HERB-DRUG INTERACTIONS: WHAT CLINICIANS NEED TO KNOW

John Neustadt, ND

The current information on herb-drug interactions is compelling. Avoiding potential or negative interactions is essential to patient safety, and understanding which herb-drug combinations work synergistically may improve clinical outcomes. Botanical medicines account for approximately 22% of all complementary and alternative medicine (CAM) therapies.[1] A 1997 survey found that up to 70% of all Americans take herbal products, and 18.4% of people on prescription medications combine them with herbs and/or vitamins.[2] Clearly, it is necessary for clinicians to have a working knowledge of herb-drug interactions.

Many clinicians are unfamiliar with this subject, however. In 2000, a survey administered at 3 educational meetings on emergency and internal medicine in Orange and Los Angeles counties, Calif., showed that participating doctors and students had "little familiarity with herbal toxicities and herb-drug interactions."[3] Furthermore, they rated their knowledge of this subject as poor. This article reviews potential and known herb-drug interactions and provides information to help clinicians estimate the relative risk of herb-drug interactions.

MECHANISMS OF INTERACTIONS

Herb-drug interactions follow the same principles as drug-drug interactions. They can be of 2 primary types: pharmacodynamic and pharmacokinetic. Pharmacodynamic interactions relate to the mechanism of action, whereas pharmacokinetics have to do with the absorption, distribution, and elimination of drugs, herbs, and other chemicals. Additionally, concomitant administration of herbs and drugs may decrease the absorption of bioactive compounds by altering the local pH or by binding the compounds in the intestinal lumen and preventing their uptake by enterocytes.

Interference With Absorption

Oral bioavailability of medications can be decreased by this latter mechanism when they are combined with soluble and insoluble fibers;[4] for example, with psyllium (*Plantago psyllium*) or tannins[4] like those found in tea (*Camellia sinensis*), pomegranate (*Punica granatum*), cinnamon (*Cinnamomum* spp), and rhubarb (*Rheum* spp). This was demonstrated in a clinical trial in which patients taking lovastatin with pectin or oat bran experienced an increase in low-density-lipoprotein (LDL) lev-

els, which returned to normal after fiber supplementation was discontinued.[5] The most likely cause of this interaction was a decrease in lovastatin absorption due to binding of lovastatin by pectins or bran fibers in the intestinal lumen.[6]

Drug Metabolism

The liver, intestines, kidneys, and lungs are the sites of drug metabolism and pharmacokinetic interactions.[7-10] Of those, the liver is the major site of drug metabolism, with the intestines playing a secondary yet potentially important role.[11] Drug metabolic pathways historically have been classified into 2 groups—phase I and phase II. These 2 phases work in sequence, with most metabolites of phase I passing through phase II. Phase I enzymes are a super family of hemoproteins called cytochrome P450s (CYP). They oxidize relatively non-polar molecules, increasing their polarity and allowing them to be excreted in the urine. The main CYP isoforms are 1A2, 2D6, 2C9, 2C19, and 3A4.[1,9,10] An estimated 60% of drugs are metabolized and excreted via the CYP3A4-dependant pathway.[12]

Phase II enzymes follow a different chemical process, which is referred to as conjugation. Phase I and phase II activities must be coordinated or the induction of phase I could cause production of too many intermediate metabolites for phase II to process. Similarly, excessive phase II substrates can lead to an increase in reactant concentrations, sometimes with fatal results. For example, CYP2E1 is the major isoform responsible for the bioactivation of acetaminophen (N-acetyl-p-amino-phenol), with CYP1A2, 2A6, 2D6, and 3A4 playing minor roles in this process.[13] When acetaminophen passes through these phase I enzymes, it metabolizes N-acetyl-p-benzoquinone-imine (NAPQI), a toxic intermediate that phase II enzymes must then reduce and conjugate with glutathione before the final substrate is excreted in the urine. Excessive phase I activity can overwhelm phase II enzymes, resulting in a build-up of NAPQI that leads to hepatic centrilobular necrosis.[13] Similarly, prodrugs, which become active only after being modified in the body, can be activated by phase I oxidation and create toxicity. Thus, induction of phase I by herbs could theoretically result in a toxic increase in serum drug concentrations, although this has not been clinically documented.[14]

Another pathway involves the transport protein p-glycoprotein (Pgp). Pgp is a membrane-bound, adenosine triphosphate (ATP)-dependent efflux pump that moves substrates out of cells.[15] It can reduce the therapeutic effect of drugs by increasing their excretion. In addition, Pgp up-regulation by cancer cells and bacteria decreases the amount of drugs that can accumulate in the cells and results in resistance (multi-drug resistance, MDR) to chemotherapeutic regimens and antibiotics. Targeting Pgp to be down-regulated is an area of active research, as it might help to decrease drug resistance and improve clinical outcomes.[16]

CYP and Pgp can be inhibited. This has been demonstrated with herbs in vitro[16-25] and in vivo.[16,26] Although, as mentioned above, this could be beneficial in some cases, inhibition of CYP and Pgp enzymes may adversely increase serum drug concentrations and could lead to ill effects. Grapefruit (Citrus paradisi) has been shown to irreversibly inhibit CYP3A4 activity in vitro,[27] and consuming as little as 200 mL (6.67 oz) can result in clinically significant increases in serum drug concentration.[28,29] Modulation of CYP and Pgp activities are important determinants of drug bioavailability, therapeutic potential, and the risk of adverse events.

Altered Metabolism

Bioactive compounds in herbs are well-known modulators of CYP and Pgp expression and activity in vitro and in vivo.[1,12] A compound isolated from Berberis (Mahonia) spp, 5'-methoxyhydnocarpin (5'-MHC), inhibits bacterial efflux pumps in vitro[30-32] and may have clinical relevance for antibiotic-resistant strains of bacteria. It may also have promise in cancer chemotherapy, as cancer cell Pgp can also be inhibited by 5'-MHC.

On the other hand, herbs or their extracts can induce cancer cell Pgp. When LS180 intestinal carcinoma cells were exposed to St John's wort (SJW, Hypericum perforatum) and its extract, hypericin, in vitro, Pgp was induced, and accumulation of the anticancer drug rhodamine 123, a Pgp substrate, decreased.[33]

Studies on the effects of herbs on CYP and Pgp activities can help to explain changes in serum concentrations in drugs when administered concomitantly with herbs. SJW has had more trials than all other herbs for potential herb-drug interactions. One placebo-controlled, randomized, blinded, parallel-group clinical trial investigated the effects of SJW extracts containing different doses of hyperforin—from 28.9 ± 0.77 mg/day (high-dose group) to 0.04 ± 0.01 mg/day (low-dose group)—for their effects on digoxin pharmacokinetics.[34] Ninety-three "healthy" volunteer men and women aged 18-40 years, were randomly assigned to 1 of 3 study phases. In each phase, the volunteers were further randomized to receive placebo or 1 of 3 SJW extracts (high, medium, and low hyperforin doses).

A 7-day run-in period was conducted during which digoxin was administered to all volunteers at dosages sufficient to reach and maintain a steady-state trough concentration of 1.0 ng/mL ± 20%. Volunteers in the high-dose hyperforin groups were further randomized into 2 groups to receive placebo or co-medication either with 300 mg SJW extract LI 160 (Jarsin 300; Lichtwer Pharma AG, Berlin, Germany) 3 times daily or other SJW preparations manufactured by the researchers delivering a range of hyperforin concentrations for 14 days. Standardized meals were served to all volunteers during the study period.

SJW extract LI 160 consumption resulted in a significant decrease in the maximum serum concentration (Cmax) of digoxin compared to placebo (–37% [95% CI, –42 to –32] vs 0.1% [95% CI, –17 to 17], respectively; P < .05), in the AUC0–24 of digoxin compared to placebo (–24.8% [95% CI, –28.3 to –21.3] vs –2.4% [95% CI, –7.8 to 3.1], respectively; P < .05), and in the digoxin trough concentration compared to placebo (–19% [95% CI, –27 to –11] vs –0.5% [95% CI, –9 to 8], respectively; P < .05). A significant inverse relationship was detected between hyperforin concentration and decreases in the maximum and trough serum concentrations of digoxin. Other in vivo human studies showed that LI 160 and comparable high-dose hyperforin-rich extracts induce intestinal CYP3A4 and Pgp,[35-37] thereby limiting the oral bioavailability of substrate drugs.

Recent research also has identified clinically relevant CYP genetic polymorphisms.[38] There are an estimated 55 human CYP isoforms,[39] and sexual dimorphisms have recently been detected for CYP1A2 and 3A4 isozymes. SJW induced CYP1A2 in females[40] but not males[41] in 2 clinical trials. Allelic variations alter CYP isozyme kinetics and explain changes in rates of drug metabolism.[42] Serum theophylline concentration, which is primarily metabolized by CYP1A2, was not affected by 300 mg SJW (TruNature®, Leiner Health Products, Carson, Calif, standardized to 0.3% hypericin) 3 times daily in males.[43] In another study, 300 mg SJW (Wild Oats Markets, Inc, Boulder, Colo, standardized to 0.3% hypericin) 3 times daily induced CYP3A4 activity to a significantly greater extent in women than in men.[44]

A time-dependent effect of drugs and herbs on CYP also exists with potentially important clinical consequences. Acute administration can decrease drug clearance, whereas long-term administration can induce drug metabolism, either by increasing protein synthesis (CYP3A) or via enzyme stabilization (CYP2E1).[11] Acute administration of the SJW extract hyperforin initially inhibited human hepatocyte CYP3A4 activity in vitro, then induced the enzyme with continued dosing.[45]

Due to difficulties in identifying the active constituents responsible for the modulation of CYP enzymes, the lack of standardization in the dietary supplements

industry, and the influence of genetic polymorphisms on drug clearance, predicting herb-drug metabolic interactions in patients is difficult. To gain a working understanding of herb-drug interactions, clinicians must be able to accurately interpret studies and apply them to their patients' specific circumstances.

ASSESSING THE EVIDENCE

The majority of data on herb-drug interactions are theoretical and based on case reports, in vitro assays, animal studies, and/or speculation.[6] Case reports are frequently cited as unequivocal evidence of dangerous interactions, despite the fact that "published case reports are often incomplete" and "do not allow us to conclude that a causal relationship exists."[6] In a search of Medline, Embase, the Cochrane Library, and the Centralised [sic] Information Service for Complementary Medicine (CISCOM), 187 cases of suspected interactions were found. However, with regard to documentation accuracy, 68.5% of these cases lacked so much information they were classified as "unable to be evaluated" and only 13% were "well-documented." Furthermore, with regard to an assessment of interactions, only 18.5% had "possible interactions."[46] The most common drug was warfarin, and the most common herb was SJW. Case reports may serve as an early warning system, but they are the weakest form of evidence and have to be interpreted critically and with great caution.

in vitro studies can point to possible molecular mechanisms for interactions between herbs and drugs, such as inducing or inhibiting CYP and Pgp activity. Most evidence for the effects of herbs on human CYP and Pgp come from in vitro assays.[17,22-24,47-52] However, doses of herbs or their extracts used in these studies often are not attainable in humans due to the oral bioavailability of the herbs. Thus, these studies do not correspond to therapeutic dosages. For in vitro pharmacokinetics to translate into useful clinical data, researchers must test clinically relevant dosages of herbs and also study the major metabolic pathway for the substrates. If a single pathway is analyzed, such as CYP induction, when Pgp is the predominate enzyme, the in vitro data are not clinically relevant.

For some herbs, in vitro evidence is not confirmed by human clinical trials, such as in the cases of milk thistle (Silybum marianum). This herb is used for its hepatoprotective properties and often is prescribed to protect the liver from potential adverse effects of hepatotoxic drugs such as diflucan. in vitro data indicate milk thistle decreases CYP3A4;[25,53] however, one trial showed that supplementation with 175 mg milk thistle (standardized to 80% silymarin) twice daily for 28 days by 12 healthy volunteers (mean age 25 ± 3.0 years) resulted in no overall change in CYP1A2, CYP2D6, CYP2E1, or CYP3A4 phenotypic expression, and no sex differences in activity.[54] For other herbs, human clinical trials support the in vitro data, which is the case for most SJW preparations tested (Table 2).

CLINICAL DECISION MAKING

Future research will continue to elaborate the complex interactions of drugs and herbs, but clinicians need to be able to provide educated, well thought-out information to patients now. If well-designed clinical trials exist for a given herb-drug interaction, then the answer is easy because data would support or discourage a specific combination of herbs and drugs. If enough in vivo data exist for a strong interaction (either induction or inhibition) between an herb and CYP or Pgp, then similar herb-drug interactions could be expected from other drugs metabolized by the same CYP and Pgp enzymes.

in vitro data and case reports may or may not be accurate and should be evaluated individually for their merit. Most clinicians do not have time to review the minutiae of these studies. In the absence of clinical trials of herb effects on drug clearance, the narrower the therapeutic window of a drug, the stronger the warnings against combining herbs and drugs. Regardless, it would be prudent to monitor appropriate laboratory values if there is any reason for concern. Taking a conservative approach when advising patients about combining herbs and drugs will help protect them against adverse interactions.

John Neustadt, ND, is the founder of Montana Integrative Medicine in Bozeman, Mont. He is a member of the American Association of Naturopathic Physicians' Scientific Affairs Committee. Dr Neustadt has written more than 100 published research reviews and is coauthor with Jonathan Wright, MD, of the book, *Thriving Through Dialysis* (Dragon Art Publishing, Auburn, Wash, 2006).

TABLE 1
LEVELS OF EVIDENCE FOR HERB-DRUG INTERACTIONS

Highest	Human clinical trials of herb effects on drug clearance or relevant laboratory parameters
	Human clinical trials of herb effects on CYP or Pgp activity, combined with a knowledge of CYP- and Pgp-drug interactions
	In vitro studies of herb effects on drug clearance
	In vitro studies of herb effects on CYP or Pgp activity, combined with knowledge of CYP- and Pgp-drug interactions
Lowest	Case reports

TABLE 2
IN VIVO CLINICAL TRIALS OF HERB-DRUG INTERACTIONS

Herb	Preparation	Design	Dose/Duration	Probe drug	Results/Conclusion
Black cohosh (*Cimicifuga racemosa*)	Black cohosh (Solaray, Inc, Park City, Utah), 1090 mg per capsule, standardized to 0.2% triterpenes glycosies	Randomized, cross-over trial N = 12 (6 men, 6 women)	1 capsule 2x/d x28 days	Midazolam (MD) and caffeine followed 24 hours later by chlorzoxazone and debrisoquin given at baseline and after supplementation	There was an approximate 7% mean decrease in CYP2D6 activity with supplementation compared to baseline (P = .02). This may not be clinically relevant, according to the authors. CYP1A2, 2E1, and 3A4 were not significantly affected. No gender-specific differences were observed. [26]
Citrus aurantium	Synephrine (General Nutrition Corp, Pittsburgh, Pa) 350 mg per capsule, standardized to 4% synephrine	Randomized, cross-over trial N = 12 (6 men, 6 women)	1 capsule 2x/d x28 days	MD and caffeine followed 24 hours later by chlorzoxazone and debrisoquin given at baseline and after supplementation	No significant differences in the ratios of MD, caffeine, chlorzoxazone, debrisoquan to their metabolites were found, which the authors interpreted to mean these herbs do not significantly influence CYP1A2, CYP2E1, CYP2D6, or CYP3A4 activity in vivo. No gender-related differences were detected. [54]
Echinacea (*Echinacea purpurea*)	Echinacea (Wild Oats Markets, Inc, Boulder, Colo), 800 mg per capsule	Randomized, cross-over trial N = 12 (6 men, 6 women)	1 capsule 2x/d x28 days	MD and caffeine followed 24 hours later by chlorzoxazone and debrisoquin given at baseline and after supplementation	No significant differences in the ratios of MD, caffeine, chlorzoxazone, debrisoquan to their metabolites were found, which the authors interpreted to mean these herbs do not significantly influence CYP1A2, CYP2E1, CYP2D6, or CYP3A4 activity in vivo. No gender-related differences were detected. [54]
	Echinacea root (Nature's Bounty, Bohemia, NY), 400 mg capsules, containing 1% phenols (caftaric, chlorogenic acid, echinacoside, and cichoric acid) per capsule	Open-label, fixed-schedule, two-period N=12 (6 men, 6 women)	1 capsule 4x/d x8 days	200 mg caffeine, 500 mg tolbutamide, and 30 mg dextromethorphan (DM) po, together with 0.05 mg/kg MD iv.	Midazolam clearance significantly increased by 34% (P = .003) and area under the curve (AUC) decreased by 23% (P = .024). [55]
Garlic (*Allium sativum L*)	Kwai garlic (Lichtwer Pharma, Eatontown, NJ), 100 mg garlic powder per tablet containing 100 g allicin potential, analyzed by the researchers to contain 1.5 ± 0.3 mg alliin and 0.03 ± 0.01 mg S-allyl-L-cysteine	Design not specified N = 14 (9 men, 6 women, all phenotyped as normal metabolizers of CYP2D6)	3 tablets 3x/d x14 days	2 mg alprazolam (ALPZ), 30 mg DM at baseline and after supplementation	No significant change in probe concentrations over baseline. [56]
	Natural Source (city and state not listed) Odourless [sic] Garlic Life Brand, 10 mg garlic extract per tablet, equivalent to 1 g fresh garlic (independently assayed, < 50 g allicin/g extract	Open, nonfasting, two-treatment, two-period, two-sequence crossover study N = 10 (5 men, 5 women)	"8 doses of garlic extract taken twice daily" x4 days. It is unclear if 1 tablet represents 1 dose or more tablets make a dose.	400 mg ritonavir at baseline and after supplementation	No significant changes in ritonavir AUC overall, and no significant gender-related differences, suggesting no net effect on p-glycoprotein (Pgp) and CYP3A4 enzymes. [57]
	Garlic oil (Wild Oats Markets, Inc, Boulder, Colo), 500 mg per capsule	Randomized, cross-over trial N = 12 (6 men, 6 women)	1 capsule 3x/d x28 days	MD and caffeine followed 24 hours later by chlorzoxazone and debrisoquin given at baseline and after supplementation	Compared to baseline, a significant 39% decrease in the 6-hydroxychlorozoxazone-to-chlorozoxazone ratio occurred after supplementation, suggesting CYP2E1 activity was inhibited (P = .030). [44]

TABLE 2 CONTINUED
IN VIVO CLINICAL TRIALS OF HERB-DRUG INTERACTIONS

Herb	Preparation	Design	Dose/Duration	Probe drug	Results/Conclusion
Ginger (*Zingiber officinalis*)	Blackmores Travel Calm Ginger (Blackmores Ltd, Balgowlah, NSW, Australia), 0.4 g ginger rhizome powder per capsule	Open-label, three-way, randomized crossover trial N = 12 men	3 capsules 3x/d x7 days	25 mg warfarin at baseline and after supplementation	No significant differences in international normalization ratio (INR, a standardized measurement of prothrombin time that is used to monitor anticoagulant therapy), platelet aggregation, warfarin clearance, and AUC occurred compared to baseline.[58]
Ginkgo (*Ginkgo biloba*)	Special extract EGb761 (Tavonin; Dr Willmar Schwabe GmbH & Co, Karlsruhe, Germany) equivalent to 2 g ginkgo leaf, 9.6 mg ginkgo flavonglycosides, 2.4 mg ginkgolides and bilobalide per capsule	Open-label, three-way, randomized crossover trial N = 12 men	2 capsules 3x/d x7 days	25 mg warfarin, 1 dose administered with or without pretreatment with ginkgo	No significant differences in INR, platelet aggregation, warfarin clearance, and AUC occurred.[58]
	Ginkgo (Ichoha Sainoshin, Aihoupu Co, Kagoshima, Japan)	N = 14 (6 men, 8 women, with Alzheimer's disease. Volunteers were allowed to continue their medications)	90 mg/day x30 days	5 mg donepezil for at least 20 weeks and until there was no fluctuation in mental status for 28 days, then supplementation was added for another 30 days	Plasma concentration of donepezil was not significantly different during ginkgo administration or 4 weeks after stopping ginkgo compared to baseline. No significant changes occurred in red blood cell cholinesterase concentration or mini-mental status exam results compared to baseline.[59]
	Ginkgold (Nature's Way Products, Springville, Utah), containing 60 mg (50:1) ginkgo leaf extract per tablet, as special extract EGb 761, standardized to 24% ginkgo flavonol glycosides and 6% terpene lactones, including ginkgolides A, B, C, as well as bilobalide and "minimal amounts" of ginkgolic acid	Three-phase study N = 12 (6 men, 6 women)	180 mg 2x/day x15 days	30 mg DM or 2 mg ALPZ at baseline and after supplementation	A 17% significant decrease in ALPZ AUC was detected for all volunteers after treatment with ginkgo compared to baseline (P < .05).[60]
	Ginkgo (Wild Oats Markets, Inc, Boulder, Colo), 60 mg per capsule, standardized to 24% flavone glycosides and 6% terpene lactones	Randomized, crossover trial N = 12 (6 men, 6 women)	1 capsule 4x/d x28 days	MD and caffeine followed 24 hours later by chlorzoxazone and debrisoquin given at baseline and after supplementation	No significant differences in the ratios of MD, caffeine, chlorzoxazone, and debrisoquan to their metabolites were found, which the authors interpreted to mean these herbs do not significantly influence CYP1A2, CYP2E1, CYP2D6, or CYP3A4 activity in vivo. No gender-related differences were detected.[44]
Goldenseal (*Hydrastis canadensis*)	Goldenseal Root Herbal Single (Nature's Way, Springville, Utah), 570 mg per capsule, standardized to 5% alkaloids (2.0% hydrastine and 2.96% berberine, as determined by the authors)	Crossover study N = 11 (6 men, 5 women)	2 capsule 2x/d x14 days	800 mg indinavir at baseline and after supplementation	No significant difference in indinavir pharmacokinetics, including Cmax, renal clearance, or half-life after supplementation compared to baseline.[61]
	Goldenseal (Wild Oats Markets, Inc, Boulder, Colo), 900 mg per capsule	Randomized, cross-over trial N = 12 (6 men, 6 women)	1 capsule 3x/d x28 days	MD and caffeine followed 24 hours later by chlorzoxazone and debrisoquin given at baseline and after supplementation	There was approximately a 40% mean reduction in CYP3A4/5 and CYP2D6 activities after supplementation compared to baseline (*P* < .0001), which may be clinically relevant, according to the authors. No gender-related differences were observed.[26]

TABLE 2 CONTINUED
IN VIVO CLINICAL TRIALS OF HERB-DRUG INTERACTIONS

Herb	Preparation	Design	Dose/Duration	Probe drug	Results/Conclusion
Hawthorne (*Crataegus oxyacantha*)	Hawthorne berry special extract WS 1442 (Dr Willmar Schwabe Pharmaceuticals, Karlsruhe, Germany), 450 mg dry extract hawthorne leaves with flowers standardized to 84.3 mg oligomeric procyanidins per capsule	Open-label, randomized, crossover trial N = 8 (4 men, 4 women)	1 capsule 2x/d x21 days with and without probe	0.25 mg digoxin daily for 10 days or digoxin daily plus hawthorne twice daily for 21 days.	No significant differences in digoxin concentration or pharmacokinetics were found between digoxin-only and digoxin + hawthorne phases.[62]
Kava kava (*Piper methysticum*)	Kava kava (Wild Oats Markets, Inc, Boulder, Colo), 1,000 mg per capsule	Randomized, cross-over trial N = 12 (6 men, 6 women)	1 capsule 2x/d x28 days	MD and caffeine followed 24 hours later by chlorzoxazone and debrisoquin given at baseline and after supplementation	An approximate 40% mean reduction in CYP2E1 activity occurred with supplementation compared to baseline (*P* = .009), which could be clinically relevant, according to the authors. CYP1A2, 2D6, and 3A4 were not significantly affected. No gender-related differences were observed.[26]
Korean ginseng (*Panax ginseng*) root	Korean ginseng root extract (Golden Glow, Queensland, Australia) 0.5 mg, standardized to 8.93 mg ginsenosides as ginsenosides per capsule	Open-label, three-treatment, three-period, three-sequence, randomized, crossover study. N = 12	2 capsules 3x/d x7 days	25 mg warfarin alone and after pretreatment with Korean ginseng	No significant changes in serum warfarin concentrations or international normalized ratio (INR) of prothrombin time were detected compared to baseline.[63]
	Panax ginseng (Wild Oats Markets, Inc, Boulder, Colo), 500 mg per capsule, standardized to 5% ginsenosides	Randomized, cross-over trial N = 12 (6 men, 6 women)	1 capsule 3x/d x28 days	MD and caffeine followed 24 hours later by chlorzoxazone and debrisoquin given at baseline and after supplementation	No significant differences in the ratios of MD, caffeine, chlorzoxazone, and debrisoquan to their metabolites were found, which the authors interpreted to mean these herbs do not significantly influence CYP1A2, CYP2E1, CYP2D6, or CYP3A4 activity in vivo. No gender-related differences were detected.[44]
Milk thistle (*Silybum marianum*)	Milk thistle (Wild Oats Markets, Inc, Boulder, Colo), 175 mg per capsule, standardized to 80% silymarins	Randomized, cross-over trial N = 12 (6 men, 6 women)	1 capsule 2x/d x28 days	MD and caffeine followed 24 hours later by chlorzoxazone and debrisoquin given at baseline and after supplementation	No significant differences in the ratios of MD, caffeine, chlorzoxazone, debrisoquan to their metabolites were found, which the authors interpreted to mean these herbs do not significantly influence CYP1A2, CYP2E1, CYP2D6, or CYP3A4 activity in vivo. No gender-related differences were detected.[54]
St. John's wort (*Hypericum perforatum*)	SJW flowering herb top (Bioglan, no city or state listed) 1 g, standardized to 0.825 mg hypericin and 12.5 mg hyperforin per tablet	Open-label, three-treatment, three-period, three-sequence, randomized, crossover study. N = 12 healthy males	1 tablet 3x/d x14 days	25 mg warfarin alone and after pretreatment with SJW	A 27% and 23% decrease in the AUC of warfarin metabolites S-warfarin and R-warfarin, respectively, was detected, as was a 21% decrease in the half-life of both metabolites, as well as a 29% and 23% increase in renal clearance of the metabolites, respectively (P < .05). INR significantly decreased by 21% compared to baseline (P < .05).[63]

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St. John's wort (*Hypericum perforatum*)	SJW (Jarsin 300; Lichtwer Pharma, Berlin, Germany), which was altered to make 150 mg high-hyperforin SJW capsules (7.0 ± 0.074 mg hyperforin) and low-hyperforin SJW capsules (0.1 ± 0.001 mg hyperforin)	Randomized, crossover trial N = 10 renal transplant patients (9 men, 1 woman, all at least 2 years post-transplant)	2 capsules 3x/d x14 days in addition to the patients normal cyclosporine dosage. After a 27-day washout period, patients switched groups.	Patients' normal cyclosporine regimen	Significantly different AUC values were noted for the 2 hyperforin concentrations ($P < .0001$). Cyclosporine AUC values for high-hyperforin SJW comedication were 45% lower (–37% to –54%) than for low-hyperforin SJW comedication ($P < .05$). 14 days of comedication with high-hyperforin SJW resulted in a 52% decrease in cyclosporine AUC ($P < .05$), a 43% decrease in Cmax and a 55% decrease in Ctrough. To maintain therapeutic serum levels of cyclosporine, the daily cyclosporine dosage had to be increased by 65% compared to baseline after 14 days of comedication with SJW ($P < .05$). The first cyclosporine dose adjustment was required 3 days after starting high-hyperforin SJW. Low-hyperforin SJW did not cause any significant changes in cyclosporine AUC. Daily cyclosporine dosages did not require adjustments during low-hyperforin SJW comedication.[64]
	St. John's wort (Wild Oats Markets, Inc, Boulder, Colo), 300 mg per capsule, standardized to 0.3% hypericin	Randomized, cross-over trial N = 12 (6 men, 6 women)	1 capsule 3x/d x28 days	MD and caffeine followed 24 hours later by chlorzoxazone and debrisoquin given at baseline and after supplementation	Supplementation produced a 98% increase (range, 17%–241%) in the mean 1-hydroxymidazolam (the metabolite of midazolam)-to-midazolam ratio compared to baseline (P < .001), indicating induction of CYP3A4. On average, women had a 74% greater increase relative to baseline than men ($P = .029$). A significant 23% mean increase in renal clearance of debrisoquin was detected ($P = .002$). The mean paraxanthine-to-caffeine ratio significantly increased by 26% ($P = .002$), indicating an induction of CYP1A2. Compared to baseline, a significant 110% increase in CYP2E1 activity occurred after supplementation, as evidenced by the rise in mean 6-hydroxychlorzoxazone-to-chlorzoxazone serum ratio.[44]
	St. John's wort (Movina; Boehringer Ingelheim, Ingelheim, Germany), 300 mg per tablet, standardized to contain 3%-6% hyperforin	Study design unspecified N = 80 males	1 capsule 3x/d x14 days	24 mg verapamil jejunal perfusion given over 100 minutes at baseline and after supplementation. A jejunal perfusion study measures tissue permeability. Drug absorption in humans correlates with the measured human effective permeability values.[65]	AUC of both enantiomers of verapamil (R-verapamil and S-verapamil) significantly decreased by 78% and 80%, respectively, after supplementation compared to baseline (P < .0001). The maximum serum concentration of both enantiomers decreased by 76% and 78%, respectively, after supplementation compared to baseline (P < .0001). AUC of the S- and R- enantiomers of norverapamil, one of the main metabolites of verapamil, also significantly decreased by 51% (P < 0.001) and 63% (P < .0001), after supplementation compared to baseline, respectively.[66]
	St. John's wort (TruNature, Carson, Calif), 300 mg per capsule, standardized to 0.3% hypericin	Randomized, double-blind, placebo-controlled crossover design N = 16 Japanese men	1 capsule 3x/d x14 days	Single oral doses of 10 mg simvastatin lactone, 20 mg pravastatin, or placebo given after 14 days SJW supplementation	AUC of simvastatin hydroxy acid, the active metabolite of simvastatin was significantly reduced by 52% after supplementation compared to placebo, respectively (P < .05). Total concentration of simvastatin lactone and simvastatin hydroxy acid was significantly decreased after supplementation compared to control (P < .05). There were no significant changes in pravastatin pharmacokinetics.[67]
	SJW extract LI160 (Lichtwer Pharma AG, Berlin), 300 mg per capsule standardized to contain 92 g hypericin, 262 g pseudohypericin, and 18.37 mg hyperforin	Single-blind, placebo-controlled parallel study N = 25 (13 men, 12 women)	1 capsule 3x/d x15 days	0.25 mg digoxin per day plus placebo or SJW	A highly significant 33% decrease in digoxin Ctrough ($P = 0.0023$), 25% decrease in digoxin AUC ($P = 0.035$) after 10 days of SJW supplementation. On day 15, a significant 25% reduction in digoxin AUC ($P = 0.035$), a significant 26% reduction in digoxin Cmax ($P = 0.0095$), and a significant 33% reduction in digoxin Ctrough on day 16 occurred ($P = .023$).[68] The effects of LI160 on serum digoxin concentrations in humans is supported by additional clinical trials.[35]

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IN VIVO CLINICAL TRIALS OF HERB-DRUG INTERACTIONS

Herb	Preparation	Design	Dose/Duration	Probe drug	Results/Conclusion
St. John's wort (*Hypericum perforatum*)	SJW extract LI160 (Lichtwer Pharma AG, Berlin, Germany), 300 mg per capsule standardized to contain 92 g hypericin, 262 g pseudohypericin, and 18.37 mg hyperforin	Controlled, open-label study N = 16 men	1 capsule 3x/d x15 days from study days 3 to 15	400 mg voriconazole prior to SJW administration, then 60 minutes after SJW on days 3 and 17	On day 1, the voriconazole AUC increased by 22% compared to control (*P* = .02), then decreased by 59% on day 15 compared to control (*P* = .0004). The authors assert that the initial increase, although significant, is not clinically relevant.[69]
	Esbericum (Schaper & Bruemmer GmbH & Co, Salzgitter, Germany), 60 mg per capsule, standardized to 0.25 mg total hypericins and 0.88 mg hyperforin	Two double-blind, placebo-controlled, parallel-group studies (A & B) N = 28	2 capsules 2x/d on days 2–10, then a single dose on day 11	(A) 1 mg ALPZ and 100 mg caffeine po on days 1 and 11 (B) 500 mg tolbutamide on days 1 and 11; 0.75 mg digoxin per day for 2 days before the first dose of tolbutamide; then 0.25 mg digoxin on days 1–11	No statistically significant changes in pharmacokinetic data were detected for any probe drug except Cmax of tolbutamide, which decreased by 10% in the SJW group compared to placebo at the end of the study period (*P* = .020).[70]
	SJW (Hypericum Buyers Club, Los Angeles, Calif), 300 mg per capsule, standardized to 0.3% hypericin	Unblinded study N = 8 (5 men, 3 women)	1 capsule 3x/d x14 days	100 mg carbamazepine twice daily for 3 days, 200 mg twice daily for 3 days, then 400 mg once daily for 14 days prior to SJW administration	No significant effect on carbamazepine pharmacokinetics by SJW was detected.[71]
	SJW (TruNature, Carson, Calif), 300 mg per capsule, standardized to 0.3% hypericin	Randomized, open-label, crossover study N = 12 healthy Japanese men	1 capsule 3x/d x15 days	400 mg theophylline on two occasions during the 15 days of SJW administration. The days on which theophylline was administered were not specified.	No significant differences in theophylline serum concentrations were found. Theophylline is primarily metabolized by CYP1A2.[43]
	SJW (Lichtwer Pharma AG, Berlin, Germany), 300 mg per tablet, containing 440 g hypericin (actual contents as measured in this study were 444 ± 20 mg SJW containing 840 ± 56 g hypericin and 1100 ± 63 g hyperforin)	Study design not specified N = 10 (2 men, 8 women)	1 capsule 3x/d x18 days with meals	0.1 mg/kg tacrolimus at baseline before SJW administration, then after 14 days of taking SJW	Tacrolimus AUC and Cmax significantly decreased with SJW coadministration (*P* = .004 and *P* = .001, respectively). Time to reach maximum concentration was not significantly changed. Reactions to coadministration varied—the average decrease in AUC was 34% (15%-64%), and the AUC in one volunteer actually increased by 31%.[72]
	SJW (Sundown; Rexall Sundown Inc, Boca Raton, Fla), 300 mg per capsule, labeled as containing 900 g hypericin	Three-period, open-label, fixed-schedule, inpatient study N = 12 healthy volunteers (3 men, 9 women; mean age 32 ± 7 years)	Part 1: control phase—no SJW; 60 mg fexofenadine Phase 2: single-dose of SJW—2 capsules SJW 1x/d plus 60 mg fexofenadine x1 day, then 2 capsules SJW 1x/d x1 day, followed by 1 capsule SJW 3x/d x14–15 days. Part 3: long-term administration of SJW—1 capsule SJW plus 60 mg fexofenadine x1 day All parts were contiguous.	60 mg fexofenadine one hour after SJW administration	A significant 45% increase in fexofenadine Cmax occurred after single-dose SJW administration (*P* < .05), which is "consistent with an inhibition of intestinal wall P-glycoprotein activity and a consequent bioavailabilty of fexofenadine." Long-term SJW administration caused a significant 35% decrease in fexofenadine Cmax (*P* < .05).[73]

TABLE 2 CONTINUED
IN VIVO CLINICAL TRIALS OF HERB-DRUG INTERACTIONS

Herb	Preparation	Design	Dose/Duration	Probe drug	Results/Conclusion
Saw palmetto (*Serenoa repens*)	Saw palmetto (Wild Oats Markets, Inc, Boulder, Colo), 160 mg per capsule, standardized to 85–95% fatty acids and sterols	Randomized, cross-over trial N = 12 (6 men, 6 women)	1 capsule 2x/d x28 days	MD and caffeine followed 24 hours later by chlorzoxazone and debrisoquin given at baseline and after supplementation	No significant differences in the ratios of MD, caffeine, chlorzoxazone, and debrisoquan to their metabolites were found, which the authors interpreted to mean these herbs do not significantly influence CYP1A2, CYP2E1, CYP2D6, or CYP3A4 activity in vivo. No gender-related differences were detected.[54]
Siberian ginseng (*Eleutherococcus senticosus*)	ProstActive (Nature's Way, Springville, Utah), 320 mg per softgel, containing 197.7 mg non-esterified fatty acids, representing 62% of the total extract. Oleic acid and lauric acid were the predominant compounds detected by the authors' independent analysis of the product	Three-phase study N = 12 (6 men, 6 women)	1 capsule per day x14 days	30 mg DM or 2 mg ALPZ at baseline and after supplementation	No significant changes in DM and ALPZ pharmacokinetics were detected. The authors conclude that at this dosage saw palmetto is "unlikely to alter the disposition of coadministered medications primarily dependent on the CYP2D6 or CYP3A4 pathways for elimination."[74]
	Siberian ginseng root extract (Nature's Way, Springville, Utah), 485 mg per capsule	N = 12 (7 men, 5 women)	1 capsule 2x/d x14 days	30 mg DM or 2 mg ALPZ at baseline and after supplementation	No significant differences in DM and ALPZ concentrations were detected after treatment with Siberian ginseng compared to baseline. Gender stratification revealed no significant differences in DM and ALPZ concentrations after treatment compared to baseline.[75]
Valerian (*Valeriana officinalis*)	Valerian (Vitamer; Lake Forest, Calif), 125 mg per capsule	Randomized, cross-over trial N = 12 (6 men, 6 women)	1 capsule 2x/d x28 days	MD and caffeine followed 24 hours later by chlorzoxazone and debrisoquin given at baseline and after supplementation	No significant differences in the ratios of MD, caffeine, chlorzoxazone, and debrisoquan to their metabolites were found, which the authors interpreted to mean these herbs do not significantly influence CYP1A2, CYP2E1, CYP2D6, or CYP3A4 activity. No gender-related differences were detected.[26]

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