Managing Drug Interactions with Medicinal Plants: Strategies for Success

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Disclosures

Dr. Erin Raney has no financial relationships to disclose.

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Learning Objectives

1. Describe the mechanism for interactions between prescription medications and commonly-used medicinal plants

2. Develop patient-specific plans to address drug-herb interactions

3. Identify professional resources for evaluating potential drug-herb interactions

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Background

- Medicinal plants are used commonly worldwide with some estimates nearing 70% of individuals
- Medicinal plants as whole plants or extracts are the origins or modern medicine and play an important historic role
- The use of prescription medications and dietary supplements is common
  - An estimated 40-60% of adults with chronic conditions use dietary supplements
  - Among patients who use prescription medications, approximately 20-25% also use dietary supplements
- The potential for herbal-drug interactions is an important focus for efficacy and safety purposes

Frontiers in Pharmacology. 2012;(3)Article 69:1-19.

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Types of Drug Interactions

Pharmacokinetic

-Interactions that affect a drug's serum concentration and final action
-Hepatic or renal injury or insufficiency
-Common metabolic pathways
  -Cytochrome P450 enzymes (e.g., CYP1A2, 2C9, 2C19, 2D6, 2E1, 3A4)
  -Uridine Diphosphate-glucuronosyltransferase conjugating enzyme (UGTs)
  -Organic anion-transporting polypeptide (OATP) drug transporters
  -P-glycoprotein transporter

Pharmacodynamic

-Actions unrelated to changes in a drug's serum concentration
-The pharmacologic action of a drug is affected; may be antagonized, neutralized, or potentiated

Frontiers in Pharmacology. 2012;(3)Article 69:1-19.

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Drug Metabolism (CYP Enzymes)

~90% of drug metabolism is through CYP1A2, 2C9, 2C19, 2D6, 2E1, 3A4

Indiana University School of Medicine

Drug Interactions Flockhart Table

https://drug-interactions.medicine.iu.edu/MainTable.aspx

- **Searchable database for prescription medications**
- **Categorized as substrates, inducers, and inhibitors of CYP450 enzymes**
- **Not intended to search for herbal product interactions**

Flockhart DA, Thacker, D., McDonald, C., Desta, Z. The Flockhart Cytochrome P450 Drug-Drug Interaction Table. Division of Clinical Pharmacology, Indiana University School of Medicine (Updated 2021). https://drug-interactions.medicine.iu.edu/. Accessed 9/26/23.

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Pharmacodynamic Interactions (examples*)

Increased blood pressure	Decreased blood glucose	Increased bleeding risk	Increased sedation/ CNS depression	Hepatotoxicity	Thyroid Effects
Bitter orange Green tea Licorice	Ashwagandha Berberine Bitter melon Cinnamon Fenugreek Red raspberry Turmeric	Flaxseed Garlic Red raspberry Saw palmetto Turmeric	Ashwagandha Kava Valerian Hops Lemon balm	Aloe Black cohosh Ginseng Green tea Kava Turmeric	Ashwagandha Lemon balm

*selected examples only: see full resources/monographs for comprehensive lists

Expert Opinion on Drug Metabolism and Toxicology. 2020;16(3):165-167; British Journal of Pharmacology 2012;75(3):603-618.; NatMed Pro https://naturalmedicines.therapeuticresearch.com/

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Who is at Highest Risk?

The following situations indicate patients or situations where outcomes of drug-dietary supplement interactions are particularly concerning:

- **Narrow therapeutic range medications**
- **Elderly**
- **Pregnancy/lactation**
- **Pediatrics**
- **Transplant**
- **Oncology**
- **HIV/ Hepatitis**

Expert Opinion on Drug Metabolism and Toxicology. 2020;16(3):165-167.

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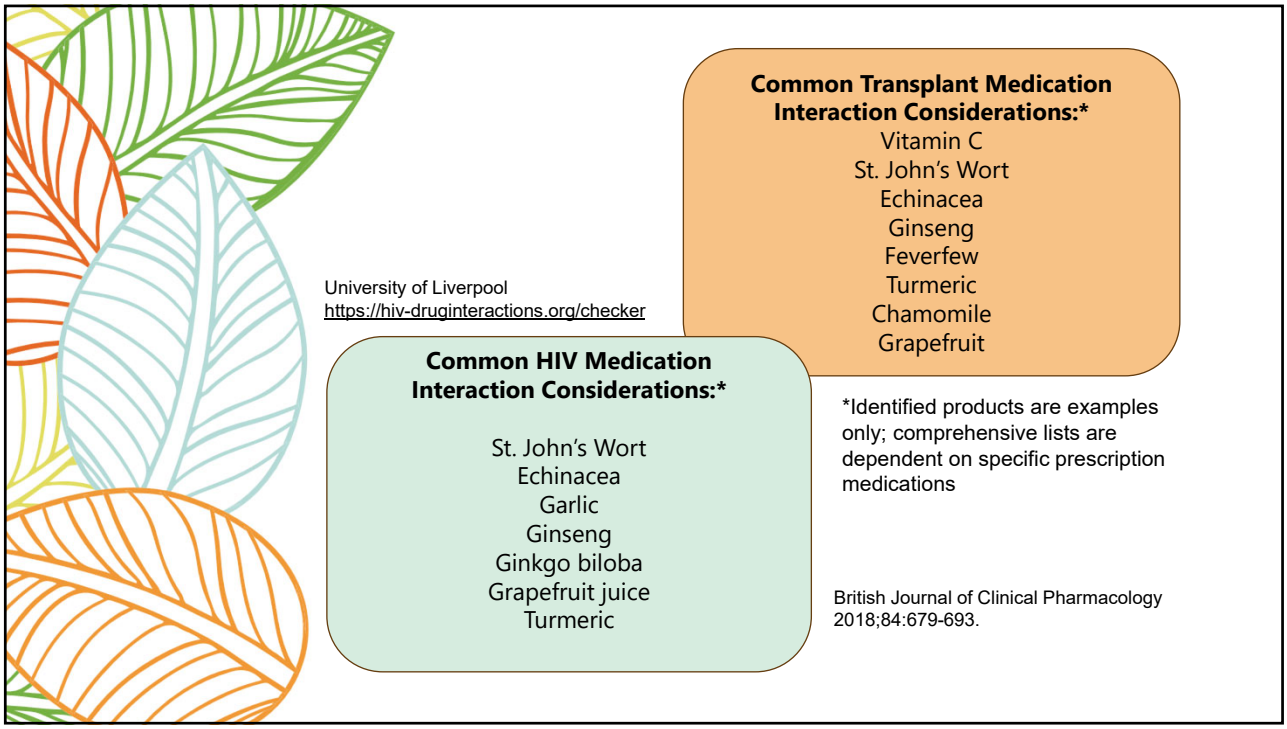

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Products with Known Interactions (examples)

Product	Example PK Interactions (see supplement monographs for comprehensive lists)
Goldenseal	Increases concentrations of medications metabolized by CYP2D6 and CYP3A4 (many antihypertensives, statins, antidepressants, protease inhibitors, hormones, others)
St. John's Wort	Reduces concentrations of medications metabolized by CYP3A4 or transported by P-gp
Ginseng (Asian)	May decrease concentrations of medications metabolized by CYP3A4
Gingko Biloba	May decrease concentrations of medications metabolized by CYP2C19 (some proton pump inhibitors, others) and 3A4

Frontiers in Pharmacology. 2012;(3)Article 69:1-19.; American Family Physician. 2017;96(2):101-106.; NatMed Pro https://naturalmedicines.therapeuticresearch.com/

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Products with Known Interactions (examples)

Product	Example PK Interactions (see supplement monographs for comprehensive lists)
Milk thistle	May decrease concentrations of medications metabolized by CYP2C9 (losartan, warfarin, phenytoin, diazepam, others)
Kava kava	May increase concentrations of medications metabolized by CYP2E1 (acetaminophen, anesthetic agents) and by CYP2C9 and 2C19 (NSAIDS, ARBS, glipizide, glyburide, valproic acid, warfarin, clopidogrel, some proton pump inhibitors, others)
Green tea	May reduce concentrations of medications transported by OATP1A1 and OATP1A2 (some statins, fluoroquinolones, beta blockers, antiretrovirals, others) May increase concentrations of medications transported by P-gp Products may contain vitamin K which may reduce INR levels in patients taking warfarin

Frontiers in Pharmacology. 2012;(3)Article 69:1-19.; American Family Physician. 2017;96(2):101-106.; NatMed Pro https://naturalmedicines.therapeuticresearch.com/

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Products with Known Interactions (examples)

Product	Example PK Interactions (see supplement monographs for comprehensive lists)
Berberine	May increase concentrations of medications metabolized by CYP2C9, 2D6, 3A4
Black cohosh	May decrease concentrations of medications transported by OATP2B1 (amiodarone, glyburide, statins, fexofenadine, others)
Garlic	Conflicting information on CYP3A4 activity (intestinal vs. hepatic) May decrease concentrations of medications transported by P-gp (colchicine, digoxin, quinidine, verapamil, tacrolimus, others)
Echinacea	May increase concentrations of medications metabolized by CYP1A2 (warfarin, theophylline, verapamil, others) and CYP3A4

Frontiers in Pharmacology. 2012;(3)Article 69:1-19.; American Family Physician. 2017;96(2):101-106.; NatMed Pro https://naturalmedicines.therapeuticresearch.com/

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A 38-year-old woman presents to her OB-GYN for an annual wellness visit. She is experiencing 2-3 episodes of breakthrough bleeding during each oral contraceptive cycle, which is a new pattern after taking the product for several years.

Her current medications:

- **Oral contraceptive (ethinyl estradiol and levonorgestrel)**
- **Escitalopram**
- **PMS Support supplement (St. John's Wort, vitamin B6, vitamin E, vitamin C)**

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Could it be a drug interaction?

St. John's Wort

- **Strong inducer of CYP3A4 and P-gp**
  - Estrogen is metabolized by CYP1A2, 3A4 and progesterone by CYP2C19, 3A4

Herbal products containing St. John's Wort (Hypericum perforatum) may induce hepatic enzymes (cytochrome P 450) and p-glycoprotein transporter and may reduce the effectiveness of contraceptive steroids. This may also result in breakthrough bleeding.

- **Pharmacodynamic effects**
  - May increase serotonergic effects when taken with escitalopram

Recommendation:

- **Rule out possible pregnancy**
- **Consider other causes of breakthrough bleeding**
- **Discontinue PMS support supplement and monitor subsequent cycle patterns for improvement.**

NatMed Pro https://naturalmedicines.therapeuticresearch.com/

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A 75-year-old man presents for a routine follow-up on his cardiac medications. He states that he has noticed leg pain increasing over the past month and his neighbor suggested that it is likely his cholesterol medication. He is requesting discontinuation of simvastatin. During the appointment he states he has started a supplement to boost his metabolism and prevent diabetes as he "already has enough health problems to deal with."

His current medications:

- **Simvastatin (taken for 10 years)**
- **"Metabolic support" supplement (berberine)**
- **Aspirin**
- **Clopidogrel**
- **Amlodipine**
- **Losartan**
- **Omeprazole**

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Could it be a drug interaction?

Berberine

- **Inhibitor of CYP2C9 and 3A4**
  - Clopidogrel, omeprazole, and losartan are metabolized by CYP2C9
  - Clopidogrel, losartan, simvastatin are metabolized by CYP3A4
- **Pharmacodynamic effects**
  - May enhance blood pressure lowering effects of losartan and amlodipine
  - May increase bleeding risk when taken with aspirin and clopidogrel

Recommendation:

- **Consider increased simvastatin levels as possible cause of leg pain; rule out other causes**
- **Assess for other markers of drug interaction (BP, bleeding)**
- **Discontinue Metabolism Support supplement and monitor for symptom improvement.**

NatMed Pro https://naturalmedicines.therapeuticresearch.com/

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A 26-year-old woman with a history of migraine headaches presents to urgent care with new onset dizziness for several days. She recently changed brands of CBD capsules which she uses to help her reduce "stress", otherwise her other medications have been stable for 2 years.

Her current medications:

- **CBD (cannabidiol) plus kava**
- **Topiramate**
- **Sumatriptan**
- **Ibuprofen**

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Could it be a drug interaction?

CBD (cannabidiol)

- **Inhibitor of CYP1A1, 1A2, 2C9, 2C19, 3A4, P-gp; substrate of 2C19, 3A4**
  - Topiramate inhibits CYP2C19, induces CYP3A4 and is a 2C9, 2C19, and P-gp substrate
  - Ibuprofen is a CYP2C9 substrate
- **Pharmacodynamic effects**
  - Additive sedative properties with CNS depressant medications

Kava kava

- **Inhibitor of CYP2C19, 2C9**
  - Topiramate inhibits CYP2C19, induces CYP3A4 and is a 2C9, 2C19, and P-gp substrate
  - Ibuprofen is a CYP2C9 substrate
- **Pharmacodynamic effects**
  - Additive sedative properties with CNS depressant medications

European Journal of Epilepsy. 2021;86:189-96.; NatMed Pro
https://naturalmedicines.therapeuticresearch.com/

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Could it be a drug interaction?

Recommendation:

- Consider and rule out other possible causes for dizziness
- Discuss options such as discontinuing both CBD and kava
- Monitor for symptom improvement
- Consider other options for stress management

European Journal of Epilepsy. 2021;86:189-96.

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Resources

Information about medicinal herbs is not as standardized or widely available as for prescription medications

Challenges with available information

- In vitro studies- provide basic information on metabolic enzymes but lacks clinical application
- In vivo studies- animal studies can be difficult to mimic human doses and physiological responses
- Case reports- difficult to determine all potential influences/ confounders
- Human studies- not required for product availability and not standardized amongst products

Actual interactions vary between plant part, growing conditions, contamination and other ingredients

Frontiers in Pharmacology. 2012;(3)Article 69:1-19.

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Resource	Comments
NatMed Pro https://naturalmedicines.therapeuticresearch.com/	Requires subscription Extensive clinical monographs for herbal products Interaction review database specifically for natural medicines
Facts & Comparisons eAnswers and Lexicomp- Natural Products Database https://www.wolterskluwer.com/en/solutions/lexicomp	Requires subscription Clinical monographs for herbal products Includes herbal products in drug interaction reviews
Micromedex https://www.merative.com/clinical-decision-support	Requires subscription Includes herbal products in drug interaction reviews Toxicology information for overdose
Memorial Sloan Kettering Cancer Center https://www.mskcc.org/cancer-care/diagnosis-treatment/symptom-management/integrative-medicine/herbs/search	Includes "Search About Herbs" section for monographs on herbal products Includes listing of known herb-drug interactions

American Family Physician. 2017;96(2):101-106.

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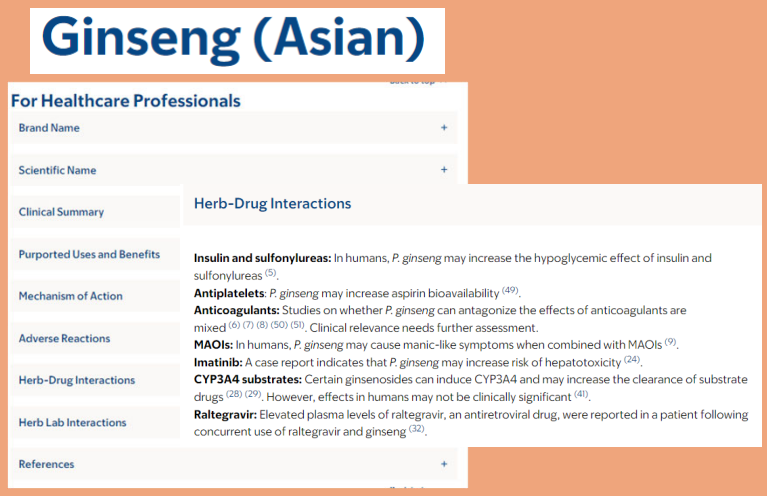
Resources



Memorial Sloan Kettering Cancer Center
https://www.mskcc.org/cancer-care/integrative-medicine/herbs/ginseng-asian#field_herb_adverse_reactions

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Resource	Comments
FDA Dietary Supplement Ingredient Directory https://www.fda.gov/food/dietary-supplements/dietary-supplement-ingredient-directory	Links to FDA actions and communications related to dietary ingredients (voluntary recalls, warning letters, safety communications) Reporting mechanism for adverse events
NIH National Cancer Institute https://www.cancer.gov/about-cancer/treatment/cam/hp	PDQ summaries on complementary and alternative medicine topics for health professionals and patients Focuses on evidence for oncology indications Section on herb-drug interactions, if applicable
NIH Office of Dietary Supplements https://ods.od.nih.gov/ https://ods.od.nih.gov/factsheets/list-all/	Fact sheets on botanicals, vitamins, minerals Section within each fact sheet on herb-drug interactions, if applicable
NIH National Center for Complementary and Integrative Health https://www.nccih.nih.gov/	Provides "Herbs at a Glance" fact sheets, including known drug interactions

American Family Physician. 2017;96(2):101-106.

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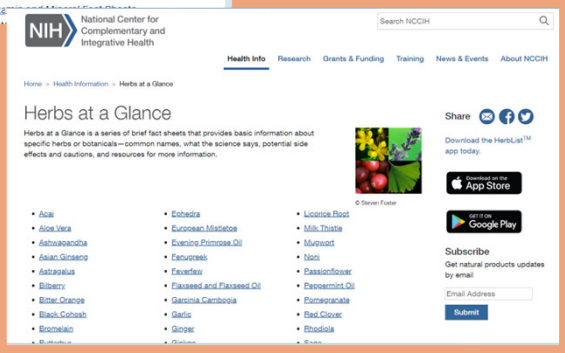
Resources

https://ods.od.nih.gov/factsheets/list-all/

https://www.nccih.nih.gov/



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Patient Assessment

Only 1/3 of individuals tell their physicians they use dietary supplements

- **Encourage patients to report dietary supplement use**
  - Incorporate assessment into medication history workflow and medical record
  - Establish an environment supportive of open communication
  - Request proactive discussion prior to initiation of supplements
- **Provide balanced product information**
  - Explain issues with product quality and consistency
  - Describe available data and resources
- **Consider effects of supplement use when evaluating medication outcomes, both at the initiation of use and longitudinally**

American Family Physician. 2017;96(2):101-106.

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Summary

- **Consider medicinal plant use in various forms when addressing adverse effects of medications**
- **Build assessment and documentation of product use into patient's medical records**
- **Utilize standardized resources when evaluating their use**

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