Complementary and Alternative Medicine for Menopausal Symptoms: A Review of Randomized, Controlled Trials

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

Background: **Women commonly use soy products, herbs, and other complementary and alternative medicine (CAM) therapies for menopausal symptoms. Randomized, controlled trials have evaluated the efficacy and short-term safety of these therapies.**

Purpose: **To review randomized, controlled trials of CAM therapies for menopausal symptoms in order to better inform practice and guide future research.**

Data Sources: **Searches of MEDLINE for articles published from January 1966 through March 2002, of the Alternative and Complementary Database (AMED) of the British Library for articles published from January 1985 through December 2000, and of the authors' own extensive files. Search terms were *hot flash/flush*, *menopause*, and *climacteric*, combined with *phytoestrogens*, *alternative medicine*, *herbal medicine*, *traditional medicine*, *Traditional Chinese Medicine* (*TCM*), *Ayurveda*, *naturopathy*, *chiropractic*, *osteopathy*, *massage*, *yoga*, *relaxation therapy*, *homeopathy*, *aromatherapy*, and *therapeutic touch*.**

Study Selection: **29 randomized, controlled clinical trials of CAM therapies for hot flashes and other menopausal symptoms were identified; of these, 12 dealt with soy or soy extracts, 10 with herbs, and 7 with other CAM therapies.**

Data Extraction: **Each author extracted information from half of the studies on the number of patients, study design, outcome measures, and results; the other author then checked these results.**

Data Synthesis: **Soy seems to have modest benefit for hot flashes, but studies are not conclusive. Isoflavone preparations seem to be less effective than soy foods. Black cohosh may be effective for menopausal symptoms, especially hot flashes, but the lack of adequate long-term safety data (mainly on estrogenic stimulation of the breast or endometrium) precludes recommending long-term use. Single clinical trials have found that dong quai, evening primrose oil, a Chinese herb mixture, vitamin E, and acupuncture do not affect hot flashes; two trials have shown that red clover has no benefit for treating hot flashes.**

Conclusions: **Black cohosh and foods that contain phytoestrogens show promise for the treatment of menopausal symptoms. Clinical trials do not support the use of other herbs or CAM therapies. Long-term safety data on individual isoflavones or isoflavone concentrates are not available.**

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For author affiliations, see end of text.

Women are frequent users of complementary and alternative medicine (CAM) therapies in many countries (1–5), including the United States, where women use CAM therapies more often than men (48.9% vs. 37.8%) (6). Many women report using these therapies for menopausal symptoms (7, 8). A national magazine received more than 15 000 responses to a survey of alternative treatments for menopausal women (7). Primary symptoms included hot flashes, joint pain, sleep problems, forgetfulness, and fatigue; hot flashes (the most common menopausal symptom for women in the United States) (9) were most commonly treated. Therapies of choice were herbal remedies, chiropractic, and meditation. Recently, dietary supplements and foods containing phytoestrogens have become increasingly popular, despite the lack of data from clinical trials.

The science of CAM therapies is still inadequate to sufficiently inform clinicians and the public of the benefits or potential risks of CAM therapies. To provide information for clinicians, we reviewed randomized, controlled clinical trials of CAM therapies for menopausal symptoms.

METHODS

Study Selection

We searched MEDLINE from January 1966 to December 2002, the Alternative and Complementary Database (AMED) of the British Library from January 1985 to December 2000, and our own extensive files. Databases were searched under the terms *hot flash/flush*, *menopause*, and *climacteric*, combined with *phytoestrogens*, *alternative medicine*, *herbal medicine*, *traditional medicine*, *Traditional Chinese Medicine* (*TCM*), *Ayurveda*, *naturopathy*, *chiropractic*, *osteopathy*, *massage*, *yoga*, *relaxation therapy*, *homeopathy*, *aromatherapy*, and *therapeutic touch*. We did not limit the search to English-language literature. Studies that examined single symptoms or conditions that are not clearly associated with menopause (for example, anxiety and lipids) were excluded. All other randomized, controlled trials, regardless of their quality, were included. A total of 29 studies were identified. Each author extracted information on the number of patients, study design, outcome measures, and results for half the studies; the other author then checked results.

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CAM THERAPIES

Herbal Remedies

Herbs used in the United States for menopausal problems include black cohosh (*Cimicifuga racemosa*), chaste tree berry (*Vitex agnus-castus*), dong quai (*Angelica sinensis*),

Table 1. **Herbs for Menopausal Symptoms***

Study, Year (Reference)	Country	Design	Patient Characteristics and Age
Black cohosh			
Jacobson et al., 2001 (10)	United States	Randomized, double-blind, placebo-controlled trial	85 women (68 completed the study) with breast cancer and daily hot flashes; 59 women were using tamoxifen concurrently Age, >18 y
Warnecke, 1985 (11)	Germany	Randomized, open, treatment-controlled trial	60 women (48 menopausal; 55 completed study) with menopausal symptoms Age, 45–60 y
Stoll, 1987 (12)	Germany	Randomized, double-blind, placebo-controlled trial	80 women (41 menopausal; 75 completed the study) with climacteric symptoms, >3 hot flashes daily, and "psychic complaints" Age, 46–58 y
Lehmann-Willenbrock and Riedel, 1988 (13)	Germany	Randomized, treatment-controlled trial	60 women (41 menopausal) with climacteric symptoms who had had hysterectomy and had at least 1 ovary Age, ≥40 y
Red clover			
Baber et al., 1999 (14)	Australia	Randomized, double-blind, placebo-controlled crossover trial	51 postmenopausal women (43 completed the study) with >3 hot flashes daily Age, 45–65 y
Knight et al., 1999 (15)	Australia	Randomized, double-blind, placebo-controlled trial	37 postmenopausal women (34 completed the study) with >3 hot flashes daily Age, 40–65
Dong quai			
Hirata et al., 1997 (16)	United States	Randomized, double-blind, placebo-controlled trial	71 postmenopausal women (61 completed the study) with >14 hot flashes weekly (any severity) or >5 hot flashes weekly (moderate or severe) Age, 45–69 y
Evening primrose oil			
Chenoy et al., 1994 (17)	United Kingdom	Randomized, double-blind, placebo-controlled trial	56 postmenopausal women (35 completed the study) with >3 hot flashes daily Age, 45–67 y
Ginseng			
Wiklund et al., 1999 (18)	Sweden	Randomized, double-blind, placebo-controlled multicenter trial	384 postmenopausal women (379 completed the study) with ≥6 hot flashes during 3 of 7 days Age, 45–65 y
Chinese herb mixture			
Davis et al., 2001 (19)	Australia	Randomized, double-blind, placebo-controlled trial	78 postmenopausal women (55 completed the study) with ≥14 hot flashes or night sweats weekly Age, 45–70 y

*CGI = Clinical Global Impression Scale; FSH = follicle-stimulating hormone; HAM-A = Hamilton Anxiety Scale; HDL = high-density lipoprotein; LH = luteinizing hormone; SDS = Self-Assessment Depression Scale; SHBG = sex hormone–binding globulin; VAS = visual analogue scale; VMI = vaginal maturation index; WHQ = Women's Health Questionnaire.
† Manufacturers: Ginsana (G115), Pharmaton, Lugano, Switzerland; Ovestin, Organon, West Orange, New Jersey; Presomen, Solvay Pharmaceuticals, Marietta, Georgia; Promensil, Novogen, Sydney, Australia; Remifemin, GlaxoSmithKline, Pittsburgh, Pennsylvania; Trisequens, Novo Nordisk, Princeton, New Jersey.
‡ Comments are italicized.

ginseng (*Panax ginseng* and other *Panax* species), evening primrose oil (*Oenethera biennis*), motherwort (*Leonurus cardiaca*), red clover (*Trifolium pratense)*, and licorice (*Glycyrrhiza glabra*). We identified 10 trials of herbs (**Table 1**) (10–19). Most studies found no significant changes in primary outcome measures. However, these studies were small, of short duration, and far from sufficient to yield definitive conclusions.

The most studied and perhaps most popular herb is black cohosh, traditionally used by Native Americans for

Table 1—**Continued**

Treatment, Dose, and Duration†	Outcome Measures	Findings and Comments‡
Remifemin tablets (40 mg/d herbal extract) vs. placebo Duration, 2 mo	Frequency and intensity of hot flashes; menopause symptom index (6 symptoms); global rating of health scale; FSH and LH levels	No significant difference between groups in frequency and intensity of hot flashes (decreased in both groups); significantly greater decrease in sweating in treatment group than in placebo group ($P = 0.04$); no changes in global rating scale or FSH and LH levels *Study duration was short; medication-induced hot flashes are more difficult to treat than naturally occurring hot flashes*
Remifemin (liquid) (40 drops twice daily) vs. conjugated estrogens (0.25 mg/d) vs. diazepam (2 mg/d) Duration, 3 mo	Kupperman index scores (modified 5 symptoms); HAM-A; SDS; CGI; VMI	Kupperman index, HAM-A, SDS, and CGI showed "highly significant reductions" with all three therapies; VMI: "trend towards estrogenic stimulation" for Remifemin and estrogen *No statistical calculations reported*
Remifemin tablets (4 mg twice daily) vs. conjugated estrogens (0.625 mg/d) vs. placebo Duration, 3 mo	Kupperman index scores (9 symptoms); hot flashes; HAM-A; VMI	Significant improvement in Kupperman index score, HAM-A ($P < 0.001$), and VMI ($P < 0.01$); no change in estrogen or placebo groups; hot flashes decreased from 4.9 to 0.7/d in Remifemin group, 5.2 to 3.2 in estrogen group, and 5.1 to 3.1 in placebo group (significance not indicated) *Lack of effect with estrogen calls other findings into question*
Remifemin tablets (4 mg of triterpene glycosides twice daily) vs. estriol (Ovestin, 1 mg/d) vs. conjugated estrogens (Presomen, 1.25 mg/d) vs. estrogen/progesterone combination (Trisequens) Duration, 6 mo	Kupperman index scores (modified 17 symptoms); LH and FSH levels	Kupperman index scores improved in all groups ($P = 0.01$); no differences among treatment groups; no changes in LH and FSH levels
Promensil (40 mg of total isoflavones) vs. placebo Duration, 7.5 mo (12 wk, then 4-wk washout, then 14 wk)	Frequency of hot flashes; symptoms (Greene menopause scale); LH, FSH, estradiol, and SHBG levels; VMI; endometrial thickness (evaluated using ultrasonography)	No difference between groups in frequency of hot flashes (decreased in both groups) or other outcome measures *Study too short to adequately assess estrogenic effects on endometrium; adverse events not mentioned*
Promensil (40 mg of total isoflavones) vs. Promensil (160 mg of isoflavones) vs. placebo Duration, 3 mo	Frequency of hot flashes; symptoms (Greene menopause scale); FSH, SHBG, and HDL cholesterol levels; VMI	No difference among groups in frequency of hot flashes (decreased in all groups), VMI, FSH level, or SHBG level; HDL cholesterol level increased significantly (18%) ($P = 0.038$) in 40-mg Promensil group only *Although total cholesterol and triglyceride tests were done, results were not reported (blood was collected when patients were not fasting)*
Dong quai (3 capsules 3 times/d; equivalent 4.5 g of dong quai root/d; standardized to 0.5 mg/kg ferulic acid) vs. placebo Duration, 6 mo	Kupperman index score; vasomotor flushes; endometrial thickness; VMI; vaginal dryness; estradiol, estrone, and SHBG levels	No difference between groups in Kupperman index scores (decreased significantly in both groups), number of hot flashes, VMI, or endometrial thickness *Dong quai is not considered estrogenic and not usually prescribed alone in Traditional Chinese Medicine*
Evening primrose oil (2000 mg with 20 mg of vitamin E) twice daily vs. placebo Duration, 6 mo	Hot flashes or sweating episodes	Frequency of daytime hot flashes decreased in placebo but not evening primrose oil group; no difference between groups in frequency of nighttime hot flashes (decreased in both groups)
Ginseng (Ginsana containing 100 mg of standardized extract G115) Duration, 4 mo (2-wk run-in, 14-wk treatment)	Hot flashes and other symptoms (VAS); Psychological General Well-Being index; WHQ (measures of quality of life); FSH and estradiol levels; endometrial thickness (evaluated using ultrasonography); VMI	No significant differences between groups in hot flashes (assessed as part of WHQ) or any main outcome measures
Chinese herbal formula (daily dose of *Rehmannia glutinosa*, 15 g; *Cornus officinalis*, 10 g; *Dioscorea opposita*, 12 g; *Alisma orientalis*, 8 g; *Paeonia suffruticosa*, 8 g; *Poria cocos*, 12 g; *Citrus reticulata*, 5 g; *Lycium chinense*, 20 g; *Albizzia julibrissin*, 15 g; *Ziziphus jujuba*, 10 g; *Eclipta prostrata*, 15 g; *Ligustrum lucidum*, 10 g) vs. bitter placebo Duration, 3 mo	Hot flashes and night sweats (by daily diary); Menopause-Specific Quality-of-Life Questionnaire scores; urinary phytoestrogen excretion	No difference between groups in frequency of vasomotor symptoms or Menopause-Specific Quality-of-Life Questionnaire score (both decreased in both groups); urinary phytoestrogen levels did not change in either group

gynecologic and other conditions. Almost all clinical studies of black cohosh have used the standardized product Remifemin (GlaxoSmithKline, Pittsburgh, Pennsylvania); however, the formulation and the dosage have changed over time. One of four randomized, controlled trials of black cohosh for hot flashes was placebo controlled (10), one used both a treatment and placebo control (12), and two were treatment controlled (11, 13). Three of the four trials found black cohosh to be beneficial for treating hot flashes.

Table 2. **Soy and Soy Extracts for Hot Flashes***

Study, Year (Reference)	Country	Study Design	Patient Characteristics and Age
Van Patten et al., 2002 (34)	Canada	Randomized, double-blind, placebo-controlled trial	157 postmenopausal women (123 completed the study) with breast cancer and hot flashes
Han et al., 2002 (35)	Brazil	Randomized, double-blind, placebo-controlled trial	82 postmenopausal women (80 completed the study) with hot flashes Age, 45–55 y
St. Germain et al., 2001 (36)	United States	Randomized, double-blind, placebo-controlled trial	91 perimenopausal women (69 completed the study) with ≥10 hot flashes weekly Age, 42–62 y
Scambia et al., 2000 (37)	Italy	Randomized, double-blind, placebo-controlled trial	39 postmenopausal women (22 completed the study); included surgical and early menopause Age, 29–63 y
Quella et al., 2000 (38)	United States	Randomized, double-blind, placebo-controlled, crossover trial	177 women (149 completed the study) with history of breast cancer and <14 hot flashes weekly; most patients were receiving tamoxifen or raloxifene Age, ≥18 y
Upmalis et al., 2000 (39)	United States	Randomized, double-blind, placebo-controlled, multicenter trial	177 postmenopausal women (117 completed the study) with ≥5 hot flashes daily Age, ≥50 y
Washburn et al., 1999 (40)	United States	Randomized, double-blind, placebo-controlled, crossover trial	51 perimenopausal women (42 completed the study) with >1 hot flash daily Age, 45–55 y
Albertazzi et al., 1998 (41)	Italy	Randomized, double-blind, placebo-controlled multicenter trial	104 postmenopausal women (79 completed the study) with ≥7 hot flashes daily Age, 45–62 y
Dalais et al., 1998 (42)	Australia	Randomized, double-blind, placebo-controlled, crossover trial	52 postmenopausal women (44 completed the study) with ≥14 hot flashes weekly Age, 45–65 y
Brzezinski et al., 1997 (43)	Israel	Randomized, placebo-controlled, unblinded trial	145 peri- and postmenopausal women (114 completed the study) with ≥1 climacteric symptom Age, 43–65 y
Murkies et al., 1995 (44)	Australia	Randomized, placebo-controlled trial	58 postmenopausal women (47 completed the study) with >14 hot flashes weekly Age, 30–70 y
Baird et al., 1995 (45)	United States	Randomized, controlled trial	97 postmenopausal women (91 completed the study) Age, 45–65 y

*FSH = follicle-stimulating hormone; HDL = high-density lipoprotein; LDL = low-density lipoprotein; LH = luteinizing hormone; SHBG = sex hormone–binding globulin; VMI = vaginal maturation index.
† Manufacturer: SOYSELECT, Indena, Settala, Milan, Italy.
‡ Comments are italicized.

Neither the identity of active compounds nor the mechanism of action of black cohosh is known. Although formononetin, an estrogenic isoflavone, was reported to have been isolated from black cohosh extract (20), another study found no formononetin in black cohosh extract (21). In addition, a recent systematic examination of extracts of

Table 2—**Continued**

Treatment, Dose, and Duration†	Outcome Measures	Findings and Comments‡
Soy beverage (90 mg of isoflavones/d) vs. control (rice beverage) Duration, 12 wk	Hot flash frequency and hot flash score (number × severity)	No difference between groups; hot flash scores decreased in both the soy group (30%) and the control group (40%). More gastrointestinal effects were reported in the soy group
Capsules containing daily dose of 150.9 mg of soy protein and 100 mg of isoflavones (69.9 mg of genistein, 18.6 mg of daidzein, 11.4 mg of glycitein) Duration, 4 mo	Kupperman index score; lipids; body mass index; blood pressure; glucose, FSH, LH, and 17β-estradiol levels	Compared with placebo, treatment decreased menopausal symptoms ($P < 0.01$), decreased total cholesterol and LDL levels ($P < 0.01$), and increased 17_{β}-estradiol levels (from 9 ± 1.2 pg/mL to 19 ± 2.2 pg/mL, $P < 0.001$). No effects on other outcome measures *This was the only study that found increased estradiol levels*
40 g/d of isoflavone-rich soy protein (80.4 mg aglycones) vs. 40 g/d of isoflavone-poor soy protein (4.4 mg/d of aglycones) vs. 40 mg/d of control (whey protein) Duration, 24 wk	Frequency and severity of hot flashes and night sweats; insomnia; fatigue; mood swings; vaginal dryness and other menopausal symptoms	No significant difference between groups in frequency or severity of hot flashes or night sweats at 12 or 24 weeks (hot flashes decreased in all groups); no changes in other outcome measures *Longest study to date; 6-wk data not presented; sporadic symptoms throughout the study (menopausal transition)*
Standardized soy extract (SOYSELECT: 400 mg/d [50 mg/d of isoflavones]) vs. placebo. After 6 wk, conjugated estrogens (0.625 mg/d) were added to treatment; after 8 wk, soy was discontinued and medroxyprogesterone acetate (10 mg/d) was added to the conjugated estrogens Duration, 12 wk (6 wk treatment, 4-wk treatment plus conjugated estrogens; 2-wk conjugated estrogens plus medroxyprogesterone acetate)	Frequency and severity of hot flashes; Greene menopause scale; VMI; endometrial thickness; pulsatility index of uterine artery; total cholesterol, HDL, LDL, triglyceride, FSH, and LH levels	Compared with placebo, treatment decreased frequency and severity of hot flashes ($P < 0.01$ and $P < 0.001$) at 6 wk; soy caused no changes in other outcome measures; conjugated estrogens caused predictable estrogenic changes in both groups
Soy tablets containing daily dose of 150 mg of isoflavones vs. placebo Duration, 8 wk (each phase, 4 wk)	Frequency and intensity of hot flashes and hot flash score (frequency × severity)	No difference between groups in hot flash score or frequency (frequency of hot flashes decreased in both groups); patients did not prefer soy over placebo
Standardized soy isoflavone extract containing 50 mg of genistein plus daidzein daily vs. placebo Duration, 12 wk	Frequency and severity of hot flashes and night sweats; SHBG and FSH levels; VMI; endometrial thickness (evaluated using ultrasonography); *N*-telopeptide; quality-of-life measures; total cholesterol, LDL, HDL, and triglyceride levels	Compared with placebo, treatment reduced frequency of hot flashes at 6 wk ($P = 0.03$); at 12 wk, treatment reduced severity of hot flashes and night sweats ($P = 0.01$), but not frequency of hot flashes or night sweats; no changes in other outcome measures *Relative lack of soy protein in supplement*
20 g of soy protein powder daily (34 mg of isoflavones) in single or split doses vs. control (isoflavone-free carbohydrate) Duration, 18 wk (each phase lasted 6 wk)	Frequency and severity of hot flashes; estrogen symptom score (including hot flashes, vaginal dryness, sleep disturbances); total cholesterol, LDL, HDL, and triglyceride levels; blood pressure	Severity of hot flashes ($P < 0.001$) and estrogen symptom score ($P < 0.05$) improved only in split-dose soy group; no differences among groups in frequency of hot flashes; compared with control, treatment (for both soy groups) decreased total cholesterol and LDL levels ($P < 0.05$); no changes in HDL or triglyceride levels; diastolic blood pressure decreased ($P < 0.01$) only in split-dose soy group *No washout between crossover; baseline number of hot flashes not reported*
60 g of isolated soy protein powder daily (40 g of protein, 76 mg of isoflavones [aglycones]) vs. control (isoflavone-free casein powder containing 40 g of protein) Duration, 12 wk	Frequency and severity of hot flashes; Kupperman index scores; blood pressure	Compared with control, treatment significantly reduced frequency of hot flashes (45% vs. 31%) at 12 wk ($P < 0.01$); no change in Kupperman index score
45 g/d (in form of bread) of soy grits (53 mg/d isoflavones) or linseed (flaxseed) vs. control (wheat meal) Duration, 28 wk (each phase lasted 12 wk, 4-wk washout)	Frequency of hot flashes; VMI; bone mineral content; bone mineral density	Compared with baseline, linseed and wheat (but not soy) decreased frequency of hot flashes; only soy improved VMI (increase of 103%) ($P < 0.04$) and bone mineral content (increase of 5.2%) ($P = 0.03$); no changes in bone mineral density *Increased bone mineral content in soy group over short time is of note*
Phytoestrogen-rich diet containing soybean food and flaxseed (1/4 caloric intake) vs. control (normal diet) Duration, 12 wk	Menopause symptom questionnaire; estradiol, LH, FSH, SHBG, and serum phytoestrogen levels	No differences between groups in menopause symptom questionnaire scores, which decreased in both groups; compared with control, treatment significantly increased SHBG levels ($P < 0.003$) and significantly decreased vaginal dryness ($P = 0.005$) and hot flash "severity score" ($P = 0.004$) assessed as part of the menopause symptom questionnaire *Report states that estradiol level did not change significantly; however, table shows estradiol decreased in both groups; no report of 6-wk data*
45 g/d of soy flour vs. 45 g/d of wheat flour Duration, 12 wk	Frequency of hot flashes and hot flash score (frequency × severity); other menopausal symptoms; VMI; lipid and FSH levels	No significant differences between groups in menopausal symptoms, frequency of hot flashes or hot flash score (decreased in both groups), or other outcome measures; no change in VMI or lipids; compared with baseline, FSH level decreased significantly only in the control group
Soy diet (1/3 caloric intake; estimated 165 mg/d of isoflavones) vs. control (usual diet) Duration, 4 wk	VMI; LH, FSH, and SHBG levels	No significant changes in any outcome measures *Hot flashes not measured; trial very short in duration*

black cohosh collected from 13 locations in the eastern United States as well as Remifemin also found no formononetin in any sample (22). Thus, other compounds must be responsible for its biological activity. Small amounts of biochanin, another isoflavone, have been isolated from *C. racemosa* roots (23). Other candidates for the

biological activity of black cohosh include triterpene glycosides, organic acids, and esters.

Black cohosh is not usually used on a long-term basis, and no clinical trials have lasted for more than 6 months. This is of concern because women using this product for "natural" hormone replacement therapy may take it for years. There are no published data from human trials about long-term safety, particularly regarding endometrial or breast stimulation. Effects on vaginal epithelium are inconclusive; two of five randomized, controlled trials that examined estrogenic effect on vaginal epithelium reported a stimulatory effect (11, 12). In vitro and in vivo studies are not consistent or sufficient. Although black cohosh may be useful for menopausal symptoms, long-term use cannot be presumed to be safe until appropriate safety studies are conducted.

Red clover contains the phytoestrogens formononetin, biochanin A, daidzein, and genistein (24). Two small, 3-month clinical trials conducted in Australia reported no significant benefit of red clover extract for hot flashes (14, 15) (**Table 1**). Several larger trials are in progress. Red clover, a Native American herb, has not been traditionally used on a long-term basis for hot flashes, and it is unknown whether long-term use would have an estrogenic effect on the breast or endometrium.

Dong quai, a Chinese herb traditionally prescribed as a tonic for women, is most commonly used as part of a mixture. It is sold in the United States for use alone or as part of newly formulated, nontraditional herbal combinations. One trial of dong quai found no benefit for hot flashes (16) (**Table 1**). It would be valuable to study Traditional Chinese Medicine (TCM) formulas, prescribed in accordance with TCM diagnostic methods. Dong quai does not contain the typically reported phytoestrogens, and the data on stimulation of estrogen receptor–positive breast cancer cells or binding to estrogen receptors (25, 26) are conflicting. Dong quai contains coumarins and can cause bleeding when administered concurrently with warfarin (27); the furocoumarins contained in dong quai can cause photosensitization (24).

Oil of evening primrose, a good source of the prostaglandin E_1 precursor γ-linolenic acid, was evaluated for hot flashes in one trial; no differences were found between a group of patients using evening primrose oil and a placebo group (17). Single-dose studies are difficult to evaluate when optimum dose and duration of treatments are unknown. Evening primrose oil is a benign treatment.

Ginseng has been used as a tonic for centuries in Asia. One trial found no benefit of ginseng over placebo for menopausal symptoms and quality-of-life measures, although there were positive effects on mood (18). Case reports link ingestion of ginseng with postmenopausal bleeding (28, 29); one case of postmenopausal bleeding occurred after topical use of a ginseng-containing face cream (30). Ginseng also reduced the international normalized ratio in one patient receiving warfarin therapy (27).

In summary, of the herbs that have been tested for hot flashes, only black cohosh has shown a beneficial effect. Questions remain about the long-term safety of most herbs.

Dietary Phytoestrogens

Many food plants contain phytoestrogens, primarily phenolic (rather than steroidal) compounds that include isoflavones, lignans, and coumestans. Isoflavone precursors are found in soy and other types of beans, clover, and alfalfa. Lignan precursors are found in whole grains, seeds (especially flaxseed [linseed]), fruits, vegetables, rye, millet, and legumes (31). Intestinal bacteria convert plant lignans to mammalian lignans (enterolactone and enterodiol) and convert conjugated isoflavones to unconjugated active isoflavones (genistein, daidzein, and equol). Phytoestrogens are estrogenic, and, thus, diet may modulate endocrine actions in the body. High dietary intake of soy products in Japan, China, and Korea has been proposed as one reason for the lower prevalence of menopausal symptoms reported in those countries (32, 33). Soy foods have become popular in the United States for treating hot flashes, despite few strong supporting clinical studies.

We identified 11 clinical trials that examined soy or isoflavone supplementation for hot flashes (**Table 2**) (34–44); one additional study of soy for menopausal women examined vaginal epithelium rather than hot flashes (45). Products studied ranged from soy foods to purified isoflavone preparations. Only 3 of 8 studies with treatment phases that lasted for more than 6 weeks showed significant improvement in hot flashes at the end of the study (35, 41, 43). The longest study to date showed no benefit for hot flashes (or other symptoms) at 24 weeks (36). Comparisons are difficult because of variations in product, dosage, scoring systems for symptoms of hot flashes, and the menopausal status of patients. Published data show only modest effects (primarily on the severity of hot flashes), and most benefits disappeared after 6 weeks (for hot flashes, even 3 months is barely adequate to appropriately assess efficacy). It is of interest that in most of these studies, symptoms decreased in all groups—often as much as 50% to 60% in placebo as well as treatment groups. Studies of longer duration must be done to determine whether this placebo effect would have declined over time in any or all groups. Additional studies of menopausal symptoms are warranted to differentiate among whole foods, soy protein, and isoflavone extracts. 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 is a benign intervention. No such presumption of safety can be made for the isolated, often high-dose, isoflavones that are currently sold over the counter.

Vitamin E

Vitamin E, recommended in many popular books for hot flashes, was the subject of poorly controlled studies in the 1940s and 1950s. A double-blind, 3-year study in 1953

compared vitamin E (50 to 100 mg/d) with two estrogen preparations, phenobarbital, and a placebo in 658 women (46). On an 11-symptom menopause index (hot flashes were not analyzed separately), more than 90% of women treated with estrogen and 43% of women treated with phenobarbital responded; vitamin E was no more effective (26%) than placebo (33%). A recent randomized, placebo-controlled crossover study tested vitamin E (400 IU vitamin E succinate twice daily) in 125 breast cancer survivors with at least 14 hot flashes weekly (47). After 4 weeks, vitamin E was associated with one less hot flash daily when compared with placebo. The difference was statistically but not clinically significant; patients did not prefer vitamin E to placebo.

Acupuncture

In a study of the effects of acupuncture on hot flashes, 24 menopausal women were randomly assigned to either an electroacupuncture group (electrical stimulation of acupuncture needles at standardized points) or to a control group (shallow acupuncture needle insertion at the same points) (48). Women were treated twice weekly for 2 weeks and then weekly for an additional 6 weeks. Hot flashes and Kupperman index scores decreased significantly ($P < 0.05$) in both groups, and there were no differences between groups. In addition, sleep dysfunction scale scores did not change. Because shallow needle insertion at correct acupuncture points would be expected to have some effect, the chosen control may have been suboptimal. Acupuncture causes tissue trauma occasionally and serious complications (including pneumothorax and cardiac tamponade) rarely. The most common serious complication has been the transmission of hepatitis viruses or other infections agents via inadequately sterilized needles (49). Disposable needles, the standard of care in the United States, obviate this concern.

Behavioral Therapies

Few studies have examined behavioral methods for moderating hot flashes. One study compared paced respiration (slow, deep breathing) with progressive muscle relaxation or nontherapeutic α-wave electroencephalographic biofeedback (control) in 33 postmenopausal women (50). Paced respiration training for 4 months significantly reduced the frequency of hot flashes by 39% ($P < 0.02$); progressive muscle relaxation training and the control intervention had no significant effect. In a more recent trial by the same investigators, 24 postmenopausal women with at least five hot flashes daily were randomly assigned to either paced respiration or biofeedback control (51). Paced respiration decreased hot flashes significantly (44% [$P < 0.001$]); no change occurred in the control group. No adverse effects were noted.

A randomized, controlled, 7-week study of the relaxation response technique involved 45 women (33 completed the study) between 44 and 66 years of age who were experiencing at least five hot flashes daily (52). The women were randomly assigned to a relaxation response group, a reading group, or a symptom-charting (control) group. The relaxation group was instructed in relaxation response techniques and asked to practice 20 minutes daily; the reading group read leisure material for 20 minutes daily. Compared to baseline, the frequency of hot flashes did not change in any group; the intensity of hot flashes decreased significantly only in the relaxation group ($P < 0.05$). State anxiety did not change in any group; trait anxiety (assessed by using the Spielberger State-Trait Anxiety Inventory) decreased significantly only in the relaxation group ($P < 0.04$). Behavioral therapies seem to be safe; an explanation for treatment effects is needed.

Wild Yam and Progesterone Creams

Topical wild yam (*Dioscorea villosa*) and "natural" (micronized) progesterone creams have been promoted for hot flashes as well as many other conditions (53). Wild yam preparations contain diosgenin, which can be converted to progesterone in a laboratory but not in the human body. A double-blind, placebo-controlled crossover trial tested wild yam cream against placebo for 3 months in 23 symptomatic menopausal women (54). The treatment and placebo groups did not differ in hot flashes or night sweats (both improved slightly in both groups). There were no changes from baseline in body weight; blood pressure; or levels of serum estradiol, serum or salivary progesterone, total cholesterol, triglyceride, high-density lipoprotein cholesterol, follicle-stimulating hormone, and glucose.

Pharmacologically active progesterone creams are also sold over the counter. A randomized, double-blind, placebo-controlled trial on the effect of progesterone cream on bone examined hot flashes as a secondary outcome (55). Healthy postmenopausal women ($n = 102$) applied one-quarter teaspoon of progesterone cream (20 mg of progesterone) or placebo daily for 1 year. The women also received daily multivitamins and calcium (1200 mg daily). The treatment did not affect bone, but among patients who initially reported hot flashes, 5 of 26 women in the control group compared with 25 of 30 women in the treatment group reported "improvement"; this difference was significant ($P < 0.001$). Eight women treated with progesterone cream had vaginal spotting. Endometrial biopsy revealed proliferative endometrium in one woman; biopsies for the other seven women retrieved insufficient tissue for diagnosis. The induction of postmenopausal bleeding is worrisome and should be explored further.

Consumers sometimes use transdermal progesterone creams as the progestin component of hormone replacement therapy; however, three studies have shown that serum levels of progesterone after application of transdermal creams are insufficient to prevent estrogenic stimulation of the endometrium (56–58).

Discussion

Hot flashes are the primary symptom for which menopausal women seek "natural" treatments. In well-designed but small trials, vitamin E, red clover, evening primrose oil, and dong quai were ineffective for hot flashes. Several controlled trials supported the use of black cohosh for menopausal symptoms; the two placebo-controlled studies that specifically examined hot flashes found opposite results. As herbs usually take longer than estrogen therapy to work, the typical 3-month pharmaceutical trial model may be too short to accurately assess the value of an herb (in all studies of herbs, duration of treatment is important). Safety data on long-term use of herbs are inadequate. Because of the popularity of black cohosh, it is extremely important to elucidate both its benefits and potential risks (especially on stimulation of endometrial or breast tissue). Behavioral approaches (such as paced respiration) are safe, have shown some initial promise, and deserve further study. There are sufficient data to discourage the use of natural progesterone cream as the progestational component of hormone replacement therapy or for the treatment of osteoporosis.

Not all herbs and dietary supplements are risk-free. Many herbs are being promoted for nontraditional uses. Newly formulated combination herbal products (often containing novel mixtures or subtherapeutic doses) should be avoided until research data are available; currently, no safety or efficacy data on such combinations have been published. The subtherapeutic doses often found in such preparations may render them harmless, but even that cannot be counted on. Although plant foods are presumed to be safe, the isolated, often concentrated components have not been tested for long-term use. Furthermore, because of the lack of adequate product quality control in the United States, it is difficult to identify the reliable supplement brands. The number of herbal products in the U.S. marketplace is growing rapidly, and recommended dosages are increasing without research supporting the need for these larger doses.

Health care providers and consumers should be aware that despite the potential usefulness of many CAM therapies, scientific research is limited. Product advertising hype far exceeds scientific knowledge, and scientific evaluation is essential to enable an informed choice among treatments. The popularity of CAM therapies and their therapeutic potential necessitate definitive safety and efficacy studies. Because herbs, vitamins, and other natural products cannot be patented, industry-sponsored research will remain limited. Federal and alternative funding sources must bridge this gap.

From Columbia University, New York, New York; and George Washington University, Washington, DC.

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Requests for Single Reprints: Adriane Fugh-Berman, MD, Department of Health Care Sciences, School of Medicine, George Washington University, 2300 K Street NW, Washington, DC 20037; e-mail, fk@columbia.edu.

Current author addresses are available at www.annals.org.

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Current Author Addresses: Dr. Kronenberg: Rosenthal Center for Complementary and Alternative Medicine, College of Physicians and Surgeons, Columbia University, 630 West 168th Street, Box 75, New York, NY 10032.
Dr. Fugh-Berman: Department of Health Care Sciences, School of Medicine, George Washington University, 2300 K Street NW, Washington, DC 20037.