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Herbs Used for Menopausal Symptoms

By Adriane Fugh-Berman, MD, and Fredi Kronenberg, PhD

THE RECENT DEFINITIVE FINDING FROM THE WOMEN'S HEALTH INITIATIVE that hormone replacement therapy (HRT) is associated with increased risk of cardiovascular events, stroke, and breast cancer has caused shock waves in both the medical and consumer community. Although it is very clear that HRT imparts no cardiovascular benefit in any population of women, HRT does help hot flashes and vaginal dryness. Even symptomatic women, however, may think twice before choosing the recently delineated risks of HRT. Alternative treatments for symptoms may well become more popular. This article will review the evidence for herbs and menopausal symptoms.

Herbs that have been used for menopause include black cohosh (*Actaea racemosa*, syn. *Cimicifuga racemosa*), chaste tree berry (*Vitex agnus-castus*), dong quai (*Angelica sinensis*), ginseng (*Panax* species), evening primrose oil (*Oenothera biennis*), wild yam (*Diascorea villosa*), motherwort (*Leonurus cardiaca*), red clover (*Trifolium pratense*), linden flower (*Tilia platyphylla*), yarrow (*Achillea millefolium*), licorice (*Glycyrrhiza glabra*), and mixtures of Chinese herbs.

Black Cohosh

Limited evidence supports the use of black cohosh for menopausal symptoms. Virtually all clinical studies of black cohosh have used the standardized product Remifemin® (however, over time the formulation has changed from liquid to tablets, and the dose has changed, so different products with the same name were tested).

Only two of five randomized, controlled trials (RCTs) of black cohosh for hot flashes were placebo-controlled (a third placebo-controlled trial examined only hormone levels).[1] Of the two randomized, double-blind, placebo-controlled trials, one study in 85 breast cancer survivors, 59 of whom were on tamoxifen, found no benefit

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of Remifemin (40 mg/d × two months) for hot flashes.[2] In an older study of 80 "climacteric" women, Remifemin (4 mg bid × three months) was more effective than conjugated estrogens (0.625 mg/d) or placebo in affecting the Kupperman menopausal symptom index and vaginal epithelium[3] (the finding that estrogen did not affect vaginal epithelium nor menopausal symptom score may render other findings untrustworthy).

Two other trials (lacking a placebo control) have compared Remifemin to estrogens. A randomized, open, three-month trial in 60 women ages 45-60 with menopausal symptoms compared Remifemin (40 drops bid) to conjugated estrogens (0.25 mg/d) or diazepam (2 mg/d); all treatments reportedly reduced scores on the Kupperman index.[4] Another randomized treatment-controlled trial in 60 symptomatic women (post-hysterectomy, but retaining at least one ovary) compared Remifemin tablets (4 mg bid) to estriol (Ovestin® 1 mg/d), conjugated estrogens (Presomen® 1.25 mg/d), or an estrogen/progesterone combination (Trisequens®) for six months; all groups improved.[5]

A placebo-controlled study in 110 menopausal women tested the effect of Remifemin 4 mg bid for two months on follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels. There was no effect on FSH levels; LH levels were reported to be lower in the treatment group at two months. However, baseline values were not reported, rendering the results difficult to interpret.[1]

The mechanism of action of black cohosh is unknown, but is probably not due to phytoestrogens. Although formononetin, an estrogenic isoflavone, was previously reported to have been isolated from black cohosh extract,[6] a recent examination of 13 populations of black cohosh, and samples of Remifemin, found no formononetin.[7] Small amounts of biochanin, another isoflavone,[8] and fukinolic acid[9] have been isolated from *C. racemosa* roots.

No clinical trials of black cohosh have been longer than six months in duration, and most are only two or three months long. Even three months is too brief to show efficacy, because hot flashes are notoriously placebo-responsive, an effect that wanes after three months. Six months is adequate to assess efficacy, but is still too short to assess long-term safety.

The effects of long-term use of black cohosh are unknown. Two of the five RCTs examined estrogenic effects of black cohosh on vaginal epithelium; both reported a stimulatory effect.[3,4] In vitro and in vivo studies are not yet consistent or sufficient. One of us (Dr. Kronenberg) is conducting a one-year study on the effects of black cohosh that will include endometrial thickness (the primary outcome is hot flashes; secondary outcomes include markers of bone metabolism and cognitive effects).

Red Clover

Red clover (*Trifolium pratense*) contains the phytoestrogens formononetin, biochanin A, daidzein, and genistein,[10] which are presumed beneficial for menopausal symptoms. Two three-month randomized, double-blind, placebo-controlled clinical trials of Promensil™ (containing 40 mg total isoflavones) conducted in Australia (one with 37 postmenopausal women, the other with 51) reported no significant benefit of red clover extract for hot flashes.[11,12]

Evening Primrose

Oil of evening primrose (*Oenothera biennis*) contains the prostaglandin E1 precursor gamma-linolenic acid.[13] Evening primrose oil (EPO, 2,000 mg and 20 mg vitamin E twice daily × six months) was evaluated for hot flashes in a randomized, double-blind, placebo-controlled clinical trial of 56 menopausal women; no benefit of EPO was found. Evening primrose oil is a benign treatment. (Although the assertion that EPO causes seizures or decreases seizure threshold in phenothiazine-

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treated patients has been repeated in many publications, there have been no reliable published reports of such an effect. EPO was briefly used to differentiate electroencephalographic findings of temporal lobe epilepsy from schizophrenia,[14] which may be the genesis of this claim.)

Yam Cream

A double-blind, placebo-controlled crossover trial found no benefit of wild yam cream over placebo in 23 symptomatic menopausal women treated for three months.[15] There was no difference between groups in incidence of hot flashes or night sweats (both improved slightly in both groups). There were no changes from baseline in body weight, blood pressure, serum estradiol or salivary progesterone levels, blood lipids, or glucose.

Ginseng

One randomized, double-blind, placebo-controlled clinical trial in 384 menopausal women tested Ginsana® (containing 100 mg *Panax ginseng* standardized extract G115 × 14 weeks) for menopausal symptoms and quality-of-life measures.[16] No effect was seen on hot flashes, endometrial thickness, vaginal maturation index, or FSH. Although no estrogenic effects were noted in this study, case reports have associated ginseng with postmenopausal bleeding;[17,18] one case occurred after topical use of a ginseng-containing face cream[19] (these products were not examined for adulterants).

Chinese Herbs

A randomized, double-blind, placebo-controlled clinical trial in 78 menopausal women found no benefit of a Chinese herb mixture for three months.[20] The same combination of herbs was given to each woman.

Dong Quai

Dong quai (*Angelica sinensis*), a Chinese herb, was tested in a randomized, double-blind, placebo-controlled clinical trial in 71 women who received capsules containing 4.5 g placebo or dong quai root/d × six months; dong quai was not superior to placebo for hot flashes.[21] Traditionally, however, dong quai is rarely used alone; it almost always is used as part of a mixture. Dong quai does not contain the typically reported phytoestrogens, and there is conflicting data on stimulation of estrogen receptor-positive breast cancer cells or binding to estrogen receptors.[22,23] Dong quai contains coumarins and can cause bleeding when administered concurrently with warfarin;[24] the furocoumarins it contains can cause photosensitization and photodermatitis.[25]

Other Herbs

No clinical trials of motherwort, linden flower, yarrow, or licorice for hot flashes have been performed. No serious adverse effects have been reported in the medical literature for linden, yarrow, or motherwort; there is very little information of any kind in the scientific literature on these herbs.

Glycyrrhizinic acid in licorice inhibits 11 β-hydroxysteroid dehydrogenase, and can cause a state of apparent mineralocorticoid excess; licorice has been associated with hypertension, hypokalemia, edema, and preterm birth.[26] However, almost all adverse effects associated with licorice have been associated with consumption of licorice candies, gums, and liqueurs, and no cases of licorice toxicity have been associated with traditional Chinese medicine, although it is a common component of herbal mixtures.

Conclusion

In summary, among herbs tested for hot flashes, limited evidence supports a beneficial effect only for black cohosh (and long-term safety questions remain). Red clover has been shown ineffective in two trials; single trials show no effect of dong quai, wild yam, evening primrose oil, ginseng, and a Chinese herb mixture. Some of the trials of herbs were quite small and may have been underpowered, but it is clear that the herbs tested so far lack a dramatic effect. ❖

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Soy and Hot Flashes

By Fredi Kronenberg, PhD, and Adriane Fugh-Berman, MD

MANY FOOD PLANTS CONTAIN PHYTOESTROGENS, compounds that have estrogen-like activity, either directly or when metabolized. Although most mammalian estrogens are steroids, the major classes of phytoestrogens (isoflavones, lignans, and coumestans) are phenolic compounds. Isoflavone precursors are found in soybeans, other beans, clover, and alfalfa.[1] Lignan precursors are found in whole grains, seeds, fruits, and vegetables, especially flaxseed (linseed), rye, millet, and legumes.[2] Lignan precursors are metabolized by gut bacteria to enterolactone and enterodiol, also termed mammalian lignans. Isoflavone precursors also are affected by gut bacteria, which remove a glycoside unit to create the active, unconjugated isoflavones, genistein, daidzein, and equol.

In the human body, these substances have some of the biological activities of human estrogens. Soybeans, various soy food products, and the constituent isoflavones genistein and daidzein have received the most study in recent years. High dietary soy intake in Japan and other Asian countries has been suggested to be the major reason for the apparently lower prevalence of menopausal symptoms.[3,4]

Hot Flashes

Clinical studies continue to explore the relationship between phytoestrogen intake, menopausal symptoms,

Table

Randomized placebo-controlled trials of phytoestrogen-containing foods and supplements for hot flashes

Subjects/Completers	Intervention	Duration	Main Findings
Phytoestrogen-containing foods			
157/123 postmenopausal women with breast cancer and hot flashes (Van Patten)[12]	Soy beverage (90 mg isoflavones/d) Control = rice beverage	12 weeks	Negative: Hot flashes decreased in both groups; no difference between groups.
69 perimenopausal women (ages 42-62), with hot flashes (St. Germain)[5]	Isoflavone-rich soy protein (40 g/d, with 80.4 mg isoflavones) Controls = isoflavone-poor soy protein (4.4 mg/d aglycones) or whey protein	24 weeks	Negative: Hot flashes decreased in both groups; no difference between groups.
51/42 perimenopausal women (ages 45-55) with hot flashes (Washburn)[13]	Soy protein powder (20 g/d, with 34 mg isoflavones) in single dose or split dose Control = complex carbohydrate	6 weeks (Crossover; total duration = 18 weeks	Mixed: No differences among groups in hot flash frequency. Hot flash severity and estrogen symptom score improved significantly only in split-dose group.
104/79 postmenopausal women with hot flashes (Albertazzi)[14]	Isolated soy protein powder (60 g/d, with 76 mg isoflavones) Control = casein powder	12 weeks	Positive: Compared to control, soy significantly reduced hot flash frequency (45% vs. 31%).
52/44 postmenopausal women with hot flashes (Dalais)[6]	45 g/d (in form of bread) of soy grits (53 mg/d isoflavones) or flaxseed Control = wheat meal	12 weeks (Crossover; total duration = 28 weeks)	Negative: Compared to baseline, flaxseed and wheat, but not soy, decreased hot flash frequency.
145/114 peri- and post-menopausal women (ages 43-65) with at least one climacteric complaint (Brzezinski)[15]	Soy foods and flaxseed constituted 1/4 of daily caloric intake Control = normal diet	12 weeks	Positive: Compared to controls, phytoestrogen group had decreased hot flash "severity score" (P = 0.004) and less vaginal dryness (P = 0.005). Total symptom scores decreased in both groups with no differences between groups.
58/47 postmenopausal women with hot flashes (Murkies)[8]	Soy flour (45 g/d) Control = wheat flour	12 weeks	Negative: Menopausal symptoms and hot flash scores decreased in both groups, with no significant differences between groups.
Soy extracts			
82/80 postmenopausal women (ages 45-55) with hot flashes (Han)[16]	Capsules containing daily dose of 150.9 mg soy protein and 100 mg isoflavones (69.9 mg genistein, 18.6 mg daidzein, 11.4 mg glycitein)	4 months	Positive: Compared to placebo, treatment decreased menopausal symptoms (P < 0.01).
39/22 surgically or naturally menopausal women (ages 29-63) (Scambia)[17]	Standardized soy extract SOYSELECT (400 mg/d, containing 50 mg/d isoflavones)	6 weeks treatment (total duration = 12 weeks, including a conjugated estrogen and medroxyprogesterone acetate phase)	Positive: Compared to placebo, treated group had reduced hot flash frequency and severity (P < 0.01 and P < 0.001) at six weeks.
82/80 postmenopausal women with hot flashes (Quella)[18]	Soy tablets (150 mg isoflavones/d, 40-45% daidzein, 10-20% glycitein)	4 weeks (Crossover; total duration = 8 weeks)	Negative: Hot flash score and frequency decreased in both groups; no difference between groups.
177/117 postmenopausal women age 50 or older with hot flashes (Upmalis)[9]	Standardized soy extract (containing 50 mg genistein + daidzein/d)	12 weeks	Mixed: Compared to placebo, treatment reduced hot flash frequency (P = 0.03), but not severity at six weeks; at 12 weeks, treatment reduced hot flash severity (P = 0.01), but not hot flash frequency or night sweats.

and long-term health concerns of menopausal women. Hot flashes, however, have received the most attention.

Eleven randomized controlled trials have examined soy or isoflavone supplementation for hot flashes. Four found a positive effect, five found a negative effect, and two found mixed effects *(see table)*. Only three of eight studies with treatment phases that lasted longer than six weeks showed significant improvement in hot flashes at the end of the study. The longest study to date (24 weeks) showed no benefit for hot flashes (or other symptoms) at 24 weeks.

Two other trials did not separately assess hot flashes and are not included in the table. An additional randomized, placebo-controlled study tested soy supplements (containing 118 mg isoflavones daily) in 94 menopausal women, 80% of whom were experiencing menopausal symptoms, an atypical assortment that included unloved feelings (we're not sure whether this means feeling unloved or reflects unpopular statements made at family meals), lightheadedness, facial hair, and dry skin. Symptoms were reported to be mostly mild, and the number of women with hot flashes is not reported. Seventy-five women completed the trial; there were no significant differences between groups in any measure.

Comparisons among studies are difficult since each study used a different product, including a high-soy diet, a soy beverage, different types of soy protein, and tablets or capsules containing soy extracts, isolated isoflavones, or a mixture. Amounts of isoflavones and protein also differed. Other differences make comparability among studies difficult. Different menopause symptom indices (particularly, different hot flash scoring systems) were used; studies included different age ranges and menopausal status of subjects (some studies included only postmenopausal women, some only perimenopausal women, and some included both). One would expect more frequent, and more severe, hot flashes in the younger women, and an increase in other symptoms such as vaginal dryness with increasing age.

Vaginal Effects

None of the studies appears to have asked women specifically about comfort during sex; one study found no effect of soy protein containing 80.4 mg isoflavones/d on vaginal dryness.[5] Several studies assessed vaginal maturation index; only one[6] of four studies[6-9] found a positive effect. Another randomized, placebo-controlled, four-week trial of soy (comprising one-third of daily calories, about 165 mg isoflavones/d) in 97 menopausal women (91 completed) found no significant effect on vaginal epithelium.[7]

Safety

Soy foods have been a staple in Asian cuisine for thousands of years and are presumed safe. Supplementing the diet with beans or bean products should not cause any problems. No such presumption of safety can be made for the isolated, often high-dose, isoflavones currently sold over the counter.

Conclusion

In most studies, only modest effects (primarily on hot flash severity) were seen, and most benefits disappeared after six weeks (for hot flashes, even three months is barely adequate to adequately assess efficacy). As in most studies of pharmaceutical estrogen therapy for menopausal symptoms, there was a large placebo effect: Symptoms decreased in all groups—often by as much as 50-60%. Longer studies must be done to determine whether this placebo effect declines over time. Additional studies are needed to determine whether there are differences among whole foods, soy protein, and isoflavone extracts in the effect on symptomatology and whether there is a dose-response relationship. It would be valuable to examine the wide range of legumes in addition to soybeans. For example, yellow split peas, black beans, lima beans, kidney beans, and red lentils all contain more genistein than soybeans (although they contain less daidzein).[10] All other beans contain far less fat than soybeans.[11]

Both epidemiological studies and randomized controlled trials suggest that diet plays a role in modulating endocrine activity. The role of diet and biological differences among populations that could explain observed differences in symptomatology remains to be determined.

The conclusions that can be drawn from the data are that soy products have at best mild-to-moderate effects on hot flashes. The effect is not dramatic. Soy foods, beans, and flaxseed are harmless, and may help individual women with menopausal symptoms. The safety of isoflavone concentrates is unknown. ❖

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CME Questions

9. For hot flashes, several clinical trials support the use of:
a. ginseng.
b. dong quai.
c. black cohosh.
d. All of the above

10. Long-term use of black cohosh is associated with:
a. no adverse effects on the endometrium.
b. endometrial thickening.
c. unknown effects on the endometrium.

11. Which of the following is associated with increased bleeding risk when combined with warfarin?
a. Evening primrose oil
b. Soybeans
c. Wild yam
d. Dong quai

12. Most phytoestrogens in food are:
a. steroidal compounds.
b. phenolic compounds.

13. Isoflavone precursors are found in:
a. beans.
b. clover.
c. alfalfa.
d. All of the above

14. The safety of isoflavone isolates:
a. has been established in randomized controlled trials.
b. is unknown.

Clinical Abstracts

With Comments by Adriane Fugh-Berman, MD

CAM Use for Menopause

Source: Newton KM, et al. Use of alternative therapies for menopause symptoms: Results of a population-based survey. *Obstet Gynecol* 2002;100:18-25.

Design/Setting/Subjects: Telephone survey of 886 women (ages 45-65; 794 white) in a health maintenance organization (Group Health Cooperative) in Washington state. Women were asked about their use of eight complementary and alternative medicine (CAM) categories: herbal, homeopathic, or naturopathic therapies; visits to a homeopathic or naturopathic physician; visits to an herbalist; dietary soy products; acupuncture; massage therapy or other bodywork; chiropractic; or relaxation and stress management. Women were asked about past or present use of the therapy category; if they had ever used it for menopausal symptoms, and if so, how helpful the therapy was.

Funding: Centers for Disease Control and Prevention (Contract # U48/CCU-009654, and the Office of Women's Health, CDC)

Results: For past and present use for any reason, relaxation or stress management was the most popular therapy reported, being utilized by 362 (43.1%) of respondents; herbal, homeopathic, or naturopathic therapies were used by 328 (37%); chiropractic by 280 (31.6%); bodywork by 261 (29.5%); dietary soy products by 203 (22.9%); acupuncture by 92 (10.4%); visits to a homeopathic or naturopathic physician 83 (9.4%); and visits to an herbalist 41 (1.2%).

For menopausal symptoms, 22.1% used at least one therapy to treat menopausal symptoms *(see comments)*; 13.1% used herbal, homeopathic, or naturopathic therapies; 9.1% used relaxation/stress management; and 7.4% used dietary soy products. Of those who used CAM therapies, more than 80% in each category reported that the therapies were somewhat or very helpful for symptom relief. Women who were not on hormone replacement therapy (HRT) were twice as likely to use alternative therapies than women on HRT. Some current HRT users reported adjuvant alternative therapy use specifically to manage menopausal symptoms: 8.1% used stress management; 8.1% used herbal, homeopathic, or naturopathic therapies; and 4.4% used dietary soy. Women with a history of breast cancer were six times more likely to use soy for menopausal symptoms than women without a history of breast cancer.

Comments: CAM use may be common for treating menopausal symptoms, but it's difficult pinning down specifics in this survey. Women were allowed to consider anything they wanted "menopausal symptoms" and weren't queried about specific therapies. The authors state that "the alternative therapy questions allowed women the broadest definition of menopause symptoms and the greatest freedom to define their choice of a therapy to treat symptoms." Why do they think that's a good thing? Even the demographic information collected is appallingly vague: Surely having the only two race/ethnicity categories as "white" and "other" went out in the 1970s.

Additionally, some of the numbers don't add up. For example, it is stated at several points that there were 886 subjects in the survey, but in the table, the number of respondents adds up to 916. It is stated that breast cancer use was associated with a sixfold increase, but this should have been qualified by the fact that the study only included 35 women with breast cancer.

There are interesting data here, but the charts are missing information and difficult to read; the tables and text don't mesh well; and the write-up obfuscates as often as it clarifies. ❖

Magnets for Hot Flashes

Source: Carpenter JS, et al. A pilot study of magnetic therapy for hot flashes after breast cancer. *Cancer Nurs* 2002;25:104-109.

Design/Setting/Subjects: A randomized, placebo-controlled, crossover pilot trial in 15 postmenopausal breast cancer survivors with hot flashes (55% on tamoxifen). Subjects were recruited from previous research subjects who had agreed to be contacted about further research studies, and from a cancer center in the southeastern United States.

Intervention: Magnets vs. a placebo device, each worn for 72 hours. Six magnetic devices (Magna-Bloc, each consisting of a hard plastic outer layer and an inner layer imbedded with four magnets of alternating polarity) were placed over acupuncture sites commonly used to treat hot flashes. There was a 10-day washout period between groups.

Outcome Measures: Ambulatory sternal skin conductance monitoring assessed hot flash frequency at baseline and at the end of each study phase. Subjects also kept a hot flash diary.

Funding: Vanderbilt-Ingram Cancer Center Support grant (IP30 CA68485) and the Vanderbilt University Joint Center for Nursing Research.

Results: Eleven women completed the study. Reasons for dropout included difficulty keeping the device attached because of perspiration (1), lack of interest (2), and itching related to the adhesive tape (1). Hot flash frequency (by skin conductance monitoring) and hot flash bother (by diary) were significantly less common during the placebo phase compared to the magnet phase ($P = 0.02$ for each). There was no difference between groups in hot flash severity, interference with daily activities, and overall quality of life. Participants rated the acceptability of both devices as high; however, 27% of subjects reported problems with the devices: itching, redness, or loose tape secondary to perspiration. By the end of the second week, 55% of participants reported itching.

Comments: This study does not support the use of magnets for treating hot flashes in breast cancer survivors. ❖

In Future Issues:

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The Calcium-Phosphate Connection

Vitamin D

Estriol Update