A regulatory science viewpoint on botanical–drug interactions

Manuela Grimstein*, Shiew-Mei Huang
Office of Clinical Pharmacology, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, MD, USA

1. Introduction

Botanical product sales and usage have increased steadily over the years driven in part by the perceived safety of natural products [1,2]. Consumers often use botanicals to promote health or to manage chronic diseases supplementing prescription medications. The most recent report from the National Health Interview Survey reveals that approximately 20% of Americans acknowledge using botanical products and 20–30% of these individuals indicated concurrent use of botanicals with prescription medications [3]. Furthermore, most patients, nearly 70%, often neglected to disclose such use to their health care providers [3]. These practices raise concerns for increased likelihood of an adverse botanical–drug interaction (BDI), and highlight the importance of improving knowledge and patient-provider communication about botanicals and risks of BDIs.

Common situations handled in clinical practice such as polytherapy, aging, chronic liver or kidney diseases, long-term drug regimens, and specific patient populations, such as those with cancer, HIV/AIDS or organ transplant are at increased risk for BDIs.

Indeed, systematic reviews of published clinical evidence identified the prescription drug classes with higher potential for interaction with botanical products. Those drug classes included antiretroviral agents, oncology drugs, immunosuppressants,
and drugs affecting the central nervous system and cardiovascular system [4–6]. Many of those drugs have a narrow therapeutic index. Clinically significant botanical–drug interactions may lead to treatment failure, as exemplified by the case-reports of St. John's wort and cyclosporine [7], and Ginkgo and efavirenz [8]. In fact, botanical products containing St. John's wort and Ginkgo had the greatest number of documented interactions with prescribed drugs as reported by a systematic literature review [4].

This report presents an overview of metabolism- and transporter-based PK interactions for the most frequently used botanical products in the US. The regulatory scientific perspectives on botanical products, including the methodologies used to evaluate potential botanical–drug interactions and labeling implications, are also discussed.

2. Mechanisms of pharmacokinetic-based botanical–drug interactions

Pharmacokinetic-based drug interactions can manifest because of changes in the absorption, distribution, metabolism, and/or excretion (ADME) pathways of the victim drug in the presence of a perpetrator. Changes in drug absorption may be mediated through modulation of intestinal uptake and efflux transporters and intestinal metabolizing enzymes; while changes in metabolism/excretion occur through inhibition/induction of metabolizing enzymes and/or modulation of hepatic/renal uptake and efflux transporters. Uptake transporters may regulate drug absorption, distribution, thus modulation of these transporters may affect plasma and tissue exposure [9].

2.1. Modulation of metabolizing enzymes

Drug-mediated inhibition of drug metabolizing enzymes is the most common mechanism underlying PK interactions [10]. Enzyme inhibition can be classified into reversible (via competitive and noncompetitive modes) and time-dependent inhibition (TDI). Unlike reversible inhibition, TDI can persist even after withdrawal of the perpetrator since recovery of enzyme activity requires de novo protein synthesis [11]. Inhibition of metabolic enzymes can manifest clinically as an increase in the systemic exposure of the victim drug due to decreased metabolic clearance or increased bioavailability [12].

The human cytochrome P450 (CYP) family of enzymes, including CYP1A2, CYP2B6, CYP2C8/9/19, CYP2D6, and CYP3A4/5 is involved in the oxidative metabolism (phase I) of most drugs used in clinical practice [10,13]. The US FDA guidance [14] recommends that these seven CYP isoforms be investigated for their contribution in the metabolism of a new drug entity, and for potential inhibition in a reversible and time-dependent manner by the entity.

Grape-fruit juice (GFJ), a popular breakfast juice in the US, is a classic example of enzyme-mediated botanical food–drug interaction.

2.1.1. GFJ: In vitro studies

Inhibition of CYP3A activity, both reversibly and in a time-dependent manner, has been demonstrated in vitro for GFJ furanocumarsins (6′,7′-dihydroxybergamottin, bergamottin and paradisin). The in vitro inhibitory constants (IC50) were in the nanomolar to micromolar range [15–17].

2.1.2. GFJ: Clinical studies

An in vivo investigation reported that enterocyte CYP3A protein expression was decreased by 47% and 62% following single and repeated (6 days) intake of GFJ. In contrast, GFJ intake did not alter intestinal CYP3A mRNA expression and liver CYP3A activity [18]. Clinical evidence of CYP3A inhibition by GFJ is provided by several prospective interaction studies. In healthy volunteers, once daily GFJ intake (200 mL/day for 3 days) simultaneous with simvastatin increased the drug AUC by 260% [19]; while GFJ intake three-times per day (900 mL/day for 3 days) 1 h before simvastatin dosing resulted in a 670% increase in the drug AUC [20]. Similarly, GFJ intake (200–600 mL single-strength, qd or bid for 2–3 days) greatly increased (85%–300% increase in AUC) exposure to nisoldipine, saquinavir, and cyclosporine [21].

These examples highlight that significant GFJ effect may occur with orally administered CYP3A substrate drugs that have low oral bioavailability due to extensive pre-systemic metabolism by intestinal CYP3A. The lower the bioavailability, the higher the likelihood of a significant interaction due to the potential higher increases in peak plasma concentration. Additional examples of GFJ-mediated interactions and drugs that are likely to interact with GFJ are listed in Table 1 and reviewed and published elsewhere [21–23]. The impact of GFJ-drug interactions on drug labeling is listed in Table 2.

Goldenseal (Hydrastis canadensis), used as an antimicrobial and for gastrointestinal disorders [24], is among the top-selling botanical products in the US [1].

2.1.3. Goldenseal: In vitro studies

In vitro investigations demonstrated the inhibitory potential of goldenseal extract and its individual isoquinoline alkaloids, berberine and hydrastine, towards CYP3A4 and CYP2D6 isoforms [25,26]. Hydrastine seems to be a more potent inhibitor of CYP3A4 (IC50 = 25 μM) than berberine (IC50 = 400 μM) [26].

2.1.4. Goldenseal: Clinical studies

Prospective clinical BDIs studies corroborated the in vitro predictions. Concomitant administration of goldenseal extract inhibited the metabolism of CYP2D6 and CYP3A index substrate drugs in healthy subjects [27–29]. For example, goldenseal supplementation [1.3 g root extract (77 mg berberine and 132 mg hydrastine), for 14 days] markedly affected midazolam pharmacokinetics (62% increase in AUC, 41% increase in Cmax and 36% reduction in oral clearance) [28]. In a controlled interaction trial in renal transplant recipients, co-administration of a goldenseal product (as berberine 0.2 g tid for 3 months) resulted in clinically relevant increase in cyclosporine (CYP3A4/P-gp substrate) steady-state blood concentrations (Caverage and Ctrough increased 35% and 88%, respectively), which may warrant reduction of cyclosporine dose [30].

Characterization of hydrastine and berberine disposition following a single dose of goldenseal extract showed that both alkaloids were readily absorbed and extensive cleared by phase I and II metabolism [31,32]. Furthermore, these studies
| Botanical [known enzyme/transporter modulator] | Metabolic enzymes and transporters affected | Effected on drug concentration (Drug example)<sup>b</sup> |
|-----------------------------------------------|---------------------------------------------|-------------------------------------------------|
| Ginkgo (*Ginkgo biloba*) [Flavonoids (e.g., quercetin, kaempferol) and terpenoids (ginkgolides A and B, and bilobalide)] | CYP1A2 (→), CYP2D6 (→), CYP2E1 (→), CYP2C19 (generally →, possible †), CYP2C9 (generally →, possible †), CYP3A4 (generally →, possible †), UGT1A1 (in vitro), P-gp (generally →, possible †), OATP (generally →, possible †) | Decrease plasma level of CYP substrates (midazolam [81], omeprazole [88], tolbutamide [87]) Increase plasma level of P-gp substrate (talinolol [82,83]) |
| Goldenseal (*Hydrastis canadensis*) [Alkaloids berberine and hydrastine] | CYP3A4 (↓) | Increase plasma level (midazolam [28,29], debrisoquine [27], cyclosporine [30,132]) Increase plasma level of CYP3A substrates or decrease plasma level of OATP substrate |
| Grapefruit juice (*Citrus x arantium*) [Flavonoids naringin/naringenin and quercetin, and furanocoumarins bergamottin, 6′,7′-dihydroxybergamottin] | Enteric CYP3A4 (↓), OATP1A2 (↓), OATP2B1(↓) | Drug category: Antihistamines (fexofenadine, terfenadine), anti-infectives (erythromycin, halofantrine, praziquantel), antiretrovirals (saquinavir), cardiovascular drugs (aliskiren, azelnidipine, celiprolol, felodipine, manidipine, nicardipine, nifedipine, nimodipine, nisoldipine, talinolol), central nervous system agents (alfentanil, buspirone, carbamazepine, diazepam, fluvoxamine, methadone, midazolam, phenytoin, sertraline, triazolam), immunosuppressants (cyclosporine, tacrolimus), statins (atorvastatin, lovastatin, simvastatin), oncology agents (etoposide) [21,23,89] Increase plasma level (losartan [121] and talinolol [133]) |
| Apple juice (*Malus pumila*) [Flavonoids hesperetin and phloridzin] | OATP1A2 (↓), OATP2B1(↓) | Decrease plasma level (Aliskiren, atenolol, celiprolol, ciprofloxacin, fexofenadine, and talinolol [21,89]) Increase plasma level |
| Orange juice (*Citrus x sinensis*) [Flavonoid hesperidin] | CYP2C9 (↓), CYP3A4 (→, possible †) | Increase plasma level |
| Milk thistle (*Silybum marianum*) [Flavonolignans silybin] | CYP1A2 (↓), CYP2D6 (↓) | Increase plasma level of CYP3A/P-gp substrate? (Metronidazole [134]) Decrease plasma level |
| St. John’s wort (*Hypericum perforatum*) [Chlorogluconol hyperforin and flavonoids (e.g., quercetin)] | CYP1A2 (↓), CYP2B6 (↓), CYP2E1(↓), CYP3A4 (↓), CYP2C9 (↓), CYP2C19 (↓), P-gp (↓) | Decrease plasma level of CYP3A/P-gp substrate? (Metronidazole [134]) Decrease plasma level |

Note: Updated from [125], Table 1.

<sup>a</sup> The enzymes and/or transporters modulating effect ([↑] increase, (↓) decrease, (→) no effect) are based on data from human studies.

<sup>b</sup> Drugs with published clinical drug-botanical interaction based on pharmacokinetic mechanism.

<sup>c</sup> References refer to comprehensive reviews of botanical drug interactions.
Table 2 – Selected examples of drug interaction information in the USPI of prescription drug products, Drug Facts of OTC products and Labels of St. John’s wort products (Note that this is not a complete list).

| Product name (Manufacturer) | Label section: Label statement |
|----------------------------|--------------------------------|
| **INSPIRA®** eplerenone tablets (Pfizer) [135] | Clinical Pharmacology-Pharmacokinetics-Drug Interactions
St. John’s wort (a CYP3A4 inducer) caused a small (about 30%) decrease in eplerenone AUC. Grapefruit juice caused a 25% increase in exposure |
| **SPRYCEL®** dasatinib tablet (Bristol-Myers Squibb) [136] | Dosage and Administration- Dose Modification
St. John’s wort may decrease dasatinib plasma concentrations unpredictably and should be avoided. Grapefruit juice may also increase plasma concentrations of dasatinib and should be avoided. |
| **NEORAL®** cyclosporine capsules, oral solution, USP (Norvatis) [137] | Drug Interactions
There have been reports of a serious drug interaction between cyclosporine and the herbal dietary supplement, St. John’s Wort. This interaction has been reported to produce a marked reduction in the blood concentrations of cyclosporine, resulting in subtherapeutic levels, rejection of transplanted organs, and graft loss. Grapefruit and grapefruit juice affect metabolism, increasing blood concentrations of cyclosporine, thus should be avoided |
| **PROCARDIA®** nifedipine capsules (Pfizer) [138] | Precautions-Drug Interactions-Other Interactions
Grapefruit Juice: Co-administration of nifedipine with grapefruit juice resulted in approximately a doubling in nifedipine AUC and Cmax with no change in half-life. The increased plasma concentrations most likely result from inhibition of CYP 3A4 related first-pass metabolism. Avoid ingestion of grapefruit and grapefruit juice while taking nifedipine. |
| **ZOCOR®** simvastatin tablets (Merck) [139] | Warnings and Precautions-Drug Interactions
The risk of myopathy and rhabdomyolysis is increased by high levels of statin activity in plasma. Simvastatin is metabolized by the cytochrome P450 isof orm 3A4. Certain drugs which inhibit this metabolic pathway can raise the plasma levels of simvastatin and may increase the risk of myopathy. These include itraconazole, ... or grapefruit juice. Combination of these drugs with simvastatin is contraindicated. |
| **ALLEGRA ALLERGY®** Fexofenadine HCl tablets (Sanofi Aventis) [140] | Warnings
When using this product do not take with fruit juices |
| St. John’s Wort Extract- Standardized Herbs 0.3% hypericin (Vitamin Shoppe®) [141] | Warning
Do not use St. John’s wort if you are pregnant, nursing or taking anti-depressants, HIV protease inhibitors (such as Indinavir) or drugs to prevent organ transplant rejection (such as Cyclosporine). Consult your physician before use if you are taking oral contraceptives, anticoagulant medication (such as Warfarin), selective serotonin reuptake inhibitors, or any other medication. |
| St. John’s Wort 300 mg Standardized Extract (Sundown® Naturals) [142] | Warning
Not intended for use by pregnant or nursing women. If you are taking any medications, or have any medical condition, consult your doctor before use. |
| Concentrated St. John’s Wort (Nature’s Sunshine®) [143] | Warning
Do not use St John’s Wort while taking any prescription drugs without advice of your prescribing physician. Do not use with prescription antidepressants, contraceptives, immunosuppressants, anticoagulants, Digoxin, blood thinners or medications for HIV, epilepsy, or cancer. |

Note: Updated from [125] Supplemental Tables 1S and 2S.

demonstrated that ingestion of commercially available extracts resulted in plasma concentrations comparable to levels determined in vitro for CYP inhibition.

BDIs may also occur because of increased expression of a protein involved in drug metabolism and/or transport, defined as induction. The most common mechanism of induction is a ligand-dependent binding and activation of nuclear receptors that function as gene transcription factors, such as AHR (aryl hydrocarbon receptor), CAR (constitutive androstane receptor) and PXR (pregnane X receptor) [33]. Clinically, enzyme induction can manifest as a decrease in the systemic exposure of the victim drug due to increased metabolic clearance or decreased bioavailability [12].

**St. John’s wort (Hypericum perforatum)** extracts are widely used for their antidepressant activity [34].

2.1.5. St. John’s wort: In vitro studies

Hyperforin, a prenylated phloroglucinol and principal active constituent of St. John’s wort, is the most potent agonist for human PXR with a binding affinity (Ki) of 27 nM [35]. The reported steady-state plasma concentrations of hyperforin (around 100–500 nM) achieved following administration of certain St. John’s wort products (300 mg–900 mg/day, containing 5% hyperforin) were around 10-fold higher than the in vitro inhibitory value [36–38]. As such, metabolizing enzymes (e.g., CYP3A) and ABC efflux transporters (e.g. P-gp)
regulated by PXR have the potential to be affected by St. John’s wort [39,40].

2.1.6. St. John’s wort: Clinical studies

Extensive clinical data support the evidence of St. John’s wort as an inducer of CYP subfamilies 2C and 3A [41–43]. Induction of intestinal and hepatic CYP3A4 by long-term St. John’s wort use (treatment periods of at least 10 days) resulted in noticeably decreased oral bioavailability (AUC and Cmax), and increased systemic clearance of concomitant drugs that are mainly, or partly, metabolized by CYP3A4, such as nevirapine [44] and verapamil [45]. In renal transplant recipients, St. John’s wort supplementation (600 mg extract qd for 14 days) markedly decreased the exposure to cyclosporine (AUC, Cmax and Ctrough reduced by 46%, 42% and 41%, respectively) [46]. Cyclosporine dose adjustment was required to maintain therapeutic levels. Following St. John’s wort administration (tid for 15 days), the exposure of repeated dosing of oxycodone (CYP3A and CYP2D6 substrate) decreased (AUC reduced 50%) in healthy volunteers. The self-reported drug effect of oxycodone also decreased significantly, demonstrating that this interaction may have the potential for clinical relevance during management of chronic pain [47]. Clinically significant St. John’s wort interaction with drug substrates of CYP2C9 [48,49] and CYP2C19 [50] via induction is also reported. St. John’s drug interaction liability has been scrutinized in recent reviews [41–43]. Table 1 lists the drug classes in which St. John’s wort use results in relevant clinical interaction.

Compared to CYP enzymes, evidence of the modulation of phase II enzymes by botanicals is limited. Phase II conjugation reactions may or may not be preceded by phase I reactions. Modulation of phase II enzymes may be of clinical significance for drugs, such as morphine and mycophenolic acid, whose conjugation reactions represent the primary metabolic pathway. Phase II conjugation reactions are catalyzed by the UDP glucuronosyl-transferase (UGT) and sulfotransferase (GST) superfamilies. The human UGT superfamily is comprised of 2 families, UGT1 and UGT2, and 3 subfamilies, UGT1A, 2A, and 2B [51].

Ginkgo (Gingko biloba L.) leaf extract is a world-wide popular botanical used for treatment of circulatory disorders [52] and improvement of cognitive function [53].

2.1.7. Ginkgo: In vitro studies

The penchant of ginkgo and its main flavonoid glycosides, quercetine, and kaempferol, to modulate UGT enzymes has been examined in vitro. Ginkgo extract and its flavonoids inhibited glucuronidation of mycophenolic acid (UGT1A7, 1A8, 1A9, and 1A10 substrate) with IC50 values of 19.1 and 5.8 μM for quercetin, and 23 μM and 7.7 μM for kaempferol, in human liver microsomes and human intestinal microsomes, respectively [54]. These in vitro inhibitory values are at least ten-fold above the expected maximum plasma concentrations for flavonoids [55]; nonetheless, micromolar levels of such perpetrators may be achieved in the intestine.

2.1.8. Ginkgo: Clinical studies

The potential for UGT-mediated interaction of ginkgo with drugs with high first-pass extraction ratio has not been investigated in clinical setting.

Milk thistle (Silybum marianum) extract is commonly used for its claimed hepatoprotective properties [56,57]. Extracts are rich in active flavonolignans, primarily silybin, silydianin, iso-silybin, and silychristine, collectively known as silymarin. Silybin is composed of a 1:1 mixture of silybin A and silybin B.

2.1.9. Milk thistle: In vitro studies

In vitro data suggested that milk thistle may inhibit UGT enzymes [58,59]. Silybin was shown to be a potent inhibitor of UGT1A1 (IC50 = 1.4 μM) and other UGTs with less potency (IC50 range = 28–79 μM) [58,60]. Silybin also inhibited CYP3A4 (Ki range = 5–160 μM) [58] and CYP2C9 (IC50 range = 8.2–18 μM) [61] activity in human liver microsomes.

2.1.10. Milk thistle: Clinical studies

Several prospective clinical studies reported minimal enzyme-based drug interaction liability with milk thistle [62,63]. For example, co-administration of milk thistle extract (80% silymarin, 200 mg tid, for 4 or 12 days) had no significant effect on the PK of intravenous irinotecan (CYP3A4/UGT1A1 substrate) in cancer patients [64]. In controlled clinical trials in healthy volunteers, milk thistle supplementation did not significantly (no statistically different from control groups) affect the exposure to the CYP3A4 substrates indinavir [65], midazolam [66], and nifedipine [67]. These finding are consistent with the low systemic levels of milk thistle flavonolignans achieved in vivo (Cmax of silybin ranged between 0.0249 and 0.257 μM) [64,68] which would be insufficient to modulate hepatic UGTs and CYPs. Following a single 600 mg dose of milk thistle extract, maximum plasma concentration for unconjugated silybin did not exceed 0.04 μM [68]. Nonetheless, intestinal concentrations of flavonolignans are likely to be higher than the observed in vitro constant values. For example, average silybin concentration of 140 μM was obtained in colorectal tissue specimens from cancer patients following high-dose silybin administration (1400 mg) [69]. It should be noted that some formulations of milk thistle products may have enhanced bioavailability (three to five-fold) compared to these conventional extract formulations [70]. These products may produce higher intestinal and systemic levels of the perpetrator constituents sufficient for inhibition of UGT and CYP activity. Therefore, further research is warranted on the effect of milk thistle on drugs cleared primarily by first pass glucuronidation, and on whether products with enhanced bioavailability may pose a risk for interactions.

2.2. Modulation of transporters

Similar to drug-metabolizing enzymes, drug-transport proteins are susceptible to decreased activity (via competitive and noncompetitive reversible inhibition) or increased expression (via induction). The ATP-binding cassette (ABC) superfamily of transporters, including ABCB1 (P-glycoprotein (P-gp), MDR1), multidrug resistance-associated protein (MRPs) and breast cancer resistance protein (BCRP) can affect the efflux of their substrates; while SLC (solute carrier) superfamily transporters, such as organic anion transporters (OATs), organic cation transporters (OCTs) and organic anion transporting polypeptides (OATPs), mainly mediate uptake (Fig. 1). These transporters are involved in oral absorption and renal and
The hepatobiliary disposition of a drug. Clinically, modulation of transporters can manifest as either increased or decreased systemic exposure depending on the site of transporter expression (i.e., apical/canalicular or basolateral/sinusoidal) and direction of flux (i.e., efflux or uptake) [9].

As a potent PXR activator, hyperforin in St. John’s wort products is implicated in the induction of P-gp [39,43].

2.2.1. St. John’s wort: Clinical studies
A 1.4-fold increase in intestinal P-gp expression was observed after a 14-day administration of St. John’s wort in healthy volunteers [71]. Accordingly, this mechanism supports the statistically significant reduction in the exposure of the P-gp substrates digoxin (25% and 35% decrease in AUC and Cmax, respectively) [72], talinolol (31% decrease in AUC) [73], and amitriptyline (22% reduction in AUC) [74] after multiple-dose supplementation of St. John’s wort extract (900 mg/day for 12–16 days). The magnitude of these effects is comparable to that observed with rifampin, a well-recognized inducer of P-gp [72]. Clinical findings suggest that the hyperforin content determines the magnitude of St John’s wort interactions, since extracts with low hyperforin content had a weak or no effect on both CYP and P-gp substrate drugs [43,75].

Ginkgo extract has also shown to be able to modulate the activity of ABC and OATPs transporters in vitro.

2.2.2. Ginkgo: In vitro studies
In Caco-2 cells, Ginkgo extract inhibited digoxin (P-gp substrate) efflux with an IC50 of 24 μg/mL [76]. The flavonoids quercetin and kaempferol inhibited OATPs 1A2 and 2B1 in transfected HEK293 cells [77]. Cell-based reporter assays showed that the flavonoids were activators of PXR, CAR and AHR [78], and the ginkolides A and B were activators of PXR at a concentration of 4 μg/mL [79].

2.2.3. Ginkgo: Clinical studies
Clinically, Ginkgo supplementation (80 mg tid for 7 days, 120 mg bid for 28 days, single 120 mg dose, respectively) did not significantly change the PK of digoxin (P-gp substrate) [80], fexofenadine (P-gp, MRP and OATP substrate) [81] and talinolol (P-gp, MRP2 and OATP substrate) [82]. To date, only two controlled trials in healthy volunteers reported increases in exposure to tanilolol (Cmax 22–25% and AUC 34–36%) caused by long-term high-dose Ginkgo extract intake (120 mg tid for 14 days) [82,83].

Several prospective clinical studies were conducted, using a variety of drugs including specific index substrates, to assess Ginkgo potential as a modulator of various CYP isoforms (e.g., CYP2C9, CYP2C19, CYP2D6, CYP3A4) and transporters (e.g., P-gp, OATPs) [84,85]. Most studies evaluated doses of 240 mg/day or lower for a maximum of 90 days, and
most utilized products formulated with the EGb761 extract (standardized to contain 22–27% flavonoid glycosides and 5–7% terpene lactones consisting of 3% ginkgolides A, B, C, and 3% bilobalide). Most studies showed no significant effect or a modest inhibitory effect [85,86]; while results implicating potential induction of CYP3A4 [81], CYP2C9 [87] and CYP2C19 [88] were seen in three studies, following ginkgo supplementation (240 mg/day of EGb761 for 28 days, 360 mg/day of EGb761 for 28 days, and 280 mg/day for 12 days of ginkgo extract, respectively). These latter results may be due to the higher dose used in some of these studies, leading to higher exposure of perpetrator constituents. The potential for PK-based interactions of ginkgo has been reviewed elsewhere [85,86]. Table 1 lists the drugs in which Ginkgo supplementation resulted in significant interaction.

Fruit juices, such as grapefruit, orange and apple, are also implicated in drug interactions mediated via inhibition of drug transporters.

2.2.4. Fruit juices: In vitro studies
In Caco-2 cells, GFJ and its flavonoids decreased the efflux of several P-gp substrates (cyclosporine, digoxin, fexofenadine, paclitaxel, saquinivir, talinolol, and vinblastine) [21,89]. In transfected HeLa cells, the flavonoids in grapefruit (naringin) and orange juice (hesperidin) showed inhibitory activity towards OATP1A2-mediated uptake of fexofenadine with IC50 values of 3.6 μM and 2.7 μM, respectively [90]. Major flavonoids present in grapefruit, orange and apple juices also demonstrated inhibitory effect on OATP2B1 uptake of estrone-3-sulfate with IC50 values ranging from 1.3 to 49.2 μM [91].

2.2.5. Fruit juices: Clinical studies
Clinically, GFJ intake did not significantly change the bioavailability of digoxin, a P-gp substrate with high oral bioavailability [92]. In controlled studies in healthy volunteers, co-administration of GFJ with fexofenadine (P-gp, MRP and OATP1A2/2B1 substrate) resulted in a marked reduction in drug exposure (43%–67% reduction in AUC) or minimal effect [89]. The variability of GFJ effect observed across studies may be attributed to different GFJ dose, including volume of ingestion and levels of perpetrator constituent(s), and timing of intake [93].

Intake of large volumes of orange juice or apple juice (1200 mL as 300 mL first dose, followed by 150 mL every 0.5 h for 3 h) greatly decreased the exposure to fexofenadine (AUC values were reduced up to 85%) [94,95]. Co-intake of GFJ, orange or apple juices (300–1200 mL) also markedly reduced the systemic exposure (AUC decreased 30%–85% of other OATP substrates such as talinolol, cefipram, atenolol and aliskiren [89,96]. Again, the effect was dependent on juice volume and variable among drugs.

As with the beta-blockers (atenolol, cefipram, talinolol), interactions of those fruit juices with substrate drugs for OATP1A2 that may have the potential for clinically relevant consequences were investigated in controlled clinical studies. GFJ intake (600 mL as 200 mL tid for 2 days) had a minor effect on levothyroxine (AUC decreased <13%) [97]; likewise, orange juice administration (355 mL) had a small impact on the exposure to ciprofloxacin and levofloxacin (AUC decreased up to 22%) [98,99].

No significant effect was also reported for other OATP substrate drugs. For example, GFJ intake (500 mL) did not affect the PK of pravastatin (OATP1B1 substrate, minimal metabolic clearance) [100]; while GTJ consumption (500 mL) resulted in a small increase (13% increase in AUC) in the oral bioavailability of pitavastatin (OATP1B1 substrate, minimal metabolic clearance) [101]. The exposure to glibenclamide (OATP2B1 substrate, extensively metabolized by CYP2C9) was also unaffected by GFJ intake (600 mL) [102].

Overall, the clinical findings suggest that fruit juices may have a greater potential for interaction with OATP1A2 drug substrates that undergoes minimal metabolic clearance.

Green-tea (Camellia sinensis) is one of the most widely consumed herbal beverages and has become the raw material for extracts used in various beverages, food products, and dietary supplements [21].

2.2.6. Green-tea: In vitro studies
In vitro studies [103–105] suggest that green tea extract and its major catechin, (−)-epigallocatechin-3-gallate, may potentially inhibit the activity of several drug transporters, including OATP1A2 (IC50 = 55 μM), OATP1B1 (IC50 = 8 μM) and OATP2B1 (IC50 = 101 μM), respectively [105].

2.2.7. Green-tea: Clinical studies
In a clinical study in healthy volunteers, both the Cmax and AUC of nadolol (OATP1A2 substrate, minimal metabolic clearance) were decreased by 85% following a 14-day pretreatment period with 700 mL/day of a green tea product. This finding suggested that inhibition of OATP1A2-mediated uptake may be a possible mechanism for the observed interaction [106]. It should be noted that the catechin level of the investigated green tea product was two-to-five-fold higher (1.54 mg/mL) than other typical green tea products (0.25–0.51 mg/mL) [103].

Further studies reflecting usual dietary fruit juice/green tea intake patterns are warranted to better assess the transported–based interaction liability associated with consumption of these beverages.

The reader is referred to a recent review of transporter-mediated botanical–drug interactions with cardiovascular drugs for further information [107].

3. Investigating botanical–drug interaction liability
In vitro systems are fundamental tools used to identify the contribution of specific phase I/II enzymes and transporters involved in drug disposition, whether a drug is a modulator (inhibitor and/or inducer) of a metabolic enzyme or transporter, and ultimately, to assess the potential for drug interactions. In principle, the guidelines proposed for an investigational drug's modulating effect [14,108–110] can be extended to a botanical drug to facilitate the development of a “new” botanical product and prospective evaluation of BDIs. To investigate hepatic metabolism-inhibition based interactions, various in vitro screening systems are commonly used: subcellular human liver tissue fractions such as reconstituted microsomal systems, recombinant CYP enzymes, and
primary human hepatocytes [111]. In vitro systems to investigate transporter-mediated interaction include membrane vesicle system, polarized cell-based, bidirectional assay for efflux transporters, or cell-based assay for uptake transporters [112]. Selection of the in vitro system should be based on the purpose of the study and the questions to be addressed [14].

There are challenges in the use of in vitro methodologies to the investigation of the inhibitory/inducible potential of botanical constituents. These limitations, elaborated in a recent review [113], include limited availability of reference standards (especially metabolites), and uncertainty regarding physiologically relevant concentrations of the constituents (free versus conjugates and other metabolites). Nonetheless, in vitro screening studies are valuable for initial evaluations and identification of botanicals with a potential for interaction in vivo, largely due to the high throughput nature of these methods and the lower costs relative to in vivo studies.

Kinetic data from in vitro studies could then be applied in quantitative models to predict the potential of the botanical product to affect the drug exposure and determine whether clinical DDI studies are necessary. These models include basic, static mechanistic and dynamic mechanistic models; the latter includes physiologically-based pharmacokinetic (PBPK). PBPK models are the most inclusive and require, besides in vitro drug interaction data, sufficient physicochemical and clinical pharmacology data (e.g., ADME and PK) of both victim drug and perpetrator, including individual constituents of botanicals that modulate enzymes and/or transporters. Hence, a well-characterized botanical product with an identification of the potential constituents that may act as enzyme and/or transporter modulator is essential to develop this quantitative framework. It is recognized that the complex and variable chemical composition inherent to botanical products, combined with the scarcity of reliable human pharmacokinetic data for such constituents, may hinder the application of this tool. While the utility of PBPK modeling for predicting the likelihood and magnitude of drug–drug interactions has been demonstrated [114]; the application of this approach in the botanical–drug interaction arena is still limited. However, this approach could potentially aid in the identification of the perpetrator constituents, evaluation of dispositional characteristics of those constituents, and description of the interactions mechanistically; advancing the efforts to predict clinical interactions from preclinical data [115].

The described examples in the review paper [115–118] highlight the use and performance of the PBPK approach in the scope of BDI. PBPK simulations accurately predicted the absence of significant clinical interaction between silybin (160 mg/day for 14 days) and the index substrates warfarin (CYP2C9) and midazolam (CYP3A). The developed PBPK model also demonstrated that the extensive intestinal and hepatic conjugation of silybin flavonolignans (silybin A and silybin B) followed by rapid clearance would likely limit silybin interaction potential to first-pass elimination of sensitive CYP substrates [116]. Subsequently, silybin PBPK model was used to predict the interaction liability between silybin and raloxifene (a UGT 1A8 and 1A10 substrate) via inhibition of intestinal glucuronidation. The modeling approach provided mechanistic understanding of the interaction and was used to inform clinical study design [115]. PBPK was also used to investigate the impact of intestinal CYP3A inhibition by the GFJ constituent 6’,7’ dihydroxybergamottin on the first-pass elimination of midazolam and simvastatin [117].

An interesting streamlined approach using in-vitro-in-silico tools was proposed to prioritize GFJ individual constituents that may act as inhibitors of intestinal OATP for further investigation. The IC50 for representative GFJ constituents from three distinct chemical classes were determined using OATP2B1-transfected cell system and the substrate estrone 3-sulfate. GFJ intestinal absorption data (unbound concentration with enterocytes) was obtained from PBPK simulations based on physiochemical properties. The ratios of unbound concentration to IC50 for each constituent were then calculated to evaluate the drug interaction liability of GFJ constituents [118].

Well-designed clinical studies using specific CYP and P-gp index substrates [108] in healthy volunteers or patients may generate the most clinically relevant interaction data. Interaction studies using a CYP cocktail of index substrates or using phenotypic measures of CYP activity have been explored to screen botanical products for their drug interaction liability [29,119]. Dedicated interaction studies may also be designed to investigate the interaction potential between a botanical product and prescription drugs likely to be co-administered. For example, three controlled studies (multiple-dose, 2-way crossover) were conducted in healthy subjects to evaluate the interaction between DW1029M (a standardized botanical extract of Morus alba L. root bark and Puerariae radix), investigated for the treatment of diabetic nephropathy, and the antidiabetic drugs metformin and linagliptin, and the antihypertensive losartan. No significant changes on the PK of metformin, losartan and linagliptin were observed because of co-administration of DW1029W [120].

Genotyping information has been incorporated in drug interaction study designs to explore the interplay of genetic polymorphisms and combined use of botanical products. Pharmacogenomic studies in humans may help identify interactions that may be more pronounced or only occur in specific population. For example, a prospective clinical BDI study showed that the magnitude of interaction of milk thistle extract (420 mg/day of silymarin, for 14 days) and losartan (CYP2C9/CYP3A substrate) was dependent upon CYP2C9 genotype [121]. In CYP2C9 wild-type subjects, losartan metabolism to its active metabolite E–3174 was reduced resulting in a two-fold increase in losartan exposure (AUC and Cmax); whereas losartan exposure was not significantly affected in subjects with CYP2C9*1/*3 genotype [121]. Likewise, pharmacogenomic studies have demonstrated that Ginkgo and St. John’s wort modulates CYP2C19 expression and activity in a genotype-dependent manner with no alteration in poor metabolizers [88,122,123]. Another study investigated the effect of PXR haplotype on St John’s wort-induced CYP3A4 activity using nifedipine (CYP3A4 index substrate). Following St John’s wort supplementation (300 mg tid, for 14 days), subjects carrying H1/H1 haplotype showed greater inducible transcriptional activity to CYP3A4 relative to subjects with H1/H2 or H2/H2 pairing. The increase on the AUC of nifedipine metabolite, dehydroxynedipine, was significantly higher (107%) in H1/H1 compared to the two other haplotype pairs (around 20–30%) [124].
Botanical products are usually comprised of multiple constituents that vary in composition, both between manufacturers and between batches from the same manufacturer [125]. This inherent variability of botanical products hinders the extrapolation of scientific findings between studies. At a minimum, BDI investigations should be conducted with a botanical product unequivocally identified. For freshly prepared material the botanical scientific name, parts used, origin of growth, methods for extraction/preparation should be noted; for commercially available products the brand name, manufacturer, lot number, ingredients, preparation directions, and manufacturing process should be stated [126]. If possible, chemical and biologic standardization of a botanical product [127] including identification and quantification of the purported perpetrator constituents should be done to ensure reproducibility of activity within studies. Quantification of the systemic exposure of the perpetrator constituent(s), whenever possible, would be of great value and could contribute to the current limit database.

Animal models (e.g., normal, transgenic, or humanized animals) may also provide valuable information regarding the potential for botanical–drug interactions. However, the predictive value of animal data alone for clinical pharmacokinetic prediction models may significantly decrease drug systemic exposure and effectiveness. Representative examples of drugs with labeling warnings about St. John’s wort dietary supplements increase by 7.9% in 2013, marking a decade of rising sales: turmeric supplements climb to top ranking in natural channel. Herbal Gram 2014;103:52–6. Representative examples of drugs with labeling warnings about St. John’s wort use are listed in Table 2. Some St. John’s wort dietary supplements also carry warning language about potential drug interactions (Table 2). If a drug has a low oral bioavailability because of extensive first-pass metabolism by intestinal CYP3A, warnings regarding concomitant ingestion of GFJ may be added to the label, depending on the drug’s exposure–response relationship. For example, USPIs for simvastatin and dasatinib carry warning language about grapefruit juice use (Table 2).

5. Conclusions and future perspective

Timely identification of drugs that may interact with botanical’s active constituents and the mechanism involved is essential for better clinical risk assessment. Guidelines and tools used to evaluate conventional drug–drug interactions can be applied to botanical–drug interactions. A streamlined approach of integrating in vitro interaction data with clinical exposure of the perpetrator constituent into quantitative prediction models may help prioritize clinical studies. Meaningful botanical–drug interaction assessment should consider inherent quality issues of botanical products, patient factors, and clinical experimental designs. While changes in victim drug PK can occur because of metabolic or transported–mediated interaction with botanicals, the clinical relevance of such interactions are dependent on factors such magnitude of effect and drug exposure–response relationship for efficacy and safety.

Regulations on prescription drug labeling content and format were set in place to highlight key drug interactions. As a risk management strategy, new drugs that are sensitive CYP3A and/or P-gp substrates may incorporate labeling language regarding concomitant use with botanicals such as St. John’s wort and GFJ. With continued improvement in our understanding of the mechanism of enzyme- and transporters-mediated botanical interactions, the risks associated with such can be better predicted, evaluated and managed, to reduce the propensity of clinically significant adverse interactions.

Disclaimer

The findings and conclusions in this work have not been formally disseminated by the United States Food and Drug Administration (FDA) and should not be construed to represent any agency determination or policy. The content of this article does not reflect the views or policies of FDA or its staff. No official support or endorsement by the FDA is intended or should be inferred.

Declaration of interests

The authors declare no conflicts of interest.

REFERENCES

[1] Lindstrom A, Ooyen C, Lynch ME, Blumenthal M, Kawa K. Sales of herbal dietary supplements increase by 7.9% in 2013, marking a decade of rising sales: turmeric supplements climb to top ranking in natural channel. Herbal Gram 2014;103:52–6.
[2] Blendon RJ, DesRoches CM, Benson JM, Brodie M, Altman DE. Americans’ views on the use and regulation of dietary supplements. Arch Intern Med 2001;161:805–10.
[3] Clarke TC, Black LI, Stussman BJ, Barnes PM, Nahin RL. Trends in the use of complementary health approaches
among adults: United States, 2002–2012. Natl Health Stat Rep 2015;79:1–16.

[4] Tsai HH, Lin HW, Simon Pickard A, Tsai HY, Mahady GB. Evaluation of documented drug interactions and contraindications associated with herbs and dietary supplements: a systematic literature review. Int J Clin Pract 2012;66:1056–78.

[5] Haeffeli WE, Carls A. Drug interactions with phytotherapeutics in oncology. Exp Opin Drug Metab Toxicol 2014;10:359–77.

[6] Fasinu PS, Gurlay BJ, Walker LA. Clinically relevant pharmacokinetic herb-drug interactions in antiretroviral therapy. Curr Drug Metabol 2006;17:52–64.

[7] Ruschitzka F, Heath TG. Predicting in vivo drug interactions. Eur J Clin Pharmacol 1977;11:131–9.

[8] Naccarato M, Young D, Gough K. A potential drug-herb interaction between Ginkgo biloba and Efavirenz. J Int Assoc Phys AIDS Care (Chic) 2012;11:98–100.

[9] Han HK. Role of transporters in drug interactions. Arch Pharm Res 2011;34:1865–77.

[10] Wienkers LC, Heath TG. Inhibition of cytochrome P450 by herbal products. Acta Pharmacol Sin 2004;25:129–36.

[11] Grimm SW, Einolf HJ, Hall SD, He K, Lim HK, Ling KH, et al. Herb-drug interaction studies. J Am Coll Nutr 1997;16:341–44.

[12] Brantley SJ, Argikar AA, Lin YS, Nagar S, Paine MF. Herb-drug interaction: challenges and opportunities for improved predictions. Drug Metab Dispos 2014;42:301–17.

[13] Paine MF, Hart HL, Ludington SS, Haining RL, Rettie AE, Zeldin DC. The human intestinal cytochrome P450 pie. Drug Metab Dispos 2006;34:880–6.

[14] US Food and Drug Administration. In vitro metabolism- and transporter-mediated drug-drug interaction studies. Guidance for industry. Draft 2017:1–47. Available at: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM581965.pdf. [Accessed 18 January 2018].

[15] Guo LQ, Yamazoe Y. Inhibition of cytochrome P450 by furanocoumarins. Acta Pharmocol Sin 2004;25:129–36.

[16] Schmiedlin-Ren P, Edwards DJ, Fitzsimmons ME, He K, Zeldin DC. The human intestinal cytochrome P450 pie. Drug Metab Dispos 2006;34:880–6.

[17] Paine MF, Widmer WW, Hart HL. A furanocoumarin-free grapefruit juice establishes furanocoumarins as the mediators of the grapefruit juice-felodipine interaction. Am J Clin Nutr 2006;85:1097–105.

[18] Lown KS, Bailey DG, Fontana RJ, Janardan SK, Adair CH, Lilja JJ, Neuvonen M, Neuvonen PJ. Effects of regular consumption of grapefruit juice on the pharmacokinetics of simvastatin. Br J Clin Pharmacol 2004;58:56–60.

[19] Park SJ, Yeo CW, Shim EJ, Kim H, Liu KH, Shin JG, et al. Pomegranate juice does not affect the disposition of simvastatin in healthy subjects. Eur J Drug Metab Pharmacokinet 2016;41:339–44.

[20] An G, Mukker JK, Derendorf H, Frye RF. Enzyme and transporter-mediated beverage–drug interactions: an update on fruit juices and green tea. J Clin Pharmacol 2015;55:1313–31.

[21] Hanley MJ, Cancalon P, Widmer WW, Greenblatt D. The effect of grapefruit on drug disposition. Expert Opin Drug Metabol Toxicol 2011;7:267–86.

[22] Bailey DG, Dresser G, Arnold MO. Grapefruit-herb interactions: forbidden fruit or avoidable consequences. CMAJ 2013;185:309–16.

[23] Chen C, Yu Z, Li Y, Fichna J, Storr M. Effects of berberine in the gastrointestinal tract - a review of actions and therapeutic implications. Am J Chin Med 2014;42:1053–70.

[24] Hanley MJ, Cancalon P, Widmer WW, Greenblatt D. The effect of grapefruit on drug disposition. Expert Opin Drug Metabol Toxicol 2011;7:267–86.

[25] Hanley MJ, Cancalon P, Widmer WW, Greenblatt D. The effect of grapefruit on drug disposition. Expert Opin Drug Metabol Toxicol 2011;7:267–86.
Hogle BC, Guan X, Folan MM, Xie W. PXR as a mediator of herb–drug interaction. JFDA 2017. https://doi.org/10.1016/j.jfda.2017.11.007.

Zhou S-F, Lai X. An update on clinical drug interactions with the herbal antidepressant St John’s wort. Curr Drug Metabol 2008;9:394–409.

Russo E, Scicchitano F, Whalley BJ, Mazzitello C, Ciriaco M, Esposito S, et al. Hypericum perforatum: pharmacokinetic, mechanism of action, tolerability, and clinical drug–drug interactions. Phytother Res 2014;28:643–55.

Borrelli F, Izzo AA. Herb-drug interactions with St John’s wort (Hypericum perforatum): an update on clinical observations. AAPS J 2009;11:710–27.

de Maat MM, Hoetelmans RM, Math t RA, van Gorp EC, Meenhorst PL, Mulder JW, et al. Drug interaction between St John’s wort and nevirapine. AIDS 2001;15:420–1.

Tannergren C, Engman H, Knutson L, Hedeland M, Bondesson U, Lennernas H. St John’s wort decreases the bioavailability of R- and S-verapamil through induction of the first-pass metabolism. Clin Pharmacol Ther 2004;75:298–309.

Bauer S, Stormer E, Johne A, Kruger H, Budde K, Neuvonen PJ, et al. Alterations in cyclosporin A pharmacokinetics and metabolism during treatment with St John’s wort in renal transplant patients. Br J Clin Pharmacol 2003;55:203–11.

Nieminen TH, Hagelberg NM, Saari TL, Neuvonen MJ, Laine K, Neuvonen PJ, et al. St John’s wort greatly reduces the concentrations of oral oxycodone. Eur J Pain 2010;14:854–9.

Jiang X, Williams KM, Laiu WS, Ammit AJ, Roufogalis BD, Duke CC, et al. Effect of St John’s wort and ginseng on the pharmacokinetics and pharmacodynamics of warfarin in healthy subjects. Br J Pharmacol 2004;145:592–9.

Xu H, Williams KM, Laiu WS, Murray M, Day RO, Mclachlan AJ. Effects of St John’s wort and CYP2C9 genotype on the pharmacokinetics and pharmacodynamics of gliclazide. Br J Pharmacol 2008;153:1579–86.

Wang LS, Zhou G, Zhu B, Wu J, Wang JG, Abd El-Aty AM, et al. St John’s wort induces both cytochrome P450 3A4-catalyzed sulfoxidation and 2C19-dependent hydroxylation of omeprazole. Clin Pharmacol Ther 2004;75:191–7.

Guillemette C, Levesque E, Harvey M, Bellemare J, Menard V. UGT genomic diversity: beyond gene duplication. Drug Metab Dispos 2004;32:587–94.

Moon YJ, Wang L, DiCenzo R. Morris ME Quercetin pharmacokinetics in humans. Biopharm Drug Dispos 2008;29:205–17.

de Avelar CR, Pereira EM, de Farias Costa PR, de Jesus RP, de Oliveira LPM. Effect of silymarin on biochemical indicators in patients with liver disease: systematic review with meta-analysis. World J Gastroenterol 2017;23:5004–17.

Abenavoli L, Capasso R, Nappi R, Capasso F. Milk thistle in liver diseases: past, present, future. Phytother Res 2010;24:1423–32.

Sridar C, Goosen TC, Kent UM, Williams JA, Hollenberg PF. Silybin inactivates cytochromes P450 3A4 and 2C9 and inhibits major hepatic glucuronosyltransferases. Drug Metab Dispos 2004;32:587–94.

Mohamed ME, Tseng T, Frye RF. Inhibitory effects of commonly used herbal extracts on UGT1A1 enzyme activity. Xenobiotica 2010;40:663–9.

Gufford BT, Chen G, Vergara AG, Lazarus P, Oberlies NH. Milk thistle constituents inhibit raloxifene intestinal glucuronidation: a potential clinically relevant natural product–drug interaction. Drug Metab Dispos 2015;43:1353–9.

Brantley SJ, Oberlies NH, Kroll DJ, Paine MF. Two flavonolignans from milk thistle (Silybum marianum) inhibit CYP2C9-mediated warfarin metabolism at clinically achievable concentrations. J Pharmacol Exp Ther 2010;332:1081–7.

Gurley BJ, Fischer EK, Gardner Z. Pharmacokinetic herb-drug interactions (part 2): drug interactions involving popular botanical dietary supplements and their clinical relevance. Planta Med 2012;78:1490–514.

Wu JW, Lin LC, Tsai TH. Drug–drug interactions of silymarin on the perspective of pharmacokinetics. J Ethnopharmacol 2009;121:85–93.

Yuan Q, Wang CW, Shi J, Lin ZX. Effects of Ginkgo biloba on the pharmacokinetics and pharmacodynamics of irinotecan. Clin Cancer Res 2005;11:7800–6.

Mills E, Wilson K, Clarke M, Foster B, Walker S, Rachlis B, et al. Milk thistle and indinavir: a randomized controlled pharmacokinetics study and meta analysis. Eur J Clin Pharmacol 2005;61:1–7.

Gurley B, Hubbard MA, Williams DK, Thaden J, Tong Y, Gentry WB, et al. Assessing the clinical significance of botanical supplementation on human cytochrome P450 3A activity: comparison of a milk thistle and black cohosh product to rifampin and clarithromycin. J Clin Pharmacol 2006;46:201–13.

Fuhr U, Beckmann-Knopp S, Jetter A, Lick U, Mengs U. The effect of silymarin on oral nifedipine pharmacokinetics. Planta Med 2007;73:1429–35.

Wen Z, Dumas TE, Schriever SJ, Hawke RL, Fried MW, Smith PC. Pharmacokinetics and metabolic profile of free, conjugated, and total silymarin flavonolignans in human plasma after oral administration of milk thistle extract. Drug Metab Dispos 2008;36:65–72.

Hoh C, Boocock D, Marczylo T, Singh R, Berry DP, Dennison AR, et al. Pilot study of oral silybinin, a putative chemopreventive agent, in colorectal cancer patients: silibinin levels in plasma, colorectum, and liver and their pharmacodynamic consequences. Clin Pharm Res 2016;12;2944–50.

Flagg TW, Godeč, Gustafson D, van Bokhoven A, Tao Y, Wilson S, et al. A study of high-dose oral silybin-phytoside followed by prostatectomy in patients with localized prostate cancer. Prostate 2010;70:848–55.

Durr D, Stieger B, Kullak-Ublick GA, Rentsch KM, Steiner C, Meier PJ, et al. St John’s wort induces intestinal P-glycoprotein. Drug Metab Dispos 2008;36:65–72.

Steinert HC, Meier PJ, et al. St John’s wort, Echinacea, clarithromycin, and rifampin on St John’s wort reduces the oral bioavailability of talinolol. Clin Pharmacol Ther 2007;81:669–78.
[74] Johne A, Schmider J, Brockmöller J, Stadelmann AM, Stormer E, Bauer S, et al. Decreased plasma levels of amitriptyline and its metabolites on comedication with an extract from St. John’s wort (Hypericum perforatum). J Clin Psychopharmacol 2002;22:46–54.

[75] Mueller SC, Majcher-Peszynska J, Mundkowski RG, Uheleke B, Klammt S, Sievers H, et al. No clinically relevant CYP3A4 induction after St. John’s wort with low hyperforin content in healthy volunteers. Eur J Clin Pharmacol 2009;65:81–7.

[76] Hellum BH, Nilsen OG. In vitro inhibition of CYP3A4 metabolism and Pglycoprotein-mediated transport by trade herbal products. Basic Clin Pharmacol Toxicol 2008;102:466–75.

[77] Fuchikami H, Satoh H, Tsujimoto M, Ohdo S, Ohtani H, Sawada Y. Effects of herbal extracts on the function of human organic anion-transporting polypeptide OATP-B. Drug Metab Dispos 2006;34:577–82.

[78] Li L, Stanton JD, Tolson AH, Luo Y, Wang H. Bioactive terpenoids and flavonoids from Ginkgo biloba extract induce the expression of hepatic drug-metabolizing enzymes through pregnane X receptor, constitutive androstane receptor, and aryl hydrocarbon receptor-mediated pathways. Pharm Res 2009;26:872–82.

[79] Satoh H, Hiura Y, Mochizuki K, Hamada M, Shimizu M. Activation of pregnane X receptor and induction of MDR1 by dietary phytochemicals. J Agric Food Chem 2008;56:5366–73.

[80] Mauro VF, Mauro LS, Kleshinski JF, Khuder SA, Wang Y, Erhardt PW. Impact of Ginkgo biloba on the pharmacokinetics of digoxin. Am J Ther 2003;10:247–51.

[81] Robertson SM, Davey RT, Voell J, Formentini E, Alfaro RM, Pennak SR. Effect of Ginkgo biloba extract on lopinavir, midazolam and fexofenadine pharmacokinetics in healthy subjects. Curr Med Res Opin 2008;24:591–9.

[82] Fan L, Mao XQ, Tao GY, Wang G, Jiang F, Chen Y, et al. Effect of Schisandra chinensis extract and Ginkgo biloba extract on the pharmacokinetics of talinolol in healthy volunteers. Xenobiotica 2009;39:249–54.

[83] Fan L, Tao GY, Wang G, Chen Y, Zhang W, He YJ, et al. Effects of Ginkgo biloba extract ingestion on the pharmacokinetics of talinolol in healthy Chinese volunteers. Ann Pharmacother 2009;43:944–9.

[84] Canter PH, Ernst E. Ginkgo biloba is not a smart drug: an updated systematic review of randomized clinical trials testing the nootropic effects of G. biloba extracts in healthy people. Hum Psychopharmacol 2007;22:265–78.

[85] Unger M. Pharmacokinetic drug interactions involving Ginkgo biloba. Drug Metab Rev 2013;45:353–85.

[86] Abad MJ, Bedoya LM, Bermejo P. An update on drug interactions with the herbal medicine Ginkgo biloba. Curr Drug Metabol 2010;11:171–81.

[87] Uchida S, Yamada H, Li XD, Maruyama S, Ohmori Y, Oki T, et al. Effects of Ginkgo biloba extract on pharmacokinetics and pharmacodynamics of tobutamide and midazolam in healthy volunteers. J Clin Pharmacol 2006;46:1290–8.

[88] Yin QQ, Tomlinson B, Wayne MM, Chow AH, Chow MS. Pharmacogenetics and herb-drug interactions: experience with Ginkgo biloba and omeprazole. Pharmacogenetics 2004;14:841–50.

[89] Bailey DG. Fruit juice inhibition of uptake transport: a new type of food–drug interaction. Br J Clin Pharmacol 2010;70:645–55.

[90] Bailey DG, Dresser GK, Leake BF, Kim RB. Naringin is a major and selective clinical inhibitor of organic anion transporting polypeptide 1A2 (OATP1A2) in grapefruit juice. Clin Pharmacol Ther 2007;81:495–502.

[91] Shirasaka Y, Shichiri M, Mori T, Nakanishi T, Tamai I. Major active components in grapefruit, orange, and apple juices responsible for OATP2B1-mediated drug interactions. J Pharm Sci 2010;102:280–8.

[92] Parker RB, Yates CR, Soberman JE, Laizure SC. Effects of grapefruit juice on intestinal P-glycoprotein: evaluation using digoxin in humans. Pharmacotherapy 2003;8:979–87.

[93] Yu J, Zhou T, Tay-Sontheimer J, Levy RH, Ragueneu-Majlessi I. Intestinal drug interactions mediated by OATPs: a systematic review of preclinical and clinical findings. J Pharm Sci 2017;106:2312–25.

[94] Dresser GK, Bailey DG, Leake BF, Schwarz UJ, Dawson PA. Fruit juices inhibit organic anion transporting polypeptide-mediated drug uptake to decrease the oral availability of fexofenadine. Clin Pharmacol Ther 2002;71:11–20.

[95] Imanaga J, Kotegawa T, Imai H. The effects of the SLCO2B1 c.1457C > T polymorphism and apple juice on the pharmacokinetics of fexofenadine and midazolam in humans. Pharmacogenet Genomics 2011;21:84–93.

[96] Tapaninen T, Neuvonen PJ, Niemi M. Orange and apple juice greatly reduce the plasma concentrations of the OATP2B1 substrate aliskiren. Br J Clin Pharmacol 2011;71:718–26.

[97] Liija J, Laitinen K, Neuvonen PJ. Effects of grapefruit juice on the absorption of levotyroxine. Br J Clin Pharmacol 2005;60:337–41.

[98] Wallace AW, Victory JM, Amsden GW. Lack of bioequivalence when levofloxacin and calcium-fortified orange juice are coadministered to healthy volunteers. J Clin Pharmacol 2003;43:539–44.

[99] Neuhoefel AL, Wilton JH, Victory JM, Heijmanowski LG, Amsden GW. Lack of bioequivalence of ciprofloxacin when administered with calcium-fortified orange juice: a new twist on an old interaction. J Clin Pharmacol 2002;42:461–6.

[100] Fukazawa I, Uchida N, Uchida E, Yasuhara H. Effects of grapefruit juice on pharmacokinetics of atorvastatin and pravastatin in Japanese. Br J Clin Pharmacol 2004;57:446–55.

[101] Ando H, Tsuruoka S, Yanagihara H, Sugimoto K, Miyata M, Yamazoe Y, et al. Effects of grapefruit juice on the pharmacokinetics of pitavastatin and atorvastatin. Br J Clin Pharmacol 2005;60:494–7.

[102] Liija J, Niemi M, Fredriksson H, Neuvonen PJ. Effects of clarithromycin and grapefruit juice on the pharmacokinetics of glibenclamide. Br J Clin Pharmacol 2007;63:732–40.

[103] Albassam AA, Markowitz JS. An appraisal of drug–drug interactions with Green tea (Camellia sinensis). Planta Med 2017;83:496–508.

[104] Knoop J, Misaka S, Singer K, Hoier E, Muller F, Glaeser H, et al. Inhibitory effects of green tea and (−)-epigallocatechin gallate on transport by OATP1B1, OATP1B3, OCT1, OCT2, MATE1, MATE2-K and P-glycoprotein. PLoS One 2015;10, e0139370.

[105] Roth M, Timmermann BN, Hagenbuch B. Interactions of green tea catechins with organic anion-transporting polypeptides. Drug Metab Dispos 2011;39:920–6.

[106] Misaka S, Yatabe J, Muller F, Takano K, Kawabe K, Glaeser H, et al. Green tea ingestion greatly reduces plasma concentrations of nadolol in healthy subjects. Clin Pharmacol Ther 2014;95:432–8.

[107] Zha W. Transporter-mediated natural product-drug interactions for the treatment of cardiovascular diseases. JFDA 2017. https://doi.org/10.1016/j.jfda.2017.11.008.

[108] US Food and Drug Administration. Clinical drug interaction studies - study design, data analysis, and clinical implications guidance for industry. Draft 2017:1–32. Available at: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf. [Accessed 18 January 2018].
Han Y, Zhao D, Zhang L, Abernethy DR, Reki D, Reynolds KS, et al. In vitro-in vivo extrapolation of metabolism and transporter-mediated drug-drug interactions overview of basic prediction methods. J Pharm Sci 2017;106:2209–13.

Reki D, Reynolds KS, Zhao D, Zhang L, Yoshida K, Sachar M, et al. Clinical drug-drug interaction evaluations to inform drug use and enable drug access. J Pharm Sci 2017;106:2214–8.

Bjornsson TD, Callaghan JT, Einolf HJ, Fischer V, Gan L, Grimm S, et al. The conduct of in vitro and in vivo drug-drug interaction studies: a pharmaceutical research and manufacturers of America (PhRMA) perspective. Drug Metab Dispos 2003;31:815–32.

Jin H, Di L. Permeability—in vitro assays for assessing drug transporter activity. Curr Drug Metabol 2008;9:911–20.

Markowitz JS, Zhu H-J. Limitations of in vitro assessments of the drug interaction potential of botanical supplements. Planta Med 2012;78:1421–7.

Zhao P, Rowland M, Huang SM. Best practice in the use of physiologically based pharmacokinetic modeling and simulation to address clinical pharmacology regulatory questions. Clin Pharmacol Ther 2012;92:17–20112.

Gufford BT, Barr JT, González-Pérez V, Layton ME, White Jr JR, Oberlies NH, et al. Quantitative prediction and clinical evaluation of an unexplored herb-drug interaction mechanism in healthy volunteers. CPT Pharmacometrics Syst Pharmacol 2015;4:701–10.

Brantley SJ, Gufford BT, Du a R, Fediuk DJ, Graf TN, Scarlett YV, et al. Physiologically based pharmacokinetic modeling framework for quantitative prediction of an herb-drug interaction. CPT Pharmacometrics Syst Pharmacol 2014;3:e107.

Fenneteau F, Poulin P, Nekka F. Physiologically based predictions of the impact of inhibition of intestinal and hepatic metabolism on human pharmacokinetics of CYP3A substrates. J Pharm Sci 2010;99:486–514.

Johnson EJ, Won CS, Kock K, Paine MF. Prioritizing pharmacokinetic drug interaction precipitants in natural products: application to OATP inhibitors in grapefruit juice. Biopharm Drug Dispos 2017;38:251–9.

Zadoyan G, Rocitta D, Klement S, Diener A, Hoerr R, Gammie T, et al. Effect of Ginkgo biloba extract EGB 761\textsuperscript{e} on human cytochrome P450 activity: a cocktail interaction study in healthy volunteers. Eur J Clin Pharmacol 2012;68:533–60.

Moon SJ, Kim SY, Lim CH, Jang HB, Kim MG, Jeon JY. Phase I and pharmacokinetic-drug-drug interaction study of metformin, losartan, and linagliptin coadministered with DW1029M in healthy volunteers. Clin Pharmacol Drug Dev 2017;6:408–19.

Han Y, Guo D, Chen Y, Chen Y, Tan Z-R, Zhou H. Effect of silymarin on the pharmacokinetics of cyclosporin A in healthy volunteers. Clin Pharmacol Ther 2006;76:225–34.

Wang LS, Zhu B, Abd El-Aty AM, Zhou G, Li Z, Wu J, et al. The influence of St John’s Wort on CYP2C19 activity with respect to genotype. J Clin Pharmacol 2004;44:577–81.

Markert C, Kastner IM, Hellwig R, Kalaft P, Schweizer Y, Hoffmann MM, et al. The effect of induction of CYP3A4 by St John’s wort on ambrisentan plasma pharmacokinetics in volunteers of known CYP2C19 genotype. Basic Clin Pharmacol Toxicol 2015;116:423–8.

Wang XD, Li JL, Su QB, Guan S, Chen J, Du J, et al. Impact of the haplotypes of the human pregnane X receptor gene on the basal and St John’s wort-induced activity of cytochrome P450 3A4 enzyme. Br J Clin Pharmacol 2009;67:255–61.

de Lima Toccafondo Vieira M, Huang SM. Botanical-drug interactions: a scientific perspective. Planta Med 2012;78:1400–15.

Won CS, Oberlies NH, Paine MF. Mechanisms underlying food-drug interactions: inhibition of intestinal metabolism and transport. Pharmaco Ther 2012;136:186–201.

van Breemen RB. Development of safe and effective botanical dietary supplements. J Med Chem 2015;58:8360–72.

Na DH, Ji HY, Park EJ, Kim MS, Liu KH, Lee HS. Evaluation of metabolism-mediated herb-drug interactions. Arch Pharm Res 2011;34:1829–42.

US Food and Drug Administration. Final rule-requirements on content and format of labeling for human prescription drug and biological products. 21 CFR Parts 201, 314, and 601. 2006. Available at, https://www.fda.gov/ohrms/dockets/98fr/06-545.pdf. [Accessed 9 September 2017].

US Food and Drug Administration. Guidance for industry: labeling for human prescription drug and biological products - implementing the PLR content and format requirements. 2013. p. 1–34. Available at: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075082.pdf., [Accessed 2 July 2017].

US Food and Drug Administration. Guidance for industry: clinical pharmacology labeling for human prescription drug and biological products. 2016. p. 1–19. Available at: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM109739.pdf, [Accessed 2 July 2017].

Xin HW, Wu XC, Li Q, Yu AR, Zhong MY, Liu YY. The effects of berberine on the pharmacokinetics of cyclosporin A in healthy volunteers. Methods Find Exp Clin Pharmacol 2006;28:25–9.

Han Y, Guo D, Chen H, Tan Z-R, Zhou H-H. Effect of continuous silymarin administration on total talinolol metabolism and disposition of metronidazole. Arzneimittelforschung 2004;54:109–13 [In German, English abstract].

Rajnarayana K, Reddy MS, Vidyasagar J, Krishna DR. Study on the influence of silymarin pretreatment on metabolism and disposition of metronidazole. Xenobiota 2009;39:694–9.

Rajnarayana K, Reddy MS, Vidyasagar J, Krishna DR. Study on the influence of silymarin pretreatment on metabolism and disposition of metronidazole. Arzneimittelforschung 2004;54:109–13 [In German, English abstract].

Pfizer. INSPIRA\textsuperscript{e} (eplerenone) tablets. USPI Revised 05 2016. 1–18. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021437s013lbl.pdf. [Accessed 14 February 2018].

Bristol-Myers Squibb. SPRYCE\textsuperscript{e} (dasatinib) tablet. USPI Revised 03 2015. 1–34. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021986s019lbl.pdf. [Accessed 14 February 2018].

Novartis. NEORAL\textsuperscript{e} (cyclosporine) Soft gelatin capsules/Oral solution. USPI Revised 03 2015. 1–32. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/050715s035,050716s038lbl.pdf. [Accessed 14 February 2018].

Pfizer. PROCARDIA\textsuperscript{e} (nifedipine) capsules. USPI 01 2015. 1–12. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/018482s052lbl.pdf. [Accessed 14 February 2018].

Merck. ZOCOR\textsuperscript{e} (simvastatin) Tablets. USPI Revised 02 2015. 1–22. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/050715s035,050716s038lbl.pdf. [Accessed 14 February 2018].

Aventis, Sanossfi. ALLEGRA ALLERGY (fexofenadine hydrochloride) tablet. Drug Facts Revised 05 2016. 1–12. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020872Orig1s038lbl.pdf. [Accessed 14 February 2018].
[141] The vitamin shoppe. St. John’s wort extract-standardized herbs. Website containing product label. Available at: https://www.vitaminshoppe.com/p/st-john-wort-extract-300-mg-240-vegetarian-capsules/vs-2127#! [Accessed 14 February 2018].

[142] Sundown Naturals. St. John’s wort 300mg standardized extract. Product Label. Available at: https://www.sundownnaturals.com//media/sundownnaturals/productimages/productlabel_65334_standardizedstjohnswort.png?h=804&w=2027&la=en&hash=35DC7316F77235CEC6931F08A5D12A6CEC5247D. [Accessed 14 February 2018].

[143] Nature’s Sunshine Products. Concentrated StJohn’s wort. Product Label. Available at: https://www.naturessunshine.com/content/us/sku/label/655.jpg. [Accessed 14 February 2018].