent results.¹¹⁶ Randomized, double-blind, placebo-controlled trials showed no beneficial effects of unrefined echinacea or echinacea capsules on symptoms of common cold or rhinovirus infection compared to placebo.^{117,118} Echinacea use has been reported to cause side effects such as nausea, dizziness and gastrointestinal upset. Echinacea inhibits hepatic enzymes CYP1A2 and CYP2C9. Echinacea has a complex effect on CYP3A4 activity, inhibiting intestinal CYP3A4 but increasing hepatic CYP3A4 activity (Table 3),¹¹⁹ therefore the effect on oral versus parenteral medications could be different. Thus, the effect of echinacea in the elderly using medications metabolized by CYP3A4 should be closely monitored or used with caution.¹²⁰

Echinacea does not change the pharmacokinetics of digoxin, a P-glycoprotein substrate,¹²¹ nor does it alter the pharmacokinetics of chlorzoxazone (CYP2E1 probe),¹²² debrisoquine (CYP2D6 probe)¹²² or tolbutamide (CYP2C9 probe).¹¹⁹ In 12 healthy subjects, after a single dose of warfarin before and after taking echinacea for 14 days, the pharmacokinetics and pharmacodynamics of warfarin were not significantly altered.¹²³ Liver toxicity with elevation of transaminases was reported in patients using echinacea,¹²⁴ and caution should be used when combining it with other medications that can harm the liver.^{52,125} Echinacea may decrease the

effects of cyclosporine and steroids because of the immunostimulant effect and complex effect on CYP3A4 activity,^{120,125} therefore transplant patients should be advised against using this herb.

St. John’s Wort

St. John’s wort or St. Joan’s wort (*Hypericum perforatum*), a perennial herb first used as a supplement by the ancient Greeks, is popular in Europe and the United States. It is used as a folk remedy for depression, anxiety, mental health conditions and sleep disturbances. Studies measuring the effectiveness of St. John’s wort in treating depression have yielded conflicting results. A large 2002 study showed the herb to be no more effective than placebo in treating moderately severe major depression.¹²⁶ Linde et al.’s Cochrane analysis¹²⁷ of St. John’s wort for major depression reviewed 29 randomized, double-blind studies comprising 5,489 people and concluded that hypericum extracts were more effective than placebo and as effective as standard antidepressants with a lesser toxicity profile for major depressive episodes. However, the authors noted studies conducted in German-speaking countries were more favorable to hypericum than others including the United States. They recommended further investigating the reasons for these differences.

Due to its potential for drug interactions St. John’s wort is not a benign supplement, and its current use as an over-the-counter medicine for depression is not endorsed by the FDA. Its active constituent hyperforin is a well-known activator of the pregnane X receptor,¹²⁸ which results in enhanced expression of the drug efflux transporter ABCB1 (P-glycoprotein)¹²⁹ and induction of CYP3A4 (Table 3), an enzyme involved in metabolism of the majority of prescription medications used in cardiovascular practice.¹³⁰ Thus, potentially serious adverse reactions can occur from coadministration with drugs metabolized through CYP3A4 or transported by P-glycoprotein. Hypotension and delayed emergence from anesthesia were associated with prior use of St. John’s wort.¹³¹ In HIV patients, it can decrease plasma levels of indinavir, resulting in failure of antiretroviral therapy.¹²⁹ It can reduce drug levels of ethinylestradiol,¹³² and women taking St. John’s wort with oral contraceptives could experience an unplanned pregnancy or increased breakthrough bleeding due to decreased efficacy.¹³³ It can increase docetaxel’s plasma clearance, reducing its efficacy and peak plasma concentration, thus causing

undertreatment of cancer patients.¹³⁴ It causes a nearly 50% decrease in cyclosporine levels in organ transplant recipients,¹³⁵ and cases of acute transplant rejection have been reported.¹³⁵⁻¹³⁷ The consequent potential for transplant rejection is a life-threatening effect and justifies abolishing use of St. John's wort in this patient population.¹³⁸ Reduced levels of digoxin also have been reported.¹³⁹ St. John's wort can alter anticoagulation properties of warfarin resulting in unstable INR values,¹⁴⁰ and bleeding complications were reported in elderly taking warfarin¹⁴¹ (Table 2 and Online Supplemental Appendix 1). It can cause hypertensive crisis with foods rich in tyramine.¹⁴² Additionally, use of St. John's wort is associated with the induction of mania or hypomania in patients suffering with bipolar disorder,¹⁴³ and it has been implicated with causing reversible photosensitivity and erythematous skin lesions after sun exposure.¹⁴⁴

Ginseng

American ginseng (*Panax quinquefolius*) and Asian ginseng (*Panax ginseng*) belong to the genus *Panax* in which the main active constituents are steroidal saponins called ginsenosides,¹⁴⁵ whereas Siberian ginseng (*Eleutherococcus senticosus*) is in the same family but not genus, with eleutherosides as the active component. These are commonly used herbs worldwide, consumed in various forms including as tea and other beverages. They are used mainly for beneficial effect in stress reduction, memory enhancement, attention deficit hyperactivity disorder, sexual dysfunction and alleviation of menopausal symptoms. They also have shown immunomodulatory, antidiabetic, anti-aging, antifatigue and anticancer properties. The content of ginsenosides in the Asian ginseng depends on the raw (white) root versus steamed (red) ginseng root. Most ginsenosides and eleutherosides were reported to have an inhibitory effect on enzymes CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4.¹⁴⁶ One case of imatinib-induced hepatotoxicity after concurrent ginseng ingestion in a patient with chronic myelogenous leukemia was reported, which resolved after short course of corticosteroids and ginseng withdrawal.¹⁴⁷ Another case reported similar findings with concomitant use of antiretroviral drug raltegravir and ginseng in an HIV-positive patient with long-term hepatitis C.¹⁴⁸ Thus, ginseng should be used with caution with other CYP3A4-metabolized drugs and in patients with preexisting liver conditions. Surprisingly, Gurley et al. noted ginseng did not affect other CYP enzymes except for slight inhibition of CYP2D6.¹⁴⁹

Ginsenosides can inhibit platelet aggregation and thromboxane formation in vitro,¹⁵⁰ prolong activated partial thromboplastin time and thrombin time in rats,¹⁵¹ and cause irreversible human platelet inhibition by panaxynol, a constituent of ginseng.¹⁵² Decreased anticoagulant effects of warfarin in a patient whose therapy had been stable previously¹⁵³ and thrombosis with a subtherapeutic INR were reported.¹⁵⁴ American ginseng also was shown to reduce warfarin effect in healthy volunteers.¹⁵⁵ In contrast, other ginseng species, including Asian ginseng¹⁵⁶ and Korean red ginseng,¹⁵⁷ did not affect warfarin's anticoagulant effect. In 12 healthy subjects, ginseng treatment for 2 weeks did not affect either the pharmacokinetics or pharmacodynamics of a single 25-mg dose of warfarin.¹⁴⁰ Long-term effects of ginseng in elderly with comorbidities have not been systematically assessed. Because of the potential for platelet inhibition in humans, ginseng use should be discontinued in patients at least 1 week before surgery.⁹⁵

There is also conflicting evidence of estrogenic properties of ginsenosides. Human studies in pregnancy and lactation are lacking, but there is in vitro evidence of teratogenicity in animal embryos with ginsenoside use. Thus, caution should be exercised with ginseng's use during pregnancy and lactation and should be avoided if possible. Ginseng may lower blood sugar levels, and this effect may be greater in patients with diabetes than in nondiabetic individuals. Hypoglycemia has been described with concomitant use of ginseng with oral hypoglycemic agents,¹⁵⁸ and its use has been reported to reduce postprandial increment of glucose in nondiabetics.¹⁵⁹ Caution is advised when using it with antidiabetic medicines or supplements that might lower blood sugar (devil's claw, ginger, fenugreek, gum and guar), and blood glucose levels may require closer monitoring and dose adjustments. Ginseng may increase cardiac repolarization and QTc interval¹⁶⁰ as well as proarrhythmic risk by additional increase in the bioavailability of antiarrhythmic agents due to reduced metabolism.¹⁶¹ Siberian ginseng was reported to reproducibly elevate digoxin concentrations, which normalized after discontinuation and increased after resumption of ginseng.¹⁶² Ginsenosides, which include more than 20 saponin glycosides with a nucleus similar in structure to steroid hormones,¹⁶³ can cause mastalgia,¹⁶⁴ functionally abnormal vaginal bleeding¹⁶⁵ and gynecomastia in males. Coingestion of American ginseng with antidepressants like phenelzine can cause side effects like nervousness, anxiousness, headache

and insomnia.¹⁶⁶ Hypertension has been reported with chronic ginseng ingestion, with normalization of blood pressure after ginseng discontinuation.¹⁶⁷

Grapefruit Juice

Grapefruit (*Citrus paradisi*) juice is commonly used for its medicinal effect in regulating glucose levels in diabetics, to prevent cancer and in lowering serum cholesterol levels in cardiovascular diseases. Active ingredients within grapefruit juice (furanocoumarins and the flavonoids naringenin and bergamottin) have an inhibitory effect on P-glycoprotein, organic anionic transporting polypeptide and CYP3A4 enzymatic activity in intestinal enterocytes, mostly affecting orally administered drugs. This can lead to elevations of the serum concentrations of drugs transported by P-glycoprotein or metabolized by CYP3A4 substrates (Table 3) and cause adverse effects. Even a single exposure to one glass of the grapefruit juice can produce clinically significant interaction, and with the half-life of CYP3A4 being > 8 hours, its reversal inhibition by grapefruit increases the bioavailability and blood levels of drugs metabolized by this enzyme (Table 3) up to 72 hours.^{168,169} Therefore, repeated juice intake can result in adverse effects even if not taken concomitantly with drugs. This effect is present whether grapefruit is taken as a whole fruit or in juice form, causing clinically relevant increase in blood concentration of affected drugs that can result in adverse effects.¹⁷⁰ Some examples include exaggerated antihypertensive response with calcium channel blockers (felodipine),¹⁷¹ increased risk of rhabdomyolysis and hepatotoxicity with statins,¹⁶⁸ hypoglycemia with antidiabetics (repaglinide), increased steady-state concentration of cyclosporine, potentiation of toxicity with antiarrhythmics with QT prolongation and torsades de pointes,¹⁷² and augmentation of antiplatelet activity of cilostazol leading to pupura.¹⁷³

There also are case reports of elevated INR and hematoma with grapefruit juice ingestion in patients previously stabilized on warfarin.¹⁷⁴ Therefore, drug interactions with grapefruit juice are a concern, especially in situations when the magnitude of interaction is large, in drugs with a narrow therapeutic index and in the elderly with multiple comorbidities and polypharmaceutical regimens. Its use in such populations should be limited and the potential for adverse grapefruit and drug interaction should be discussed with the elderly taking drugs metabolized through CYP3A (Table 3)

or transported through P-glycoprotein to avoid any potential adverse effect.

Federal Regulation of Herbal Supplements

Herbal supplements are “medicinal” products of plant origin that are not officially recognized as drugs nor intended for use as conventional foods, but are considered part of treatment modalities in integrative medicine. Unlike drug products that must be proved safe and effective before marketing, herbal or dietary supplements do not need prior FDA authorization before being marketed except for “new dietary ingredients” marketed after October 15, 1994, which only require demonstration of safety and not efficacy by submitting a premarket notification 75 days prior to the launch of the new product. However, the FDA does require manufacturers to register with its agency.

The U.S. Dietary Supplement Health and Education Act of 1994 defines and regulates dietary supplements.¹⁷⁵ Under the act, supplements are effectively regulated by the FDA for Good Manufacturing Practices under 21 CFR Part 111.¹⁷⁶ The current Good Manufacturing Practices (cGMP) final rule¹⁷⁷ ensures consistency by requiring information about manufacturing, packing, labeling, identity, quality, strength, purity and composition in the manufacture of dietary supplements. However, without validated analytical standards and methods to detect the active ingredients of the vast majority of herbal supplements, it is difficult for the FDA to detect potency or dosing requirements for these herbal products. The cGMP final rule requires that manufacturers, not the FDA, determine the quality specifications for their products, and companies that want to use less stringent specifications can do so without penalty.¹⁷⁸

Manufacturers may make three types of claims for their dietary supplement products: health claims, structure/function claims and nutrient content claims. These claims are not endorsed by the FDA, and the manufacturer is solely responsible for ensuring the accuracy and truthfulness of these claims. Thus, by law, if a dietary supplement makes a claim, it must state a “disclaimer” that the FDA has not evaluated the claim. The disclaimer also must state that this product is not intended to “diagnose, treat, cure or prevent any disease,” because only a drug can legally make such a claim. Manufacturers, packagers and distributors of

dietary supplements are required to report any serious adverse events to the FDA within 15 business days after being notified (i.e. consumer complaints), but they are not required to do any active surveillance and reporting on their own. They also need to provide any additional medical information they obtain within a year of the adverse event report.

Consumers and other health care providers are encouraged to report similar adverse events to the FDA. The FDA has intervened by identifying harmful dietary supplements or potential contamination, but while FDA's curbing measures have had some impact, it has not been enough to restrict the access of hazardous botanicals to general consumers when manufacturers can simply introduce new similar formulations.¹⁷⁹ With the limited resources available to the FDA, and presence of 1,800 manufacturers and more than 75,000 products in the supplement market,¹⁷⁸ enforcement of existing laws is difficult.¹⁸⁰ The FDA cannot fully accomplish its mission of consumer protection without increased resources and regulations on the industry.

Limitations of Scientific Evidence on Efficacy and Safety

Most of the scientific knowledge on herbal remedies and herb-drug interactions comes from in vitro studies, animal studies and case reports; there is a lack of validated controlled clinical trials. Information about pharmacokinetics, pharmacodynamics, efficacy and safety of herbal products in the elderly population with cardiovascular diseases,¹⁸¹ who also have multiple comorbidities and take different medicines, is particularly limited.¹⁸² Lack of safety data for cardiovascular disease patients is a recurring phenomenon in herbal medicine, with no rigorous attention given to adverse events or interactions with prescription drugs.¹³ Even when data are available for other populations, typically healthy volunteers or low-risk patients without comorbid conditions, findings are often questionable because of a lack of consistency in research methods, small number of subjects, absence of placebo groups, lack of standardization of supplements and absence of data on herb-drug interactions. Thus, findings for specific herbal products are of limited usefulness for making decisions about efficacy or safety. The dramatic increase of dietary supplement sales in the last two decades has unmasked several herbal adverse effects and life-threatening herb-drug interactions as discussed in this review,

particularly with the use of St. John's wort. The elderly are particularly susceptible to herb-mediated changes to CYP activity and should be properly instructed to avoid supplements that can increase adverse effects.^{149,183} For example one study reported ginseng inhibited CYP2D6 in elderly but not younger subjects.¹⁸⁴

Most of the information about drug-herb interactions comes from clinical practice, but a systematic assessment of such interactions by collecting data from clinical studies may provide additional insights. In addition, the system for reporting adverse effects needs to be closely followed by consumers, health care providers and manufacturers to report adverse interactions as emphasized by the Institute of Medicine.¹⁸⁵

Inadequate Quality Control Measures

Herbal and dietary supplement manufacturers in the United States include a blanket warning on labels rather than specifying adverse effects and potential interactions.^{133,186,187} Additionally, herbal products may be contaminated with other substances, contain attenuated quantity or quality of active ingredients¹⁸⁸ or many not contain the intended ingredient at all, causing variations in their side effect profiles.¹⁸⁹ A 2013 study of 44 popular supplements sold by 12 companies showed most of the herbal products tested were of poor quality, often diluted or replaced by cheap fillers like soybean, wheat and rice.¹⁹⁰ A recent investigation by the New York Attorney General's office into store-brand supplements at four national retailers showed all but five of the 24 products tested to be either contaminated or replaced by another plant product.¹⁹¹

Despite FDA guidelines mandating manufacturers to avoid contamination, supplements repeatedly have been reported to contain adulterant compounds, including other herbs, heavy metals,^{28,192} anabolic steroids²² or prescription drugs¹⁹³ as well as contaminant microbials,²⁷ pesticides and other compounds²⁶ that put unsuspecting consumers at risk of adverse side effects and herb-drug interactions. Several cases of potentially life-threatening hepatotoxicity (leading to liver transplantation in some) attributed to Herbalife® products (Los Angeles, CA) marketed for promoting energy, fitness and weight control were recently documented.¹⁹⁴ In an analysis of 20 herbal/dietary supplements marketed as natural slimming products, eight formulations contained sibutramine, five had sibutramine with phenolphthalein and one was adulterated with

synephrine.²¹ Sibutramine has a potential for abuse or addiction and elevates blood pressure and heart rate, posing significant risk to patients with heart disease, heart failure, arrhythmias or stroke,¹⁹⁵ while phenolphthalein is known to have carcinogenic properties. In June 2011, two New Jersey dietary supplement companies were forced to shut down all manufacturing and distribution following FDA investigation into violations of misbranding food labels, selling products containing a major food allergen and having unhygienic conditions; a dead rodent cut in half along with rodent excreta and pellets were found on a blender motor platform, and bags of raw ingredients were gnawed through by rodents and covered with rodent urine and feces.¹⁹⁶

No package inserts for herbal supplements describing potential adverse events or drug interactions are required, and patients have no way of distinguishing safe from potentially harmful supplements. Direct-to-consumer advertisement featuring extravagant, unsubstantiated and dubious health claims by the supplement industry¹⁹⁷ continues despite regulatory guidelines. The Federal Trade Commission provides oversight and guidance but relies on advertisement surveillance for enforcement of its guidelines rather than approval before use. Thus, despite levying millions of dollars of fines yearly, misleading marketing campaigns continue to thrive.¹⁹⁸

Underreporting of Adverse Herb Reactions and Herb-Drug Interactions

An FDA-commissioned study estimated receiving less than 1% of all adverse events associated with dietary supplements.¹⁹⁹ Many herb-related adverse events are underreported by patients or clinical practitioners,²⁰⁰ probably for a multitude of reasons. Consumers perceive herbal products as “natural remedies” carrying minimal to no risk,²⁰¹ and are thus unable to correlate any adverse effects and more likely to blame prescription medicines when encountering a side effect. Most complementary medicine users fail to disclose herbal product use to their physicians.²⁰² Consumers may lack direction on how to file a complaint or may assume it is the role of the health care provider once informing them of an adverse event. Health providers have limited training on herbal adverse effects, toxicities and herb-drug interactions,²⁰³ and may underrecognize their occurrence. A prospective study looking into web-based questionnaires administered to health care providers noted that approximately 73% of physician respondents did not know how or where to

report adverse events related to dietary supplements.²⁰⁴ The Dietary Supplements Information Expert Committee has recommended enhancing data collection approaches, improving coordination of adverse event-related surveillance programs, strengthening education programs for public and health care sectors and conducting further research into safety of dietary supplements.²⁰⁵ Reports of suspected or documented adverse events may be submitted voluntarily to the FDA’s MedWatch program²⁰⁶ or other organizations such as a poison control center.

Public Misperception of Benefits of Herbal Supplementation

The public seems to believe that dietary supplements, like pharmaceuticals, undergo scrutiny and rigorous research before marketing. According to a nationwide interactive poll of 1,010 respondents, 59% of the respondents believed the supplements were approved by a government agency before being sold, 68% believed that listing potential side effects on labels was a requirement and 55% believed that supplement manufacturers were required to make scientific evidence-backed safety claims.²⁰⁷ Similarly, the PEW Internet and American Life Project reported 52% of users to have visited health sites believed “almost all” or “most” health information on the Internet is credible.²⁰⁸ While some media sources provide a wealth of accurate information, others contain false, unsubstantiated information or even conflicting statements. For example, in a study of Internet marketing of herbal products¹⁹⁷ at least 81% of websites were found to make one or more health claims, with more than 50% claiming to treat, prevent, diagnose or cure specific diseases despite regulations barring such statements. Another study investigating 12 weight-loss supplements sold online identified eight ingredients with reported life-threatening cardiac adverse effects or death.²⁰⁹ Warning about potential adverse effects did not appear on the web pages. One product’s list of ingredients included ma huang (Chinese ephedra), even though marketing of ephedra-containing products is banned in the United States. The popular belief that natural supplements confer health benefits²¹⁰ without potential for harm²¹¹ makes consumers vulnerable to making choices that could be deleterious.

Knowledge Barriers Between Patients and Providers Regarding Herb-Drug Interactions

Many herbal supplements contain active ingredients that have strong biological effects and can make them unsafe in certain situations, especially when consumed

in large amounts or taken with drugs that can alter their pharmacokinetic and pharmacodynamics parameters. Despite increased educational initiatives and the large body of literature on herbal remedies, there remains a considerable knowledge gap on herb-related safety issues among both health care providers²¹² and health store employees²¹³ who are usually the first point of contact for consumers interested in buying herbal remedies. This lack of knowledge exchange can result in distribution of inconsistent information that can heighten confusion and spread false messages, thus further complicating issues. Physicians are advised to be aware of potential therapeutic benefits of complementary and alternative medicinal agents while at the same time wary of their unwanted risks, toxicities and potential interactions. Better recognition of herb profiles will allow physicians to identify herb-drug interferences, antagonisms and synergies and assist in formulating better goal-driven individualized health care plans.

Initiatives like the Dietary Supplement Verification Program from U.S. Pharmacopeia can ensure that products are labeled correctly and devoid of contaminants. It is also important for health care providers to develop good communication with their patients and create a comfortable environment for discussing herbs and other supplements. Consumers are encouraged to consult with their medical providers when concomitantly using nutraceuticals with prescription drugs. It is prudent to work with preparations manufactured by companies that adhere to Good Manufacturing Practices pharmaceutical standards. However, many of these products are not readily available to the public over the counter. Without the same oversight for herbal products that is required for allopathic medicine, the public risks self-medicating with substances that are potentially ineffective, deleterious or both, leading to harmful consequences.

Conclusions

Most medications, herbal preparations and nutraceuticals have notable effects on biochemical pathways and can influence wound healing, metabolic processes, coagulation and cardiovascular function. They also can interact with other prescribed drugs. A large portion of the data available regarding the effects of herbal medicines is anecdotal and lacks proper evidence regarding safety in the elderly with multiple comorbidities. Quality control standards are highly variable and marketing of many products misleading

or potentially harmful when used by the vulnerable population taking multiple medicines.

Public and health practitioners need to be reminded that herbal supplements are bioactive compounds and could have adverse effects when combined with medications whose effectiveness and safety can be altered by natural products such as St. John's wort or grapefruit juice. General guidelines or expert opinion-based recommendations have been provided in peer-reviewed journals, but national guidelines are needed. The National Center for Complementary and Integrative Health provides information about commonly used herbs and their potential for drug interactions. Major academic centers (e.g. Mayo Clinic, Memorial Sloan-Kettering Hospital and University of Maryland) also provide this information, and links to these sites are provided in Online Supplemental Appendix 2.

Patient-Friendly Recap

- Herbal products are sold as dietary supplements and not subject to the same regulatory standards as pharmacological drugs.
- The FDA previews “dietary ingredients” for safety, but not for effectiveness.
- Elderly patients with comorbidities using multiple medications and dietary supplements are at increased risk of adverse interactions.
- Unlike drugs, supplements are not intended to treat, diagnose, prevent or cure diseases, and such claims need to be proven scientifically before accepted by the public or health care providers.
- Products sold as “natural” are not always safe. Always remember — safety first.

Funding Sources

Dr. Jahangir is supported by a grant from the National Heart, Lung, and Blood Institute (R01 HL101240) and intramural research funding from Aurora Health Care. The content in this article is solely the responsibility of the authors and does not necessarily represent the official views of the NHLBI or National Institutes of Health.

Conflicts of Interest

None.

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