

## CLINICALLY SIGNIFICANT PHARMACOKINETIC DRUG-HERBAL DIETARY SUPPLEMENTS INTERACTIONS

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**ABSTRACT** Most commercially available botanical supplements exhibit considerable variability in phytochemical profiles, and label claims for "standardized" marker compounds can deviate considerably from actual content. Such variations can have significant influence on results of clinical studies evaluating dietary supplements efficacy or its herb-drug interaction risk.

There are also plant extracts that can influence the drug disposition or can act as inhibitors or inducers of CYP isoforms.

In summary, dosage forms containing standardized herbal extracts, when administered at per label recommended doses, do not pose a risk for clinically relevant herb-drug interactions. However, daily doses exceeding these doses or prolonged treatment may increase prospects for interactions.

**KEYWORDS:** pharmacokinetic, herb-drug interaction, dietary supplements, metabolic enzymes, transporter activity.

### INTRODUCTION

By now, plants that were most likely responsible to produce clinically important herb-drug interactions were those whose active principles act as inhibitors of cytochrome P450 (CYP) enzyme activity (e.g., *Hydrastis canadensis*, *Piper nigrum*, *Cimicifuga racemosa*, *Schisandra chinensis*) or function as ligands for orphan nuclear receptors (e.g., *Hypericum perforatum*).

The aim of this paper is to assess the clinical relevance over the risk of the interactions that popular dietary supplements may pose when taken concomitantly with conventional medications.

### MATERIALS AND METHODS

Dietary supplements containing active principles that act as inducers or inhibitors of cytochrome P450 were subjected for investigation for clinically relevant interactions with the allopathic drugs.

A retrospective study of data collected from scientific literature was made.

We investigated pharmacokinetic interactions between drugs and different dietary supplements that may interfere important pharmacokinetic phases of the

drug in organism: biotransformation, transport and distribution to the target organ.

In Romania, among the most popular medicinal plants that can induce interactions with allopathic drugs are:

- *Echinacea* sp. with immunosuppressant medications (cyclosporine), corticosteroids (prednisone, prednisolone), anabolic steroids, amiodarone, methotrexate, ketoconazole,
- *Allium sativum* with antiplatelet drugs (aspirin, ticlopidine, clopidogrel), anticoagulants (warfarin) and insulin,
- *Crataegus* species (Hawthorn) with digoxin, coronary vasodilators (theophylline, caffeine, papaverine, sodium nitrate, adenosine and epinephrine), cardiovascular drugs for heart failure, high blood pressure, angina, arrhythmias and CNS depressants,
- nettle leaves (*Urtica dioica*) with anticoagulants (warfarin),
- Passion flower (*Passiflora incarnata*) with CNS depressants and monoamine oxidase inhibitors (phenelzine and tranylcypromine),
- St John's Wort (*Hypericum perforatum*) with antidepressants, barbiturates (phenobarbital), bromocriptine, CNS stimulants, digoxin, monoamine

oxidase inhibitors, selective serotonin-reuptake inhibitors (paroxetine, sertraline, fluoxetine, fluvoxamine, citalopram) and reserpine.

## RESULTS AND DISCUSSION

### Black Cohosh

*Actaea racemosa* L. (syn. *Cimicifuga racemosa* L. (family *Ranunculaceae*) or black cohosh, is a perennial herb native to North America used traditionally for female reproductive system ailments and is now popular for the relief of menopausal symptoms such as hot flashes, and osteoporosis. For this purpose it is ranked among the 10 top-selling supplements in the United States (Shams et al., 2010). Spiroketal triterpene glycosides are believed to be responsible for black cohosh's pharmacological activity even though they are not phytoestrogens (Vioreck et al., 2005).

The scientific literature showed that black cohosh does not appear to be a potent modulator of human drug metabolism. *In vitro* studies found that isolated triterpene glycosides act as relatively weak inhibitors ( $IC_{50} > 100 \mu M$ ) of human CYP3A4, while whole extracts elicited greater inhibition. Responsible for this is a possible synergistic action of fukinolic and cimicifugic acids, compounds that are potent ( $IC_{50} < 13 \mu M$ ) inhibitors *in vitro* of CYP1A2, 2D6, 2C9, and 3A4 (Tsukamoto et al., 2005; Huang et al. 2010).

However, by comparing to standard dose of clarithromycin (500 mg daily for 7 days) or rifampicin (600 mg daily for 7 days), black cohosh supplement (40–80 mg extract daily for 14 days) produced no demonstrable effects on digoxin and midazolam pharmacokinetics (Gurley, 2006). These findings suggest that black cohosh is not a potent modulator of human CYP3A4 or ABCB1 activity *in vivo*.

Based on the currently available data, standardized black cohosh supplements, when taken at recommended doses, pose little risk for herb-drug interactions.

### Echinacea spp.

Echinacea species (e.g., *Echinacea purpurea* L. Moench, *E. angustifolia* DC., *E. pallida* Nutt.) of the family *Asteraceae* are North American species whose roots and aerial parts have been used traditionally for immune stimulatory properties and for prevention of the common cold (Basch, 2005). Echinacea is placed among the 10 top selling botanicals in the U.S. for many years.

Other PSMs like caffeic acid esters (e.g., cichoric acid, echinacoside), polysaccharides, and alkenes are also considered to contribute to Echinacea's activity. Because commercially available Echinacea supplements often consist of extracts from various species and plant parts, important variation in phytochemical profile and content is common reported among products.

Recent studies concluded that alkamides exhibit at least mild to moderate inhibition of CYP3A4 in most of the model systems tested, dependent upon alkamide content (Toselli, 2009).

Using the CYP3A assay of midazolam concluded that 8 days of *E. purpurea* supplementation selectively modulated CYP3A activity in the intestine (inhibition) and liver (induction) of healthy volunteers (Gorski et al., 2004).

Mild inhibitory effects were observed for CYP1A2 and CYP2C9, while CYP2D6 was unaffected.

Treatment at healthy adults with supplements with *E. purpurea* for either 14 (800 mg extract daily) or 30 days (1500 mg extract daily) produced no clinically significant changes in CYP phenotypes (Gurley et al., 2008).

Another study reported that 28 days of *E. purpurea* supplementation in healthy volunteers (500 mg three times daily) produced modest reductions in midazolam plasma concentration, but had no significant effects on the pharmacokinetics of lopinavir and ritonavir (CYP3A4 substrates), or fexofenadine (Penzak et al., 2010).

Fourteen days of supplementation with a standardized *E. purpurea* product (800 mg extract daily) had no effect on digoxin pharmacokinetics in healthy volunteers (Gurley et al., 2012).

Thus, *E. purpurea* will produce no clinically relevant interactions with co-administered drugs. So, based on relevant studies, it seems that dietary supplements with standardized Echinacea extracts, at recommended doses, are not likely to yield alkamide concentrations sufficient enough to highly modulate human CYP and carrier membrane transport proteins *in vivo*. Therefore, Echinacea supplements have minimal risks for interacting with most conventional drugs.

### Allium spp.

Allium species, such as garlic (*Allium sativum* L.) and onions (*Allium cepa* L.) are a rich source of sulfur-containing compounds, which are volatile and are responsible for the characteristic flavor of these species.

Previous studies have confirmed that prolonged administration of these sulfur-compounds induced hepatic and intestinal murine CYP subfamilies (e.g., CYP1A, CYP2B, CYP3A), in addition to various transferases (e.g., GSTs, UGTs) through activation of CAR and Nrf2 nuclear receptors (Fisher et al., 2007).

The ability of garlic to inhibit CYP appears dependent upon product type and composition. *In vitro* assessments of allicin, fresh garlic, or commercially prepared supplements (e.g., garlic oil and garlic powder) either found no effect or modest inhibition (< 50%) of human CYP2C9, CYP2C19, and CYP3A4 isoforms. However, a freeze-dried garlic supplement,

produced significant inhibition of CYP3A4 in vitro (> 95%).

Different types of processing can significantly vary its phytochemical composition, e.g. lyophilization may stabilize those organosulfur compounds responsible for inhibiting CYP3A4. Studies on aged garlic extracts (AGE) showed no inhibition of the major CYP isoforms present in human liver microsomes (Greenblatt et al., 2006).

Based upon in vitro and in vivo findings, garlic's effects on transporter activity also appear dependent upon the hydrophilicity of specific organosulfur compounds.

Results of the interactions between garlic and several drugs upon the biotransformation pathways (e.g., acetaminophen, alprazolam, caffeine, chlorzoxazone, cyclosporine, debrisoquine, docetaxel, dextromethorphan, midazolam, omeprazole, ritonavir, saquinavir, warfarin) revealed that only drugs that are substrates of CYP2E1 are significantly affected.

Administration of diallyl sulfide (0.2mg/kg) to healthy volunteers reduced plasma 6-hydroxychlorzoxazone /chlorzoxazone ratio (a measure of CYP2E1 activity) by 31% (Loizou, 2001).

Other studies confirmed that only lipophilic and not hydrophilic, organosulfur compounds were CYP2E1 inhibitors. Lately studies confirmed that prolonged garlic oil supplements (500 mg, three times daily for 28 days) inhibited human CYP2E1 activity in both young and elderly adults by 40% and 25%, respectively. However, no modulatory effects were noted for CYP1A2, CYP2D6, or CYP3A4 (Gurley et al., 2012, (Greenblatt et al., 2006)).

On contrary, 21 days of twice daily supplementation with garlic powder (9 mg alliin and 23mg alliin) reduced significantly the maximum plasma concentrations (C<sub>max</sub>) of the protease inhibitor saquinavir (Gurley, 2012).

A mild effect on ritonavir was observed after a four-day course of garlic extract (5mg, twice daily) (Gurley, 2012).

No clinically important garlic-mediated interactions have been reported for warfarin, a substrate for CYP2C9 and 3A4. However, large doses of alliin (150 mg daily) did reduce the metabolism of omeprazole by inhibiting CYP2C19 activity.

No significant effects were observed in the pharmacokinetic of simvastatin (a CYP3A4 substrate) or pravastatin.

Taken together these findings, we can conclude that most commercially available garlic supplements pose only a limited risk for producing clinically important herb-drug interactions.

Presently, only human CYP2E1 appears to be inhibited by garlic oil products, but because only a few drugs are substrates of CYP2E1 and most of those have fairly broad therapeutic index.

### Ginkgo biloba

Today, dosage forms incorporating *G. biloba* leaf extracts are used throughout the world for treatment of insufficient blood flow, memory deficits, cognitive disorders, Alzheimer's disease, depression, vertigo, tinnitus and intermittent claudication (Chan et al., 2007).

It is one of the most intensely studied botanicals in the world.

Much of the research has focused on products formulated with EGb 761, an extract produced by the German company Schwabe. EGb 761 is a standardized extract containing 24% flavonoid glycosides (e.g., quercetin, kaempferol, isorhamnetin), 6% terpene lactones (3.1% ginkgolides A, B, C, and J and 2.9% bilobalide), 5–10% organic acids, and other constituents (Chan et al., 2007).

Other compounds present in *G. biloba* may have allergenic, immunotoxic and other undesirable properties (e.g., ginkgetin, amentoflavone, ginkgolic acids, ginkgotoxin and others) and therefore they are removed during plant processing.

Discrepancies among clinical studies concerning efficacy may be due to significant interproduct variability in phytochemical content and biopharmaceutical characteristics of ginkgo extract dosage forms.

In many in vitro experimental systems, ginkgo extracts, individual terpene lactones and flavonoid glycosides have been shown to inhibit various metabolic enzymes and transporters.

Aglycones of quercetin, kaempferol and isorhamnetin seem to have the greatest inhibitory capacity, while ginkgolides and bilobalide exhibit the least and in many cases, no effect.

Prolonged administration of *G. biloba* extracts to rats, often in high doses, not only induced a multitude of metabolic enzymes, but reduce efficacy for several drugs: nicardipine, tolbutamide, phenobarbital, propranolol, cyclosporine and theophylline.

Concomitant administration of *G. biloba* also enhanced the hepatotoxicity of acetaminophen via CYP3A induction (Gurley et al., 2012).

Evidence from in vitro and animal investigations clearly points to *G. biloba* extracts and their constituents as inducers of metabolic enzymes and transporter activity.

Over 29 prospective clinical trials assessing the effect of *G. biloba* supplements on the pharmacokinetics of a variety of drugs have been published. The drugs included: aspirin, alprazolam, antipyrine, bupropion, caffeine, chlorzoxazone, cilostazol, clopidogrel, dapsone, debrisoquine, dextromethorphan, diazepam, diclofenac, digoxin, donepezil, endogenous steroids, fexofenadine, flurbiprofen, lopinavir, mephenytoin, metformin,

midazolam, nifedipine, omeprazole, talinolol, ticlopidine, tolbutamide, voriconazole and warfarin. The majority of these studies followed a *G. biloba* supplementation with a dose of 240 mg leaf extract twice daily from 3 to 90 days, while others utilized smaller doses. In most studies, products containing the standardized EGb 761 extract were tested.

Of the 29 studies, 23 observed no significant effects of *G. biloba* on drug disposition, 5 observed a modest inhibitory effect and 3 demonstrated evidence of CYP3A4, CYP2C9 and CYP2C19 induction (Gurley et al., 2012).

In conclusion, dosage forms containing standardized *G. biloba* extracts, when administered at doses of 240mg/day or less, do not pose a risk for clinically relevant herb-drug interactions. However, daily doses exceeding 240 mg/day may increase prospects for interactions.

### Ginseng spp.

Asian ginseng (*Panax ginseng*) and American ginseng (*Panax quinquefolius* L.) are the most widely used and extensively studied from the *Panax* species (family *Araliaceae*).

*P. ginseng* root has used for more than 2000 years in traditional Chinese medicine as an adaptogen (a plant that increases resistance to stress and fatigue) and a restorative tonic.

More than 40 ginsenosides have been identified in the roots of *P. ginseng* and *P. quinquefolius*.

Ginseng root extracts are often standardized in a particular percentage (~ 4%) and ratio of ginsenosides.

Conclusions of clinical and nonclinical evidence on drug interactions with ginseng extracts and their effects on metabolic enzymes and transporters are particularly confusing. There were cited variability in ginsenoside type and content, in degree of absorption, poor membrane permeability, interindividual differences in gut microflora (Chen et al., 2008).

Concerns regarding possible ginseng-drug interactions first appeared when two case reports speculated that ginseng reduced warfarin anticoagulation (Janetzky et al., 2007).

Subsequent clinical trials with *P. ginseng*, however, have failed to observe any influence on warfarin pharmacokinetics or pharmacodynamics.

Several prospective human trials have investigated the effects of *P. ginseng* and *P. quinquefolius* supplements on human drug disposition. Warfarin was examined the most. Results of the clinical trials were divided in two categories: no effect or mild induction of CYP2C9 substrate (Janetzky et al., 2007).

As a result, there is no clinically evidence that links ginseng supplementation to potentially harmful drug interactions.

### Methylenedioxyphenyl (MDP) Compounds

Popular botanical supplements known to contain substantial quantities of MDP-PSMs include goldenseal (*Hydrastis canadensis*), kava kava (*Piper methysticum*), black pepper (*Piper nigrum*), and *Schisandra* spp. In these species, MDP-compounds often function as insecticides, but when they are administered to humans they can act as inhibitors of CYPs. Prolonged administration of MDP-containing compounds has also been shown to induce CYP1A and CYP2B expression in several animal species (Murray, 2000).

In China, berberine (an OTC remedy for diarrhea of bacterial origin) has also been shown to significantly increase the AUC, Cmax and trough concentrations of the immunosuppressive drug cyclosporine.

### Goldenseal

Extracts of goldenseal root (*Hydrastis canadensis* L.; family *Ranunculaceae*) are often taken as an antimicrobial to prevent common colds and upper respiratory tract infections.

Gurley et al. (2005) first observed that goldenseal supplements significantly inhibited CYP2D6 and CYP3A4 in healthy volunteers. In subsequent investigations with the CYP3A4 substrate midazolam, Gurley et al. further demonstrated that 14 days of goldenseal supplementation (~ 209 mg isoquinoline alkaloids daily) significantly increased midazolam AUC, Cmax and elimination half-life. The effects were similar to those noted for clarithromycin (1000 mg daily), a well-recognized inhibitor.

However, recent clinical evidence, indicates that goldenseal's effect on digoxin disposition in humans is not significant. Given that goldenseal significantly inhibit both CYP3A4 and CYP2D6 activity (the two most important drug metabolizing enzymes in humans), its herb-drug interaction potential is considerable.

### Kava kava

Kava kava (*Piper methysticum* G. Forst.; family *Piperaceae*) dietary supplements are used for the alleviation of stress, anxiety, or insomnia.

Reports linking kava use to liver toxicity have led to the removal of these products from Australia, Canada, and several European countries. Possible hepatotoxic side effects of kava prompted the FDA to issue warnings associated with kava supplementation correlated to prolonged usage (> 60 days) and co-medication with prescription drugs or other botanical supplements. Modulation of human drug metabolism and/or transport has been cited as the mechanism responsible for kava-induced liver toxicity.

*In vitro* data points to kava as an inhibitor of various CYPs (Ulbricht, 2005).

However, consumption of commercially available kava supplements at label recommendations is not



likely to affect the efficacy or toxicity of conventional medications.

### Schisandra spp.

Berry extracts of *Schisandra* species (*Schisandra chinensis* (Turcz.) Baill. and *S. sphenanthera* Rehder & E. H. Wilson) are often prescribed for their adaptogenic and hepatoprotective properties.

In the United States, extracts of *S. chinensis* and *S. sphenanthera* are often incorporated into dietary supplement formulations.

Previous studies pointed *Schisandra* (especially, gomisins B, C, and G) as both substrates and inhibitors of ABC efflux transporters in vitro and both competitive and noncompetitive inhibitors of human CYP isoforms.

The inhibitory effect of gomisin C was stronger than that of ketoconazole, a well-known potent CYP3A4 inhibitor.

Studies investigating *Schisandra*'s effect on xenobiotic metabolism demonstrated its inhibition or induction action, each dependent upon the duration of administration.

When single doses of *Schisandra* extracts ( $\leq 250$  mg/kg) were administered to rats concomitantly with CYP3A and/or ABCB1 substrates (e.g., midazolam, nifedipine, paclitaxel, tacrolimus), an increase in drug's AUCs was noted, suggesting inhibition. However, when administration periods exceeded 6 days, rat metabolic enzymes and transporter function were consistently induced.

When *Schisandra* was administered once or for up to 14 consecutive days, AUCs of talinolol (ABCB1 substrate), tacrolimus (CYP3A4/ABCB1 substrate) and midazolam (CYP3A4 substrate) were increased 1.5-, 2.1-, and 2.0-fold, respectively.

According to the clinical data currently available, *Schisandra* extracts pose a significant risk for elevating blood levels of drugs that are CYP3A and/or ABCB1 substrates (Iwata et al., 2004).

### Milk Thistle

Extracts of milk thistle fruits yield a complex of flavanolignans and flavonoids collectively known as silymarin. Milk thistle extracts are used for their antioxidant and hepatoprotective properties for treating various liver diseases (e.g., cirrhosis, hepatitis, hepatotoxicity) (Miguez et al., 1994).

Components of standard milk thistle extracts, as a general rule, have very low oral bioavailability and short elimination half-lives. Even when milk thistle extract (700 mg) was administered every 8 hours for 7 days, the maximum steady state concentrations of silybin A and B rarely exceeded 1.5  $\mu\text{g/mL}$  (Hawke et al., 2010).

However, systemic concentrations of silybin and isosilybin may be 3–5-fold higher in patients with

cirrhotic or nonalcoholic fatty liver disease, which may account for milk thistle's benefit in these populations.

A considerable number of prospective human studies have examined milk thistle's drug interaction potential. Supplements containing standard milk thistle extracts had no significant effects on the clinical pharmacokinetics of aminopyrine (nonspecific CYP), caffeine (CYP1A2), chlorzoxazone (CYP2E1), debrisoquine (CYP2D6), digoxin (ABCB1 substrate), indinavir (CYP3A4 substrate), irinotecan (CYP3A4/UGT1A1 substrate), midazolam (CYP3A4), nifedipine (CYP3A4 substrate), phenylbutazone (nonspecific CYP), ranitidine (CYP3A4/ABCB1 substrate) and rosuvastatin (ABCB1 substrate).

More concerning is a recent finding that silymarin inhibits the metabolism of losartan to its active metabolite E-3174, and that the interaction is dependent upon CYP2C9 genotype. In patients with the CYP2C9\*1/\*1 genotype, a 14-day course of silymarin produced a 2-fold increase in losartan AUC and C<sub>max</sub> (Han et al., 2009).

A recent clinical trial of Siliphos (a complex of silymarin with phosphatidylcholine) for treatment of chemotherapy-related hepatotoxicity in childhood acute lymphoblastic leukemia suggests no adverse interactions between milk thistle and methotrexate, 6-mercaptopurine or vincristine during the 28-day course of supplementation.

Therefore, based upon the clinical data, the drug interaction risk for milk thistle products appears minimal (Gurley et al., 2008).

### St. John's Wort

St. John's wort (*Hypericum perforatum* L.; family *Hypericaceae*) is the most studied botanical dietary supplement in the world.

Many clinical trials have demonstrated its efficacy comparable to standard antidepressants, but with fewer side effects than conventional antidepressive agents (trial, 2002).

The popularity of St. John's wort has also been attributed to the fact that it's one of the most problematic dietary supplements with regard to herb-drug interactions.

Both the antidepressant effect and drug interaction potential of St. John's wort is correlated to the extract's content in hyperforin, a bicyclic polyprenylated acylphloroglucinol found exclusively in *Hypericum* species. As an antidepressant, hyperforin functions as broad-based neurotransmitter reuptake inhibitor of serotonin, dopamine, norepinephrine, glutamate and gamma-aminobutyric acid. Hyperforin does not interact directly with uptake transporters, but increases intracellular sodium concentration, thereby inhibiting gradient-driven neurotransmitter reuptake.

While recognized as a natural antidepressant, SJW is also well known for its ability to induce the activity of several metabolic enzymes and transporters, thereby reducing the efficacy of a multitude of prescription medications (ivabradine, digoxin, warfarin, mephenytoin, amitriptyline, voriconazole, fexofenadine, simvastatin, atorvastatin, midazolam, alprazolam, quazepam, indinavir, talinolol, verapamil, nifedipine, cancer chemotherapeutics, hormonal contraceptives, hypoglycemic drugs (gliclazide), cyclosporine, methadone, omeprazole, chlorzoxazone).

Several clinical studies have demonstrated that *Hypericum* extracts containing less than 1% hyperforin are less likely to produce clinically significant herb-drug interactions (Mueller et al., 2004).

However, considering that only few *Hypericum* products are specifically labeled as having low hyperforin content to avoid significant drug interactions, consumers should avoid concomitant use with prescription medications.

## CONCLUSIONS

Most herbal dietary supplements pose only minimal risks for modulating human drug metabolism. However, some plant compounds act as mechanism-based inhibitors of CYPs and therefore may potentiate the toxicity of allopathic medications, while potent nuclear receptor ligands like hyperforin may dramatically reduce drug efficacy.

Since the vast majority of these botanicals have not evaluated in a clinical setting considering that most has a historic use. However, in vitro studies and case reports suggest that many botanical supplements may indeed be potent modulators of human drug disposition.

Therefore we should be aware that there is a risk of potential drug-herb interaction that should be considered when using herbs or supplements with prescription or over-the-counter medications.

As a general safety guideline we recommend to inform the physician and pharmacist of any herbs or supplements that recently have used when taken concomitantly with an allopathic drug.

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