The Herbal Factor
Understanding the Potential Herb-Drug Interactions

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Target Audience: Pharmacists
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Activity Type: Knowledge-based
Disclosures

Dr. Gurley has served as an expert witness in several dietary supplement-related legal cases.

The American Pharmacists Association is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.
Learning Objectives

1. Make attendees aware of the prevalence of concomitant use of herbal dietary supplements and conventional medications in the U.S.
2. Make attendees aware that herbal dietary supplements can interact with conventional medications either through pharmacodynamic and/or pharmacokinetic mechanisms.
3. Provide examples of clinically relevant herb-drug interactions.
4. Provide clinical evidence that commonly used botanical supplements can modulate the activities of drug metabolizing enzymes and transporters.
5. Emphasize that most herbal supplements do not pose a serious threat for herb-drug interactions on account of formulation issues.
6. Novel formulations and adulteration with prescription drugs may predispose some dietary supplements to drug interactions.
1. Assessment Question

Which of the following issues can contribute to the incidence of herb-drug interactions?

A. Variability in product content and potency.
B. Patient’s lack of notification of supplementation usage to health care providers.
C. Lack of safety and efficacy studies prior to marketing.
D. Adulteration with conventional medications.
E. All of the above.
2. Assessment Question

Which of the following herbal formulations is most likely to produce pharmacodynamic herb-drug interactions?

A. St. John’s wort
B. Ephedra-free formulations
C. Goldenseal
D. Black pepper-containing formulations
3. Assessment Question

Which botanical dietary supplement interacts with most drugs by rendering them ineffective?

A. Echinacea
B. Ginseng
C. Ginkgo biloba
D. St. John’s wort
4. Assessment Question

Which category of dietary supplements is most likely to be adulterated with a prescription medication?

A. Weight-loss supplements
B. Sexual performance enhancement supplements
C. Exercise performance enhancement (i.e., body building) supplements
D. All of the above
Before they were herb-drug interactions

- Phytochemical-mediated changes in xenobiotic metabolism have been recognized for several decades.

- Until 1991, most phytochemical-mediated changes in xenobiotic metabolism were considered novelties.
  - Cruciferous vegetables – inhibit hepatic CYP2E1 activity
    - Chemoprevention (e.g. broccoli)

- In 1991, the novelty wore off.
  - Grapefruit juice – inhibits intestinal CYP3A4 activity
    - GFJ increased oral bioavailability of several drugs

- In 1994, DSHEA increased the number of novel phytochemicals available for consumption.
Potential for Herb-Drug Interactions

- “An estimated 15 million adults in 1997 took prescription medications concurrently with herbal remedies and/or high dose vitamins (18.4% of all prescription users).”

- “This estimate includes nearly 3 million adults aged 65 years or older.”

*JAMA, 280:1569, 1998*
Recent surveys suggest that ~20-35% of Rx drug users take botanical supplements concomitantly.

Approx. 70% of supplement users take Rx drugs.

Less than 40% of patients reveal use of herbal dietary supplements to health care professionals.
Factors contributing to herb-drug interactions

- Products containing multiple herb components.
- Formulations utilizing concentrated plant extracts.
- Presence of multiple phytochemicals that have not been characterized for pharmacological activity.
Partial Listing of Known Constituents of typical St. John’s wort Extracts

**Naphthodianthrones**
- hypericin
- pseudohypericin
- protohypericin
- protopseudohypericin
- cyclopseudohypericin

**Xanthones**
- 1,3,6,7-tetrahydroxyxanthone
- kielcorin

**Phloroglucinol derivatives**
- hyperforin
- hydroperoxycadiforin
- adhyperforin

**Flavonoids**
- luteolin
- 13, 118-biapigenin
- amentoflavone
- hyperin
- catechin derivatives
- epicatechin derivatives
- quercitin
- kaempferol
- hyperoside
- quercitrin
- isoquercitrin
- rutin
- myricetin

**Essential Oils**
- methyl-2-octane
- pinenes
- terpineol
- geraniol
- limonene
- caryophyllene
- humulene
Initial recognition of possible herb-drug interactions

• **Case Reports**
  Case reports appearing in the peer-reviewed medical literature often serve as initial indicators of possible herb-drug interactions. Case reports usually cannot establish causation, but may help generate hypotheses for possible mechanisms.

• **Adverse Event Reports (AERs)**
  Herb-drug interactions may underlie many AERs submitted to the FDA’s MedWatch program or Poison Control Centers across the U.S.

• **In vitro screenings**
  Effects of phytochemicals on purified enzymes/transporters or isolated cell lines expressing human drug metabolizing enzymes/transporters.

• **Prospective in vivo studies**
  Assess various effects of botanicals using human subjects.
Potential mechanisms for herb-drug interactions

**Pharmacodynamic interactions:**

- Botanicals having pharmacological properties similar to or opposite those of conventional Rx.
  - Caffeine-containing dietary supplements
    - *Ephedra*-free weight-loss supplements
  - Licorice
Caffeine-containing beverages (coffee and tea) have been a mainstay in western and eastern societies for hundreds of years.

Natural caffeine sources: coffee, tea (green or black), cocoa, guarana, yerba maté, kola nut, guayusa, yaupon holly, others.

Multi-ingredient, caffeine-containing dietary supplements are relatively new entities, making their debut in the early 1990s.
Natural Caffeine Sources: Historical Timeline

- **Coffee and tea:** 1500’s – present
- **Colas:** 1880’s – present
- **Chocolate candy:** 1880’s – present
- **Energy drinks:** 1990 – present
- **Ephedra-containing DS:** 1994 – 2004 (caffeine + ephedrine alkaloids)
- **Ephedra-free DS:** 2004 – present (caffeine + other natural sympathomimetics)
Caffeine Pharmacology

- **Caffeine** (1,3,7-trimethylxanthine) is one of the most widely consumed and heavily studied stimulants in history.

- As a phytochemical, caffeine has excellent oral bioavailability, a small apparent volume of distribution, and is not highly protein bound.

- Readily crosses the blood brain barrier.

- **Dose-dependent CNS and cardiovascular stimulant effects** (mood enhancement, wakefulness, anxiety, increased heart rate, elevated blood pressure, coronary and peripheral vasoconstriction, tremors, seizures) are due to:
  - **Nonselective adenosine antagonist** ($A_1$ and $A_{2A}$ receptors).
  - **Nonselective inhibitor of phosphodiesterases and accumulation of cAMP**.
  - **Activation of ryanodine receptor channels**.
  - **Inhibitor of GABA neurotransmission**.

  *(Only at higher serum concentrations [>25 µg/mL] do the last three mechanisms contribute to caffeine pharmacodynamics.)*

- Tolerance may develop with chronic exposure.
As a general rule, caffeine-containing beverages have an excellent safety profile.

Safety concerns with caffeine-containing beverages are typically associated with either over-indulgence, or individual sensitivities.

The safety profile for multi-ingredient, caffeine-containing dietary supplements, however, is less clear.
Caffeine Adverse Event Citations in the Medical Literature

Figure 1. Citation counts for articles about caffeine adverse effects in the PubMed® and Web of Science (WOS)™ databases by year.

Why do multi-ingredient, caffeine-containing dietary supplements sometimes produce adverse health effects?

- Overindulgence and/or underlying health issues.
- Taken concomitantly with other prescription stimulants:
  - e.g., amphetamines, methylphenidate, sibutramine, etc.
- Formulated with other naturally occurring stimulants:
  - e.g., ephedrine alkaloids, synephrine, phenylethylamines, yohimbine, forskolin, etc.
- Adulterated with prescription or illicit stimulants:
  - e.g., sibutramine, DMAA, BMPEA, etc.
- Consumers expressing genetic polymorphisms of receptors, enzymes, and transporters involved in caffeine disposition.
  - e.g., $A_{2A}$, COMT, CYP1A2, hERG, etc.
- Often taken in combination with vigorous exercise.
  - products frequently marketed as exercise performance enhancers.
Ephedra Case Reports

ADVERSE CARDIOVASCULAR AND CENTRAL NERVOUS SYSTEM EVENTS ASSOCIATED WITH DIETARY SUPPLEMENTS CONTAINING EPHEDRA ALKALOIDS

Ischemic stroke after using over the counter products containing ephedra

Seizure Activity and Unresponsiveness after Hydroxycut Ingestion

Ischemic stroke in a user of Thermadrene: A case study in alternative medicine

Adverse Cardiovascular Events Temporally Associated With Ma Huang, an Herbal Source of Ephedrine
Ephedra (Ma-huang) Supplements

- Natural source of ephedrine-type alkaloids: ephedrine, pseudoephedrine, methylephedrine, norephedrine, norpseudoephedrine (C-IV).

- Content of ephedrine alkaloids vary. (species, location, growing conditions, time of harvest, method of processing)

- Often formulated with multiple botanicals whose interactions have yet to be thoroughly investigated (guarana, *Citrus aurantium*, etc.).
Methamphetamine

Ephedrine

Phenylpropanolamine

Synephrine
Ephedra (Ma-huang) Supplements
(Ephedrine/caffeine combinations)

- Ephedra-containing dietary supplements frequently formulated with natural sources of caffeine (guarana, green tea, kola nut, Yerba maté).

- OTC products containing multiple ephedrine alkaloids or ephedrine/caffeine combinations ("amphetamine look-alikes") were prohibited by FDA in 1983.
Ephedra (Ma-huang) Supplements
(Ephedrine/caffeine combinations: herb-herb intx.)

- Ephedrine/caffeine potentiate each others cardiovascular and CNS stimulant effects.

- Ephedrine/caffeine has 1/5–1/10 the potency of (+)amphetamine.

- Phytochemicals (catechins, xanthones, tannins) present in natural CFE sources (green tea, guarana, kola nut) potentiate sympathomimetic activity of EPH/CFE by inhibiting COMT or MAO.

- EPH/CFE significantly lowers cerebral blood flow.
Ephedrine and Caffeine Pharmacokinetics

EPH alkaloids and CFE from *Ephedra* DS are bioavailable and exhibit similar Tmax values.

Toxicity concerns exacerbated when taken in conjunction with exercise!

Exercise and Ephedra DS were a common feature of AERs and case reports.
In 2004, the FDA removed Ephedra-containing DS from the U.S. market due to an increased risk of adverse health effects. Ephedra-free DS quickly supplanted their problematic namesakes.
Case reports with merit: *Ephedra-free*

**Hypertensive Urgency Associated With Xenadrine EFX Use**

**Vasospasm and Stroke Attributable to Ephedra-Free Xenadrine: Case Report**

**Case report**

**Malignant hypertension and acute aortic dissection associated with caffeine-based ephedra-free dietary supplements: a case report**

**A Case of Severe Exercise-Induced Rhabdomyolysis Associated with a Weight-Loss Dietary Supplement**
Ephedra Alternatives

- Natural sources of caffeine are now the most frequently used substitutes for Ephedra.

- Caffeine sources: Guarana, Green tea, Kola nut, Yerba maté, combinations of each.

- Typical recommended servings can contain as much caffeine as 3-6 cups of regular coffee, sometimes more.

- Are high dose caffeine products safer?
Randomized clinical trial with 3 popular Ephedra-free supplements

- 12 subjects, 4 Ephedra-free DS, 2 capsules t.i.d for 3 days.
- BP, HR, ECG monitored daily and baseline.
- Significant increase in SBP, DBP, HR, and abnormal ECG activity.
- Other effects: N&V, headache, insomnia, etc.
- Caffeine dose and complexity of formulation may contribute to effects.
- Two products heavily contaminated with Bacillus species

Pharmacodynamic herb-drug interaction considerations of “Ephedra-free” supplements

- Consumers of “ephedra-free” supplements may be obese with underlying cardiovascular disease.

- Such consumers may take antihypertensive and other cardiovascular medications concomitantly.

- Study suggests that “ephedra-free” may not be “trouble-free” in certain consumers.

Licorice root extract formulations
*(Glycyrrhiza glabra)*

- Found in many multi-ingredient weight-loss supplements

- **Interaction mechanism:**
  Chronic use leads to sodium retention, potassium depletion due to mineralocorticoid effect of glycyrhizic acid and its metabolite (monoglucuronyl-18β-glycyrrhetinic acid) which inhibits 11-β-hydroxysteroid dehydrogenase.

- **Interactions:**
  Antihypertensives (diuretics), antiarrhythmics

- **Consequences:**
  Hypertension, hypokalemia, arrhythmias
Potential mechanisms for herb-drug interactions

**Pharmacokinetic mechanism:**
- Affect drug absorption, distribution, metabolism, excretion.
- Modulation of drug metabolizing enzymes in small intestine and liver. (e.g. CYPs, UGTs, GSTs, SULTs, etc.)
- Modulation of drug transporting proteins in small intestine, liver, blood brain barrier. (e.g. P-glycoprotein, OATP, OCT, etc)
Approximate percentage of drugs metabolized by CYP enzymes
Pharmacokinetic effect of CYP and/or Pgp modulation
Herb-drug interactions:
St. John’s wort (*Hypericum perforatum*)

- **Indication:** Antidepressive
- **Efficacy:** Good (product-dependent)
- **Drug Interaction Risk:** Very High! Renders most drugs ineffective
Effect of SJW on CYP3A4 Phenotype

**Young**: [Average increase = 98%] (Range = 17%-240%)

**Elderly**: [Average increase = 141%] (Range = 58%-725%)


Gurley et al., *Drugs & Aging* 2006; 46:201-213
Effect of SJW on Cyclosporine Trough Concentrations

Heart TXP with rejection

Liver TXP with rejection
(Karliova et al. *J. Hepatol.* 2000; 33:853)

Kidney TXP with rejection
(Barone et al. *Transplantation* 2001; 71:239
What makes St. John’s wort so problematic?

**Mechanism:**
Induction of CYPs (e.g., CYP3A4, 2C9, 2C19, 2E1) and efflux transporters (e.g., ABCB1, ABCG2)
Binds to hPXR to induce CYP and ABC gene expression

**Responsible phytochemicals:**
Hyperforin, adhyperforin

Most potent hPXR ligand yet discovered!
(Ki ≈ 25nM)
More potent than rifampin!
What makes St. John’s wort so problematic?

600 mg/day rifampin (C) similar to 24 mg/day hyperforin (D) with regard to effects on digoxin PCK.

What makes St. John’s wort so problematic?

- CYP3A4 and P-gp responsible for metabolism and transport of ≥50% of conventional drugs.

- Hyperforin responsible for antidepressive activity.

- SJW products once standardized for hypericin (0.3%), yet hypericin exhibits no anti-depressive activity nor does it affect CYP.

- SJW products now standardized to hyperforin. (Hyperforin content not always indicated on label.)
<table>
<thead>
<tr>
<th>Product</th>
<th>Hyperforin (mg/g)</th>
<th>Hypericin (mg/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A&lt;sub&gt;1&lt;/sub&gt;</td>
<td>13.6</td>
<td>0.25</td>
</tr>
<tr>
<td>A&lt;sub&gt;2&lt;/sub&gt;</td>
<td>3.8</td>
<td>0.30</td>
</tr>
<tr>
<td>B</td>
<td>5.3</td>
<td>0.30</td>
</tr>
<tr>
<td>C</td>
<td>10.0</td>
<td>0.30</td>
</tr>
<tr>
<td>D</td>
<td>7.4</td>
<td>0.28</td>
</tr>
<tr>
<td>E</td>
<td>1.1</td>
<td>0.35</td>
</tr>
<tr>
<td>F</td>
<td>1.1</td>
<td>0.24</td>
</tr>
</tbody>
</table>
What makes St. John’s wort so problematic?

- **Interaction Mechanism:**
  Induces CYP3A4, CYP2C9, CYP2E1, other CYPs as well as P-gp and other efflux transporters.

- **Interactions:**
  Cyclosporine, digoxin, warfarin, BCPs, simvastatin, indinavir, midazolam, verapamil, irinotecan, omeprazole, many others…

- **Consequences:**
  Numerous!! Renders most medications ineffective!
Herb-drug interactions: Goldenseal (*Hydrastis canadensis*)

- **Indication:** Numerous
  Colds, URTIs, mask urine Rx screens

- **Efficacy:** Poor

- **Drug Interaction Risk:** Likely!
  Inhibits metabolism of many drugs
Effect of goldenseal on CYP3A4 & 2D6:

Gurley et al., Clin. Pharmacol Ther., 2008; 83:61-69
What makes goldenseal problematic?

- *In vivo* activity of CYP3A4 & 2D6 reduced by 40% (clinically relevant).

- CYP3A4 & 2D6 responsible for metabolism of ≥75% of conventional drugs.

- Two isoquinoline alkaloids (hydrastine and berberine) are *mechanism-based* inhibitors CYP isoforms.
Goldenseal isoquinoline alkaloids

broken circle = methylenedioxyphenyl (MDP) moiety

Historical perspective of goldenseal’s effect on CYP3A4

- During the American Civil War quinine (Cinchona bark) was one of the few effective febrifuges available to both armies.
- Quinine was in short supply in the Confederate army.
- Goldenseal was often administered with quinine to prolong its antipyretic effects and reduce its dose.
- Quinine is a CYP3A4 substrate.
Other MDP-containing botanicals

*Piper longum & Piper nigrum* (black pepper)
Effect of *Piper nigrum* on nevirapine
Other MDP-containing botanicals
(Schizandra chinensis)
Effect of *Schizandra* on tacrolimus

Schizandra extract increases tacrolimus absorption
Resveratrol (1 gram/day) decreases the activity of various CYPs, especially CYP2C9

Effect of *resveratrol* on diclofenac AUC

Resveratrol (500 mg/day) markedly increases AUC of diclofenac, a CYP2C9 substrate

Bedada et al., *Phytother. Res.* 2015; DOI: 10.1002/ptr.5539
Green tea (700 ml/day) decreases nadolol absorption, reduces cumulative renal excretion of nadolol, and reduces its antihypertensive effect.

What makes green tea problematic?

- Green tea catechins inhibit OATP1A2-mediated uptake both \textit{in vitro} and \textit{in vivo}.
- Green tea catechins inhibit other uptake transporters \textit{in vitro} (e.g., OATP2B1), thus green tea may adversely affect other drugs whose absorption is OATP-mediated.
- Green tea is one of the world’s most popular beverages and is a component of many weight-loss supplements.

![Epigallocatechin gallate (EGCG)](image)
Many popular botanical supplements do not appear to pose a serious drug interaction risk; however, the vast majority have yet to be studied in a clinical setting.
Bioavailability of most phytochemicals is poor

- Echinacea
- Black cohosh
- Saw palmetto
- Ginkgo biloba

- **Systemic effects of many botanical DS are minimal due to:**
  - **poor dosage form performance**
    (inadequate dosage form disintegration and/or dissolution)
  - **extensive pre-systemic metabolism**
Emerging technologies for improving phytochemical bioavailability

- Recognizing that many “active” phytochemicals have poor aqueous solubility (and/or permeability) and undergo significant first-pass effects, new formulation technologies have been implemented to improve dissolution and bioavailability.

- None of these new botanical formulations have been evaluated for their drug interaction potential in humans!
  - Liposomes
  - Phytosomes (complexes of phosphatidylcholine and polyphenols)
  - Self-emulsifying drug delivery systems (SEDDS)
  - Nanoparticles
  - Phytochemical inhibitors of xenobiotic metabolism (e.g., piperine)
Emerging Technologies: Phytosomes

**Definition:** complexes of phosphatidylcholine and various polyphenolic phytochemicals (e.g., flavonoids).

**Advantages:** improved stability and shelf life; phytochemical bioavailability can be improved 2-6 fold. May improve permeability and/or solubility. Several products are commercially available:

- milk thistle
- curcumin
- green tea catechin polyphenols
- grape seed proanthocyanidins
- *Ginkgo biloba*

**Disadvantages:** limited primarily to polyphenolics.
Phytosomes: An example with Silybin (milk thistle)

Absorption: Silybin vs. Milk Thistle (mg/ml)

- Milk Thistle
- Silybin

Hours

0 2 4 6
Certain categories of dietary supplements have been plagued by problems of adulteration with prescription medications.

- Weight-loss supplements
- Exercise performance enhancers
- Sexual performance enhancers

Some herb-drug interactions are actually drug-drug interactions in disguise

Many herbs of commerce are also prone to adulteration with plant species that are cheaper and less effective.
Sexual performance enhancement supplements are especially prone to adulteration and removal from the market by the FDA. 

- sildenafil, tadalafil, vardenafil, or various synthetic analogs of these are frequently encountered.

Almost on a daily basis, the FDA submits warning letters to manufacturers about adulterated herbal sex/male enhancement products. Thousands of such products have been removed from the market.
Adulteration: Anabolic steroids and analogs

- Many sports and/or exercise performance enhancement supplements are prone to adulteration with synthetic anabolic steroids and anabolic steroid analogs.
- Serious toxicities can result from prolonged usage.

Hepatotoxicity Associated With Dietary Supplements Containing Anabolic Steroids

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http://www.fda.gov/bbs/topics/NEWS/2008/NEW01933.html
Many adulterated products originate from foreign countries (e.g., China, India, Brazil, etc.)
Conclusions

- Botanical supplements can interact with conventional medications.
  - Mechanism(s) may be pharmacodynamic (similar pharmacology) or pharmacokinetic (e.g. induction or inhibition of drug metabolizing enzyme/transporter activity).

- Many popular botanicals pose little risk for drug interactions; yet, most botanicals have not been evaluated in vivo.

- Novel dosage forms may increase the risk for herb-drug interactions.

- Supplements adulterated with prescription Rx may give rise to drug-drug interactions.
Information Resources

www.nccih.nih.gov
www.ods.od.nih.gov
www.consumerlab.com

ConsumerLab.com

www.naturaldatabase.therapeuticresearch.com

Natural Medicines Comprehensive Database

Natural Standard
The Authority on Integrative Medicine
Further reading


Which Brands to Buy?

- The United States Pharmacopoeia (USP) sets standards for drug and dietary supplement quality.

- Supplement manufacturers whose products meet the USP’s stringent standards display the USP quality verification certificate on the label.