Pharmacokinetic Herb-Drug Interactions (Part 2): Drug Interactions Involving Popular Botanical Dietary Supplements and Their Clinical Relevance

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- solute carrier membrane transport proteins
- botanical dietary supplements
- black cohosh
- *Echinacea*
- garlic
- *Ginkgo biloba*
- ginseng
- goldenseal
- kava
- black pepper
- piperine
- *Schisandra*
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- methylenedioxyphenyl-containing compounds

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Abstract

In Part 2 of this review, a critical examination of the pertinent scientific literature is undertaken in order to assess the interaction risk that popular dietary supplements may pose when taken concomitantly with conventional medications. Botanicals most likely to produce clinically important herb-drug interactions are those whose phytochemicals act as mechanism-based inhibitors of cytochrome P450 enzyme activity (e.g., *Hydrastis canadensis, Piper nigrum, Schisandra chinensis*) or function as ligands for orphan nuclear receptors (e.g., *Hypericum perforatum*). In addition, several external factors unrelated to phytochemical pharmacology can augment the drug interaction potential of botanical supplements.

Nonstandard Abbreviations

ABC:	ATP-binding cassette
AhR:	aryl hydrocarbon receptor
AUC:	area under the plasma concentration-time curve
CAR:	constitutive androstane receptor
CYP:	cytochrome P450 enzyme
DSHEA:	Dietary Supplement Health and Education Act
GMPs:	good manufacturing practices
GST:	glutathione S-transferase
MDR1:	multidrug resistance protein 1
MDP:	methylenedioxyphenyl
MDZ:	midazolam
NADPH:	nicotinamide adenine dinucleotide phosphate
OATP:	organic anion transporting polypeptide
OTC:	over-the-counter
P-gp:	P-glycoprotein
PSM:	plant secondary metabolite
PXR:	pregnane xenobiotic receptor
SLC:	solute carrier membrane transport protein
SULT:	sulfotransferase
UGT:	uridine diphosphate glycosyltransferase
UM:	ultra-rapid metabolizer
XME:	xenobiotic metabolizing enzyme

Introduction

In Part 1 of this review, a discussion of the origins and mechanisms underlying herb-drug interactions was presented. In Part 2, a critical assessment of the available clinical evidence regarding herb-drug interaction potentials for several popular botanical supplements sold in the United States is provided. While the number of botanicals selected for review is not extensive, the approach taken to discern whether a botanical extract poses a risk for producing clinically significant herb-drug interactions can be extended to any supplement formulation. (For definitions of abbreviations regarding various drug metabolizing enzymes and transporters, see Part 1 of this review.)

Black Cohosh

Actaea racemosa L, (syn. *Cimicifuga racemosa* [L.] Nutt.; family Ranunculaceae) or black cohosh, is a perennial herb native to North America used traditionally by Native Americans for female repro-

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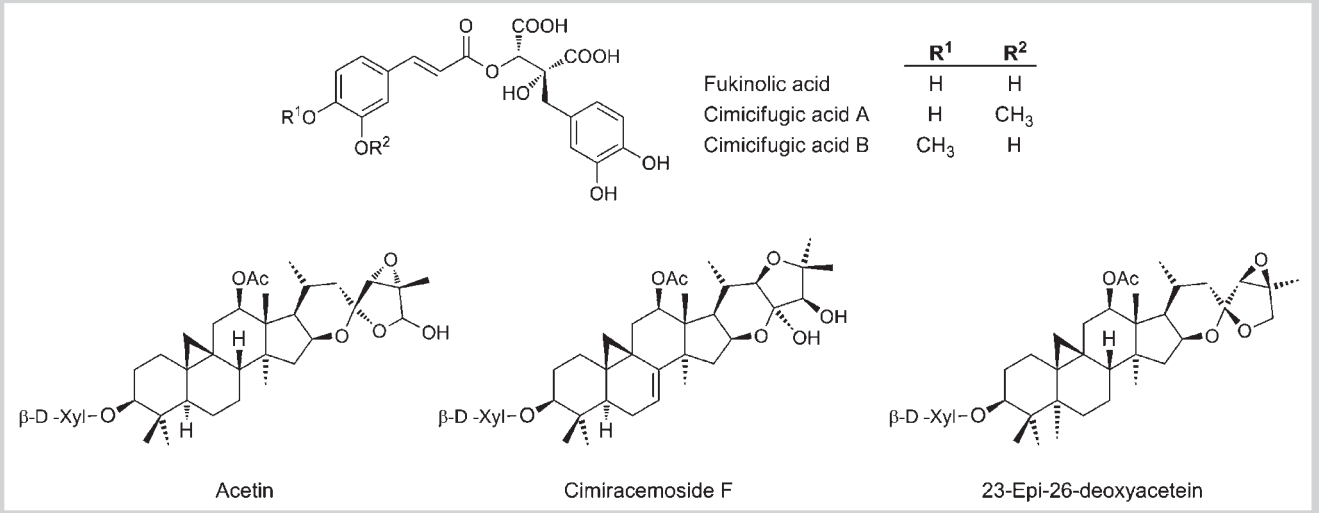

Fig. 1 Representative phytochemicals (triterpene glycosides, phenylpropanoids) present in black cohosh.

ductive system ailments and is now popular for the relief of menopausal symptoms such as hot flashes [1,2]. The purported ability of black cohosh to help alleviate climacteric symptoms, premenstrual syndrome, and osteoporosis has secured its ranking among the 10 top-selling supplements in the United States [3]. Spiroketal triterpene glycosides (**Fig. 1**) are believed responsible for black cohosh's pharmacological activity even though they are not phytoestrogens [4,5]. As such, most commercial black cohosh products are chemically standardized to triterpene glycosides, with 23-*epi*-26-deoxyactein (also known as 27-deoxyactein) being the most abundant congener [6].

At present, black cohosh does not appear to be a potent modulator of human drug metabolism. *In vitro* studies found individual triterpene glycosides to be relatively weak inhibitors (IC_{50} > 100 µM) of human CYP3A4 [7,8], while whole extracts elicited greater inhibition, a finding suggestive of synergy [7]. The inhibitory effects of whole black cohosh extracts may stem not from triterpene glycosides but rather fukinolic and cimicifugic acids. These compounds are potent (IC_{50} < 13 µM) inhibitors of CYP1A2, 2D6, 2C9, and 3A4 *in vitro* [8]; however, their quantities vary considerably among commercially available black cohosh products [9], a factor that can profoundly affect their inhibitory activity *in vivo*. In human liver microsomes, IC_{50} values for CYP2B6, 2C19, and 2E1 were approximately 50, 30, and 10 µg/mL, respectively, for methanolic extracts of black cohosh [10]. However, when compared to standard regimens of clarithromycin (500 mg daily for 7 days) or rifampin (600 mg daily for 7 days), black cohosh supplementation (40–80 mg extract daily delivering 3–6 mg triterpene glycosides for 14 days) produced no demonstrable effects on digoxin and MDZ pharmacokinetics [11,12]. These findings suggest that black cohosh is not a potent modulator of human CYP3A4 or ABCB1 activity *in vivo*. Black cohosh supplementation also had no clinically significant effects on phenotypic measures of human CYP1A2, 2E1, or 2D6 activity [13]. When administered orally, black cohosh's principal triterpene glycoside, 23-epi-26-deoxyactein, reaches the systemic circulation intact, albeit in very low concentrations (< 10 ng/mL) [6]. This apparent lack of biotransformation bolsters the idea that black cohosh triterpene glycosides are unlikely to be inhibitors of human XMEs *in vivo*. Black cohosh extracts incorporating DMSO as a cosolvent moderately inhibited (~ 47%) uptake of estrone-3-sulfate, a SLCO2B1 substrate, into human embryonic kidney cells stably expressing the transporter [14]. Whether this effect translates to the *in vivo* condition remains to be determined.

As with most commercially available botanical supplements, black cohosh products exhibit considerable variability in phytochemical profiles, and label claims for "standardized" marker compounds can deviate considerably from actual content [9]. Such variations can have considerable influence on how results of clinical studies evaluating black cohosh efficacy or its herb-drug interaction potential are interpreted. Nevertheless, based on the currently available data, standardized black cohosh supplements, when taken at recommended doses, pose little risk for herb-drug interactions.

Interaction risk: low.

Echinacea spp.

▼

Echinacea species (e.g., *Echinacea purpurea* [L.] Moench, *E. angustifolia* DC., *E. pallida* [Nutt.] Nutt.) of the family Asteraceae are North American perennials whose roots and aerial parts have been used traditionally for a variety of medicinal purposes [15, 16]. *Echinacea* formulations containing either root or whole plant extracts are marketed for their "immune stimulatory" properties and for prevention of the common cold [15,16]. *Echinacea*'s popularity as an immune stimulator has placed it among the 10 top-selling botanicals in the U.S. for many years. While evidence from *in vitro* and animal studies lend credence to *Echinacea* preparations as immunomodulators, clinical findings remain equivocal. (For reviews of clinical efficacy see references [15–19].) The three species most commonly encountered are chemically dissimilar. Both *E. purpurea* and *E. angustifolia* contain alkamides as their major lipophilic constituents, although of differing structural types (**Fig. 2**). By contrast, the lipophilic fraction of *E. pallida* is characterized by polyacetylenes and is practically devoid of alkamides. These phytochemical dissimilarities also extend to their respective plant parts (i.e., roots vs. aerial parts). As PSMs, polyacetylenes and alkamides are natural pesticides that, when ingested in relatively high amounts, can be toxic. In low concentra-

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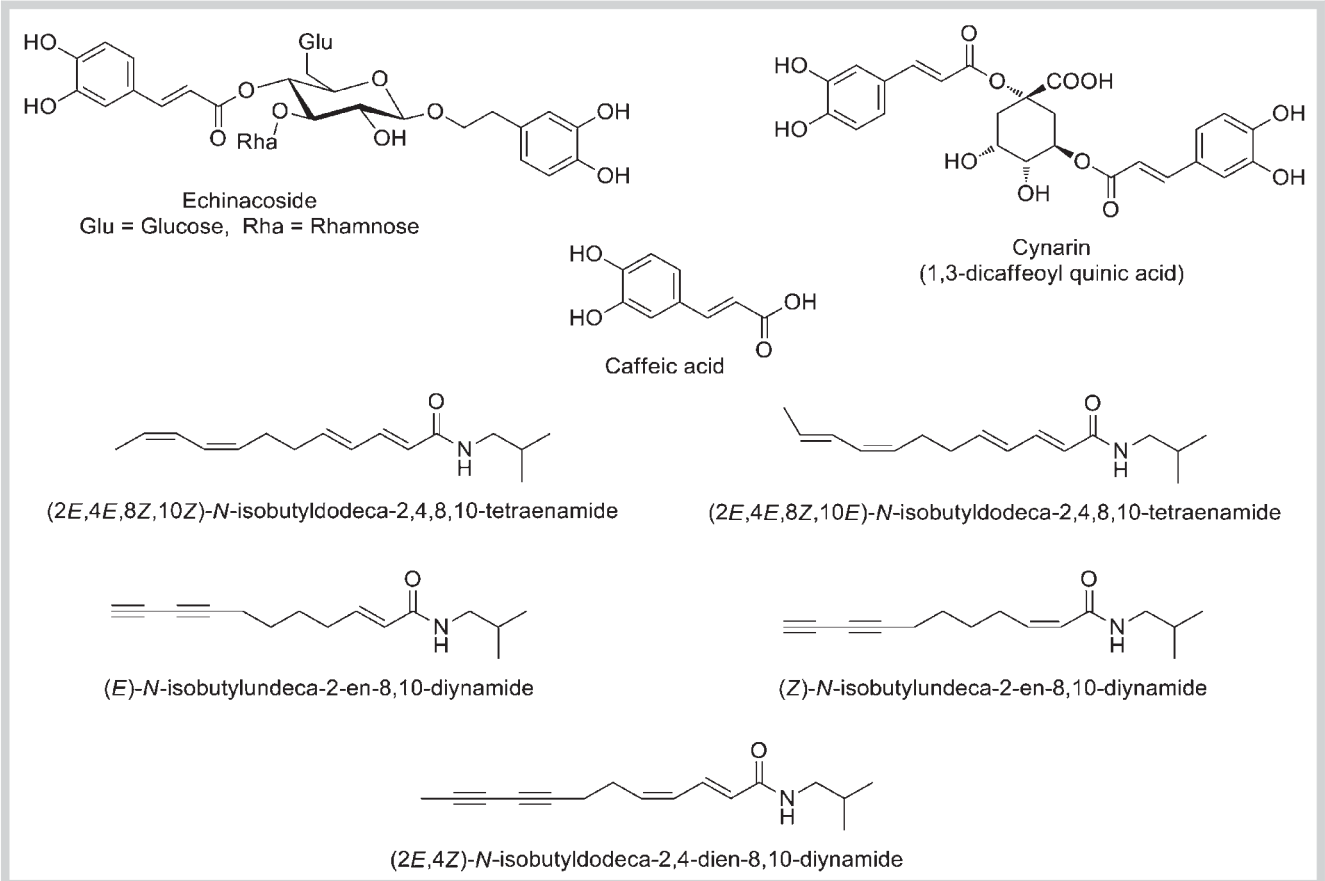

Fig. 2 Representative phytochemicals (alkamides, phenylpropanoids) present in *Echinacea* species.

tions, however, alkamides appear to have beneficial effects [20]. Other PSMs like caffeic acid esters (e.g., cichoric acid, echinacoside), polysaccharides, and alkenes are also thought to contribute to echinacea's activity. Because commercially available *Echinacea* supplements often consist of extracts from various species and plant parts, considerable variation in phytochemical profile and content is common among products [16,21].

Permeability [22,23] and pharmacokinetic [24–26] studies indicate that several alkamides, but not caffeic acid conjugates, cross the intestinal mucosa reaching the systemic circulation intact. Following single doses of *Echinacea* alkamides (~11 mg) administered as tablets manufactured from ethanolic liquid extracts, plasma concentrations varied considerably with maximum plasma levels not exceeding 350 ng/mL [26]. Individual *Echinacea* alkamides are metabolized to varying degrees by several human CYPs, but when combined (as in an extract), metabolism is markedly reduced [27–29]. This appears to arise from (2*E*)-*N*-isobutylundeca-2-ene-8,10-diynamide (**Fig. 2**), which contains a terminal alkyne and may act as a mechanism-based inhibitor [27]. A considerable number of *in vitro* studies have examined the XME and ABCB1 modulatory effects of echinacea extracts and individual PSMs [30–44]. A recent review of the bulk of these studies concluded that alkamides exhibit at least mild to moderate inhibiton of CYP3A4 in most of the model systems tested, with the magnitude dependent upon alkamide content [29]. This conclusion is strengthened by a recent animal study, in which standardized *E. purpurea* extracts reduced rat CYP3A mRNA levels by 40% [45]. Expression of CYP1A mRNA, however, was increased by 80%. Mild inhibitory effects on ABCB1- [43,44] and SLCO2B1-mediated [14] transport have also been demonstrated.

Very few prospective clinical studies examining the interaction potential of *Echinacea* supplements have been conducted in humans. Using the CYP3A probe midazolam, Gorski et al. concluded that 8 days of *E. purpurea* supplementation selectively modulated CYP3A activity in the intestine (inhibition) and liver (induction) of healthy volunteers [46]. The authors concluded that due to *Echinacea*'s seemingly opposing effects on intestinal and hepatic CYP3A4, any interaction would depend upon the substrate's hepatic and intestinal extraction ratio. Mild inhibitory effects were observed for CYP1A2 and CYP2C9, while CYP2D6 was unaffected. In this instance, however, *Echinacea*'s effect pales in comparison to those reported by these same investigators for known CYP3A4 inhibitors (e.g., clarithromycin) and inducers (rifampin) of midazolam metabolism [47,48]. It would appear that *Echinacea*'s effect on CYP3A expression is modest at best, as neither standardized extracts nor purified alkamides upregulated CYP3A4 mRNA levels when exposed to HepG2 cells for 96 hours [41]. In contrast, rifampin exposure increased CYP3A4 mRNA expression by 3.8-fold. Using various phenotypic probe drug ratios to assess CYP1A2, CYP2D6, CYP2E1, and CYP3A4 activity, Gurley et al. found that healthy adults supplemented with *E. purpurea* for either 14 (800 mg extract daily) [49] or 30 days (1500 mg extract daily) [50] produced no clinically significant changes in CYP phenotypes. More recently, Penzak et al. reported that 28 days of *E. purpurea* supplementation in healthy volunteers (500 mg three times daily) produced modest reductions in midazolam AUC

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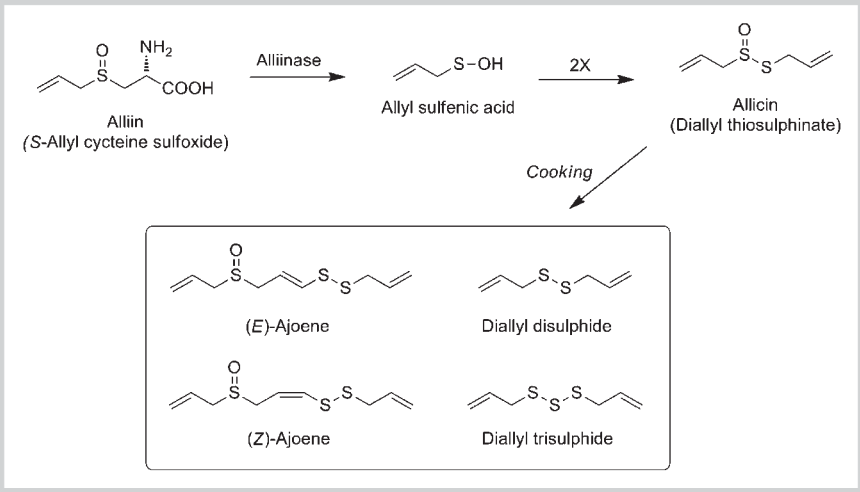

Fig. 3 Representative phytochemicals (sulfur-containing compounds) present in garlic.

(27% decrease), but had no significant effects on the pharmacokinetics of lopinavir and ritonavir (CYP3A4 substrates), or fexofenadine (a purported ABCB1 and SLCO substrate) [51]. This study, like that of Gorski et al., suggests that *E. purpurea* may have mild inductive effects on human CYP3A4 *in vivo*. However, when compared to rifampin's effects on the pharmacokinetics of CYP3A4 substrates [12,48], any clinically important drug interactions with *Echinacea* seem remote.

To date, only two clinical studies have evaluated *Echinacea*'s impact on drug transporters. Fourteen days of supplementation with a standardized, well-characterized *E. purpurea* product (800 mg extract daily) had no effect on digoxin (an ABCB1 substrate) pharmacokinetics in healthy volunteers [52]. By contrast, 7 days of rifampin (600 mg daily) or clarithromycin (500 mg daily) produced marked reductions and increases, respectively, in digoxin AUC, a finding that underscores *Echinacea*'s clinically insignificant effect on these transporters. In addition, the pharmacokinetics of fexofenadine, a nonspecific ABCB1 and SLCO substrate, were not impacted by 28 days of *E. purpurea* supplementation [51]. Taken together, these data render it unlikely that *E. purpurea* will produce clinically relevant interactions with coadministered drugs through ABC or SCLO modulation.

Based on the collected evidence to date, it appears that dietary supplements formulated with standardized *Echinacea* extracts – when ingested per label recommendations – are not likely to yield alkamide concentrations sufficient enough to dramatically modulate human CYP, ABC, and SLCO isoforms *in vivo*. Therefore, *Echinacea* supplements pose minimal risks for interacting with most conventional medications, an opinion concordant with that of other recent reviews [29,53].

Interaction risk: low.

Garlic

▼

Members of the family Alliaceae have been an important part of the human diet for thousands of years. *Allium* species, such as garlic (*Allium sativum* L.) and onions (*Allium cepa* L.), are a rich source of sulfur-containing compounds, many of which are volatile and give rise to the characteristic flavor and aroma of these species. Fresh garlic has little smell but tissue damage by cutting, crushing, or biting results in alliin (2-propenyl-*L*-cysteine sulfoxide) (**Fig. 3**) being cleaved by the enzyme alliinase resulting in the formation of allicin (diallyl thiosulfinate), which gives crushed garlic its characteristic smell. Because allicin is very unstable to heat, cooking results in its degradation to a number of organosulfur compounds including diallylsulfides and ajoenes [54] (**Fig. 3**). Bad breath, which follows the ingestion of garlic products, is due to a range of sulfide compounds that appear in the systemic circulation and expired air.

Garlic is reputed to have benefits for protection against cardiovascular diseases, cancer, microbial infections, and vampires! Although there is some evidence for the first two effects, the rest are largely the result of speculation and folklore [54]. The putative anti-hypercholesterolemic effect of garlic supplements makes them one of the most widely used botanical supplements in the United States. Their efficacy, however, remains in doubt due to conflicting results from numerous published clinical trials [55–58]. This is probably a function of the type of product used, its quality, and poor characterization of the phytochemical agent(s) responsible for garlic's lipid lowering effect.

Three general categories of garlic supplements are available commercially (garlic oil, dehydrated garlic powder, and aged garlic extract) each with their own unique composition of purported bioactive components [59–61]. Within these products a plethora of organosulfur compounds, steroid saponins, and other phytochemicals have been identified [54,59–62]. Of these, the oil-soluble organosulfur compounds including allyl thiosulfinates (e.g., allicin), alkyl sulfides (e.g., diallyl sulfide), vinyldithiins, and ajoene have received the most attention (**Fig. 3**). Allicin has long been touted as the agent responsible for garlic's lipid lowering effects, yet the compound is unstable in the gastrointestinal tract, is not bioavailable, and is rarely found in commercial products [59–61]. Allicin's degradation products, diallyl sulfide, diallyl disulfide, diallyl trisulfide, dithiin, and ajoene, may contribute to the lowering of serum cholesterol levels; however, many products, particularly those containing garlic oil, have relatively poor efficacy [63,64]. In addition, many *in vivo* studies indicate that garlic oil and individual alkyl sulfides, most notably diallyl sulfide and allylmethylsulfide, inhibit murine and human CYP2E1 [65–68]. This is likely a result of the CYP2E1-catalyzed biotransformation of diallyl sulfide to diallyl sulfoxide and diallyl sulfone, in which the latter is a mechanism-based inhibitor of the enzyme [66,69]. Despite inhibition of human CYP2E1 *in vitro*, few interactions involving garlic products and CYP2E1 substrates have been reported, a consequence that probably reflects the paucity

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of drugs metabolized by this enzyme. Conversely, prolonged administration of diallyl sulfide and diallyl disulfide induced other hepatic and intestinal murine CYP subfamilies (e.g., CYP1A, CYP2B, CYP3A), in addition to various transferases (e.g., GSTs, UGTs) [65, 70–76] through activation of CAR and Nrf2 nuclear receptors [77].

The ability of garlic to inhibit other human CYP isoforms also 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 [32, 78] or modest inhibition (< 50%) of human CYP2C9, CYP2C19, and CYP3A4 isoforms [79, 80]. A freeze-dried garlic supplement, however, produced significant inhibition of CYP3A4 *in vitro* (> 95%) [80]. Because the chemistry of garlic is complex and because different types of processing can significantly alter its phytochemical composition, lyophilization may stabilize those organosulfur compounds capable of inhibiting CYP3A4. Aged garlic extracts (AGE), on the other hand, do not appear to inhibit any of the major CYP isoforms present in human liver microsomes [81]. This may stem from a dearth of oil-soluble organosulfur compounds in AGE and a preponderance of water-soluble components (e.g., *S*-allyl-*L*-cysteine, saponins) [59]. The shift from oil- to water-soluble ingredients arises from the aging process and subsequent aqueous extraction, which makes AGE distinct from the other types of garlic products.

Based upon *in vitro* and murine *in vivo* findings, garlic's effects on transporter activity also appear dependent upon the hydrophilicity of specific organosulfur compounds. The preponderance of *in vitro* data regarding ABC isoforms implies that garlic's oil-soluble organosulfur compounds are not potent inhibitors of the efflux transporter ABCB1 [80, 82–85] but may, however, induce ABCC2 expression [85]. Interestingly, lipophilic compounds (e.g., diallyl sulfide, diallyl disulfide) increased ABCB1 efflux through rat ileum but not through Caco-2 cell monolayers [86]. When exposed to both Caco-2 cell monolayers and the rat intestine at high concentrations (~ 12 µg/mL), water-soluble compounds in AGE (e.g., *S*-allyl-*L*-cysteine) induced the activity of ABCB1, ABCC2, and SLCO transporters [86, 87]. In a HepG2 cell line, however, ABCC2 activity was reduced, suggesting that AGE-mediated regulation of ABCC2 proteins in the liver is different from that in the intestine [88]. Tissue-specific regulation of ABCC2 activity has also been observed for other xenobiotics [89], and this may only add to the difficulties of predicting garlic-drug interactions.

A modest number of prospective human studies have investigated the drug interaction potential of garlic supplements or purified garlic organosulfur compounds [90–102]. Owing to the variety of products evaluated and diverse dosages of garlic phytochemicals administered, results have been mixed. A number of drugs, whose biotransformation pathways run the gamut of human XMEs, have been assessed (e.g., acetaminophen, alprazolam caffeine, chlorzoxazone, cyclosporine, debrisoquine docetaxel dextromethorphan, midazolam, omeprazole, ritonavir, saquinavir, warfarin), yet the evidence implies that only substrates of CYP2E1 are significantly affected [90, 92, 98]. The first prospective study by Gwilt et al. found that daily administration of aged garlic extract (~ 19 mg *S*-allyl-*L*-cysteine) produced no significant effects on the pharmacokinetics of acetaminophen, a putative CYP2E1 substrate [91]. Later, Loizou and Crocker observed that administration of diallyl sulfide (~ 0.2 mg/kg) to healthy volunteers reduced plasma 6-hydroxychlorzoxazone/chlorzoxazone ratios (a phenotypic measure of CYP2E1 activity) by an average of 31% [92]. This finding confirmed in humans what had been previously observed in murine models that lipophilic, and not hydrophilic, organosulfur compounds were CYP2E1 inhibitors. Subsequent studies confirmed that prolonged garlic oil supplementation (500 mg, three times daily for 28 days) inhibited human CYP2E1 activity in both young [90] and elderly adults [98] by almost 40% and 25%, respectively; however, no modulatory effects were noted for CYP1A2, CYP2D6, or CYP3A4. In contrast, 21 days of twice daily supplementation with garlic powder (~ 9 mg allicin and 23 mg alliin) reduced by 50% the mean AUC, 8-hour trough concentrations, and mean maximum plasma concentrations (C_{max}) of the protease inhibitor saquinavir [93]. The authors concluded that the garlic powder supplement might have induced intestinal CYP3A4 and/or P-gp, since saquinavir is a substrate for both proteins. A similar, although less dramatic, effect on ritonavir AUC, was observed after a four-day course of garlic extract (5 mg, twice daily) [94]. Subsequent studies examining the prolonged effects of garlic supplementation on other CYP3A4 substrates, however, failed to note any significant changes [95–97]. Nor have any clinically important garlic-mediated interactions been reported for warfarin, a recognized substrate for CYP2C9 and 3A4 [100, 101]. However, large doses of the organosulfur compound allicin (~ 150 mg daily) did reduce the metabolism of omeprazole by inhibiting CYP2C19 activity in individuals both homozygous and heterozygous for the *CYP2C19*1* allele, but not for those homozygous for *CYP2C19*2* [102]. Interestingly, the CYP3A4-mediated omeprazole sulfone pathway was not affected. Reductions in saquinavir and ritonavir concentrations noted in early studies appear attributable to garlic-mediated upregulation of intestinal ABCB1 or ABCC2 activity as was demonstrated in several recent *in vitro* investigations [84–89]. The extent to which garlic supplementation affects human ABC and SLCO substrates *in vivo* was recently addressed in healthy volunteers receiving a standardized garlic extract for 21 days [103]. A 31% increase in the duodenal expression of human ABCB1 correlated with a modest reduction in saquinavir AUC while no significant effects were noted in the pharmacokinetic parameters of simvastatin (a CYP3A4 substrate) or pravastatin (an SLCO1B1 substrate).

Taken together the accumulated findings imply 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 indicies, this interaction is not cause for great concern. On the other hand, prolonged consumption of garlic extract appears to modestly induce the human efflux transporter ABCB1. Accordingly, prolonged exposure to concentrated garlic extracts may reduce the efficacy of drugs whose disposition is strongly dependent on ABCB1.

Interaction risk: low.

Ginkgo biloba

▼

Termed living fossils, ginkgo trees (family Ginkgoaceae) have existed since the early Jurassic period 150 million years ago. The lone species that avoided extinction (*Ginkgo biloba* L.) is now cultivated in Asia, Europe, North America, New Zealand, and Argentina. Ginkgo is a popular ornamental tree recognizable by its unusual fan-shaped leaves that turn bright yellow in autumn. In Asia, the tree has long been held sacred for its therapeutic value. Today, dosage forms incorporating *G. biloba* leaf extracts are used throughout the world for treatment of insufficient blood flow,

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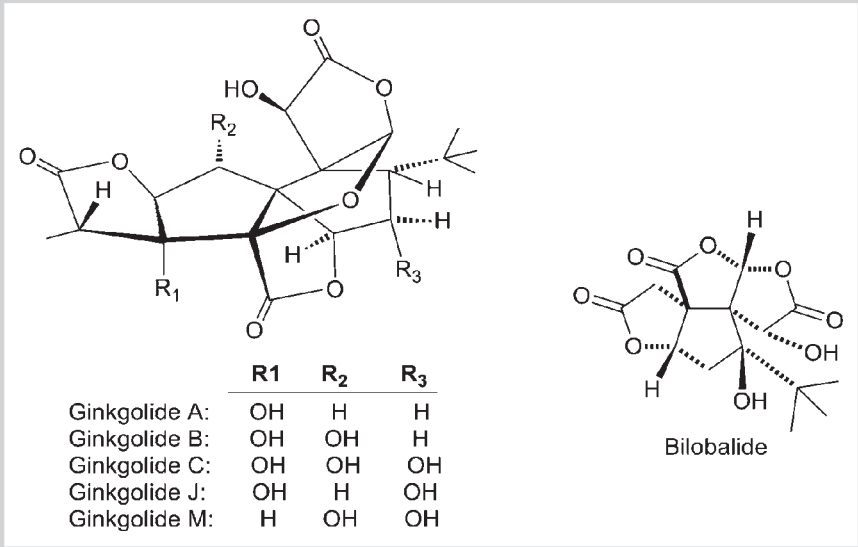

Fig. 4 Representative phytochemicals (terpene lactones, flavonoid glycosides) present in *Ginkgo biloba*.

memory deficits, cognitive disorders, Alzheimer's disease, depression, vertigo, tinnitus, and intermittent claudication [104]. Ginkgo's popularity has made it one of the most intensely studied botanicals in the world. Currently more than 2500 articles related to *G. biloba* have been published in the medical literature.

Clinical trials on the efficacy of *G. biloba* extracts are numerous and controversial [105–109]. Much of the research has centered on products formulated with EGb 761, an extract produced by the German company Schwabe. EGb 761 is a standardized, concentrated 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 [104]. Several other companies produce ginkgo extracts with similar chemical profiles. Terpene lactones are unique to *G. biloba* and include the ginkgolides, a group of diterpene trilactones (e.g., ginkgolide A, B, C, J, M), and bilobalide, a sesquiterpene lactone (**Fig. 4**). *G. biloba* flavonoids occur principally as glycoside derivatives, with quercetin, kaempferol, and isorhamnetin being the most prevalent. Other PSMs present in *G. biloba* that may have allergenic, immunotoxic, and other undesirable properties (e.g., ginkgetin, amentoflavone, ginkgolic acids, ginkgotoxin, and others) are typically removed during processing [104].

Discrepancies among clinical studies regarding efficacy may be traced to significant interproduct variability in phytochemical content and biopharmaceutical characteristics of ginkgo extract dosage forms (e.g., disintegration, dissolution, bioavailability) [110, 111]. These same discrepancies may also underly the confusion surrounding the herb-drug interaction potential of *G. biloba*. Depending upon which experimental model is utilized, different interpretations of ginkgo's drug interaction capabilities emerge. In many *in vitro* experimental systems, ginkgo extracts [14, 33, 35, 38, 112–119], as well as individual terpene lactones [110, 111, 115–120] and flavonoid glycosides [14, 115–123] have been shown to inhibit various XMEs and transporters, although in most instances IC_{50} values were well in excess of 20 µM. Aglycones of quercetin, kaempferol, and isorhamnetin seem to have the greatest inhibitory capacity [116, 119–126], while ginkgolides and bilobalide exhibit the least and in many cases, none at all [79, 116–119, 123, 124, 127]. In contrast, ginkgo extracts and individual terpene lactones appear capable of inducing the expression of several CYP, UGT, and ABC isoforms in rat [128–130] and human primary hepatocytes [113, 114, 130, 131] as well as human mammary epithelial cells [132]. Cell-based reporter assays in HepG2 [121, 131] and LS180 [133] and other cell lines [132, 134] revealed that ginkolides A and B are activators of PXR, whereas quercetin and kaempferol activated PXR, CAR, and AhR. Bilobalide exerted no effects on nuclear receptors in these assays. The discovery that specific ginkgolides and flavonoids are ligands for several xenobiotic receptors provides an explanation for a host of recent *in vivo* studies in which prolonged administration of *G. biloba* extracts to rats, often in high doses, not only induced a multitude of XMEs [135–140] but reduced efficacy for several drug substrates: nicardipine [141], tolbutamide [142], phenobarbital [143], propranolol [144], cyclosporine [145], and theophylline [146]. Concomitant administration of *G. biloba* also enhanced the hepatotoxicity of acetaminophen via CYP3A induction [147]. However, several of these *in vivo* studies contradicted cell-based reporter assay findings when bilobalide was implicated as an XME activator [148–150].

Evidence from *in vitro* and animal investigations clearly points to *G. biloba* extracts and their constituents as inducers of XME and transporter activity. These findings have led investigators to warn of significant drug interactions with *G. biloba*. Clinical evidence substantiating these claims, however, is not as compelling. To date, 29 prospective clinical trials assessing the effect of *G. biloba* supplementation on the pharmacokinetics of a variety of drugs, including several specific CYP probes, have been published [90, 98, 139, 151–176]. Twenty-nine different drugs whose metabolism or transport is mediated by various CYP isoforms (e.g., CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4) or transporters (e.g., ABCB1, SLCO1B1, SLCO2B1) were evaluated. The drugs included aspirin [167], alprazolam [161], antipyrine [152], bupropion [174], caffeine [90, 98, 154], chlorzoxazone [90, 98, 154], cilostazol [162], clopidogrel [162], dapsone [154], debrisoquine [90, 98, 154], dextromethorphan [157], diazepam [175], diclofenac [163], digoxin [156], donepezil [159], endogenous steroids [139, 161], fexofenadine [170], flurbiprofen [164], lopinavir [170], mephenytoin [154], metformin [169], midazolam [90, 98, 166, 170], nifedipine [153, 158], omeprazole [151], talinolol [172, 173], ticlopidine [165, 176], tolbutamide [163, 166], vorico-

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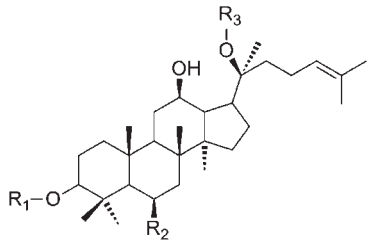

Compound	R_1	R_2	R_3
Protopanaxadiol derivatives			
Rb_1	-Glc^2-^{1}Glc	-H	-Glc^6-^{1}Glc
Rb_2	-Glc^2-^{1}Glc	-H	-Glc^6-^{1}Arap
Rc	-Glc^2-^{1}Glc	-H	-Glc^6-^{1}Araf
Rd	-Glc^2-^{1}Glc	-H	-Glc
Rg_3	-Glc^2-^{1}Glc	-H	-H
Rh_2	-Glc	-H	-H
Compd K (C-K)	-H	-H	-Glc
20(*S*)-protopanaxadiol (Ppd)	-H	-H	-H
Protopanaxatriol derivatives			
Re	-H	-O-Glc^2-^{1}Rha	-Glc
Rg_1	-H	-O-Glc	-Glc
Rg_2	-H	-O-Glc^2-^{1}Rha	-H
Rh_1	-H	-OGlc	-H
Rf	-O-Glc^2-^{1}Glc	-H	-H
20(*S*)-protopanaxatriol (Ppt)	-H	-OH	-H

Fig. 5 Representative phytochemicals (ginsenosides) present in the *Panax* species.

nazole [171], and warfarin [155, 160, 168]. The majority of these studies followed a *G. biloba* supplementation regimen of 240 mg leaf extract twice daily from as few as 3 to as many as 90 days, while others utilized smaller doses. In addition, most utilized products containing the standardized EGb 761 extract. Of the 29 studies (many of which evaluated more than one drug), 23 observed no significant effects of *G. biloba* on drug disposition, 5 observed a modest inhibitory effect [153, 154, 166, 172, 173], and 3 demonstrated evidence of CYP3A4 [168], CYP2C9 [164], and CYP2C19 [151] induction. Moreover, when compared to FDA guidelines on drug interaction criteria [177, 178], those few studies demonstrating a modulatory effect of *G. biloba* on drug disposition do not appear to be clinically important.

Discrepancies in *G. biloba's* effect on rat and human XMEs *in vivo* do not appear to reflect species differences in PXR activation [129, 179], but rather seem to be dose related [136, 139]. Most rat studies administered *G. biloba* extracts at 100 mg/kg/day, a dose comparable to 1300 mg/day or greater in humans; however, most human studies incorporated doses of 240 mg/day or less.

Additionally, several studies have assessed the pharmacokinetics of ginkgolides and bilobalide in human volunteers. Following 240 mg doses of standardized *G. biloba* extracts, C_{max} values for ginkgolides and bilobalide rarely exceeded 40 ng/mL [180–182], concentrations well below the 4000 ng/mL at which ginkgolides A and B activated PXR *in vitro* [133]. It is possible that concentrations exceeding 40 ng/mL may be achieved within intestinal enterocytes, but this depends upon disintegration and dissolution profiles of individual dosage forms (characteristics that can vary considerably between brands [183, 184]), as well as the permeability of individual terpene lactones or flavonol glycosides. In Caco-2 and MDR1-MDCK cell monolayers, ginkgolides and bilobalide exhibited low absorptive permeability and high efflux [185]; two conditions that would further preclude their exposure to enteric XMEs.

In summary, dosage forms containing standardized *G. biloba* extracts, when administered at doses of 240 mg/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.

Interaction risk: low, at doses 240 mg/day or lower.

Ginseng spp.

Of the five major *Panax* species (family Araliaceae) worldwide, Asian ginseng (*Panax ginseng* C.A. Meyer) and American ginseng (*Panax quinquefolius* L.) are the most widely used and extensively studied. *P. ginseng* root has an almost 2000-year history of use in traditional Chinese medicine (TCM) as an adaptogen (a plant that increases resistance to stress and fatigue) and a restorative tonic. Today, ginseng root, either as a TCM or dietary supplement, is one of the most popular herbs in the world; used to improve libido and sexual performance, prevent cancer, regulate blood sugar, lower blood pressure, improve cognition, fight fatigue, and boost immunity [186]. With the possible exception of its mild hypoglycemic effect, ginseng's efficacy remains questionable, as many clinical trials have produced confounding results [187–189]. Ambiguity in clinical findings may be linked to differences in the ginsosenoside content of products evaluated.

Ginsenosides, a group of triterpene glycosides (steroidal saponins), are unique to *Panax* species. More than 40 ginsenosides have been identified in the roots of *P. ginseng* and *P. quinquefolius*. Ginsenoside nomenclature employs the designation Rx, where x represents the retention factor (Rf) value from the sequence of spots (from bottom to top) on thin-layer chromatography plates. Ginsenosides exhibit considerable structural variation. They differ from one another by the type, number, and site of attachment of sugar moieties. The two major subtypes of ginsenosides – protopanaxadiol and protopanaxatriol – are classifed according to the arrangement and number of sugar (glucose, rhamnose, xylose, and arabinose) residues on the steroidal skeleton [190]. Rb1, Rb2, Rc, and Rd are examples of protopanaxadiol ginsenosides, while Re, Rf, Rg1, and Rg2 are examples of protopanaxatriols (**Fig. 5**). *P. ginseng* and *P. quinquefolius* differ significantly in type and proportion of ginsenosides, with *P. ginseng* having a high Rg1 : Rb1 ratio and *P. quinquefolius* a low Rg1 : Rb1 ratio [191]. Such distinctions may account for differences in purported efficacy between the two species. Ginseng root extracts are often standardized to contain a particular percentage (~4%) and ratio of ginsenosides. When ingested, ginsenosides undergo partial hydrolytic deglycosylation in the stomach and are further deglycosylated in the large intestine through enzymatic glucosidase activity of gut microflora [190, 192–194]. It is these metabolites (e.g., compound K, **Fig. 5**) that ultimately reach the systemic circulation and are alleged to have pharmacologic activity [192, 194–196].

From a drug interaction perspective, clinical and nonclinical evidence regarding ginseng extracts and their effects on XMEs and transporters is particularly confusing. This confusion stems from an assortment of variables affecting ginsenoside disposition.

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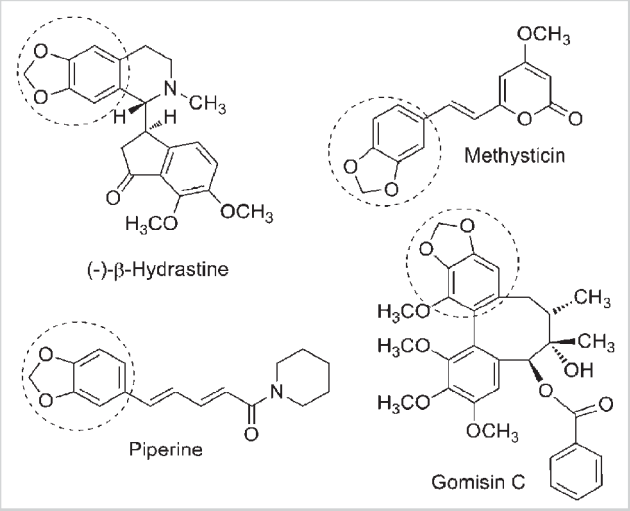

Fig. 6 Representative methylenedioxyphenyl-containing phytochemicals (broken circle = methylenedioxyphenyl moiety).

These include, but are not limited to, variability in ginsenoside type and content [190, 191], degree of preabsorptive deglycosylation [192–195], poor membrane permeability [197], interindividual differences in gut microflora [192–194], and enteric efflux by ABC transporters [198, 199]. It is now clear that highly polar, extensively glycosylated ginsenosides (e.g., Rb1, Rb3, Rg3, Re, Rg1, Rg2) are relatively weak modulators of human XMEs and transporters [37, 120, 200–207]. Ginsenoside concentrations necessary to inhibit most CYPs and transporters *in vitro* are not only high (> 50 µM), but are not likely to be realized *in vivo*, especially if normal dosing recommendations of ginseng products are followed [37, 120, 127, 200–207]. This also holds true for the even higher ginsenoside concentrations (> 100 µM) required for inducing CYP1A1 [208], CYP2C9, and CYP3A4 [200] activity in human liver cells and microsomes. However, the products of ginsenoside hydrolysis (e.g., deglycosylated metabolites) have been shown to competitively inhibit a variety of CYPs and transporters, oftentimes at concentrations well below 20 µM [203–208].

Only a limited number of animal studies have examined the effects of orally administered ginseng extracts (> 30 mg/kg) on drug disposition. From these, it appears that *P. ginseng* or *P. quinquefolius* either mildly induce [209–211] or have no significant effects [212–214] on rat XMEs and ABCB1 activity *in vivo*. Substantially more prospective human trials have investigated the effects of *P. ginseng* and *P. quinquefolius* supplementation on human drug disposition, with the CYP2C9 substrate, warfarin, being examined the most. Like the murine studies, clinical results fall into two catgories: no effect [90, 98, 215–219] or mild induction [217, 220–222].

Concerns regarding possible ginseng-drug interactions first surfaced when two case reports speculated that ginseng reduced warfarin anticoagulation [223, 224]. As single case reports cannot establish causation, a prospective clinical trial by Yuan et al. demonstrated that international normalized ratios (INR, a measure of anticoagulation), peak plasma warfarin levels, and warfarin AUCs were reduced by *P. quinquefolius* in healthy volunteers, and these effects reached statistical significance [221]. Subsequent clinical trials with *P. ginseng*, however, have failed to observe any influence on warfarin pharmacokinetics [216, 222] or pharmacodynamics [216, 218, 222]. Such discrepancies may reflect the disparity in ginsenoside profiles between *P. ginseng* and *P. quinquefolius*; however, several methodological concerns have been raised about the Yuan et al. study including it being underpowered, that inadequate sampling was used to determine AUC, and a non-stereoselective assay was used to measure warfarin enantiomers [222]. Therefore, it appears that whatever effect(s) *P. quinquefolius* extracts might have on human CYP2C9 activity, their magnitude does not reach clinical significance. As a result, the available evidence that links ginseng supplementation to potentially harmful drug interactions remains unconvincing.

Interaction risk: low.

Methylenedioxyphenyl-Containing Phytochemicals

The plant kingdom is replete with species that harbor phytochemicals whose structures contain methylenedioxyphenyl (MDP) moieties (**Fig. 6**). 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-containing PSMs (MDP-PSMs) often function as insecticides [225], but when consumed by humans they can act as mechanism-based inhibitors of CYPs [226, 227]. This type of inhibition is thought to arise from CYP-dependent oxidation of the methylenedioxy carbon to a carbene that subsequently interacts with CYP heme iron to produce a stable heme-adduct, termed a metabolic-intermediate (MI) complex [227]. It is through the formation of MI complexes that CYP isoforms are inactivated by MDP-PSMs [227, 228]. Because MDP-PSMs can function as mechanism-based CYP inhibitors, they pose significant risks for herb-drug interactions.

Prolonged administration of MDP-containing compounds has also been shown to induce CYP1A and CYP2B expression in several animal species [227–229]. Induction of CYPs by MDP-PSMs may be mediated by AhR or through mechanisms that promote protein stabilization [228, 229]. Whether CYP inhibition or induction predominates *in vivo* may depend upon the length and bulk of MDP side chains as well as the individual CYP isoform examined [230]. MDPs with long bulky side chains appear to be more potent inhibitors of CYP1A2, CYP2C9, CYP2D6, and CYP3A4, whereas CYP2B6 and CYP2C19 are not inactivated [230].

Goldenseal

Extracts of goldenseal root (*Hydrastis canadensis* L.; family Ranunculaceae), a perennial herb indigenous to eastern North America, are often taken as an antimicrobial to prevent common colds and upper respiratory tract infections. Often formulated with *Echinacea* species, goldenseal ranks among the top-selling botanicals in the United States.

Goldenseal's medicinal properties are attributed to several isoquinoline alkaloids, of which berberine and hydrastine (**Fig. 7**) are the most prevalent. Both berberine and hydrastine are MDP-PSMs that inhibit various CYP isoforms *in vitro* [10, 30, 31, 34, 36, 37, 231]. Using fluorometric microtiter plate assays, Budzinski et al. first noted that commercial extracts of *Hydrastis canadensis* were potent *in vitro* inhibitors of CYP3A4 [30]. Follow-up investigations by these authors found that goldenseal reduced CYP3A-mediated conversion of testosterone to its 6*β*-hydroxy metabolite by 88% [31]. Chatterjee and Franklin later confirmed the inhibition of testosterone 6*β*-hydroxylation by goldenseal extracts and ex-

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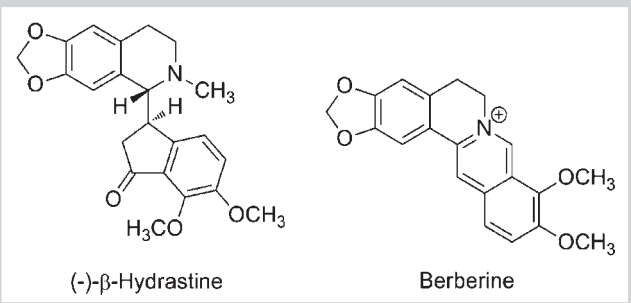

Fig. 7 Representative phytochemicals (isoquinoline alkaloids) present in goldenseal.

tended their findings to include individual isoquinoline alkaloids [231]. They demonstrated that hydrastine was a more potent inhibitor of CYP3A4 (IC_{50} = 25 µM) than berberine (IC_{50} = 400 µM).
It is seldom that prospective clinical studies corroborate *in vitro*-based predictions of CYP-mediated herb-drug interactions; however, goldenseal appears to be an exception. Using phenotypic measures of CYP activity, Gurley et al. first observed that goldenseal supplementation significantly inhibited CYP2D6 and CYP3A4 in healthy volunteers [13]. In subsequent investigations with the CYP3A4 probe midazolam, Gurley et al. further demonstrated that 14 days of goldenseal supplementation (~ 209 mg isoquinoline alklaoids daily) significantly increased midazolam AUC, C_{max}, and elimination half-life, and that the effects were proportional to those produced by the well-recognized, mechanism-based inhibitor clarithromycin (1000 mg daily) [232]. In addition, goldenseal's inhibition of human CYP2D6 *in vivo* was confirmed with other commercially available supplement brands [49]. Interestingly, another prospective study evaluating the influence of goldenseal supplementation on the pharmacokinetics of indinavir (a protease inhibitor and CYP3A4 substrate) failed to register any significant effects [233]. This discrepancy may stem from the relatively high oral bioavailability of indinavir, which renders it a less effective probe for assessing herb-mediated changes in CYP3A activity. Thus, goldenseal may have its greatest impact on those CYP3A substrates exhibiting high intestinal metabolism and low oral bioavailability.
In China, berberine (an OTC remedy for diarrhea of bacterial origin) has also been shown to significantly increase the AUC, C_{max}, and trough concentrations of the immunosuppressive drug cyclosporine [234,235]. Since cyclosporine is both a CYP3A4 and ABCB1 substrate, the activity of both of these proteins could conceivably be affected by hydrastine and berberine. There is convincing *in vitro* and animal evidence that berberine is a substrate for certain ABC isoforms [236–240], and thus, it may compete with other ABC substrates for efflux across intestinal and canalicular membranes. Recent clinical evidence, however, indicates that goldenseal's effect on digoxin (an ABCB1 substrate with a narrow therapeutic index) disposition in humans is not significant [241]. Therefore, goldenseal's propensity for eliciting herb-drug interactions appears limited to those mediated by CYPs.
Dissolution profiles of commercially available goldenseal supplements reveal that berberine and hydrastine are rapidly and completely released from extract formulations [242], producing intestinal luminal concentrations comparable to those required for CYP inhibition *in vitro* [241]. In humans, both berberine and hydrastine are readily absorbed and extensively metabolized, with berberine phase I metabolites being preferentially sulfated, while those of hydrastine are primarily glucuronidated [243]. Extensive metabolism is conducive to the formation of MI complexes and may explain goldenseal's penchant for CYP inhibition. Given that goldenseal isoquinoline alkaloids significantly inhibit both CYP3A4 and CYP2D6 activity (the two most important drug metabolizing enzymes in humans), its herb-drug interaction potential is deemed considerable.
Interaction risk: high.

Kava kava

Kava kava (*Piper methysticum* G. Forst.; family Piperaceae) has long been a traditional beverage consumed among South Pacific islanders to imbue psychotropic, hypnotic, and anxiolytic effects [244]. Since the 1990s, commercial kava extracts formulated as tablets and/or capsules have been marketed as dietary supplements for the alleviation of stress, anxiety, or insomnia [244, 245]. Reports linking kava use to liver toxicity have led to the removal of these products from Australia, Canada, and several European countries, and prompted the FDA to issue warnings of possible hepatotoxic side effects associated with kava supplementation [244]. For those case reports documenting possible kava-related hepatotoxicity, prolonged usage (> 60 days), and co-medication with prescription drugs or other botanical supplements were frequent and confounding variables [244]. Modulation of human drug metabolism and/or transport has been postulated as an underlying mechanism for kava-induced liver toxicity. Accordingly, a significant body of literature exists exploring kava's ability to alter XME and transporter activity. The preponderance of *in vitro* data points to kava as an inhibitor of various CYPs and ABCB1 [79,245–251], whereas other evidence suggests kava may activate PXR to induce CYP and ABCB1 activity [252–254]. In accordance to kava phytochemicals acting as nuclear receptor ligands, most studies that administered high doses of kava extracts to murine species for prolonged periods observed an induction in CYP1A and 3A activity and expression [250,255–258].
The kavalactones (e.g., kavain, dihydrokavain, methysticin, dihydromethysticin, yangonin, desmethoxyyangonin) are a collection of phytochemicals unique to kava (**Fig. 8**). Of these, methysticin and dihydromethysticin are both MDP-PSMs and potent (≤ 10 µM) mechanism-based inhibitiors of CYPs *in vitro* [247,249]. Dihydromethysticin, like some other MDP-containing compounds, also appears to induce CYP3A isoforms *in vitro* through activation of human PXR [253]. In addition, both methysticin and dihydromethysticin have good dissolution profiles in simulated intestinal fluid at pH values greater than 4, a property favorable for producing gut lumen concentrations in excess of 10 µM [242]. As a result, one might anticipate that kava supplementation would significantly modulate human XMEs and transporters *in vivo*. To date, only five prospective clinical studies have attempted to evaluate the drug interaction potential of kava and the results have been mixed [13,49,232,241,259]. Russman et al. found that in chronic users of traditional kava-containing beverages (e.g., 7–27 g kavalactones per week) significantly reduced CYP1A2 activity, yet this practice had no effect on the phenotypic markers of CYP2C19, 2D6, 2E1, or 3A4 function [259]. In contrast, Gurley et al. observed that 30 days of kava supplementation in healthy volunteers had no effect on the phenotypic markers of CYP1A2, CYP2D6, or CYP3A4 activity; however, CYP2E1 activity was significantly reduced [13].
Discrepancies between these studies with regard to kava's effect on CYP1A2 and 2E1 may be traced to variations in extract compo-

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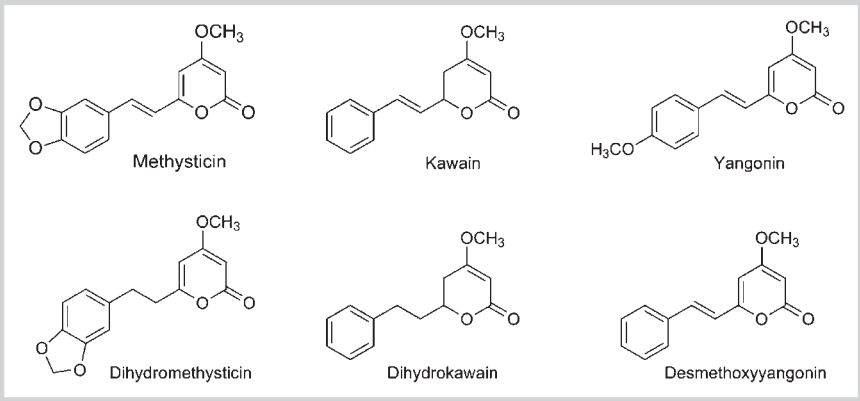

Fig. 8 Representative phytochemicals (kava lactones) present in kava kava.

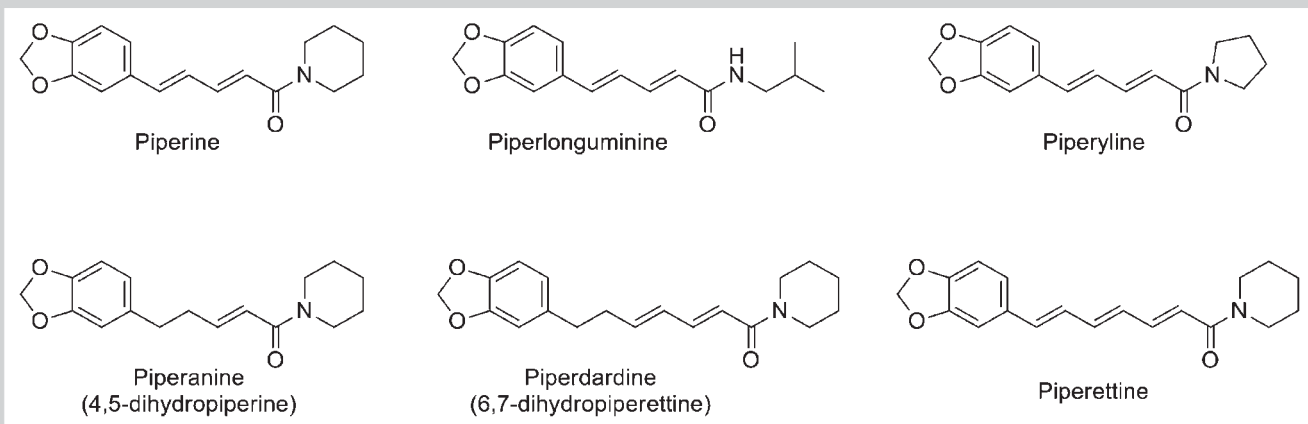

Fig. 9 Representative phytochemicals (piperamides) present in black pepper.

sition. Traditional kava beverages are made from aqueous extractions of *P. methysticum* root, whereas formulations of many commercially available kava supplements are products of nonaqueous solvent extractions. Kavalactone profiles can vary considerably among the two extraction processes [245]. Subsequent studies conducted by Gurley's group found that, when compared to known CYP inducers and inhibitors, 14 days of supplementation with well-characterized kava products had no clinically relevant effects on human CYP2D6, CYP3A4, or ABCB1 activity [52, 232, 241].

The apparent low potency of methysticin and dihydromethysticin as mechanism-based inhibitors *in vivo* may stem from the structure of their MDP side chains. In examining a series of MDP-containing compounds, Nakajima et al. noted that those with short, nonbulky side chains were less effective inhibitors of CYP activity [230]. This, coupled with the fact that kava extracts often have lower amounts of methysticin and dihydromethysticin compared to the isoquinoline alkaloid content of goldenseal, may explain the difference in herb-drug interaction potentials for these two MDP-containing species. In short, consumption of commercially available kava supplements per product label recommendations is not likely to affect the efficacy or toxicity of conventional medications.

Interaction risk: low.

Black pepper/piperine

Dried ground black pepper (*Piper nigrum* L.; family Piperaceae) has been used since antiquity as both a flavoring agent and medicine [260]. In fact, for almost two millennia *Piper* species (e.g., *P. nigrum* and *P. longum*) have been essential components of several Ayurvedic medicine preparations [261]. Black pepper is one of the most commonly used spices and may be found on nearly every dinner table in the industrialized world. Black pepper is produced from green unripe berries of the pepper plant; the fruits are dried following a heat treatment that releases browning enzymes from the cell walls [262]. The spiciness of black pepper is due to the MDP-containing phytochemical, piperine, and related pungent alkaloids known as piperamides [260] (**Fig. 9**). These compounds function as insecticides in the pepper plant [263–265], but in mammalian systems they are inhibitors of various XMEs [266–277] and transporters [278–283]. While inhibition is clearly the most prevalent finding, especially upon acute exposure, several animal studies report upregulation of GSTs [284], certain CYPs [285, 286], and ABCs [278, 280, 281] with long-term exposure to piperine, a finding in line with other studies examining chronic feeding of MDP-PSMs.

Piperine's ability to inhibit drug metabolism was first recognized by Atal et al. more than 30 years ago when its administration to rats increased the oral bioavailability of the alkaloids sparteine and vasicine by factors of two and three, respectively [266]. In addition, piperine increased the pharmacodynamic effects of hexobarbital and zoxazolamine in a dose-dependent fashion [266].

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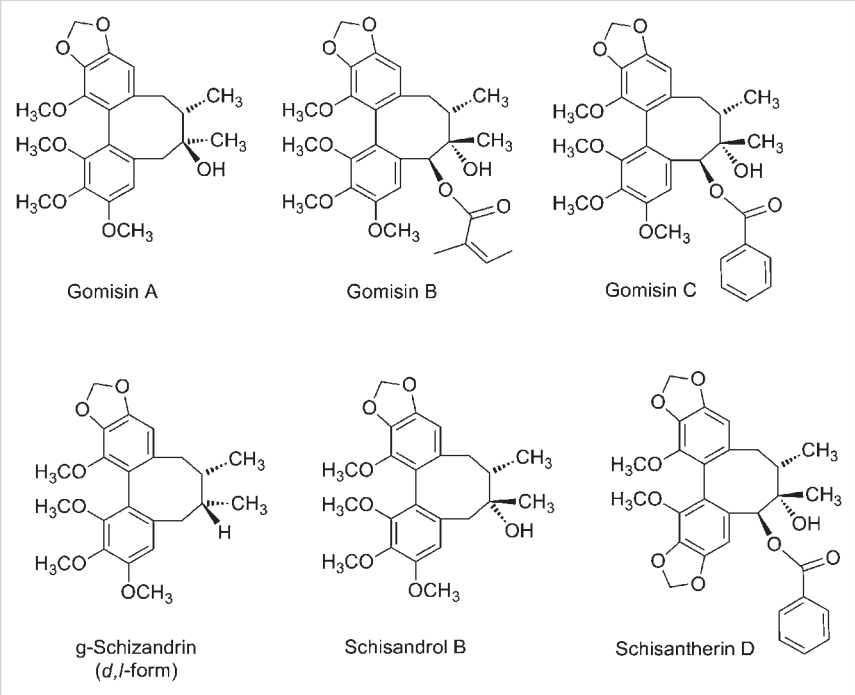

Fig. 10 Representative methylenedioxyphenyl-containing phytochemicals present in *Schisandra* species.

Follow-up studies by Atal's group observed that piperine administration was a noncompetitive inhibitor of various murine hepatic monoxygenases as well as UGTs [267]. Subsequent studies confirmed piperine's effect on murine XMEs [268–273] and also found that it and other piperamides were selective inhibitors of human CYP3A4, CYP2D6, and ABCB1 *in vitro* [274, 275, 277, 282]. Piperine's inhibitory effect on UGTs is more pronounced in intestinal epithelial cells than hepatocytes [270]. Moreover, structure–activity relationship studies involving more than 35 separate analogues revealed that piperine is especially suited for CYP inhibition [273]. Modifications to either the MDP moiety or piperidine side chain significantly reduced its potency [273]. (Millions of years of plant-animal warfare have clearly optimized piperine pharmacology.) In addition to its inhibitory effects on XMEs and ABCB1, piperine may also promote drug absorption by modulating the permeability characteristics of intestinal membranes as well as through stimulating increases in microvilli length [287].

One of the most compelling aspects of piperine is its ability to dramatically enhance the oral absorption of concomitantly administered medications [266, 279, 283, 288–293]. To date, every prospective human trial investigating black pepper's and/or piperine's effect on drug pharmacokinetics has demonstrated a profound improvement in oral bioavailability. Drugs affected and the observed percent increase in mean AUC include phenytoin (16–133%) [289, 291, 292], rifampicin (69%) [288], propranolol (103%) [290], theophylline (96%) [290], and nevirapine (170%) [293]. In practically every case, piperine's effect can be considered clinically relevant. This is especially so for drugs with narrow therapeutic indices.

Recognizing piperine's utility as a bioavailability enhancer, many dietary supplement manufacturers incorporate *P. nigrum* or *P. longum* extracts into botanical formulations as a means of improving phytochemical efficacy. This positive herb-herb interaction is best exemplified by curcumin, a dietary phytochemical in tumeric with promising chemopreventative properties but exceedingly poor oral bioavailability due to extensive CYP- and UGT-mediated metabolism [294–295]. When administered with 5 mg of piperine, a twofold increase in curcumin AUC was observed in healthy volunteers [294]. In another study, 20 mg of piperine produced an almost 20-fold increase in curcumin AUC [296]. Similar bioavailability enhancing effects on green tea polyphenols have also been reported [297]. As an added benefit to enhancing phytochemical bioavailability, piperine also has a broad safety profile [260].

When used in quantities typical for flavoring food, black pepper is not likely to affect the disposition of most medications. However, excessive use of black pepper or intake of dietary supplements formulated with *P. nigrum* or *P. longum* extracts may produce clinically significant interactions with drugs. This may be of particular concern when CYP3A and/or ABCB1 substrates are ingested concomitantly with piperine or piperamides in excess of 10 mg.

Interaction risk: high.

Schisandra spp.

Preparations of fruits from woody vines in the family Schisandraceae are a staple in traditional Chinese, Japanese, and Russian medicine [298]. Among their many uses, 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 [298, 299]. In the United States, extracts of *S. chinensis* and *S. sphenanthera* are often incorporated into multicomponent dietary supplement formulations.

A host of unique MDP-PSMs including gomisins A–C, schisandrin, schisandrol B, and schisantherin D are found in *Schisandra* species (**Fig. 10**). Like many MDP-PSMs, those present in *Schisandra* species are modulators of mammalin XMEs and transporters. Recognition of these properties is important as *Schisandra* products are often taken in conjunction with conventional medications in China, Japan, Russia, and other Asian countries. In addition, dietary supplements containing *Schisandra* extracts are becoming

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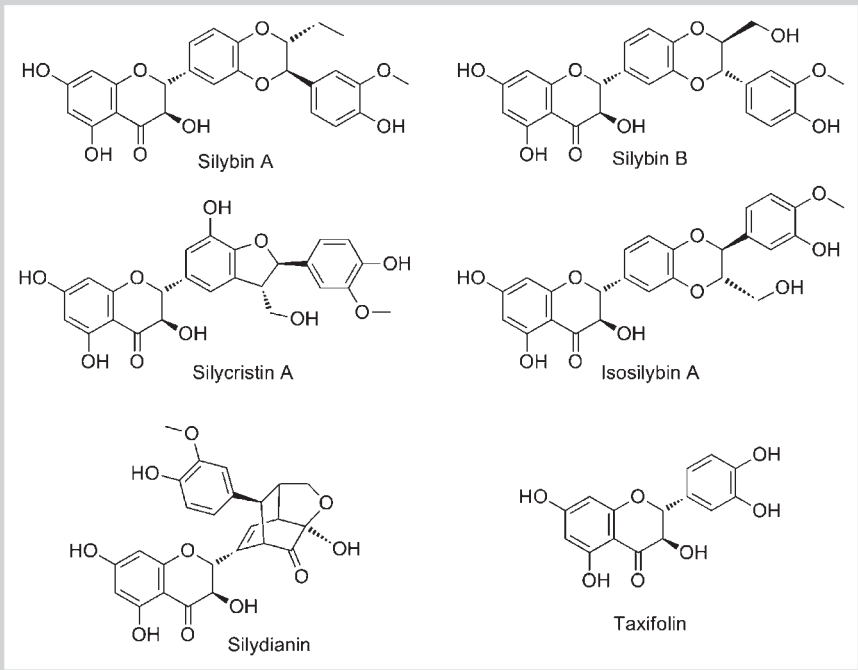

Fig. 11 Representative phytochemicals (flavanolignans) present in milk thistle.

more popular in many Western cultures. This too may increase the chance of *Schisandra*-related herb-drug interactions.

Ample evidence points to *Schisandra* MDP-PSMs as both substrates and inhibitors of ABC efflux transporters *in vitro* [300–306]. A number of *in vitro* studies also point to *Schisandra* MDP-PSMs as both competitive and noncompetitive inhibitors of murine and human CYP isoforms [307–312]. In particular, gomisins B, C, and G were shown to be particularly effective inhibitors of human CYP3A4 with IC_{50} values < 1.5 µM [308]. In the presence of NADPH, gomisin C's inactivation of CYP3A4 was time- and concentration-dependent, as well as irreversible, characteristics indicative of mechanism-based inhibition. Moreover, the inhibitory effect of gomisin C was stronger than that of ketoconazole, a known potent CYP3A4 inhibitor [308]. In contrast, reporter gene assays demonstrated that *S. chinensis* extracts and its constituents, schisandrin and schisandrol, activated rat and human PXR [310], whereas certain natural gomisin H analogues (e.g., tigloylgomisin H, angeloylgomisin H) significantly activated phase II detoxification gene expression via the Nrf2 nuclear receptor pathway [313].

Of the available animal studies investigating *Schisandra*'s effect on xenobiotic metabolism, two outcomes emerged (inhibition or induction), each dependent upon the duration of administration. When single doses of *Schisandra* extracts (≤ 250 mg/kg) were administered to rats concomitantly with CYP3A and/or ABCB1 substrates (e.g., midazolam [311], nifedipine [309], paclitaxel [314], tacrolimus [312]), drug AUCs more than doubled, suggesting inhibition. However, when administration periods exceeded 6 days, rat XME and transporter function were consistently induced [310, 311, 315, 316].

Unlike the murine study results, prospective clinical trials assessing *Schisandra*'s effect on CYP3A and/or ABCB1 substrate pharmacokinetics were not biphasic. Whether *Schisandra* was administered once or for up to 14 consecutive days, AUCs of talinolol (ABCB1 substrate) [172], tacrolimus (CYP3A4/ABCB1 substrate) [317, 318], and midazolam (CYP3A4 substrate) [319] were increased 1.5-, 2.1-, and 2.0-fold, respectively. Based on these data, it appears that *Schisandra* is a potent inhibitor, not an inducer, of human XMEs and transporters. Such species differences may stem from the fact that humans not only received lower mg/kg doses of *Schisandra*, but that gomisin C concentrations necessary for PXR activation in humans are twice those required for murine species [311]. Accordingly, the clinical data currently available strongly suggests that *Schisandra* extracts pose a significant risk for elevating blood levels of drugs that are CYP3A and/or ABCB1 substrates.

Interaction risk: high.

Milk Thistle

▼

Silybum marianum L. Gaertn. (family Asteraceae), commonly known as milk thistle, is an herbaceous plant native to the Mediterranean region, although it has been naturalized throughout the world [320]. Extracts of milk thistle fruits (achenes) yield a collection of flavanolignans and flavonoids collectively known as silymarin [320, 321]. The principal phytochemical components in silymarin are silybin A, silybin B, isosilybin A, isosilybin B, silychristin, isosilychristin, silydianin, and taxifolin [321] (**Fig. 11**). Milk thistle extracts are touted for their antioxidant and hepatoprotectant properties, and their utility as therapy for treating various liver diseases (e.g., cirrhosis, hepatitis, hepatotoxicity) has been examined in numerous clinical trials [322–326]. While many smaller trials have revealed improvements in various clinical indicies, several larger studies have yielded equivocal results. However, an unequivocal conclusion gleaned from the clinical studies is that milk thistle has an excellent safety profile [322–326].

Milk thistle is one of the few popular botanicals in which the pharmacokinetic profile of its principal phytochemicals has been thoroughly examined in humans [327–331]. Components of standard milk thistle extracts, as a general rule, have very low oral bioavailability and short elimination half-lives. This stems from a combination of the poor water solubility of silymarin phy-

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tochemicals coupled with extensive presytemic metabolism (both phase I and II) and biliary secretion. As an example, C_{max} values for unconjugated silybin A and B (the two most prevalent flavanolignans in milk thistle products) rarely exceeded 20 ng/mL for single 600 mg doses of milk thistle extract in healthy volunteers [330]. 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 µg/mL [331]. At doses exceeding 1500 mg daily, there was also evidence of nonlinear pharmacokinetics [331]. Liver disease, however, does increase milk thistle flavanolignan exposure. Systemic concentrations of silybin and isosilybin diastereomers may be 3–5-fold higher in patients with cirrhotic or nonalcoholic fatty liver disease, which may account for milk thistle's purported efficacy in these populations [329, 331].

Given its popularity as one of the most utilized botanical supplements in the world, milk thistle's ability to modulate human XMEs and transporters has received considerable attention. A variety of *in vitro* methodologies have been utilized to assess the effect of milk thistle extracts or individual flavanolignans on XME [10, 36, 37, 112, 332–340], ABC efflux transporter [36, 37, 112, 337, 341–346], and SLC1B1 uptake transporter [347] activity. The majority of studies are in general agreement that flavanolignan concentrations in excess of 10 µM are required for inhibition of most CYP isoforms, and even higher concentrations are needed for ABCB1 and ABCG2 inhibition. Of all the CYP isoforms tested, CYP2C9 appears to be the most sensitive with IC_{50} values ~ 8 µM for human liver microsomes. At concentrations exceeding 30 µM, silybin diastereomers have been reported to function as mechanism-based inhibitors of CYP2C9 and 3A4 [336]. UGT1A1, however, may be the XME most easily inhibited by milk thistle with an IC_{50} value of 1.4 µM [336]. SLC1B1 also exhibited an IC_{50} value less than 4 µM for silymarin [347].

Because milk thistle flavanolignans exhibit poor oral bioavailability, several technologies have been employed to enhance this property [348]. One of the more successful has been complexation of silymarin components with phosphatidylcholine. Marketed as Silipide® and Siliphos®, these phosphatidylcholine complexes, or phytosomes, exhibit improvements in flavanolignan bioavailability three to five times those of conventional milk thistle extract formulations [348–352]. In addition, recent clinical studies in prostate cancer patients have shown that doses of Siliphos® ranging from 2.5 to 20 grams daily for up to 4 weeks produced C_{max} values between 10 and 100 µM for unconjugated silybin diastereomers [353, 354]. Conceivably, these concentrations are sufficient for inhibition of various XMEs and efflux transporters, and episodes of hyperbilirubinemia reported in these studies may indeed reflect inhibition of UGT activity [353, 354].

To date, a considerable number of prospective human studies have examined milk thistle's drug interaction potential. Supplementation regimens utilizing standard milk thistle extracts had no observable effects on the clinical pharmacokinetics of aminopyrine (nonspecific CYP probe) [355], caffeine (CYP1A2 probe) [50], chlorzoxazone (CYP2E1 probe) [148], debrisoquine (CYP2D6 probe) [49, 50], digoxin (ABCB1 substrate) [11], indinavir (CYP3A4 substrate) [356–358], irinotecan (CYP3A4/UGT1A1 substrate) [359], midazolam (CYP3A4 probe) [12, 50], nifedipine (CYP3A4 substrate) [360], phenylbutazone (nonspecific CYP probe) [355], ranitidine (CYP3A4/ABCB1 substrate) [361], and rosuvastatin (ABCB1/SLC1A1 substrate) [347]. Taken together, these findings imply that standard milk thistle products generate flavanolignan concentrations *in vivo* that are incapable of affecting most human XMEs and transporters. However, a few clinical studies challenge this assumption. For example, 14 days of silymarin supplementation (140 mg thrice daily) increased the AUC of talinolol (ABCB1 substrate) in healthy volunteers by 36% (a finding suggestive of ABCB1 inhibition); however, this effect is not considered clinically relevant [362]. In contrast, 140 mg of silymarin administered to healthy adults for 9 days reduced the mean AUC for metronidazole (CYP3A4/ABCB1 substrate) by 29% [363], and while this effect hints at possible induction, it too is of little clinical concern. More concerning is a recent finding that silymarin inhibits the metabolism of losartan to its active metabolite E-3174, and that the magnitude of the interaction is dependent upon *CYP2C9* genotype [364]. In subjects with the *CYP2C9*1/*1* genotype, a 14-day course of silymarin produced a 2-fold increase in losartan AUC and C_{max}, but these parameters were not affected in subjects with the *CYP2C9*1/*3* genotype. This finding supports that of Brantley et al. who noted that CYP2C9 appeared most vulnerable to inhibition by clinically achievable concentrations of silybin B [340].

At present, no prospective studies have examined the effects of phytosomal milk thistle preparations on the pharmacokinetic profiles of conventional medications. As such, it remains to be seen whether milk thistle products with enhanced bioavailability pose a greater risk for herb-drug interactions. A recent clinical trial of Siliphos® for treatment of chemotherapy-related hepatotoxicity in childhood acute lymphoblastic leukemia suggests otherwise, as investigators observed no adverse interactions between milk thistle and methotrexate, 6-mercaptopurine, or vincristine during the 28-day course of supplementation [365]. Therefore, based upon the existing clinical data, the drug interaction risk for milk thistle products appears minimal.

Interaction risk: low.

St. John's Wort

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With more than 2000 peer-reviewed articles published on its safety and efficacy, St. John's wort (*Hypericum perforatum* L.; family Clusiaceae) is the most studied botanical dietary supplement in the world. *Hypericum perforatum* is a yellow-flowering, perennial herb indigenous to Europe that has been introduced to many temperate areas of the world and grows wild in many meadows. The common name comes from its traditional flowering and harvesting on 24 June, the birthday of John the Baptist (St. John's Day).

Extracts of *H. perforatum* have gained international recognition for their antidepressant activity although the efficacy of many St. John's wort (SJW) products remains questionable [366]. Nevertheless, many clinical trials have demonstrated efficacy superior to placebo and comparable to standard antidepressants but with fewer side effects than conventional antidepressive agents [367]. When used as a single agent, a favorable risk/benefit ratio has made St. John's wort one of the most readily consumed dietary supplements in the world. In turn, the popularity of SJW has also contributed to its distinction as being one of the most problematic dietary supplements with regard to herb-drug interactions.

Both the antidepressant effect and drug interaction potential of SJW hinge upon the extract's content of hyperforin, a bicyclic polyprenylated acylphloroglucinol found exclusively in *Hypericum* species [368] (**Fig. 12**). As an antidepressant, hyperforin functions as broad-based neurotransmitter reuptake inhibitor, affect-

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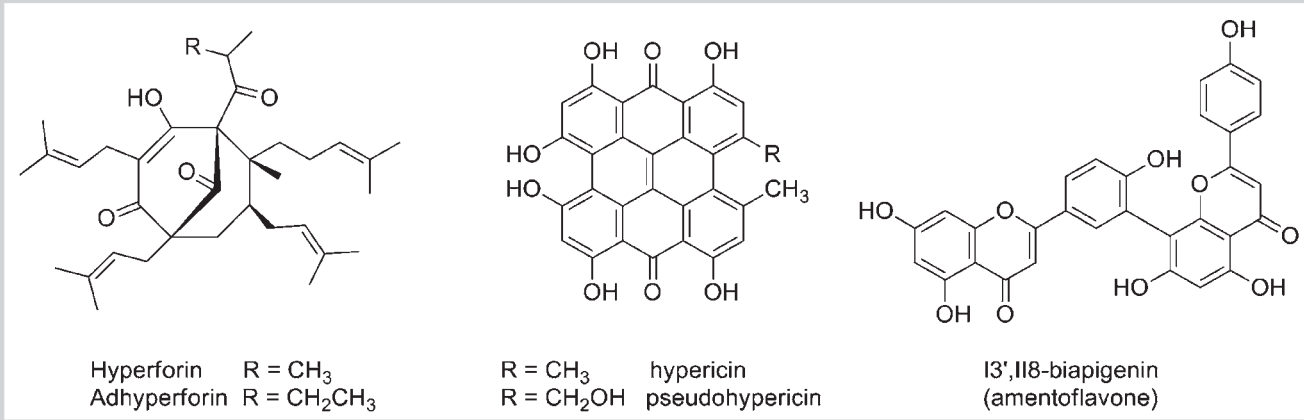

Fig. 12 Representative phytochemicals (phloroglucinols, napthodianthrones, flavonoid glycosides) present in St. John's wort.

ing the synaptosomal uptake of serotonin, dopamine, norepinephrine, glutamate, and gamma-aminobutyric acid with similar efficiency. Hyperforin's mode of action appears unique in that the phytochemical does not interact directly with uptake transporters but elevates intracellular sodium concentration, thereby inhibiting gradient-driven neurotransmitter reuptake [368]. As previously mentioned in Part 1 of this review, recent investigations reveal that hyperforin and other SJW-related phytochemicals (e.g., adhyperfroin, hypericins, flavanol glycosides) act synergistically through both pharmacodynamic and pharmacokinetic mechanisms to alleviate depression [369].

While recognized as a natural antidepressant, SJW is equally well known for its ability to induce the activity of several XMEs and transporters, thereby reducing the efficacy of a multitude of prescription medications. As discussed in Part 1 of this review, the clinical severity of SJW-mediated interactions was first recognized in 1999–2000. At that time, several clinics around the world reported that concomitant use of SJW and cyclosporine produced dramatic reductions in blood levels of the immunosuppressant among organ transplant recipients resulting in graft rejection. Since that time, a plethora of clinical studies have borne out SJW's effect on the pharmacokinetics of various medications [370–374].

Hyperforin, a principal mediator of SJW's antidepressive action, lies at the heart of the herb's drug interaction potential. The prenylated phloroglucinol is a high-affinity ligand for human PXR, an orphan nuclear receptor selectively expressed in the liver and intestine that mediates the induction of XME and efflux transporter gene transcription [375–377]. According to one estimate, hyperforin is the most potent PXR activator discovered to date [375], with a half-maximal effective concentration (EC_{50}) of 23 nM – a value well below plasma concentrations often achieved in humans (~100–300 nM) [378, 379]. (Unlike many of the unique phytochemicals described previously, hyperforin is bioavailable and exhibits an elimination half-life of 8–12 hours, thus allowing for significant accumulation with repeated dosing [378, 379].) Of the XMEs and transporters regulated by PXR, those most affected by SJW are CYP subfamilies 2C and 3A as well as several ABC efflux transporters [370–373]. As a result, more than 70% of all prescription medications are susceptible to SJW-mediated interactions, the consequences of which are decreased oral bioavailability, enhanced systemic clearance, and reduced drug efficacy.

As with all botanicals, phytochemical content can vary considerably and such is the case with hyperforin [380, 381]. Most SJW extracts are currently standardized to contain 3% hyperforin, yet many brands may possess amounts well below this value. Several clinical studies have demonstrated that SJW extracts containing less than 1% hyperforin are less likely to produce clinically relevant herb-drug interactions [381–384]. Unfortunately for consumers, few SJW products are specifically labeled as having low hyperforin content. Accordingly, to avoid significant drug interactions, consumers should avoid concomitant use of SJW and prescription medications.

In addition to content variability, another factor affecting the magnitude of hyperforin's effect on CYP3A expression and drug efficacy is PXR haplotype. Like many CYPs, PXR is polymorphic, and certain mutations produce significant functional defects in terms of CYP3A transcription. Recent studies indicate that individuals with the H1/H1 haplotype pair appear more susceptible to SJW-mediated CYP3A induction than subjects with H1/H2 or H2/H2 pairings [385]. Furthermore, once SJW has been discontinued, as much as a week may be required before CYP3A activity returns to basal levels [386].

SJW's penchant for producing herb-drug interactions has been scrutinized in several recent reviews [370–374]. ▶ **Table 1** summarizes those drugs in which SJW produces clinically significant interactions.

Interaction risk: high.

Conclusions and Future Perspectives

▼

Humans possess a complex system of gastrointestinal XMEs and transporters that are proficient at precluding absorption and facilitating elimination of numerous structurally diverse dietary phytochemicals. As a result, most botanical dietary supplements pose only minimal risks for modulating human drug metabolism. However, several distinct PSMs can either inactivate or highjack the controls of this innate gastrointestinal defense network. MDP-PSMs, functioning as mechanism-based inhibitors of CYPs, may potentiate the toxicity of allopathic medications, whereas potent nuclear receptor ligands like hyperforin may dramatically reduce drug efficacy. What differentiates these PSMs as significant modulators of human drug disposition from the multitude of others is their combination of favorable physicochemical prop-

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Table 1 Drug interactions with St. John's wort confirmed in human studies.

Drug category	Effect of SJW on drug conc.	Reference
Antianginals		
Ivabradine	decrease plasma level of drug	[389]
Antiarrhythmics		
Digoxin	decrease plasma level of drug	[49, 390–392]
Anticoagulants		
Warfarin	decrease plasma level of drug	[168, 216]
Anticonvulsants		
Mephenytoin	decrease plasma level of drug	[393]
Antidepressants		
Amitriptyline	decrease plasma level of drug	[391]
Antifungals		
Voriconazole	decrease plasma level of drug	[394]
Antihistamines		
Fexofenadine	mixed, generally decreases plasma level of drug	[395–397]
Antihyperlipidemics		
Simvastatin	decrease plasma level of drug	[398]
Atorvastatin	decrease plasma level of drug	[399]
Anxiolytics		
Midazolam	decrease plasma level of drug	[90, 98, 384, 386, 395, 397, 400]
Alprazolam	decrease plasma level of drug	[401, 402]
Quazepam	decrease plasma level of drug	[403]
Antivirals		
Indinavir	decrease plasma level of drug	[356]
Nevirapine	decrease plasma level of drug	[404]
β-adrenergic blockers		
Talinolol	decrease plasma level of drug	[405]
Calcium channel blockers		
Verapamil	decrease plasma level of drug	[406]
Nifedipine	decrease plasma level of drug	[153, 385]
Cancer chemotherapeutics		
Irinotecan	decrease plasma level of drug	[407]
Imatinib	decrease plasma level of drug	[408, 409]
Hormonal contraceptives		
Ethinylestradiol	decrease plasma level of drug	[410–412]
Norethindrone	decrease plasma level of drug	[410, 411]
Ketodesogestrel	decrease plasma level of drug	[412]
Hypoglycemic drugs		
Gliclazide	decrease plasma level of drug	[413]
Immunosuppressants		
Cyclosporine	decrease plasma level of drug	[395, 414–416]
Tacrolimus	decrease plasma level of drug	[417–419]
Opioids		
Methadone	decrease plasma level of drug	[420]
Proton pump inhibitors		
Omeprazole	decrease plasma level of drug	[421]
Skeletal muscle relaxants		
Chlorzoxazone	decrease plasma level of drug	[90, 98]
5α-reductase inhibitors		
Finasteride	decrease plasma level of drug	[422]

erties and unique pharmacophores. As discussed in previous sections, many PSMs modulate human XMEs and transporters *in vitro*, but due to various factors, this activity is rarely realized *in vivo*.

Recognizing that poor dissolution characteristics represent major obstacles to phytochemical bioavailability and efficacy, several dietary supplement manufacturers have recently incorporated novel methods of formulating botanical extracts as a means of improving oral absorption [387, 388]. Such innovative formulation technologies include liposomes, self-emulsifying microemulsions, microspheres, phosphatidylcholine complexation (phytosomes), and nanoparticles, as well as the incorporation of piperine as a CYP3A4 and ABCB1 inhibitor [387, 388]. In each instance, when compared to conventional extract formulations, the oral bioavailability of various phytochemicals can be increased several fold. To date, no clinical assessments of the herb-drug interaction potential of botanical extracts incorporating these novel formulations have been reported. Accordingly, many botanicals whose drug interaction potential is minimized when administered as conventional dry extracts may increase significantly upon ingestion of formulations utilizing novel delivery systems. Phytochemicals that heretofore had been casualties of man's xenobiotic defense system may emerge as inducers and/or inhibitors of human XMEs and transporters. Improved phytochemical delivery, therefore, may open up a new theater of operations in the "drug war" between humans and plants.

Currently, thousands of botanical supplements are available in the United States and abroad, and hundreds of new products are introduced onto the market each year. Not surprisingly, the vast majority of these botanicals have yet to be evaluated in a clinical setting. From a practical perspective, most may not warrant clinical study; logistics alone clearly preclude such an endeavor. Nevertheless, *in vitro* studies and compelling case reports suggest that many more botanical supplements may indeed be potent modulators of human drug disposition.

Conflict of Interest

▼

The authors declare no conflict of interest.

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