

NHPs USED IN MENOPAUSE:

Hormonal	<ul style="list-style-type: none"> Black cohosh Chasteberry Dong quai Flaxseed 	<ul style="list-style-type: none"> Red clover Soy Wild yam/natural progesterone
Misc	<ul style="list-style-type: none"> Evening primrose oil 	

MENOPAUSAL SYMPTOMS:

- Decrease in estrogen and progesterone production and imbalance leads to symptoms
- Increased life expectancy
- Most common:
 - Vasomotor symptoms (hot flashes & night sweats)
 - Occur in 85% of women but usually subside within a few years
 - Vulvovaginal dryness
 - Sleep disturbances

MEASURING HOT FLASHES:

- Studies show that 10-58% of women report that taking the placebo is effective at treating hot flashes
- ≥ 2 fewer hot flashes/day than placebo = clinical difference
- Trials need to be long enough (≥ 8 weeks) in order to translate findings to the long term

MOVE TOWARDS MORE NATURAL ALTERNATIVES:

- > 2002: WHI studies – potential negative effects of hormone therapy on CV health and breast cancer
- 40-50% of women in Western countries use CAM therapies for menopausal symptoms

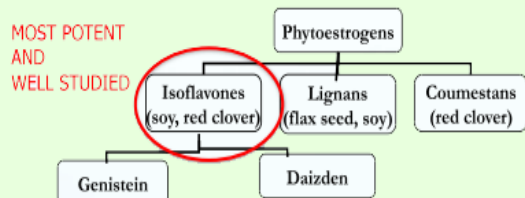
CONFUSING TERMS: bioidentical vs. natural hormones, phytoestrogens

BIOIDENTICAL HORMONE REPLACEMENT THERAPY (BHRT):

- Structurally and functionally equivalent to human hormones
- Sources:
 - Synthetic** (ex// Estrace)
 - "Natural" or plant based**
 - Natural progesterone = wild yam, soy
 - Bioidentical estrogen = 17 beta estradiol (plants)
- Even when derived from a natural source it must be synthetically modified to be identical to a human hormone
 - Not in "natural form" when given to patient

WHY THE INTEREST IN PHYTOESTROGENS?

- 10-20% of Asian women experience hot flashes compared to 85% of North American women
 - Believed to be because of their high consumption of soy protein in the diet (25-150 mg per day)
 - North Americans consume 1 mg per day
- Phytoestrogens are **plant-based products** that are:
 - Structurally similar to estradiol (E2)
 - Able to bind to estrogen receptors
 - Has very weak estrogen-like activity (100 – 10000x weaker)
- Classification of phytoestrogens



ISOFLAVONES (SOY):

BOTANY	<ul style="list-style-type: none"> <i>Glycine max</i> 95% are attached to sugar molecules (glycosides) <ul style="list-style-type: none"> Active form aglycone (w/o sugar) – genistein, daidzein Contain lignans and beta-phytosterols
MOA	<ul style="list-style-type: none"> Isoflavones are structurally similar to estradiol and selective estrogen receptor modifiers (SERMs) <ul style="list-style-type: none"> Stimulates estrogen receptors in some tissues while blocking the effect in others Estrogen effects are much weaker Genistein has higher affinity for ERβ receptor (20-30 x) <ul style="list-style-type: none"> Found in CNS, blood vessels, vagina, heart bones NOT breast or uterus Bioactive metabolite equol is more potent than daidzein <ul style="list-style-type: none"> Only 30% of population have gut micro-flora to produce equol (compared to 50-60% Asians)
VSM	<ul style="list-style-type: none"> Overall, results are fairly positive Maximum benefit for relieving hot flushes: 1-2 less per day <ul style="list-style-type: none"> HRT: 2.5 – 3 per day No evidence that soy ↓ hot flashes in breast cancer survivors May be more effective in women who have ≥ 4 hot flashes/day If patients are going to respond, they will by 12 weeks
OSTEO-POROSIS	<ul style="list-style-type: none"> Genistein binds ERβ in bone <i>In vitro</i> – soy isoflavones stimulate proliferation and differentiation of bone cells 2 meta analyses <ul style="list-style-type: none"> ↓ spine BMD and BMC compared to placebo ↓ bone resorption marker by 14% <ul style="list-style-type: none"> Similar to estrogen or bisphosphonate therapy Effects more significant at > 90 mg isoflavones/day when taken for at least 3-6 months Only effective with lower levels of estrogen (i.e. post-menopause)
ADRs	<ul style="list-style-type: none"> Well tolerated orally Higher doses (150 mg/day isoflavones) used for 5 years has shown endometrial thickening Epidemiological studies show inverse relationship between soy consumption and breast cancer incidence <ul style="list-style-type: none"> May ↓ risk in pre-menopausal women but ↑ risk in post Foods are safe but avoid over supplementing
CIs	<ul style="list-style-type: none"> Possible estrogenic and anti-estrogenic effects <ul style="list-style-type: none"> Caution in hormone-sensitive cancers (avoid supplements) Pregnancy (food safe, supplements not)
Dis	<ul style="list-style-type: none"> Competes with other sources of estrogen <ul style="list-style-type: none"> Avoid if taking tamoxifen (dose), SERMs, HRT Avoid MAOI if using fermented soy products (tyramine → HTN)
DOSE	<ul style="list-style-type: none"> 20-60 g per day of soy protein providing 34 – 100 mg isoflavones has been used in studies <ul style="list-style-type: none"> 1 g soy protein = 1-3 mg of isoflavones Best not to exceed 100 mg isoflavones per day May be some benefit in products than contain > 30 mg genistein Food sources (soy protein with intact isoflavones) have been own to be more beneficial in some trials – <i>good place to start</i>

FLAX SEED (LINSEED):

- Richest source of lignans (seed contains lignans, OIL DOES NOT)
- Most common source of ALA (55% of seed is ALA)
- Not well studied – 2 RCTs showed that flax seed (25 g/d) decreased VMS (NSS)
- Safety concerns
 - Oil may have anti-platelet properties (caution if on warfarin)
 - Seed has phytoestrogenic properties (avoid in estrogen-sensitive cancers)

RED CLOVER:

BOTANY	<ul style="list-style-type: none"> <i>Trifolium pretense</i> – use leaves and flowers of plant 4 isoflavones: daidzein, genistein, formononetin, biochanin A Other constituents: coumaric acid
MOA	<ul style="list-style-type: none"> Same as soy
EVIDENCE	<ul style="list-style-type: none"> Modest decrease in hot flashes, maybe night sweats (NSS) SS in women with ≥ 5 hot flashes/day or post-menopausal
CIs	<ul style="list-style-type: none"> Same as soy
Dis	<ul style="list-style-type: none"> Avoid with tamoxifen, SERMs, HRT Cation with anti-coagulant/anti-platelets (contains coumaric acid)

BLACK COHOSH:	
BOTANY	<ul style="list-style-type: none"> • <i>Actaea racemosa</i> – root stock (rhizome) part of plant used • Native to Eastern North America • Constituent standardized to 2.5% triterpene glycosides
MOA	<ul style="list-style-type: none"> • Has estrogen-like effects but doesn't bind to estrogen receptor • May have SERM-like activity
EVIDENCE	<ul style="list-style-type: none"> • Overall, evidence does show it's effective at reducing hot flushes • Thought to be alternative for reducing hot flushes in women on tamoxifen BUT not shown to be more effective than placebo • Doubts remain – 40 mg daily dose NSS at reducing VMS
SAFETY	<ul style="list-style-type: none"> • Mild GI effects, otherwise well tolerated • Does not increase endometrial thickness
ESTROGEN SENSITIVE CANCERS	<ul style="list-style-type: none"> • Not shown to stimulate breast cancer cells <i>in vitro</i> but not proven to be clinical studies • Not studied for more than 2 months in women hormone-sensitive cancers • UNTIL MORE IS KNOWN, AVOID BLACK COHOSH
CIs	<ul style="list-style-type: none"> • Liver disease (due to potential hepatotoxicity) • Pregnancy
DIs	<ul style="list-style-type: none"> • Hepatotoxic drugs?

CRANBERRY (ALTERNATIVE TO ABX IN UTI):	
BOTANY	<ul style="list-style-type: none"> • <i>Vaccinium macrocarpon</i> • Major constituent = proanthocyanidins (PAC A&B)
MOA	<ul style="list-style-type: none"> • Proposed to inhibit adherence of <i>E. coli</i> to the urogenital mucosa (maybe only A-type PAC)
FORMS	<ul style="list-style-type: none"> • Pure juice (pH 2.5 = unpalatable) • Cranberry cocktail (10-20% juice by volume) • Good alternative: capsules
MIXED EVIDENCE	<ul style="list-style-type: none"> • Very well studied but conflicting findings due to study heterogeneity • More consistency in positive results for prevention of uncomplicated UTIs • NSS reducing occurrence of symptomatic UTI
DOSE	<ul style="list-style-type: none"> • Dry cranberry juice extract 300-400 mg BID • 8-16 ounces daily of pure cranberry juice
ADRs	<ul style="list-style-type: none"> • Studies using juice have huge drop-out rate
CIs	<ul style="list-style-type: none"> • Be cautious of consuming large amounts of cranberry juice in diabetics due to high sugars
DIs	<ul style="list-style-type: none"> • Warfarin (may increase INR) – mixed findings

OTHER PRODUCTS:	
CHASTE BERRY	<ul style="list-style-type: none"> • No evidence that it is effective • May have estrogenic effects
DONG QUAI	<ul style="list-style-type: none"> • Used in TCM for hot flashes (usually combo w/ herbs) • <i>May</i> have some estrogenic effects • No evidence that it is effective • DO NOT RECOMMEND – some constituents believed to be carcinogenic
EVENING PRIMROSE OIL	<ul style="list-style-type: none"> • No evidence that it reduces hot flashes • One study: placebo was more effective !!!

NHPs USED FOR PMS:		
	Efficacy	Safety
Chasteberry <i>Vitex agnus castus</i>	<ul style="list-style-type: none"> • Possibly effective • Significant improvement in PMS sx compared to placebo in 7 RCTs • Use for ≥ 3 cycles 	<ul style="list-style-type: none"> • Well tolerated • Avoid: hormone sensitive cancers or if using dopaminergic medication
Evening primrose oil	<ul style="list-style-type: none"> • Insufficient studies • May be no different than placebo but small studies = lack statistical power 	<ul style="list-style-type: none"> • DI: anti-coags • CI: history of seizures (may lower threshold)
Calcium	<ul style="list-style-type: none"> • Likely effective • Both food and supplements (1200 mg) reduce PMS symptoms • Best evidence for PMS sx 	<ul style="list-style-type: none"> • Space from meds • DI: IV ceftriazone • CI: renal insufficiency
Vitamin B6	<ul style="list-style-type: none"> • Possibly effective • Can help w/ mood sx 	<ul style="list-style-type: none"> • Well tolerated
Magnesium	<ul style="list-style-type: none"> • Limited evidence • Took 2 months to see benefit 	<ul style="list-style-type: none"> • High doses can cause diarrhea

SUMMARY OF MENOPAUSE NHPs:		
	Efficacy	Safety
Wild yam	<ul style="list-style-type: none"> • NOT EFFECTIVE unless used as a source to synthesize natural progesterone 	<ul style="list-style-type: none"> • Well tolerated
Soy	<ul style="list-style-type: none"> • Very well studied • Appears to be more benefit with products containing ≥ 30 mg genistein; possibly effective • Best evidence of the phytoestrogens • May increase spine BMD 	<ul style="list-style-type: none"> • No proliferation of endometrium • Avoid in hormone sensitive cancers • DI: estrogenic therapy, avoid MAOIs • CI: best to avoid with hx of breast cancer (foods okay!)
Flax seed	<ul style="list-style-type: none"> • Not well studied • May be small benefit in decreasing VMS 	<ul style="list-style-type: none"> • DI: warfarin (oil only) • CI: seed in estrogen sensitive cancers
Red clover	<ul style="list-style-type: none"> • Mixed evidence; heterogeneity of studies a problem • May be more evidence for red clover in post-menopausal women with severe VMS 	<ul style="list-style-type: none"> • Same as soy • DI: anti-platelet, anti-coagulants?
Black cohosh	<ul style="list-style-type: none"> • Mixed evidence • Cochrane & JAMA: no • Beer: yes 	<ul style="list-style-type: none"> • CI: liver disease, hormone sensitive cancer

	Mood	Cramps	Breast	Fluid retention	Has
Chasteberry	X	X	X	X	X
Evening primrose					
Calcium	X	X		X	
Vitamin B6	X		x		
Mg2+	X			X	

Onset: chasteberry = 3 months, calcium = 3 months, Mg = 2 months