

Natural Health Product Interactions with Medication

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ABSTRACT: Natural health products (or dietary supplements) refer to those products found in oral dosage forms, containing 1 or more active ingredients considered to be a nutrient, an herbal product, or any other nonnutrient/nonherbal substance. Their use continues to increase in the general population and in patients seen by nutrition support clinicians. Aside from an appraisal of product safety and effectiveness, attention should be paid to the potential for these product ingredients to interact with medication. Estimates are that at least 15 million adults in the United States are at risk for supplement-drug interactions. These can occur through both pharmacokinetic and pharmacodynamic mechanisms. This review describes the influence of dietary supplements on both the disposition and the effect of medication and provides numerous examples. Patients at greatest risk for interactions are those with chronic disease, who use multiple medications—particularly those with a narrow therapeutic range—have genetic variants in drug metabolism, impaired organ function, and are at either end of the age spectrum. Knowledge of the specific effects on drug absorption, metabolism, and effect is still incomplete. Relative to the large number of possible interactions between supplements and medication, only a small number of combinations have been examined or reported. The greatest limiting factor remains the quality or reliability of the existing evidence, as many widely accepted interactions are only theoretical based either on *in vitro* data or known pharmacology. A distinction needs to be clearly drawn between “documented” interactions and “potential” interactions. Although drug-drug interactions have been widely recognized, supplement-drug interactions may be as important to recognize, report, and manage.

The use of natural health products, also referred to as dietary supplement products, continues to

increase in the general population. Many of the patients seen by nutrition support clinicians, regardless of the setting, are likely to be consuming supplements or have an interest in doing so. The nutrition support clinician is in a unique position to evaluate dietary supplement data and provide each patient with appropriate guidance.¹ Aside from an appraisal of product safety and effectiveness, attention should be paid to the potential for these natural health products to interact adversely with medication. Evidence that many supplements have pharmacologic activity that could lead to adverse interactions when consumed with medications has grown; however, there is inadequate information to estimate the potential magnitude of this problem.² A valuable discussion of natural products was included in this journal a few years ago and correctly pointed to the potential for drug interactions.³ Use has continued to increase since then, as has the potential for interactions between these products and medication. Increased use of both medications and natural products, along with acceptance of such practice by segments of the health care system, can only increase the potential for interactions. This review will describe the influence of dietary supplements on both the disposition and the effect of medication.

For the purpose of this paper, the term *natural health product* will be used interchangeably with the term *dietary supplement*. This will refer to those products found in oral pharmaceutical dosage forms, containing 1 or more active ingredients considered to be a nutrient, an herbal, or other botanical product, or any other nonnutrient/nonherbal substance, as included in the regulatory definition of dietary supplements.⁴ Nutrition bars, meal replacements, or enteral nutrition formulations are not included. Any adverse clinical outcomes associated with a patient's decision to discontinue a medication in favor of a dietary supplement product are also not included in this discussion. Interactions between natural health products (the initiator) and drugs (the object of the interaction) need to be seen within the broader scope of drug-nutrient interactions (Table 1).¹ This paper's focus is on the third of the 5 types of interaction listed in Table 1, with dietary supplement ingredients as the precipitating factor. An interaction would have a defined location and

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Table 1
Classification of drug-nutrient interactions

Precipitating factor	Object of interaction	Potential consequence	Example (precipitant: object/consequence)
Altered nutritional status	Drug	Treatment failure Drug toxicity	Obesity: atracurium/↓ effect; PCM: salicylate/↑ toxicity
Food or food component	Drug	Treatment failure Drug toxicity	Food: indinavir/↓ absorption; GFJ: simvastatin/↑ toxicity
Specific nutrient or other DS	Drug	Treatment failure Drug toxicity	Vit K: warfarin/↓ effect; Vit E: warfarin/↑ effect
Drug	Nutritional status	Altered nutritional status	Valproic acid: weight gain
Drug	Specific nutrient	Altered nutrient status	Methotrexate: folate deficit

↓, Decreased; ↑, increased; DS, dietary supplement; GFJ, grapefruit juice; PCM, protein-calorie malnutrition; Vit, vitamin.

mechanism of effect in keeping with a recently described classification system.^{5,6}

Earlier reviews describing the overall health risks from dietary supplements⁷⁻¹¹ were followed by a number of papers in the past few years, which addressed specific aspects of the supplement-drug interaction issue.¹²⁻²⁰ Detailed descriptions of many case reports can be found in these publications. More recent reviews focus on interactions that involve a particular supplement, class of drug, or patient population.²¹⁻³⁰ Several pocket handbooks have also been compiled recently that describe many dietary supplement-drug interactions.^{31,32} As an example of how widespread the interest in the topic has become, a review of supplement-drug interactions in animals even exists.³³ Studies revealing the absence of an interaction between a supplement and medication are also being published.³⁴⁻³⁶ As more of these latter findings are noted, tables listing safe combinations of supplements with drugs can eventually be provided as a guide to patient care.

Interaction Risk

Although recent estimates are that about 50% of Americans use prescription medication, 40% use vitamins and mineral supplements, and at least 14% use herbals and other natural products,² the increasing emphasis on self-care among people further increases consumption patterns of pharmacologically active substances. The extent of potentially adverse, clinically significant interactions between supplements and medication is just not known. Supplements used on a chronic basis by a patient may pose the greatest risk for influencing drug disposition. Patients at greatest risk for interactions are those with chronic disease, who use multiple medications, particularly those drugs with a narrow therapeutic range, have genetic variants in drug metabolism, impaired organ function, and are at either end of the age spectrum.

A recent Canadian survey identified that of people using at least 1 natural health product, more than half combined this use with a drug.³⁷ Potential

supplement-drug interactions were identified in 28% of people using natural health products and medication concurrently, with one-third of those classified as moderate or major clinical significance.³⁷ Patients with chronic disease states are not only likely to be using medication regimens but also dietary supplements.¹ About 11% of patients with cardiovascular disease, diabetes, and psychiatric disorders reported use of supplements with their prescription regimens, with some at risk for commonly recognized interactions.³⁸ A more recent finding was that about 40% of patients with cardiovascular disease use nutritional supplements.³⁹ Close to 60% of those using the narrow therapeutic index drugs digoxin, warfarin, sotalol, or amiodarone were using an oral supplement concurrently. An incidental finding in a group of surgical patients, half of whom were using dietary supplements, was that a significant number were receiving anticoagulant medications along with supplements known to have anticoagulant effects.⁴⁰ As more is learned about genetic variability of drug-metabolizing enzymes and transporters, the role that this variability plays in interactions will likely become more prominent. A survey of community-dwelling elderly identified significant use of dietary supplements (6 product average per subject) and prescribed medication (3 per subject).⁴¹ Interaction potential was not described, however. Twenty-seven percent of an older cohort attending a memory clinic were either current or past users of natural health products, and herb-drug interactions were identified in 27% of the current users.⁴² More than half of elderly patients seen at 1 primary care clinic and using dietary supplements were consuming at least 1 potentially interacting combination with their medication.²⁵ Almost half of caregivers reported giving their children natural products, and two-thirds of those interviewed did not think that these products could interact with medications.⁴³

Relative to the vast number of permutations for interactions between supplements and medication, only a small number of combinations have been examined or reported. Much attention has been paid to the most common supplements and to the drugs

with narrow therapeutic indices (ie, ratio of upper-to-lower therapeutic concentrations or dose is small) and a potential for significant adverse effects.

Warfarin is the most commonly cited drug, and St John's wort is the most commonly cited supplement, in the way that grapefruit juice is the most commonly cited food involved in interactions with medication. Although not likely overstated, interactions with other supplements (or juices) have not been studied as closely yet in most cases. Natural health products that contain a combination of ingredients can possess internal interactions between those ingredients, which then may interact with a medication.⁴⁴ Interpretations of cases in which multi-ingredient supplement products are implicated are difficult to assign to any 1 ingredient in most cases.

Warfarin, an anticoagulant, is an example of a medication with a narrow therapeutic margin (ie, subtherapeutic and toxic effects can occur across a small range of drug dose or concentrations). Of patients seen in a warfarin anticoagulation clinic, 26% claimed to have used an herbal medicine the week before their appointment, with some products capable of enhancing or inhibiting the drug's effect, although no patient manifested obvious bleeding or a thromboembolic event.³⁰ Other narrow margin drugs include digoxin, phenytoin, and calcineurin inhibitors. Drugs with relatively small therapeutic windows like these are most likely to be involved in clinically relevant interactions with the introduction of supplementation. In the case of digoxin, other cardiac glycoside-like compounds have been found in a number of natural products of botanical origin.

Although often considered detrimental, not all interactions are associated with adverse outcomes. A number of supplements have been used to augment the effect of pharmaceuticals or reduce their toxicity. For example, coadministration of ascorbic acid with iron supplements may enhance iron absorption, especially in anemic patients and those with gastrectomy.^{45,46} Pyridoxine limits adverse nervous system effects of isoniazid, whereas riboflavin may reverse the lactic acidosis associated with nucleoside reverse transcriptase inhibitors.^{47,48} Folic acid supplementation minimizes fenofibrate-induced hyperhomocysteinemia and methotrexate-induced hematologic toxicity.^{49,50} Carnitine may offer benefit to patients with Alzheimer disease not responding well to donepezil or rivastigmine.⁵¹ Supplements that enhance drug efficacy or reduce toxicity are not always predictable in their effect, however, and only in rare instances could these combinations be recommended.

Integrating the use of supplements into current pharmacotherapeutic approaches to patient care must still take into account the issues of product safety, efficacy, and quality.^{1,11,52,53} This includes evaluation of their interaction potential with medication regimens, to which little attention has been paid until recently.¹⁸

Nature of the Evidence

The questions most commonly posed are whether a particular supplement can be initiated in a patient already receiving medication, or whether a particular supplement could be responsible for an observed change in drug response. Many of the documented and potential interactions may be relatively minor, but others can be serious and even life-threatening.¹⁸ Although space limitations in a review do not allow discussion of each reported interaction and the strength of association or causality, each documented report is considered as a comparable event.

The greatest limiting factor remains the quality or reliability of the existing evidence. A survey of the leading 44 dietary supplement manufacturers revealed that 10 report drug interactions to be an important issue, but only 2 allocate funds to study them.⁵⁴ Reviewing the most widely claimed interactions, <15% are well documented.¹⁵ Therefore, a distinction needs to be clearly drawn between documented interactions (see Tables 2 to 5) and potential interactions (see Tables 4 and 6).

Although some interactions between natural products and medications have been documented,

Table 2
Documented nutrient supplement-drug interactions

Nutrient ingredient	Drug	Comment
Ascorbic acid	Warfarin	↓ Drug effect
Calcium	Fluoroquinolones*	↓ Drug absorption
	Iron	↓ Drug absorption
	Levothyroxine	↓ Drug absorption
	Tetracyclines	↓ Drug absorption
	Zinc	↓ Drug absorption
Folic acid	Fenofibrate	No change in effect†
	Phenytoin	↓ Drug level
Iron	ACE-inhibitors‡	↓ Drug absorption
	Levodopa	↓ Drug absorption
	L-Dopa/carbidopa	↓ Drug absorption
	Methyldopa	↓ Drug absorption
	Mycophenolate	↓ Drug absorption
	Zinc	↓ Drug absorption
Magnesium	Digoxin	↓ Drug absorption
Minerals (divalent, trivalent)	Fluoroquinolones*	↓ Drug bioavailability
	Penicillamine	↓ Drug bioavailability
	Tetracyclines	↓ Drug absorption
Potassium	ACE Inhibitors‡	↑ Hyperkalemia risk
Pyridoxine (high dose)	Levodopa	↓ Drug effect
Vitamin E	Aspirin	↑ Drug effect
	Digoxin	↑ Drug bioavailability
	Warfarin	↑ Drug effect
Vitamin K	Warfarin	↓ Drug effect
Zinc	Fluoroquinolones*	↓ Drug absorption
	Tetracyclines	↓ Drug absorption

↓, Decreased; ↑, increased; INR, international normalized ratio.

*Ciprofloxacin, gatifloxacin, levofloxacin.

†Reduces drug-induced hyperhomocysteinemia.

‡Benazepril, captopril, enalapril, fosinopril, lisinopril, quinapril, ramipril.

Table 3
Documented herbal supplement–drug interactions

Herbal ingredient	Drug	Comment
Betel nut (<i>Areca catechu</i>)	Antipsychotics*	↑ Drug toxicity
Boldo (<i>Peumus boldus</i>)	Warfarin	↑ Drug effect
Capsicum (<i>Capsicum annuum</i>)	Theophylline	↑ Drug absorption
Danshen (<i>Salvia miltorrhiza</i>)	Warfarin	↑ Drug effect
Devil's claw (<i>Harpagophytum procumbens</i>)	Warfarin	↑ Drug effect
Dong quai (<i>Angelica sinensis</i>)	Warfarin	↑ Drug effect
Fenugreek (<i>Trigonella</i> sp.)	Warfarin	↑ Drug effect
Garlic (<i>Allium sativum</i>)	Protease inhibitors†	↓ Drug concentrations
	Warfarin	↑ Drug effect
Ginger (<i>Zingibar</i> sp)	Phenprocoumon	↑ Bleeding risk
Ginkgo (<i>Ginkgo biloba</i>)	Trazodone	↑ Drug effect
	Antiplatelet agents‡	↑ Bleeding risk
	Nifedipine	↑ Drug effect
	Omeprazole	↓ Drug effect
Ginseng (<i>Panax ginseng</i> , <i>P. quinquefolius</i>)	Warfarin	↓ Drug effect
	Phenelzine	↑ Drug effect
Green tea (<i>Camellia sinensis</i>)	Warfarin	↓ Drug effect
Kava (<i>Piper methysticum</i>)	Alprazolam	↑ Drug effect
	Levodopa	↓ Drug effect
	Spiroolactone	↓ Drug effect
	Indinavir	↓ Drug concentrations
	Warfarin	↑ Drug effect
Licorice (<i>Glycyrrhiza glabra</i>)	Lithium	↓ Drug levels
Milk thistle (<i>Silybum marianum</i>)	See Table 4	See Table 4
Papaya (<i>Carica papaya</i>)	Barbiturates	↑ Drug effect
Psyllium (<i>Plantago</i> spp)		
St. John's wort (<i>Hypericum perforatum</i>)		
Valerian (<i>Valeriana officinalis</i>)		

↓, Decreased; ↑, increased; INR, international normalized ratio.

*Fluphenazine.

†Amprenavir, indinavir, nelfinavir, ritonavir, saquinavir.

‡Aspirin, clopidogrel.

many other widely accepted interactions are theoretically based either on *in vitro* data or known pharmacology. The potential for an interaction

between several herbal products and warfarin, for example, although widely accepted has only been actually reported for a few.⁵⁵ With time, some of

Table 4
St John's wort–drug interactions

Documented interaction	Comment	Potential interaction	Comment
Alprazolam	↓ Drug effect	Amiodarone	↓ Drug level/effect
Amitriptyline	↓ Drug level/effect	Amsacrine	↓ Drug effect
Cyclosporine	↓ Drug level/effect	Carbamazepine	↓ Drug level/effect
Digoxin	↓ Drug level/effect	Diltiazem	↓ Drug level/effect
Imatinib	↓ Drug level	Etoposide	↓ Drug effect
Indinavir	↓ Drug level/effect	Omeprazole	↑ Photosensitivity
Irinotecan	↓ Drug level	Protease inhibitors	↓ Drug level/effect
Midazolam	↓ Drug level	Triptans	Serotonin syndrome
Nifedipine	↓ Drug level	Verapamil	↓ Drug level/effect
Oral contraceptives	↓ Drug effect	Other CYP3A4 substrate	↓ Drug level/effect
SSRIs*	Serotonin syndrome	Other P-gp substrate	↓ Drug level/effect
Simvastatin	↓ Drug level		
Tacrolimus	↓ Drug level/effect		
Talinolol†	↓ Drug level		
Theophylline	↓ Drug level		
Warfarin	↓ Drug effect		

↓, decreased; ↑, increased; SSRIs, selective serotonin reuptake inhibitors; P-gp, P-glycoprotein.

*Fluoxetine, paroxetine, sertraline.

†Not available in the United States.

Table 5
Documented other supplement-drug interactions

Other ingredient	Drug	Comment
Carnitine	Thyroid hormone	↓ Drug effect
Chondroitin	Warfarin	↑ Drug effect
CoEnzyme Q	Warfarin	↓ Drug effect
Fish oil	Warfarin	↑ Drug effect
	Antidepressants*	↑ Drug effect
Glucosamine†	Antidiabetics‡	↓ Drug effect
5-Hydroxy-tryptophan	Carbidopa	↑ Scleroderma risk
Ipriiflavone	Theophylline	↑ Drug effect
Melatonin	Nifedipine	↓ Drug effect
	Warfarin	↓ Drug effect
Pectin	Lovastatin	↓ Drug absorption
Policosanol	Aspirin	↑ Drug effect
S-Adenosyl-methionine	Clomipramine	Serotonin syndrome risk
Soy	Warfarin	↓ Drug effect
Tryptophan	MAO inhibitors§	↑ Drug effect
	Fluoxetine	↑ Drug effect

*Fluoxetine, paroxetine, sertraline.

†Based on an IV preparation, not an oral supplement.

‡Insulin.

§Isocarboxazid, phenelzine, tranylcypromine.

these well-founded potential interactions may come to be recognized clinically and documented in a patient case or prospective evaluation. The nature of the clinical evidence remains predominantly single case reports and case series, although formal investigations into interactions have begun. Of course, causality is hardly established through case reports, but it serves the purpose of selecting interactions to study prospectively. A longstanding theoretical interaction between ginger and anticoagulants was recently confirmed in a case report of a woman experiencing an elevated international normalized ratio (INR) and epistaxis with this combination.⁵⁶ By way of comparison, theoretical drug-drug interactions between prescription drugs can be confirmed in case reports even well after the drugs have been on the market.⁵⁷ The numbers of published case reports describing supplement-drug interactions outnumber clinical trials evaluating such interactions. The interactive effects on absorption and metabolism can be studied *in vitro*, but poor correlation between *in vitro* and *in vivo* findings regarding supplement-drug interactions can occur for a number of reasons.¹⁹ This includes poor bioavailability from the product, large interindividual variability in absorption of the active constituents, and interproduct or interlot variability of the active constituents. This frequent lack of correlation lessens the ability to accurately predict supplement-drug interactions from *in vitro* data.

Estimates are that at least 15 million adults in the United States are at risk for supplement-drug interactions.⁵⁸ An evaluation of 169 possible herb-drug interactions (13 natural health products, 13

drug classes) identified 39 pairs with potential for interaction. Of these, clinical evidence existed for only 31% of them, most of poor quality (ie, others remain theoretical).⁵⁹ Many natural products have the potential to interact with warfarin, whereas only a small number have been documented thus far.^{55,60}

Given the nature of the data, the incidence of clinically important supplement-drug interactions is not known. For an interaction to manifest clinically, factors beyond the interacting agents may be important (eg, age, genetics, nutritional status, organ function). This could explain the manifestation of an interaction in one patient but not another. For example, the elderly patient receiving warfarin is more likely to bleed at a lower INR than would a younger patient.⁶¹ The poor quality of many dietary-supplement products may also account for some of the variability in clinical manifestation. The quality of the reports themselves may be suspect. But armed with all of this, the reader can make use of the accompanying tables. These tables will need ongoing revision as the data grow in number and quality. Although most supplement-drug interactions have not been confirmed in prospective study, those reported in the literature from single cases to multiple case series are included as "documented" otherwise considered theoretical, even with *in vitro* evidence for enzyme induction/inhibition, until reported in a patient.

Mechanisms of Interaction

Interactions between natural health products (ie, dietary supplements) and medications can come about through both pharmacokinetic and pharmacodynamic mechanisms.⁶² Pharmacokinetic interactions occur because of altered oral drug absorption, induction or inhibition of drug metabolizing enzymes, altered drug protein binding, or altered drug excretion. Although each may play a role, most attention has been directed at drug transporters and metabolizing enzymes as a focal site for many interactions.

Drug-metabolizing enzymes (eg, cytochrome P450 enzymes [CYPs], uridine diphosphoglucuronyl transferases [UGTs], glutathione S-transferases) and drug transporters (P-glycoprotein, organic anion transporting polypeptides [OATPs]) are responsible for the disposition of a drug. These transport and enzyme proteins are widespread but are particularly found at the intestine and liver. Any substance (eg, natural product) may interact with a drug by altering any one or a combination of these systems to result in a clinical response other than expected. Knowledge of the sites of drug metabolism and transport (Table 7) is important to identifying mechanisms of interactions. For example, many of the common herbal ingredients can induce or inhibit the activity of the various CYP enzymes and may be more complex mechanistically than previously considered.⁶³ The CYP3A isoenzyme is responsible for

Table 6
Some other potential supplement-drug interactions from A to Z

Ingredient	Drug	Comment	
Alfalfa (<i>Medicago sativa</i>)	Anticoagulants	↓ Drug effect	
	Oral contraceptives	↓ Drug effect	
Aloe (<i>Aloe vera</i>)*	Antidiabetics	↑ Drug effect	
	Antiplatelet agents	↑ Drug effect	
	Digoxin	↑ Drug effect	
	Diuretics	↑ Hypokalemia	
	Antidiabetics	↑ Drug effect	
α-Lipoic acid	Warfarin	↑ Drug effect	
Angelica root (<i>Angelica</i> sp)	Warfarin	↑ Drug effect	
Arnica flower (<i>Arnica montana</i>)	Warfarin	↑ Drug effect	
Ascorbic acid	Cotrimoxazole	↑ Drug absorption	
	Disulfiram	↓ Drug effect	
	Estrogens	↑ Drug effect	
	Mexilitene	↓ Drug effect	
	Propranolol	↓ Drug absorption	
	Bilberry (<i>Vaccinium myrtillus</i>)	Anticoagulants	↑ Drug effect
		Antidiabetics	↑ Drug effect
	Black cohosh (<i>Cimicifuga racemosa</i>)	Antihypertensives	↑ Drug effect
		Digoxin	↑ Drug absorption
		Iron salts	↓ Drug absorption
Bromelain	Anticoagulants	↓ Drug effect	
	Antiplatelet agents	↑ Drug effect	
Calcium	Etidronate	↓ Drug absorption	
	Tamoxifen	↑ Hypercalcemia	
	Antiplaetlet agents	↑ Drug effect	
Capsicum (<i>Capsicum</i> sp)	Antiplaetlet agents	↑ Drug effect	
Cascara (<i>Rhamnus purshiana</i>)	Corticosteroids	↑ Hypokalemia	
	Digoxin	↑ Drug effect	
Cat's claw (<i>Uncaria tomentosa</i>)	Cyclosporine	↑ Drug effect	
	Protease inhibitors	↑ Drug effect	
Chamomile (<i>Matricaria chamomilla</i>)	Sedatives	↑ Drug effect	
	Simvastatin	↑ Drug effect	
	Warfarin	↑ Drug effect	
	Prolactin inhibitors	↓ Drug effect	
Chasteberry (<i>Vitex agnus-castus</i>)	Warfarin	↓ Drug effect	
Chlorella	Anticoagulants	↑ Drug effect	
Chondroitin	Anticoagulants	↑ Drug effect	
Chromium	Antidiabetics	↑ Drug effect	
Cocoa (<i>Theobroma cacao</i>)	Antidiabetics	↓ Drug effect	
Dandelion (<i>Taraxacum officinale</i>)	Antidiabetics	↑ Drug effect	
	Diuretics	↑ Drug effect	
	Lithium	↑ Drug levels	
	Antiplatelet agents	↑ Drug effect	
	Triazolam	↑ Drug effect	
Danshen (<i>Salvia bowelyana</i>)	Antiplatelet agents	↑ Drug effect	
Dehydroepiandrosterone, DHEA	Triazolam	↑ Drug effect	
Dong quai (<i>Angelica sinensis</i>)	Antiplatelet agents	↑ Drug effect	
Echinacea (<i>Echinacea</i> spp)	Immunomodulators	Altered drug effect	
	Protease inhibitors	↑ Drug effect	
Elder (<i>Sambucus nigra</i>)	Antidiabetics	↑ Drug effect	
Evening primrose (<i>Oenothera biennis</i>)	Anticoagulants	↑ Drug effect	
	Antiplatelet agents	↑ Drug effect	
	Phenothiazines	↑ Seizure risk	
	Fluoroquinolones	↓ Drug absorption	
	Antiplatelet agents	↑ Drug effect	
Fennel (<i>Foeniculum vulgare</i>)	Antiplatelet agents	↑ Drug effect	
Feverfew (<i>Tanacetum parthenium</i>)	Antidepressants	↑ Drug effect	
Fish oil	Antiplatelet agents	↑ Drug effect	
	Antipsychotics	↑ Drug effect	
Flaxseed (<i>Linum usitatissimum</i>)	Warfarin	↑ Drug effect	
Folic acid	Doxycycline	↓ Drug effect	
Garcinia (<i>Garcinia cambogia</i>)	Warfarin	↓ Drug effect	
Garlic (<i>Allium sativum</i>)	Anticoagulants	↑ Drug effect	
	Antidiabetics	↑ Drug effect	
	Antiplatelet agents	↑ Drug effect	
	Cyclosporine	↓ Drug effect	
	NNRTIs	↓ Drug effect	

(Continued)

Table 6 (Continued)

Ingredient	Drug	Comment
Germanium	Loop diuretics	↓ Drug effect
	Anticoagulants	↑ Drug effect
Ginger (<i>Zingiber officinale</i>)	Antiplatelet agents	↑ Drug effect
	Anticoagulants	↑ Drug effect
Ginkgo (<i>Ginkgo biloba</i>)	Antiepileptics	↓ Drug effect
	MAO inhibitors	↑ Drug effect
	Cyclosporine	↓ Drug absorption
	Calcium channel blocker	↓ Drug effect
	Anticoagulants	Altered drug effect
	Antidiabetics	↑ Drug effect
Ginseng (<i>Panax spp</i>)	Antiplatelet agents	↑ Drug effect
	Immunomodulators	Altered drug effect
	MAO inhibitors	↑ Drug effect
	Anticoagulants	↓ Drug effect
Goldenseal (<i>Hydrastis canadensis</i>)	Antihypertensives	↓ Drug effect
	Immunomodulators	Altered drug effect
	Anticoagulants	↑ Drug effect
Grape seed extract	Antiplatelet agents	↑ Drug effect
	CNS depressants	↑ Drug effect
Hawthorn (<i>Crataegus laevigata</i>)	Antiarrhythmics	Altered drug effect
	Digoxin	↑ Drug effect
Hydrazine	CNS depressants	↑ Drug effect
	Immunosuppressant	↑ Drug effect
	Clozapine	↑ Drug levels
	Haloperidol	↑ Drug levels
	Theophylline	↑ Drug levels
	Tacrine	↑ Drug levels
	Antidiabetics	↓ Drug effect
Juniper (<i>Juniperus communis</i>)	Diuretics	↑ Drug effect
	Lithium	↑ Drug levels
Kava (<i>Piper methysticum</i>)	Antiepileptics	↑ Drug effect
	CNS depressants	↑ Drug effect
Lemon balm (<i>Melissa officinalis</i>)	CNS depressants	↑ Drug effect
	Antihypertensives	↓ Drug effect
Licorice (<i>Glycyrrhiza glabra</i>)	Antiplatelet agents	↑ Drug effect
	Corticosteroids	↑ Drug effect
	Digoxin	↑ Drug effect
	Diuretics	↑ Hypokalemia
	Nitrofurantoin	↓ Drug absorption
	Warfarin	↓ Drug effect
	Antidepressants	↓ Drug effect
	CNS depressant	↑ Drug effect
	Immunomodulators	Altered drug effect
	CYP3A substrate	↑ Drug effect
Milk thistle (<i>Silybum marianum</i>)	Carbamazepine	↓ Drug effect
	Digoxin	↑ Drug effect
N-acetyl cysteine	Warfarin	↑ Drug effect
	CNS depressants	↑ Drug effect
Oleander (<i>Nerium oleander</i>)	Antiepileptics	↑ Drug effect
	Iron salts	↓ Drug absorption
Passionflower (<i>Passiflora incarnata</i>)	Neuroleptics	↑ Drug effect
	Anticoagulants	↑ Drug effect
Peppermint (<i>Mentha piperita</i>)	Digoxin	↓ Drug effect
	Warfarin	↑ Drug effect
Phenylalanine	CNS depressants	↑ Drug effect
	Antiepileptics	↑ Drug effect
Policosanol	Iron salts	↓ Drug absorption
	Neuroleptics	↑ Drug effect
Psyllium (<i>Plantago spp</i>)	Anticoagulants	↑ Drug effect
	Digoxin	↓ Drug effect
Pyridoxine (high dose)	Hydralazine	↓ Drug effect
	Isoniazid	↓ Drug effect
Quercetin	Digoxin	↑ Drug absorption
	Fluoroquinolones	↓ Drug effect
Red clover (<i>Trifolium pratense</i>)	Warfarin	↑ Drug effect
	Estrogens	Altered drug effect
Resveratrol	Antidiabetics	↓ Drug effect
	Antihypertensives	↓ Drug effect
Rosemary (<i>Rosmarinus officinalis</i>)	L-dopa/carbidopa	↓ Drug effect
	SSRIs	↑ Drug toxicity
S-Adenosyl-methionine	SSRIs	↑ Drug toxicity
	Triptans	↑ Drug effect

(Continued)

Table 6 (Continued)

Ingredient	Drug	Comment
St John's wort (<i>Hypericum perforatum</i>)	(See Table 4)	
Saw palmetto (<i>Serenoa repens</i>)	Hormone therapy	↓ Drug effect
Shark cartilage	Calcium	Hypercalcemia risk
Soy protein	Thyroid hormone	↓ Drug absorption
Tyrosine	L-dopa	↓ Drug effect
Uva ursi (<i>Arctostaphylos uva-ursi</i>)	Iron	↓ Drug absorption
Valerian (<i>Valeriana officinalis</i>)	CNS depressants	↑ Drug effect
	Antiepileptics	↑ Drug effect
Vitamin A	Isotretinoin	↑ Drug effect
	Valproic acid	↑ Drug effect
Vitamin D	Digoxin	↑ Drug effect
Vitamin E	Antidiabetics	↑ Drug effect
Willow (<i>Salix alba</i>)	Warfarin	↑ Drug effect
Xanthan gum	Antidiabetics	↑ Drug effect
Yohimbe (<i>Pausinystalia yohimbe</i>)	Antihypertensives	↓ Drug effect
	MAO inhibitors	↑ Hypertension
Zinc	Immunomodulators	Altered drug effect

↓, Decreased; ↑, increased; increased drug effect includes toxicity; CNS, central nervous system; MAO, monoamine oxidase; NNRTIs, nonnucleoside reverse transcriptase inhibitors; SSRIs, selective serotonin reuptake inhibitors.

*Based on oral use.

the oxidative metabolism of more than half of the currently used medication. P-glycoprotein, a product of the *MDR1* gene, is an efflux pump, able to export a wide range of substances across the cell membrane. At the intestinal tract, it serves to keep unwanted substances from being absorbed systemically by transporting them back toward the lumen and to local CYP enzymes. As p-glycoprotein structure and function are studied more closely, substrate interactions may become even clearer.⁶⁴ The supplement-drug interactions at these sites may be antagonistic or synergistic in their effect.⁶⁵ The effect of natural products on other enzyme systems and drug transporters is still not widely studied.

A supplement ingredient or combination may therefore interfere with any of the various steps

involved in absorption of a drug or in its metabolism. The effects of supplements on hepatic drug-metabolizing enzymes may need to take phenotype into account using accepted drug markers.⁶⁶ *In vitro* screening of enzyme inhibition or induction can be used to decide which natural products require further *in vivo* interaction studies. Using this method, the inhibitory effects of St John's wort, echinacea, valerian, and fish oil products on several CYP isoenzymes were confirmed.⁶⁷ Mechanistically, a large number of dietary supplement ingredients have the potential for toxicity and interaction with CYP activity.⁶⁸ Interactions demonstrated through *in vitro* study may not occur to the same degree *in vivo*, depending on the bioavailability and concentration achieved. Although *in vitro* data support an influ-

Table 7
Selected drug substrates of enzymes and transporters

CYP1A2	CYP2C9	CYP2C19	CYP2D6	CYP2E1	CYP3A	P-Glycoprotein	UGT	GST
Clozapine	Celecoxib	Amitriptyline	Amitriptyline	APAP	Alprazolam	Amiodarone	Ketoprofen	APAP
Mexiletine	Glyburide	Citalopram	Carvedilol	Dapsone	Amiodarone	Cyclosporine	Lamotrigine	Busulfan
Tacrine	Phenytoin	Diazepam	Citalopram	Enflurane	Amprenavir	Digoxin	Lorazepam	Valproic acid
Theophylline	S-Warfarin	Fluoxetine	Codeine		Amitriptyline	Diltiazem	Morphine	
Verapamil		Nelfinavir	Fluoxetine		Bosentan	Doxorubicin	Propofol	
		Omeprazole	Haloperidol		Buspiron	Loperamide	Zidovudine	
		Phenytoin	Metoprolol		Cyclosporine	Saquinavir		
		Sertraline	Nefazodone		Dapsone	Tacrolimus		
			Ondansetron		Erythromycin			
			Propranolol		Felodipine			
			Risperidone		Indinavir			
			Tramadol		Losartan			
					Lovastatin			

APAP, acetaminophen; CYP, cytochrome P450; GST, glutathione S-transferases; UGT, uridine diphosphate glucuronyl-transferases.

ence of enzyme inhibition or induction, the concentrations that can be achieved *in vivo* are critical to the likelihood of true interactions. For these pharmacokinetic interactions to be clinically significant they would ultimately have to decrease drug efficacy or increase drug toxicity, either of which needs to be recognized and addressed.

Pharmacodynamic interactions may result in additive, synergistic, or antagonistic effects of the supplement combination with a drug. Medication possessing antiplatelet activity, or with the potential for depressing the central nervous system, or with the potential to cause organ toxicity, could be of further risk when used with dietary supplements that share these pharmacologic activities.

Poor dietary supplement quality, including adulteration with drugs, could also play a role in the interaction potential between supplements and medication.^{1,9,53,69,70} Drug-drug interactions can often be predicted according to known characteristics of a drug's absorption, distribution, metabolism, excretion, or effect; however, this is less predictable for supplement-drug interactions.⁷¹ Less well-described characteristics of many supplement ingredients explain this poor predictability. Attempts at making these predictions in the absence of characteristic data result in lists of interactions of theoretical or potential concern (Table 6).

Influence of Nutrient Supplements on Medication

Individual vitamin and mineral supplements have the potential to alter drug absorption, metabolism, and effect, as do those containing peptides and amino acids (see Tables 2 and 6). Other substances included with nutrient ingredients may also play a role. The solubilizer Cremophor, known to inhibit the intestinal P-glycoprotein efflux pump *in vitro*, may be found in some vitamin products. This castor oil derivative was recently shown to increase the bioavailability of digoxin in humans as a result.⁷²

Vitamins

Ascorbic acid is noted to increase the absorption and overall bioavailability of the antimicrobial cotrimoxazole, not otherwise predicted by *in vitro* study.⁷³ It appears from a single-dose study that ascorbic acid supplementation of 2 g daily decreases the bioavailability of propranolol.⁷⁴ High doses of ascorbic acid can impair acetaminophen metabolism, although the clinical consequence is of minor significance unless using both agents chronically in the setting of impaired hepatic and renal function.⁷⁵ Discontinuation of daily ascorbic acid supplementation in a patient taking an oral contraceptive has been reported to cause heavy breakthrough bleeding suggesting decreased drug clearance with supplementation.^{76,77} Although 1 g of vitamin C may not be

problematic with warfarin, higher doses of ascorbic acid may interfere with the drug's anticoagulant activity when taken together.⁷⁸ Ascorbic acid can increase the chromosomal damage in peripheral blood lymphocytes induced by mitomycin-C *in vitro*.⁷⁹

Supplementation with folic acid in patients receiving phenytoin may increase the metabolism of the drug, leading to loss of seizure control.⁸⁰⁻⁸³ The activity of doxycycline appears to be inhibited by water-soluble vitamins, particularly folic acid, according to an *in vitro* study.⁸⁴

Supraphysiologic doses of the various vitamin E isoforms may play a role in drug interactions.⁸⁵ Even the formulation may make a difference. A water-soluble formulation of vitamin E increases the bioavailability of digoxin by inhibiting the activity of P-glycoprotein, although pharmacodynamics were not affected in the subjects studied.⁸⁶ Vitamin E reduces platelet aggregation, more so with mixed tocopherols than with α -tocopherol alone.⁸⁷ This may be additive to the clinical effects of antiplatelet (eg, aspirin) and anticoagulant (eg, warfarin) medication. Vitamin E may also potentiate the effect of insulin.

Warfarin's therapeutic effect is diminished by supplements containing vitamin K, even at a dose of 25 μ g in susceptible patients.⁸⁸ Although vitamin K intake can influence degree of anticoagulation in an individual patient, CYP2C9 genotype and age may have more to do with interpatient warfarin dose variability than does vitamin K.⁸⁹ For this reason, and because some level of vitamin K is still required in patients receiving warfarin chronically to prevent possible reductions in bone mineral density,⁹⁰ vitamin K intake is not contraindicated in anticoagulated patients. Maintaining consistent amounts is recommended while avoiding drastic changes in vitamin K intake. Discontinuation of a vitamin K-containing supplement in a patient stabilized on warfarin can result in significant elevations of the INR.⁹¹ Close patient monitoring and follow-up of INR values are required.

Multivitamin supplements did not enhance the immunologic response to influenza vaccine administration.³⁴ Supplementation with vitamin A to mothers and infants receiving oral polio vaccine had no effect on antibody responses.⁹²

Minerals

Iron supplements may interfere with the absorption of angiotensin-converting enzyme inhibitors by forming a complex within the gastrointestinal tract.⁹³ Iron was noted to significantly reduce the absorption of the immunosuppressant mycophenolate mofetil in one report but not in a controlled trial.^{36,94} Iron supplements were shown to impair intestinal absorption of a therapeutic dose of zinc, but not the absorption of a therapeutic dose of copper, in a group of subjects with an ileostomy.⁹⁵

Large doses of calcium supplements caused treatment failure as a result of drug malabsorption in a woman receiving levothyroxine for hypothyroidism.⁹⁶ Mineral supplementation (eg, calcium, iron, magnesium, zinc) can also interfere significantly with the oral absorption of quinolone antibiotics (eg, ciprofloxacin, gatifloxacin, levofloxacin, norfloxacin)⁹⁷⁻¹⁰⁰ and tetracyclines and possibly the bisphosphonates. Although multivalent ion-containing supplements interact with the fluoroquinolones, likely by chelation, when calcium supplementation is administered as part of a beverage (eg, orange juice), there may exist the added factor of competition for intestinal transport.^{97,101} Spacing mineral supplements at least 2-3 hours apart from medication may minimize these interactions.

Mineral supplementation may also increase the risk from drugs with the inherent potential to elevate mineral concentrations. Calcium supplementation may potentially increase the risk of hypercalcemia with the antiestrogen tamoxifen. Potassium supplementation, particularly in patients with poor renal function, increases the risk of hyperkalemia associated with the angiotensin-converting enzyme inhibitors.¹⁰²

Antioxidants

The use of nutrients that possess antioxidant activity by patients treated with chemotherapy as a way to decrease adverse drug effects can occur at the risk of diminishing therapeutic effect of the medication.¹⁰³ This important area remains understudied.^{104,105} The potential exists for micronutrient supplementation to either enhance or antagonize chemotherapeutic regimens, according to *in vitro* data, which is likely also a dose-related phenomenon. In a small group of patients with cancer receiving cisplatin chemotherapy, vitamin E supplementation appeared to decrease peripheral neurotoxicity.¹⁰⁶ The influence of antioxidants on medication goes beyond chemotherapy.

Antioxidant micronutrients (vitamin C, vitamin E, β -carotene, selenium) attenuated the beneficial effects on lipid profiles seen in patients with coronary disease treated with the simvastatin-niacin combination regimen.^{107,108} Specifically, the rise in HDL-cholesterol by the drug combination was blunted by the use of the nutrient supplements. The use of nutrient supplements in patients enrolled in clinical drug trials is often overlooked and may need to be evaluated for potential interactions. For example, in a trial testing finasteride's value in primary prostate cancer prevention, 44% of the participants used a multivitamin, 35% used single vitamin C or vitamin E supplements, and 10% to 15% used an antioxidant mixture or other single nutrient supplements on a regular basis.¹⁰⁹ One supplement intended for prostate cancer management contained surreptitious amounts of several drugs.^{110,111} Although supplement use may not interfere with

finasteride's disposition or effect and may even have additive or synergistic effects, this should be evaluated formally. Other drug trials in which patients may be expected to be using nutrient supplements will need to identify any potential interaction before full study enrollment. For example, the use of high-dose folic acid and vitamin B₁₂ did not impair the low-density lipoprotein (LDL)-cholesterol lowering effect of simvastatin ahead of a trial using this combination.¹¹² Repeated daily doses of vitamin C or vitamin E did not significantly influence the pharmacokinetics of linezolid, an antimicrobial with purported dependence on reactive oxygen species for its clearance.³⁵

Protein

The impact that individual amino acids or protein supplements may have on drug disposition and effect are not yet well described. Protein supplements may influence drug bioavailability and have the potential to increase drug metabolism.¹¹³ Any differences in the interaction potential that may exist between protein sources (eg, casein, soy, whey) are not well described. Some drugs may be substrate for intestinal peptide transporters (eg, angiotensin-converting enzyme inhibitors). An arginine salt of ibuprofen significantly decreased the time to analgesic effect compared with ibuprofen alone, with increased duration of effect.^{114,115} The effect may be just the result of enhanced solubility for the ibuprofen rather than altered transport. Specific amino acid supplements have the potential to compete with drugs that use the same group of transporters for absorption (eg, gabapentin, baclofen, methyl dopa, L-dopa). The same could be said for all medications that take advantage of nutrient specific transporters for their absorption.

Influence of Herbal Supplements on Medication

The addition of herbal products to a drug regimen has the potential to diminish or amplify the effect of a drug through pharmacodynamic means (Table 3 and 6). Altered drug pharmacokinetics by an herbal may also translate to interference with the expected drug response. Much has been described for St John's wort and a few other popular herbals and their impact on drug absorption, metabolism, and effect. A variety of herbal medicines is known to have an influence on drug-metabolizing enzymes. Depending on the active constituents of each, the result may be enzyme induction or enzyme inhibition.¹¹⁶ Inhibition or induction of CYP enzymes by some active constituents may approach the effects from the anti-infectives ketoconazole or rifampin, respectively.^{117,118} Occasionally, increased drug effect when combined with an herbal product may be accounted for by an indirect mechanism. For exam-

ple, herbal ingredients with diuretic or laxative effects could decrease serum potassium levels, which in turn increase the risk of digoxin toxicity.

St John's Wort

Although St John's wort's safety profile is otherwise promising, accumulated evidence points to the potential for significant interactions with medication.¹¹⁹ St John's wort can reduce the bioavailability of a number of drugs through increased activity of CYP3A4 and P-glycoprotein (Table 4).¹²⁰ At least 1 of the >2 dozen bioactive components of St John's wort is a potent ligand for the pregnane X receptor, a receptor in the cell nucleus that regulates the expression of CYP3A4.¹²¹ This activation was found to be comparable with an established CYP3A4 inducer. This indicates that caution should be used in the use of any medication metabolized by this enzyme. The ability of St John's wort to induce intestinal CYP3A4 and P-glycoprotein, reducing substrate bioavailability, was greater than the induction of hepatic CYP3A4.¹²² St John's wort may increase CYP3A4 activity to a greater extent in women than in men. The influence of St John's wort on drug-metabolizing enzymes was not recognized in an animal study evaluating several plant species over 20 years ago,¹²³ as it is now. The *in vitro* enzyme inhibition does not seem to extend to CYP1A2, CYP2C9, or CYP2D6.¹²⁴

In vitro data are not always predictive of *in vivo* effects. For example, pharmacokinetic interactions are based on CYP3A4, CYP1A2, and CYP2C9 induction by St John's wort, thereby increasing the clearance of drugs metabolized through these pathways.¹²⁵ The induction of CYP3A4 by St John's wort after only 2 weeks of use caused a significant increase in alprazolam clearance and would be expected to do the same for other CYP3A4 substrates.¹²⁶ Activity of CYP2D6 was not influenced in this study. St John's wort, by inducing CYP2C9 increases the clearance of warfarin, thereby decreasing its therapeutic effect. Seven days of use is likely to be a threshold for CYP and P-glycoprotein effects. Given the widespread use of this supplement ingredient, the limited number of reported interactions may be explained in part by the large number of products not meeting label claims for content.¹²⁷ Duration of use, and actual content of active constituents, determines the significance of an interaction with St John's wort.

Data generated from single-dose studies may differ from those obtained following multiple dosing. For example, St John's wort increased the bioavailability of fexofenadine after a single dose of each; however, with repeated dosing there was no apparent effect on the pharmacokinetics of the drug.¹²⁸ The influence of repeated doses on therapeutic effects of other drugs can be significant. The reduced bioavailability of oral contraceptives can lead to therapeutic failure of this form of contracep-

tion.^{129,130} Numerous reports exist describing the interference of St John's wort with cyclosporine and other immunosuppressant drugs, but not mycophenolate, in transplant patients, with rejection the unfortunate clinical consequence in several cases.¹³¹⁻¹³⁷ This effect becomes apparent by the third day of supplementation.¹³⁶ Clearance of the tyrosine kinase inhibitor imatinib was increased significantly after use of St John's wort as a result of CYP3A4 induction.¹³⁸ Increased P-glycoprotein activity likely explains the reduced bioavailability of digoxin after repeated doses with St John's wort.¹³⁹ Induction of CYP3A4 or P-glycoprotein results in significantly reduced drug levels of indinavir.¹⁴⁰ Extrapolation to other drugs in a class should be done carefully, however. For example, whereas a typical dose of St John's wort reduces bioavailability and plasma levels of simvastatin and its metabolite, it has no influence on pravastatin, which is metabolized by non-CYP pathways.^{141,142}

Pharmacodynamic interactions potentially resulting in the serotonin syndrome can occur when St John's wort is used with other serotonergic drugs. The interaction between St John's wort and the serotonergic antidepressants can occur as a result of additive serotonin effects and an inhibition of drug metabolism.¹⁴³ One of the constituents of St John's wort, hypericin, may antagonize the effects of the chemotherapeutic drugs etoposide and amsacrine at the level of topoisomerase II.¹⁴⁴ Additionally, a constituent of St John's wort is identified as a photosensitizing agent with the potential to cause more rapid epidermal erythema upon ultraviolet light exposure.²¹ When combined with other known photosensitizing medications, this risk from St John's wort can be increased.

Ginkgo

Ginkgo may significantly reduce the absorption of cyclosporine, possibly through an effect on intestinal CYP3A4 and P-glycoprotein.¹⁴⁵ Active constituents of ginkgo also have the potential to inhibit hepatic CYP3A4 activity *in vitro* in a dose-dependent fashion.¹⁴⁶ Ginkgo extracts can also increase the activity of CYP2C19, increasing the metabolism of omeprazole.¹⁴⁷ A ginkgo extract had no apparent effect on CYP2D6, however.¹⁴⁸ Interactions with ginkgo are also more likely caused by pharmacodynamic than pharmacokinetic mechanisms. Its inhibition of platelet activating factor increases the risk of bleeding in patients using anticoagulants or antiplatelet agents.^{149,150} Ginkgo may increase the effects of trazodone and nifedipine.^{151,152} Ginkgo may decrease the effect of antiepileptics, although this pharmacodynamic effect may be caused by contaminants.

Garlic

Garlic increases hepatic CYP3A4 expression *in vitro*.¹¹⁸ It is unlikely that garlic supplements sig-

nificantly induce (or inhibit) CYP3A4 or CYP2D6 *in vivo*, but this does not rule out an effect on other CYP isoenzymes, transferases, or an influence on P-glycoprotein activity.^{19,153} Garlic inhibits CYP2E1, which has fewer known substrate and no documented interactions to date. Garlic supplements reduced plasma saquinavir concentrations by about 50%, as studied in healthy volunteers after 21 days of garlic supplement intake.¹⁵⁴ Short-term administration of garlic supplements inconsistently decreased the bioavailability of another protease inhibitor, ritonavir, under single-dose conditions.¹⁵⁵ An interaction between garlic and warfarin is most likely pharmacodynamic in character, although inhibition of CYP remains a possibility.

Ginseng

Active constituents of ginseng do have the potential to induce or inhibit CYP3A4 activities in a dose-dependent fashion.^{118,146} But given the low concentration of ginsenosides after oral consumption, ginseng is unlikely to significantly influence CYP activity *in vivo*. It appears that ginseng (*Panax ginseng*) may interact with warfarin, the antidepressant phenelzine, and ethanol, although other product ingredients may be implicated.¹⁵⁶ Addition of ginseng to a regimen of warfarin in a patient with a mechanical heart valve led to loss of drug effect until the supplement was discontinued.¹⁵⁷ *Eleutheria* species differ from true ginseng species and seem not to alter CYP2D6 or CYP3A4 activities.¹⁵⁸

Kava

An *in vitro* study of kava extract and individual kavalactones indicates significant inhibition of CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, and CYP4A9/11 activity.¹⁵⁹ Kava's increased *in vitro* expression of hepatic CYP3A4 was also reported elsewhere.¹¹⁸ However, according to traditional use *in vivo*, kava extracts do have the potential to inhibit CYP1A2 but not CYP2D6, CYP2C19, CYP2E1, or CYP3A4 activity.¹⁶⁰ Aside from its potential role in hepatotoxicity, kava can cause drowsiness, which can be additive with other CNS-depressant drugs, including the benzodiazepines.¹⁶¹ Kava also has the potential to cause Parkinsonian symptoms, which would interfere with the efficacy of anti-Parkinson drug regimens used by a patient.¹⁶²

Milk Thistle

Milk thistle contains a group of active flavonoids referred to collectively as silymarin, the main constituent being silibinin. This latter compound has been shown to have variable inhibitory effects on individual human CYP isoenzymes, UGT1A6/9, and P-glycoprotein *in vitro*.¹⁶³⁻¹⁶⁵ The clinical significance of drug interactions following this inhibition remains to be determined, particularly for CYP3A4 and CYP2C9 substrates, the ones most likely to be

involved according to *in vivo* concentrations. The unchanged or slightly reduced (rather than increased) concentrations of the protease inhibitor indinavir when associated with milk thistle use were therefore unexpected according to these findings.¹⁶⁶

Echinacea

According to *in vitro* data, echinacea appears to inhibit CYP1A2 activity and CYP3A activity at the intestine, thereby increasing oral drug bioavailability.¹⁶⁷ But according to *in vivo* data, echinacea can actually induce hepatic CYP3A activity, causing increased systemic drug clearance.¹⁶⁸ There are as yet no documented interactions with any medication serving as substrates for these enzymes.

Other Herbs

Herbal products from mineral-rich plants (eg, *Sanguisorba officinalis*) have the same potential to interact with the fluoroquinolones as discussed earlier.¹⁶⁹ An extract from the angelic root may inhibit hepatic CYP activity and would be expected to influence drugs whose clearance is dependent on intrinsic hepatic clearance.¹⁷⁰ A compound herbal product, Wu-chu-yu-tang, includes *Evodiae fructus*, which may increase CYP1A2 activity and the metabolism of drugs that are substrates for this enzyme.¹⁷¹ Black cohosh exhibits significant inhibition of P-glycoprotein, arresting the transport of digoxin in an *in vitro* model.¹⁷² Feverfew and valerian can alter digoxin transport as well, but to a lesser degree. Cat's claw and goldenseal may inhibit CYP3A4 activity, thereby potentially influencing the bioavailability and effect of the many drug substrates of this enzyme. Other potential interactions based on animal data include citrus herbs significantly increasing cyclosporine bioavailability, likely through inhibition of intestinal P-glycoprotein.^{173,174} Green tea extracts, although not altering CYP3A4 activity, may induce UGT1A1 activity, which could potentially increase the clearance of the active metabolite of the chemotherapeutic drug irinotecan.¹⁷⁵ Licorice (*Glycyrrhiza glabra*) roots or an active constituent extracted from it (glycyrrhizin) may activate hepatic glucuronidation enzymes (UGT1 family) involved in the metabolism of several drugs.¹⁷⁶ No clinical data are as yet available describing such an interaction, which could be beneficial in clearing toxins. These potential interactions need to be evaluated in clinical studies.

The herbal preparation PC-SPES may interfere with the effectiveness of microtubule-modulating drugs, including paclitaxel used in prostate cancer.¹⁷⁷ Dong quai may contain photosensitizers, increasing the potential risk of drug-induced phototoxicity. Herbal products containing ingredients with diuretic properties (eg, horsetail, juniper, parsley, uva ursi) may increase the risk of toxicity from lithium, a mood stabilizer. A renal transplant

patient receiving cyclosporine therapy developed rhabdomyolysis after consuming a monacolin-containing ("statin-like") herbal product.¹⁷⁸

Additive, Synergistic, or Antagonistic Effects

Patients receiving warfarin should avoid use of supplements that can themselves increase the risk of bleeding or the risk of thrombosis. A 61-year-old man maintained on warfarin developed gum bleeding, epistaxis, and skin bruising, with an INR >6 after consumption of quilinggao, a combination Chinese herbal product, that includes constituents with antiplatelet or antithrombotic activity.¹⁷⁹ Another herbal formula containing six herbs, Kangen-Karyu, appears to possess antithrombotic activity that may be synergistic with warfarin, although there is no documented pharmacokinetic interaction with warfarin.¹⁸⁰ Herbals with anticoagulant properties can be additive to medications with the same actions. Additive anticoagulant effects could occur with coumarin-containing plants, including sweet melilot and sweet woodruff, despite the fact that coumarin is only a weak anticoagulant unless converted to dicoumarol in improperly stored products. Additive effects with warfarin can also include salicylate-containing herbals, including willow bark and meadowsweet. Warfarin's pharmacologic effect can also be enhanced by dong quai or fenugreek, whereas danshen decreases warfarin clearance, but all may result in an increased INR and place the patient at risk for bleeding.^{181,182} Conversely, a variety of plants contain vitamin K, which could antagonize the effect of warfarin. Green tea is such an herbal product; however, there is a potential that warfarin absorption may become altered as a result of other ingredients in this herbal product. Profound anticoagulation was reported in a patient consuming danshen with warfarin after mitral valve replacement and in another with rheumatic heart disease.^{183,184} According to animal data, both *R*- and *S*-warfarin plasma concentrations at steady state are increased significantly after danshen administration as a result of decreased volume of distribution and clearance.¹⁸⁵

Additive effects between an herbal product and a prescribed drug can extend to end-organ toxicity, as well. A number of herbal medicines associated with dose-related or idiosyncratic hepatotoxicity (eg, chaparral, comfrey, germander, kava, ma huang, pennyroyal, spirulina) still appear in supplement products. The pyrrolizidine alkaloids are found across a number of plant species and can account for much of the hepatotoxicity. A report of patients requiring liver transplantation for fulminant hepatic failure determined that 50% were associated with herbal exposure.¹⁸⁶ The possibility exists that, in combination with patented medicines having their own inherent risk for hepatic toxicity, the risk would be increased.¹⁸⁷

Influence of Other Supplements on Medication

There is currently much less information available to describe the impact of the nonnutrient/nonherbal dietary supplement ingredients on drug disposition and effect. Reports that describe supplement use in patients presumably using prescribed medication rarely evaluate interactions. According to what little is known about the mechanisms and pharmacologic effects of these supplement ingredients, a number of potential interactions can be ascribed to some of the more commonly used products in this group (Tables 5 and 6). Clearly, much remains to be studied about drug interactions with these supplements. As more is learned, expanded tables can be expected. Although several ingredients listed in this somewhat arbitrary category can be found in the normal diet, they are not officially recognized as nutrients.

Fiber

The use of fiber-containing supplements can reduce the bioavailability of some drugs as the result of dose-dependent but usually nonspecific adsorption of drug to the fiber. In the case of levothyroxine, this requires much higher drug doses to overcome the interaction.¹⁸⁸ The interaction may vary, depending on the fiber source, although this has not been closely examined. For example, pectin may reduce absorption of lovastatin, a lipid-lowering drug.¹⁸⁹ The mechanism may be more complex than just adsorption in the case of flaxseed-containing supplements. Although not a fiber, activated charcoal found in a dietary supplement product also reduced drug bioavailability by adsorption.¹⁹⁰

Phytochemicals

Polyphenolic phytochemicals (ie, phenolic acids, flavonoids, lignans, stilbenes) are widespread in the food supply and as constituents of many herbs. But as isolated ingredients, they have been included in dietary supplement products, and on their own each constitutes a nonnutrient/nonherbal ingredient. Many polyphenols are metabolized or transported through the same mechanisms as medications. Although not documented yet clinically, polyphenols could influence the bioavailability of therapeutic drugs when consumed in adequate quantities.¹⁹¹ A number of flavonoids (eg, quercetin, luteolin, galangin, kaempferol) have the potential to interact with medications according to their *in vitro* inhibition of enzymes and transporters at physiologic levels.^{165,192} Compounds from the flavonol family of flavonoids (eg, quercetin, kaempferol, catechin) that may be contained in dietary supplements may interfere with absorption of copper and iron by decreasing the levels of metallothionein at intestinal cells.¹⁹³ According to an animal model, administration of pharmacologic doses of quercetin signifi-

cantly increased the bioavailability of digoxin, likely as a result of interfering with P-glycoprotein, with the potential for toxicity of this narrow indexed drug.¹⁹⁴ Quercetin may also induce CYP3A4, likely through mechanisms other than the pregnane X receptor.¹¹⁸ Grape seed extract can also increase CYP3A4 expression *in vitro*.¹¹⁸ UGT enzymes may be inhibited or induced by polyphenols as well. Bioflavonoids (as found in fruit juices) are inhibitors of intestinal OATP, thereby reducing the bioavailability of that transporter's substrates (eg, fexofenadine).

Soy Isolates

The supplementation of a soy beverage resulted in subtherapeutic INR in a 70-year-old man otherwise stable on warfarin therapy, which returned to therapeutic levels within 2 weeks of discontinuing the soy product.¹⁹⁵ The exact mechanism remains to be determined, but may include effects on drug absorption through P-glycoprotein and OATP, or drug clearance. Soy extracts containing isoflavones (daidzein, genistein) seem to have no effect on CYP3A activity in healthy subjects.¹⁹⁶ The semisynthetic soy derivative ipriflavone may inhibit CYP1A2 and CYP2C9 activity.¹⁹⁷ Unlike soy extracts, this derivative would be expected to increase warfarin's effect by reducing drug metabolism. Genistein increased the level of metallothionein, and daidzein supplementation may inhibit CYP1A2 activity and the metabolism of theophylline, resulting in greater drug exposure at a given dose.¹⁹⁸

Other

Glucosamine may theoretically decrease sensitivity to insulin and oral antidiabetic agents but was not seen when administered at common doses in a group of diabetic patients.¹⁹⁹ Chondroitin may increase the effect of anticoagulants and has only recently been documented in a patient receiving warfarin using high doses of a combination glucosamine-chondroitin product.²⁰⁰

Melatonin has potentially additive effects with central nervous system depressants and potential interference with immunosuppressive therapy. S-adenosyl-methionine has potential additive activity with antidepressants, triptans, anticoagulants, and antiplatelet agents. Large loading doses of creatine have the potential to increase the nephrotoxicity of other medications, although not documented clinically.

The hormone dehydroepiandrosterone (DHEA), marketed as a dietary supplement, had no apparent effect on prednisone pharmacokinetics in a small group of healthy women.²⁰¹ However, DHEA did decrease the metabolism of the benzodiazepine triazolam to variable extent, likely according to interindividual CYP concentrations.²⁰² This hormone is a

substrate of OATP and could potentially interact with drugs transported by this mechanism (eg, β -lactam antibiotics, methotrexate, pravastatin).

Carnitine can be transported by the organic cation transporting polypeptides, which are also responsible for drug transport (eg, procainamide, quinidine, valproic acid). Carnitine may decrease the effect of thyroxine.²⁰³ Although no drug interactions have been reported with pyruvate, as a substrate for the monocarboxylate transporter it could be evaluated with drug substrate for this transporter (eg, atorvastatin, valproic acid).

The interaction that occurs between coenzyme Q10 and warfarin to interfere with the anticoagulant effects of the drug is most likely the result of the structural similarity between the supplement ingredient and vitamin K.

The addition of fish oil supplements to the regimen of patients using warfarin for anticoagulation may increase the INR beyond the therapeutic range.²⁰⁴ Eicosapentaenoic acid supplementation may augment the effect of antidepressant medication in patients with unipolar depressive disorders and antipsychotic medication in patients with schizophrenia.^{205–207} Supplementation with plant stanols and sterols has not been closely evaluated for potential interference with the absorption and therapeutic effect of medication (eg, cyclosporine).²⁰⁸

The influence of prebiotics (eg, fructo-oligosaccharide) or probiotics has not been adequately studied either. However, there is a suggestion based on an *in vitro* study that the probiotic *Lactobacillus casei* increases activity of the human small intestinal oligopeptide transporter, hPEPT1, that also serves as a transporter for a number of drugs (eg, angiotensin-converting enzyme inhibitors, β -lactam antibiotics).²⁰⁹ The potential for interaction between probiotics and antibiotics also begs for closer evaluation.

Virtually no data are available on drug interactions with many of the other more popular nonnutrient/nonherbal natural products, including α -lipoic acid, dimethylsulfone (MSM), shark cartilage, or individual carotenoids (eg, lutein, lycopene).

Summary

Dietary supplements generally have the potential to interact with prescribed medication and can put individual patients at great risk.^{15,18} Our knowledge of specific effects on drug absorption, metabolism, and effect is still incomplete. A paucity of case reports and especially prospective studies evaluating interaction potential is evident. A more comprehensive and validated list of documented interactions between dietary supplements and medications than that listed here will need significant, high-quality research attention.^{59,210} Individual supplement products or ingredients may be added to or removed from these tables as more data accumulate.

Beyond the potential risks involved from a true supplement-drug interaction is the realization that many may present in practice but go unrecognized, unacknowledged, or undocumented. They may be mistaken for signs of inadequate therapeutic dosing or inherent drug toxicity. A clinically significant interaction between a supplement ingredient or product and a medication can be reported to the FDA's MedWatch program (go to <http://www.fda.gov/medwatch/report/hcp.htm>). Interactions should be reported as a means of sharing the information with other health care providers. Several clinical management options exist for patients receiving a supplement-drug combination with a clinically relevant interaction. This includes discontinuing one of the agents, adjusting doses or administration schedules to minimize the interaction, or switching to another drug in the same therapeutic category that has been shown not to interact with the supplement.

Until now, drug-drug interactions have been more widely recognized and may be more likely associated with adverse effects, including fatal events; however, the story of supplement-drug interactions is still being written.

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