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ProCE, Inc.
848 W. Bartlett Road
Suite 9E
Bartlett, IL 60103
www.ProCE.com

Herbal-Drug Interactions

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Mary L. Chavez, Pharm.D.

Professor

Department of Pharmacy Practice

Midwestern University

College of Pharmacy-Glendale

Glendale, Arizona

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LEARNING OBJECTIVES

1. Describe the prevalence and nature of herbal-drug interactions.
2. List factors that can complicate the determination of actual herbal-drug interactions.
3. Describe the role of pharmacodynamics in herbal-drug interactions.
4. Describe the role of cytochrome P-450 and P-glycoproteins in pharmacokinetic herbal-drug interactions.
5. Recognize herbal-drug interactions that may occur with warfarin and with medications that treat diabetes.
6. Recognize drugs that may interact with St. John's wort.

ABSTRACT: The general public's use of herbals has increased over the past 10 years. Aside from the need to appraise these products for safety and efficacy, health care providers and the public need to know whether interactions might occur when these products are used in combination with conventional drugs. Most of the current evidence concerning interactions between natural products and drugs is based on known or suspected pharmacologic activity,

data derived from in vitro studies, or anecdotal case reports that frequently lack pertinent information. The relevance of such information in terms of severity and outcome is questionable. More recently, there have been some reliable, documented case reports, in vivo studies, and clinical trials that have evaluated herbal-drug interactions. Results have sometimes been contradictory, and much more research is needed. The purpose of this article is to provide an evidence-based discussion and information to educate patients about potential herbal-drug interactions.

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INTRODUCTION

Use of complementary and alternative medicine (CAM) in the United States (U.S.) has risen over the last 10 years.^{1,2} Indeed, the dietary supplement industry is currently estimated to be a \$20 billion industry, and according to data from the U.S. Food and Drug Administration (FDA), there were 29,000 dietary supplements on the market in 2004. In 2002, the U.S. Department of Health and Human Services (DHHS) conducted a National Health Interview Survey (NHIS). The results estimated that approximately 62% of U.S. adults over 18 years of age use some type of CAM,

including mind-body therapies (e.g., yoga, meditation, prayer), alternative medicine (e.g., acupuncture, chiropractic care, folk medicine), and biologically based therapies (herbals and other dietary supplements). Reasons cited by users of CAM are presented in Table 1.²

Not only has the prevalence of use of natural medicine increased, but the pattern of use has also changed. Self-directed herbal use increased by 10% between 1997 and 2002.³ Of concern, researchers estimated that 18% of patients who took prescription medications in 1997 also used herbal products or high-dose multivitamins. As a result, an estimated 15 million adults were at risk for dietary supplement drug interactions. Studies have also found that less than 40% of users of CAM disclose use to their physician.⁴ This is despite the frequent reports in the lay and medical literature about the potential adverse effects and herbal-drug interactions associated with use. Perhaps many users are not aware that dietary supplements are marketed without documentation of safety and efficacy.

Currently, herbal products are regulated by the Dietary Supplement Health and Education Act (DSHEA) of 1994.⁵ Under DSHEA, herbal products and other dietary supplements (including vitamins, minerals, amino acids, enzymes, and organ tissues) are not regulated by the FDA as conventional prescription or over-the-counter medications or as food additives. Accordingly, the FDA has the burden of proving that a supplement is harmful rather than requiring that the manufacturer prove that the supplement is safe or effective. In addition, manufacturers are responsible for labeling of dietary supplements. Under the DSHEA, any claim that a supplement can prevent, treat, or cure a specific disease, as well as information

regarding herbal-drug interactions is prohibited on the label.^{5,6}

Currently, manufacturers of dietary supplements are not required to follow good manufacturing practices (GMPs) for drugs, but are required to abide by the regulations of GMPs for food. The FDA is currently finalizing its rule for GMPs specific for dietary supplements.⁶ Testing of the quality of more than 1,200 dietary supplement products by the independent laboratory www.ConsumerLab.com found that one in 4 products lacked the labeled ingredients or had other serious problems, such as unlisted ingredients or contaminants.⁷ This creates a problem when evaluating the validity of herbal-drug interactions. Contaminants or undisclosed pharmaceuticals may actually be responsible for suspected herbal-drug interactions.

Determination of Herbal-Drug Interactions

Recent research estimates 50% of adult Americans use at least one prescription medication and 7% of adult Americans take 5 or more prescription drugs. Among prescription drug users, 16% also take herbal supplements;⁸ however, the prevalence of clinically significant interactions between herbals and medications is unknown. A factor that may account for the lack of data on the true prevalence of herbal-drug interactions is that information needed to determine whether an interaction has occurred is often unavailable owing to the following:

1. A lack of information concerning the “contents” of the herbal product
2. Incomplete or inaccurate product information
3. Multiple ingredients

Additionally, patients may not inform health care providers of suspected interactions, or they do not attribute the reaction to the natural product.

The FDA maintains the MedWatch system for reporting adverse events, including those for both conventional drugs and dietary supplements. A total of 320,860 adverse events were reported to the system in 2002.⁹ This number included adverse events secondary to interactions. The data, however, did not separate drug versus herbal interactions. In another report published by the DHHS, investigators estimated that less than 1% of all dietary supplement—related drug interactions are reported to the FDA.¹⁰ The report cites several limitations to the adverse event reporting system, including limited availability of medical records for the reported adverse events, lack of product ingredient information for the substances involved in the adverse event, and limited information on the product by the manufacturers.¹⁰ The lack of available clinical data for many herbal products also serves as a barrier for post-marketing safety assessment of herbal products.

The Nature of Herbal-Drug Interactions

Most natural products, unlike conventional drugs, are a complex mixture of chemical constituents. Often a complete characterization of the bioactive compounds from an herbal is unknown. Additionally, the chemical makeup of natural products varies depending on the part of the plant used (bark, stems, leaves, roots, rhizomes), climate, growing conditions, harvesting, and storage conditions. Combination products composed of multiple natural products complicate matters further.

Not only does the complex nature of a natural product complicate the determination of herb-drug interactions, but also the

manufacturing process (e.g., drying process and extraction methods) contributes to the overall complexity. As previously mentioned, because herbal products are not regulated by the FDA, there are no standards for herbal products. Indeed, herbal products have been found to be misidentified and/or substituted or adulterated with other natural products or unwanted substances.¹⁰ Recently, the FDA issued a warrant for the seizure of imported ginseng slated for the manufacture of dietary supplements attributable to contamination by pesticides.¹¹

Misidentification can occur when inexperienced harvesters choose the incorrect plant. As an example, a number of European women developed severe nephrotoxicity after consuming a Chinese weight-loss product that contained *Aristolochia fangchi*, which was probably inappropriately substituted for the anticipated *Stephania tetrandia*. The mistake may have occurred because of confusion with the Chinese names for the 2 plants (*Guang fang ji* and *Han fang ji*, respectively).¹² The FDA responded by issuing warnings and a recall of all supplements containing aristolochic acid.¹³

Another important limiting factor concerning herbal-drug interactions is the reliability of the existing evidence. A survey of 44 of the leading dietary supplement manufacturers revealed that only 10 of 15 respondents considered interactions to be an important issue, and only 2 allocated funds to study herbal-drug interactions.¹⁴ A systematic review of published case reports, case series, or clinical trials of herb-drug interactions found that only 13% were well documented using a 10-point scoring system that assessed interaction probability developed by Fugh-Berman and Ernst.¹⁵

The efficacy, safety, and quality of dietary supplements have been the concern of several organizations. The United States Pharmacopoeia and National Formulary (USP-NF) has developed official public monographs for nutritional and dietary supplements, and has also launched the Dietary Supplement Verification Program (DSVP).¹⁶ Under DSVP, dietary supplements are evaluated by the USP according to stringent manufacturing practices. If the product meets the DSVP standards, it will be granted the DSVP certification mark. The DSVP certification mark signifies the product contains the ingredients that are listed on the label in the declared amounts and strengths, that the product is manufactured under GMPs according to the USP-NF, that the product meets stringent standards of purity, and that the product meets specified limits of contaminants. The DSVP certification mark is not intended to imply safety or efficacy of dietary supplement ingredients, but should help to assure consumers, health care professionals, and supplement retailers that the product was manufactured under GMPs for purity and has been tested for potential contaminants and accuracy of ingredient labeling.¹⁶ A list of USP-Verified Dietary Supplements is available at the USP Web site <http://www.usp.org/USPVerified/>.

Although many herbal-drug interactions are likely to be negative in nature, it is important to realize that some interactions may have a beneficial effect on drug therapy. For example, “statin” drugs decrease the biosynthesis of endogenous coenzyme Q10, and adverse effects owing to statin therapy may be secondary to the decrease in tissue levels of coenzyme Q10.^{17,18} Thus, supplementation with coenzyme Q10 by patients on statin therapy may help prevent adverse effects. Another example is the use of silymarin (milk thistle

extract) for prevention of drug-induced hepatotoxicity. Researchers have found that 800 mg daily of silymarin was associated with a significant decrease in malondialdehyde (a polyunsaturated fatty acid oxidation product) and improvement in liver function tests in women who were receiving long-term phenothiazine or buyrophenone therapy.¹⁹ Dietary supplements that enhance drug efficacy or reduce adverse effects are not always predictable and, therefore, only in rare instances can the use of these types of combinations be recommended.²⁰

Evidence for Herbal-Drug Interactions

Data from the NHIS based on 31,044 U.S. adults over 18 years of age, found that 19% used natural products in 2002.² The top dietary supplement used in 2002 is presented in Table 2. Few clinical studies exist concerning herbal-drug interactions with these dietary supplements. The evidence of interactions among such commonly used dietary supplements is often based on presumed pharmacologic activity, data derived from in vitro or animal studies, or anecdotal single case reports and case series. Therefore, there is limited information to guide clinical decision making and to inform patients of safety issues related to herbal-drug interactions.

Mechanisms of Herbal-Drug Interactions

Interactions between herbals and medications can be caused by either pharmacodynamic or pharmacokinetic mechanisms. Pharmacodynamic interactions can occur when an herbal product produces additive, synergistic, or antagonist activity in relation to the conventional drug with no change in the plasma concentration of either herbal product or drug.²⁰ Pharmacodynamic interactions are related to the pharmacologic activity of the interacting agents and can

affect organ systems, receptor sites, or enzymes. A pharmacodynamic interaction may occur when herbals that possess antiplatelet activity are administered with antiplatelet/anticoagulant drugs, thus increasing the risk for bleeding. Other examples are when herbals that depress the central nervous system (CNS), such as kava, are administered with CNS depressant drugs or when herbals that may lower blood glucose are given with antidiabetic drugs. An example of an antagonistic interaction is when an herbal with high caffeine content, such as guarana, is administered with a sedative-hypnotic. In addition, herbals with the potential to cause organ toxicity may cause further risk of toxicity when drugs with similar toxicity are administered concurrently, such as when the hepatotoxic herbal comfrey is given with large and prolonged doses of acetaminophen.²¹

Pharmacokinetic interactions occur when an herbal changes the absorption, distribution, metabolism, protein binding, or excretion of a drug that results in altered levels of the drug or its metabolites. Most of the current evidence of pharmacokinetic drug interactions involves metabolizing enzymes and drug transporters.²⁰ Although drug interactions can involve enzymes such as glutathione S-transferases and uridine diphosphoglucuronyl transferases (UGTs), most herbal-drug interactions are related to oxidative metabolism by the cytochrome P-450 system (CYP) or by the effect of a herbal on the efflux drug transporter P-glycoprotein.²⁰

The CYP system is a family of monooxygenase enzymes that are mainly found in intestinal and liver cells and catalyzes several Phase I metabolic processes, including oxidation, hydroxylation, S- and O-demethylation, and oxidative deamination of more than 70% of

prescription drugs.²² The CYP isoenzymes, which have been found to be involved in significant pharmacokinetic reactions in humans, include CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4. More than half of all medications undergo metabolism by CYP3A4 substrates.²⁰ Because some herbals and various drugs may be substrates of the same CYP isoenzyme, either product may inhibit or induce the activity of the CYP isoenzyme when ingested concomitantly.²³

The P-glycoprotein drug transporter is a glycoprotein encoded by the MDR1 gene and functions as a transmembrane efflux transporter that pumps drugs out of cells.²⁴ P-glycoproteins are found in many tissues and especially in organs responsible for drug absorption or elimination, such as the intestine, liver, and kidneys.²⁵ In the intestinal tract, as drug molecules attempt to pass from the lumen through the intestinal wall to the portal blood system, P-glycoproteins can transport the molecule back toward the lumen and toward the local CYP enzymes. Drugs can then be eliminated from the body. Thus, P-glycoprotein-mediated drug efflux has the effect of limiting the rate and extent of drug absorption from the intestinal tract. Drugs that are substrates of CYP3A4 often affect P-glycoproteins as well.²⁶

Table 3 lists some common CYP450 and P-glycoprotein substrates. In vitro screenings for potential inhibition or induction of CYP enzymes by various herbals are being conducted.²³ In addition, in vitro models are used to evaluate the effect of herbals on particular transporter systems, including the P-glycoprotein MDR1-encoded transporter. St. John's wort affects both the MDR1-encoded transporter and CYP3A4 enzymes.²³

Various in vitro assay methods for determining whether an herbal affects metabolic enzymes or drug transporters are used. These assays generally use subcellular fractions of human liver tissues, whole-cell models of isolated human hepatocytes, liver slices, or human cancer cell lines.²⁹ Changes in the activity or concentration of enzymes or transporters can be demonstrated through use of selective chemical inhibitors of specific CYP enzymes or transporter systems. In vitro assays, however, do not necessarily correlate with in vivo and human metabolism. Further in vivo studies and clinical investigations are needed to validate in vitro herbal-drug interactions.

Absorption of drugs can be impaired when herbs that contain hydrocolloidal fibers, gums, and mucilage are taken together. Such herbals include aloe gel, flaxseed, marshmallow, psyllium, and rhubarb.³⁰ These herbals can bind to drugs that can prevent absorption and, subsequently, reduce systemic availability. As an example, psyllium can inhibit the absorption of lithium, and there are case reports of reduced lithium serum concentrations when lithium was taken concurrently with psyllium.³⁰ Likewise, herbal laxatives such as aloe latex, buckthorn, cascara sagrada, rhubarb, and senna can cause loss of fluids and potassium and can potentially increase the risk of toxicity with digoxin.^{21,31,32}

Potential pharmacokinetic interactions can occur with displacement of a drug from protein binding sites. Drug displacement of highly protein-bound drugs by another compound may result in increased activity of the displaced drug. Although displacement of protein-bound drugs has been described as a source for potential drug interactions, there are no documented reports of herbal-drug interactions

attributable to displacement of drugs from protein-binding sites.²³

Change in renal clearance of a drug is another potential mechanism for producing herbal-drug interactions. Herbals that can inhibit tubular uptake or in other ways that can interfere with the renal clearance of a drug should be considered as having potential to produce pharmacokinetic herbal-drug interactions.²³

Making decisions on whether an herbal-drug interaction occurs based on data from in vitro or animal test models is inadequate. Results from these models need to be further evaluated using well conducted clinical trials to validate the clinical significance. Even still, the reliability of clinical studies must also be assessed. Researchers investigated the extent in which published, randomized controlled trials assessed the content of the herbal supplements used in the studies.³³ They found that only 12 (15%) of 81 studies reported performing tests to quantify actual contents. The results from many of these controlled trials may have been of little value, since the identity, purity, quality, strength, and composition of the supplements were not confirmed.

Risk for Herbal-Drug Interactions

The risk of having an herbal-drug interaction is based on a variety of factors and not solely based on the pharmacologic and pharmacokinetic characteristics of the herbal. One important factor that increases the likelihood of having an herbal-drug interaction is concomitant use of an herbal with drugs that have a narrow therapeutic index. Such drugs include digoxin, antiepileptic drugs, antineoplastic agents, immunosuppressants, and warfarin.³⁴ Patient populations who are at increased risk for having herbal-drug interactions include the elderly, critical care patients, patients

undergoing surgical procedures, patients with liver or renal disease, and patients receiving multiple medications.

Documented Herbal-Drug Interactions

As previously addressed, most herbal-drug interactions are theoretical or are based on suspected pharmacologic activity or in vitro data. Although it is commonly felt that warfarin interacts with several herbals, actual documentation has only been reported for a few herbals. St. John's wort is the most studied herbal, and has the most evidence for significant interactions with medications. Documented herbal-drug interactions of reliable case reports, case series, or clinical investigations are presented in Table 4. This table does not include case reports of unlikely or unevaluable herbal-drug interactions using the criteria developed by Fugh-Berman and Ernst.¹⁵

Warfarin-Herbal Drug Interactions

Warfarin is known to interact with many drugs and, owing to its narrow therapeutic index, interactions can result in potentially fatal consequences if either bleeding complications arise or if subtherapeutic levels occur. Herbals can also interact with warfarin, but the risk of herbal-warfarin interactions is difficult to characterize because of the limited number and nature of existing case reports.^{36,37} Herbals that may interact with warfarin are presented in Table 5.

Herbals that decrease platelet aggregation, inhibit platelet-activating factor, or contain salicylates may increase the risk for bleeding. Interactions between warfarin and these herbals should be considered theoretical at the moment. Still, until additional research becomes available, it would be judicious to discourage use of any of these herbs in patients taking warfarin or

for those who are undergoing any type of surgical procedure.

Some herbals contain coumarin derivatives, and bleeding could occur when these herbals are taken with warfarin despite coumarin being only a weak anticoagulant. Notably, coumarins can be converted to dicoumarol when preparations are stored improperly.²⁰

Vitamin K foods include green, leafy vegetables and certain vegetable oils; consuming appreciable amounts of these vitamin K-containing foods can antagonize warfarin. Some herbals also contain appreciable amounts of vitamin K, and consumption may also antagonize warfarin therapy. Case reports of vitamin K antagonism of warfarin by fiddleheads³⁸ and noni juice³⁹ have been documented. There is a case report of a 44-year-old man on chronic warfarin therapy with international normalized ratio (INR) [for anticoagulant monitoring] values of 2.5-3.5, who experienced a reduction in response to warfarin (INR 1.14 and 1.37) after consuming a large amount of green tea (one-half to 1 gallon daily) for about one week.⁴⁰ Within one week after discontinuing green tea, his INR returned to an appropriate value (INR 2.5). The amount of vitamin K in dried green tea leaves is higher (1428 mcg of vitamin K/100 g of leaves) than in dried black tea leaves (262 mcg of vitamin K/100 g of dried black tea leaves). Brewing green tea lowers the amount of vitamin K (0.3 mcg of vitamin K/100 g brewed tea), although the actual concentration of vitamin K in the final product varies depending on the dilution and the amount of tea leaves used to brew tea.⁴⁰ The reported interaction between green tea and warfarin may be attributable to the antiplatelet of green tea and not the vitamin K content.^{21,40} Drinking significant amounts of green tea should be avoided in patients receiving warfarin,

although smaller amounts may not produce any appreciable clinical reduction in INR values.

Several published case reports support potentiation of warfarin by herbals resulting in INR. Case reports include interaction with danshen (*Salvia miltiorrhiza*), boldo (*Peumus boldus*) (in combination with fenugreek), dong quai (*Angelica sinensis*), garlic, ginger, ginseng, *Ginkgo biloba*, Lycium (*Lycium barbarum*), and papaya.^{21,35} The causality of these cases reports remains to be determined.

Warfarin is a racemic mixture of 2 stereoisomers consisting of *R*- and *S*-warfarin enantiomers. Most of the anticoagulant activity is attributed to the *S*-enantiomer. The principal enzyme responsible for the metabolism of *S*-warfarin is CYP2C9, while *R*-warfarin is partially metabolized by CYP1A2 and CYP3A4.^{37,41} Drugs or herbals that modulate the expression and activity of CYP2C9 could affect warfarin plasma concentration and anticoagulant response.

There is a case report that suggests ginkgo potentiates the effect of warfarin.⁴² In vitro studies have shown that constituents of ginkgo are capable of inhibiting CYP2C9.⁴¹ A controlled study, however, failed to demonstrate that *Ginkgo biloba* influenced the clinical effect of warfarin.⁴³

There is a clinical trial in which St John's wort significantly induced the apparent clearance of both *S*- and *R*-warfarin, which resulted in a significant reduction in the pharmacologic effect of warfarin. The antagonism of warfarin by St. John's wort was likely owing to induction of CYP2C9.⁴⁴

In a randomized, placebo-controlled study in healthy young volunteers, American ginseng

antagonized the effect of warfarin. The effect was overall modest, but most subjects had a reduction in INR values warfarin area under the curve (AUC), with some individuals having substantial changes.⁴⁵ The results are supported by 2 case reports of patients stabilized on warfarin who developed decreased INR values with use of Asian ginseng.^{46,47} The case reports suggest that Asian ginseng should be avoided in patients receiving warfarin because of the risk of thrombotic complications. In a randomized, open-label, 3-way crossover study, however, co-administration of a single dose of ginseng to healthy volunteers did not affect INR values, platelet aggregation, or pharmacokinetics of *S*- and *R*-warfarin.⁴⁸ Even though there are conflicting results, patients receiving warfarin should avoid ginseng; the mechanism for the interaction is unknown. Current evidence suggests that the ginseng constituent ginsenoside Rd can significantly inhibit both CYP2C9 and CYP3A4 in vitro, but the concentration needed to inhibit CYP2C9 may not be physiologically possible with consumption of ginseng alone.⁴¹ Further investigation is needed to evaluate the effect of ginseng on CYP isoenzymes in humans.

Herbal-Antidiabetic Drug Interactions

Two national surveys examined the prevalence and pattern of use of CAM among individuals with diabetes. One study using 1996 Medical Expenditure Panel Survey data found that individuals with diabetes were 1.6 times more likely to use CAM than persons without diabetes.⁴⁹ Data from a nationally representative survey conducted from 1997 to 1998 found that 35% of respondents with diabetes used CAM to treat their condition.⁵⁰

Some herbals may decrease blood glucose levels, which may cause detrimental

interactions when administered with antidiabetic drugs and could interfere with the clinical management of diabetic patients.²¹ The results from published efficacy studies of herbals used for treatment of diabetes is presented in Table 6; however, there are no documented case reports or clinical trials of herbals interacting with antidiabetic medications. Current evidence of possible interactions is based on preliminary studies that found that specific herbals decrease blood glucose levels or improve insulin sensitivity.

In February 2000, California state officials discovered 5 Chinese herbals contained the antidiabetic drugs glyburide and phenformin.⁵² The California Department of Health Services' Food and Drug Branch launched an investigation of the products after a diabetic patient in northern California suffered from several episodes of hypoglycemia after consuming one of the products. As a result, the FDA advised consumers to immediately stop using the 5 herbal products because the products were unsafe attributable to adulteration and because the individual were not being monitored by a physician. The 5 Chinese antidiabetic herbal remedies were Diabetes Hypoglycose Capsules, Pearl Hypoglycemic Capsules, Tongyi Tang Diabetes Angel Pearl Hypoglycemic Capsules, Tongyi Tang Diabetes Angel Hypoglycemic Capsules, and Zhen Qi Capsules.⁵² It is surmised, therefore, that potential interactions with some antidiabetic herbal products may be caused by adulteration.

St. John's Wort Drug Interactions

St. John's wort extracts are widely used for treatment of mild to moderate depression.⁵³ St. John's wort contains many chemical constituents, including phloroglucinols (hyperforin), naphthodianthones (hypericin and pseudohypericin), flavonoids, and

xanthenes.⁵⁴ Recent in vitro studies, numerous cases reports, and clinical studies have shown that St. John's wort is associated with clinically significant drug interactions. Indeed, the FDA has issued a warning to the medical community about the use of St. John's wort in combination with cyclosporine, citing 2 cases of acute rejection in 2 patients who were given heart transplants.⁵⁵

Early studies suggested that hypericin was the primary active constituent, but current evidence indicates that hyperforin is probably the active antidepressant constituent.⁵⁶ The antidepressant mechanism of action is multiple, and proposed mechanisms include inhibition of serotonin reuptake, increase in serotonergic and dopaminergic receptors, and increase affinity for GABAergic receptors.⁵⁷

In vitro studies and case reports suggest that St. John's wort induces CYP1A2, CYP2C9, CYP2C19, and CYP3A4.⁵⁸⁻⁶⁰ Research has also shown that constituents of St. John's wort, particularly hyperforin, are potent modulators of the nuclear xenobiotic pregnane X receptor, which regulates CYP3A.⁶⁰ Clinical investigations suggest that short-term administration of St. John's wort does not induce CYP3A4 but longer treatment (10 days to 2 weeks) is required.⁵⁵

Studies have also shown that St. John's wort induces P-glycoproteins.^{24,61} There is a case report of an 80-year-old man on long-term digoxin therapy who developed nodal bradycardia and bigeminy after consuming St. John's wort herbal tea (2,000 ml/day).⁶² Since digoxin is a known substrate of P-glycoprotein, this may account for the significant decrease in digoxin serum concentrations when St. John's wort is given with digoxin. The interaction of St. John's wort and digoxin varies depending on the

preparation, particularly with the hyperforin content and dose.⁶³

Case reports have shown that serotonin syndrome is possible when St. John's wort is given with selective serotonin reuptake inhibitors (SSRIs).³⁵ This pharmacodynamic interaction occurs because of overstimulation of 5HT-1_A receptors in the central nervous system (CNS). Symptoms associated with serotonin syndrome can include mental status changes, tremor, autonomic instability, gastrointestinal complaints, headache, myalgias, and motor restlessness.^{64,65} Use of St. John's wort with serotonergic drugs such as buspirone, dextromethorphan, meperidine, monoamine oxidase inhibitors, SSRIs, tricyclic antidepressants, and triptans should be avoided.

Conclusion

Documented evidence demonstrates that herbals can interact with prescribed medications and can put patients at risk. The interactions often involve drug metabolizing enzymes and drug transporter systems, although pharmacodynamic interactions can also be involved. Many herbals may increase the risk for bleeding when combined with warfarin owing to

various factors such as intrinsic antiplatelet activity or by induction of warfarin metabolism. Patients receiving warfarin therapy should be discouraged from using herbals and other dietary supplements. Interactions with antidiabetic drugs are currently theoretical, but caution should be warranted with use of herbals and antidiabetic drugs because of the risk of hypoglycemia. Drugs that prominently metabolized by CYP3A4 and are eliminated by the P-glycoprotein transporter are likely to interact with St John's wort. Based on case reports and clinical investigations, St. John's wort appears to interact with many prescription drugs, including antidepressants, antiretroviral agents, certain anticancer drugs, digoxin, immunosuppressant drugs, and oral contraceptives. Pharmacists and other health care providers must take an active role in learning about herbals and other dietary supplements to make informed decisions. It is imperative that patients are asked about their use of herbal supplements to assess for potential herbal-drug interactions. In addition, suspected herbal-drug interactions should be reported to the FDA's Adverse Event Reporting Program at <http://www.fda.gov/medwatch/how.htm>.

Table 1. Selected Reasons for Using Complementary Medicine by Adults in 2002²

Reason	Percent of Users
CAM combined with conventional medical treatment would likely help	54.9
CAM would be interesting to try	50.1
Conventional medical treatments would not ameliorate health-related problems	28.0
CAM was suggested by a conventional medical professional	26.0
Conventional medical treatment is too expensive	13.0

Table 2. Top Dietary Supplements Reported by Users of Herbal Therapy in 2002²

Dietary Supplement	% of Herbal Users Reporting Product Use*	Standard Error
Echinacea	40.3	0.80
Ginseng (unspecified species)	24.1	0.67
Ginkgo biloba	21.1	0.65
Garlic	19.9	0.63
Glucosamine with or with chondroitin	14.9	0.58
St. John's wort	12.0	0.53
Peppermint	11.8	0.52
Fish oils, omega fatty acids	11.7	0.53
Ginger	10.5	0.51
Soy	9.4	0.49
Chamomile	8.6	0.44
Bee pollen or royal jelly	7.0	0.41
Kava kava	6.6	0.41
Valerian	5.9	0.38
Saw palmetto	5.8	0.35

*Respondent may have used more than one dietary supplement

Table 3. Clinically Significant Cytochrome P450 and P-Glycoprotein Substrates^{27,28}

Cytochrome P450 Isoenzyme	Substrates	Inhibitors	Inducers
1A2	Acetaminophen Amitriptyline Caffeine Clomipramine Clozapine Cyclobenzaprine Estinyl estradiol Fluvoxamine Haloperidol Imipramine Mexiletine Naproxen Olanzapine Ondansetron Pentazocine Propranolol Ropivacaine Tacrine Theophylline Tizanidine	Amiodarone Cimetidine Fluoroquinolones Fluvoxamine Methoxsalen Mibefradil	Broccoli Brussel sprouts Char-grilled meat Insulin Modafinil Nafcillin Omeprazole Tobacco

	Verapamil <i>R</i> -Warfarin Zileuton Zolmitriptan		
2B6	Bupropion Cyclophosphamide Efavirenz Ifosfamide Methadone	Thiotepa Ticlopidine	Phenobarbital Rifampin
2C8	Paclitaxel Torsemide Amodiaquine Cerivastatin Repaglinide	Trimethoprim Quercetin Glitazones Gemfibrozil Montelukast	Rifampin
2C9	Amitriptyline Celecoxib Diclofenac Fluoxetine Fluvastatin Glyburide Glipizide Ibuprofen Irbesartan Lorsartan Meloxicam Naproxen Nateglinide Phenytoin Piroxicam Rosiglitazone Tamoxifen Tolbutamide Torsemide <i>S</i> -Warfarin	Amiodarone Fluconazole Fluvastatin Fluvoxamine Isoniazid Lovastatin Phenylbutazone Probenicid Sertraline Sulfamethoxazole Sulfaphenazole Teniposide Trimethoprim Zafirlukast	Rifampin Secobarbital
2C19	Amitriptyline Carisoprodol Citalopram Clomipramine Cyclophosphamide Diazepam Fluoxetine Hexobarbital Imipramine Indomethacin Lansoprazole Mephenytoin	Chloramphenicol Cimetidine Felbamate Fluoxetine Fluvoxamine Indomethacin Ketoconazole Lansoprazole Modafinil Omeprazole Oxcarbazepine Probenicid	Carbamazepine Norethindrone Prednisone Rifampin

	Mephobarbital Nelfinavir Nilutamide Omeprazole Pantoprazole Phenobarbitone Phenytoin Primidone Progesterone Propranolol Teniposide <i>R</i> -Warfarin	Ticlopidine Topiramate	
2D6	Amitriptyline Amphetamine Aripiprazole Atomoxetine Carvedilol Chlorpheniramine Chlorpromazine Clomipramine Codeine Desipramine Dextromethorphan Duloxetine Encainide Flecainide Fluoxetine Fluvoxamine Haloperidol Imipramine Lidocaine Metoclopramide Metoprolol Mexiletine Nortriptyline Ondansetron Paroxetine Perphenazine Profafenone Propranolol Risperidone Sertraline Tamoxifen Thioridazine Timolol Tramadol	Amiodarone Bupropion Celecoxib Chlorpromazine Chlorpheniramine Clemastine Cimetidine Citalopram Clomipramine Cocaine Diphenhydramine Doxepin Doxorubicin Duloxetine Escitalopram Fluoxetine Halofantrine Hydroxyzine Red-Haloperidol Levomopromazine Metoclopramide Methadone Mibefradil Moclobemide Paroxetine Perphenazine Quinidine Ranitidine Ritonavir Sertraline Terbinafine Ticlopidine Tripeleminamine	Dexamethasone Rifampin

	Tricyclic antidepressants Venlafaxine		
2E1	Acetaminophen Caffeine Chlorzoxazone Dapsone Enflurane Ethanol Halothane Isoflurane Isoniazid Sevoflurane Theophylline Venlafaxine	Disulfiram	Ethanol Isoniazid
3A4,5,7	Alfentanyl Alprazolam Amlodipine Aripiprazole Astemizole Atrovastatin Buspirone Cafergot Caffeine Cerivastatin Chlorpheniramine Cisapride Clarithromycin Cocaine Codeine Cyclosporine Dapsone Dextromethorphan Diazepam Diltiazem Docetaxel Doxycycline Eplerenone Ergotamine Erythromycin (Not 3A5) Ethinyl estradiol Ethosuximide Etoposide Felodipine Fentanyl	Amiodarone Aprepitant Chloramphenicol Cimetidine Ciprofloxacin Clarithromycin Delaviridine Diethyl- Dithiocarbamate Diltiazem Erythromycin Fluconazole Fluvoxamine Gestodene Grapefruit Juice Indinavir Itraconazole Ketoconazole Mifepristone Nefazodone Nelfinavir Norfloxacin Norfluoxetine Mibefradil Ritonavir Star Fruit Verapamil	Barbiturates Carbamazepine Efavirenz Glucocorticoids Modafinil Nevirapine Phenobarbital Phenytoin Pioglitazone Rifabutin Rifampin St. John's wort Troglitazone

	Finasteride Fluconazole Fluoxetine Haloperidol Hydrocortisone Ifosfamide Imatinib mesylate Imipramide Indinavir Irinotecan Isradipine Intraconazole LAAM Lidocaine Loratadine Lovastatin Methadone Midazolam Nefedipine Nicardipine Nifedipine Nimodipine Nisoldipine Nitrendipine Nelfinavir Omeprazole Odanestron Paclitaxel Paroxetine Pimozide Progesterone Propranolol Quetiapine Quinidine (Not 3A5) Quinine Ritonavir Salmeterol Saquinavir Sildenafil Simvastatin Sirolimus Tacrolimus (FK506) Tamoxifen Telithromycin Terfenidine Testosterone		
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	Trazodone Triazolam Venlafaxine Verapamil Vincristine Zaleplon Zolpidem		
P-Glycoprotein	Amiodarone Cyclosporine Digoxin Diltiazem Doxorubicin Loperamide Saquinavir St. John's wort Tacrolimus		

Table 4. Documented Herbal-Drug Interactions^{20, 21,35}

Herbal	Drug	Comment	Mechanism
Betel nut (<i>Areca catechu</i>)	Procyclidine	Betel nut has cholinergic activity	↓ drug effect
Boldo (<i>Peumus boldus</i>) (in combination with fenugreek)	Warfarin	Boldo constituents have antiplatelet activity	↑ bleeding risk
Capsicum (<i>Capsicum annuum</i>)	ACE inhibitor	Increased risk of cough	↑ drug toxicity
Danshen (<i>Salvia miltorrhiza</i>)	Warfarin	Danshen decreases half-life of warfarin	↑ drug effect
Dong quai (<i>Angelica sinensis</i>)	Warfarin	Dong quai contains coumarin derivatives; danshen decreases half-life of warfarin	↑ drug effect
Fenugreek (<i>Trigonella</i> species) in combination with boldo	Warfarin	Fenugreek constituents have antiplatelet activity	↑ bleeding risk
Fiddleheads	Warfarin	Fiddleheads contains vitamin K	↓ drug effect
Garlic (<i>Allium sativum</i>)	Warfarin	Garlic has antiplatelet activity	↑ drug effect
Garlic (<i>Allium sativum</i>)	Saquinavir	Induction of CYP3A4 enzymes	↓ drug effect
Ginger (<i>Zingiber officinale</i>)	Phenprocoumon	Ginger can inhibit thromboxane synthetase and/or decreases platelet aggregation	↑ bleeding risk
Ginkgo (<i>Ginkgo biloba</i>)	Aspirin	Ginkgo has antiplatelet activity	↑ bleeding risk
Ginkgo (<i>Ginkgo biloba</i>)	Haloperidol	Ginkgo may scavenge free radicals produced by hyperdopaminergic activity	↓ drug toxicity
Ginkgo (<i>Ginkgo biloba</i>)	Ibuprofen	Ginkgo has antiplatelet activity	↑ bleeding risk
Ginkgo (<i>Ginkgo biloba</i>)	Omeprazole	Induction of CYP2C19 enzymes	↓ drug effect
Ginkgo (<i>Ginkgo biloba</i>)	Trazodone	Ginkgo may have GABA-ergic activity	↑ drug effect
Ginkgo (<i>Ginkgo biloba</i>)	Valproic acid	Contaminants of leaf/seed that may contain neurotoxins	↑ drug toxicity
Ginseng, American (<i>Panax quinquefolius</i>)	Warfarin	Unknown	↓ drug effect
Ginseng, Asia (<i>Panax ginseng</i>)	Phenelzine	Unknown	↑ drug toxicity
Ginseng, Siberian (<i>Eleutherococcus senticosus</i>)	Digoxin	False elevation of digoxin by unknown mechanism	No effect
Green tea (<i>Camellia sinensis</i>)	Warfarin	Green tea contains vitamin K	↓ drug effect
Kava (<i>Piper methysticum</i>)	Alprazolam	Additive CNS depressant effect	↑ drug effect
Kava (<i>Piper methysticum</i>)	Levodopa	Kava may antagonize dopamine	↓ drug effect
Lycium (<i>Lycium barbarum</i>)	Warfarin	Induction of CYP2C9 by Lycium	↑ bleeding risk

Noni juice (<i>Morinda citrifolia</i>)	Warfarin	Noni juice contains vitamin K	↓ drug effect
Papaya	Warfarin	Unknown	↑ drug effect
Peppermint oil (<i>Mentha piperita</i>)	Nifedipine	Increases oral bioavailability	↑ drug effect
Psyllium (<i>Plantago</i> species)	Carbamzepine	Psyllium decreases absorption	↓ drug effect
Psyllium (<i>Plantago</i> species)	Lithium	Psyllium decreases absorption	↓ drug effect
St. John's wort (<i>Hypericum perforatum</i>)	Alprazolam	Induction of CYP3A4	↓ drug effect
St. John's wort (<i>Hypericum perforatum</i>)	Amitriptyline	Induction of CYP3A4	↓ drug effect
St. John's wort (<i>Hypericum perforatum</i>)	Buspirone	Induction of serotonin syndrome	↑ drug toxicity
St. John's wort (<i>Hypericum perforatum</i>)	Chlorzoxazone	Induction of CYP2C19	↓ drug effect
St. John's wort (<i>Hypericum perforatum</i>)	Cyclosporine	Induction of CYP3A4 and modulation of P-glycoprotein	↓ drug effect
St. John's wort (<i>Hypericum perforatum</i>)	Digoxin	Modulation of P-glycoprotein	↓ drug effect
St. John's wort (<i>Hypericum perforatum</i>)	Fenoxfenadine	Modulation of P-glycoprotein	↓ drug effect
St. John's wort (<i>Hypericum perforatum</i>)	General anesthetic agents (fentanyl, propofol, sevoflurane)	Delayed emergence by unknown mechanism	↑ drug toxicity
St. John's wort (<i>Hypericum perforatum</i>)	Imatinib	Induction of CYP3A4	↓ drug effect
St. John's wort (<i>Hypericum perforatum</i>)	Indinavir	Induction of CYP3A4	↓ drug effect
St. John's wort (<i>Hypericum perforatum</i>)	Irinotecan	Modulation of P-glycoprotein	↓ drug effect
St. John's wort (<i>Hypericum perforatum</i>)	Loperamide	Induction of serotonin syndrome	↑ drug toxicity
St. John's wort (<i>Hypericum perforatum</i>)	Mephytoin	Induction of CYP2C19	↓ drug effect
St. John's wort (<i>Hypericum perforatum</i>)	Methadone	Induction of withdrawal symptoms	↑ drug toxicity
St. John's wort (<i>Hypericum perforatum</i>)	Midazolam	Induction of intestinal CYP3A4	↓ drug toxicity
St. John's wort (<i>Hypericum perforatum</i>)	Nefazodone	Induction of serotonin syndrome	↑ drug toxicity
St. John's wort (<i>Hypericum perforatum</i>)	Nevirapine	Induction of CYP3A4 and modulation of P-glycoprotein	↓ drug effect
St. John's wort (<i>Hypericum perforatum</i>)	Omeprazole	Induction of both CYP3A4 and CYP2C19	↓ drug effect
St. John's wort (<i>Hypericum perforatum</i>)	Oral contraceptives	Induction of CYP3A4 and modulation of P-glycoprotein	↓ drug effect
St. John's wort (<i>Hypericum perforatum</i>)	Paroxetine	Induction of serotonin syndrome	↑ drug toxicity

St. John's wort (<i>Hypericum perforatum</i>)	Phenprocoumon	Decreased bioavailability	↓ drug effect
St. John's wort (<i>Hypericum perforatum</i>)	Ritonavir	Induction of CYP3A4 and modulation of P-glycoprotein	↓ drug effect
St. John's wort (<i>Hypericum perforatum</i>)	Rosiglitazone	Induction of CYP2C8	↓ drug effect
St. John's wort (<i>Hypericum perforatum</i>)	Sertraline	Induction of serotonin syndrome	↑ drug toxicity
St. John's wort (<i>Hypericum perforatum</i>)	Simvastatin	Induction of CYP3A4	↓ drug effect
St. John's wort (<i>Hypericum perforatum</i>)	Tacrolimus	Induction of CYP3A4	↓ drug effect
St. John's wort (<i>Hypericum perforatum</i>)	Theophylline	Induction of CYP1A2 (only in female subjects)	↓ drug effect
St. John's wort (<i>Hypericum perforatum</i>)	Trazodone	Induction of serotonin syndrome	↑ drug toxicity
St. John's wort (<i>Hypericum perforatum</i>)	Venlafaxine	Induction of CYP3A4 and modulation of P-glycoprotein	↓ drug effect
St. John's wort (<i>Hypericum perforatum</i>)	Verapamil	Induction of intestinal CYP3A4	↓ drug effect
St. John's wort (<i>Hypericum perforatum</i>)	Voriconazole	Induction of CYP2C19, CYP3A4, and CYP2C9	↓ drug effect
St. John's wort (<i>Hypericum perforatum</i>)	Warfarin	Induction of CYP2C9	↓ drug effect
Soy (<i>Glycine max</i>)	Warfarin	Unknown	↓ drug effect

Table 5. Herbs That May Interact with Anticoagulant Therapy²¹

Salicylate-Containing Herbs	Coumarin-Containing Herbs	Herbs with Antiplatelet or Antithrombotic Activity	Vitamin K-Containing Herbs
Meadowsweet Red clover Willow bark	Angelica Asafoetida Astragalus Bishop's weed Black haw Celery Deertongue Dong quai Fenugreek German chamomile Manna Marsh blazing star Neem Northern prickly ash Red clover Roman chamomile Rupturewort Sweet clover Sweet woodruff Tonka bean	Allspice Andrographis Angelica Arnica Asafoetida Bishop's weed Black tea Bladderwrack Bogbean Boldo Borage Bromelain Buchu Burdock Capsicum Cat's claw Cinchona Clove Coltsfoot Deertongue Danshen Dong quai Epimedium Fenugreek Feverfew Flaxseed Asian ginseng Siberian ginseng Garlic Ginger Ginkgo Green tea Guarana Guggul Holy basil Honey suckle Horse chestnut Jiaogulan Kudzu Oolong tea Pau D'arco Safflower Saw palmetto	Alfalfa Chlorella Cornsilk Fiddleheads Great plantain Noni Parsley Smartweed Stinging nettle Watercress

		Sea buckthorn Soy Sweet vernal grass Tumeric Yarrow	
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Table 6. Clinical Studies that Evaluated Herbal Supplements for the Treatment of Diabetes⁵¹

Herbal	Total Number of Subjects	Type of Diabetes	Dose	Proposed Mechanism of Action	Outcome
American ginseng (<i>Panax quinquefolius</i>)	10	Type 2	Placebo or 3, 6, or 9 g ground root at 120, 80, 40, or 0 min before a 25-g oral glucose challenge	Increases glucose uptake, modulates insulin secretion, decreases carbohydrate absorption	Significant reduction in postprandial glucose compared with placebo irrespective of dose and time of administration ($P < 0.05$ for all values)
Asian ginseng (<i>Panax ginseng</i>)	12	Type 2	100 mg, 200 mg or placebo daily for 8 weeks	Increases glucose uptake, modulates insulin secretion, decreases carbohydrate absorption	Significant reduction in glycosylated hemoglobin with 200 mg dose only ($P < 0.05$)
Bitter melon (<i>Momordica charantia</i>)	100	Type 2	One dose, amount unspecified	Increases insulin uptake, inhibits gluconeogenesis, enhances glucose oxidation	Significant reduction ($P < 0.001$) of both fasting and post-prandial serum glucose
Cinnamon (<i>Cinnamomum cassia</i>)	60	Type 2	1, 3, or 6 g of cinnamon or placebo daily for 40 days	Increases insulin release, promotes glycogen synthesis	Significant decrease in glucose compared with placebo ($P < 0.05$); significant decrease in total cholesterol, triglycerides and LDL-cholesterol compared with placebo ($P < 0.05$)

Fenugreek (<i>Trigonella foenum-graecum</i>)	10	Type 1	Defatted seed powder in unleavened bread twice daily for 10 days	Delays gastric emptying, slows carbonate absorption, increases number of insulin receptors, increases insulin peripheral sensitivity	Significant decrease in fasting blood ($P < 0.01$), total cholesterol ($P < 0.001$), LDL-cholesterol ($P < 0.01$), and triglycerides ($P < 0.01$)
	60	Type 2	Seed powder 25 grams twice daily for 6 months		Significant reduction in 24-hour glucose excretion, total cholesterol, LDL, and VLDL cholesterol and triglycerides ($P < 0.001$, all values)
Gymnema (<i>Gymnema sylvestre</i>)	64	Type 1	200 mg twice daily for 6 to 30 months in addition to insulin	Increases glucose uptake, stimulates beta-cells, increases number of beta-cells, increases insulin release	Significant decrease in glycoslyated hemoglobin compared with placebo ($P < 0.001$)
	22	Type 2	400 mg daily for 18 to 20 months in addition to a sulfonylurea		Significant decrease in glycoslyated hemoglobin compared with placebo ($P < 0.001$) and average fasting glucose ($P < 0.001$) from baseline
Prickly pear cactus (<i>Opuntia streptacantha</i>)	32	Type 2	One dose of 500 grams broiled nopal, 500 grams broiled zucchini, or 400 mL of water	Slows carbohydrate absorption, decreases lipid absorption, increases insulin release	Significant reduction in fasting glucose with nopal ($P < 0.001$).

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