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Review Article

A regulatory science viewpoint on botanical–drug interactions

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ABSTRACT

There is a continued predisposition of concurrent use of drugs and botanical products. Consumers often self-administer botanical products without informing their health care providers. The perceived safety of botanical products with lack of knowledge of the interaction potential poses a challenge for providers and both efficacy and safety concerns for patients. Botanical–drug combinations can produce untoward effects when botanical constituents modulate drug metabolizing enzymes and/or transporters impacting the systemic or tissue exposure of concomitant drugs. Examples of pertinent scientific literature evaluating the interaction potential of commonly used botanicals in the US are discussed. Current methodologies that can be applied to advance our efforts in predicting drug interaction liability is presented. This review also highlights the regulatory science viewpoint on botanical–drug interactions and labeling implications.

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,

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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 furanocumarins (6′,7′-dihydroxybergamottin, bergamottin and paradisins). The *in vitro* inhibitory constants (IC_{50}) 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 (IC_{50} = 25 μM) than berberine (IC_{50} = 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

Table 1 – Effect of botanical product extracts and their active constituents on metabolic enzymes and transporters.

Botanical [known enzyme/transporter modulator]	Metabolic enzymes and transporters affected[a]	Effected on drug concentration (Drug example)[b]
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 ↑), (UGT1A ↓ *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 (↓) CYP2D6 (↓)	*Increase plasma level* (midazolam [28,29], debrisoquine [27], cyclosporine [30,132])
Grapefruit juice (*Citrus x arantium*) [Flavonoids naringin/naringenin and quercetin, and furanocoumarins bergamottin, 6′7′-dihydroxybergamottin]	Enteric CYP3A4 (↓) OATP1A2 (↓) OATP2B1(↓)	*Increase plasma level of CYP3A substrates or decrease plasma level of OATP substrate* 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] [c]
Apple juice (*Malus pumila*) [Flavonoids hesperetin and phloridzin] Orange juice (*Citrus x sinensis*) [Flavonoid hesperidin]	OATP1A2 (↓) OATP2B1(↓)	*Decrease plasma level* (Aliskiren, atenolol, celiprolol, ciprofloxacin, fexofenadine, and talinolol [21,89]) [c]
Milk thistle (*Silybum marianum*) [Flavonolignans silybin]	CYP2C9 (↓), CYP3A4 (↔, possible↑) CYP1A2 (↔), CYP2D6 (↔) CYP2E1 (↔), UGT1A1 (↔) OATP1B1 (↔), P-gp (↔,possible↓)	*Increase plasma level* (losartan [121] and talinolol [133]) *Decrease plasma level of CYP3A/P-gp substrate?* (Metronidazole [134])
St. John's wort (*Hypericum perforatum*) [Phloroglucinol hyperforin and flavonoids (e.g., quercetin)]	CYP1A2 (↑) CYP2B6 (↑) CYP2E1(↑) CYP3A4 (↑) CYP2C9 (↑) CYP2C19 (↑) P-gp (↑)	*Decrease plasma level* Drug category: Antihistamines (e.g., fexofenadine), antivirals (indinavir, lamivudine, nevirapine), cardiovascular drugs (digoxin, ivabradine, nifedipine, talinolol, verapamil, warfarin), central nervous system agents (amitriptyline, alprazolam, buspirone,methadone,midazolam, phenytoin, sertraline), hypoglycaemic agents (gliclazide), immunosuppressants (cyclosporine, tacrolimus), statins (atorvastatin, simvastatin), oncology agents (imatinib, irinotecan), proton pump inhibitors (cimetidine, omeprazole) [4,41–43] [c]

Note: Updated from [125], Table 1.

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

[b] Drugs with published clinical drug–botanical interaction based on pharmacokinetic mechanism.

[c] 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
INSPRA®	*Clinical Pharmacology-Pharmacokinetics-Drug Interactions*
eplerenone tablets (Pfizer) [135]	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®	*Dosage and Administration- Dose Modification*
dasatinib tablet (Bristol-Myers Squibb) [136]	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®	*Drug Interactions*
cyclosporine capsules, oral solution, USP (Norvatis) [137]	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®	*Precautions-Drug Interactions-Other Interactions*
nifedipine capsules (Pfizer) [138]	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®	*Warnings and Precautions-Drug Interactions*
simvastatin tablets (Merck) [139]	The risk of myopathy and rhabdomyolysis is increased by high levels of statin activity in plasma. Simvastatin is metabolized by the cytochrome P450 isoform 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®	*Warnings*
Fexofenadine HCl tablets (Sanofi Aventis) [140]	When using this product do not take with fruit juices
St. John's Wort Extract- Standardized Herbs	*Warning*
0.3% hypericin (Vitamin Shoppe®) [141]	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	*Warning*
(Sundown® Naturals) [142]	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	*Warning*
(Nature's Sunshine®) [143]	Do not use St Jonh's Wort while taking any prescription drugs without advice of your prescribing physician. Do not use with prescription antidepressants, contraceptives, immunossupressants, 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 [4,41–43]. 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 [4,41–43]. 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*. Gingko extract and its flavonoids inhibited glucuronidation of mycophenolic acid (UGT1A7, 1A8, 1A9, and 1A10 substrate) with IC_{50} 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 gingko 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 flavanolignans, primarily silybin, silydianin, isosilybin, 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 (IC_{50} = 1.4 μM) and other UGTs with less potency (IC_{50} range = 28–79 μM) [58,60]. Silybin also inhibited CYP3A4 (Ki range = 5–160 μM) [58] and CYP2C9 (IC_{50} 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 milt 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

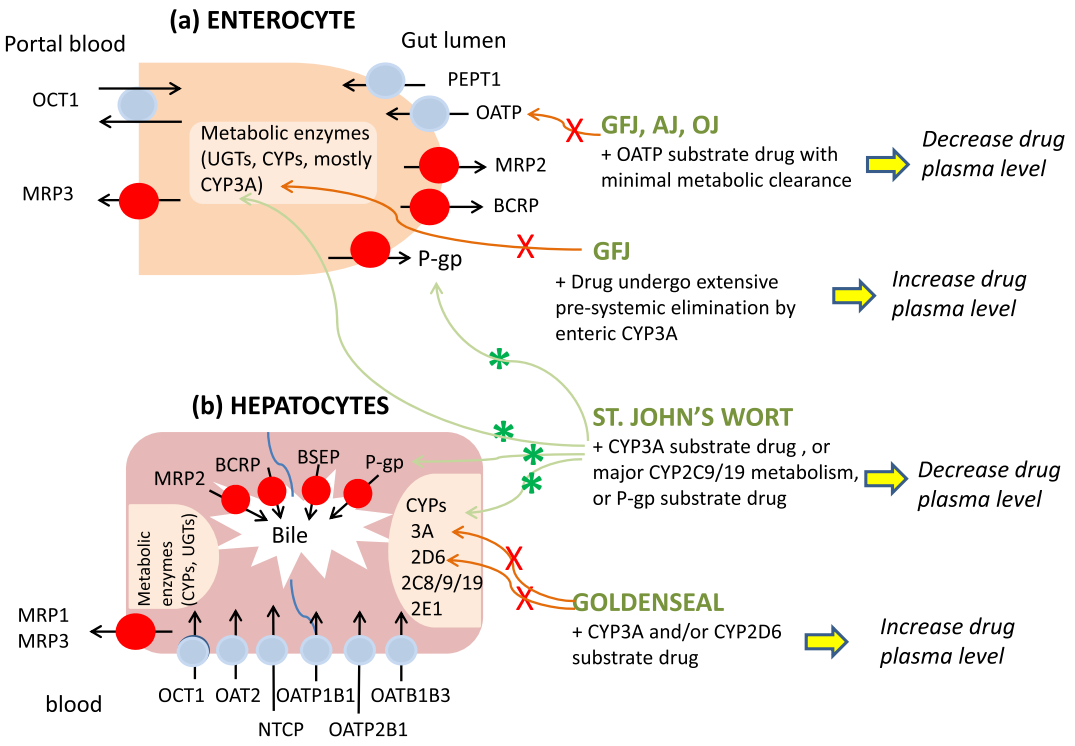

Fig. 1 – Schematic representation of selected examples of possible mechanism for enzyme- and transporter-mediated botanical–drug interactions in the intestinal epithelial (a) and liver cells (b) with effect on victim drug exposure. [*] Indicates induction of the metabolic enzyme or drug transporter. [X] Indicates inhibition of metabolic enzyme or drug transporter. Abbreviations: GFJ: grapefruit juice; OJ: orange juice; AJ: apple juice; CYP; cytochrome P450 enzymes; BSEP, bile salt export pump; BCRP: breast cancer resistance protein; MRP: multidrug resistance associated protein; NTCP: sodium taurocholate cotransporting polypeptide; OAT: organic anion transporter; OATP: organic anion transporting polypeptide; OCT: organic cation transporter; P-gp: P-glycoprotein; PEPT1: peptide transporter 1; UGT; Uridine 5′-diphospho-glucuronosyltransferase family of enzymes.

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 IC_{50} 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 IC_{50} 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 IC_{50} 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 GF1J 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, celiprolol, atenolol and aliskiren [89,96]. Again, the effect was dependent on juice volume and variable among drugs.

As with the beta-blockers (atenolol, celiprolol, 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 botanical 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 (IC_{50} = 55 μM), OATP1B1 (IC_{50} = 8 μM) and OATP2B1 (IC_{50} = 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 IC_{50} 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 IC_{50} 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, dehydronifedipine, 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; while 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 interaction is limited because of interspecies differences in protein specificity and inhibitor selectivity [128].

4. Drug interactions: considerations for labeling

Regulations of prescription drug labeling (71 FR 3922) [129] recommend that the clinically significant drug interactions (i.e., prescription or over-the-counter drugs or foods that interact in clinically significant ways with the product) be referenced in the "Highlights–Drug Interactions" section of its United States Prescribing Information (USPI) [130]. Specific actionable instructions for preventing and managing the drug interaction should be included in the "Drug interactions" section of USPI [130]. Essential information may be also stated in the "Drug Interaction", "Dosage and Administration, "Contraindications", "Warnings and Precautions", and "Clinical Pharmacology" sections [131].

For botanicals or foods with established drug interaction liability, such as St. John's wort and GFJ, labeling language for interactions can be based on the metabolic and dispositional characteristics of the drugs being labeled without clinical data characterizing the interaction. For example, cautionary language regarding the use of St. John's wort is added to the label of drugs which are substrates for CYP3A and/or P-gp and induction of these pathways may significantly decrease drug systemic exposure and effectiveness. 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. Guidances 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.

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