Phenotyping Studies to Assess the Effects of Phytopharmaceuticals on *In Vivo* Activity of Main Human Cytochrome P450 Enzymes

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Abstract

The extensive use of herbal drugs and their multiple components and modes of action suggests that they may also cause drug interactions by changing the activity of human cytochrome P450 enzymes. The purpose of the present review is to present the available data for the top 14 herbal drug sales in the U.S. Studies describing the effects of herbal drugs on phenotyping substrates for individual CYPs were identified by a comprehensive MEDLINE search. Drugs included *Allium sativum* (Liliaceae), *Echinacea purpurea* (Asteraceae), *Serenoa repens* (Arecaceae), *Ginkgo biloba* (Ginkgoaceae), *Vaccinium macrocarpon* (Ericaceae), *Glycine max* (Fabaceae), *Panax ginseng* (Araliaceae), *Actea racemosa* (Ranunculaceae), *Hypericum perforatum* (Hypericaceae), *Silybum marianum* (Asteraceae), *Camellia sinensis* (Theaceae), *Valeriana officinalis* (Valerianaceae), *Piper methysticum* (Piperaceae), and *Hydrastis canadensis* (Ranunculaceae) preparations. We identified 70 clinical studies in 69 publications. The majority of the herbal drugs appeared to have no clear effects on most of the CYPs examined. If there was an effect, there was mild inhibition in almost all cases, as seen with garlic or kava effects on CYP2E1 and with soybean components on CYP1A2. The most pronounced effects were induction of CYP3A and other CYPs by St. John's wort and the inhibitory effect of goldenseal on CYP3A and CYP2D6, both being borderline between mild and moderate in magnitude. With the exceptions of St. John's wort and goldenseal, the information currently available suggests that concomitant intake of the herbal drugs addressed here is not a major risk for drugs that are metabolized by CYPs.

Abbreviations

$AUC_{(0-\infty)}$:	area under the concentration-time curve from 0 to infinity
C_{max}:	maximum serum concentration
CI:	confidence interval
CYP:	cytochrome P450 enzyme
EGCG:	epigallocatechin gallate
EMA:	European Medicines Agency
FDA:	Food and Drug Administration
GABA:	gamma-aminobutyric acid
GBE:	*Ginkgo biloba* extract
(d)GTE:	(decaffeinated) green tea extract
INR:	international normalized ratio of prothrombin time
LSS:	limited sampling strategy
p:	p value
Poly E:	Polyphenon E®
rac:	racemic
SJW:	St. John's wort
$t_{1/2}$:	elimination half-life

Introduction

Herbal drugs are claimed to exert their unique mode of action by the complex interplay of many different constituents. Beyond actions of various constituents on more than a single target, it is postulated to also arise from mutual interactions of related chemical moieties at both the pharmacokinetic and pharmacodynamic level. It is therefore not surprising that herbal drugs may also have an effect on the activity of cytochrome P450 enzymes (CYPs), the most important enzyme family to mediate phase I metabolism of small molecule drugs and other human xenobiotics. This became particularly obvious when St. John's wort was recognized to be a potent inducer of CYP3A [1] and other proteins involved in pharmacokinetics, and the detection of the inhibitory effects of grapefruit juice on gut wall CYP3A was a

reminder that natural products may be involved in drug interactions [2].

Nowadays, there is general agreement that the potential of herbal drugs to cause drug-drug interactions needs to be assessed as thoroughly as for non-herbal drugs, including interactions at the level of CYP-mediated metabolism. *In vitro* studies with herbal drugs probably are less reliable than those with individual chemicals because both effective concentrations *in vitro* as well as *in vivo* processing of the complex mixtures can hardly be predicted. Because not all potential combinations with other drugs can be tested, the effect of drugs on individual enzymes is usually assessed using the phenotyping approach. Phenotyping for a CYP enzyme, i.e., quantification of its actual *in vivo* activity in an individual, is performed by administration of a selective substrate for this enzyme and subsequent determination of appropriate pharmacokinetic metrics closely reflecting enzyme activity [3]. Phenotyping substrates are usually marketed drugs with therapeutic indications, which are chosen mainly based on their selectivity for the CYP to be examined, on tolerability, and on availability. The standard design of a respective clinical study is a crossover design with administration of the phenotyping agents in both periods, combined with coadministration of the drug to be tested at its highest chronic therapeutic dose in one period [3]. Current regulatory guidance has adopted this procedure and also provides recommendations on individual phenotyping agents [4,5].

It is beyond the scope of this review to evaluate all individual substances and metrics used to quantify the effects of herbal drugs on individual CYPs in detail; for a respective assessment, see [3]. CYP phenotyping drugs recommended by the FDA [4,5] include the following: CYP1A2, theophylline, caffeine; CYP2B6, efavirenz, bupropion; CYP2C8, amodiaquine, cerivastatin, repaglinide, rosiglitazone; CYP2C9, warfarin, tolbutamide; CYP2C19, omeprazole, esoprazole, lansoprazole, pantoprazole; CYP2D6, metoprolol, desipramine, dextromethorphan, atomoxetine; CYP2E1, chlorzoxazone; CYP3A4, midazolam, buspirone, felodipine, lovastatin, eletriptan, sildenafil, simvastatin, triazolam. The EMA list is more limited, comments on the lack of exhaustive validation of some agents, and also occasionally asks for monitoring of specific reactions. The FDA created and posted an additional extensive list in 2011 [6] presenting sensitive substrates (as mentioned in the 1999 document "Guidance for Industry: *In Vivo* Drug Metabolism/Drug Interaction Studies – Study Design, Data Analysis, and Recommendations for Dosing and Labeling", which formally is still valid today) and substrates with a narrow therapeutic range, but provides little advice on the selection of the individual agent. While caffeine, warfarin, tolbutamide, and midazolam, and most respective metrics derived from plasma concentrations may be considered as fully validated (with the limitations described above) [3], caveats apply for the other listed substances, as additional metabolic pathways are known and/or validation data are limited. Several substances present in EMA and FDA lists had been withdrawn from the market prior to generation of the lists.

A combination of substances in a phenotyping cocktail in order to address a panel of CYPs in a single clinical study has been studied extensively [3,7,8]. There should be no mutual interaction of the drugs within a cocktail; an excellent example how to study this in detail has been published [9]. The EMA guidance addresses cocktail studies, while for the FDA, only semiofficial information is available (see [10,11]), showing that the FDA also accepts data from cocktail studies. While in general the cocktail approach appears to be appropriate, the inclusion of "historical" substances with limited validation and/or affinity to several CYPs such as dapsone or quinidine may compromise the results for other cocktail components.

Pharmacokinetic metrics, which reflect CYP activity best, may be metabolic ratios of a metabolite over a parent drug in plasma or urine, clearance of the parent drug, or partial clearance via a specific pathway, depending on the individual phenotyping substrate used. It is desirable to use metrics without the need of drawing many blood samples during the entire concentration vs. time profile of the phenotyping drug in order to keep burdens for both study participants and investigators as low as possible. Some metrics can indeed be derived using a limited sampling strategy (LSS) or even from a single sample [3]. However, the most recent 2010 EMA (draft) guidelines on the investigation of drug interactions (CPMP/EWP/560/95/Rev. 1 – Corr.) as well as the respective FDA guidance website [12] ask explicitly for the determination of complete area under the curve (AUC) values of phenotyping substrates, requiring at least 8–10 samples per study period, and discourages the use of single concentrations and metabolic ratios. The reason for this reluctance to accept metrics derived using an LSS probably is that their validation is limited to the quantification of baseline activity in individuals without major diseases with effects on pharmacokinetics and in the absence of factors with a major impact on pharmacokinetics. However, any effects of interacting drugs may not be limited to the activity of the CYP to be investigated, but may also affect absorption, secondary metabolism, and other pharmacokinetic processes of the phenotyping substrate. Because of their multiple ingredients, herbal drugs would be at risk to unexpectedly exert such additional effects. LLS-based metrics presumably are less robust to such effects, with the risk that these would either be erroneously identified as an effect on CYP activity, or that existing effects on CYPs would be hidden. While the confounding mechanism could then be identified by a change in the entire concentration vs. time profile of the phenotyping drug, these may well go unnoticed with LLS-based metrics only. Furthermore, LLS and complete sampling may also reach different results in interaction studies [13] because the concentration of interacting moieties and, thus, the extent of interaction change during a dosing interval – which is only partially covered by an LLS.

A second caveat concerns the estimation of the sample size required in interaction studies with herbal drugs. We repeatedly observed that the apparent intraindividual variability of phenotyping agent pharmacokinetics was clearly higher than reported in previous studies with small molecule drugs [14,15]. The reason for this observation is unclear; one could speculate that nonspecific effects on gastrointestinal motility are involved. A higher safety margin when calculating the sample size appears to be the only way to handle this problem as long as the mechanisms are unclear.

The regulatory (i.e., safety) purpose of interaction studies with any drugs including herbal drugs is to investigate the maximal extent of interaction for maximal exposure towards the "perpetrator". To this end, effects on phenotyping metrics should be larger rather than smaller than the true effects on CYP activity (sensitive metrics). In contrast, true effects on CYP activity for a given dose would theoretically be required to adapt the dose of concomitantly given drugs subject to this interaction. For the latter approach, changes in enzyme activity could then be incorporated in simulations to predict the extent of interactions with other drugs [11]; however, as these methods are at an early stage, the former approach currently still seems to be more appropriate.

In summary, the phenotyping approach is the method of choice to study the potential of drugs including herbal drugs to change CYP activity and thus the pharmacokinetics of their drug substrates, but much expertise and very close attention to the details of individual studies is required in order to understand the consequences of respective results. More research is needed especially to achieve better transferability of results to quantitatively predict effects of other drug substrates in treated patients.

Methods

The aim of the present review was to give a concise overview on herb-drug interactions in human clinical studies, especially phenotyping and phenotyping cocktail studies, with respect to the major human drug metabolizing cytochrome P450 enzymes.

A literature search was conducted in MEDLINE (as accessed via PubMed on December 2, 2011) using the search terms of the plant's name in combination with "cytochrome P450", plus "drug interaction" or "herb-drug interaction". The search was limited to English and German language papers. For further information, reviews and additional publications from all reference lists were read and relevant data were extracted. The discussion of case reports, animal data as well as *in vitro* experiments were not the primary objective of the present review and were not included.

Results

We identified 70 clinical studies in 69 publications. An overview of the data is presented in **Table 1** (at the end of the paper). Herb-drug interactions were present for 10 of the top 14 selling botanicals in the U.S. for 2006, including garlic with 2 drugs (chlorzoxazone, saquinavir), echinacea with 3 drugs (caffeine, midazolam, tolbutamide), ginkgo with 3 drugs (midazolam, omeprazole, tolbutamide), soy with 2 drugs (caffeine, theophylline), ginseng with 1 drug (debrisoquine), black cohosh with 1 drug (debrisoquine), St. John's wort with 19 drugs (alprazolam, atorvastatin, chlorzoxazone, cortisol, cyclosporine, desogestrel, ethinyl estradiol, gliclazide, imatinib, indinavir, ivabradine, mephenytoin, midazolam, norethindrone, omeprazole, quazepam, verapamil, voriconazole, and warfarin), kava with 1 drug (chlorzoxazone), and goldenseal with 2 drugs (debrisoquine, midazolam).

In addition to the 14 plants described in detail (see discussion), we found positive herb-drug interactions for *Angelica dahurica* with 1 drug (caffeine), *Scutelleria baicalensis* with 3 drugs (bupropion, chlorzoxazone, losartan), grapes/red wine with 4 drugs (buspirone, caffeine, dextromethorphan, losartan), and curcuma with 1 drug (caffeine).

The following detailed description of the respective botanicals is sorted in descending order of their U.S. sales ranking according to Blumenthal et al. [16].

Garlic [*Allium sativum* (L.) (Liliaceae)]

Garlic is the most popular herbal remedy. Postulated pharmacological actions of garlic include antibacterial, antiviral, antifungal, antihypertensive, blood glucose lowering, antithrombotic, antimutagenic, and antiplatelet actions [17]. Responsible for these activities are organosulfur compounds like alliin, allicin, diallyl disulfide, ajoene, and many others [18]. When the bulb is processed, alliin reacts with the enzyme allinase to produce the active constituent of garlic, allicin. Allicin is the compound often used to standardize many garlic formulations [19]. Garlic is available in different forms of pharmaceutical preparations, such as dry powder products, oil-macerated, volatile garlic oil, and juices of fresh garlic [20].

A clinical study assessed the effect of short-term administration of garlic supplements on single-dose ritonavir [21], a protease inhibitor that is mainly metabolized by CYP3A4 [22]. Acute dosing of this garlic extract over 4 days did not significantly alter the pharmacokinetics of ritonavir. In another trial, 11 female patients with metastatic breast cancer were treated with the CYP3A4 substrate docetaxel and garlic for 12 consecutive days. Garlic supplementation had no statistically significant effects on the pharmacokinetic profile of docetaxel when administered over the short term (4 days) or long term (12 days) [23]. A further study investigated the effect of garlic (over 12 days) on CYP2C9 activity by using warfarin as the probe substrate and showed no effect on pharmacokinetics or pharmacodynamics of the probe [24]. Another clinical study with 14 normal volunteers found no influence of garlic on the activity of CYP3A4 and CYP2D6 by a consecutive intake of garlic for 14 days [25]. In contrast, other studies showed an effect of garlic preparations by long-term use longer than 14 days: A clinical study with 10 healthy volunteers demonstrated that long-term (21 days) use of garlic caplets led to a significant decline in the plasma concentrations of saquinavir [26], an HIV-1 protease inhibitor that is metabolized by CYP3A4 [22]. The similarity in the magnitude of the decreases in AUC (−51%), C_{max} (−54%), and concentration at 8 hours (C_8) (−49%) suggested that garlic affected the bioavailability of saquinavir rather than its systemic clearance [26]. A cocktail interaction study in 12 healthy elderly subjects (mean = 67 years) who took garlic oil for 28 days showed no significant effects on CYP1A2, CYP2D6, and CYP3A4 activity, but it produced a significant decrease in CYP2E1 activity [27].

In summary, garlic appears to have only a minor potential to cause herb-drug interactions, with CYP2E1 as the only identifiable target. The saquinavir case needs further investigation.

Echinacea [*Echinacea purpurea* (L.) Moench (Asteraceae)]

Echinacea has anti-inflammatory and immunomodulating properties and is widely used for the treatment of the upper respiratory tract [28]. Echinacea preparations are made from the roots and/or other parts of the plant by juicing, alcohol extraction, infusion, decoction, or consumed as tablets or capsules [29]. Echinacea preparations are not chemically standardized. The constituent base is complex, consisting of phenols (cichoric and caftaric acid), polysaccharides, and alkylamides. The immunomodulatory effect was reported to be caused by alkylamides, which bind to human cannabinoid receptors 1 and 2, and inhibit tumor necrosis factor α [30].

With a sales ranking of #2 in the U.S. market [16], it is very important to determine the ability of echinacea to effect metabolic drug-drug interactions. Clinical studies indicate conflicting data about the effect of echinacea on the hepatic drug oxidation system. In a cocktail interaction study with 12 healthy volunteers, CYP1A2 was inhibited as assessed by a reduced oral clearance of the CYP1A2 probe caffeine (−27%, $p = 0.049$), there was a minor inhibitory effect on CYP2C9 (−11%, $p = 0.001$), while there was no effect on CYP2D6 or CYP3A4 [31]. Two further clinical studies determined the influence of echinacea on CYP3A4. In one of these studies, 13 healthy volunteers were dosed with lopinavir-ritonavir and the probe substrate midazolam. Neither lopinavir

nor ritonavir pharmacokinetic parameter values were significantly altered after 14 days of echinacea administration [32]. The other study in 12 healthy male volunteers conducted with warfarin, a substrate of CYP2C9 and CYP3A4 for S-warfarin, and CYP3A4 and CYP1A2 for R-warfarin [33], found no clinically significant pharmacokinetic and pharmacodynamic interaction [34]. In a cocktail interaction study with 12 healthy volunteers determined by Gurley et al. [35], long-term supplementation of echinacea had no effect on CYP1A2, CYP2D6, CYP2E1, or CYP3A4 activity [35]. The same research group assessed the influence of echinacea on the activity of CYP2D6 in a clinical study with 18 normal volunteers, again with no effects [36].

In summary, the results of all described studies propose that echinacea has a fairly low capability for causing herb-drug interactions with human cytochrome P450 enzymes.

Saw palmetto [*Serenoa repens* (W. Bartram) Small (Arecaceae)]

Saw palmetto is the most popular herbal remedy used to alleviate the symptoms related to benign prostatic hyperplasia [37]. It has an ability to improve urologic symptoms and urine flow measures comparable to that of finasteride [35]. Saw palmetto extracts gained from the ripe, dried fruit have anti-inflammatory and spasmolytic properties. Most saw palmetto extracts are composed of mixtures of fatty acids including capric, caprylic, lauric, linoleic, linolenic, myristic, oleic, palmitic, and stearic acids, which typically account for 80–90% of the extract [38].

There are only two clinical studies that have assessed the impact of saw palmetto on human cytochrome P450 enzymes. A cocktail interaction study with 12 healthy volunteers demonstrated that saw palmetto had no significant modulatory effects on CYP1A2, CYP2D6, CYP2E1, and CYP3A4 [35]. Another clinical study with 12 normal volunteers determined whether saw palmetto affects the activity of CYP2D6 and CYP3A4. For the probe substrates dextromethorphan (CYP2D6 activity) and alprazolam (CYP3A4 activity), the results indicated a lack of effect [38].

Overall, saw palmetto extract at generally recommended doses seems to be an unlikely candidate for CYP-mediated herb-drug interactions.

Ginkgo [*Ginkgo biloba* (L.) (Ginkgoaceae)]

Ginkgo extract is a popular herbal remedy used for a variety of disorders. EGb 761® special extract, for example, is a dry extract from *Ginkgo biloba* leaves (drug-extract ratio 35–67 : 1) that has been adjusted to 22–27% ginkgo flavonoids and 5.0–7.0% terpene lactones consisting of 2.8–3.4% ginkgolides A, B, C and 2.6–3.2% bilobalides, with a ginkgolic acid content less than 5 ppm [39]. EGb 761® interferes with various pathomechanisms relevant to dementing disorders [40–42]. A large number of clinical studies suggest that *Ginkgo biloba* extract (GBE) may have beneficial effects on memory, cognition, and the vascular system [43–47].

For an herbal drug to be taken by elderly people, often with several chronic diseases, the ability of GBE to cause metabolic drug-drug interactions should be known. The literature exhibits conflicting data, particularly on long-term treatment of 12 days and more. A clinical study in 11 healthy volunteers assessed the effect of GBE on the activity of CYP2C9 using flurbiprofen as a substrate. The subjects took 2 × 60 mg EGb 761® tablets thrice daily for 1 day. There was no significant difference between ginkgo or placebo treatment in any of flurbiprofen's kinetic parameters [48]. Another research group also could not find any effect of ginkgo, neither inducing nor inhibiting, on CYP1A2, CYP3A4 and CYP2C9 activity using racemic warfarin as a probe drug in 12 healthy male subjects, who took ginkgo for 7 consecutive days [49]. Using a cocktail phenotyping approach, a study with 18 healthy volunteers provided evidence that EGb 761® had no clinically relevant inhibitory or inducing effects towards human CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 when administered at chronic therapeutic doses for 8 days [15]. A clinical study with 18 healthy Chinese subjects investigated the potential herb-drug interaction between ginkgo and omeprazole, a widely used CYP2C19 substrate [50]. The volunteers had taken ginkgo tablets 2 × 70 mg twice daily for 12 days. In this study, plasma concentrations of omeprazole were significantly decreased and 5-hydroxyomeprazole as its metabolite significantly increased following ginkgo administration in comparison to baseline indicating an induction of CYP2C19 [50]. In contrast, a clinical study performed in 14 Chinese volunteers examined the possible effects of ginkgo as an inducer of CYP2C19 on single-dose pharmacokinetics of voriconazole [51]. Ginkgo pretreatment for 12 days did not significantly affect pharmacokinetic parameters of voriconazole [51]. A clinical study evaluated as the primary objective the effect of GBE on the exposure of lopinavir, an HIV protease inhibitor metabolized by CYP3A4, in 14 healthy volunteers [52]. The secondary objectives were to compare ritonavir exposure pre- and post-GBE, and assess the effect of GBE on single doses of the probe drug midazolam. *Ginkgo biloba* extract decreased midazolam $AUC_{(0-\infty)}$ by 34% ($p = 0.03$) and C_{max} by 31% ($p = 0.03$) but did not significantly affect the exposures of lopinavir and ritonavir [52]. A clinical study performed in 14 healthy male volunteers determined the effects of GBE on the pharmacokinetics of bupropion, a substrate of CYP2B6. *Ginkgo biloba* extract administration of 240 $mg \cdot day^{-1}$ (two 60-mg capsules taken twice daily) for 14 days did not significantly alter the basic pharmacokinetic parameters of bupropion [53]. Another clinical study with 12 healthy volunteers assessed the influence of GBE on the activity of CYP2D6 and CYP3A4 for about 14 days. For the probe substrates dextromethorphan (CYP2D6 activity) and alprazolam (CYP3A4 activity), no statistical differences were observed between baseline and post-GBE treatment indicating a lack of effect on CYP2D6 and CYP3A4 [54]. In a cocktail interaction study with 12 healthy volunteers and treatment duration of 28 days, no significant effect on CYP1A2, CYP2D6, CYP2E1, and CYP3A4 activity for *Ginkgo biloba* was found [27]. But other studies observed that ginkgo inhibits CYP3A4 [55, 56]. A study with 15 subjects showed that the geometric mean midazolam $AUC_{(0-\infty)}$ prior to GBE administration was reduced by 34% after GBE administration [55]. The outcome of the study of Uchida and colleagues performed in 10 male healthy volunteers was an inhibiting effect of GBE on CYP3A4 activity as shown by an increased $AUC_{(0-\infty)}$ by 25% and decreased oral clearance by 26% of midazolam, and an inducing effect on CYP2C9 activity according to a reduced $AUC_{(0-\infty)}$ by 16% of tolbutamide [56]. A pharmacokinetic study in healthy volunteers conducted with diazepam as a substrate of CYP2C19 did not suggest the presence of an herb-drug interaction [57].

Altogether, it appears that GBE may have some effect on the activity of CYP enzymes when applied in patients, probably depending on the preparation used.

Cranberry [*Vaccinium macrocarpon* (Aiton) (Ericaceae)]

Cranberries are primarily cultivated for consumption as foods and beverages [58]. Products of the cranberry industry include fresh fruit (5%), juices (60%), sauces, dried fruit, and ingredients (35%), such as frozen fruit, juice concentrates, and spray-dried

powders [59, 60]. Cranberry juice contains phytochemicals such as proanthocyanidins, flavonols, and quercetin [61]. The juice and concentrated extracts of cranberries are increasingly popular among consumers because of its use for the prevention and adjunctive treatment of urinary tract infections [58]. Moreover, cranberry juice shows efficacy in reducing urinary tract infections by acidifying the urine [62] and in reducing bacteriuria in elderly persons [63]. It also features positive effects against drug-resistant bacteria [64].

The large popularity of cranberry juice should give reason to examine its ability to cause herb-drug interactions. There are only a few data available. A clinical study in 8 healthy volunteers investigated the potential interaction between cranberry juice and diclofenac, a substrate of CYP2C9. An intake of 180 mL of cranberry juice twice a day for 5 days did not change the pharmacokinetics of diclofenac [65]. Another clinical study evaluated the effect of cranberry juice and other beverages on CYP2C9 activity. Fourteen healthy volunteers received flurbiprofen as a probe substrate for CYP2C9 in combination with 8 oz. of cranberry juice. None of the beverages altered CYP2C9-mediated clearance of flurbiprofen in humans [66]. Further investigations on CYP2C9 in clinical studies showed that cranberry juice also had no interaction potential on the pharmacokinetics of warfarin [67, 68]. In addition to CYP2C9, Lilja and colleagues assessed the effect of cranberry juice on the activities of CYP1A2 and CYP3A4. Ten healthy volunteers took 200 mL cranberry juice thrice daily for 10 days. They observed no effects of cranberry juice on the pharmacokinetics of tizanidine (as CYP1A2 probe) and midazolam (as the CYP3A4 probe) [68]. Another clinical study in 12 healthy male volunteers revealed that an intake of 240 mL of cranberry juice did not affect the pharmacokinetics of cyclosporine as a substrate of CYP3A [69].

In summary, daily ingestion of more than 1 glass of cranberry juice seems not to alter the activities of cytochrome P450 enzymes.

Soy [*Glycine max* (L.) Merr. (Fabaceae)]

Soy is a plant native to East Asia, commonly grown for its bean, which has been reported to have various health benefits. Soybeans provide ample amounts of α-linolenic acid [70] and significant amounts of isoflavones. Three soybean isoflavones, genistein, daidzein, and glycitein, and their various glycoside forms account for roughly 50, 40, and 10%, respectively, of total isoflavone content [71]. Epidemiological and experimental researchers have provided extensive information on the anti-estrogenic effects of soy isoflavones on human health [72]. In China, Japan, Korea, and other countries in the Far East as well as lately in Western countries, the bean and products made from it such as soy sauce, soy flour, soy milk, and tofu are a popular part of the diet.

Hence, it is very important to take the ability of soy for an herb-drug interaction into account. A clinical study performed in 20 healthy volunteers examined the potential effect of daidzein on CYP1A2 activity and on the pharmacokinetics of theophylline as a probe substrate [73]. Plasma concentrations and derived parameters including $AUC_{(0–48)}$, C_{max}, and $t_{1/2}$ were significantly increased by approximately one-third [73]. Another clinical study investigated the effect of 1 g genistein once daily for 14 days on the caffeine-based metrics of CYP1A2 and CYP2A6 in 18 healthy female volunteers [74]. Genistein decreased the urinary caffeine metabolite ratio used to assess CYP1A2 activity by 41%, whereas the urinary ratio for CYP2A6 activity increased by 47%, suggesting that genistein inhibited CYP1A2 and induced CYP2A6 [74]. A clinical study in 18 healthy Chinese female volunteers provided no effects of soy extract on the pharmacokinetics of losartan as a substrate of CYP2C9 and CYP3A4 [75]. A clinical study assessed the drug interaction potential of soy extract on CYP3A using the urinary excretion of the 6β-hydroxycortisol/cortisol ratio as a marker of enzyme induction. Twenty healthy subjects received a soy extract containing 50 mg isoflavones twice daily for 14 days. The soy extract had no effect [76].

Altogether, soybean constituents may be weak inhibitors of CYP1A2, which translates into clinical relevance only in extraordinary situations.

Asian ginseng [*Panax ginseng* (L.) (Araliaceae)]

Asian ginseng (ginseng) is marketed for a wide range of indications, which include erectile dysfunction, cancer prevention, enhanced physical function, and improved cognitive functions [77]. Ginseng extracts are generally standardized to ginsenosides. Ginsenosides are a class of steroid glycosides and triterpene saponins [78]. The roots of *Panax ginseng* contain at least 25 different triterpene saponins [79]. Ginsenosides Rb1, Rb2, Rc, Rd, Re, Rf, and Rg1 are reported as major constituents and each ginsenoside has been shown to have different pharmacological effects, including immune system modulation, antistress activities, and antihyperglycemic activities, anti-inflammatory, antioxidant, and anticancer effects, antiplatelet, antithrombotic, vasodilatory, cardiotonic, angiogenic, and neuroprotective effects [79–82].

For an herbal drug to be widely used by the elderly community for a variety of indications, the ability of ginseng to cause metabolic drug-drug interactions should be determined. Clinical studies in humans have shown that *Panax ginseng* has no effect on a number of CYP enzymes [77]. In a cocktail interaction study with 12 healthy elderly volunteers (mean = 67 years), *Panax ginseng* inhibited CYP2D6 activity assessed using debrisoquine urinary recovery ratios significantly, but only by 7.0% [27]. No significant effect on CYP1A2, CYP3A4, or CYP2E1 activity for *Panax ginseng* was found [27]. One trial investigated the interaction between warfarin and *Panax ginseng* in ischemic stroke patients. Twenty-five patients were enrolled in the study; twelve patients in the ginseng group received *Panax ginseng* and warfarin for 2 weeks, and the control group (n = 13) received only warfarin for the same duration of time. There were no statistically significant differences between the ginseng group and control group [80]. Another study in 12 healthy male subjects conducted to investigate the effect of ginseng on the pharmacokinetics and pharmacodynamics of warfarin found no clinically significant changes in AUC, $t_{1/2}$, and apparent total clearance [83]. This study confirmed that ginseng had no effect on the activity of CYP1A2, CYP3A4, or CYP2C9 in healthy volunteers [83]. Another clinical study could also not show any effect of *Panax ginseng* on CYP3A. Twenty healthy subjects received 100 mg *Panax ginseng* standardized to 4% ginsenosides twice daily for 14 days. The urinary excretion of the 6β-hydroxycortisol/cortisol ratio was used as a marker of CYP3A induction but no significant alteration was observed for *Panax ginseng* [76].

In summary, it appears that Asian ginseng has no effect on the activity of CYP enzymes *in vivo*.

Black cohosh [*Actaea racemosa* (L.) Nutt. (Ranunculaceae)]

Extracts of black cohosh are made from the roots and rhizomes of the plant. Black cohosh preparations (tinctures or tablets of dried materials) are commonly used as an alternative to hormone ther-

apy in perimenopausal women to treat symptoms such as hot flashes, vaginal dryness, and mood swings [19,84].

A few clinical studies conducted the effect of black cohosh on human cytochrome P450 enzymes. A cocktail interaction study with 12 healthy volunteers showed no significant effects of black cohosh on CYP1A2, CYP2E1, and CYP3A4 activity, but it did have an effect on CYP2D6 [85]. Black cohosh exhibited a statistically significant decrease in the CYP2D6 phenotype ($p = 0.02$), but the magnitude of the result (~ 7.0% reduction) is not clinically relevant [85]. In another clinical study with 18 normal volunteers, Gurley et al. assessed the influence of black cohosh only on the activity of CYP2D6 to corroborate their earlier findings. This time, comparisons of pre- and post-supplementation of 8-hour debrisoquine urinary recovery ratios revealed no statistically significant effects on CYP2D6 [36]. Another pharmacokinetic study in 19 healthy volunteers conducted with midazolam as a substrate of CYP3A also did not suggest the presence of an herb-drug interaction [86].

In summary, black cohosh appears to have no clinically relevant effects on cytochrome P450 activity.

St. John's wort [*Hypericum perforatum* (L.) (Hypericaceae)]

St. John's wort (SJW) is an herbaceous perennial plant native to Europe. Extracts obtained from the aerial parts of *Hypericum perforatum* have been recommended traditionally for a wide range of medical conditions [87]. St. John's wort is commonly used to treat mild-to-moderate depression but is also used to treat anxiety, obsessive-compulsive disorder, and premenstrual syndrome [19]. The extracts of SJW contain numerous pharmacologically active ingredients, including naphthodianthrones (e.g., hypericin and its derivatives) and phloroglucinols derivatives (e.g., hyperforin, which inhibits the reuptake of a number of neurotransmitters, including serotonin) [87]. The most common recommended dose is 900 mg per day standardized to 0.3% hypericin to treat depression [19].

Several clinical studies have clearly revealed that SJW may alter CYP activity. Many of the interaction studies indicate that SJW is a potent inducer of CYP3A4, CYP2E1, and CYP2C19, with no effect on CYP1A2, CYP2D6, or CYP2C9 [20,77]. The effect of SJW on CYP3A4 is seen after long-term treatment. Markowitz et al. assessed the effects of SJW on CYP2D6 and CYP3A4 activity. Seven normal subjects received 3 times daily a commercial SJW formulation (Solaray®) 300 mg, standardized to 0.3% hypericin for 4 days. Dextromethorphan (CYP2D6 activity) and alprazolam (CYP3A4 activity) were administered as probe substrates. No statistically significant differences were found in any estimated pharmacokinetic parameter for alprazolam or dextromethorphan for this short-term treatment [88]. A cocktail interaction study with 12 healthy volunteers examined the effect of SJW on CYP activity. Tolbutamide (CYP2C9), caffeine (CYP1A2), dextromethorphan (CYP2D6), oral midazolam (intestinal wall and hepatic CYP3A), and intravenous midazolam (hepatic CYP3A) were administered before, with short-term SJW dosing (900 mg), and after 2 weeks of intake (300 mg 3 times a day) to determine CYP activities [89]. Short-term administration of SJW had no effect on CYP activities. Long-term SJW administration caused a significant ($p < 0.05$) increase in oral clearance of midazolam and a corresponding significant decline in oral bioavailability [89]. There are many other clinical studies that confirm these findings. Another clinical cocktail interaction study assessed the influence of SJW on the activity of CYP1A2, CYP2D6, and CYP3A4. Eight healthy male and 8 healthy female subjects were treated with SJW extract ($3 \times 300\ mg \cdot day^{-1}$) for 14 days [90]. After 2 weeks of treatment with SJW, the mean increase in the 6β-hydroxycortisol/cortisol molar concentration ratio in urine, used as an index of activity of CYP3A4, was 85%. Additionally, the authors found a slight (but not significant) increase in the paraxanthine/caffeine ratio in saliva after SJW. However, most of the subjects exhibiting an apparent induction of CYP1A2 were females [90]. No influence of SJW on CYP2D6 activity was found [90]. A clinical cocktail interaction study performed in 12 elderly subjects (mean = 67 years) assessed the pre- and post-supplementation phenotypic ratios for CYP3A4, CYP1A2, CYP2E1, and CYP2D6 [27]. Twenty-eight days of SJW supplementation resulted in a 141% increase in the mean one-hour 1-hydroxymidazolam/midazolam serum ratio ($p < 0.001$) [27]. Similar to its effect on CYP3A4, SJW produced significant increases in CYP2E1 activity ($p = 0.006$). No statistically significant differences in mean values were noted for CYP1A2 and CYP2D6 [27]. In a later clinical study performed by the same researchers [36], no significant differences were observed among the mean baseline debrisoquine urinary recovery ratio by supplementation of 14 days of SJW. In contrast to Wenk and colleagues, no sex-related changes in CYP phenotypes were noted. Two further clinical studies suggested that SJW is an inducer of CYP3A4 following 14 days of treatment [91,92]. There are also two clinical studies which determined the effect of SJW on CYP2C19 activity. In each study, 12 healthy volunteers received a 300-mg SJW tablet 3 times daily for 14 days. In one study, the activities of CYP2C19 and CYP1A2 were measured using mephenytoin and caffeine, respectively [93], and in the other study, the activities of CYP2C19 and CYP3A4 were measured using omeprazole [94]. In both studies, it was found that SJW treatment significantly increased CYP2C19 activity.

Furthermore, clinical data imply that hyperforin content affects the extent of SJW interactions, since extracts with a low hyperforin amount had a weak or no effect on CYP activity. A clinical study compared the effects of 2 SJW preparations with high and low hyperforin content on the pharmacokinetics of cyclosporine. In a crossover study, 10 renal transplant patients were randomized into 2 groups and received SJW extract 300 mg (two 150 mg capsules) 3 times a day (total dose, 900 mg/d) containing low or high concentrations of hyperforin for 14 days in addition to their regular regimen of cyclosporine [95]. The study showed a significant difference between the effects of the 2 SJW preparations on cyclosporine pharmacokinetics. The area under the plasma concentration-time curve, within one dosing interval (AUC_{0-12}; $p < 0.0001$), values with high hyperforin SJW comedication were 45% lower (95% CI − 37% to − 54%; $p < 0.05$) than for low hyperforin SJW [95]. Arold and colleagues performed two clinical interaction studies with 28 healthy volunteers in each study. In study A, alprazolam (CYP3A4) and caffeine (CYP1A2), and in study B, tolbutamide (CYP2C9) and digoxin (p-glycoprotein), were given as probe substrates, respectively. The participants received SJW with a low hyperforin content (Esbericum® capsules; $240\ mg \cdot day^{-1}$, 3.5 mg hyperforin) or placebo for 10 days. No statistically significant differences were found in the primary kinetic parameters between the placebo group and the SJW group at the end of both studies [96]. Another two clinical studies conducted by Mueller and colleagues evaluated the effect on CYP3A function of SJW preparations with a wide range from very low to high hyperforin content. In the first study, 42 healthy volunteers were randomized into 6 different SJW medication groups for 14 days. A single oral dose of midazolam was used as a probe substrate.

All SJW preparations tested resulted in a decrease in midazolam AUC, although the extent of the effect differed [97]. St. John's wort extract with a hyperforin content of 41 mg/day decreased midazolam AUC_{0-12} by 79.4% (95% CI − 88.6 to − 70.1). St. John's wort powder tablets with a hyperforin content of 12 mg/day resulted in a decrease of 47.9% (95% CI − 59.7 to − 36.2), while SJW powder tablets with an amount of 0.13 mg/day of hyperforin reduced midazolam AUC_{0-12} by only 21.1% (95% CI − 33.9 to − 8.3) [97]. The second study evaluated the effect of an SJW powder only with a low hyperforin content on CYP3A function. Twenty healthy male volunteers received SJW as capsules containing 500 mg *Hyperici herba* powder with 0.06 mg total hyperforin per capsule and had to take two capsules per day, for 14 days. Midazolam $AUC_{0-\infty}$ was reduced by 11.3% (95% CI − 22.8 to 0.21) indicating a significant but mild induction of CYP3A function [98]. No significant changes were observed after SJW treatment regarding midazolam C_{max}, t_{max}, and $t_{1/2}$ ($p > 0.05$) [98].

Apart from using probe drugs in clinical interaction studies to show that SJW is a potential inducer of CYP3A4, CYP2E1, and CYP2C19, SJW has also been shown to have the ability to clinically interact with a number of frequently used drugs. St. John's wort may reduce the efficacy of oral contraceptives (e.g., induction of ethinyl estradiol-norethindrone metabolism [99,100]; decrease in serum 3-ketodesogestrel concentrations [101]), may reduce the pharmacokinetics of imatinib by increasing its clearance [102,103], may interact with cardiovascular drugs (e.g., decreased plasma concentrations of atorvastatin [104], ivabradine [105], and R- and S-verapamil [106]), may induce the apparent clearance of both S- and R-warfarin, which in turn resulted in a significant reduction in the pharmacological effect of *rac*-warfarin [83], may interact with drugs acting on the central nervous system (e.g., decreased plasma concentration of quazepam [107], alprazolam [92], and midazolam [27,89,97,99]), may reduce plasma voriconazole concentrations after long-term but not short-term administration [108], may alter gliclazide pharmacokinetics [109], and may reduce the AUC of the HIV-1 protease inhibitor indinavir [110].

In summary, clinical evidence of the effects of SJW on CYP enzymes is undisputed. There are numerous studies which have shown that the inducing effect of SJW depends on treatment duration and the preparation, primarily the amount of hyperforin. Patients and physicians should be well informed about the interaction potential of St. John's wort.

Milk thistle [*Silybum marianum* (L.) Gaertn. (Asteraceae)]

Extracts of milk thistle are recognized for the treatment of liver injury. The active principle is a mixture of flavolignans called Silymarin [20]. Silymarin is made from the seeds of milk thistle and is composed of six closely related flavonolignans (silibinin, isosilybin A, isosilybin B, silychristin, isosilychristin, silydianin) and one flavonoid (taxifolin) [111]. Silibinin, the major active constituent of silymarin, consists of 2 diasteroisomers, silybin A and silybin B [111,112]. Silymarin has cytoprotective, antioxidative, and radical scavenging as well as anti-inflammatory and antifibrotic properties [14]. It is used to self-treat hepatic disorders, including hepatitis C and cirrhosis, and as a hepatoprotectant, particularly for mushroom poisoning [113].

For a popular herbal product to be taken for hepatoprotection and chemoprevention, the ability of milk thistle extract to cause metabolic drug-drug interactions should be known. Several *in vivo* studies in humans indicate that milk thistle has no effect on the hepatic drug oxidation system. A clinical study was conducted to examine the effect of silymarin on cytochrome P450 3A4. Sixteen healthy male volunteers were administered with immediate release nifedipine as a CYP3A4 test drug either alone or with the coadministration of silymarin. The coadministration of silymarin for 1 day did not considerably change the extent of absorption or metabolism of nifedipine but might decrease the absorption rate. Silymarin was not a potent CYP3A4 inhibitor *in vivo* [14]. Van Erp and colleagues investigated the effect of milk thistle on the pharmacokinetics of irinotecan, a substrate for CYP3A4. Neither short-term intake (4 days) nor long-term intake (12 days) of milk thistle showed significant effects on irinotecan clearance [114]. Gurley et al. investigated the *in vivo* effect of milk thistle on human cytochrome P450 three times. A clinical study with 19 normal subjects assessed the clinical significance of milk thistle supplementation on human cytochrome P450 3A activity. The study's purpose was to compare the effect of milk thistle on CYP3A to a clinically recognized inducer, rifampin, and inhibitor, clarithromycin. In contrast to rifampin and clarithromycin, no significant changes in the probe substrate midazolam pharmacokinetics were observed as a result of milk thistle supplementation [86]. In a similar study, 18 healthy volunteers were administered with a standardized milk thistle extract to assess the effect on cytochrome P450 2D6. The study conducted with debrisoquine as a substrate of CYP2D6 also did not suggest the presence of an herb-drug interaction [36]. In a cocktail interaction study with 12 healthy volunteers, he and his colleagues determined long-term supplementation of milk thistle extracts on CYP1A2, CYP2D6, CYP2E1, or CYP3A4 activity. They found no statistically significant differences in mean CYP1A2, CYP2D6, CYP2E1, or CYP3A4 phenotypic ratios [35].

In summary, current data suggest that milk thistle has no major effects on the activity of CYP enzymes when applied in patients.

Green tea [*Camellia sinensis* (L.) Kuntze (Theaceae)]

After withering the freshly picked leaves, a brief heating, roasting, or steaming prevents the fermentation of the tea leaves. For this reason, almost all active ingredients such as catechins (70%), minor flavonols (10%), and polymeric flavonoids (20%) contained in the fresh leaves will remain [19]. The main catechin component of green tea is epigallocatechin gallate (EGCG) that accounts for 50–80% of the catechins in green tea [115,116]. Polyphenon E® (Poly E), for example, is a widely used concentrated green tea extract (GTE) from green tea leaves. It contains a total catechin fraction of 89% with EGCG as the main component accounting for 65% of the material followed by 9.0% epicatechin, 6.6% epicatechin gallate, 3.8% epigallate catechin, 1.0% catechin, 0.2% gallocatechin, and 0.2% catechin gallate [117]. Green tea, GTE, and its major active compound ECGC demonstrated antioxidant, anticarcinogenic, anti-inflammatory, antiatherogenic, immunomodulatory, and chemopreventive properties [118–121]. It has antiatherosclerotic effects on dysfunctional vessels in smokers through increasing the level of nitric oxide and reducing oxidative stress [122,123]. Green tea may have cardiovascular protecting effects through inhibition of angiotensin-converting enzyme activity [124]. Standardized green tea compounds are effective for decreasing blood pressure, low-density lipoprotein cholesterol, and oxidative stress [125].

The large variety of assumed medical uses of green tea imply that the potential for drug interactions could be high. A clinical study with 11 healthy volunteers assessed the influence of decaffeinated GTE (dGTE) on the activity of CYP2D6 and CYP3A4. The probe substrates dextromethorphan (CYP2D6 activity) and al-

prazolam (CYP3A4 activity) were administered orally at baseline, and again after treatment with four dGTE capsules (< 1 mg caffeine) per day for 14 days. No significant differences in dextromethorphan and alprazolam pharmacokinetics were observed at baseline and after treatment with dGTE indicating a lack of effect on CYP2D6 and CYP3A4 [126]. In a clinical cocktail interaction study with 42 healthy volunteers, no clinically significant effects on CYP1A2, CYP2C9, CYP2D6, and CYP3A4 activity for GTE were found [127]. The study participants received a cocktail of CYP metabolic probe drugs, including caffeine, losartan, dextromethorphan, and buspirone for assessing the activity of CYP1A2, CYP2C9, CYP2D6, and CYP3A4, respectively. The subjects underwent 4 weeks of green tea catechin intervention at a dose that contains 800 mg EGCG daily. The intervention did not alter the phenotypic indices of CYP1A2, CYP2C9, and CYP2D6, but resulted in a 20% increase ($p = 0.01$) in the area under the plasma buspirone concentration-time profile, suggesting a small reduction in CYP3A4 activity [127].

Overall, both authors concluded that repeated green tea catechin administration is unlikely to modify the disposition of medications metabolized by CYPs.

Valerian [*Valeriana officinalis* (L.) (Valerianaceae)]

Valerian is a popular remedy prepared from its roots, rhizomes (underground stems), and stolons (horizontal stems). The root is chiefly used for medicinal benefits. It can be found in capsule, tea, tablet, or liquid extract forms. The most abundant constituents of valerian are monoterpenes and sesquiterpenes, including the genus-specific valepotriates and valerenic acid [128]. Valerian root also contains appreciable levels of gamma-aminobutyric acid (GABA) [129] and has sedative, anxiolytic, and hypnotic properties [130]. It is often taken to help alleviate insomnia. There are several clinical studies to evaluate the evidence of efficacy of valerian as a treatment for insomnia [131–134].

A clinical study with 12 normal volunteers assessed the influence of a valerian supplement on the activity of CYP2D6 and CYP3A4. The probe substrates dextromethorphan (CYP2D6 activity) and alprazolam (CYP3A4 activity) were administered orally at baseline, and again after exposure to two valerian tablets nightly for 14 days. Valerian showed no clinically relevant effects on the disposition of medications primarily dependent on the CYP2D6 or CYP3A4 pathways for metabolism [135]. In a clinical interaction study with 12 healthy volunteers, the study participants received valerian for 28 days. Probe drug cocktails of caffeine for CYP1A2 activity and midazolam for CYP3A4 activity, followed 24 hours later by debrisoquine for CYP2D6 activity and chlorzoxazone for CYP2E1 activity to avoid potential interference, were administered before (baseline) and at the end of supplementation. Valerian had no significant effect on any CYP phenotypes [85].

In summary, valerian appears unlikely to produce CYP-mediated herb-drug interactions.

Kava [*Piper methysticum* (G.) Forst. (Piperaceae)]

Kava is still a popular herbal beverage. The commercial products, if not withdrawn from the market for hepatotoxicity, are prepared from dried rhizomes of the kava plant, and the more contemporary dosage form is a capsule, which usually contain a standard 30% of kavalactones. The constituents of kava extract are kavalactones, kawain, methysticin, dihydromethysticin, desmethoxyyangonin, and dihydrokawain [19]. Kavalactones, the assumed active principles, are predominantly concentrated in the plant's rhizome rather than in its upper stems or leaves [136]. Kavalactones effects are a slight numbing of the gums and mouth, and vivid dreams. Kava has been reported to improve cognitive performance and promote a cheerful mood [137]. Kava has anxiolytic and sedative properties and is often suggested to alleviate the symptoms of anxiety [138].

There are only a few clinical studies which revealed the clinical influence of potential interactions mediated by cytochrome P450 enzymes. A clinical study performed by Gurley and colleagues assessed the kava supplementation on human CYP3A activity using midazolam as a phenotypic probe. Sixteen healthy volunteers received kava for 14 days. Midazolam disposition was not affected by kava supplementation [139]. The same research group assessed the influence of kava on the activity of CYP2D6 in a clinical study with 18 healthy volunteers. Kava was not a potent modulator of human CYP2D6 *in vivo* [36]. A cocktail interaction study in 12 healthy subjects for 28 days showed no significant effects on CYP1A2, CYP2D6, and CYP3A4 activity for kava, but significantly reduced phenotypic ratios for CYP2E1 (~ 40%, $p = 0.009$) [85].

In summary, kava may interact with CYP2E1 substrates. Thus, concomitant ingestion of kava and drugs that are CYP2E1 substrates may increase their therapeutic and adverse effects.

Goldenseal [*Hydrastis canadensis* (L.) (Ranunculaceae)]

Goldenseal is used as a versatile herbal remedy and has many different medicinal properties. Its roots and rhizomes, which internally are bright yellow in color, have been used as a traditional medicine for the treatment of infection, inflammation, and as an immune system booster. It is taken orally to treat upper respiratory infections and gastrointestinal tract disorders [140]. Modern herbalists consider it an alternative anticatarrhal, anti-inflammatory, antiseptic, astringent, bitter tonic, laxative, and muscular stimulant [140]. Commercial preparations of goldenseal may be purchased in tincture form or as a liquid extract [141]. Goldenseal extract contains isoquinoline alkaloids, including berberine, (+)- and (−)-hydrastine, and lesser amounts of hydrastinine [142]. Chemically, these three goldenseal alkaloids possess a methylenedioxyphenyl moiety, which, in studies of cytochrome P450 (P450) -dependent drug metabolism, frequently give rise to inhibition [142].

Gurley et al. determined the effects of goldenseal supplementation only on human CYP3A activity. Sixteen healthy volunteers received goldenseal for 14 days. Statistically significant increases ($p < 0.05$) in midazolam $AUC_{(0-\infty)}$ (62%), elimination half-life (57%), and C_{max} (41%) were observed after goldenseal extract supplementation. Goldenseal reduced midazolam apparent oral clearance by 36% ($p < 0.001$) [139]. The same research group conducted a clinical assessment in 18 healthy volunteers on the effects of goldenseal only on human CYP2D6 activity. Pre- and post-supplementation phenotypic trait measurements were determined for CYP2D6 using 8-hour debrisoquine urinary recovery ratios. Comparisons of pre- and post-supplementation 8-hour debrisoquine urinary recovery ratios revealed significant inhibition (~ 50%) of CYP2D6 activity for goldenseal [36]. In a cocktail interaction study, 12 healthy volunteers received goldenseal for 28 days. The probe drug cocktail of midazolam (for CYP3A4/5 activity) and caffeine (CYP1A2 activity), followed 24 hours later by chlorzoxazone (CYP2E1 activity) and debrisoquine (CYP2D6 activity), were administered before (baseline) and at the end of supplementation. Goldenseal produced significant reductions in CYP2D6 ($p < 0.0001$) and CYP3A4/5 ($p < 0.0001$) phenotypes [85].

Overall, goldenseal seems to be a mild to moderate inhibitor of CYP3A4/5 and CYP2D6. Accordingly, patients should refrain from taking goldenseal supplements concomitantly with prescriptive medications, particularly those extensively metabolized by CYP2D6 and CYP3A4/5.

Other herb-drug interactions

In addition to the herbs described above, there are further plants with therapeutic benefits, which have been investigated with regard to effects on the human cytochrome P450 drug metabolizing system. A clinical study in 12 healthy male subjects showed no effect of ginger [*Zingiber officinale* (R.) (Zingiberaceae)] on the pharmacokinetic parameters of S- or R-warfarin [49]. A cocktail interaction study investigated the effects of multiple doses of three herbal medicines on metabolic activities of CYP1A2, 2C9, 2C19, 2D6, 2E1, and 3A4 [143]. The roots of *Angelica tenuissima* (L.) [Apiaceae], *Angelica dahurica* (L.) [Apiaceae], and *Scutellaria baicalensis* (L.) [Lamiaceae] were administered to 24 healthy male volunteers. *Angelicae tenuissimae radix* had no influences on CYP activities. *Angelicae dahuricae radix* significantly decreased CYP1A2 activity to 10% of baseline activity (95% CI 0.05–0.21). *Scutellariae radix* showed significant changes in CYP2C9 and CYP2E1 activities. Baseline values for losartan as a CYP2C9 probe were decreased to 71% (0.54–0.94) and the metabolic activity of chlorzoxazone as a CYP2E1 probe showed a 1.42-fold (1.03–1.97) increase [143]. Furthermore, in another study with 17 healthy male subjects, baicalin, a flavone glucuronide of baicalein extracted from *Scutellariae radix*, significantly induced CYP2B6 activity as measured by bupropion hydroxylation (an average 63% increase in the AUC ratio of hydroxybupropion over bupropion and an 87% increase in the AUC of hydroxybupropion) [144]. There are also several other single constituents of plants which may have effects on cytochrome P450 enzymes. For example, resveratrol as the main non-flavonoid polyphenol found in red wine and grapes [*Vitis vinifera* (L.) (Vitaceae)] has a wide range of biological and pharmacological activities including antioxidant, anti-inflammatory, antimutagenic, and anticarcinogenic effects [145]. A cocktail interaction study in 42 healthy volunteers determined the effect of pharmacological doses of resveratrol on CYP1A2, CYP2C9, CYP2D6, and CYP3A4. Resveratrol intervention was found to inhibit the phenotypic indices of CYP3A4, 2D6, and 2C9, and to induce the phenotypic index of 1A2 [146]. Curcumin, a yellow curry spice extracted from the rhizome of *Curcuma longa* (L.) [Zingiberaceae], is a polyphenolic non-flavonoidic that displays anti-inflammatory and antioxidant activities [145]. A clinical study with 16 unrelated, healthy Chinese men investigated the effect of curcumin on the activities of CYP1A2 and CYP2A6 using caffeine as a probe drug. Cytochrome P450 1A2 activity was decreased by 28.6% (95% CI 15.6–41.8; $p < 0.000$), while increases were observed in CYP2A6 (by 48.9%; 95% CI 25.3–72.4; $p < 0.000$) [147].

Limitations

Reported drug-herb interaction studies used a broad range of specific preparations of the respective herbs. The information on these preparations is sparse in many of the studies, and even if commercial products have been used, other batches will have different compositions and thus may have different potentials do cause drug-drug interactions. Phytopharmaceuticals composed of different fractions from parts of a plant (leaves, roots, seeds, fruit, other parts) may have completely different compositions. Thus, any extrapolation of the data gathered here to other products is flawed to an unknown extent. Furthermore, many studies used invalid phenotyping metrics and/or had small numbers of participants without proper estimation of the sample size required to answer the scientific question. The published literature thus provides only a rough estimate to which extent marketed drugs prepared from specific plants or other preparations of these plants, such as infusions, would indeed cause clinically relevant drug interactions in patients.

Conclusions

Our article provides a brief description of clinical interaction studies between phytopharmaceuticals and human cytochrome P450 enzymes for the top 14 common botanicals sales in the U.S. The majority of the herbal drugs appeared to have no clear effects on most of the CYPs examined. If there were an effect, the herbal drugs would qualify as mild inhibitors (less than a 2-fold change in enzyme activity) in almost all cases, e.g., in the case of inhibition of CYP2E1 by garlic and by kava or for inhibitory effects of soybean components on CYP1A2. The most pronounced effects were the well-known induction of several members of the CYP family by St. John's wort and the inhibitory effect of goldenseal on CYP3A and CYP2D6, both being borderline between mild and moderate (more than 2-fold but less than 5-fold) in magnitude. With these two exceptions, concomitant intake of herbal drugs is not a major risk for drugs that are metabolized by CYPs.

Conflict of Interest

No conflict of interest is to be declared.

Table 1 Reported clinical studies on the effects of herbal drugs and/or respective components on cytochrome P450 enzymes in humans.

Prescribed drug	Actually used probe drug for CYP isoform	Sample size	Dosage and duration of treatment	Preparation and content	Study design	Clinical result of interaction, magnitude of change in % of PK parameters (p value)	Possible mechanism, involved CYP	Ref.
Garlic								
Alprazolam	Alprazolam	14	3 × 600 mg twice daily for 14 days	Coated tablets with 600 µg allicin	Phenotyping at baseline vs. end of herb treatment	No effect on alprazolam pharmacokinetics	None, CYP3A4	[25]
Caffeine	Caffeine	12	500 mg thrice daily for 28 days	Garlic oil	Open-label, randomized study; phenotyping at baseline vs. end of supplement phase	No effect on caffeine pharmacokinetics	None, CYP1A2	[27]
Chlorzoxazone	Chlorzoxazone	12	500 mg thrice daily for 28 days	Garlic oil	Open-label, randomized study; phenotyping at baseline vs. end of supplement phase	Decreased 6-hydroxychlorzoxazone/chlorzoxazone serum ratios, 22% (p = 0.005)	Inhibition of CYP2E1	[27]
Debrisoquine	Debrisoquine	12	500 mg thrice daily for 28 days	Garlic oil	Open-label, randomized study; phenotyping at baseline vs. end of supplement phase	No effect on debrisoquine urinary recovery ratio	None, CYP2D6	[27]
Dextromethorphan	Dextromethorphan	14	3 × 600 mg twice daily for 14 days	Coated tablets with 600 µg allicin	Phenotyping at baseline vs. end of herb treatment	No effect on dextromethorpan pharmacokinetics	None, CYP2D6	[25]
Docetaxel	Docetaxel	10	600 mg twice daily for 12 days	Garlic tablets with 3600 µg allicin	Prospective pharmacokinetic study; garlic coadministration in 1st cycle of docetaxel treatment	No effect on docetaxel pharmacokinetics	None, CYP3A4	[23]
Midazolam	Midazolam	12	500 mg thrice daily for 28 days	Garlic oil	Open-label, randomized study; phenotyping at baseline vs. end of supplement phase	No effect on midazolam pharmacokinetics	None, CYP3A4	[27]
Ritonavir	Ritonavir	10	2 × 5 mg twice daily for 4 days	Garlic powder in liquid-filled soft gelatin capsules	Open, two-treatment, two-period, two-sequence, randomized, crossover study; ritonavir administration at end of supplement phase	No effect on ritonavir pharmacokinetics	None, CYP3A4	[21]
Saquinavir	Saquinavir	10	4000 mg twice daily for 21 days	Garlic caplets with 3.6 mg/caplet allicin and 4.8 mg/caplet allin	Two-treatment, three-period, single-sequence, longitudinal study; saquinavir administration at end of garlic supplementation in period two	Decreased mean saquinavir AUC 51% (p = 0.007), mean C_8 49% (p = 0.002) and mean C_{max} 54% (p = 0.006)	Not known, CYP3A4	[26]
Rac-warfarin	*Rac*-warfarin	12	2 × 500 mg thrice daily for 14 days	Enteric-coated garlic tablets containing 2000 mg of fresh garlic bulb equivalent to 3.71 mg of allicin per tablet	Open-label, three-treatment, randomized crossover study; warfarin administration alone vs. after 2 weeks of pretreatment with garlic	No effect on either S-warfarin or R-warfarin pharmacokinetics	None, CYP2C9	[67]
	Rac-warfarin	48	5 mL twice daily for 12 weeks	Aged garlic extract with 305 g/L of extracted solids	Double-blind, randomized, placebo-controlled pilot study	No effect on warfarin pharmacokinetics and pharmacodynamics	None, CYP2C9	[24]

cont.

Table 1 *Continued*

Prescribed drug	Actually used probe drug for CYP isoform	Sample size	Dosage and duration of treatment	Preparation and content	Study design	Clinical result of interaction, magnitude of change in % of PK parameters (p value)	Possible mechanism, involved CYP	Ref.
Echinacea								
Caffeine	Caffeine	12	400 mg 4 times daily for 8 days	*Echinacea purpurea* root	Two-period, open-label, fixed-schedule study; phenotyping before vs. after a short course of echinacea	Reduced oral clearance of caffeine by 27 % (p = 0.49)	Inhibition of CYP1A2	[31]
	Caffeine	12	800 mg twice daily for 28 days	*Echinacea purpurea* (no standardization)	Open-label study randomized for supplementation sequence	No effect on caffeine pharmacokinetics	None, CYP1A2	[35]
Chlorzoxazone	Chlorzoxazone	12	800 mg twice daily for 28 days	*Echinacea purpurea* (no standardization)	Open-label study randomized for supplementation sequence	No effect on chlorzoxazone pharmacokinetics	None, CYP2E1	[35]
Debrisoquine	Debrisoquine	12	800 mg twice daily for 28 days	*Echinacea purpurea* (no standardization)	Open-label study randomized for supplementation sequence	No effect on debrisoquine pharmacokinetics	None, CYP2D6	[35]
	Debrisoquine	12	800 mg twice daily for 28 days	*Echinacea purpurea* extract, standardized to 2.2 mg isobutylamides per capsule	Open-label study randomized for supplementation sequence	No effect on debrisoquine pharmacokinetics	None, CYP2D6	[36]
Dextromethorphan	Dextromethorphan	12	400 mg 4 times daily for 8 days	*Echinacea purpurea* root	Two-period, open-label, fixed-schedule study; phenotyping before vs. after a short course of echinacea	No effect on dextromethorphan pharmacokinetics	None, CYP2D6	[31]
Lopinavir	Midazolam	13	500 mg thrice daily for 28 days	*Echinacea purpurea* fresh liquid extract 8 : 1 (250 mg) softgel capsules	Open-label study on the steady-state pharmacokinetics of lopinavir and ritonavir	No effect on lopinavir pharmacokinetics	None, CYP3A4	[32]
Midazolam	Midazolam	12	400 mg 4 times daily for 8 days	*Echinacea purpurea* root	Two-period, open-label, fixed-schedule study; phenotyping before vs. after a short course of echinacea	No effect on midazolam pharmacokinetics	None, CYP3A4	[31]
	Midazolam	13	500 mg thrice daily for 28 days	*Echinacea purpurea* fresh liquid extract 8 : 1 (250 mg) softgel capsules	Open-label study on the steady-state pharmacokinetics of lopinavir and ritonavir	Modest decrease in midazolam $AUC_{(0-\infty)}$ by 27 % (p = 0.008)	Not known, CYP3A4	[32]
	Midazolam	12	800 mg twice daily for 28 days	*Echinacea purpurea* (no standardization)	Open-label study randomized for supplementation sequence;	No effect on midazolam pharmacokinetics	None, CYP3A4	[35]
Ritonavir	Midazolam	13	500 mg thrice daily for 28 days	*Echinacea purpurea* fresh liquid extract 8 : 1 (250 mg) softgel capsules	Open-label study on the steady-state pharmacokinetics of lopinavir and ritonavir	No effect on ritonavir pharmacokinetics	None, CYP3A4	[32]
Tolbutamide	Tolbutamide	12	400 mg 4 times daily for 8 days	*Echinacea purpurea* root	Two-period, open-label, fixed-schedule study; phenotyping before vs. after a short course of echinacea	Reduced oral clearance of tolbutamide by 11 % (p = 0.001)	Inhibition of CYP2C9	[31]

cont.

Table 1 *Continued*

Prescribed drug	Actually used probe drug for CYP isoform	Sample size	Dosage and duration of treatment	Preparation and content	Study design	Clinical result of interaction, magnitude of change in % of PK parameters (p value)	Possible mechanism, involved CYP	Ref.
Warfarin	Warfarin	12	675 mg 4 times daily for 7 days	A mixture of 600 mg of *Echinacea angustifolia* root and 675 mg of *Echinacea purpurea* root standardized to 5.75 mg of total alkamides per tablet	Open-label, randomized, three-treatment, crossover study; administration of single dose of warfarin vs. after two weeks of pretreatment with echinacea	No effect on warfarin pharmacokinetics	None, CYP2C9	[34]
Saw palmetto								
Alprazolam	Alprazolam	12	320 mg once daily for 14 days	ProstActive capsules containing 197.7 mg of non-esterified fatty acids, representing 62% of the total extact	Phenotyping before vs. after pretreatment of saw palmetto	No effect on alprazolam pharmacokinetics	None, CYP3A4	[38]
Caffeine	Caffeine	12	160 mg twice daily for 28 days	Standardized to 85% to 95% fatty acids and sterols	Open-label study randomized for supplementation sequence	No effect on caffeine pharmacokinetics	None, CYP1A2	[35]
Chlorzoxazone	Chlorzoxazone	12	160 mg twice daily for 28 days	Standardized to 85% to 95% fatty acids and sterols	Open-label study randomized for supplementation sequence	No effect on chlorzoxazone pharmacokinetics	None, CYP2E1	[35]
Debrisoquine	Debrisoquine	12	160 mg twice daily for 28 days	Standardized to 85% to 95% fatty acids and sterols	Open-label study randomized for supplementation sequence	No effect on debrisoquine pharmacokinetics	None, CYP2D6	[35]
Dextromethorphan	Dextromethorphan	12	320 mg once daily for 14 days	ProstActive capsules containing 197.7 mg of non-esterified fatty acids, representing 62% of the total extact	Phenotyping before vs. after pretreatment of saw palmetto	No effect on dextromethorphan pharmacokinetics	None, CYP2D6	[38]
Midazolam	Midazolam	12	160 mg twice daily for 28 days	Standardized to 85–95% fatty acids and sterols	Open-label study randomized for supplementation sequence	No effect on midazolam pharmacokinetics	None, CYP3A4	[35]
Ginkgo								
Alprazolam	Alprazolam	12	120 mg twice daily for 14 days	EGb 761 tablets standardized to 24% ginkgo flavonol glycosides and 6% terpene lactones as well as bilobalide	Phenotyping at baseline vs. treatment with ginkgo	No effect on alprazolam pharmacokinetics	None, CYP3A4	[54]
Bupropion	Bupropion	14	2 × 60 mg twice daily for 14 days	*Ginkgo biloba* capsules standardized with a minimum of 24% ginkgo flavone glycosides and 6% terpene lactones	Randomized, 2-phase crossover study; voriconzole administration before vs. after pretreatment with ginkgo	No effect on bupropion pharmacokinetics	None, CYP2B6	[53]
Caffeine	Caffeine	12	60 mg 4 times daily for 28 days	*Ginkgo biloba* standardized to 24% flavone glycosides and 6% terpene lactones	Open-label, randomized study; phenotyping at baseline vs. end of supplement phase	No effect on caffeine pharmacokinetics	None, CYP1A2	[27]

cont.

Table 1 *Continued*

Prescribed drug	Actually used probe drug for CYP isoform	Sample size	Dosage and duration of treatment	Preparation and content	Study design	Clinical result of interaction, magnitude of change in % of PK parameters (p value)	Possible mechanism, involved CYP	Ref.
	Caffeine	18	120 mg twice daily for 8 days	EGb 761 tablets	Open-label, randomized, threefold crossover, cocktail study; pretreatment with ginkgo vs. phenotyping at the end of treatment	No effect on caffeine pharmacokinetics	None, CYP1A2	[15]
	Caffeine	18	240 mg once daily for 8 days	EGb 761 tablets	Open-label, randomized, threefold crossover, cocktail study; pretreatment with ginkgo and placebo vs. phenotyping at the end of treatment	No effect on caffeine pharmacokinetics	None, CYP1A2	[15]
Chlorzoxazone	Chlorzoxazone	12	60 mg 4 times daily for 28 days	*Ginkgo biloba* standardized to 24% flavone glycosides and 6% terpene lactones	Open-label, randomized study; phenotyping at baseline vs. end of supplement phase	No effect on chlorzoxazone pharmacokinetics	None, CYP2E1	[27]
Cortisol	Omeprazole	18	2 × 70 mg twice daily for 12 days	Each tablet contains 70 mg of standardized *Ginkgo biloba* leaf extract (16.04 mg of flavonol glycosides and 4.77 mg of terpene lactones)	Open-label, sequential design; phenotyping at baseline vs. end of 12-day treatment period	No effect on cortisol pharmacokinetics	None, CYP3A	[50]
Debrisoquine	Debrisoquine	12	60 mg 4 times daily for 28 days	*Ginkgo biloba* standardized to 24% flavone glycosides and 6% terpene lactones	Open-label, randomized study; phenotyping at baseline vs. end of supplement phase	No effect on debrisoquine pharmacokinetics	None, CYP2D6	[27]
Dextromethorphan	Dextromethorphan	12	120 mg twice daily for 14 days	EGb 761 tablets	Phenotyping at baseline vs. treatment with ginkgo	No effect on dextromethorphan pharmacokinetics	None, CYP2D6	[54]
	Dextromethorphan	18	120 mg twice daily for 8 days	EGb 761 tablets	Open-label, randomized, threefold crossover, cocktail study; pretreatment with ginkgo vs. phenotyping at end of treatment	No effect on dextromethorphan pharmacokinetics	None, CYP2D6	[15]
	Dextromethorphan	18	240 mg once daily for 8 days	EGb 761 tablets	Open-label, randomized, threefold crossover, cocktail study; pretreatment with ginkgo and placebo vs. phenotyping at end of treatment	No effect on dextromethorphan pharmacokinetics	None, CYP2D6	[15]
Diazepam	Diazepam	12	120 mg twice daily for 28 days	Each tablet contains 40 mg of standardized *Ginkgo biloba* extract (9.6 mg flavonol glycosides and 2.4 mg terpene lactones)	Open-label, sequential design; phenotyping at baseline vs. at end of treatment with ginkgo	No effect on diazepam pharmacokinetics	None, CYP3A4	[57]
Flurbiprofen	Flurbiprofen	11	2 × 60 mg thrice a day for 1 day	EGb 761 tablets	Randomized, two-way crossover study; phenotyping at baseline vs. at end of treatment with ginkgo or placebo	No effect on flurbiprofen pharmacokinetics	None, CYP2C9	[48]

cont.

Table 1 *Continued*

Prescribed drug	Actually used probe drug for CYP isoform	Sample size	Dosage and duration of treatment	Preparation and content	Study design	Clinical result of interaction, magnitude of change in % of PK parameters (p value)	Possible mechanism, involved CYP	Ref.
Lopinavir	Midazolam	14	120 mg twice daily for 14 days	Capsules containing 29.2% flavonol glycosides and 5.1% terpene lactones of total content	Open-label investigation on the steady-state pharmcokinetics of lopinavir and ritonavir; phenotyping at baseline vs. at end of treatment of ginkgo administration	No effect on lopinavir pharmacokinetics	None, CYP3A4	[52]
Midazolam	Midazolam	12	60 mg 4 times daily for 28 days	*Ginkgo biloba* standardized to 24% flavone glycosides and 6% terpene lactones	Open-label, randomized study; phenotyping at baseline vs. at end of supplement phase	No effect on midazolam pharmacokinetics	None, CYP3A4	[27]
	Midazolam	18	120 mg twice daily for 8 days	EGb 761 tablets	Open-label, randomized, threefold crossover, cocktail study; pretreatment with ginkgo vs. phenotyping at end of treatment	No effect on midazolam pharmacokinetics	None, CYP3A4	[15]
	Midazolam	18	240 mg once daily for 8 days	EGb 761 tablets	Open-label, randomized, threefold crossover, cocktail study; pretreatment with ginkgo and placebo vs. phenotyping at end of treatment	No effect on midazolam pharmacokinetics	None, CYP3A4	[15]
	Midazolam	15	120 mg twice daily for 28 days	Capsules containing 29.2% flavonol glycosides and 5.1% terpene lactones of total content	Single-sequence, longitudinal investigation; phenotyping at baseline vs. at end of treatment with *Ginkgo biloba* extract	Mild-moderate reduced $AUC_{(0-\infty)}$ for midazolam	Not known, CYP3A4	[55]
Midazolam	Midazolam	14	120 mg twice daily for 14 days	Capsules containing 29.2% flavonol glycosides and 5.1% terpene lactones of total content	Open-label investigation on the steady-state pharmcokinetics of lopinavir and ritonavir; phenotyping at baseline vs. end of treatment of ginkgo administration	Decreased midazolam $AUC_{(0-\infty)}$ by 34% ($p = 0.03$) and C_{max} by 31% ($p = 0.03$)	Induction of CYP3A	[52]
	Midazolam	10	2 × 60 mg thrice daily for 28 days	EGb 761 tablets	Phenotyping before vs. after administration of *Ginkgo biloba* extract	Increased $AUC_{(0-\infty)}$ by 25% and decreased oral clearance by 26% for midazolam	Inhibition of CYP3A4	[56]
Omeprazole	Omeprazole	18	120 mg twice daily for 8 days	EGb 761 tablets	Open-label, randomized, threefold crossover, cocktail study; pretreatment with ginkgo vs. phenotyping at end of treatment	No effect on omeprazole pharmacokinetics	None, CYP2C19	[15]
	Omeprazole	18	240 mg once daily for 8 days	EGb 761 tablets	Open-label, randomized, threefold crossover, cocktail study; pretreatment with ginkgo and placebo vs. phenotyping at end of treatment	No effect on omeprazole pharmacokinetics	None, CYP2C19	[15]
	Omeprazole	18	2 × 70 mg twice daily for 12 days	Each tablet contains 70 mg of standardized *Ginkgo biloba* leaf extract (16.04 mg of flavonol glycosides and 4.77 mg of terpene lactones)	Open-label, sequential design; phenotyping at baseline vs. end of 12-day treatment period	Decrease in the AUC ratio of omeprazole to 5-hydroxyomeprazole by 54.4% ($p < 0.01$)	Induction of CYP2C19	[50]

cont.

Table 1 *Continued*

Prescribed drug	Actually used probe drug for CYP isoform	Sample size	Dosage and duration of treatment	Preparation and content	Study design	Clinical result of interaction, magnitude of change in % of PK parameters (p value)	Possible mechanism, involved CYP	Ref.
Ritonavir	Midazolam	14	120 mg twice daily for 14 days	Capsules containing 29.2% flavonol glycosides and 5.1% terpene lactones of total content	Open-label investigation on the steady-state pharmcokinetics of lopinavir and ritonavir; phenotyping at baseline vs. end of treatment of ginkgo administration	No effect on ritonavir pharmacokinetics	None, CYP3A4	[52]
Tolbutamide	Tolbutamide	18	120 mg twice daily for 8 days	EGb 761 tablets	Open-label, randomized, threefold crossover, cocktail study; pretreatment with ginkgo vs. phenotyping at end of treatment	No effect on tolbutamide pharmacokinetics	None, CYP2C9	[15]
	Tolbutamide	18	240 mg once daily for 8 days	EGb 761 tablets	Open-label, randomized, threefold crossover, cocktail study; pretreatment with ginkgo and placebo vs. phenotyping at end of treatment	No effect on tolbutamide pharmacokinetics	None, CYP2C9	[15]
	Tolbutamide	10	2 × 60 mg thrice daily for 28 days	EGb 761 tablets	Phenotyping before vs. after administration of *Ginkgo biloba* extract	Slightly decreased $AUC_{(0-\infty)}$ by 16% for tolbutamide	Induction of CYP2C9	[56]
Voriconazole	Voriconazole	14	120 mg twice daily for 12 days	Ginkgo biloba capsules standardized with a minimum of 24% flavone glycosides and 6% terpene lactones	Randomized, two-phase crossover design; phenotyping at baseline (without pretreatment) vs. after pretreatment with *Ginkgo biloba*	No effect on voriconazole pharmacokinetics	None, CYP3A4	[51]
Rac-warfarin	*Rac*-warfarin	12	2 × 40 mg thrice daily for 7 days	EGb 761 tablets	Randomized, open-label, three-treatment, three-period, three-sequence, crossover study; phenotyping alone vs. after 7 days pretreatment with ginkgo	No effect on either S- or R-warfarin pharmacokinetics	None, CYP2C9	[49]
Cranberry								
Cyclosporine	Cyclosporine	12	240 mL once a day for 1 day	Concentrated cranberry juice	Open-label, randomized, three-way crossover study with three sequences; phenotyping with water intake (baseline) vs. with juice intake (treatment)	No effect on the overall disposition of cyclosporine	None, CYP3A	[69]
Diclofenac	Diclofenac	8	180 mL once a day for 1 day	Concentrated cranberry juice containing 27% cranberry	Open-label, two-period, crossover design; phenotyping with water intake (baseline) vs. pretreatment with cranberry juice	No change in pharmacokinetics of diclofenac	None, CYP2C9	[65]
Flurbiprofen	Flurbiprofen	14	8 oz. a day for 1 day	Concentrated cranberry juice	Crossover design; phenotyping with water (baseline) vs. cranberry juice placebo vs. cranberry juice	No effect on flurbiprofen pharmacokinetics	None, CYP2C9	[66]
Midazolam	Midazolam	10	200 mL thrice daily for 10 days	Concentrated cranberry juice was diluted with tap water (1 : 4 vol/vol)	Randomized, two-phase crossover study; phenotyping with water (baseline) vs. pretreatment with cranberry juice	No effect on midazolam pharmacokinetics	None, CYP3A4	[68]

cont.

Table 1 *Continued*

Prescribed drug	Actually used probe drug for CYP isoform	Sample size	Dosage and duration of treatment	Preparation and content	Study design	Clinical result of interaction, magnitude of change in % of PK parameters (p value)	Possible mechanism, involved CYP	Ref.
Tizanidine	Tizanidine	10	200 mL thrice daily for 10 days	Concentrated cranberry juice was diluted with tap water (1 : 4 vol/vol)	Randomized, two-phase crossover study; phenotyping with water (baseline) vs. pretreatment with cranberry juice	No effect on tizanidine pharmacokinetics	None, CYP1A2	[68]
Rac-warfarin	*Rac*-warfarin	10	200 mL thrice daily for 10 days	Concentrated cranberry juice was diluted with tap water (1 : 4 vol/vol)	Randomized, two-phase crossover study; phenotyping with water (baseline) vs. pretreatment with cranberry juice	No effect on either S-warfarin or R-warfarin pharmacokinetics and pharmacodynamics	None, CYP2C9	[68]
	Rac-warfarin	12	2 × 500 mg thrice daily for 14 days	Two capsules with cranberry juice concentrate are equivalent to 57 g of fruit per day	Open-label, three-treatment, randomized crossover study; warfarin administration alone or after two weeks of pretreatment with cranberry	No effect on either S-warfarin or R-warfarin pharmacokinetics but pharmacodynamics (increased mean $AUC_{(INR)}$ by approx. 30 %)	None, CYP2C9	[67]
Soy								
Caffeine	Caffeine	18	1000 mg once daily for 14 days	Genistein tablets	Phenotyping once before vs. once at end of treatment with genistein	Decreased urinary paraxanthine ratio by 41 % and increased urinary 1,7-dimethylurate ratio by 47 %	Inhibition of CYP1A2 and induction of CYP2A6	[74]
Cortisol	Cortisol	20	50 mg twice daily for 14 days	Capsules with soy extract containing 50 mg isoflavones (10.9 mg daidzein and 16.5 mg genistein)	Phenotyping at baseline vs. at end of pretreatment	No alteration of urinary 6β-hydroxycortisol/cortisol ratio	None, CYP3A4	[76]
Losartan	Losartan	18	2 × 1000 mg twice daily for 14 days	Genistein Soy Complex tablets	Open-label, two-phase study; phenotyping at baseline vs. at end of pretreatment	No effect on pharmacokinetics of losartan or its metabolite E-3174	None, CYP2C9	[75]
Theophylline	Theophylline	10	200 mg twice daily for 10 days	200 mg daidzein	Single-blind, placebo-controlled, parallel study; phenotyping at baseline vs. after daidzein or placebo coadministration	Increased theophilline $AUC_{(0-48)}$ by ~ 34 % ($p < 0.05$), $AUC_{(0-\infty)}$ by ~ 34 % ($p < 0.05$), C_{max} by ~ 24 % ($p < 0.05$) and $t_{1/2}$ by ~ 41 % ($p = 0.011$)	Inhibition of CYP1A2	[73]
Ginseng								
Caffeine	Caffeine	12	500 mg thrice daily for 28 days	*Panax ginseng* standardized to 5 % ginsenosides	Open-label, randomized study; phenotyping at baseline vs. end of supplement phase	No effect on caffeine pharmacokinetics	None, CYP1A2	[27]
Chlorzoxazone	Chlorzoxazone	12	500 mg thrice daily for 28 days	*Panax ginseng* standardized to 5 % ginsenosides	Open-label, randomized study; phenotyping at baseline vs. end of supplement phase	No effect on chlorzoxazone pharmacokinetics	None, CYP2E1	[27]
Cortisol	Cortisol	20	100 mg twice daily for 14 days	*Panax ginseng* 100 mg standardized to 4 % ginsenosides	Phenotyping at baseline vs. at end of pretreatment	No alteration of urinary 6β-hydroxycortisol/cortisol ratio	None, CYP3A	[76]
Debrisoquine	Debrisoquine	12	500 mg thrice daily for 28 days	*Panax ginseng* standardized to 5 % ginsenosides	Open-label, randomized study; phenotyping at baseline vs. end of supplement phase	Decreased debrisoquine urinary recovery ratios of 7 % ($p = 0.003$)	Inhibition of CYP2D6	[27]

cont.

Table 1 *Continued*

Prescribed drug	Actually used probe drug for CYP isoform	Sample size	Dosage and duration of treatment	Preparation and content	Study design	Clinical result of interaction, magnitude of change in % of PK parameters (p value)	Possible mechanism, involved CYP	Ref.
Midazolam	Midazolam	12	500 mg thrice daily for 28 days	*Panax ginseng* standardized to 5% ginsenosides	Open-label, randomized, phenotyping at baseline vs. end of each supplement phase	No effect on midazolam pharmacokinetics	None, CYP3A4	[27]
Warfarin	Warfarin	12	500 mg thrice daily for 14 days	Aqueous extract of 9.2% *Panax ginseng* equivalent to 100 mg crude root	Randomized, open-label, controlled study; warfarin intake with *Panax ginseng* vs. warfarin intake only	No effect on warfarin pharmacokinetics	None, CYP2C9	[80]
Rac-warfarin	*Rac*-warfarin	12	2 × 500 mg thrice daily for 7 days	Capsules containing extract equivalent to 0.5 g *Panax ginseng* root and 8.93 mg ginsenosides	Open-label, three-treatment, three-period, three-sequence, randomized, crossover study; warfarin intake alone vs. after 7 days' pretreatment with ginseng	No effect on warfarin pharmacokinetics	None, CYP2C9	[83]
Black cohosh								
Caffeine	Caffeine	12	1090 mg twice daily for 28 days	Black cohosh root extract capsules standardized to 0.2% triterpene glycosides	Open-label study; phenotyping at baseline vs. at the end of supplementation	No effect on caffeine pharmacokinetics	None, CYP1A2	[85]
Chlorzoxazone	Chlorzoxazone	12	1090 mg twice daily for 28 days	Black cohosh root extract capsules standardized to 0.2% triterpene glycosides	Open-label study; phenotyping at baseline vs. at the end of supplementation	No effect on chlorzoxazone pharmacokinetics	None, CYP2E1	[85]
Debrisoquine	Debrisoquine	12	1090 mg twice daily for 28 days	Black cohosh root extract capsules standardized to 0.2% triterpene glycosides	Open-label study; phenotyping at baseline vs. at the end of supplementation	Decreased debrisoquine urinary recovery ratios of 7%	Inhibition of CYP2D6	[85]
	Debrisoquine	18	40 mg twice daily for 14 days	Black cohosh extract standardized to 2.5% triterpene glycosides per tablet	Open-label study randomized for supplementation sequence	No effect on debrisoquine pharmacokinetics	None, CYP2D6	[36]
Midazolam	Midazolam	12	1090 mg twice daily for 28 days	Black cohosh root extract capsules standardized to 0.2% triterpene glycosides	Open-label study; phenotyping at baseline vs. at the end of supplementation	No effect on midazolam pharmacokinetics	None, CYP3A4	[85]
	Midazolam	19	40 mg twice daily for 14 days	Black cohosh extract standardized to 2.5% triterpene glycosides	Open-label study; phenotyping at baseline vs. at the end of supplementation	No effect on midazolam pharmacokinetics	None, CYP3A4	[86]
St. John's wort								
Alprazolam	Alprazolam	28	240 mg twice daily with low hyperforin for 10 days	Capsules containing 60 mg SJW extract, with 0.25 mg of total hypericins and 0.88 mg hyperforin	Double-blind, placebo-controlled, parallel-grouped study; phenotyping at baseline vs. at end of treatment with SJW or placebo	No effect on alprazolam pharmacokinetics	None, CYP3A4	[96]

cont.

Table 1 *Continued*

Prescribed drug	Actually used probe drug for CYP isoform	Sample size	Dosage and duration of treatment	Preparation and content	Study design	Clinical result of interaction, magnitude of change in % of PK parameters (p value)	Possible mechanism, involved CYP	Ref.
Alprazolam	Alprazolam	7	300 mg thrice daily for 4 days	Capsules standardized to 0.3% hypericin	Two-phase study; phenotyping at baseline vs. at end of treatment	No effect on alprazolam pharmacokinetics	None, CYP3A4	[88]
	Alprazolam	12	300 mg thrice daily for 14 days	Tablets containing 300 mg of SJW extract standardized to 0.12% to 0.3% hypericin	Open-label crossover study with fixed treatment order; phenotyping at baseline vs. at end of treatment	A twofold decrease in AUC for alprazolam plasma concentration vs. time ($p < 0.001$) and a twofold increase in alprazolam clearance ($p < 0.001$)	Induction of CYP3A4	[92]
	Alprazolam	16	300 mg twice daily for 28 days	Tablets containing 300 mg of active substance	Randomized, open, crossover study; SJW (active treatment) vs. vitamin product (control)	Increased serum level of LDL cholesterol by appr. 30% ($p = 0.02$) and increase in total cholesterol by approx. 30% ($p = 0.02$)	Induction of CYP3A4	[104]
Caffeine	Caffeine	28	240 mg twice daily with low hyperforin for 10 days	Capsules containing 60 mg SJW extract, corresponding to 0.25 mg of total hypericins and 0.88 mg hyperforin	Double-blind, placebo-controlled, parallel-grouped study; phenotyping at baseline vs. at end of treatment with SJW or placebo	No effect on caffeine pharmacokinetics	None, CYP1A2	[96]
	Caffeine	12	300 mg thrice daily for 14 days	Tablets containing 0.3% hypericin and 4% hyperforin	Two-phase, randomized, placebo-controlled crossover study; pretreatment with SJW or placebo vs. phenotyping at end of intake	No effect on caffeine pharmacokinetics	None, CYP1A2	[93]
	Caffeine	12	3 × 300 mg once daily for 2 days	Capsules containing 900 µg hypericin	Three-period, open-label, fixed schedule study; phenotyping at baseline vs. at end of treatment	No effect on caffeine pharmacokinetics	None, CYP1A2	[89]
	Caffeine	12	300 mg thrice daily for 14 days	Capsules containing 900 µg hypericin	Three-period, open-label, fixed schedule study; phenotyping at baseline vs. at end of treatment	No effect on caffeine pharmacokinetics	None, CYP1A2	[89]
	Caffeine	16	300 mg thrice daily for 14 days	SJW extract containing 900 µg hypericin	Open study; phenotyping at baseline vs. at end of treatment	No effect on caffeine pharmacokinetics	None, CYP1A2	[90]
	Caffeine	12	300 mg thrice daily for 28 days	*Hypericum perforatum* standardized to 0.3% hypericin	Open-label, randomized study; phenotyping at baseline vs. at end of supplement phase	No effect on caffeine pharmacokinetics	None, CYP1A2	[27]
Chlorzoxazone	Chlorzoxazone	12	300 mg thrice daily for 28 days	*Hypericum perforatum* standardized to 0.3% hypericin	Open-label, randomized study; phenotyping at baseline vs. at end of supplement phase	A 26% ($p = 0.006$) rise in the 6-hydroxychlorzoxazone/chlorzoxazone serum ratio	Induction of CYP2E1	[27]
Cortisol	Cortisol	16	300 mg thrice daily for 14 days	SJW extract containing 900 µg hypericin	Open study; phenotyping at baseline vs. at end of treatment	Increased 6β-hydroxycortisol/cortisol molar concentration ratio in urine of 85%	Induction of CYP3A4	[90]
	Cortisol	13	300 mg thrice daily for 14 days	Tablets standardized to 0.3% hypericin	Unblinded, multiple-dose, single-treatment study; phenotyping at baseline vs. at end of treatment	Increased urinary 6β-hydroxycortisol/cortisol ratio of 114% ($p = 0.003$)	Induction of CYP3A4	[91]

cont.

Table 1 *Continued*

Prescribed drug	Actually used probe drug for CYP isoform	Sample size	Dosage and duration of treatment	Preparation and content	Study design	Clinical result of interaction, magnitude of change in % of PK parameters (p value)	Possible mechanism, involved CYP	Ref.
Cyclosporine	Cyclosporine	10	300 mg thrice daily with low hyperforin for 14 days	Capsule containing 0.1 mg total hyperforin, 0.45 mg total hypericin and 15.6 mg total flavonoids	Randomized crossover study; phenotyping at baseline vs. at end of treatment	No effect on cyclosporine pharmacokinetics	None, CYP3A4	[95]
	Cyclosporine	10	300 mg thrice daily with high hyperforin for 14 days	Capsule containing 7.0 mg total hyperforin, 0.45 mg total hypericin and 16.16 mg total flavonoids	Randomized crossover study; phenotyping at baseline vs. at end of treatment	Decreased $AUC_{(0-12)}$ for cyclosporine by 52% ($p < 0.05$)	Induction of CYP3A4	[95]
Debrisoquine	Debrisoquine	18	300 mg thrice daily for 14 days	St. John's wort extract standardized to 3% hyperforin	Open-label study randomized for supplementation sequence	No effect on debrisoquine pharmacokinetics	None, CYP2D6	[36]
	Debrisoquine	12	300 mg thrice daily for 28 days	*Hypericum perforatum* standardized to 0.3% hypericin	Open-label, randomized study; phenotyping at baseline vs. end of supplement phase	No effect on debrisoquine pharmacokinetics	None, CYP2D6	[27]
Desogestrel	Desogestrel	18	300 mg thrice daily for 28 days	SJW extract standardized to 0.3% hypericin	Oral contraceptive intake before (control) vs. cotreatment with SJW extract	Decreased 3-ketodesogestrel $AUC_{(0-24)}$ by ~ 44% ($p = 0.001$) and C_{max} by ~ 18% ($p = 0.005$) during cycle A and by ~ 42% ($p = 0.001$) and by ~ 23% ($p < 0.001$) during cycle B, respectively	Inhibition of CYP2C9/CYP2C19 and/or induction of CYP3A4	[101]
Dextromethorphan	Dextromethorphan	7	300 mg thrice daily for 4 days	Capsules standardized to 0.3% hypericin	Two-phase study; phenotyping at baseline vs. at end of treatment	No effect on dextromethorphan pharmacokinetics	None, CYP2D6	[88]
	Dextromethorphan	12	300 mg thrice daily for 14 days	Tablets containing 300 mg of an SJW extract standardized to 0.12% to 0.3% hypericin	Open-label crossover study with fixed treatment order; phenotyping at baseline vs. at end of treatment	No effect on dextromethorphan pharmacokinetics	None, CYP2D6	[92]
	Dextromethorphan	12	3 × 300 mg once daily for 2 days	Capsules containing 900 µg hypericin	Three-period, open-label, fixed schedule study; phenotyping at baseline vs. at end of treatment	No effect on dextromethorphan pharmacokinetics	None, CYP2D6	[89]
Dextromethorphan	Dextromethorphan	12	300 mg thrice daily for 14 days	Capsules containing 900 µg hypericin	Three-period, open-label, fixed schedule study; phenotyping at baseline vs. at end of treatment	No effect on dextromethorphan pharmacokinetics	None, CYP2D6	[89]
	Dextromethorphan	16	300 mg thrice daily for 14 days	SJW extract containing 900 µg hypericin	Open study; phenotyping at baseline vs. at end of treatment	No effect on dextromethorphan pharmacokinetics	None, CYP2D6	[90]
Ethinyl estradiol	Midazolam	12	300 mg thrice daily for 28 days	SJW extract	Oral contraceptive intake before (control) vs. cotreatment with SJW extract	Increased mean CL_{oral} of ethinyl estradiol by 47%, increased midazolam CL_{oral} by 50%	Induction of CYP3A4	[99]
	Ethinyl estradiol	16	300 mg thrice daily for 28 days	SJW extract	Placebo-controlled, single-blind sequential study; oral contraceptive intake before (control) vs. cotreatment with SJW extract	Reduced AUC of ethinyl estradiol by 14% ($p = 0.016$)	Induction of CYP3A4	[100]

cont.

Table 1 *Continued*

Prescribed drug	Actually used probe drug for CYP isoform	Sample size	Dosage and duration of treatment	Preparation and content	Study design	Clinical result of interaction, magnitude of change in % of PK parameters (p value)	Possible mechanism, involved CYP	Ref.
	Ethinyl estradiol	18	300 mg thrice daily for 28 days	SJW extract standardized to 0.3 % hypericin	Oral contraceptive intake before (control) vs. cotreatment with SJW extract	No effect on ethinyl estradiol pharmacokinetics	None, CYP3A4	[101]
Gliclazide	Gliclazide	21	300 mg thrice daily for 15 days	SJW extract	Sequential crossover, two-treatment study; gliclazide alone vs. at end of treatment with SJW	Reduced gliclazide $AUC_{(0-\infty)}$ by 33 % and decreased C_{max} by 22 %	Not known, CYP2C9	[109]
Imatinib	Imatinib	10	300 mg thrice daily for 14 days	SJW	Open-label, complete crossover, fixed-sequence, pharmacokinetic study; imatinib administration before vs. at end of treatment with SJW	Reduction of $AUC_{(0-\infty)}$ of imatinib by 32 % ($p = 0.0001$) and reduced C_{max} by 29 % ($p = 0.005$)	Induction of CYP3A4	[102]
	Imatinib	12	300 mg thrice daily for 14 days	SJW extract	Open-label, two-period, fixed-sequence study; imatinib administration before vs. at end of treatment with SJW	Increased imatinib clearance by 43 % ($p < 0.001$), decreased $AUC_{(0-\infty)}$ by 30 % ($p < 0.001$)	Induction of CYP3A4	[103]
Indinavir	Indinavir	8	300 mg thrice daily for 14 days	SJW preparation standardized to 0.3 % hypericin	Open-label study; indinavir administration at baseline vs. at end of treatment with SJW	Reduced $AUC_{(0-8)}$ of indinavir by 57 % ($p = 0.0008$)	Induction of CYP3A4	[110]
Ivabradine	Ivabradine	12	300 mg thrice daily for 14 days	SJW tablets	Open-label, two-period, non-randomized, phase I, pharmacokinetic study; ivabradine administration at baseline vs. at end of treatment with SJW	Decreased C_{max} by 51 % ($p < 0.01$) and AUC_{∞} by 61 % ($p < 0.01$) for ivabradine	Induction of CYP3A4	[105]
Mephenytoin	Mephenytoin	12	300 mg thrice daily for 14 days	Tablets containing 0.3 % hypericin and 4 % hyperforin	Two-phase, randomized, placebo-controlled crossover study; pretreatment with SJW or placebo vs. phenotyping at end of intake	Raised urinary 4′-hydroxymephenytoin excretion by 151.5 % ($p = 0.0156$)	Induction of CYP2C19	[93]
Midazolam	Midazolam	42	6 different concentrations of hyperforin for 14 days	Coated tablets with 300 mg of dried *Hypericum herba* containing 0.13–41.25 mg hyperforin, 1.08–4.86 mg hypericins and 17.92–80.64 mg flavonoids	Open-label, randomized, interaction study with six parallel SJW medication groups; phenotyping at baseline vs. at end of treatment with SJW	All SJW preparations tested resulted in a decrease in midazolam AUC. The extent of midazolam AUC decrease correlated significantly with increasing the HYF dose ($r = 0.765$, $p < 0.001$)	Induction of CYP3A4	[97]
	Midazolam	12	3 × 300 mg once daily for 2 days	Capsules containing 900 µg hypericin	Three-period, open-label, fixed schedule study; phenotyping at baseline vs. at end of treatment	No effect on midazolam pharmacokinetics	None, CYP3A4	[89]
	Midazolam	12	300 mg thrice daily for 14 days	Capsules containing 900 µg hypericin	Three-period, open-label, fixed schedule study; phenotyping at baseline vs. at end of treatment	> 50 % ($p < 0.05$) decrease in midazolam AUC_{oral} and C_{max}, a 21 % ($p < 0.05$) decrease in midazolam $AUC_{intravenous}$	Induction of CYP3A4	[89]
	Midazolam	12	300 mg thrice daily for 28 days	*Hypericum perforatum* standardized to 0.3 % hypericin	Open-label, randomized, phenotyping at baseline vs. end of each supplement phase	A 141 % ($p < 0.001$) increase in mean 1-hydroxymidazolam/midazolam serum ratio	Induction of CYP3A4	[27]

cont.

Table 1 *Continued*

Prescribed drug	Actually used probe drug for CYP isoform	Sample size	Dosage and duration of treatment	Preparation and content	Study design	Clinical result of interaction, magnitude of change in % of PK parameters (p value)	Possible mechanism, involved CYP	Ref.
	Midazolam	20	500 mg twice daily with low hyperforin for 14 days	SJW capsules containing 500 mg *Hyperici herba* powder	Open-label, one-sequence crossover study; phenotyping at baseline vs. at end of treatment with SJW	No effect on midazolam pharmacokinetics	None, CYP3A4	[98]
	Midazolam	12	300 mg thrice daily for 28 days	SJW extract	Oral contraceptive intake before (control) vs. cotreatment with SJW extract	Reduced oral $AUC_{(0-\infty)}$ by 35% ($p = 0.076$), reduced oral C_{max} by 16% ($p = 0.214$) and increased oral clearance of midazolam by 45% ($p = 0.007$)	Induction of CYP3A4	[99]
Norethindrone	Midazolam	12	300 mg thrice daily for 28 days	SJW extract	Oral contraceptive intake before (control) vs. cotreatment with SJW extract	Reduced $AUC_{(0-24)}$ by 12% ($p = 0.15$), reduced C_{max} by 7% ($p = 0.045$) and increased oral clearance of norethindrone by 14% ($p = 0.042$)	Induction of CYP3A4	[99]
	Norethindrone	16	300 mg thrice daily for 28 days	SJW extract	Placebo-controlled, single-blind sequential study; oral contraceptive intake before (control) vs. cotreatment with SJW extract	Reduced AUC of norethindrone by 14% ($p = 0.021$)	Induction of CYP3A4	[100]
Omeprazole	Omeprazole	12	300 mg thrice daily for 14 days	SJW extract tablets containing 0.3% total hypericin and 4% hyperforin	Two-phase, randomized, placebo-controlled crossover study; pretreatment with SJW or placebo vs. omeprazole intake at end of treatment	Increased C_{max} and $AUC_{(0-\infty)}$ of 5-hydroxyomeprazole by 38.1% ($p = 0.028$) and by 37.2% ($p = 0.005$); increased C_{max} and $AUC_{(0-\infty)}$ of omeprazole sulfone by 155.5% ($p = 0.001$) and by 158.7% ($p = 0.017$)	Induction of CYP2C19 and CYP3A4	[94]
Quazepam	Quazepam	13	300 mg thrice daily for 14 days	SJW caplets standardized to 0.3% hypericin	Randomized, double-blind, crossover study; pretreatment with SJW or placebo vs. quazepam intake at end of treatment	Reduced $AUC_{(0-48)}$ by 55% ($p < 0.05$) and C_{max} by 8.7% ($p < 0.05$)	Induction of CYP3A4	[107]
Tolbutamide	Tolbutamide	28	240 mg twice daily with low hyperforin for 10 days	Capsules containing 60 mg SJW extract, corresponding to 0.25 mg of total hypericins and 0.88 mg hyperforin	Double-blind, placebo-controlled, parallel-grouped study; phenotyping at baseline vs. at end of treatment with SJW or placebo	No effect on tolbutamide pharmacokinetics	None, CYP2C9	[96]
	Tolbutamide	12	3 × 300 mg once daily for 2 days	Capsules containing 900 µg hypericin	Three-period, open-label, fixed schedule study; phenotyping at baseline vs. at end of treatment	No effect on tolbutamide pharmacokinetics	None, CYP2C9	[89]
	Tolbutamide	12	300 mg thrice daily for 14 days	Capsules containing 900 µg hypericin	Three-period, open-label, fixed schedule study; phenotyping at baseline vs. at end of treatment	No effect on tolbutamide pharmacokinetics	None, CYP2C9	[89]
Rac-verapamil	*Rac*-verapamil	8	300 mg thrice daily for 14 days	SJW tablets containing 3% to 6% hyperforin	Phenotyping at baseline vs. at end of treatment	Decreased AUC by 78% ($p < 0.0001$) for R-verapamil and by 80% ($p < 0.0001$) for S-verapamil and decreased C_{max} by 76% ($p < 0.0001$) for R-verapamil and by 78% ($p < 0.0001$) for S-verapamil	Induction of CYP3A4	[106]

cont.

Table 1 *Continued*

Prescribed drug	Actually used probe drug for CYP isoform	Sample size	Dosage and duration of treatment	Preparation and content	Study design	Clinical result of interaction, magnitude of change in % of PK parameters (p value)	Possible mechanism, involved CYP	Ref.
Voriconazole	Voriconazole	16	300 mg thrice daily for 15 days	SJW extract	Open-label, controlled, fixed-dose schedule study; phenotyping at baseline vs. at end of treatment	Reduced $AUC_{(0-\infty)}$ by 59% ($p = 0.0004$) of voriconazole after 15 days	Induction of CYP2C19	[108]
Rac-warfarin	*Rac*-warfarin	12	1000 mg thrice daily for 14 days	Tablets containing standardized dry extract equivalent to 1 g *Hypericum perforatum*, 0.825 mg hypericin and 12.5 mg hyperforin	Open-label, three-treatment, three-period, three-sequence, randomized, crossover study; warfarin intake alone vs. after 14 days' pretreatment with St. John's wort	Reduced $AUC_{(0-\infty)}$ by 27% ($p < 0.05$) for S-warfarin and by 23% ($p < 0.05$) for R-warfarin, induced apparent clearance of both S- and R-warfarin by 29% ($p < 0.05$) and by 23% ($p < 0.05$), respectively	Induction of CYP1A2 and/or CYP3A4 and CYP2C9	[83]
Milk thistle								
Caffeine	Caffeine	12	175 mg twice daily for 28 days	Standardized to 80% silymarins	Open-label study randomized for supplementation sequence	No effect on caffeine pharmacokinetics	None, CYP1A2	[35]
Chlorzoxazone	Chlorzoxazone	12	175 mg twice daily for 28 days	Standardized to 80% silymarins	Open-label study randomized for supplementation sequence	No effect on chlorzoxazone pharmacokinetics	None, CYP2E1	[35]
Debrisoquine	Debrisoquine	12	175 mg twice daily for 28 days	Standardized to 80% silymarins	Open-label study randomized for supplementation sequence	No effect on debrisoquine pharmacokinetics	None, CYP2D6	[35]
	Debrisoquine	18	300 mg thrice daily for 14 days	Milk thistle extract standardized to 80% silymarin per capsule	Open-label study randomized for supplementation sequence	No effect on debrisoquine pharmacokinetics	None, CYP2D6	[36]
Irinotecan	Irinotecan	6	200 mg thrice daily for 14 days	Standardized capsules containing 200 mg milk thistle seed extract (containing 80% silymarin)	Irinotecan administration before vs. after treatment with milk thistle capsules	No effect on irinotecan clearance	None, CYP3A4	[114]
Midazolam	Midazolam	12	175 mg twice daily for 28 days	Standardized to 80% silymarins	Open-label study randomized for supplementation sequence	No effect on midazolam pharmacokinetics	None, CYP3A4	[35]
	Midazolam	19	300 mg thrice daily for 14 days	Milk thistle standardized to 80% silymarin	Open-label study; phenotyping at baseline vs. at the end of supplementation	No effect on midazolam pharmacokinetics	None, CYP3A4	[86]
Nifedipine	Nifedipine	16	2 × 140 mg twice a day for 1 day	Silymarin capsules containing 173.0–186.7 mg dry extract from milk thistle fruits [36–44:1], equivalent to 140 mg silymarin, calculated as silibinin	Open, within-subject crossover design with period-balanced randomly allocated sequences: nifedipine administration at baseline vs. at end of treatment	No effect on nifedipine pharmacokinetics	None, CYP3A4	[14]
Green tea								
Alprazolam	Alprazolam	11	211 mg green tea catechins for 14 days	Decaffeinated green tea capsules containing 2 mg catechin, 11 mg epicatechin, 18 mg epigallocatechin, 126 mg epigallocatechin gallate, 0.9 mg caffeine	Phenotyping at baseline vs. treatment with ginkgo	No effect on alprazolam pharmacokinetics	None, CYP3A4	[126]

cont.

Table 1 *Continued*

Prescribed drug	Actually used probe drug for CYP isoform	Sample size	Dosage and duration of treatment	Preparation and content	Study design	Clinical result of interaction, magnitude of change in % of PK parameters (p value)	Possible mechanism, involved CYP	Ref.
Buspirone	Buspirone	42	800 mg EGCG daily for 28 days	Polyphenon E (decaffeinated green tea extract) capsules with 200 mg EGCG/capsule	Cocktail study; phenotyping at baseline vs. at end of treatment	No effect on buspirone pharmacokinetics	None, CYP3A4	[127]
Caffeine	Caffeine	42	800 mg EGCG daily for 28 days	Polyphenon E	Cocktail study; phenotyping at baseline vs. at end of treatment	No effect on caffeine pharmacokinetics	None, CYP1A2	[127]
Dextromethorphan	Dextromethorphan	11	211 mg green tea catechins for 14 days	Decaffeinated green tea capsules containing 2 mg catechin, 11 mg epicatechin, 18 mg epigallocatechin, 126 mg epigallocatechin gallate, 0.9 mg caffeine	Phenotyping at baseline vs. treatment with ginkgo	No effect on dextromethorphan pharmacokinetics	None, CYP2D6	[126]
	Dextromethorphan	42	800 mg EGCG daily for 28 days	Polyphenon E	Cocktail study; phenotyping at baseline vs. at end of treatment	No effect on dextromethorphan pharmacokinetics	None, CYP2D6	[127]
Losartan	Losartan	42	800 mg EGCG daily for 28 days	Polyphenon E	Cocktail study; phenotyping at baseline vs. at end of treatment	No effect on losartan pharmacokinetics	None, CYP2C9	[127]
Valerian								
Alprazolam	Alprazolam	12	2 × 500 mg nightly for 14 days	Tablets containing 500 mg dry valerian root extract with 5.51 mg valerenic acid	Open-label, fixed treatment order, crossover study; phenotyping at baseline vs. pretreatment with valerian extract	No effect on alprazolam pharmacokinetics	None, CYP3A4	[135]
Caffeine	Caffeine	12	125 mg thrice daily for 28 days	Valerian root extract (no standardization claim)	Open-label study; phenotyping at baseline vs. at the end of supplementation	No effect on caffeine pharmacokinetics	None, CYP1A2	[85]
Chlorzoxazone	Chlorzoxazone	12	125 mg thrice daily for 28 days	Valerian root extract (no standardization claim)	Open-label study; phenotyping at baseline vs. at the end of supplementation	No effect on chlorzoxazone pharmacokinetics	None, CYP2E1	[85]
Debrisoquine	Debrisoquine	12	125 mg thrice daily for 28 days	Valerian root extract (no standardization claim)	Open-label study; phenotyping at baseline vs. at the end of supplementation	No effect on debrisoquine pharmacokinetics	None, CYP2D6	[85]
Dextromethorphan	Dextromethorphan	12	2 × 500 mg nightly for 14 days	Tablets containing 500 mg dry valerian root extract with 5.51 mg valerenic acid	Open-label, fixed treatment order, crossover study; phenotyping at baseline vs. pretreatment with valerian extract	No effect on dextromethorphan pharmacokinetics	None, CYP2D6	[135]
Midazolam	Midazolam	12	125 mg thrice daily for 28 days	Valerian root extract (no standardization claim)	Open-label study; phenotyping at baseline vs. at the end of supplementation	No effect on midazolam pharmacokinetics	None, CYP3A4	[85]
Kava								
Caffeine	Caffeine	12	1000 mg twice daily for 28 days	Kava kava root extract (no standardization claim)	Open-label study; phenotyping at baseline vs. at the end of supplementation	No effect on caffeine pharmacokinetics	None, CYP1A2	[85]

cont.

Table 1 *Continued*

Prescribed drug	Actually used probe drug for CYP isoform	Sample size	Dosage and duration of treatment	Preparation and content	Study design	Clinical result of interaction, magnitude of change in % of PK parameters (p value)	Possible mechanism, involved CYP	Ref.
Chlorzoxazone		12	1000 mg twice daily for 28 days	Kava kava root extract (no standardization claim)	Open-label study; phenotyping at baseline vs. at the end of supplementation	Reduced 6-hydroxychlorzoxazone/chlorzoxazone serum ratios by ~ 40% ($p = 0.009$)	Inhibition of CYP2E1	[85]
Debrisoquine	Debrisoquine	12	1000 mg twice daily for 28 days	Kava kava root extract (no standardization claim)	Open-label study; phenotyping at baseline vs. at the end of supplementation	No effect on debrisoquine pharmacokinetics	None, CYP2D6	[85]
	Debrisoquine	18	136.3 mg thrice daily for 14 days	Kava kava rhizome extract standardized to 75 mg kavalactones per capsule	Open-label study randomized for supplementation sequence	No effect on debrisoquine pharmacokinetics	None, CYP2D6	[36]
Midazolam	Midazolam	12	1000 mg twice daily for 28 days	Kava kava root extract (no standardization claim)	Open-label study; phenotyping at baseline vs. at the end of supplementation	No effect on midazolam pharmacokinetics	None, CYP3A4	[85]
	Midazolam	16	1227 mg thrice daily for 14 days	Kava kava rhizome extract standardized to 75 mg kavalactones per capsule	Open-label study; phenotyping at baseline vs. at the end of supplementation	No effect on midazolam pharmacokinetics	None, CYP3A4	[139]
Goldenseal								
Caffeine	Caffeine	12	900 mg thrice daily for 28 days	Goldenseal root extract (no standardization claim)	Open-label study; phenotyping at baseline vs. at the end of supplementation	No effect on caffeine pharmacokinetics	None, CYP1A2	[85]
Chlorzoxazone	Chlorzoxazone	12	900 mg thrice daily for 28 days	Goldenseal root extract (no standardization claim)	Open-label study; phenotyping at baseline vs. at the end of supplementation	No effect on chlorzoxazone pharmacokinetics	None, CYP2E1	[85]
Debrisoquine	Debrisoquine	12	900 mg thrice daily for 28 days	Goldenseal root extract (no standardization claim)	Open-label study; phenotyping at baseline vs. at the end of supplementation	Reduced debrisoquine urinary recovery ratios by 40% ($p < 0.05$)	Inhibition of CYP2D6	[85]
	Debrisoquine	18	1070 mg thrice daily for 14 days	Root extract standardized to 24.1 mg isoquinoline alkaloids per capsule	Open-label study randomized for supplementation sequence	Reductions in debrisoquine urinary recovery ratios by 47% ($p < 0.05$)	Inhibition of CYP2D6	[36]
Midazolam	Midazolam	12	900 mg thrice daily for 28 days	Goldenseal root extract (no standardization claim)	Open-label study; phenotyping at baseline vs. at the end of supplementation	Reduced 1-hydroxymidazolam/midazolam serum ratios by 40% ($p < 0.05$)	Inhibition of CYP3A4/5	[85]
	Midazolam	16	1323 mg thrice daily for 14 days	Goldenseal root extract standardized to 24.1 mg isoquinoline alkaloids	Open-label study; phenotyping at baseline vs. at the end of supplementation	Increase ($p < 0.05$) in midazolam $AUC_{(0-\infty)}$ by 62%, elimination half-life by 57%, and C_{max} by 41%	Inhibition of CYP3A	[139]
Ginger								
Rac-warfarin	*Rac*-warfarin	12	3 × 400 mg thrice daily for 7 days	Capsules containing extract equivalent to 0.4 g of ginger rhizome powder	Randomized, open-label, three-treatment, three-period, three-sequence, crossover study; phenotyping alone vs. after 7 days pretreatment with ginkgo	No effect on S- and R-warfarin pharmacokinetics	None, CYP2C9	[49]

cont.

Table 1 *Continued*

Prescribed drug	Actually used probe drug for CYP isoform	Sample size	Dosage and duration of treatment	Preparation and content	Study design	Clinical result of interaction, magnitude of change in % of PK parameters (p value)	Possible mechanism, involved CYP	Ref.
Angelica tenuissima								
Caffeine	Caffeine	8	2000 mg thrice daily for 13 days	Encapsuled aqueous extract equivalent to 2 g of herb	Open-label, parallel group study; phenotyping at baseline vs. at end of treatment	No effect on caffeine pharmacokinetics	None, CYP1A2	[143]
Chlorzoxazone	Chlorzoxazone	8	2000 mg thrice daily for 13 days	Encapsuled aqueous extract equivalent to 2 g of herb	Open-label, parallel group study; phenotyping at baseline vs. at end of treatment	No effect on caffeine pharmacokinetics	None, CYP2E1	[143]
Dextromethorphan	Dextromethorphan	8	2000 mg thrice daily for 13 days	Encapsuled aqueous extract equivalent to 2 g of herb	Open-label, parallel group study; phenotyping at baseline vs. at end of treatment	No effect on caffeine pharmacokinetics	None, CYP2D6	[143]
Losartan	Losartan	8	2000 mg thrice daily for 13 days	Encapsuled aqueous extract equivalent to 2 g of herb	Open-label, parallel group study; phenotyping at baseline vs. at end of treatment	No effect on caffeine pharmacokinetics	None, CYP2C9	[143]
Midazolam	Midazolam	8	2000 mg thrice daily for 13 days	Encapsuled aqueous extract equivalent to 2 g of herb	Open-label, parallel group study; phenotyping at baseline vs. at end of treatment	No effect on caffeine pharmacokinetics	None, CYP3A4	[143]
Omeprazole	Omeprazole	8	2000 mg thrice daily for 13 days	Encapsuled aqueous extract equivalent to 2 g of herb	Open-label, parallel group study; phenotyping at baseline vs. at end of treatment	No effect on caffeine pharmacokinetics	None, CYP2C19	[143]
Angelica dahurica								
Caffeine	Caffeine	8	2000 mg thrice daily for 13 days	Encapsuled aqueous extract equivalent to 2 g of herb	Open-label, parallel group study; phenotyping at baseline vs. at end of treatment	Decreased metabolic ratio of caffeine to 10% of baseline activity ($p < 0.001$)	Inhibition of CYP1A2	[143]
Chlorzoxazone	Chlorzoxazone	8	2000 mg thrice daily for 13 days	Encapsuled aqueous extract equivalent to 2 g of herb	Open-label, parallel group study; phenotyping at baseline vs. at end of treatment	No effect on chlorzoxazone metabolic ratio	None, CYP2E1	[143]
Dextromethorphan	Dextromethorphan	8	2000 mg thrice daily for 13 days	Encapsuled aqueous extract equivalent to 2 g of herb	Open-label, parallel group study; phenotyping at baseline vs. at end of treatment	Slightly increase in dextromethorphan metabolic ratio	None, CYP2D6	[143]
Losartan	Losartan	8	2000 mg thrice daily for 13 days	Encapsuled aqueous extract equivalent to 2 g of herb	Open-label, parallel group study; phenotyping at baseline vs. at end of treatment	No effect on losartan metabolic ratio	None, CYP2C9	[143]
Midazolam	Midazolam	8	2000 mg thrice daily for 13 days	Encapsuled aqueous extract equivalent to 2 g of herb	Open-label, parallel group study; phenotyping at baseline vs. at end of treatment	No changes in plasma concentration of midazolam	None, CYP3A4	[143]
Omeprazole	Omeprazole	8	2000 mg thrice daily for 13 days	Encapsuled aqueous extract equivalent to 2 g of herb	Open-label, parallel group study; phenotyping at baseline vs. at end of treatment	No effect on omeprazole metabolic ratio	None, CYP2C19	[143]
Scutellaria baicalensis								
Bupropion	Bupropion	17	500 mg thrice daily for 14 days	Baicalin capsules	Two-phase, two-treatment, sequential study; bupropion intake at baseline vs. at end of treatment	Increased hydroxybupropion $AUC_{(0-\infty)}$ by 87% ($p < 0.01$) and C_{max} by 73% ($p < 0.01$)	Induction of CYP2B6	[144]

cont.

Table 1 *Continued*

Prescribed drug	Actually used probe drug for CYP isoform	Sample size	Dosage and duration of treatment	Preparation and content	Study design	Clinical result of interaction, magnitude of change in % of PK parameters (p value)	Possible mechanism, involved CYP	Ref.
Caffeine	Caffeine	8	2000 mg thrice daily for 13 days	Encapsuled aqueous extract eq. to 2 g of herb	Open-label, parallel group study; phenotyping at baseline vs. at end of treatment	No effect on caffeine metabolic ratio	None, CYP1A2	[143]
Chlorzoxazone	Chlorzoxazone	8	2000 mg thrice daily for 13 days	Encapsuled aqueous extract eq. to 2 g of herb	Open-label, parallel group study; phenotyping at baseline vs. at end of treatment	A 1.42-fold ($p = 0.039$) increase in metabolic ratio of chlorzoxazone after multiple administration	Induction of CYP2E1	[143]
Dextromethorphan	Dextromethorphan	8	2000 mg thrice daily for 13 days	Encapsuled aqueous extract eq. to 2 g of herb	Open-label, parallel group study; phenotyping at baseline vs. at end of treatment	No effect on dextromethorphan metabolic ratio	None, CYP2D6	[143]
Losartan	Losartan	8	2000 mg thrice daily for 13 days	Encapsuled aqueous extract eq. to 2 g of herb	Open-label, parallel group study; phenotyping at baseline vs. at end of treatment	Decreased metabolic ratio of losartan to 71 % ($p = 0.024$) of baseline value	Inhibition of CYP2C9	[143]
Midazolam	Midazolam	8	2000 mg thrice daily for 13 days	Encapsuled aqueous extract eq. to 2 g of herb	Open-label, parallel group study; phenotyping at baseline vs. at end of treatment	No changes in plasma concentration of midazolam	None, CYP3A4	[143]
Omeprazole	Omeprazole	8	2000 mg thrice daily for 13 days	Encapsuled aqueous extract eq. to 2 g of herb	Open-label, parallel group study; phenotyping at baseline vs. at end of treatment	No effect on omeprazole metabolic ratio	None, CYP2C19	[143]
Grapes/red wine								
Buspirone	Buspirone	42	2 × 500 mg once daily for 28 days	Caplets containing 500 mg resveratrol plus inert pharmaceutical excipients	Phenotyping at baseline vs. at end of treatment	A 33 % ($p = 0.01$) increase in buspirone AUC	Inhibition of CYP3A4	[146]
Caffeine	Caffeine	42	2 × 500 mg once daily for 28 days	Caplets containing 500 mg resveratrol plus inert pharmaceutical excipients	Phenotyping at baseline vs. at end of treatment	A 16 % ($p = 0.0005$) decrease in caffeine/paraxanthine ratio	Induction of CYP1A2	[146]
Dextromethorphan	Dextromethorphan	42	2 × 500 mg once daily for 28 days	Caplets containing 500 mg resveratrol plus inert pharmaceutical excipients	Phenotyping at baseline vs. at end of treatment	A 70 % ($p = 0.01$) increase in post-intervention dextromethorphan/dextrorphan molar ratio	Inhibition of CYP2D6	[146]
Losartan	Losartan	42	2 × 500 mg once daily for 28 days	Caplets containing 500 mg resveratrol plus inert pharmaceutical excipients	Phenotyping at baseline vs. at end of treatment	A 171 % ($p < 0.0001$) increase in CYP2C9 phenotypic index	Inhibition of CYP2C9	[146]
Curcuma								
Caffeine	Caffeine	16	2 × 500 mg once daily for 14 days	Curcumin capsules	A two-phase, crossover design; caffeine administration at baseline vs. at end of treatment	Decreased plasma $AUC_{(0-\infty)}$ of paraxanthine by 46.6 % ($p = 0.032$) and decreased urinary excretion by 36.4 % ($p < 0.000$), increased urinary excretion of 1,7-dimethylurate by 77.3 % ($p = 0.036$)	Inhibition of CYP1A2 and induction of CYP2A6	[147]

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