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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.





## Q1 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. 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. *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. 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. *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



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