What Clinicians Should Know About Botanicals

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Chair: USP Dietary Supplement Admissions, Evaluation and Labeling Expert Committee

Author of National Geographic’s
- Fortify Your Life
- Healthy At Home
- Life Is Your Best Medicine
- Guide to Medicinal Herbs
What Clinicians Really Face

• 62-year-old man type 2 diabetes, hypertension, dyslipidemia, GERD, back pain, knee osteoarthritis: taking metformin, lisinopril, simvastatin, esomeprazole, and acetaminophen.

• During 20-minute office visit, he reports his back and knee pain are getting progressively worse and wants something “natural.”

• He has brought in two products containing 15 herbs and asks if it is okay to take them.

• Are they safe? Will they interact with his meds? Will they help?
Take 2 capsules 2 times day

Take 4 capsules 2-3 times per day.
“Made in US FDA Regulated Facility”
Real World: Real Confusion

- No training in the use of botanical remedies.
- Too little time during appointments for counseling.
- Labels are often difficult to read and interpret.
- Dosing of different extracts makes recommendations difficult.
- Concerns over safety and potential drug interactions.
- Concerns over quality.
- Finding unbiased resources.
Herb-Drug Interactions (HDI)

- **Human pharmacokinetic studies** are the gold standard for evaluating clinical consequences of potential HDI.
- **Preclinical data** suggests many herbs interact with drugs, BUT many predicted HDI have shown no clinically significant effects. To minimize discrepancies, the same botanical material or extract should be used at all stages of study.
- More crucial the drug or narrower the therapeutic window—*interactions must be closely monitored.*
- There are numerous HDI checkers on the Internet.

Sprouse AA, van Breemen RB. *Drug Metab Dispos* 2016;44:162-171
<table>
<thead>
<tr>
<th>Common Name (Latin Binomial)</th>
<th>Preclinical Interactions</th>
<th>Clinical Interactions</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Inhibition</td>
<td>Induction</td>
</tr>
<tr>
<td>Gingko (Ginkgo biloba)*</td>
<td>CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A (Ohnishi et al., 2003; Yale and Glurich, 2005; OATP2B1 (Fuchikami et al., 2006)</td>
<td>—</td>
</tr>
<tr>
<td>Ginseng (Panax spp.)*</td>
<td>CYP1A2, CYP2A6, CYP2C9, CYP2D6, CYP3A4, UGT2B15 (Anderson et al., 2003); CYP2C9, CYP2C19, CYP2D6, CYP3A4 (Foster et al., 2002)</td>
<td>—</td>
</tr>
<tr>
<td>Goldenseal (Hydrastis Canadensis)</td>
<td>CYP2D6, CYP2C9, CYP2C19, CYP3A4 (Budzinski et al., 2000; Chatterjee and Franklin, 2003; Foster et al., 2003)</td>
<td>—</td>
</tr>
<tr>
<td>Green tea (Camellia sinensis)*</td>
<td>CYP1A2 (Netsch et al., 2006); CYP3A4 (Moore et al., 2000); OATP2B1 (Mao et al., 2013)</td>
<td>—</td>
</tr>
<tr>
<td>Isoflavones [e.g., soy (Glycine max) and red clover, (Trifolium pretense)]</td>
<td>Soy: CYP1A2, CYP2A6, CYP2C9, CYP2D6 (Modarai et al., 2006); CYP3A4 (Li and Doshi, 2011); OATP22B1 (Mao et al., 2013)</td>
<td>CYP3A4 (Modarai et al., 2006)</td>
</tr>
</tbody>
</table>

From: Sprouse AA, van Breemen RB. *Drug Metab Dispos* 2016;44:162-171
NATURAL MEDICINES

The most authoritative resource available on dietary supplements, natural medicines, and complementary alternative and integrative therapies.

LEARN MORE
One example of a drug-supplement interaction checker.

Available through many academic and medical institutions.

**RED** represents a very serious interaction

**Yellow** is moderate risk

**Green** is typically theoretical or low risk

Authoritative, up-to-date assessment on potential herbal-supplement-drug induced liver injury.

https://www.ncbi.nlm.nih.gov/books/NBK547852/

Accessed January 17, 2023
### Quality Concerns

- Domestically produced **products** generally better quality than imported from China/ India.
- **3rd party testing** (e.g., USP, NSF, CL, NNFA) **quality indicator**.
- Steer patients away from most herbal products in **weight loss, sexual enhancing, or bodybuilding** categories.
- **Consumer Labs** can be a useful website for assessing quality.

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**Tables on Left From FDA:**


Accessed November 3, 2022
Elderberry Systematic Review

- Elderberry *may not* reduce the risk of developing the common cold.
- It *may* reduce duration and severity of colds, evidence is uncertain.
- It *may* reduce duration of influenza, evidence is uncertain.
- Compared to oseltamivir, elderberry-containing product may be associated with lower risk of influenza complications and AE.
- There is no evidence that it overstimulates the immune system.

Cranberry for Recurrent UTI

- **American Urological Association**: “Clinicians may offer cranberry prophylaxis for women with rUTIs.”

- **Only non-antibiotic prophylaxis** the AUA Guideline recommends.

- **Products should provide minimum 36 mg/d PAC** — this is minimum amount required to promote bacterial anti-adhesion activity and contribute to UTI prevention.

### Supplement Facts

<table>
<thead>
<tr>
<th>Serving Size: 1 capsule</th>
<th>% Daily Value</th>
</tr>
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<tbody>
<tr>
<td>Servings Per Container: 30</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Amount Per Capsule</th>
<th>% Daily Value</th>
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<tbody>
<tr>
<td>Urophenol™ - 240 mg</td>
<td></td>
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<tr>
<td>Cranberry (125:1)</td>
<td>t</td>
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<tr>
<td>(Vaccinium macrocarpon) fruit extract providing 15% proanthocyanidins (PACs) = 36 mg PAC per DMAC/A2</td>
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First Line Therapy: Nonpharmacologic Options

- Convert prenatal to folic acid supplement only
- Ginger capsules 250 mg four times daily
- Consider P6 acupressure with wrist bands

If persistent symptoms

Pharmacologic Options

Vitamin B6 (pyridoxine) 10-25 mg orally (either taken alone or in combination with doxylamine 12.5 mg orally), 3-4 times per day. Adjust schedule and dose according to severity of patient's symptoms.

OR

Vitamin B6 (pyridoxine) 10 mg/doxylamine 10 mg combination product, two tablets orally at bedtime initially up to four tablets per day (one tablet in morning, one tablet in midafternoon and 2 tablets at bedtime.)
Peppermint Leaf (Mentha piperita)

- Meta-analysis RCTs: soluble fiber, antispasmodic drugs, peppermint oil, and gut-brain neuromodulators for IBS. Most studies of low risk of bias.

- Peppermint essential oil ranked first for efficacy when global symptoms used as outcome measure, and tricyclic antidepressants ranked first for efficacy when abdominal pain used as the outcome measure.

- Dose 0.2 ml in enteric coated caps BID-TID

Now Back To Our Patient
**Take 2 capsules 2 times day**

<table>
<thead>
<tr>
<th>Serving Size: 2 Vegetarian Capsules</th>
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<tbody>
<tr>
<td>Servings Per Container: 30</td>
<td></td>
</tr>
<tr>
<td><strong>Amount</strong></td>
<td><strong>% Daily Value</strong></td>
</tr>
<tr>
<td>Per Serving</td>
<td></td>
</tr>
<tr>
<td>White Willow Extract (Salix alba) (bark)</td>
<td></td>
</tr>
<tr>
<td>Salicin (15%)</td>
<td></td>
</tr>
<tr>
<td>Devil's Claw Extract 1.8:1 (Harpagophytm procumbens) (root)</td>
<td></td>
</tr>
<tr>
<td>400 mg</td>
<td>**</td>
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<tr>
<td>60 mg</td>
<td></td>
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<tr>
<td>Theracurmin Curcumin† Extract from Turmeric (Curcuma longa) (root)</td>
<td></td>
</tr>
<tr>
<td>60 mg</td>
<td>**</td>
</tr>
<tr>
<td>Boswellia Extract (Boswellia serrata) (gum)</td>
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<tr>
<td>Boswellic Acid (60%)</td>
<td></td>
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<tr>
<td>150 mg</td>
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<tr>
<td>90 mg</td>
<td></td>
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<tr>
<td>Ultra Fruit Polyphenol Complex [blueberry, bilberry, cranberry, grape, pomegranate, raspberry, strawberry]</td>
<td></td>
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<tr>
<td>100 mg</td>
<td>**</td>
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</table>

**Take 4 capsules 2-3 times per day.**

“Made in US FDA Regulated Facility”

<table>
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<th>Supplement Facts</th>
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<tr>
<td>Serving Size: 4 capsules</td>
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<tr>
<td>Servings Per Container: 15</td>
<td></td>
</tr>
<tr>
<td><strong>Amount</strong></td>
<td><strong>% Daily Value</strong></td>
</tr>
<tr>
<td>Per Serving</td>
<td></td>
</tr>
<tr>
<td>Proprietary herbal blend</td>
<td>2.6 g</td>
</tr>
</tbody>
</table>

Cramp Bark, Jamaica Dogwood (Bark), Black Haw (Bark), Rosemary, Kava Kava (Root), Passion Flower, Valerian (Root), Mexican Wild Yam (Root), Red Raspberry (Leaf), Lobelia (Leaf), St. John's Wort
Willow Bark (*Salix* spp.)

- Studies show efficacy back pain and arthritis.
- Willow bark supplements deliver up to 240 mg of salicin, can be metabolized to 113 mg salicylic acid. (This product 60 mg salicin per serving)
- Low-dose aspirin (62 mg of salicylic acid) must include guidelines on use in pregnant women/children; info on blood coagulation.
- USP panel recommended same labeling for dietary supplements.

Turmeric Rhizome (*Curcuma longa*)

- Tuft’s systematic review: curcumin significantly **more effective** than placebo and equivalent to NSAIDs for **pain relief** and functional improvement in knee osteoarthritis.\(^1\)
- Low aqueous solubility of curcumin and **rapid metabolism and elimination** lead to questions about formulation/delivery.
- **Adverse effects:** primarily GI.

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Dose: 1000-1200 mg per day of standardized extract (95% curcumin). May contain piperine or be liposomal bound: Meriva.
Caution with piperine 20 mg/d – multiple drug interactions

Devil’s Claw  
(*Harpagophytum procumbens* DC. Ex Meisn.)

- Analgesic, anti-inflammatory, digestant.
- Native to southern and eastern Africa.
- Dried, secondary tubers used as analgesic for centuries.
- Studies confirm beneficial effect for back pain and osteoarthritis.
- Safety review of 28 clinical trials found few adverse effects, up to 8% of patients report diarrhea with higher dosing.

Jamaican Dogwood Root Bark  
(*Piscidia piscipula* L. Sarg.)

- Root bark used for general pain and as a sedative.
- Contains rotenone, a neurotoxic pesticide. Environmental research suggests it may be a causative agent for Parkinson’s disease and it is being used as a modeling tool for the disease.¹
- The safety, especially long-term of orally ingested Jamaican dogwood root bark is unclear.

Lobelia Leaf/Herb \((\text{Lobelia inflata L.})\)

- Lobelia long-used as a **bronchodilator**, antispasmodic, and sedative.
- Also known as “**puke-weed**”—is a **potent emetic** and can cause nausea, vomiting, diarrhea, coughing, dizziness, tremors, and throat irritation.

- **Vomiting usually occurs before significant toxicity**, however, can cause convulsions and respiratory depression.
- Potent alkaloids partial nicotinic agonists.
- FDA considers it an “unsafe herb.”
In Closing…

• With increasing rates of multimorbidity, polypharmacy is the norm, not the exception.

• The burden on clinicians to counsel patients on the safe and effective use of botanical products is overwhelming, complex, and time consuming.

• While serious AER are not common, they do and will happen. Better predictive tools are necessary for decision making.