Viewpoint

Unlocking the Goldenseal Reveals the Complexities of Natural Product–Drug Interactions

Botanical natural products are a rich source of diverse phytochemicals that allow for the continued development of novel therapeutic agents and dietary supplements. Natural products are widely promoted for their putative health benefits and are generally perceived to be safe. Less appreciated is that clinically significant drug interactions can and do occur with natural product use (Gurley et al., 2008; Borrelli and Izzo., 2009; Bailey et al., 2013). Where natural product–drug interactions have been identified, there is often a lack of robustness in the experimental approach leading to an insufficient mechanistic understanding of the interactions, the causative agents, or the potential clinical relevance of the interactions (Roe et al., 2016). One such notable botanical natural product–drug interaction is with goldenseal (Hydrastis canadensis) and midazolam, a cytochrome P450 (CYP) 3A4/5 substrate.

Goldenseal is primarily consumed for its antiviral, antimicrobial, antiobesity, and hypoglycemic activity (Heidarian et al., 2014; Guo et al., 2016; Mandal et al., 2020). The two main bioactive phytoconstituents found in goldenseal are berberine and (−)-β-hydrastine (Weber et al., 2003). Although berberine and (−)-β-hydrastine exhibit therapeutic benefits, they both inhibit hepatic microsomal cytochrome P450 (P450) enzymes, including CYP3A4/5, raising concerns about possible drug interactions (McDonald et al., 2020). Reinforcing this concern, goldenseal was reported to increase concentrations of midazolam in human subjects (Nguyen et al., 2021). Building on this earlier work, the manuscript by Nguyen et al. (2023) takes an integrative experimental approach involving human intestinal microsomes, clinical pharmacokinetics, and physiologic-based pharmacokinetic (PBPK) modeling to advance the understanding of goldenseal–midazolam drug interactions and their clinical significance.

Nguyen et al. began with IC_{50} shift experiments. Briefly, human intestinal microsomes were pre-incubated for 30 minutes with and without berberine and (−)-β-hydrastine in the presence and absence of NADPH (an electron donor for P450 reactions). This was followed by a secondary incubation containing NADPH and midazolam. The key result was a leftward shift in the dose-response inhibition for (−)-β-hydrastine, pre-incubated with NADPH, which shows a time-dependent inhibition (TDI) is occurring. This is important as it demonstrates that TDI is possible if (−)-β-hydrastine is converted to a Phase I metabolite that more potently inhibits CYP3A or through a mechanism-based inhibition where the (−)-β-hydrastine metabolite forms a covalent adduct with the enzyme or haem group. A second set of experiments confirmed this by showing that longer pre-incubations and higher (−)-β-hydrastine concentrations resulted in greater inhibition of midazolam metabolism. While berberine also demonstrated TDI, the data strongly suggest that (−)-β-hydrastine is the more potent inhibitor of the two compounds. Interestingly, berberine demonstrated a biphasic effect with lower concentrations (<5 μM) increasing intestinal microsomal metabolism of midazolam. Subsequent reversible enzyme inhibition assays confirmed this result suggesting that berberine (<5 μM) allosterically activates CYP3A. While (−)-β-hydrastine and berberine rapidly dissolved from the goldenseal capsules in a simulated in vitro intestinal fluid model, (−)-β-hydrastine had higher permeability than berberine in the Caco-2 human intestinal cell model. These results suggest that in humans, (−)-β-hydrastine should enter intestinal cells more rapidly than berberine, which would better facilitate CYP3A inhibition (Fig. 1).

One of the strengths of the manuscript by Nguyen et al. was to determine whether the intestinal microsomal interaction translated to a significant change in midazolam pharmacokinetics in humans. This was achieved through an open-label two-arm clinical study of 16 healthy adult males (n = 8) and females (n = 8).

ABBREVIATIONS: AUC, area under the plasma concentration versus time curve; CYP, cytochrome P450; PBPK, physiologically based pharmacokinetics; TDI, time-dependent inhibition.
In the baseline phase, subjects received 2.5 mg of midazolam syrup. In the drug interaction phase, they took 1 g of goldenseal three times a day for six days followed by a single dose (2.5 mg) of midazolam on day 6. In the chronic dosing study, there was a significant 31% increase in the maximal midazolam concentration and a 40% increase in systemic exposure as measured by the area under the curve (AUC0-12 or AUC0-inf). In an acute study performed in eight of the subjects, a single large (3 g) dose of goldenseal increased maximum midazolam concentration by 43% and AUC by 65%. There was a small (20%) but significant increase in the elimination half-life with chronic but not acute goldenseal. These findings are consistent with intestinal CYP3A inhibition as the primary site of the interaction; however, the increased half-life in the chronic study suggests that hepatic CYP3A inhibition could have a minor contribution to the changes in midazolam pharmacokinetics.

In the final phase of the study, a PBPK modeling approach was used to study the effect of goldenseal on midazolam pharmacokinetics in humans. It was concluded that the PBPK models closely predicted (-)-β-hydrastine and berberine pharmacokinetics after acute and chronic dosing of 1 g of goldenseal. When (-)-β-hydrastine and berberine models were combined with the default Simcyp midazolam pharmacokinetic model, the PBPK predicted midazolam pharmacokinetics were within 1.2-fold of those observed in clinical trials. With the inhibitor model validated, the study then probed how changing one or more parameters in the PBPK model impacted the goodness of fit. When TDI or (-)-β-hydrastine was removed from the model, or the midazolam dose was switched to intravenous, the previously observed inhibitory effect was lost. Together, these results provide further support for the intestine as the primary site of the interaction; however, the increased half-life in the chronic study suggests that hepatic CYP3A inhibition could have a minor contribution to the changes in midazolam pharmacokinetics.

Among ongoing discussions about the safety of natural product supplement use and their clinical implications, the study by Nguyen et al., is timely and important for consumers, healthcare providers and researchers. Through the application of their previously derived in vitro pharmacokinetic constants to the in silico PBPK modeling combined with additional in vitro and clinical pharmacokinetic studies in the current manuscript, the authors provide a robust and novel perspective on the complex nature of goldenseal-mediated drug interactions and their potential clinical importance. A particularly important finding is the prediction of an inhibitory interaction that is sustained at a clinically significant level for up to 24 hours. This further affirms that even with the spacing of goldenseal and other oral medications, a drug interaction is possible.
Although the study by Nguyen et al. advances the understanding of goldenseal-mediated drug interactions, there are minor weaknesses and limitations. First, midazolam is an excellent CYP3A probe substrate, but it is most often administered intravenously, where it would not be susceptible to the goldenseal intestinal CYP3A interaction. Therefore, to expand on the clinical relevance, future studies should focus on evaluating the co-treatment of goldenseal phytoconstituents with at-risk, orally administered drugs with low to moderate bioavailability that are highly metabolized by intestinal CYP3A, such as lipid-lowering agents (e.g., simvastatin), cardiovascular and antihypertensive agents (e.g., amiodarone and nifedipine), central nervous system-acting medications (e.g., buspirone), immunosuppressant agents (e.g., cyclosporine), anti-infectives (e.g., erythromycin), antineoplastic agents (e.g., crizotinib), and urinary tract agents (e.g., dipherenacin) (Bailey et al., 2013). An additional minor limitation is that Nguyen et al. did not assess or comment on the potential impact of the interaction on other benzodiazepines. Based on known metabolic pathways, the goldenseal-CYP3A interaction would be predicted to impact other CYP3A-metabolized benzodiazepines (e.g., diazepam, triazolam, alprazolam) but not those primarily metabolized by phase II pathways (e.g., lorazepam and clonazepam) (Riss et al., 2008). A second interesting path for future research would be to test this prediction by assessing the pharmacokinetic interactions between goldenseal phytoconstituents and other orally administered benzodiazepines. One limitation that Nguyen et al. does address is the complexity of studying botanical extracts due to the presence of various other bioactive phytoconstituents. This is significant for goldenseal, as the reversible CYP3A inhibitory effect by an unknown phyto constituent was unmasked with higher doses of goldenseal. As Nguyen et al., did not attempt to identify the unknown goldenseal phytoconstituent in this manuscript, we believe that it should be a future priority to better understand goldenseal–drug interactions. In addition, previous reports from PBPK modeling show noteworthy interactions between goldenseal and ABCB1 transporters (Adiwidjaja et al., 2022). We suggest conducting clinical pharmacokinetic studies to assess the impact of inhibiting intestinal ABCB1 on the bioavailability of ABCB1 substrates to identify or exclude additional interactions of concern. The final limitation that should be addressed is the inclusion of more diverse populations in future clinical and PBPK modeling studies to recognize and subsequently highlight situations that are therapeutically safe or pose the highest risk for clinically significant goldenseal–drug interactions.

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References


