

Herb-Drug Interactions: Focus on Pharmacokinetics

By Jerry M. Cott, PhD

ABSTRACT

Recent literature regarding drug-drug, herb-drug, and food-drug interactions must not be ignored; nor can they always be taken at face value. Studies have shown that *St. John's wort* (SJW) (*Hypericum perforatum*) can reduce plasma levels of indinavir, cyclosporin, digoxin, and possibly other drugs as well. Current knowledge regarding the metabolism of these medications suggests that the cytochrome P450 (CYP) drug metabolizing enzyme systems cannot account for all these effects. It has been reported that the P-glycoprotein (Pgp) transmembrane pump is also induced by SJW. Medications that are substrates of both CYP 3A4 and Pgp are of particular concern and may pose special interaction risks when combined with certain foods or botanical products such as SJW.

CNS Spectrums 2001;6(10):827-832

INTRODUCTION

It is essential for clinicians to be aware of the data that is available regarding natural products that are being used by consumers.^{1,2} Herb-drug interactions can be of two primary types: pharmacokinetic and pharmacodynamic. Dynamic interactions are those having to do with the mechanism of action (eg, where the drug actions may be in opposition or in addition to each other). Only kinetic interactions will be considered here. Although some pharmacokinetic information on herbal medicines is available,³ more is needed. Interactions of botanical products with a prescribed medication could increase or decrease the action of the drug, either of which could result in adverse effects.

Rather than a laundry list of reported interactions, this article will summarize the primary types of kinetic interactions, as well as specific reports concerning psychotherapeutic herb-drug interactions, especially those regarding *St. John's wort* (SJW) (*Hypericum perforatum*).

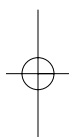
LIVER ENZYMES

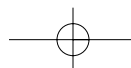
The cytochrome P450 (CYP) system is a family of enzymes particularly concentrated in the liver and intestinal mucosa, but also found in the kidneys, skin, lung, and other tissues. These enzymes are important for phase I drug metabolism. They predominantly catalyze oxidation, reduction, and hydrolysis reactions, which increase polarity of lipophilic compounds. Although 12 gene families have been identified, three categories of these enzymes are of the greatest significance in humans: CYP 2C, CYP 2D6,

and CYP 3A4.^{4,5} CYP 2C (particularly 2C9 and 2C19) is responsible for the metabolism of many anticonvulsants, proton pump inhibitors, antidepressants, and nonsteroidal anti-inflammatory drugs (NSAIDs). CYP 2D6 is found in the liver, intestine, kidney, and brain, where it mediates oxidative metabolism of many medications. This enzyme shows genetic polymorphism, and "poor metabolizers" make up approximately 7% of the Caucasian population. CYP 3A4 is the most abundant hepatic enzyme and accounts for the oxidation of over half of all medications subject to oxidative metabolism. Orally-administered substrates of CYP 3A4 undergo a significant extrahepatic metabolism prior to absorption. Although the activity of CYP 3A4 is distributed monomorphically, there is significant interindividual variation. The benzodiazepine alprazolam is a rather pure substrate for CYP 3A4 and is used as a marker in this enzyme.

Many foods and drugs induce or inhibit (or both) the activity of CYP enzymes. For example, multiple oral dosing (twice daily for 10 days) of grapefruit juice to rats has been reported to inhibit the intestinal metabolism of nifedipine while simultaneously inducing liver microsomal metabolism.⁶ Induction is a slow process, because it depends on the rate of synthesis of the new enzyme. It is usually noticeable after a few days, and may be maximal after 2 weeks. Inhibition is more rapid, and can become maximal within the first 24 hours of exposure to the inhibitor. Likewise, it may reverse more rapidly.

Herbal products usually contain numerous pharmacologically active constituents, including essential oils, tannins, coumarins, anthraquinones, saponins, glycosides, anthocyanins, alkaloids, and flavonoids, all of which may potentially participate in herb-drug interactions. In vitro studies have shown the ability of plant saponins to inhibit the CYP enzymes.⁷ Some coumarins may also inhibit specific CYP isoenzymes.^{8,9} Although a large amount of in vitro data is related to the effects of flavonoid compounds to inhibit CYP isoenzymes,^{10,11} the effects on the enzymes may vary with the tissue being studied.¹² A synergy between the coumarins and the flavonoids may be important in regard to grapefruit inhibition.⁸ The flavonoid quercetin is a constituent of many herbal products, including SJW. It has been shown to inhibit CYP 3A4 in vitro.¹³ The bioflavonoid constituents in grapefruit juice (naringenins and/or coumarins) inhibit intestinal CYP 3A4, and may cause clinically significant drug interactions with felodipine, cyclosporine, terfenadine, and





Feature Article

diazepam.¹⁴⁻¹⁶ Cruciferous vegetables such as Brussels sprouts and broccoli induce CYP 1A2.^{17,18} This enzyme metabolizes many carcinogens, including tobacco-related compounds and charbroiled meat.

Although *in vitro* screening is a common and noninvasive means of screening for potential drug interactions mediated by the cytochromes, it has considerable limitations that may prevent generalization to clinical situations. For instance, *in vitro* drug and enzyme concentrations must approximate those attained *in vivo*, because enzyme specificity may be lost at elevated concentrations. False positives may be generated when crude extracts are incubated directly with human liver cells (often at thousands of times normal plasma levels). The incubates often contain many constituents that would never be absorbed if ingested. Additional contributing factors difficult to simulate are genetic and environmental influences on enzyme expression (the extent of protein binding, hepatic blood flow, and nonhepatic elimination). Finally, the phase II enzymes are subject to polymorphism, can be induced and inhibited, and are subject to rate-limiting kinetics such as the availability of cofactors, and the overall redox status of the organism.

Thus, clinical studies are by far the most useful measure of metabolic alterations because they incorporate the variables mentioned above and take into account the effects of stomach acids, digestive enzymes, transport systems, absorption, and so forth.

Direct (*in vivo*) evidence of SJW interaction with CYP enzymes is inconclusive. Isolated constituent studies suggest the possibility of both inhibition and induction of CYP 3A4. Of human studies on CYP 3A4, results are conflicting. There is evidence that shows a lack of interaction with CYP 2D6 and CYP 1A2.

In Vitro

Commercially available SJW extracts were examined for the potential to inhibit the human CYP enzymes 1A2, 2C9, 2C19, 2D6, and 3A4.¹⁹ Crude SJW methanolic extracts showed inhibition of all these enzymes at very high concentrations. The concentration required to inhibit by 50% (IC₅₀) ranged from 10 mg/mL–1,000 mg/mL. The flavonoid compound I3,I18-biapiogenin inhibited 3A4, 2C9, and 1A2 activities with IC₅₀ values of 0.08, 4.0, and 3.7 mg/mL, respectively. Hyperforin inhibited 2D6, 2D9, and 3A4 with IC₅₀ values of 1.6, 4.4, and 2.3 mg/mL, respectively. The significance of this data is unknown because the concentrations were higher than those attained clinically (eg, hyperforin C_{max} level=~150 ng/mL).²⁰ In addition, the activities of isolated chemical constituents may not be relevant to whole or crude plant extracts.

Experimental evidence for isolated constituents is limited. Moore²¹ has found that within physiologically relevant concentrations, the SJW constituent hyperforin induces CYP 3A4 in hepatocyte cells via the pregnane X nuclear receptor (K_i=27 nM)

In Vivo

One study to evaluate effects on CYP 3A4 was conducted with 13 healthy volunteers who were given 300-mg standardized extract SJW tid for 14 days. Urinary excretion ratios (over 24 hours) of 6-beta-hydroxycortisol/cortisol were used as an index of CYP 3A4 activity both before and after 14 days of SJW treatment. A significant increase (114%) in ratios was shown, and the authors concluded that SJW is an inducer of CYP 3A4.²²

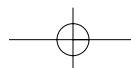
In another study, the effects of SJW on the activity of CYP 2D6 and CYP 3A4 were assessed in seven normal volunteers.²³ Probe substrates included dextromethorphan (for CYP 2D6 activity) and alprazolam (for CYP 3A4 activity). The drugs were orally administered with and without the coadministration of a standardized 300-mg extract of SJW tid for 3 days. Urinary concentrations of dextromethorphan and dextrophan were quantified. Plasma samples were collected (0–60 hours) for alprazolam pharmacokinetic analysis sufficient to estimate time of maximum plasma concentration (T_{max}), C_{max}, half life (t_{1/2}), and area under the curve (AUC). No statistically significant differences were found in any estimated pharmacokinetic parameters, suggesting that short-term treatment with SJW is unlikely to inhibit CYP 2D6 or CYP 3A4 activity. The dose regimen, however, was too short to draw conclusions regarding induction.

Similar probe methodology was used to examine CYP 3A4 and CYP 2D6 in 16 healthy volunteers who were grouped into extensive or poor metabolizers. SJW extract (300 mg tid) was administered for eight days. There was a tendency for induction of CYP 3A4, but there was no effect on CYP 2D6. No significant inhibitory effect on either enzyme was observed after an acute dose of SJW.²⁴ The same group of investigators, using a caffeine probe methodology, also reported on the effect on CYP 1A2 and the phase II enzyme N-acetyltransferase (NAT2) of acute and 8-day SJW treatment in 16 subjects using a caffeine probe methodology. The results showed no significant interactions with CYP 1A2 or NAT2 metabolic pathways.²⁵

***P*-GLYCOPROTEIN**

P-glycoprotein (Pgp) is an adenosine triphosphate (ATP)-dependent pump that moves substrates out of cells. It is an inducible membrane transport protein that was initially discovered by cancer researchers studying multidrug resistance to certain cytotoxic anticancer drugs.²⁶ This resistance was found to result in cross-tolerance or cross-resistance to structurally unrelated compounds due to an overexpression of a family of transporter proteins (Pgp) under the control of the multidrug-resistance gene (MDR-1).²⁷ Pgp is found in normal human renal, intestinal, and biliary epithelia, and in the adrenals, testis, and pregnant uterus where it is a barrier to xenobiotic accumulation and a determinant of the oral bioavailability of many drugs.²⁸ It is also found in both the choroid plexus and cerebral endothelium where it contributes to the blood-brain barrier and limits entry of drugs into the brain.²⁹ Pgp is expressed in normal human T-lym-





phocytes, where it appears to participate in the transport of cytokines (IL-2, IL-4, and IFN- γ).³⁰

Pgp can also be affected by a range of naturally-occurring compounds. Some of these, such as grapefruit juice, also modulate CYP enzymes,⁹ although this may be a random rather than an intrinsic linkage between the two systems.³¹ With drugs that are substrates of both Pgp and CYP 3A4 (such as indinavir and cyclosporin), presystemic metabolism would take place in a synergistic fashion.³² This could result in large decreases in plasma levels by agents that induce expression of both proteins. Reactive oxygen species (ROS) downregulate the expression of Pgp.³³ Because many medicinal plant constituents are antioxidants, this mechanism could play a significant role in the proposed interactions. Several naturally-occurring flavonoids (many of which are antioxidants) bind the protein with high affinity.³⁴ Rosemary (*Rosmarinus officinalis*) extracts appear to inhibit transport into cells expressing Pgp by preventing the binding of the substrate to the Pgp protein.³⁵ The antioxidants in rosemary are polyphenols, rather than flavonoids.³⁶ Methoxyflavones from orange juice are reported to inhibit Pgp-mediated transport of vinblastine into Caco-2 cells,³⁷ whereas the antioxidant flavones quercetin and kaempferol induced expression of UDP-glucuronosyltransferases and Pgp protein in Caco-2 cell monolayers.³⁸

SJW has recently been reported to induce Pgp, as well as CYP 3A4. The administration of SJW extract to rats or humans for 14 days resulted in a 3.8-fold and 1.4-fold increase of intestinal Pgp expression, respectively.³⁹

ST. JOHN'S WORT: DRUG INTERACTIONS

Although SJW shows monoamine oxidase (MAO) inhibition *in vitro*, this effect has not been displayed *in vivo*, nor have there been any reported cases of MAO inhibitor-associated hypertension in humans using SJW.⁴⁰ Although SJW has been reported to inhibit serotonin, norepinephrine, and dopamine uptake into synaptosomes *in vitro*,⁴¹ the concentrations required are unrealistically high. In fact, a recent study suggests that the reported uptake inhibition is only an artifact of the assay system. It does not bind to the serotonin uptake site like a true uptake inhibitor; rather it releases monoamines in a similar way to reserpine.⁴² SJW was the subject of a recent monograph that includes a review of its pharmacology and toxicology.⁴³

Cyclosporine

The acute rejection of cardiac grafts in two male patients in their early 60s was recently reported.⁴⁴ In both cases, immunosuppression was maintained with a standard triple therapy of azothiaprime, cyclosporine, and corticosteroids. Both patients were hospitalized due to early signs of rejection 3 weeks after beginning standardized SJW at 300 mg tid. In both cases, cessation of SJW led to an increase in cyclosporine levels. Both patients were eventually stabilized and recovered.⁴⁴ In another report, a 29-year-old woman

who had received a cadaveric kidney and pancreas transplant with stable organ function and stable cyclosporine concentrations began self-medicating with SJW. After taking SJW supplements for 4–8 weeks, her cyclosporine concentrations became subtherapeutic; this was associated with organ rejection. Four weeks after stopping SJW, her cyclosporine concentrations returned to therapeutic levels.⁴⁵

Cyclosporine is known to be a substrate of CYP 3A4, but CYP 3A4 induction by SJW may not be responsible for the entire cyclosporine interaction. Much of the oral bioavailability variation in cyclosporine was ascribed previously to CYP 3A4 variability. However, this variation is now known to be caused by Pgp, variably reducing the rate of intestinal absorption.⁴⁶ Thus, SJW extracts may have reduced oral bioavailability of cyclosporin by inducing Pgp, as well as CYP 3A4.³⁹ In any event, the potential interaction of SJW with cyclosporine is extremely serious; therefore, coadministration of the two agents should be avoided.

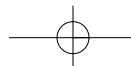
Digoxin

Currently, there is no direct evidence for an influence of SJW extracts or isolated compounds on Pgp activity or expression. However, the recent clinical study on the digoxin-SJW interaction implies that Pgp modulation may also be involved here, because digoxin is a known substrate of Pgp transport but is not metabolized by CYP enzymes. Healthy volunteers were brought to steady state after 5 days of treatment with digoxin.⁴⁷ The subjects continued to receive digoxin (0.25 mg/day) either with placebo (n=12) or SJW 900 mg/day (LI160; n=13) for another 10 days. No statistically significant changes were observed after the initial dose of SJW extract. However, 10 days of treatment with the extract resulted in a 25% decrease of digoxin AUC ($P=.0035$) and a reduction in trough concentrations and C_{max} of 33% ($P=.0023$) and 26% ($P=.0095$), respectively.

Human Immunodeficiency Virus Protease Inhibitors

Human immunodeficiency virus (HIV) patients are very likely to be taking a number of medications concurrently. They are also likely to be taking SJW for various reasons. Several reports suggest extreme caution should be used with respect to the potential for drug interactions in this sensitive group of patients. Piscitelli and colleagues⁴⁸ carried out a clinical study on the effects of SJW on plasma levels of the HIV protease inhibitor indinavir in healthy, non-HIV subjects. A baseline steady state with indinavir (three 800-mg doses) over 24 hours was established, and after a fourth dose on the next day, kinetic parameters were established. The same dose regimen was repeated after 14 days of standardized SJW extract consumption at 300 mg tid. There was a large (57%) reduction in the indinavir AUC after SJW therapy. Although the exact mechanism of this interaction is unclear, indinavir is a substrate of CYP 3A4. However, as with cyclosporin, indinavir is also a substrate of Pgp.⁴⁹





Feature Article

Warfarin

A crossover study examined the effect of SJW extract (LI160) on a single dose of phenprocoumon (an anticoagulant closely related to warfarin) in 10 healthy males 18–50 years of age.⁵⁰ Subjects received SJW (300 mg tid) or placebo for 11 days; on day 11 each subject received a single dose of phenprocoumon (12 mg). SJW resulted in a significant decrease (~17%; $P=.007$) in the AUC of free phenprocoumon compared with placebo.

A letter to *The Lancet* from the Swedish Medical Products Agency (MPA) reported seven cases in which patients who had been stabilized on warfarin had experienced reduced bleeding times during SJW consumption.⁵¹ No thromboembolic complications were noted, and either the SJW was discontinued or the warfarin dose was adjusted. The authors suggested the cause to be an interaction between SJW and CYP 2C9 (the primary liver enzyme associated with warfarin metabolism), although there was no direct evidence for this. Another possible explanation for the interaction is reduced intestinal absorption due to induction of Pgp.

Oral Contraceptives

The same *Lancet* letter cited above⁵¹ also mentions reports of intermenstrual (n=8) or changed (n=1) menstrual bleeding in women (23–31 years of age) who had been taking long-term oral contraceptives and had recently started taking SJW (within the previous week in five of the cases). No details are given, but the authors suggest that induction of CYP 3A4 by SJW is responsible, because steroids are known substrates of CYP 3A4. These reports resulted in the Swedish MPA contacting marketers of SJW and requesting that a warning be added to the labeling and that studies on the extent and implications of these interactions be carried out. To date, there have been no reports of decreased plasma levels of steroid hormones or unwanted pregnancies associated with SJW.

Theophylline

Increased bioavailability of theophylline in human subjects (increased C_{max}, AUC, and elimination half-life) has been reported when the drug is combined with certain food substances, including piperine from black pepper⁵² and a high-carbohydrate, low-protein diet.⁵³ Theophylline has been reported to be metabolized (by demethylation) to a significant degree by CYP 1A2 in human liver microsomes.^{54,55} As already noted, CYP 1A2 enzymes are induced by tobacco, charbroiled meat, and cruciferous vegetables. There is no in vivo data showing a potential for CYP 1A2 and SJW interaction. On the contrary, an 8-day treatment with SJW in 16 subjects showed no effects on CYP 1A2.²⁵ Although an interaction between theophylline and SJW has been cited dozens of times in the literature, the published report referred to is a single case of a 42-year-old woman. She smoked half a pack of cigarettes daily and had taken 11 prescription medications in addition to SJW for the previous

2 months. On cessation of SJW, her plasma theophylline levels rose within 7 days.⁵⁶ This same article also provided in vitro data suggesting induction of CYP 1A2 with pure hypericin at concentrations several hundred times greater than levels found in plasma. The case is hard to evaluate and does not constitute evidence for a SJW-theophylline interaction. CYP 2E1 may also be involved in theophylline metabolism.⁵⁷ Alcohol is known to induce this enzyme, but no mention was made in the report of alcohol consumption or other dietary factors having influenced CYP 1A2. Until additional in vivo data are available for SJW and CYP 1A2, little can be said about interaction potential.

Carbamazepine

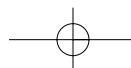
Eight healthy volunteers received 100 mg of carbamazepine bid for 3 days, 200 mg bid for 3 days, and then 400 mg once daily for 14 days. On the last day, blood samples were taken. Then, for an additional 14 days, the subjects took 300 mg SJW (0.3% hypericin) tid with meals and carbamazepine (400 mg/day) for an additional 14 days. On day 35, plasma samples were analyzed for carbamazepine and its metabolite, carbamazepine-10,11-epoxide. There were no significant differences in carbamazepine concentrations at peak, trough, or AUC before and after the administration of SJW.⁵⁸ This suggests that SJW is either not a particularly powerful CYP 3A4 inducer, or that it cannot induce carbamazepine metabolism beyond the extent to which it induces itself.

INTERACTIONS OF OTHER PSYCHOACTIVE BOTANICALS

Ginkgo Interactions

Some of the observed effects of ginkgo leaf extract, particularly the constituent ginkgolide B, are thought to involve the inhibition of platelet-activating factor (PAF).⁵⁹ Thus, theoretically, ginkgo could have anticoagulant effects. There have been several reports of bleeding associated with ginkgo treatment. The first was a case of spontaneous bilateral subdural hematoma in a 33-year-old Korean woman who was also treated with acetaminophen and ergotamine/caffeine.⁶⁰ It has been reported that a subdural hematoma occurred in a patient who combined coumadin with ginkgo, and spontaneous bleeding from the iris occurred in a patient who was also receiving chronic aspirin after bypass surgery.⁶¹ In a recent case, a 61-year-old man who had been taking ginkgo at a daily dose of 120–160 mg experienced subarachnoid hemorrhage and a mildly increased bleeding time of 6 minutes.⁶² No other medications were mentioned in this report. All of these patients recovered. In an ex vivo mouse model, the antiplatelet and antithrombotic effects on adenosine diphosphate-induced platelet aggregation by oral treatment with ticlopidine was enhanced by coadministration of the ginkgo extract EGb 761.⁶³ A clinical trial examining bleeding time was conducted in human volunteers.⁶⁴ EGb 761 had no effect on this parameter by itself and did not





increase the effect of aspirin. Authors of another clinical trial designed to evaluate effects of ginkgo on blood sugar reported no changes in coagulation tests that included fibrinogen, prothrombin time, and partial thromboplastin time.⁶⁵ Despite the lack of anticoagulant activity in these clinical trials, ginkgo theoretically reduces platelet aggregation by inhibiting PAF. Thus, caution would suggest that concurrent use of anticoagulants should probably be avoided. No other interactions are known.

Kava

In contrast to some earlier German reports,⁶⁶ a recent clinical trial showed an additive effect of kava and alcohol on impairment and cognition. The hypnotic actions of kava and alcohol were also reported to be additive when given together to mice.⁶⁷

One anecdotal report⁶⁸ suggests kava may interact with benzodiazepine metabolism. A 54-year-old man on daily doses of alprazolam, cimetidine, and terazosin was hospitalized after experiencing an acute change in mental status 3 days after he began taking kava. He recovered from his lethargy and disorientation within several hours. This report was titled: "Coma From the Health Food Store: Interaction Between Kava and Alprazolam." No other interactions have been reported.

CONCLUSION

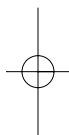
Reports of interactions of medications and botanicals are becoming increasingly common and are often alarmist in tone. The application of certain pharmacokinetic principles is necessary to aid in determining the clinical relevance of some of these reports. SJW is capable of inhibiting CYP 3A4 acutely and inducing it after repeated doses. It can also induce the drug-transport protein Pgp. Thus, drugs that are substrates of both systems (eg, indinavir and cyclosporine) are of particular concern. Naturally-occurring dietary constituents can also have major effects on drug availability. However, once this information is better understood it can be put to use. For example, the combination of grapefruit juice with expensive medications such as protease inhibitors, sildenafil, or cyclosporine would allow the use of smaller doses (effects could be offset by induction of Pgp, however). Unexpected pharmacokinetic interactions are always undesirable. More in vivo data is badly needed to make sense of the plentiful but contradictory in vitro data. Lists of substrates, inducers, and inhibitors of the various enzymes systems are updated regularly and can be found on the Internet at medicine.iupui.edu/flockhart/.

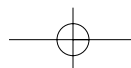
At this point in time, it would appear that SJW, ginkgo, and kava do not pose a significant risk of interaction with the majority of commonly used medications. Patients who are prescribed any of the specific medications that require precise plasma levels in order to be efficacious while minimizing toxicity should be monitored closely, and should be cautioned about possible serious interactions with other medications as well as many foods. The patients would be

well advised to avoid experimenting with herbal medicines without the knowledge of their healthcare provider. **CNS**

REFERENCES

1. Fugh-Berman A, Cott JM. Dietary supplements and natural products as psychotherapeutic agents. *Psychosom Med*. 1999;61:712-728.
2. Wong AH, Smith M, Boon HS. Herbal remedies in psychiatric practice. *Arch Gen Psychiatry*. 1998;55:1033-1044.
3. De Smet PA, Brouwers JR. Pharmacokinetic evaluation of herbal remedies: basic introduction, applicability, current status and regulatory needs. *Clin Pharmacokinet*. 1997;32:427-436.
4. Hardman JG, Limbird LE, Molinoff PB, et al, eds. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. New York, NY: McGraw-Hill; 1996:11-14.
5. Caraco Y. Genetic determinants of drug responsiveness and drug interactions. *Ther Drug Monit*. 1998;20:517-524.
6. Mohri K, Uesawa Y, Sagawa K-I. Effects of long-term grapefruit juice ingestion on nifedipine pharmacokinetics: induction of rat hepatic P-450 by grapefruit juice. *Drug Metab Dispos*. 2000;28:482-486.
7. Kim HJ, Chun YJ, Park JD, et al. Protection of rat liver microsomes against carbon tetrachloride-induced lipid peroxidation by red ginseng saponin through cytochrome P450 inhibition. *Planta Med*. 1997; 63:415-418.
8. Tirillini B. Grapefruit: the last decade acquisitions. *Fitoterapia*. 2000;71 (suppl 1):S29-S37.
9. Ohnishi A, Matsuo H, Yamada S, et al. Effect of furanocoumarin derivatives in grapefruit juice on the uptake of vinblastine by Caco-2 cells and on the activity of cytochrome P450 3A4. *Br J Pharmacol*. 2000; 130:1369-1377.
10. Obermeier MT, White RE, Yang CS. Effects of bioflavonoids on hepatic P450 activities. *Xenobiotica*. 1995;25:575-584.
11. Henderson MC, Miranda CL, Stevens JF, et al. In vitro inhibition of human P450 enzymes by prenylated flavonoids from hops, *Humulus lupulus*. *Xenobiotica*. 2000;30:235-251.
12. Ueng YF, Shyu CC, Lin YL, et al. Effects of baicalin and wogonin on drug-metabolizing enzymes in C57BL/6J mice. *Life Sci*. 2000;67:2189-2200.
13. Li Y, Wang E, Patten CJ, et al. Effects of flavonoids on cytochrome P450-dependent acetaminophen metabolism in rats and human liver microsomes. *Drug Metab Dispos*. 1994;22:566-571.
14. Lown KS, Bailey DG, Fontana RJ, et al. Grapefruit juice increases felodipine oral availability in humans by decreasing intestinal CYP3A protein expression. *J Clin Invest*. 1997;99:2545-2553.
15. Fuhr U. Drug interactions with grapefruit juice: extent, probable mechanism and clinical relevance. *Drug Saf*. 1998;18:251-272.
16. Ozdemir M, Aktan Y, Boydag BS, et al. Interaction between grapefruit juice and diazepam in humans. *Eur J Drug Metab Pharmacokinet*. 1998;23:55-59.
17. Kall MA, Vang O, Clausen J. Effects of dietary broccoli on human in vivo drug metabolizing enzymes: evaluation of caffeine, oestrone and chlorzoxazone metabolism. *Carcinogenesis*. 1996;17:793-799.
18. Fontana RJ, Lown KS, Paine MF, et al. Effects of a char-grilled meat diet on expression of CYP3A, CYP1A, and P-glycoprotein levels in healthy volunteers. *Gastroenterology*. 1999;117:89-98.
19. Obach RS. Inhibition of human cytochrome P450 enzymes by constituents of St. John's wort, an herbal preparation used in the treatment of depression. *J Pharmacol Exp Ther*. 2000;294:88-95.
20. Biber A, Fischer H, Romer A, et al. Oral bioavailability of hyperforin from hypericum extracts in rats and human volunteers. *Pharmacopsychiatry*. 1998;31(suppl 1):36-43.
21. Moor LB, Goodwin B, Jones SA, et al. St. John's wort induces hepatic drug metabolism through activation of the pregnane X receptor. *Acad Sci U S A*. 2000;97:7500-7502.
22. Roby CA, Anderson GD, Kantor E, et al. St John's wort: effect on CYP3A4 activity. *Clin Pharmacol Ther*. 2000;67:451-457.





Feature Article

23. Markowitz JS, DeVane CL, Boulton DW, et al. Effect of St. John's wort (*Hypericum perforatum*) on cytochrome P-450 2D6 and 3A4 activity in healthy volunteers. *Life Sci*. 2000;66:PL133-PL139.
24. Ereshefsky B, Gewertz N, Lam YWF, et al. Determination of SJW differential metabolism at CYP2D6 and CYP3A4 using dextromethorphan probe technology. In: *Abstracts from the 39th Annual Meeting of the New Clinical Drug Evaluation Unit*; June 1999; 130. Boca Raton, FL.
25. Gewertz N, Ereshefsky B, Lam YWF, et al. Determination of differential effects of St. John's wort on the CYP1A2 and NAT2 metabolic pathways using caffeine probe technology. In: *Abstracts from the 39th Annual Meeting of the New Clinical Drug Evaluation Unit*. 1999; 131. Boca Raton, FL.
26. Johnstone RW, Ruefli AA, Smyth MJ. Multiple physiological functions for multidrug transporter P-glycoprotein? *Trends Biochem Sci*. 2000;25:1-6.
27. Yu, D. K. The contribution of P-glycoprotein to pharmacokinetic drug-drug interactions. *J Clin Pharmacol*. 1999;39:1203-1211.
28. Tanigawara, Y. Role of P-glycoprotein in drug disposition. *Ther Drug Monit*. 2000;22:137-140.
29. Sugiyama Y, Kusuhara H, Suzuki H. Kinetic and biochemical analysis of carrier-mediated efflux of drugs through the blood-brain and blood-cerebrospinal fluid barriers: importance in the drug delivery to the brain. *J Control Release*. 1999;62:179-186.
30. Drach J, Gsur A, Hamilton G, et al. Involvement of P-glycoprotein in the transmembrane transport of interleukin-2 (IL-2), IL-4, and interferon-gamma in normal human T lymphocytes. *Blood*. 1996;88:1747-1754.
31. Kim RB, Wandel C, Leake B, et al. Interrelationship between substrates and inhibitors of human CYP3A and P-glycoprotein. *Pharm Res*. 1999;16:408-414.
32. Hochman JH, Chiba M, Nishime J, et al. Influence of P-glycoprotein on the transport and metabolism of indinavir in Caco-2 cells expressing cytochrome P-450 3A4. *J Pharmacol Exp Ther*. 2000;292:310-318.
33. Wartenberg M, Fischer K, Hescheler J, et al. Redox regulation of P-glycoprotein-mediated multidrug resistance in multicellular prostate tumor spheroids. *Int J Cancer*. 2000;85:267-274.
34. Maitrejean M, Comte G, Barron D, et al. The flavanolignan silybin and its hemisynthetic derivatives: a novel series of potential modulators of P-glycoprotein. *Bioorg Med Chem Lett*. 2000;10:157-160.
35. Plouzek CA, Ciolino HP, Clarke R, et al. Inhibition of P-glycoprotein activity and reversal of multidrug resistance in vitro by rosemary extract. *Eur J Cancer*. 1999;35:1541-1545.
36. Offord EA, Mace K, Avanti O, et al. Mechanisms involved in the chemoprotective effects of rosemary extract studied in human liver and bronchial cells. *Cancer Lett*. 1997;114:275-281.
37. Takanaga H, Ohnishi A, Yamada S, et al. Polymethoxylated flavones in orange juice are inhibitors of P-glycoprotein but not cytochrome P450 3A4. *J Pharmacol Exp Ther*. 2000;293:230-236.
38. Bock KW, Eckle T, Ouzzine M, et al. Coordinate induction by antioxidants of UDP-glucuronosyltransferase UGT1A6 and the apical conjugate export pump MRP2 (multidrug resistance protein 2) in Caco-2 cells. *Biochem Pharmacol*. 2000;59:467-470.
39. Dürr D, Stieger B, Kullak-Ublick GA, et al. St John's wort induces intestinal P-glycoprotein/MDR1 and intestinal and hepatic CYP3A4. *Clin Pharmacol Ther*. 2000;68:598-604.
40. Cott JM. In vitro receptor binding and enzyme inhibition by *Hypericum perforatum* extract. *Pharmacopsychiatry*. 1997;30(suppl. 2):108-112.
41. Müller WE, Rolli M, Schäfer C, et al. Effects of *Hypericum* extract (LI160) in biochemical models of antidepressant activity. *Pharmacopsychiatry*. 1997;30(suppl 2):102-107.
42. Gobbi M, Valle FD, Ciapparelli C, et al. *Hypericum perforatum* L. extract does not inhibit 5-HT transporter in rat brain cortex. *Naunyn Schmiedebergs Arch Pharmacol*. 1999;360:262-269.
43. Upton R, Graff A, Williamson E, et al. American Herbal Pharmacopoeia and Therapeutic Compendium on St. John's wort *Hypericum perforatum*: Quality control, analytical and therapeutic monograph. *HerbalGram*. 1997;40 (suppl):1-32.
44. Ruschitzka F, Meier PJ, Turina M, et al. Acute heart transplant rejection due to Saint John's wort. *Lancet*. 2000;355:548-549.
45. Barone GW, Gurley BJ, Ketel BL, et al. Drug interaction between St. John's wort and cyclosporine. *Ann Pharmacother*. 2000;34:1013-1016.
46. Lown KS, Mayo RR, Leichtman AB, et al. Role of intestinal P-glycoprotein (mdr1) in interpatient variation in the oral bioavailability of cyclosporine. *Clin Pharmacol Ther*. 1997;62:248-260.
47. John A, Brockmoller J, Bauer S, et al. Pharmacokinetic interaction of digoxin with an herbal extract from St. John's wort (*Hypericum perforatum*). *Clin Pharmacol Ther*. 1999;66:338-345.
48. Piscitelli SC, Burstein AH, Chaït D, et al. Indinavir concentrations and St. John's wort. *Lancet*. 2000;355:547-548.
49. Choo EF, Leake B, Wandel C, et al. Pharmacological inhibition of P-glycoprotein transport enhances the distribution of HIV-1 protease inhibitors into brain and testes. *Drug Metab Dispos*. 2000;28:655-660.
50. Maurer A, John A, Bauer S, et al. Interaction of St. John's wort extract with phenprocoumon. *Eur J Clin Pharmacol*. 1999;55:A22.
51. Yue Q-Y, Bergquist C, Gerdén B. Safety of St. John's wort (*Hypericum perforatum*). *Lancet*. 2000;355:576-577.
52. Bano G, Raina RK, Zutshi U, et al. Effect of piperine on bioavailability and pharmacokinetics of propranolol and theophylline in healthy volunteers. *Eur J Clin Pharmacol*. 1991;41:615-617.
53. Walter-Sack I, Klotz U. Influence of diet and nutritional status on drug metabolism. *Clin Pharmacokinet*. 1996;31:47-64.
54. Ha HR, Chen J, Freiburghaus AU, et al. Metabolism of theophylline by cDNA-expressed human cytochromes P-450. *Br J Clin Pharmacol*. 1995;39:321-326.
55. Lee H, Yeom H, Kim YG, et al. Structure-related inhibition of human hepatic caffeine N3-demethylation by naturally occurring flavonoids. *Biochem Pharmacol*. 1998;55:1369-1375.
56. Nebel A, Schneider BJ, Baker RK, et al. Potential metabolic interaction between St. John's wort and theophylline. *Ann Pharmacother*. 1999;33:502.
57. Kharasch ED, Thummel KE, Mhyre J, et al. Single-dose disulfiram inhibition of chlorzoxazone metabolism: a clinical probe for P450 2E1. *Clin Pharmacol Ther*. 1993;53:643-650.
58. Burstein AH, Horton RL, Dunn T, et al. Lack of effect of St John's wort on carbamazepine pharmacokinetics in healthy volunteers. *Clin Pharmacol Ther*. 2000;68:605-612.
59. Braquet P. Proofs of involvement of PAF-acether in various immune disorders using BN 52021 (ginkgolide B): a powerful PAF-acether antagonist isolated from *Ginkgo biloba* L. *Adv Prostaglandin Thromboxane Leukot Res*. 1986;16:179-198.
60. Rowin, J, Lewis, SL. Spontaneous bilateral subdural hematomas associated with chronic *Ginkgo biloba* ingestion. *Neurology*. 1996; 46:1775-1776.
61. Rosenblatt M, Mindel J. Spontaneous hyphema associated with ingestion of ginkgo biloba extract. *N Engl J Med*. 1997;336:1108.
62. Vale S. Subarachnoid haemorrhage associated with ginkgo biloba. *Lancet*. 1998;352:36.
63. Kim YS, Pyo MK, Park KM, et al. Antiplatelet and antithrombotic effects of a combination of ticlopidine and ginkgo biloba ext (EGb 761). *Thromb Res*. 1998;91:33-38.
64. Busse W. EGb 761 has no effect on bleeding time in human volunteers. Paper presented at: "Nature's Medicine: Potions or Poisons," College of Pharmacy at Nova Southeastern University; April 6-8, 2001; Davie, Florida.
65. Kudolo GB. The effect of 3-month ingestion of *Ginkgo biloba* extract on pancreatic beta-cell function in response to glucose loading in normal glucose tolerant individuals. *J Clin Pharmacol*. 2000;40:647-654.
66. Foo H, Lemon J. Acute effects of kava, alone or in combination with alcohol, on subjective measures of impairment and intoxication and on cognitive performance. *Drug Alcohol Rev*. 1997;16:147-155.
67. Jamieson DD, Duffield PH. Positive interaction of ethanol and kava resin in mice. *Clin Exp Pharmacol Physiol*. 1990;17:509-514.
68. Almeida JC, Grimsley EW. Coma from the health food store: interaction between kava and alprazolam. *Ann Intern Med*. 1996;125:940.

