

What Clinicians Should Know About Botanicals



Tieraona Low Dog, MD, ABOIM

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

Tieraona Low Dog, M.D.







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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?

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



Take 2 capsules 2 times day

Supplement Facts		
Serving Size: 4 capsules		
Servings Per Container: 15		
	Amount Per Serving	%Daily Value
Proprietary herbal blend	2.6 g	†
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		



Take 4 capsules 2-3 times per day.
"Made in US FDA Regulated Facility"

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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

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

Common Name (Latin Binomial)	Preclinical Interactions		Clinical Interactions		
	Inhibition	Induction	Inhibition	Induction	No Effect
Ginkgo (<i>Ginkgo biloba</i>) ^a	CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A (Ohnishi et al., 2003; Yale and Glurich, 2005); OATP2B1 (Fuchikami et al., 2006)	—	—	—	CYP1A2, CYP2D6, CYP2E1, CYP3A4 (Gurley et al., 2002); MDR1 (Mauro et al., 2003)
Ginseng (<i>Panax spp.</i>) ^{a, b}	CYP1A2, CYP2A6, CYP2C9, CYP2D6, CYP3A4, UGT2B15 (Anderson et al., 2003); CYP2C9, CYP2C19, CYP2D6, CYP3A4 (Foster et al., 2002)	—	—	—	CYP1A2, CYP2D6, CYP2E1, CYP3A4 (Gurley et al., 2002); CYP3A4 (Anderson et al., 2003)
Goldenseal (<i>Hydrastis Canadensis</i>)	CYP2D6, CYP2C9, CYP2C19, CYP3A4 (Budzinski et al., 2000; Chatterjee and Franklin, 2003; Foster et al., 2003)	—	CYP2D6 (Gurley et al., 2005, 2008); CYP3A4/CYP3A5 (Gurley et al., 2005)	—	CYP1A2, CYP2E1 (Gurley et al., 2005)
Green tea (<i>Camellia sinensis</i>) ^a	CYP1A2 (Netsch et al., 2006); CYP3A4 (Moore et al., 2000); OATP2B1 (Mao et al., 2013)	—	—	—	CYP2D6, CYP3A4 (Chatterjee and Franklin, 2003); ECGC: CYP1A2 (Chow et al., 2006); CYP2D6, CYP2C9, CYP3A (Wang et al., 2001)
Isoflavones [e.g., soy (<i>Glycine max</i>) and red clover, (<i>Trifolium pretense</i>)]	Soy: CYP1A2, CYP2A6, CYP2C9, CYP2D6 (Modarai et al., 2006); CYP3A4 (Li and Doshi, 2011); OATP2B1 (Mao et al., 2013)	CYP3A4 (Modarai et al., 2006)	—	—	Soy: CYP3A4 (Modarai et al., 2006)

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Clear Print

Search Matches (Click to Add)

- A & C Plus Fenugreek by Vitality Products Inc
- A & D
- A & D
- A & D
- A & D
- A & D
- A & D

Selected Agents (Click to Remove)

- Plavix (Clopidogrel)
- Lovastatin
- Captopril
- Green Tea Extract
- Curcumin 500 with Bioperine by Pure Encapsulations
- St John's Wort by BioAid Health Products

Results Summary (Click for Details)

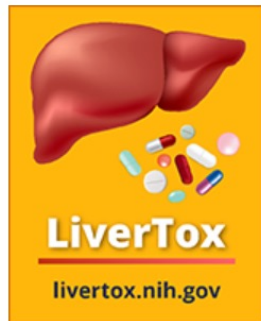
Click on any interaction below for more information.

Lovastatin <<interacts with>> ST. JOHN'S WORT (Hypericum perforatum) contained in "St John's Wort by BioAid Health Products"	View Details
Interaction Rating = Major Do not take this combination.	
Plavix <<interacts with>> ST. JOHN'S WORT (Hypericum perforatum) contained in "St John's Wort by BioAid Health Products"	View Details
Interaction Rating = Major Do not take this combination.	
Captopril <<interacts with>> ST. JOHN'S WORT (Hypericum perforatum) contained in "St John's Wort by BioAid Health Products"	View Details
Interaction Rating = Moderate Be cautious with this combination.	
Lovastatin <<interacts with>> BLACK PEPPER contained in "Curcumin 500 with Bioperine by Pure Encapsulations"	View Details

- 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

Natural Medicines Database. <https://naturalmedicines-therapeuticresearch-com.ezproxy2.library.arizona.edu/#C>. Accessed November 15, 2022

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LiverTox

Clinical and Research Information on Drug-Induced Liver Injury

Bethesda (MD): [National Institute of Diabetes and Digestive and Kidney Diseases](#); 2012-.

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New In LiverTox
Smallpox drugs used
for Monkeypox
Brincidofovir
Tecovirimat

2022 Survey Results
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LiverTox[®] provides up-to-date, unbiased and easily accessed information on the diagnosis, cause, frequency, clinical patterns and management of liver injury attributable to prescription and nonprescription medications and selected herbal and dietary supplements. The LiverTox site is meant as a resource for both physicians and patients as well as for clinical academicians and researchers who specialize in idiosyncratic drug induced hepatotoxicity.

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

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Date	Product ¹	Firm	Firm Address	Source/URL(s)	Subject	Action	Program Area(s)	Additional Outcome
08/02/2022	SANGTER Energy Supplement, 3000mg	Distributor RFR, LLC	Miami, FL	sangter.com and retail stores	Undeclared sildenafil	Recall	Drugs	
07/28/2022	Honeymoon Exclusive For Men & Women	n/a	n/a	Examination of imported goods	Undeclared tadalafil and sildenafil	Public Notification		
07/25/2022	Sustango	Ultra Supplement LLC	Wilmington, DE	amazon.com	Undeclared tadalafil	Recall	Drugs	
07/22/2022	Lipopastilla + Gold Max	n/a	n/a	lipopastillas.com	Undeclared sibutramine and phenolphthalein	Public Notification		
07/15/2022	Adam's Secret Extra Strength Blue	n/a	n/a	adamssecret.com	Undeclared tadalafil	Public Notification	Drugs	
07/15/2022	Adam's Secret Extra Strength Purple	n/a	n/a	adamssecret.com	Undeclared tadalafil and sildenafil	Public Notification	Drugs	
07/15/2022	Adam's Secret Extra Strength Amazing Black	n/a	n/a	adamssecret.com	Undeclared tadalafil	Public Notification	Drugs	
07/15/2022	Adam's Secret Extra Strength 300 Platinum (White Packaging)	n/a	n/a	adamssecret.com	Undeclared tadalafil	Public Notification	Drugs	
06/27/2022	Launch Sequence Capsules	Loud Muscle Science, LLC	n/a	amazon.com, amazon.ca, ebay.com, and retail stores	Undeclared tadalafil	Recall	Drugs	
06/27/2022	Launch Sequence Euphoria Capsules	Loud Muscle Science, LLC	n/a	amazon.com, amazon.ca, ebay.com, and retail stores	Undeclared tadalafil	Recall	Drugs	

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.

Tables on Left From FDA:

[.fda.gov/scripts/sda/sdNavigation.cfm?filter=&sortColumn=1d&sd=tainted_supplements_cder&page=1](https://www.fda.gov/scripts/sda/sdNavigation.cfm?filter=&sortColumn=1d&sd=tainted_supplements_cder&page=1)

Accessed November 3, 2022

Elderberry Systematic Review

Elderberry supplement sales skyrocketed to \$320 million in 2020: ABC report

By Stephen Daniells

15-Sep-2021 - Last updated on 15-Sep-2021 at 22:41 GMT



© S847 / Getty Images

- 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.

Wieland LS, et al. *BMC Complement Med Ther* 2021 Apr 7;21(1):112.

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Cranberry for Recurrent UTI



Supplement Facts

Serving Size: 1 capsule
Servings Per Container: 30

Amount Per Capsule	% Daily Value
Urophenol™ - 240 mg	†
Cranberry (125:1) (Vaccinium macrocarpon) fruit extract providing 15% proanthocyanidins (PACs) = 36 mg PAC per DMAC/A2	

- **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**.

Recurrent Uncomplicated Urinary Tract Infections in Women: AUA/CUA/SUFU Guideline (2019) www.auanet.org/guidelines/recurrent-uti Accessed 1/13/23

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ACOG PRACTICE BULLETIN

Clinical Management Guidelines for Obstetrician–Gynecologists

NUMBER 189, JANUARY 2018

(Replaces Practice Bulletin 153, September 2015)

Committee on Obstetric Practice—This Practice Bulletin was developed by the American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Obstetrics in collaboration with Susan M. Ramin, MD.

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

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).

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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



Black CJ, et al. *Lancet Gastroenterol Hepatol*. 2019 Dec 16. pii: S2468-1253(19)30324-3.

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Now Back To Our Patient

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Serving Size: 2 Vegetarian Capsules		
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Boswellia Extract (Boswellia serrata) (gum)	150 mg	**
Boswellic Acid (60%)	90 mg	**
Ultra Fruit Polyphenol Complex [blueberry, bilberry, cranberry, grape, pomegranate, raspberry, strawberry]	100 mg	**



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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.**

Oketch-Rabah H, Marles RJ, Jordan SA, Low Dog, T. United States Pharmacopeia Safety Review of Willow Bark *Planta Med* 2019; 85(16): 1192-1202

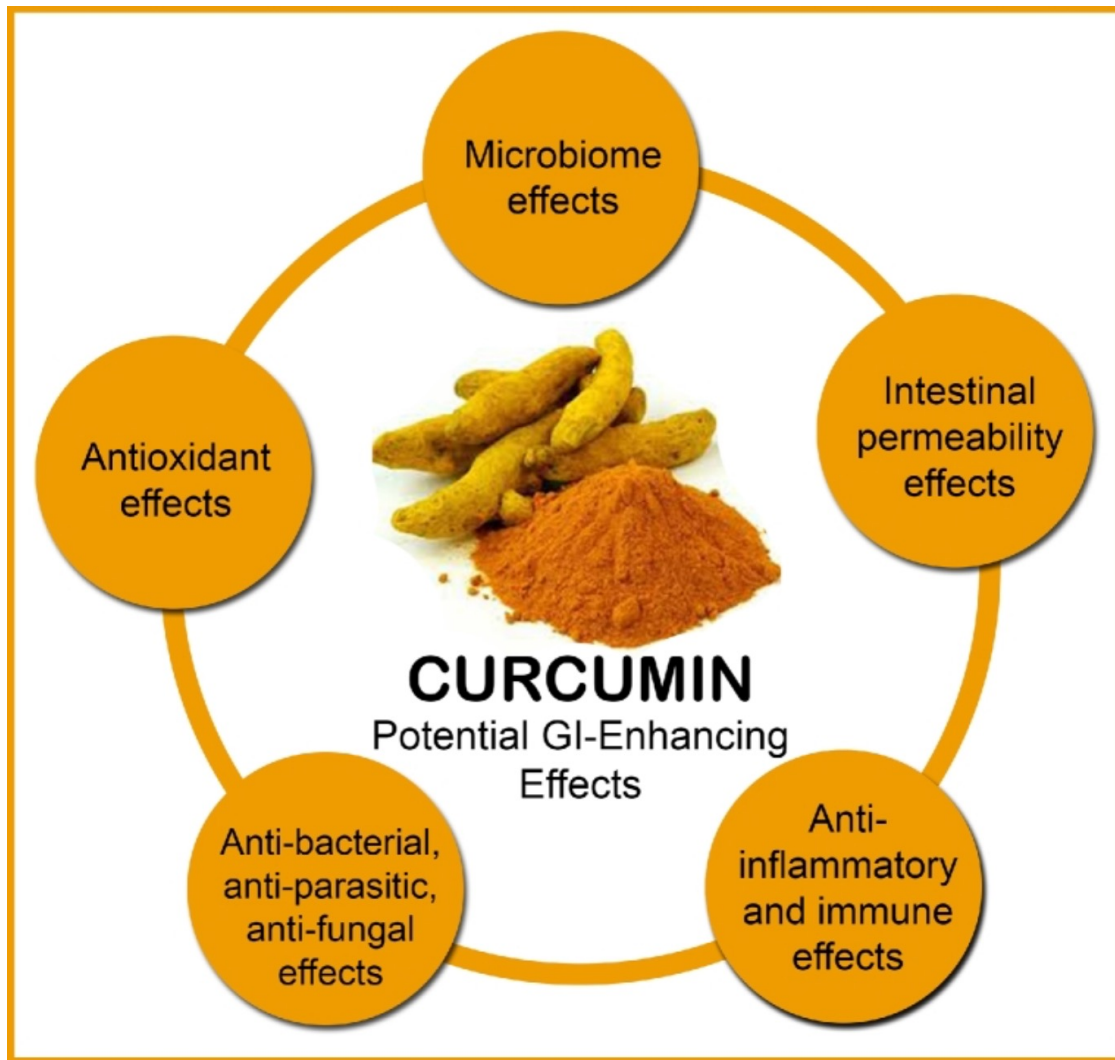
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Turmeric Rhizome (*Curcuma longa*)

- 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.



1. Bannuru RR, et al. Efficacy of curcumin and Boswellia for knee osteoarthritis: Systematic review and meta-analysis. *Semin Arthritis Rheum* 2018 Mar 10. pii: S0049-0172(18)30002-7



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

From: Lopresti A. The Problem of Curcumin and Its Bioavailability: Could Its Gastrointestinal Influence Contribute to Its Overall Health-Enhancing Effects?

Adv Nutr 2018 Jan; 9(1): 41–50.

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.**

Parenta C, et al. *Nat Prod Res* 2016 Jun;30(11):1248-55; Dragos D, et al. *Nutrients* 2017; Jan; 9(1): 70.

Menghini L, et al. *Phytother Res* 2019 Sep;33(9):2152-2162.

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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**.

1. Richardson JR, et al. Neurotoxicity of Pesticides. *Acta Neuropathol* 2019



Lobelia Leaf/Herb (*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.”



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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.



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