

## Evidence-based drug–herbal interactions

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### Abstract

Due to the growing use of herbals and other dietary supplements healthcare providers and consumers need to know whether problems might arise from using these preparations in combination with conventional drugs. However, the evidence of interactions between natural products and drugs is based on known or suspected pharmacologic activity, data derived from in vitro or animal studies, or isolated case reports that frequently lack pertinent information. The usefulness of such information is questionable. More recently an increasing number of documented case reports, in vivo studies, and clinical trials have evaluated herbal–drug interactions. Results have sometimes been contradictory and more research is needed. Since there is a lack of rigorous studies that can establish the clinical significance of herb–drug interactions, an evidence-based evaluation of the current literature concerning commonly used herbal–drug interactions, as well as other dietary supplements, was conducted.

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### Introduction

Use of complementary and alternative medicine (CAM) in the United States has been increasing in recent years (Eisenberg et al., 1998). Indeed, the dietary supplement industry is currently estimated to be a \$20 billion industry and according to recent statistics from the Food and Drug Administration (FDA), there are at least 29,000 dietary supplement products on the market. Dietary supplements are defined by the Dietary Supplement and Health Education Act (DSHEA) of 1994 (Anon, 1995) and include such products as herbals, vitamins, minerals, sports nutrition supplements, weight management products, specialty supplements and other oral dosage forms intended to supplement the diet (Anon, 2005a).

Dietary supplements are not regulated by the Federal Food and Drug Administration (FDA) as conventional prescription or over-the-counter (OTC) medications or as food additives, and at the present time manufacturers of dietary supplements are not required to follow good manufacturing practices (GMP) as for drugs, but are required to abide by GMPs for food. Manufac-

turers do not have to provide the FDA proof that dietary supplements are effective or safe but they are not permitted to market unsafe products. Once a dietary supplement is marketed, the FDA has to prove that the product is unsafe in order to prohibit its use and be able to remove the product from the market (Anon, 2005a).

### Determination of herbal–drug interactions

#### *Adverse event reporting (AER)*

Reporting of adverse drug events is currently limited. The FDA maintains the MedWatch system for reporting adverse events, including those for both conventional drugs and dietary supplements. In 2002, 320,860 adverse events were reported to the system (Anon, 2002). However, the MedWatch system does not separate drug versus herbal interactions. In addition, a report published by the Department of Health and Human Services (DHHS) estimated that less than 1% of all drug–dietary supplement interactions are reported to the FDA (Anon, 2001). The DHHS report cites several limitations to the AER system including limited availability of medical records for the reported adverse events, lack of product ingredient information for the

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substances involved, and limited information on products by the manufacturers (Anon, 2001). A published review of widely claimed interactions found that <15% were well documented (Fugh-Berman and Ernst, 2001). The lack of available clinical data for many herbal products serves as a barrier for post marketing safety assessment of herbal products.

### The nature of herbal–drug interactions

Natural products, unlike conventional drugs, provide a complex mixture of bioactive entities, which may or may not provide therapeutic activity. Often a complete characterization of all the chemical constituents from a natural product is unknown. Additionally, chemical makeup of a natural product may vary depending on the part of the plant processed (stems, leaves, roots), seasonality and growing conditions. Combination products composed of multiple natural products complicate matters further.

Not only does the complex nature of natural products complicate the determination of drug–herbal interactions, but the manufacturing process contributes to the overall complexity as well. Because herbal products are not regulated by the FDA, as previously stated, there are no standards for herbal products. Indeed, some products have been found to be misidentified, substituted and/or adulterated with other natural products or unwanted substances. Testing of the quality of more than 1200 dietary supplement products by the independent laboratory ConsumerLab.com found that 1 in 4 dietary supplement products lacked the labeled ingredients or had other serious problems such as unlisted ingredients or contaminants (Anon, 2005b). This creates a problem when evaluating the validity of drug–herbal interactions.

### Evidence for herbal–drug interactions

Herbal–drug interactions can be characterized as either pharmacodynamic (PD) or pharmacokinetic (PK) in nature. PD interactions may occur when constituents of herbal products have either synergistic or antagonist activity in relation to a conventional drug. As a result, concentration-dependent activity of a therapeutic molecule is altered at the site of action at the drug-receptor level. PK interactions result from alteration of absorption, distribution, metabolism, or elimination of a conventional drug by an herbal product or other dietary supplements. Although many drug–herbal 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 coenzyme Q10 and adverse effects secondary to “statin” drugs may be due to the resultant decrease in tissue levels of coenzyme Q10 (Folkers, et al., 1990; Rundek et al., 2004). Thus, supplementation with coenzyme Q10 by patients on statin therapy may be beneficial.

The evidence of interactions between some commonly used herbal products and other dietary supplements and drugs is usually based on known or suspected pharmacological activity, data derived from in vitro or animal studies, or isolated case

Table 1

Evaluation of the probability of herbal–drug interactions (1 point per item)<sup>a</sup>

1 point each

Adequate patient history (age, sex, relevant medical conditions) is reported
Concurrent diseases, conditions, or other medications associated with adverse event (including dosing)
Concomitant medications are documented (including dosing)
Description of interactors is adequate
Obvious alternate explanations have been excluded
Chronology is complete
Time sequence of drug administration to adverse event is reasonable
Adverse event is adequately described
Event ceases upon stopping drug
Event recurs upon rechallenge

Adapted from Fugh-Berman and Ernst (2001).

<sup>a</sup> Likely (8–10 points), possible (4–7 points), or unevaluable (0–3 points).

reports that frequently lack pertinent information. The usefulness of such information is questionable. Since there is need for an evidence-based approach that evaluates herbal–drug interactions, this article will review the current evidence for some common herbal–drug interactions. In addition, a review of warfarin–herbal drug interactions and St. John’s wort–drug interactions will be presented.

### Evaluation of herbal–drug interactions

Fugh-Berman and Ernst (2001) have developed a rubric for the determination of the reliability of case reports on drug–herbal interactions. The probability of an interaction is scored using a 10-point scale, where one point is given for each of 10 items such as patient medical history and event chronology (Table 1). The sum is totaled and an interaction is deemed likely (8–10 points), possible (4–7 points), or unevaluable (0–3 points). The scoring system can be used to determine whether case reports involving herbal–drug interactions contain the appropriate information to be considered reliable. Examples of using this approach are presented in Table 2.

### Evaluation of herbal–drug interactions

#### *Echinacea–drug interactions*

There have been no specific case reports of echinacea–drug interactions. However, due to the potential immunostimulatory nature of echinacea, some sources raise the issue that concomitant use with immunosuppressants is contraindicated. To date, this contraindication is speculative since documentation is lacking (Blumenthal, 2003a). Evidence from in vitro and in vivo studies suggests potential interactions with substrates of cytochrome P450 3A4 (CYP3A) or CYP1A2 (Gorski et al., 2004). No clinical studies have assessed the potential nature of interactions involving CYP3A4 or CYP1A2.

#### *Garlic–drug interactions*

There are several case reports of patients who experienced spontaneous bleeding during and following surgery

Table 2  
Examples of the evaluation of herbal–drug interactions using the evaluation method developed by Fugh-Berman and Ernst (2001)

Dietary supplement	Anticoagulant	Subject(s)	Other drugs	Signs and symptoms of interaction	Mechanism	Reliability	Reference
Danshen	Warfarin	62-year-old male with mitral valve replacement	Digoxin, furosemide, captopril	Increased INR*	Additive effect due to coumarin content in danshen	Likely	Izzat et al. (1998)
Dong quai	Warfarin	46-year-old female with history of stroke, rheumatic heart, atrial fibrillation	Digoxin, furosemide	2-fold increase in prothrombin time and INR	Possible inhibition of platelet activity by dong quai	Likely	Page and Lawrence (1999)
Garlic	Warfarin	1 patient	Unknown	Increased INR, hematuria	Unknown; possible inhibition of platelet aggregation	Unevaluable	Sunter, 1991
<i>Ginkgo biloba</i>	Warfarin	70-year-old female with hypertension, MI, atrial fibrillation, coronary bypass and gait disorder	None	PT <sup>#</sup> —16.9, PTT <sup>±</sup> —35.5, left parietal hemorrhage	Ginkgo inhibits platelet aggregation	Possible	Matthews (1998)
<i>Ginkgo biloba</i>	Sodium valproate	78-year-old man	Temezepam, aspirin, tampril	Generalized tonic-clonic seizures	Contaminants of leaf/seed which may contain neurotoxins	Possible	Granger (2001)
<i>Panax Ginseng</i>	Warfarin	47-year-old male with heart valve replacement	Diltiazem, NTG, salsalate	Decreased INR	Unknown	Possible	Janetzky and Morreale (1997)
<i>Panax Ginseng</i>	Phenelzine	64-year-old woman	Unknown	Headache, insomnia, tremulousness	Unknown	Unevaluable	Shader and Greenblatt (1985)
St. John's wort	Warfarin	Case series of 7 patients	Unknown	Decreased INR	Induction of warfarin CYP2C9 metabolism	Unevaluable	Yue et al. (2000)
St. John's wort	Cyclosporin	61-year-old woman with heart transplant	Unknown	Decrease cyclosporin serum concentration and rejection reaction	Induction of CYP3A4 and PgP <sup>≈</sup>	Possible	Bon et al. (1999)
St John's wort	Digoxin	80-year-old man	Unknown	Nodal bradycardia and bigeminy	Induction PgP	Unevaluable	Andelic (2003)

\*INR=international ratio, <sup>#</sup>PT=prothrombin time, <sup>±</sup>PTT=partial thromboplastin time, <sup>≈</sup>PgP=*p*-glycoprotein transporter.

which were linked to prior ingestion of garlic (Rose et al., 1990; Burnham, 1995; German et al., 1995). Inhibition of platelet aggregation by bio-organic constituents of garlic has been demonstrated both in vitro (Ariga et al., 2000; Briggs et al., 2000) and in vivo (Steiner and Li, 2001; Rahman and Billington, 2000). A discussion of the interaction of garlic with warfarin will occur later in this paper.

Garlic may induce hepatic CYP3A4 metabolism of saquinivir resulting in decreased plasma drug levels (Piscitelli et al., 2002). Ten healthy patients were administered 1200 mg of saquinivir three times a day with meals on days 1–4, 22–25, and 36–39. On days 5–25 patients were given 2 garlic capsules twice daily, each containing 4.64 mg allicin and 11.2 mg allin. Mean saquinivir area under the curve (AUC), mean maximum concentration ( $C_{max}$ ) and 8 h plasma levels decreased 51%, 54%, and 49%, respectively. AUC, maximum concentration and 8 h plasma levels returned to 65%, 61%, and 71% of baseline values, respectively, following a 10 day washout period. The authors hypothesized possible induction of hepatic CYP3A4 metabolism and/or induction of *p*-glycoproteins as the mechanism for decreased saquinivir levels. Patients taking saquinivir should be advised to minimize their consumption of garlic or garlic supplements.

### *Ginkgo biloba*–drug interactions

*G. biloba* has been reported to cause spontaneous bleeding in patients who are generally healthy (Rowin and Lewis, 1996; Gilbert, 1997; Fong and Kinnear, 2003; Fessenden et al., 2001; Destro et al., 2005), possibly due to the antiplatelet effects of the ginkgolide B component (Rosenblatt and Mindel, 1997; Meisel et al., 2003). Case reports of *G. biloba* possible interactions resulting in bleeding have been reported with aspirin, ibuprofen, and warfarin. In one case report of possible herbal–drug interaction, a 70-year-old male with a history of coronary bypass and taking aspirin 325 mg daily for 3 years experienced a spontaneous hemorrhage in the right eye 2 weeks after a regimen of 40 mg twice daily of *G. biloba* was begun (Rosenblatt and Mindel, 1997). Another report of possible herbal–drug interaction involved a 71-year-old male patient taking 40 mg of *G. biloba* extract daily for over 2 years for the treatment of occasional dizziness (Meisel et al., 2003). The patient began taking ibuprofen 600 mg daily for osteoarthritis and 4 weeks after the regimen was begun, the patient suffered a cerebral hemorrhage, resulting in coma and death. A case report of *G. biloba* and warfarin will be discussed later. Concurrent use of *G. biloba* with anticoagulants, aspirin and ibuprofen should be avoided.

There is a unevaluable case report in a 5-year toxicological study on traditional remedies and food supplements of an

interaction between *G. biloba* and a thiazide diuretic (no further information provided) in an elderly woman who took the combination and developed elevated blood pressure, which returned to normal when both agents were discontinued (Shaw et al., 1997). This reaction has not been evaluated in clinical trials.

*G. biloba* may act as an antagonist of gamma-aminobutyric acid (GABA) activity at benzodiazepine binding sites (Huang et al., 2004). Therefore, its use in patients taking drugs which are ligands for benzodiazepine binding sites should be avoided. A case report of interactions of possible interactions with *G. biloba* and trazodone has been reported. In one case, an 80-year-old female patient had been taking 3.5 mg of bromazepam daily for restlessness, anxiety, and irritability for an unspecified amount of time (Galluzzi et al., 2000). The patient was diagnosed with Alzheimer's disease and 5 mg donepezil at bedtime and 600 mg vitamin E twice a day were added to her medication regimen in order to improve cognitive function and behavior. The medication regimen was discontinued 3 months later since no improvement was observed. The patient was switched from bromazepam to trazadone 20 mg twice daily with the addition of *G. biloba* 80 mg daily. Three days following the change in the dosing regimen, the patient lapsed into a coma, which was reversed immediately upon intravenous administration of 1 mg flumazenil, suggesting a link with the GABAergic system.

There is a case report of a possible interaction with *G. biloba* and valproate. In one report, two separate patients suffered seizures when *G. biloba* and valproate sodium were administered concomitantly (Granger, 2001). The first patient was a 78-year-old male with well-controlled epilepsy on a dosing regimen of 1200 mg of valproate sodium daily for at least 18 months. He suffered 3 generalized tonic-clonic seizures 2 weeks after a *G. biloba* regimen of 120 mg daily was begun. The patient remained seizure-free 8 months following discontinuation of the *G. biloba*. The second patient, an 84-year-old female patient with severe dementia, had been free of seizures for 2 years on a regimen of 1600 mg valproate sodium daily. Upon recommendation of her psychiatrist, the patient began taking 120 mg of *Ginkgo* daily and 12 days following addition of the supplement she was admitted to the hospital in status epilepticus. Seizures ceased within 2 h after administration of intravenous diazepam and the patient remained seizure free for at least 4 months after discontinuation of *G. biloba*.

In clinical trials, *G. biloba* has been reported to interact with CYP450 isoenzymes, potentially resulting in metabolic drug interactions, although the results are contradictory (Yin et al., 2004; Markowitz et al., 2003a; Yang et al., 2003; Smith et al., 2001). In one controlled trial, 18 healthy patients were administered omeprazole 40 mg a day prior to and 1 day following a regimen of 140 mg *G. biloba* extract twice daily for 12 consecutive days (Yin et al., 2004). The ratio of omeprazole to 5-hydroxyomeprazole AUC decreased 67.5% while urinary excretion of 5-hydroxyomeprazole decreased 13–44%. The authors hypothesized that *G. biloba* extract induced CYP2C19 while inhibiting urinary excretion of 5-hydroxyomeprazole. The effect of *G. biloba* on CYP3A4 activity is inconclusive as several studies have published conflicting results. In one clinical trial, 10 mg of nifedipine was admin-

istered to 21 healthy patients prior to and following a course of 120 mg *G. biloba* extract daily for 18 days (Smith et al., 2001). Plasma levels of nifedipine increased 29%, 30 min after administration following short term *Ginkgo* administration, suggesting an inhibition of CYP3A4 activity. In contrast, Markowitz et al. (2003a) showed a slight decrease in alprazolam AUC (17%) with no change in half-life indicating *G. biloba* did not interact with CYP3A4.

*G. biloba* is hypothesized to have an antioxidant effects, resulting in enhanced activity of haloperidol (Zhang et al., 2001a,b; Zhou et al., 2004). In 3 clinical trials, the effectiveness of 0.25 mg/kg/day haloperidol was enhanced when co-administered with 360 mg daily of *G. biloba*, as measured using the Scale of Assessment of Positive (SAPS) or Negative Symptoms Scale (SANS) (Zhang et al., 2001a,b; Zhou et al., 1999). In addition, 2 of the studies measured a decrease in superoxide dismutase levels, suggesting *Ginkgo* extract was able to scavenge free radicals produced by hyperdopaminergic activity (Zhang et al., 2001a; Zhou et al., 1999).

#### *Ginseng–drug interactions*

*Ginseng* is commonly available as Asian *ginseng* (*Panax ginseng*) and American *ginseng* (*Panax quinquefolius* L.) which are taxonomically similar plants but differ chemically in their content of ginsenosides and slightly in biological activity (Blumenthal, 2003b). There are unevaluable case reports of *ginseng* interacting with loop diuretics and with phenelzine (Becker et al., 1996; Shader and Greenblatt, 1985; Jones and Runikis, 1987). Preliminary clinical studies suggest that American (Vuksan et al., 2000a,b, 2001; Sievenpiper et al., 2003) and Asian *ginseng* (Sotaniemi et al., 1995) may increase the risk for hypoglycemia based on preliminary studies and, therefore, concomitant use of *ginseng* with anti-diabetic medication may increase the risk for hypoglycemia.

An unevaluable interaction between *ginseng* (species not specified) and loop diuretics has been reported, necessitating careful monitoring with concomitant use of the two products. In the case report, a 63-year-old male with glomerulonephritis taking furosemide and cyclosporine (doses not specified) experienced edema and hypertension 10 days after starting a regimen of 10–12 tablets of a *ginseng* product which also contained germanium (Becker et al., 1996). The patient was stabilized after 240 mg of furosemide administered intravenously every 8 h and the *ginseng* product was discontinued. The patient was discharged on a dose of 80 mg of furosemide twice daily. A similar cycle was observed upon rechallenge with the *ginseng* product. Although a temporal relationship for the interaction exists, the exact nature of the interaction is unknown as the germanium component in the *ginseng* product may have resulted in the interaction. Long-term use of germanium has been associated with chronic renal failure (Becker et al., 1996).

There are two unevaluable case reports of *ginseng*–phenelzine interaction which suggest that use of *ginseng* with MAO inhibitors should be avoided. In both cases the species of *ginseng* was not specified. In the first case report, a 64-year-old female patient took phenelzine in combination with *ginseng* and experienced

headache, insomnia, and tremulousness (Shader and Greenblatt, 1985). In a second report, a 42-year-old female patient who took phenelzine 45 mg daily, triazolam 0.5 mg at bedtime and lorazepam 1 mg four times daily experienced manic-like symptoms when she initiated use of ginseng and bee pollen (Jones and Runikis, 1987).

There is a case report of a possible interaction with Siberian ginseng (*Eleutherococcus senticosus*) and digoxin of elevated serum digoxin levels without symptoms of toxicity attributed (McRae, 1996). A 74-year-old male taking digoxin 0.25 mg daily for over 10 years experienced elevated digoxin levels after starting Siberian ginseng. Digoxin levels did not decrease when the digoxin regimen was lowered to 0.125 mg and 0.25 mg on alternating days nor when digoxin was discontinued. However, serum digoxin levels returned to normal when Siberian ginseng was stopped. Upon rechallenge with Siberian ginseng 9 months later, digoxin levels again increased and decreased to normal when the product was discontinued. The nature of the interaction is unknown but Siberian ginseng contains eleutherosides which may have interfered with the digoxin assay. The authors speculated that the elevated digoxin levels were caused by cardiac glycoside-like constituents since the product was assayed and found to be free of digoxin and digitoxin. However, the product was not assayed for the presence of eleutherosides and, therefore, it is not known whether the product actually contained Siberian ginseng. A well known herbal expert has hypothesized that the product may have been adulterated with silk vine (*Periploca sepium*) which is reported to contain cardiac glycosides. Silk vine is a frequent adulterant of *E. senticosus* (Awang, 1996).

#### Glucosamine/chondroitin–drug interactions

Glucosamine and chondroitin are used as dietary supplements for management of symptoms associated with osteoarthritis and are generally considered to be safe. There are no case reports of serious adverse events related to glucosamine and/or chondroitin supplementation. A single case of a possible interaction with warfarin reports possible additive anticoagulation effect in a patient receiving warfarin and high doses of a combination glucosamine–chondroitin product (Rozenfeld et al., 2004).

#### Warfarin–herbal drug interactions

Warfarin exerts its anticoagulant activity by interfering with the hepatic conversion of the vitamin K-dependent clotting factors II (prothrombin), VII, IX and X. In addition, warfarin inhibits activation of vitamin K-dependent regulatory proteins C and S (Rehulkova, 2001; Hirsh et al., 1992). Fluctuations in the ingestion of sources of vitamin K such as green, leafy vegetables and certain vegetable oils may effect the hypoprothrombinemic response to warfarin, and therefore may require dosage adjustment of warfarin dosage. Patients should be routinely counseled as to which foods contain vitamin K and periodic monitoring of international ratio (INR) is essential in patients receiving warfarin therapy.

Herbals can impact the pharmacokinetics of warfarin by decreasing its absorption from the gastrointestinal tract, or by altering its metabolic clearance. Oral warfarin is available as a racemic mixture of *R*- and *S*-enantiomers (Greenblatt and von Moltke, 2005). Inhibition of metabolism of *S*-warfarin is more important clinically because this isomer is 5 times more pharmacologically active than the *R* form (Hirsh et al., 1992). The main enzyme responsible for *S*-warfarin metabolism is CYP2C9 and any factor that modifies the expression and activity of CYP2C9 can influence the anticoagulant response (Greenblatt and von Moltke, 2005). Many warfarin–drug interactions have been attributed to the metabolic inhibition of the *S*-enantiomer by CYP2C9 (Rehulkova, 2001; Wittkowsky, 2001). It is less likely that significant warfarin–drug or herbal interactions would occur if the minor CYP3A4 metabolic pathway of *S*-warfarin is inhibited. The less potent *R*-warfarin is primarily eliminated by CYP1A2 and interactions are unlikely to occur when the CYP1A2 pathway is competitively inhibited by other drugs or herbals (Wittkowsky, 2001).

In vitro studies have found that various whole extracts from herbals and isolated herbal components inhibit CYP2C9 activities in human liver microsomes (Zhou et al., 2003). The application of in vitro data to assess the risk for in vivo herbal–drug interactions involves a number of pharmacokinetic assumptions such as bioavailability of the product, interindividual variability in absorption, distribution and clearance of the active constituents, and interproduct or interlot variability of the active constituents (Strandell et al., 2004).

A number of herbals and other natural substances may potentially interfere with warfarin therapy. However, information is usually limited to the pharmacological activity of the herbal constituents and therefore, the clinical significance of potential herbal–warfarin interactions is unclear (Heck et al., 2000; Greenblatt and von Moltke, 2005). Possible mechanisms which result in herbal–warfarin interactions include decreased warfarin absorption, decreased platelet aggregation, decreased serum levels of thromboxane, prostaglandin or phospholipase A<sub>2</sub>, decreased synthesis of cyclooxygenase, inhibition of platelet-activating factor, conversion of fibrin to fibrinogen and inhibition of CYP2C9, and vitamin K and coumarin content (Stenton et al., 2002). However, coumarins are weak anticoagulants unless converted to dicoumarol when improperly stored (Boullata, 2005). The nature of the clinical evidence of warfarin–herbal interactions remains predominantly single case reports and case series although proper clinical studies of interactions have begun (Engelsen et al., 2002; Yuan et al., 2004; Jiang et al., 2004; Maurer et al., 1999; Kim and White, 1996; Corrigan and Ulfers, 1981).

#### Warfarin–coenzyme Q10 interactions

Coenzyme Q10 is structurally similar to menaquinone (vitamin K<sub>2</sub>), and may possess procoagulant properties (Heck et al., 2000). However, studies in rats found that coenzyme Q10 did not decrease hypoprothrombinemic response, protein binding, and absorption and distribution of *S*- and *R*-enantiomers

but produced a significant increase in the total clearance of both *R*- and *S*-warfarin (Zhou and Chan, 2001). There are four unevaluable case reports of coenzyme Q10 interacting with warfarin (Landbo and Almdal, 1998; Spigest, 1994). However, the results of a placebo-controlled, double-blind, crossover study demonstrated that 100 mg of coenzyme Q10 daily had no effect on INR in patients receiving stable long-term warfarin therapy (Engelsen et al., 2002). Even though there is conflicting evidence, patients receiving concomitant therapy with warfarin and coenzyme Q10 should be closely monitored.

#### *Warfarin–danshen interactions*

Animal studies in rats have demonstrated oral administration of danshen extract for 3 days significantly altered the overall pharmacokinetics of both *R*- and *S*-warfarin and increased the plasma concentrations of both enantiomers (Chan et al., 1995). There are three published case reports (1 likely and 2 possible) of danshen interacting with warfarin (Tam et al., 1995, Yu et al., 1997). Therefore, patients who consume danshen in combination with warfarin may increase their risk for bleeding.

#### *Warfarin–dong quai interactions*

Dong quai contains coumarin derivatives (Sheu et al., 1987) and data from a study in rabbits showed significantly lower prothrombin times when dong quai was administered concomitantly with warfarin (Lo et al., 1995). Also, there is a case report showing dong quai is likely to interact with warfarin (Page and Lawrence, 1999). Concurrent use of dong quai with warfarin should be avoided.

#### *Warfarin–garlic interactions*

The current evidence that garlic may interact with warfarin is mainly based on case reports of patients who ingested excessive amounts of garlic and developed platelet disorders and/or hemorrhage (Morris et al., 1995; Rose et al., 1990; German et al., 1995; Samson, 1982). There is an unevaluable report of 2 patients who developed elevated INR with concomitant use of garlic and warfarin (Sunter, 1991). In vitro studies have found that garlic oil and the constituent ajoene inhibits platelet aggregation induced by various aggregating agents (Bordia et al., 1998; Apitz-Castro et al., 1986; Lawson et al., 1992). But results of studies that evaluated the effect of garlic on platelet function in humans have been conflicting. A double-blind, placebo-controlled study in 14 men found garlic had no significant effect on platelet aggregation (Morris et al., 1995) and platelet aggregation was not altered with a 10-day course of garlic capsule in 4 healthy subjects. However, continued ingestion of large quantities of raw garlic cloves inhibited platelet aggregation (Samson, 1982) and consumption of essential oil of garlic produced a dose-related inhibition of platelet aggregation in 6 health adults (Bordia, 1978). Patients using warfarin should be cautioned regarding the possible risk of increased bleeding with ingestion of garlic.

#### *Warfarin–ginger interactions*

There is a case report of epistaxis, which can be defined as likely, with significant increase in INR and prolonged PTT that occurred in a 76-year-old female patient taking phenprocoumon (unspecified dose), 1 g colecalciferol, 62.5 mg captopril, 3 mg piretanide, 40 mg isosorbide mononitrate, and 0.1 mg digoxin daily (Kruth et al., 2004). Several weeks prior to the incident, the patient reported she began consumption of unspecified amounts of pieces of dried ginger and ground dried ginger in tea. Both INR and PTT were stabilized by administering vitamin K<sub>1</sub> 10 mg intravenously and 10 mg orally on the third and sixth days following the incident. Phenprocoumon was resumed and the patient's INR was stabilized. There is a report of inhibition of arachidonic acid induced platelet aggregation in a male volunteer who consumed large, unspecified quantities of ginger marmalade (15% raw ginger) (Dorso et al., 1980). However, other studies using either dried (Lumb, 1994) or raw (Srivastava, 1989; Janssen et al., 1996) ginger did not show any effect on platelet function or serum thromboxane levels. Although the evidence for an interaction with ginger and warfarin is inconclusive, patients taking anticoagulants should be advised against consuming large amounts of ginger without consulting their healthcare provider.

#### *Warfarin–*G. biloba* interactions*

Ingestion of 120 mg daily of standardized *G. biloba* extract for 3 months nonselectively inhibited cyclooxygenase-1 (COX-1) mediated thromboxane A<sub>2</sub> and COX-2 mediated prostaglandin-1<sub>2</sub> in patients with type 2 diabetes mellitus. Ginkgolide B, a constituent in *G. biloba*, has been shown to decrease platelet aggregation and ginkgolide B displaces platelet-activating factor (PAF) from its binding sites, thus potentially decreasing blood coagulation (Kudolo et al., 2002).

In a case report of possible interaction in a 78-year-old female stabilized on warfarin (unspecified dose) for 5 years following a coronary artery bypass began taking *G. biloba* (unspecified dose) (Matthews, 1998). Two months following the initiation of *G. biloba*, the patient suffered apraxia, a change in mild to moderate cognitive deficits and an inability to feed herself. A CT-scan revealed a left parietal hemorrhage. The patient's cognitive functions improved following 1 month of rehabilitation and discontinuation of *G. biloba*. However, there is preliminary evidence that suggests *G. biloba* does not increase INR in patients consuming warfarin (Engelsen et al., 2002). Nonetheless, patients on warfarin therapy should be advised to avoid concurrent use of *G. biloba*.

#### *Warfarin–American ginseng (*Panax quinquefolium* L.) interactions*

American ginseng is native to North America and is a distinct species which is related to Asian ginseng but has some differences in chemical constituents. A randomized, placebo-controlled study in 20 healthy young volunteers showed American ginseng antagonized the efficacy of warfarin (Yuan et

al., 2004). Subjects received warfarin 5 mg daily for 3 days during weeks 1 and 4, and American ginseng 1 g twice daily or placebo for 2 weeks. American ginseng produced a modest reduction in INR, peak warfarin levels, and warfarin area under the curve. Therefore, patients receiving warfarin should avoid American ginseng.

#### *Warfarin–Asian ginseng (P. ginseng) interactions*

Ginsenosides are considered the active constituents in Asian ginseng root and in vitro evidence suggests that ginsenosides may inhibit platelet aggregation and inhibit the conversion of fibrinogen to fibrin (Park et al., 1996; Yun et al., 2001). A study in 20 volunteers found that Asian ginseng 100 mg standardized to 4% ginsenosides twice daily for 14 days did not significantly change urinary 6- $\beta$ -OH-cortisol/cortisol ratio, which suggests that Asian ginseng does not induce CYP3A4 (Anderson et al., 2003).

In a case report (defined as possible), a 47-year-old male with a mechanical heart valve experienced a decreased INR 2 weeks after a stabilized regimen of ginseng three times daily (no further information of product) was begun (Janetzky and Morreale, 1997). His drug regimen also included diltiazem, nitroglycerin, and salsalate. The patient's INR of 3–4 had been stable for at least 9 months prior to the event on a dosing regimen of warfarin 5 mg daily, decreased to 1.5 upon use of ginseng supplement, and returned to normal after ginseng was discontinued. In a similar report of a possible interaction, a 58-year-old male with mechanical bileaflet aortic valve was admitted to the hospital with acute anterospectral myocardial infarction and diabetic ketoacidosis. The patient had been optimally maintained on warfarin until 3 months prior to admission, when his INR became unsteady. Echocardiography showed thrombosis on the valve. The author reported that the inability to maintain therapeutic INR levels was likely due to self-treatment with a commercial ginseng product (assumed to be Asian ginseng) for an unspecified time (Rosado, 2003). These case reports suggest that Asian ginseng should be avoided in patients receiving warfarin because of the risk of thrombotic complications. However, a randomized, open-label, three-way crossover study of co-administration of ginseng and warfarin in 12 healthy volunteer did not affect INR, platelet aggregation or pharmacokinetics of *S*- and *R*-warfarin (Jiang et al., 2004).

#### *Warfarin–green tea interaction*

There is a case report of a possible interaction in a 44 year-old patient who was on stable warfarin therapy for a mechanical heart valve. The patient experienced a decreased INR after consuming a large amount of green tea (1 gal/day for 1 week.) (Taylor and Wilt, 1999). Oral administration of the probe drugs dextromethorphan (CYP2D6 activity) and alprazolam (CYP3A4 activity) to 11 healthy volunteers demonstrated that decaffeinated green tea (*Camellia sinensis*) extract did not induce CYP2D6 and 3A4 pathways (Donovan et al., 2004). A study using rabbit whole blood found that green tea is a potent inhibitor of thrombin stimulated platelet thromboxane formation which suggests green

tea extract may be beneficial for treatment of vascular disease, but may also increase the risk of bleeding when used in combination with antiplatelet and anticoagulant drugs (Ali and Afzal, 1987). Therefore, patients on warfarin therapy should not consume large quantities of green tea.

#### *Warfarin–omega fatty acid interactions*

Omega fatty acids, such as those found in fish oil supplements, may potentially interact with anticoagulants. In one case report, a 67-year-old female experienced an increased INR when fish oil and warfarin were administered concurrently (Buckley et al., 2004). The patient had been taking 1 g of fish oil daily in addition to 1.5 mg warfarin daily with a stable INR of 2.8 for at least 5 months. When the dose of fish oil was increased to 2 g daily, the patient's INR rose to 4.3. A decrease in the warfarin dose to 1 mg daily and fish oil to 1 g daily resulted in a subtherapeutic INR while a return to the original regimen of 1.5 mg warfarin and 1 g fish oil daily returned the INR to the normal maintenance levels. The authors hypothesized eicosapentaenoic and docosahexaenoic acids in fish oil effected platelet aggregation or vitamin K dependent coagulation factors. However, results of a placebo-controlled, randomized, double-blinded, parallel study in 16 patients taking stable doses of warfarin suggested that 3 to 6 g of fish oil daily does not significantly affect INR (Bender et al., 1998). Therefore, although the results are conflicting, concomitant use of fish oil (omega fatty acids) with warfarin could theoretically increase the risk of bleeding.

#### *Warfarin–saw palmetto interactions*

Although saw palmetto is generally well tolerated, there is some evidence that the herb may interact with anticoagulation therapy. Administration of 2 probe medications with saw palmetto at commonly recommended doses to 12 healthy subjects demonstrated that saw palmetto did not effect CYP3A4 activity (Markowitz et al., 2003b). An increase in INR in two male patients taking warfarin was reported (defined as unevaluable) with an herbal product containing saw palmetto, curbicin, and vitamin E (Yue and Jansson, 2001). In one patient, the INR returned to normal upon administration of vitamin K, while the INR stabilized in the other patient once the herbal product was discontinued. Although the likely nature of the interaction was a result of the vitamin E component of the product, saw palmetto cannot be ruled out without further investigation. There is a case report of severe intraoperative hemorrhage in a patient taking saw palmetto alone. The patient's bleeding time was elevated and returned to normal within a few days of discontinuing saw palmetto (Cheema et al., 2001). Therefore, patients receiving anticoagulation therapy should be closely monitored with concomitant administration of products containing saw palmetto.

#### *Warfarin–soy interactions*

A single case report of an unevaluable interaction between soy and warfarin has been reported (Cambria-Kiely, 2002). A 70-year-old male with a history of coronary artery bypass and

coronary artery disease taking warfarin 3 mg daily for 7 months in addition to digoxin 0.125 mg daily, atenolol 25 mg daily, lansoprazole 30 mg daily, and lorazepam 0.5 mg twice daily as needed began drinking 480 mL of soy milk daily. Four weeks after starting soy milk consumption, the patient's INR decreased from 2.3 to 1.6, and returned to normal after soy milk was discontinued. Probe extracts administered to 20 volunteers who received a soy extract containing 50 mg isoflavones twice daily found no significantly altered urinary 6- $\beta$ -OH-cortisol/cortisol ratio suggesting soy extract does not induce CYP3A4 (Anderson et al., 2003). Unhydrolyzed soy extract had little effect on CYP1A2, CYP2A6, and CYP2D6 but hydrolyzed soy extract inhibited CYP2C9 and CYP3A4. Patients undergoing anticoagulation therapy should be cautioned against use of large amounts of soy products or should be closely monitored for changes in anticoagulation.

#### *Warfarin–vitamin C interactions*

There have been two case reports of high doses of vitamin C (16 g daily) interacting with warfarin, possibly by causing diarrhea and reducing warfarin absorption (Rosenthal, 1971; Smith et al., 1972). Lower doses of 5 to 10 g daily may reduce warfarin absorption although the effect does not appear to be clinically significant. (Weintraub and Griner, 1974; Feetam et al., 1975; Smith et al., 1972).

#### *Warfarin–vitamin E interactions*

Evidence suggests that daily consumption of more than 400 IU of vitamin E with concomitant warfarin might prolong INR and increase the risk of bleeding due to interference with production of vitamin K-dependent clotting factors (Corrigan, 1982; Corrigan and Marcus, 1974). Vitamin E also potentiates the antiplatelet activity of aspirin in collagen-stimulated platelets (Celestini et al., 2002). Supplementation with 1000 IU *RRR*- $\alpha$ -tocopherol daily for 12 weeks antagonized vitamin K-dependent clotting factors in men and women not taking warfarin (Booth et al., 2004). The risk for interaction between warfarin and vitamin E interaction is probably higher in patients deficient in vitamin E (Corrigan, 1982). A small double-blind clinical trial in which 21 subjects taking chronic warfarin therapy demonstrated doses of 1200 IU were safe in patients taking warfarin, although it is unclear if warfarin is safe in all populations who are concurrently taking vitamin E (Kim and White, 1996).

#### **St. John's wort–drug interactions**

The adverse drug reaction database of the WHO Collaborating Centre for International Drug Monitoring has received 67 case reports of drug interactions with St. John's wort (Mannel, 2004). These case reports suggest St. John's wort induces CYP3A4 and intestinal *p*-glycoprotein. Drugs which are likely to interact as determined by case reports or clinical trials include the immunosuppressants cyclosporine (Bauer et al., 2003) and tacrolimus (Hebert et al., 2004; Bolley et al., 2002), the HIV

protease inhibitor indinavir (Picitelli et al., 2000), the HIV reverse transcriptase inhibitor nevirapine (de Maat et al., 2001), the antineoplastic drugs irinotecan (Mathijssen et al., 2002), imatinib mesylate (Smith et al., 2004), and the benzodiazepines alprazolam (Markowitz et al., 2003c), midazolam (Markowitz et al., 2000), and quazepam (Kawaguchi et al., 2004), amitriptylline (Johns et al., 2002), digoxin (Johns et al., 1999; Mueller et al., 2004), fenoxfenadine (Wang et al., 2002), methadone (Eich-Hochli et al., 2003), simvastatin (Sugimoto et al., 2001), omeprazole (Wang et al., 2004c), theophylline (Nebel et al., 1999), verapamil (Tannergren et al., 2004), and warfarin (Yue et al., 2000). The efficacy of oral contraceptives is likely to be impaired with concurrent St. John's wort (Schwarz et al., 2003). There is a published case report of delayed emergence with use of St. John's wort and general anesthesia (Crowe and McKeating, 2002; Hall et al., 2003). The current available evidence suggests that all herbal medicines including St. John's wort should be discontinued 2 weeks prior to surgery (Hodges and Kam, 2002).

Combining St. John's wort with serotonin selective re-uptake inhibitors and other antidepressants may increase the risk for serotonin syndrome and other central nervous system reactions, and therefore should be avoided. Case reports of likely or possible serotonin syndrome associated with use of St. John's wort have been reported with buspirone, loperamide, nefazodone, paroxetine, sertraline, and venlafaxine (Dannawi, 2002; Fugh-Berman and Ernst, 2001).

Research has demonstrated that constituents of St. John's wort, particularly hyperforin, are potent ligands ( $K(i)=27$  nM) for the nuclear xenobiotic pregnane X receptor which regulates CYP3A (Moore et al., 2000; Watkins et al., 2003). In vitro studies (Obach, 2000) and human studies (Mai et al., 2004; Wang et al., 2004a) have shown that hyperforin and St. John's wort induce CYP3A4. Data suggests that short-term administration of St. John's wort does not induce CYP3A4 and longer treatment is required in order for St. John's wort to induce CYP3A4. Using substrate probes before and after 4 days of co-administration of St. John's wort, researchers found that St. John's wort did not produce significant differences in pharmacokinetic parameters (Markowitz et al., 2000, 2003c). However, administration of St. John's wort long term significantly increased urinary 6- $\beta$ -hydroxycortisol/cortisol ratios which is a surrogate marker for CYP3A4 activity. (Roby et al., 2000; Bauer et al., 2002; Wang et al., 2001). Studies have also found that St. John's wort induces the orphan nuclear receptor *p*-glycoprotein which acts as a key regulator of MDR-1 and many other gene drug transporters (Zhou et al., 2004; Durr et al., 2000; Hennessy et al., 2002). Studies in LS180 cells suggest St. John's wort also induces expression of CYP1A2 (Karyekar et al., 2002). A probe substrate study in humans suggest St. John's wort does not inhibit CYP2D6 (Markowitz et al., 2000; Wang et al., 2004b).

#### **Conclusion**

Based on current evidence from in vitro, in vivo and clinical studies, herbals and other dietary supplements interact

with many drugs. Still, drug–herbal interactions are difficult to evaluate because of the lack of reliability of these products. The interactions often involve drug-metabolizing enzymes and drug transporter systems, although pharmacodynamic interactions can also be involved. Because the pharmacokinetic and pharmacodynamic characteristics of most herbal and other dietary supplements are not completely recognized, potential interactions are not often predictable. Potential interactions are more likely to occur with drugs with narrow therapeutic indexes. The evidence-based evaluation used in the study can be used to evaluate the reliability of case reports.

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