

Botanicals in Women's Health



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Disclosure

- Tieraona Low Dog, MD has the following to disclose:
 - Health Advisory Board: Pharmaca
 - Director of Scientific & Regulatory Affairs: Healthy Lifestyle Brands
 - Consultant/Spokesperson: FoodState
- This talk will not discuss off-label and/or investigational use of pharmaceuticals or devices not yet approved by the FDA.

Learning Objectives

- Participants will be able to identify physiologic actions of plants commonly used in herbal products
- Participants will be able to discuss the evidence of safety and benefit for botanicals commonly used in the management of PMS, dysmenorrhea and menopause.

What is Her Story?



Spring: The Maiden

- Menarche/Menstruation
- Adolescence
- Emotional well-being



Key Supplements



- Multivitamin/mineral with iron
- Magnesium
- ✓ Calcium intake
- ✓ Vitamin D
- Pre/probiotic rich foods
- Herbal teas with chamomile, lemon balm, raspberry leaf, tulsi, etc.

Iron

- Low iron levels make it hard to thermoregulate, pay attention and focus, and causes muscle weakness with exertion.
- 10% of women ages 12-49 have iron deficiency, rates higher among black and Hispanic women.
- RDA is 18 mg/d (8 mg after menopause)

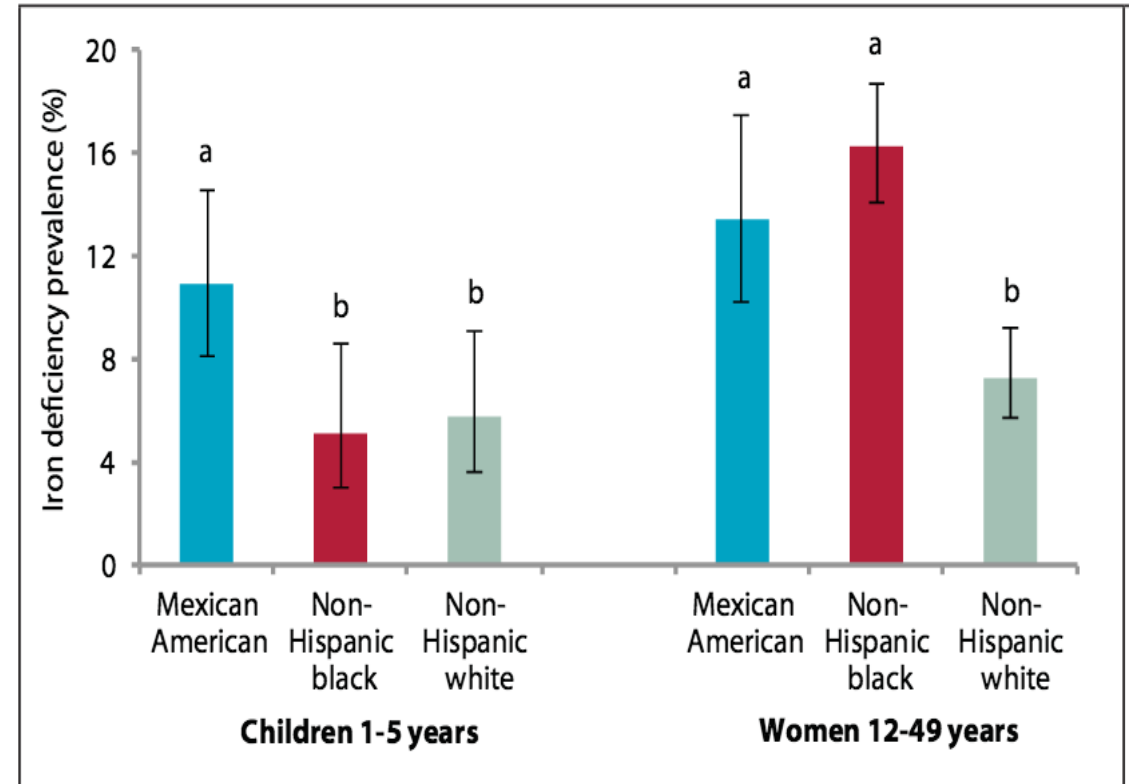


Figure H.3.a. Age-adjusted prevalence estimates of low body iron stores (< 0 mg/kg) in U.S. children and women by race/ethnicity, National Health and Nutrition Examination Survey, 2003–2006.

Error bars represent 95% confidence intervals. Bars not sharing a common letter differ within children and women ($p < 0.05$). Age adjustment was done using direct standardization.

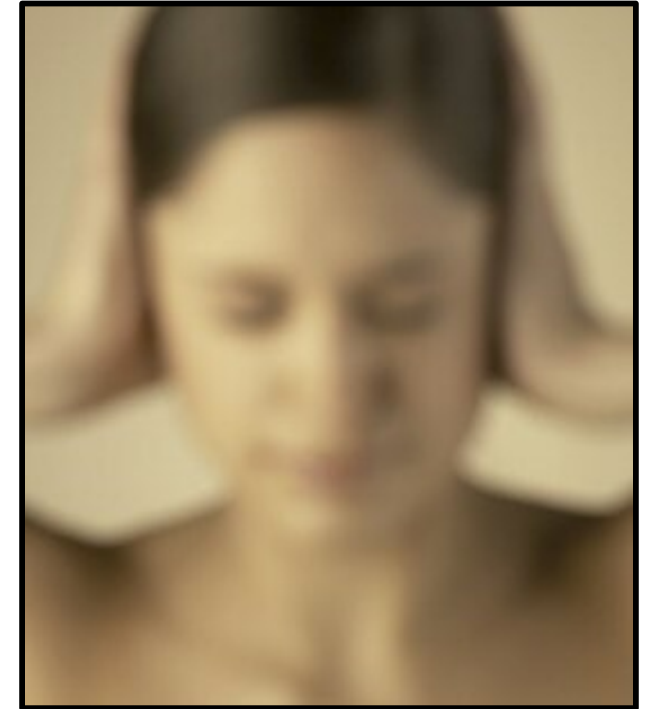
Premenstrual Syndrome

- Emotional and behavioral symptoms
 - Tension or anxiety
 - Depressed mood
 - Crying spells
 - Mood swings and irritability or anger
 - Appetite changes and food cravings
 - Trouble falling asleep
 - Social withdrawal
 - Poor concentration

- Physical signs and symptoms
 - Joint or muscle pain
 - Headache
 - Fatigue
 - Weight gain from fluid retention
 - Abdominal bloating
 - Breast tenderness
 - Acne flare-ups
 - Constipation or diarrhea

Calcium and PMS

- Two systematic reviews of PMS treatments concluded there was sufficient evidence to recommend calcium for PMS.
- Given that many women, especially adolescents, do not meet the adequate intake recommendations for dietary calcium, a 3-month trial of 500 mg BID calcium is reasonable.

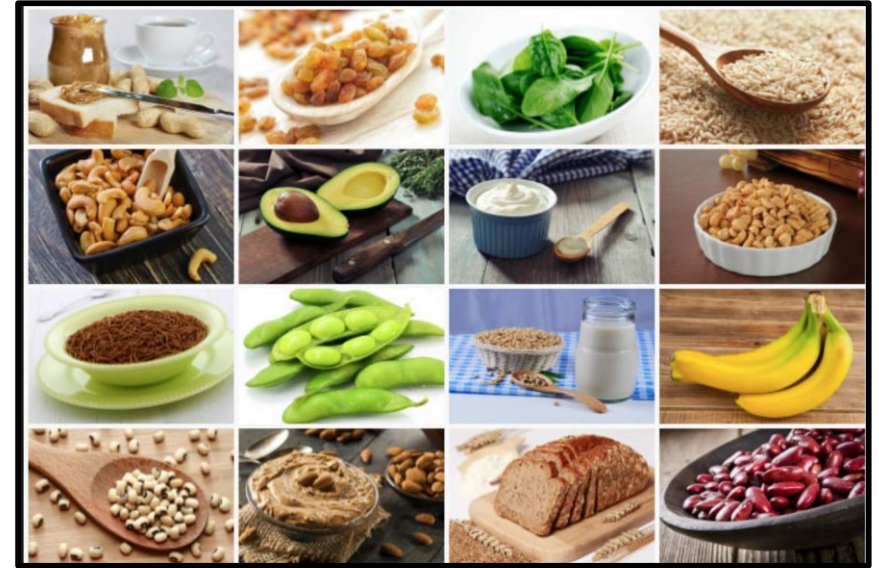


Freeman EW. *Expert Opin Pharmacother* 2010; 11(17):2879-89

Whelan AM, et al. *Can J Clin Pharmacol* 2009; 16(3):e407-29

Magnesium

- Review concluded “promising results” that magnesium is beneficial for dysmenorrhea.
- 4-month study found combination of 200 mg magnesium and 50 mg vitamin B6 superior to placebo in relieving PMS symptoms.
- Canadian Headache Society gave magnesium citrate a strong recommendation for prophylaxis of migraine.
- Magnesium may be particularly beneficial for menstrual migraine prophylaxis.



Tepper DE. *Headache* 2014; 54(2):403-8.

Guerrera MP, et al. *Am Fam Physician* 2009; 80(2):157-62

Fathizadeh N, et al. *Iran J Nurs Midwifery Res.* 2010; 15(Suppl 1):401-5.



ChasteBerry Fruit

(*Vitex agnus castus*)

- Chasteberry is obtained from the dried ripe fruit of the chaste tree and has been used as a women's health botanical since ancient Greece
- German health authorities approve for irregular menses PMS, and breast tenderness.
- In PMDD, one study found Vitex equivalent to fluoxetine, in another fluoxetine outperformed Vitex.
- One study found Vitex comparable to bromocriptine for reducing serum prolactin levels and ameliorating cyclic mastalgia.
- Systematic review, however, "13 of 14 studies with placebo, dietary supplements, or herbal preparations as controls reported positive effects of *Vitex agnus castus* on total premenstrual syndrome symptoms. Unfortunately most of the trials are associated with a *high risk of bias.*"

Dante G, et al. *J Psychosom Obstet Gynaecol* 2011; 32(1):42-51
Van Die MD, et al. *Planta Med* 2013; 79(7):562-75
Verkaik S, et al. *Am J Obstet Gynecol* 2017; Feb 22. pii: S0002-9378(17)30319-8.

Mechanisms and Dose

- Rapid decline in β -endorphin levels causes mild opiate-withdrawal syndrome, leading to an increase in pain, headache, mood swings, and water retention. Vitex is agonist at mu-receptors.
- Vitex binds dopamine receptors in the hypothalamus and anterior pituitary, inhibiting release of prolactin.
 - Prolactin plays a role in breast stimulation and may result in cyclical mastalgia.
- Study in men found: 120 mg chaste tree extract increased PRL, 240 mg had no effect and 480 mg decreased PRL.
- In general, dose 400-500 mg 1-2 times per day of crude herb.



Webster DE, et al. *J Ethnopharmacol* 2006; 106(2):216-21
Carmichael AR. *Evid Based Complement Alternat Med* 2008; 5(3):247-50
Merz PG, et al. *Exp Clin Endocrinol Diabetes* 1996; 104(6):447-53

Supplement Facts

Serving Size: 30 Drops (1 ml)

Servings Per Container: 30

	Amount Per Serving	% Daily Value
Extract Organic Chaste Tree berry (<i>Vitex agnus- castus</i>) in Organic Grain Alcohol USP (60- 70%), and Water.		†

Minimum Dry Herb Strength Ratio: 1:4

†Daily Value not established.

Supplement Facts

Serving Size: 1 Capsule

	Amount Per Serving:	% DV
Vitex (fruit)	400 mg	**

**Daily Value (DV) not established.

Supplement Facts

Serving Size: 2 Vegetarian Capsules

Servings per Container: 60

	Amount Per Serving	% Daily Value
Calories	5	
Total Carbohydrate	2 g	<1%†
Sugars	1 g	
Vitamin C (as Ascorbic Acid)	30 mg	50%
D-Mannose	1,000 mg	*
Cranberry (<i>Vaccinium macrocarpon</i>) (berry extract) (as CranActin Cranberry AF Extract)	400 mg	*



St. John's Wort

(*Hypericum perforatum*)

- University of Leeds randomized 36 women (18-45 years old) with regular menses and PMS to a cross-over, placebo controlled trial.
- Women underwent two-cycle placebo run in, then randomly assigned 900 mg/d SJW extract (0.18% hypericin, 3.38% hyperforin) or placebo for two cycles, placebo wash out, and then crossed over.
- SJW was statistically superior to placebo in improving physical and behavioral symptoms of PMS ($p < 0.05$).
- SJW effective for mild forms of depression. Primary concern is herb-drug interactions.

Canning S, et al. CNS Drugs 2010; 24(3):207-25

Dysmenorrhea

Uterine Tonic – raspberry, black cohosh, yarrow, lady's mantle, dong quai, motherwort, partridge berry, black haw/cramp bark

Uterine Anti-spasmodic – black cohosh, dong quai, black haw/cramp bark, pulsatilla, chamomile, yarrow, motherwort, Jamaican dogwood, peony

Uterine Anti-inflammatory – Chamomile, yarrow, motherwort, dong quai, peony, black cohosh, blue cohosh, black haw/cramp bark

Circulatory Stimulant (Uterine) – dong quai, ginger, cinnamon, peony

Uterine Astringent – yarrow, lady's mantle, shepherd's purse, raspberry, cranesbill

Black Haw

(*Viburnum prunifolium*)



- Valued in early American medicine for its effectiveness in easing uterine cramping, whether spasmodic dysmenorrhea or threatened miscarriage.
- Black haw was officially entered into the United States Pharmacopoeia in 1882 and remained in the National Formulary until 1960.
- Darkness in our history, “It was for a long time customary for planters to compel their female slaves to drink an infusion of black haw daily whilst pregnant to prevent abortion...”

Felter HW, Lloyd JU. *King's American Dispensatory* 18th Ed. 3rd Rev. Vol. II. Eclectic Medical Publications, Portland, 1983. Page 2059-62.

Studies

- Iridoid glucosides have relaxant effects on uterine, jejunum and trachea tissue *in vitro*.
- Esculetin and scopoletin are known to relieve muscle spasms.
- Salicin is analgesic and anti-inflammatory.
- There has been very little work done since the early 1960s, which confirmed uterine relaxant properties.
- No clinical trial data available for review.
- Dose: 1 gram 4-6 times per day acutely.

Cometeo, et al. J Ethnopharmacol 2009; 123(2): 201-7

Dietz BM, et al. Pharamcol Rev 2016; 68(4): 1026–1073.



Yarrow

(*Achillea millefolium*)

- Was widely used for the treatment of spasmodic gastrointestinal disorders, hepatobiliary, gynecological disorders, against inflammation and wound healing.
- Superior for menopausal flooding and heavy menses.
 - Flavonoids act as antispasmodic on smooth muscle
- Anxiolytic in animal studies
- 90 day safety study rats – negative for adverse events
- Dose: 1 gram 1-4 times per day

Ali SL, et al. Pharmacognosy, Phytochemistry and Pharmacological Properties of *Achillea millefolium* L.: A Review. *Phytother Res* 2017; 2017 Jun 15. doi: 10.1002/ptr.5840.

Dang Gui

(*Angelica sinensis*)

- Dang gui used in TCM for at least 2000 years
 - Diagnosis of blood stasis (amenorrhea, dysmenorrhea, endometriosis)
- Lei Gong's Treatise on Preparation of Materia Medica (588 AD), "The root is a tonic of the blood and promotes blood circulation; it regulates the menstrual cycle and stops menstrual pain..."
- Tonic for women with fatigue, low vitality, or who are recovering from illness.
- Merck introduced to the Western world in 1899 under trade name Eumenol®, a product that was said to positively effect menstrual disorders.



Studies

- Ligustilide has anti-inflammatory effects and enhances microcirculation of uterus, which could contribute to the mechanisms of relief of menstrual symptoms
- One uncontrolled study found dang gui alone and in combination relieved dysmenorrhea.
- No randomized, placebo-controlled, clinical trials evaluating the efficacy of dong quai for PMS.
- May cause excessive bleeding in women prone to menorrhagia, although, hematopoietic effects have been documented. This is consistent with its “blood building” effect in TCM.



Dang Gui Root. American Herbal Pharmacopoeia 2003

Formulation

Acute Pain Formula:

Black haw/crampbark	60ml
Black cohosh	30ml
Ginger (10%)	<u>10ml</u>
	100ml

Dose: 2ml every 20-40 minutes for 3 doses and then 2ml every 3-4 hours

Acute Pain Formula:

Black haw/crampbark	70ml
Kava	20ml
Ginger (10%)	<u>10ml</u>
	100ml

Dose: 2ml every 20-40 minutes for 3 doses and then 2ml every 3-4 hours

Supplement Facts

Serving Size 1 Capsules

Serving Per Container 24

	Amount Per Serving	% Daily Value
Proprietary Blend	335 mg	†
Black Haw (Viburnum prunifolium) stem bark		
Cramp Bark (Viburnum opulus) bark		
Yarrow (Achillea Millefolium) flower		
Kava Kava (Piper methysticum) rhizome/root		

† Daily Value not established.

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THE BODY

More Evidence Cranberries Don't Prevent Urinary Tract Infections

Many think the fruit raises urine acidity and has a bacteria-battling compound

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Cranberry Fruit

(*Vaccinium macrocarpon*)

- Study of 147 women (~86 years old) in nursing home taking cranberry extract BID (36 mg proanthocyanidins per capsule) found no significant difference in presence of bacteriuria plus pyuria over placebo.
- Bacteriuria is common in elders, original focus of study was prevention of clinical UTI. Less than 4% of these participants met criteria for recurrent UTI.
- Another review found cranberry products ***decreased UTI recurrences about 30%-40% in premenopausal women with rUTIs***, but were less effective than low-dose antimicrobial prophylaxis.



Juthani-Mehta M, et al. Effect of Cranberry Capsules on Bacteriuria Plus Pyuria Among Older Women in Nursing Homes: A Randomized Clinical Trial. *JAMA* 2016; 8;316(18):1879-1887.
Beerepoot M, et al. Non-antibiotic Prophylaxis for Urinary Tract Infections. *Pathogens* 2016; 5(2): pii: E36.

Supplement Facts

Serving Size: 1 Scoops (2.7 g)

Servings Per Container: 30

	Amount Per Serving	%Daily Value
Calories	10	
Total Carbohydrate	2 g	<1%†
Sugars	2 g	††
D-Mannose	2 g	0%
Cran Naturelle Organic Whole Cranberry Powder (Vaccinium macrocarpon)	515 mg	††

Supplement Facts

Serving Size: 2 Vegetarian Capsules

Servings per Container: 60

	Amount Per Serving	% Daily Value
Calories	5	
Total Carbohydrate	2 g	<1%†
Sugars	1 g	
Vitamin C (as Ascorbic Acid)	30 mg	50%
D-Mannose	1,000 mg	*
Cranberry (Vaccinium macrocarpon) (berry extract) (as CranActin Cranberry AF Extract)	400 mg	*

Autumn: The Transition

- The meno pause
- Hearts open and whole



Key Supplements



- Multivitamin/mineral (no iron after menopause)
- Calcium/Magnesium/Vit K
- ✓ Vitamin D or 2000 IU/d
- ✓ Omega 3 index if indicated



Herbal Options

- Adaptogens
- Nervine relaxants/tonics
- Mental focus
- Hypnotic/Sedative
- Aphrodisiacs
- Symptom relief hot flashes/night sweats

Research

- Hot flashes – black cohosh, soy, St. John's wort, sage, Siberian rhubarb, licorice, pycnogenol
- Diminished libido – maca
- Anxiety – kava, black cohosh
- Depression – St. John's wort
- Quality of life – *Panax ginseng*

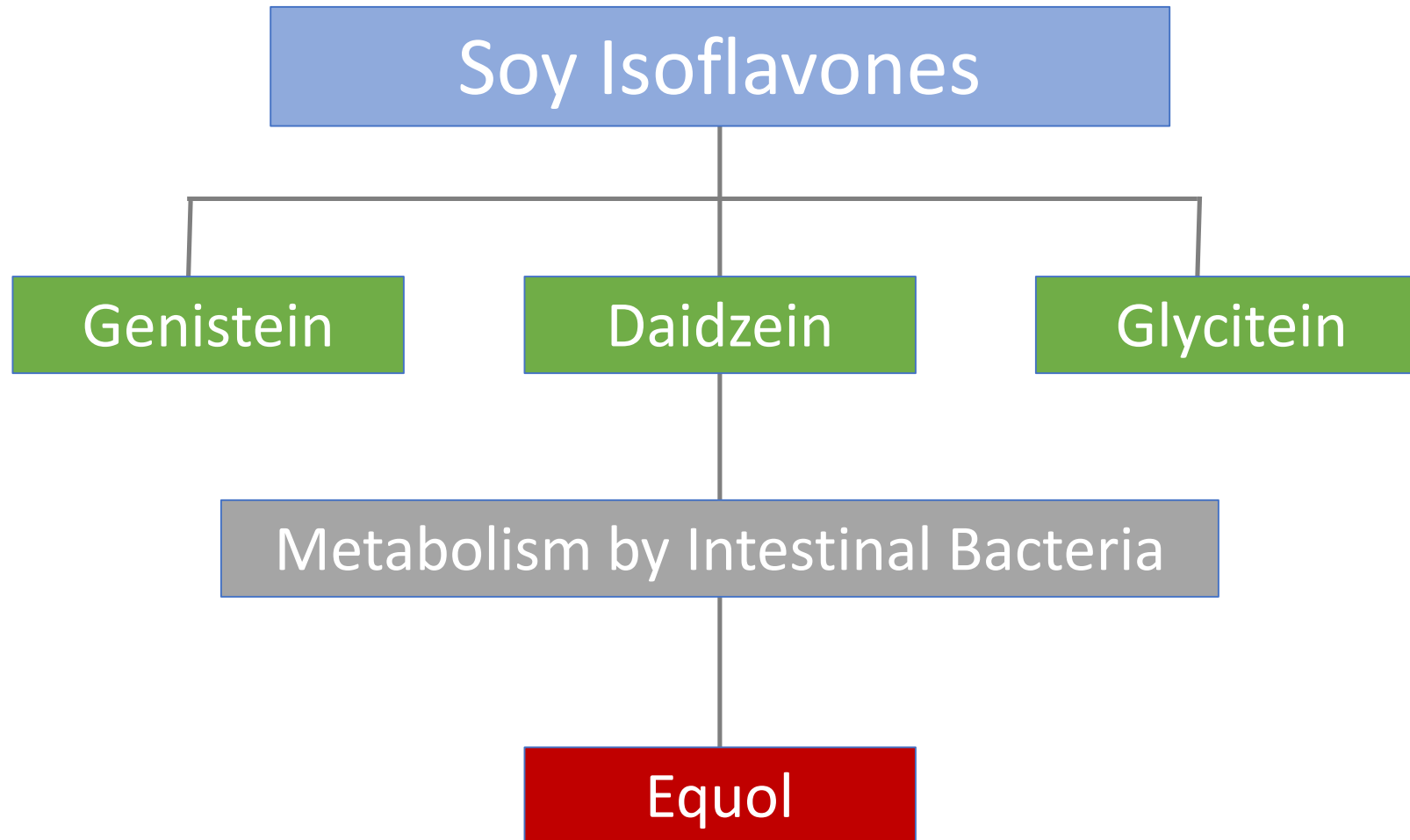
*Note: Siberian rhubarb has been studied but all research done on one cohort by one research team.



Soybean (*Glycine max*)

- Soybean notable for its total protein content and quality of soy protein is higher than that of other plant proteins and similar to animal protein.
- Soybean oligosaccharides are prebiotics.

Messina M. Nutrients 2016; 8(12): 754



Only about 25% of non-Asians and 50% of Asians host the intestinal bacteria that convert daidzein into the isoflavonoid equol, which is thought to be highly active.

Soy and Soy Isoflavones

- 2012 meta-analysis: ingestion of soy isoflavones (median, 54 mg) significantly reduced frequency of hot flashes by 20.6% ($P < 0.00001$) and severity by 26%, above and beyond that of placebo.
- Isoflavone supplements providing > 18.8 mg of genistein (40 mg isoflavones from whole soybean) were *more than twice as potent* at reducing hot flash frequency than lower doses.
- S-equol supplements of 10-30 mg/day for non-equol producing women significantly reduced mood symptoms in one trial.

Taku K, et al. *Menopause*. 2012 Jul;19(7):776-90.

Thomas AJ, et al. *Maturitas* 2014; 78(4):263-76.

Position Statement NAMS: *Menopause* 2015 Nov; 22(11):1155-72

Soy and Cancer

- The European Food Safety Authority (EFSA) concluded after a multi-year investigation that in postmenopausal women, soy isoflavones do not adversely affect the breast, thyroid or uterus.
- The North American Menopause Society concluded that soy isoflavones do not increase risk of breast or endometrial cancer.
- Positions by the American Cancer Society and the American Institute for Cancer Research are that soy foods can be safely consumed by women with breast cancer.

Panel on Food Additives and Nutrient Sources added to Food Scientific opinion on the risk assessment for peri- and post-menopausal women taking food supplements containing isolated isoflavones. EFSA J. 2015;13:4246.

Messina M. *Nutrients* 2016; 8(12): 754

Black Cohosh Root/Rhizome

(*Actaea racemosa*, *Cimicifuga racemosa*)



- Anti-inflammatory, antispasmodic, nervine relaxant
- Cooling, balances pitta/kapha
- More than 18 studies found black cohosh eases hot flashes/night sweats, mood and joint pain.
- Two 12-month NIH funded studies failed to show any benefit for black cohosh over placebo for menopausal hot flashes.
- May be particularly useful for those with joint pains, anxiety and depression

Geller, et al. *Menopause* 2009; 16(6):1156-66

Newton, et al. *Maturitas* 2008; 61(1-2):181-93.

Mahady, et al. *Menopause* 2008; 15:628-38.

Black Cohosh, and more...

- Historically black cohosh used for melancholy and rheumatic pain.
- Systematic review found black cohosh significantly reduced depression and anxiety in all studies.
- Lower estrogen results in decline in norepinephrine and serotonin, leading to a change in thermoregulation in the hypothalamus.
- UIC researchers found crude extracts display 5-HT₇ receptor binding activity and block serotonin reuptake. 5-HT₇ receptors involved in mood, learning, memory, sleep, thermoregulation and circadian rhythm.
- Rare but possible relationship between black cohosh and liver damage. Dose of extract 40-80 mg 1-2 times per day or 500-1000 mg per day of crude root.

Powell, et al. *J Agric Food Chem* 2008; 56:11718-26
Geller SE, Studee L. *J Womens Health* (Larchmt). 2005 Sep;14(7):634-49.
Nikolic D, et al. *Biomed Chromatogr* 2014; 28(12):1647-51.
Mahady GB, Low Dog T, et al. *Menopause* 2008; 15(4 Pt 1):628-38.



Valerian

(*Valeriana officinalis*)

- Serotonergic activity reported for valerian; valerenic acid identified as a potential partial agonist of the 5-HT_{5A}.
- RDBPCT of 68 women receiving 255 mg valerian capsules three times daily for 8 weeks showed a significant reduction in hot flash frequency and intensity.
- 8-week study: 60 postmenopausal women (45–60 years old) showed a significant improvement in menopausal symptoms with 530 mg of valerian root capsules twice a day.

Taavoni S, et al. *Complement Ther Clin Pract* 2013; 19:193–196

Izadjoo M, et al. *Int J Rev Life Sci* 2015; 5:220–226.

St. John's Wort

(*Hypericum perforatum*)



- Several studies show SJW extract reduces hot flashes and improves quality of life with/without black cohosh.
- Systematic review confirms SJW superior to placebo for relief of menopause symptoms.
- Dose: 900-1500 mg/d standardized extract.
- Numerous herb drug interactions,

Liu YR, et al. *Climacteric* 2014; 17(4):325-35

Hops

(*Humulus lupulus*)

- Hypnotic, antispasmodic
- Overwrought, over-stimulated, irritable
- Contains 8-prenylnaringenin (8-PN), greater affinity for ER-alpha than beta but 70-fold less potent than estradiol.
- No uterotrophic activity noted. Unclear degree of effect with oral dosing.



Chadwick LR, et al. *Phytomedicine* 2006; 13(1-2):119-31

Hops: Studies for Menopause

- RPCT: 67 menopausal women over 12 weeks receiving hops extract standardized to 100 or 250 μg 8-PN or placebo showed significant effects at 6 weeks for lower dose. No effect observed at higher doses and lower dose was not significantly different from placebo after 12 weeks.
- Study using 500 mg/d hops versus placebo (120 women, 90 days) showed a statistically significant reduction in menopausal symptoms and a dramatic reduction in hot flashes. (No placebo response, extract not described, etc.)

Heyerick A, et al. 2006; *Maturitas* 54:164–175

Aghamiri V, et al. *Complement Ther Clin Pract* 2016 23:130–135.

Maca

(*Lepidium meyenii*)

- Maca used in South America for centuries for infertility and menopause.
- Systematic review of 4 RCTs found favorable effects for maca on menopause related symptoms; three studies conducted by same research group.
- Systematic review that included two trials in women found a positive effect on sexual dysfunction or libido in menopausal women.
- Dose is generally 3 grams per day.
- Significant concerns over adulteration/quality in supply chain have been identified.



Lee MS, et al. *Maturitas*. 2011 Nov;70(3):227-33.

Shin BC, et al. *BMC Complement Altern Med* 2010; 10:44.

Pycnogenol (French maritime pine bark)



- DBPCT 170 perimenopausal women treated with 30 mg pycnogenol or placebo twice daily over a period of 3 months.
- Strong placebo response, however, pycnogenol was especially effective for improving vasomotor and insomnia/sleep problem symptoms, which were significantly better after 4 and 12 weeks than placebo ($p < 0.05$).

Kohama T, et al. *J Reprod Med* 2013; 58(1-2): 39-46

Other Botanicals

- Sage (*Salvia officinalis*)
- Motherwort (*Leonurus cardiaca*)
- Chaste tree (*Vitex agnus castus*)
- Ginseng (*Panax ginseng*)
- Hops (*Humulus lupulus*)
- Kava (*Piper methysticum*)
- Siberian rhubarb (*Rheum rhaponticum*)
- Lady's mantle (*Alchemilla vulgaris*)
- Yarrow (*Achillea millefolium*)
- Schisandra (*Schisandra chinensis*)
- Bacopa (*Bacopa monnieri*)

Shatavari (*Asparagus racemosus*)

- Adaptogen
- Cooling, moistening
- Potent anti-inflammatory
- Pacifies pitta, anxiolytic
- For hot flashes, improves depression, sexual vitality
- Prokinetic, decreases hyperacidity
- Dose is 2-3 grams per day.



Supplement Facts

Serving Size 1 Cup Brewed Tea

Servings Per Container 16

	Amount Per Serving	%DV
Calories	0	
All Herbal Ingredients:		
Organic shatavari root [API]**	1008 mg	†
Proprietary Blend:	792 mg	
Organic cardamom seed		†
Organic marshmallow leaf		†

† Daily Value (DV) not established.

Motherwort

(*Leonurus cardiaca*)

- Cooling bitter nervine relaxant.
- Used for *transitions* in a woman's life
- Many women report that it helps hot flashes and anxiety
- Pharmacological studies have confirmed its antibacterial, antioxidant, anti-inflammatory and analgesic activity, as well as its effects on the heart and the circulatory system. Sedative and hypotensive activity has been demonstrated in clinical trials.
- Dose: 500 mg 1-3 times per day



Wojtyniak K, et al. *Leonurus cardiaca* L. (motherwort): a review of its phytochemistry and pharmacology. *Phytother Res* 2013; Aug;27(8):1115-20

Sage

(*Salvia officinalis*)

- Sage has long been used to ease menopause related hot flashes.
- Only one small open study has been conducted – it showed that a fresh sage preparation significantly reduced hot flashes.
- Basic science data suggests a possible estrogenic activity secondary to flavonoids present in the leaves, though this effect appears mild.
- Best to use aqueous preparations long-term or low dose tincture due to presence of thujone.



Bommer S, et al. *Adv Ther* 2011; 28(6):490-500
Rahte S, et al. *Planta Med* 2013; 79(9):753-60

Damiana

(Turnera diffusa, T. aphrodisiaca)

- Widely used by indigenous peoples of Central America and northern Mexico; was one of the most important plants of the ancient Mayas. Used extensively for asthma/respiratory complaints. Also used as a tonic and to restore sexual vigor.
- A review of the science confirms it has antianxiety, antiaromatase, antibacterial, antidiabetic, antioxidant, adaptogenic, antiobesity, antispasmodic, cytotoxic, gastroprotective, hepatoprotective, and aphrodisiac activities.

Szewczyk K, et al. J Ethnopharmacol 2014; 152(3):424-43.

Schisandra chinensis

- Adaptogen
- Mental focus, endurance
- Warm, drying – good for incontinence, specific for sweats
- Improves fatigue
- Liver protectant
- Watch for drug interactions



Meno-Smoothie

- 12-16 ounces almond milk
- 1 tsp. maca powder (4 grams)
- 1 tsp. shatavari powder (3 grams)
- ½ tsp amalaki powder (2 grams)
- 1-2 tsp flax seeds, powdered
- ½ cup Greek yogurt
- ½ cup strawberries
- ¼ tsp cinnamon powder



Women's health is a state of well-being in which a woman feels creative, strong and wise. Her innate healing power is vital and intact. She feels valued and heard. She is free to choose and decide; she honors her own rhythms and journey.