

# Herbal and Dietary Supplement–Drug Interactions in Patients with Chronic Illnesses

PAULA GARDINER, MD, MPH, *Harvard Medical School, Boston, Massachusetts*

RUSSELL PHILLIPS, MD, *Beth Israel Deaconess Medical Center, Boston, Massachusetts*

ALLEN F. SHAUGHNESSY, PharmD, *Tufts University Family Medicine Residency Program at Cambridge Health Alliance, Cambridge, Massachusetts*

Herbs, vitamins, and other dietary supplements may augment or antagonize the actions of prescription and nonprescription drugs. St. John's wort is the supplement that has the most documented interactions with drugs. As with many drug-drug interactions, the information for many dietary supplements is deficient and sometimes supported only by case reports. Deleterious effects are most pronounced with anticoagulants, cardiovascular medications, oral hypoglycemics, and antiretrovirals. Case reports have shown a reduction in International Normalized Ratio in patients taking St. John's wort and warfarin. Other studies have shown reduced levels of verapamil, statins, digoxin, and antiretrovirals in patients taking St. John's wort. Physicians should routinely ask patients about their use of dietary supplements when starting or stopping a prescription drug, or if unexpected reactions occur. (*Am Fam Physician*. 2008;77(1):73-78. Copyright © 2008 American Academy of Family Physicians.)

About one in four persons taking prescription medication also take a dietary supplement.<sup>1,2</sup> According to the National Center for Complementary and Alternative Medicine (NCCAM), a dietary supplement can be a vitamin, a mineral, an herb or other botanical, an amino acid, or other such substances or their constituents. These supplements have demonstrated pharmacologic action used to produce therapeutic results.<sup>3</sup> Even supplements that do not have a documented pharmacologic action can affect the absorption, metabolism, and disposition of other drugs.

The research literature regarding interactions between each of these supplements and other medications is rapidly and continually evolving. This review focuses on the use of dietary supplements in patients with chronic conditions, in whom the risk for dietary supplement–drug interaction is the greatest (*Table 1*).<sup>4-30</sup> The information is based on a review of several sources, including the Medline, Embase, and Cinahl databases and an authoritative drug interaction reference.<sup>31</sup> *Table 2* lists resources available to check for drug interactions with dietary supplements.

Asthma, insomnia, depression, chronic gastrointestinal disorders, pain, memory problems, and menopausal symptoms are the medical conditions for which supplements are most commonly used.<sup>32,33</sup> Patients at high risk for interactions, such as those with seizure disorders, cardiac arrhythmia, or congestive heart failure, often report dietary supplement use.<sup>2</sup> These patients tend to take more prescription medications, especially medications with a narrow therapeutic index.

## Regulation of Dietary Supplements

Dietary supplements are not subjected to the same rigorous safety and efficacy trials and premarketing approval process required of prescription drugs. As a result, there is often incomplete knowledge regarding interactions between dietary supplements and drugs, especially among patients with chronic diseases.

Marketed products containing dietary supplements may vary significantly. Even different batches of the same product from the same manufacturer may differ in content and potency. Previously in the United States, dietary supplement products may not have

**Table 1. Herbal and Dietary Supplement–Drug Interactions**

<i>Herbal or dietary supplement</i>	<i>Drug</i>	<i>Comment</i>	<i>Recommendation*</i>
<b>Patients taking oral anticoagulants</b>			
Cranberry (juice)	Warfarin (Coumadin)	Interaction possible based on seven reports of increased INR, although a clinical study showed no interactions <sup>4,7</sup>	Suspect an interaction if INR elevated
Fish oil	Warfarin	Interaction possible, with case reports showing an elevated INR, although a clinical study showed no effect of fish oil on anticoagulation status <sup>8,9</sup>	Suspect an interaction if INR elevated
Garlic	Warfarin	Interaction unlikely based on a clinical study that found garlic is relatively safe and poses no serious hemorrhagic risk for closely monitored patients taking warfarin oral anticoagulation therapy <sup>10</sup> One review found no case reports of interactions with garlic and warfarin <sup>11</sup>	Suspect an interaction if bruising or bleeding occurs despite an appropriate INR
Ginkgo	Warfarin	Interaction possible, though controlled clinical studies show no effect of ginkgo on the kinetics or dynamics of warfarin <sup>12,13</sup>	Experts recommend caution, although available research does not support this conclusion
	Aspirin	Interaction suspected based on four case reports of spontaneous bleeding <sup>14,15</sup>	Suspect an interaction if spontaneous bleeding occurs
Ginseng	Warfarin	Interaction possible based on conflicting research findings American ginseng ( <i>Panax quinquefolius</i> ) reduces blood concentrations of warfarin <sup>16,17</sup> Coadministration of warfarin with Asian ginseng ( <i>Panax ginseng</i> ) did not affect the pharmacokinetics or pharmacodynamics of warfarin <sup>18</sup>	Avoid combination if possible
St. John's wort	Warfarin	Interaction suspected based on decreases in INR in case reports and in a study in 12 healthy volunteers <sup>18</sup>	Evaluate warfarin response when St. John's wort is initiated or stopped
Vitamin E (> 400 IU daily)	Warfarin	Interaction suspected based on a single patient (with rechallenge), resulting in an increase in INR <sup>19</sup> One clinical trial showed no interaction <sup>20</sup>	Evaluate warfarin response when vitamin E is used in combination
<b>Patients taking cardiovascular medications</b>			
Eleuthero ( <i>Eleutherococcus senticosus</i> )	Digoxin	Possible increase in digoxin levels without clinical signs (case report) <sup>21</sup>	Monitor digoxin level when eleuthero is initiated or stopped
St. John's wort	Digoxin	Suspected decrease in digoxin levels without clinical signs in a controlled study <sup>22</sup>	Monitor digoxin level when St. John's wort is initiated or stopped
	Verapamil (Calan)	Interaction suspected based on decreased bioavailability in a study in eight healthy volunteers <sup>23</sup>	Increase verapamil dose, if necessary, if diminished response occurs
	Statins	Interaction suspected based on decreased plasma blood levels in a clinical study <sup>24</sup>	Monitor serum lipid levels after St. John's wort is added
<b>Patients taking psychiatric medications</b>			
Ginkgo	Atypical antidepressant (trazodone [Desyrel])	Interaction possible based on one case report of coma <sup>25</sup>	Evaluate for emotional and/or behavioral changes in patient response after ginkgo is initiated or stopped
Ginseng	Monoamine oxidase inhibitors	Interaction possible based on two case reports of manic-like symptoms, headache, and tremulousness <sup>17</sup>	Avoid combination if possible
St. John's wort	SSRIs	Interaction suspected based on case reports of drowsiness or serotonin syndrome <sup>26</sup>	Taper off St. John's wort when initiating an SSRI
	Benzodiazepines	Interaction suspected based on pharmacokinetic studies showing decreased serum levels (25 to 50 percent) without clinical signs <sup>27-29</sup>	Adjust the dose of benzodiazepine as needed
	Tricyclic antidepressants	Interaction possible based on decreased amitriptyline plasma levels but no clinical effects in a study of 12 depressed patients <sup>27,30</sup>	Monitor patient response after St. John's wort is initiated or stopped

INR = International Normalized Ratio; SSRI = selective serotonin reuptake inhibitor.

\*—All recommendations have a strength of recommendation taxonomy (SORT) evidence rating of C (consensus, disease-oriented evidence, usual practice, expert opinion, or case series). For information about the SORT evidence rating system, see <http://www.aafp.org/afpsort.xml>.

Information from references 4 through 30.

contained what they were labeled to contain. However, in June 2007 the U.S. Food and Drug Administration (FDA) released “good manufacturing practices” for the dietary supplement industry.<sup>34</sup>

### Types of Interactions

Interactions with dietary supplements can be of two types. Pharmacodynamic interactions occur when the intrinsic action of a dietary supplement augments or antagonizes the activity of another drug. Pharmacokinetic interactions result from changes in metabolism, excretion, or (infrequently) absorption or protein binding of the active aspect of the dietary supplement or the drug, resulting in more-pronounced or diminished pharmacologic activity.

The evidence supporting dietary supplement–drug interactions, just as with drug–drug interactions, varies widely. There is no process for systematic evaluation of dietary supplement products for possible interactions with prescription medications. As a result, our knowledge of interactions is incomplete and based on animal studies, case reports, case series, historical contraindications, extrapolation from basic pharmacology data, or the rare clinical trial. Many recommendations regarding dietary supplement–drug interactions are based on conjecture rather than research.

### Interaction Risks in Specific Patient Populations

The following section reviews potential effects of dietary supplements in patients taking anticoagulants, cardiovascular medications, psychiatric medications, laxatives, diabetes medications, or medications for human immunodeficiency virus (HIV) infection.

#### PATIENTS RECEIVING ANTICOAGULANTS

Case reports have shown interactions between the anticoagulant warfarin (Coumadin) and St. John’s wort, ginkgo, garlic, and ginseng.<sup>11,17</sup> Studies have demonstrated that St. John’s wort increases the metabolism of warfarin, leading to diminished serum levels.<sup>18,35–37</sup> However, the clinical response to the combination has not been quantified.

Ginkgo does not interact with warfarin or aspirin directly, but has demonstrated antiplatelet activity.<sup>12,38</sup> In combination with nonsteroidal anti-inflammatory drugs, especially aspirin, ginkgo has been reported to cause severe bleeding, including intracranial bleeding.<sup>39–41</sup>

Garlic has intrinsic antiplatelet activity. However, one clinical trial has demonstrated that garlic is safe and poses no serious hemorrhagic risk for monitored patients taking warfarin.<sup>10</sup>

A low-quality clinical study found no effect of Asian ginseng (*Panax ginseng*) in combination with warfarin.<sup>18</sup> American ginseng (*Panax quinquefolius*), a separate plant, decreases warfarin serum levels in humans, resulting in less anticoagulation.<sup>16</sup> Eleuthero (*Eleutherococcus senticosus*) has not been studied; however, it contains a constituent that inhibits platelet aggregation.

Vitamin E and fish oil are often mentioned in reviews of supplement–drug interactions.<sup>42,43</sup> In a clinical study of 16 patients, fish oil (3 to 6 g daily) did not affect coagulation status in patients receiving warfarin.<sup>8</sup>

Vitamin E may have an effect on bleeding time. In vitro studies demonstrate potentiation of the antiplatelet effect of aspirin by vitamin E.<sup>44</sup> However, clinical trials with and without warfarin and vitamin E show no increased risk of bleeding even though high doses of vitamin E may antagonize vitamin K.<sup>20,45,46</sup>

Cranberry juice, although implicated in case reports, has not been shown to affect coagulation in a controlled study.<sup>4</sup>

Given the narrow therapeutic index of warfarin and the serious consequences associated with small changes, the anticoagulation status in patients taking dietary supplements should be carefully monitored whenever they initiate or stop taking any supplement, or when a new bottle of the same product is used, until the effect in the individual patient is known. Specifically, patients receiving American ginseng should be monitored when changing products or even bottles of the same product.<sup>47</sup>

#### PATIENTS RECEIVING CARDIOVASCULAR MEDICATIONS

Of all the supplements used by patients who have cardiac disease, St. John’s wort, used to treat mood disorders, is associated with the most interactions. It decreases serum levels of verapamil (Calan) and statins.<sup>23,24,48</sup> Blood pressure and lipid levels, respectively, should be monitored closely if a patient is taking one of these drugs and St. John’s wort.

The suspected mechanisms of St. John’s wort interactions are by the induction of cytochrome P450 (CYP450) isoenzymes CYP3A4, CYP2C9, and CYP1A2, and the transport protein P-glycoprotein, leading to decreased concentration of medications.<sup>36</sup> In one study, St. John’s wort decreased digoxin blood levels by 25 percent, most likely by inducing the P-glycoprotein, which decreases the bioavailability of digoxin.<sup>22,49</sup> Ginseng is another commonly used herb that has been reported to cause an increase in digoxin serum levels in a case report of one patient.<sup>21</sup> Digoxin levels should be monitored in patients taking eleuthero or St. John’s wort.

**Table 2. Sources of Information About Herbal and Dietary Supplement–Drug Interactions**

Organization/product	Web site	Comments
ePocrates Online Premium*	<a href="http://www.epocrates.com">http://www.epocrates.com</a>	Uses natural medicine database
HerbMed by the Alternative Medicine Foundation†	<a href="http://www.herbmed.org">http://www.herbmed.org</a>	Directly linked to PubMed
Medscape* drug interaction checker	<a href="http://www.medscape.com/druginfo/druginterchecker">http://www.medscape.com/druginfo/druginterchecker</a>	Searches prescription and over-the-counter drugs, and dietary supplements
Medwatch, the FDA Safety Information and Adverse Event Reporting Program	<a href="http://www.fda.gov/medwatch">http://www.fda.gov/medwatch</a>	Online form to report all suspected drug–dietary supplement interaction
NCCAM	<a href="http://nccam.nih.gov">http://nccam.nih.gov</a>	NIH-sponsored center, has useful patient information
Natural Medicines Comprehensive Database*	<a href="http://www.naturaldatabase.com">http://www.naturaldatabase.com</a>	Thorough and up-to-date information; has a drug–supplement interaction program
Natural standard	<a href="http://www.naturalstandard.com">http://www.naturalstandard.com</a>	Thorough monographs, including herb–drug interactions
Tatro, DS. Drug Interaction Facts. St. Louis, Mo.: Facts and Comparisons, 2006	<a href="http://www.factsandcomparisons.com">http://www.factsandcomparisons.com</a>	Helpful textbook on interactions for medications as well as dietary supplements

FDA = U.S. Food and Drug Administration; NCCAM = National Center for Complementary and Alternative Medicine; NIH = National Institutes of Health.

\*— Requires a subscription.

†— Information is free for 40 herbal products; for others, a fee is charged.

#### PATIENTS RECEIVING PSYCHIATRIC MEDICATIONS

Although it probably is not its inherent mechanism of action in the treatment of depression, St. John's wort may have an effect on serotonin levels. It has been associated with serotonin syndrome in patients also receiving a selective serotonin reuptake inhibitor (SSRI).<sup>50</sup> St. John's wort should be tapered off when an SSRI is initiated.<sup>51</sup> Patients should be cautioned not to initiate St. John's wort when receiving these drugs.

St. John's wort decreases serum levels of psychiatric medications metabolized by the CYP450 enzyme system. It has been shown to affect serum levels of benzodiazepines and tricyclic antidepressants, although these changes may not result in a clinical effect.<sup>27,28,30</sup>

#### PATIENTS TAKING BULK LAXATIVES

Psyllium and related bulk-forming laxatives are dietary supplements often not considered to be medications by many patients. However, they can slow or diminish absorption of many drugs. Psyllium can reduce carbamazepine (Tegretol) absorption and serum levels.<sup>52</sup> Additionally, there is a case report showing that psyllium decreased the absorption of lithium.<sup>53</sup> As a general rule, bulk laxatives such as psyllium should not be taken at the same time as other medications; their use should be separated by several hours to allow absorption to occur.

#### PATIENTS RECEIVING DIABETES MEDICATIONS

Supplement–drug interactions are not well documented in patients being treated for diabetes. However, a number of supplements have intrinsic effects on serum glucose.

Ginseng has hypoglycemic activity in patients with diabetes, and this effect might be additive in patients taking oral hypoglycemics or insulin. Chromium and psyllium also have hypoglycemic effects.<sup>54–56</sup> The effect of these supplements is unpredictable in individuals, and no specific changes in hypoglycemic doses are needed unless blood glucose changes occur.

#### PATIENTS RECEIVING HIV MEDICATIONS

Most antiretrovirals are metabolized via the CYP3A4 and P-glycoprotein systems. Dietary supplements that induce these systems may decrease serum levels of the antiretrovirals. St. John's wort is the dietary supplement with the most evidence of an effect on these systems.<sup>57</sup> Limited clinical research has demonstrated reductions in antiretroviral serum concentrations in patients taking garlic and vitamin C.<sup>58,59</sup> Milk thistle, *Echinacea* species, and goldenseal inhibit CYP450 enzymes in vitro, but not to a clinically relevant effect.<sup>57,60</sup> The effectiveness of HIV therapy should be monitored in patients taking these supplements, particularly St. John's wort. Because of the risk of a dangerous interaction, patients taking antiretrovirals should be discouraged from using St. John's wort.

#### General Considerations with Dietary Supplements

Physicians should advise patients about the safety and effectiveness of the products they are using or are considering using. Most patients do not realize the great variability among dietary supplements. Several groups

have set up standards for production, bioavailability, and purity of dietary supplements, including the United States Pharmacopeia Convention, Consumer Labs, and the NSF International. Products approved by any of these organizations will be marked with their seal.

Two out of three patients taking prescription medications and supplements do not tell their physician about their dietary supplement use, perhaps because they do not consider supplements to be legitimate drugs or to carry risks.<sup>2</sup> Therefore, all patients should be asked about their use of dietary supplements. Rather than closed, yes or no questions, physicians should ask, "What vitamins, herbs, and other supplements do you use? What about teas, tinctures, or natural products?" These supplements should be treated as other drugs and recorded in the patient record.

## The Authors

PAULA GARDINER, MD, MPH, is an assistant professor at the Boston (Mass.) University Family Medicine Residency Program. At the time this article was written she was a clinical research fellow at the Osher Institute, Division for Research and Education in Complementary and Integrative Medical Therapies, Harvard Medical School, Boston, Mass.

RUSSELL PHILLIPS, MD, is a general internist and chief of the Division of General Medicine and Primary Care at Beth Israel Deaconess Medical Center, Boston, Mass., and he directs the Harvard Medical School Research Fellowship Program in Complementary and Integrative Medicine. He received his medical degree from Stanford University School of Medicine, Stanford, Calif.

ALLEN F. SHAUGHNESSY, PharmD, is associate program director of the Tufts University Family Medicine Residency Program at Cambridge (Mass.) Health Alliance. He received his undergraduate degree in pharmacy from Temple University, Philadelphia, Penn., and completed his doctor of pharmacy degree and fellowships in faculty development and primary care public health policy development at the Medical University of South Carolina, Charleston.

*Address correspondence to Paula Gardiner, MD, Department of Family Medicine, Boston University, Dowling 5, 1 Boston Medical Center Place, Boston, MA 02118 (e-mail: paula.gardiner@bmc.org). Reprints are not available from the authors.*

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