TRANSPORTER INHIBITION BY HERBAL SUPPLEMENTS – POTENTIAL DRUG-DIETARY SUPPLEMENT INTERACTIONS

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ABSTRACT

Membrane transporters are known to affect the absorption (A), distribution (D), metabolism (M), and elimination (E) of drugs. The presence of drugs that inhibit these transporters can have profound effects on the safety profiles of co-medications, and has led regulatory agencies to focus their attention on transporter-mediated drug-drug interactions. Largely unregulated is the field of herbal supplements/neutraceuticals. Many of these compounds are touted as having drug-like benefits, while the potential for drug-like adverse events is left unsaid. Green Tea extract-based dietary supplements have been widely consumed for their purported beneficial health effects, such as weight reduction. However, tea polyphenols may also inhibit the activities of both drug-metabolizing enzymes and drug transporters, potentially resulting in adverse drug effects. In addition, tea catechins may upregulate or downregulate the expression of the drug-metabolizing enzymes and transporters, altering the ADME properties of co-medications. In order to investigate the action of supplements on drug transporters, we have studied the effects of a panel of widely used supplements on transporters shown to be clinically important for drug absorption and disposition. While the supplements studied had little to no effect on the organic cation transporter OCT2 and only modest effects on the efflux transporter p-glycoprotein, many of them had profound inhibitory effects on the organic anion transporting polypeptides OATP1B1 and OATP1B3, including green tea extract, black cohosh, Ginkgo biloba, and St. John's wort. Green tea extract was also shown to strongly inhibit the organic anion transporters OAT1 and OAT3. Since inhibition of these transporters by drugs can result in adverse drug effects for co-medications, inhibition of these transporters by supplements can potentially lead to adverse drug effects for co-medications as well.

BACKGROUND

Drug-drug interactions are a common problem during drug treatment. These interactions may decrease drug efficacy or cause serious, even fatal, adverse events. A number of drugs have been withdrawn from the market due to drug-drug interactions that were only discovered post-marketing.

Regulatory agencies, such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA), have published guidelines to help the pharmaceutical industry design safety studies to investigate such potential drug-drug interactions that may occur with new investigational pharmaceuticals[1,2]. Many clinically relevant drug interactions can be predicted (and thus avoided) from well designed, mechanistically based in vitro studies on the effects of these drugs towards metabolic enzymes and transporters.

However, drug interactions are not limited to concomitant medications. Foods, such as grapefruit juice, are well known to also alter drug pharmacokinetic properties. In addition, herbal supplements can also result in drug interactions, leading to adverse events.

The use of herbal supplements has been steadily increasing, with ~20% of Americans using herbal supplements and up to 30% using herbal supplements concurrently with conventional drugs[3,4,5]. In addition, use of herbal supplements and nonprescription medications is underreported to health care providers[6]. Unlike investigational new drugs, herbal supplements are generally not studied for their potential to cause drug interactions prior to marketing.

The general lack of knowledge of the interaction potential of herbal supplements, coupled with their widespread yet under-reported use, presents challenges for health care providers and significant safety concerns for patients.

In order to investigate potential drug-herbal supplement interactions, we have tested several common herbal supplements on transporters known to be involved in drug-drug interactions.

MATERIALS AND METHODS

For SLC transporters, MDCK-II cells were transfected using a novel *in situ* transfection technology, Opti-Expression, which allows consistent and effective transfection of polarized cell monolayers. Cells were either transfected with plasmids encoding the SLC transporters or a plasmid encoding green fluorescent protein (GFP) as mock control. For P-gp, MDCK-MDR1 cells were grown in polarized monolayers. For BCRP, Caco-2 cells that had been selected for enhanced BCRP and lower P-gp activity were grown in polarized monolayers.

St. John's Wort and echinacea were obtained from Ikhlas Kahn at the University of Mississippi School of Pharmacy, green tea extract was obtained from Amax NutraSource, Inc., black cohosh was obtained from PlusPharma, Inc., and Ginkgo biloba extract was obtained from the Midwest Research Institute.

RESULTS

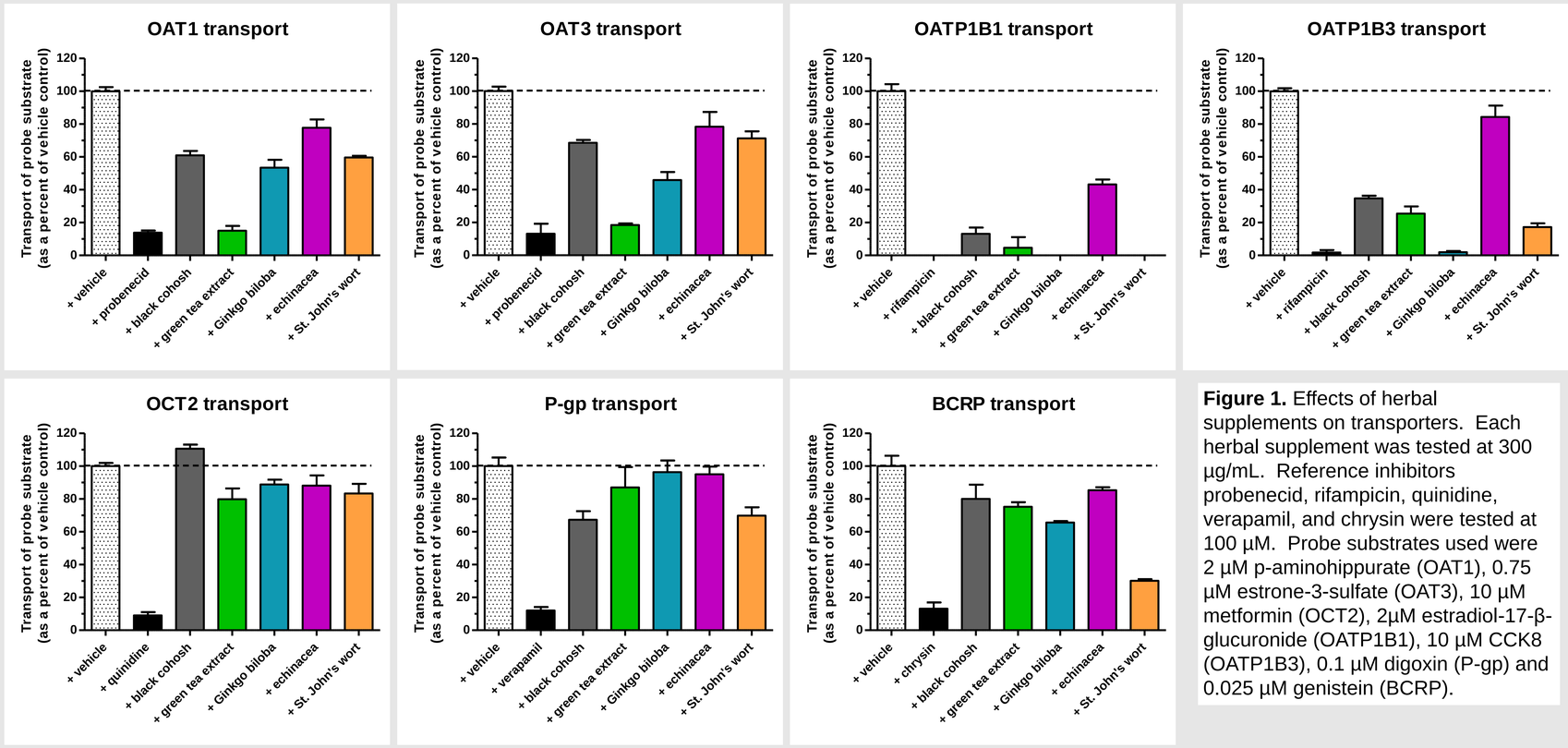

Figure 1. Effects of herbal supplements on transporters. Each herbal supplement was tested at 300 µg/mL. Reference inhibitors probenecid, rifampicin, quinidine, verapamil, and chrysin were tested at 100 µM. Probe substrates used were 2 µM p-aminohippurate (OAT1), 0.75 µM estrone-3-sulfate (OAT3), 10 µM metformin (OCT2), 2µM estradiol-17-β-glucuronide (OATP1B1), 10 µM CCK8 (OATP1B3), 0.1 µM digoxin (P-gp) and 0.025 µM genistein (BCRP).

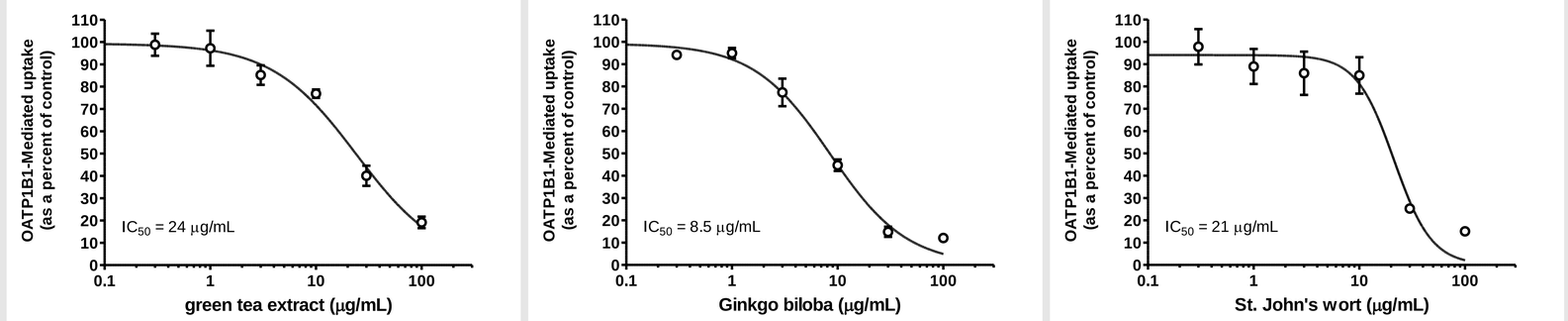

Figure 2. IC_{50} determinations of herbal supplements against OATP1B1. Supplements were studied at 0.3 - 100 µg/mL. The probe substrate was 2 µM estradiol-17β-D-glucuronide. The IC_{50} values were determined by non-linear regression using GraphPad Prism. Data represent the mean and standard deviation of triplicate samples.

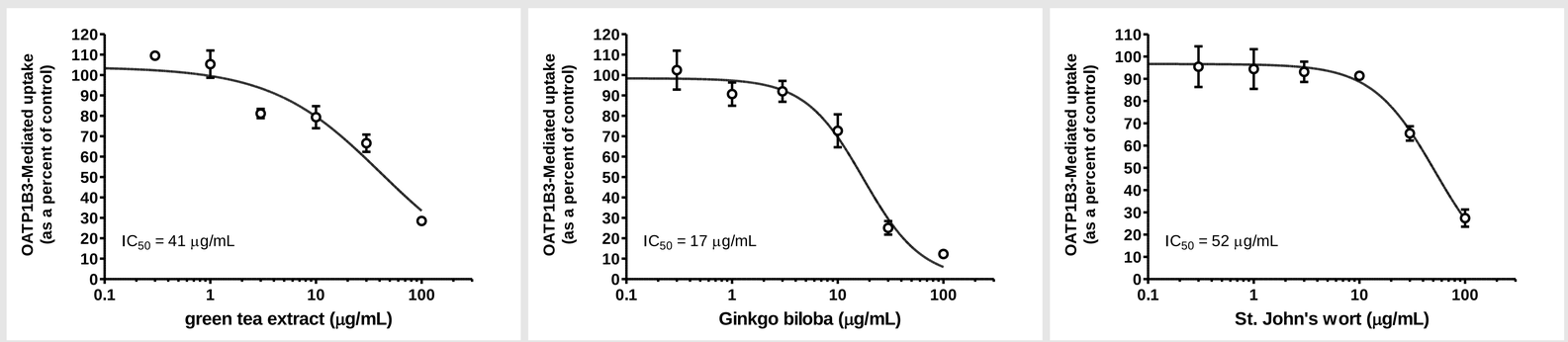

Figure 3. IC_{50} determinations of herbal supplements against OATP1B3. Supplements were studied at 0.3 - 100 µg/mL. The probe substrate was 10 µM CCK8. The IC_{50} values were determined by non-linear regression using GraphPad Prism. Data represent the mean and standard deviation of triplicate samples.

DISCUSSION

Herbal supplements have been shown to significantly inhibit transporters that are responsible for uptake of drugs into kidney proximal tubules (OAT1, OAT3) and into liver hepatocytes (OATP1B1, OATP1B3) for elimination.

Of the herbal supplements tested in this study, green tea extract is the most potent inhibitor of OAT1 and OAT3, while black cohosh, green tea extract, Ginkgo biloba, and St. John's wort were all potent inhibitors of OATP1B1 and OATP1B3.

Inhibition of OAT1 and OAT3 may result in adverse events for drugs that are normally substrates of these transporters, such as adefovir, acyclovir, ciprofloxacin, tenofovir, ceftriaxone, and others.

Inhibition of OATP1B1 and OATP1B3 may result in adverse events for drugs that are normally substrates of these transporters, such as statins, taxanes, protease inhibitors, glyburide, rifampin, valsartan, and others.

CONCLUSIONS

While herbal supplements are often used to manage various common chronic diseases, they can increase the likelihood of adverse events for concomitantly taken prescription medications[5]. Identification of drugs that may interact with herbal supplements and the mechanism involved is essential for better risk management.

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