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FOR CLINICIANS WHO PROVIDE CARE FOR WOMEN

Complementary and alternative medicine preparations used to treat symptoms of menopause

► MAIDA TAYLOR, MD, MPH, FACOG

Since the publication of the results of the Women's Health Initiative (WHI), women distressed by menopausal symptoms have been desperate to find therapies they perceive to be safer than conventional pharmaceutical estrogens and progestogens. While menopause consultants continue to debate the merits or deficiencies of the WHI, and as the pendulum of professional opinion oscillates, women are increasingly confused. Is estrogen therapy good, or

is it bad? Is it good alone, but bad with a progestin? Are hormones helpful if taken early in the menopausal transition, but dangerous later on?

The complexities of the new recommendations regarding the initiation of hormone therapy are bewildering: the postulated cardiovascular benefits of initiating hormone treatment early, during the *window of opportunity*, contradict the postulated breast protection gained by the interposition of the *gap*, a delay in initiating therapy. This is indeed a mixed message, and women are baffled. Small wonder that so many women have lost faith in conventional pharmaceuticals and perceive that the medical establishment is collaborating with drug companies to turn normal aging into a vast tableau of pathology.

Immediately after the WHI, as the use of menopausal hormone therapy declined, the use of both over-the-counter (OTC) remedies and pharmaceutical alternatives accelerated.¹

The same woman who distrusts doctors and drugs, regrettably, may

suspend disbelief when entering a health food store or strolling the supplement aisle at her local big box retailer. Many Americans hold the misapprehension that OTC supplements are tested by the FDA when they actually may be marketed without documentation of efficacy or safety. Although manufacturing standards are set by the US Pharmacopeia (USP), the organization has no legal enforcement powers. In addition, the FDA is hampered by underfunding and understaffing in its efforts to detect manufacturing defects.

Potential deficiencies in OTC supplements include lack of standardization of active ingredients (if known); adulteration with active drugs, steroids, or unknown substances; contamination with heavy metals or pesticides; and highly variable amounts of constituents, which are affected by growing conditions and extraction techniques. Indeed, taking unproven, untested supplements is tantamount to enrolling in an unmonitored, unsupervised clinical trial.

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Maida Taylor, MD, MPH, FACOG

Clinical Professor
Department of Obstetrics, Gynecology and
Reproductive Sciences
University of California, San Francisco
San Francisco, California

Disclosures

Dr Taylor reports that she has served as a consultant to Chemo France and Spain, Everett Laboratories, PharmaDerm, and Sempra Laboratories.

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► CYNTHIA K. SITES, MD



Beyond estrogen for menopausal symptoms

How many times have we heard our patients say, “I can’t take estrogen for my hot flashes because of my health issues”? Or, “Estrogen alone is not enough for me”? If this sounds familiar, perhaps this issue of *Menopausal Medicine* will provide useful advice for these patients.

In her article, Maida Taylor, MD, MPH, FACOG, discusses the evidence for a variety of complementary and alternative therapies for menopausal symptoms. The known safety and efficacy of botanicals, including those that act as hormones or selective estrogen receptor modulators (SERMs) and those that act centrally to modulate the secretion or metabolism of neurotransmitters, are explored.

Armed with all of this new information, we will be in a better position to answer patient questions about the next botanical compound.

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American Society for Reproductive Medicine
1209 Montgomery Hwy., Birmingham, AL 35216
(205) 978-5000 • asrm@asrm.org • www.asrm.org

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Defining complementary and alternative medicine

Complementary and alternative medicine (CAM) encompasses several systematic medical practices based on models of health and disease that differ from the medical physiology that underpins Western medicine.

Traditional Chinese medicine equates health as the balance of the essential life force, qi (pronounced *chee*), and the therapeutic goal is often to normalize the flow of qi through the body. Mind-body systems of medicine view health as an equilibrium between the conscious and unconscious mind on bodily functions. Manipulative and body-based systems, such as chiropractic, osteopathy, and massage, aim to rebalance or realign the body with manual manipulation. Meditation, hypnosis, music, and prayer are part of this sphere, as are energy-modulating modalities, like therapeutic touch, qigong (a Chinese system that integrates physical postures, breathing techniques, and focused attention), and magnets, which are said to alter bioelectric fields in or around the body.

The most commonly employed CAM remedies, however, are biologic-based therapies, such as botanical medicine, dietary supplements (including vitamins and minerals), and orthomolecular medicine.²

CAM treatments used for menopausal symptoms

Virtually every culture employs some folk method or botanical remedy for treatment of menopausal symptoms. According to the Study of Women Across the Nation (SWAN), during menopause, the most commonly used botanical medicines are soy supplements, glucosamine, flaxseed oil, ginkgo, black cohosh, and

TABLE Botanicals said to be useful for menopausal symptoms

HORMONE MEDIATORS/MODULATORS

- Alfalfa (*Medicago sativa*)
- Black cohosh (*Actaea racemosa*)
- Chasteberry (*Vitex agnus-castus*)
- Aniseed, dill, fennel, fenugreek (all members of the dill family)
- Dong quai (*Angelica sinensis*)
- Evening primrose (*Oenothera biennis*) oil
- Flaxseed (*Linum usitatissimum*)
- Gotu kola (*Centella asiatica*)
- Green tea (*Camellia sinensis*)
- Hops (*Humulus lupulus*)
- Kudzu (*Pueraria lobata*)
- Licorice (*Glycyrrhiza glabra*) (also mineralocorticoid activity)
- Maca (*Lepidium peruvianum*)
- Milk thistle (*Silybum marianum*)
- Red clover (*Trifolium pratense*)
- Rhubarb (*Rheum rhaponticum*)
- Sarsaparilla (*Smilax regelii*)
- Sage (*Salvia officinalis*)
- Soy (*Glycine max*) and its derivatives, daidzein, genistein, S–equol, and other isoflavones
- Wild yam (*Dioscorea villosa*)

CENTRAL/NEUROTRANSMITTER MEDIATORS

- Ginkgo (*Ginkgo biloba*)
- Kava kava (*Piper methysticum*)
- *Panax ginseng* (also said to be estrogenic)
- St. John's wort (*Hypericum perforatum*)
- Valerian (*Valeriana officinalis*)

ginseng.³ The **TABLE** lists botanicals said to be useful in treating menopausal symptoms.

The Natural Medicines Comprehensive Database divides botanicals used for menopause into 2 groups: those that are purportedly hormonally active, functioning as estrogens or as selective estrogen receptor modulators (SERMs); and those that alter the function of central neuroreceptors, possibly modulating secretion or metabolism of serotonin and other neurotransmitters, thus mimicking the mode of action of selective serotonin reuptake inhibitors (SSRIs).⁴

Isoflavones

Three types of polyphenolic compounds are said to be estrogenic: the isoflavones, lignans, and coumestans.⁵ In animal studies, these phytochemicals induce disturbances in estrus cycles. Sheep that graze on red clover and cattle fed whole soy may be rendered sterile. By interfering with the animal's reproductive life cycle, these substances act as "birth control" in the grazing population, protecting the plant species from overpredation.⁶

Soy and soy derivatives

Soy, or soya (scientific name, *Glycine*

max, L), is a major source of protein in Asian diets, specifically fermented soy products like tempeh, miso, and tamari.⁷ Although soy is not a traditional treatment for menopausal symptoms, it is nonetheless promoted as a panacea.

It is a widely circulated myth that Asian women do not suffer the symptoms of menopause because they eat a soy-based diet. Caution must be exercised when comparing symptom profiles of women of different racial/ethnic groups. The SWAN investigation provides excellent data on menopausal symptoms experienced by women of different racial/ethnic groups. For example, although hot flashes are less common in Asian women, more than 90% of Japanese American women evidence of some sort menopausal distress, most commonly, shoulder and neck pain.^{8,9}

Metabolism of soy varies by region and ethnicity. In the soy bean, isoflavones are bound to a sugar moiety and are classed as glycosides. Fermentation and digestion cleave the sugar moiety and produce the aglyconic forms of the isoflavones, which are more potent metabolites. Soy isoflavone glycosides are genistin, daidzin, and glycitin, while the aglycones are genistein, daidzein, and glycitein.

Further action by intestinal bacteria converts aglycone daidzein into an even more active molecule, equol. Approximately 60% to 70% of Western and European populations do not have the requisite intestinal flora for this enzymatic conversion.¹⁰ Therefore, data derived from studies done with Asian subjects may not be reproducible in other racial groups. Yet soy continues to be promoted as a functional food to ease hot flashes, preserve bone mineral, and improve lipid profile. Specific isoflavone isolates, such as genistein, and an isoflavone metabolite of daidzein, S-equol, are also sold

as remedies. Isoflavone isolates are also extracted from red clover.

Several large literature reviews have been done on the clinical efficacy of soy for menopausal symptoms. Reviewers at the Cochrane Collaborative were unable to perform a meta-analysis of the impact of soy protein and isoflavones on vasomotor symptoms due to the highly variable study designs and great range of soy types used in the research protocols.¹¹ The Cochrane review authors found that, generally, the amount of isoflavones recommended ranged from 35 to 134.4 mg, and hot flashes generally decreased by 40% to 50%; these reductions were approximately 15% greater than those seen with placebo. No dose-response relationship was apparent. Studies have failed to consistently demonstrate whether equol producers respond better than non-equol producers.

Caution must be exercised when comparing symptom profiles of women of different racial/ethnic groups.

Other studies have failed to demonstrate estrogenic activity in natural soy, as evidenced by no changes in vaginal maturation index, follicle-stimulating hormone (FSH) level, sex hormone binding globulin (SHBG) level, and markers of bone turnover.^{12,13}

Many women do not like soy, while others are troubled by gastrointestinal bloating and gas after eating soy.¹⁴ To avoid these symptoms, isoflavone isolates and concentrates are proffered as alternatives, assuming that the soy proteins can be removed while the supposed active ingredient can be retained, often

concentrating these purported bioactive components.

Bolaños et al performed a meta-analysis of the literature on “soy dietary supplement,” “soy extract,” or “isoflavone concentrate” (genistein or daidzein) for hot flashes.¹⁵ Overall, the standardized mean difference in the number of hot flashes was calculated to be -0.39 (95% CI, -0.53 to -0.25) in favor of soy. For soy “concentrate,” “extract,” and “dietary supplement,” the differences were -0.45 (95% CI, -0.64 to -0.25), -0.51 (95% CI, -0.79 to -0.22), and -0.20 (95% CI, -0.46 to -0.06), respectively. While these changes were statistically significant, the authors noted that the reductions were probably not clinically significant and that their review was inconclusive.

The North American Menopause Society recently published a report on the efficacy of isoflavones in ameliorating menopausal symptoms. Hundreds of papers were reviewed. The conclusions were similar to those of the Cochrane group: soy isoflavones at best “are modestly effective,” and some soy derivatives, like genistein and S-equol, may be somewhat better.¹⁶

Equol is a metabolite of daidzein and is produced by the action of intestinal bacteria. Using biofermentation, a Japanese pharmaceutical company is manufacturing S-equol from soy germ. The rationale for administering S-equol is to circumvent the lack of beneficial intestinal flora in non-equol producers. Several studies of S-equol have been done; all used the Japanese Menopausal Symptom Score, which is heavily weighted with quality-of-life scales. S-equol in a dosage of 10 mg 3 times a day was associated with significant improvements in mood and anxiety. No changes were noted in levels of FSH, luteinizing hormone (LH), estradiol, or progesterone.^{17,18}

Genistein, an aglycone isoflavone,



is being studied as single agent for menopausal symptoms. The genistein used in recent trials is a non-soy derived product. In a study of bone and cardiovascular risk factors, a subset of symptomatic subjects was segregated from the larger study *after randomization*. After 12 weeks, women taking genistein had a 56.4% reduction in the mean number of hot flushes, while the placebo group evidenced no diminution in symptoms during an entire year of study, a finding inconsistent with the natural course of menopause and findings from randomized clinical trials. Subjects in the genistein group also reported significantly fewer hot flushes per day ($P=.010$) and a decrease in total duration of hot flushes per day ($P=.009$) at week 12 versus subjects in the placebo group.¹⁹

In a more recent 12-week trial, subjects on genistein ($n=32$) demonstrated a 51% reduction (9.7 to 4.7/day) in the number of hot flushes by week 12 ($P=.049$), compared with a 30% reduction in the placebo group (9.8 to 7.0/day).²⁰

Daidzein is another aglycone isoflavone, also abundant in soy, that is being considered as a single therapy for menopausal symptoms. One study demonstrated that, at 8 weeks, vasomotor symptom frequency declined in the 40-mg daidzein group by 43% and, in the 60-mg daidzein group, by 41%, versus a 32% decrease in the placebo arm. At 12 weeks, the reductions were 52%, 51%, and 39%, respectively. Quality-of-life scores improved in all groups. None of these findings, however, reached statistical significance.²¹

Red clover

Red clover (scientific name, *Trifolium pratense*) is the richest plant source of isoflavones, and an extract is promoted for the treatment of menopausal symptoms. The Cochrane Collaborative

performed a meta-analysis of trials that used one specific red clover extract product (Promensil) and found that the weighted mean decrease in hot flushes across the trials was -0.6 (95% CI, -1.8 to 0.6) per day, a decrease not clinically relevant.¹¹

Black cohosh is the most popular botanical for menopausal symptoms. The active ingredients of black cohosh are not defined and its mechanism of action has not been clearly elucidated.

In another study, Geller and Studee compared red clover to black cohosh and conjugated equine estrogen (CEE) plus medroxyprogesterone acetate (MPA) and, again, demonstrated a lack of efficacy.¹³

Other botanicals Black cohosh

Black cohosh (scientific name, *Actaea racemosa* L, previously known as *Cimicifuga racemosa*) is the most popular botanical for menopausal symptoms. The most widely used and best-studied commercial formulation available in the United States is Remifemin,²² made from an extract of the rhizome. It is also the referenced product studied in clinical trials in peer-reviewed journals.

The active ingredients of black cohosh are not defined and its mechanism of action has not been clearly elucidated. Proposed mechanisms of action suggest that it may act as a SERM, may stimulate serotonergic pathways, or may act through antioxidant and anti-inflammatory pathways.²³

Numerous clinical trials of black cohosh have been published, but

many had methodologic deficits. Meta-analyses and reviews of the available studies have all reached similar conclusions: at present, there is insufficient conclusive data documenting the efficacy of black cohosh for menopausal symptoms.

The best-designed studies of black cohosh have been negative. In a crossover study, Pockaj et al found that women who received black cohosh reported a 20% reduction in the hot flush score, while women on placebo had a 27% decrease.²⁴

In a 4-arm trial comparing black cohosh, red clover, placebo, and combination hormone therapy using CEE plus MPA, only hormone therapy provided statistically significant reduction in symptoms. After 12 months, hot flushes declined 34% in the black cohosh arm, 57% in the red clover arm, and 63% in the placebo arm, while the hormone-treated group realized a 94% reduction in symptoms.²⁵

Tice et al compared black cohosh and other botanicals with placebo and also found no statistically significant improvements with any of the products tested.²⁶

Between 30 and 60 cases of hepatotoxicity possibly associated with black cohosh have been reported. Several agencies and regulatory bodies have reviewed the data in detail. The National Institutes of Health stated that there is no plausible mechanism that might explain a link between black cohosh and hepatotoxicity. Nonetheless, the USP Botanical Expert Committee issued a directive that black cohosh products should carry a warning, particularly regarding use in persons with compromised liver function.²⁷⁻²⁹

Dong quai

Dong quai, also known as *Angelica sinensis*, dang gui, and tang kuei, is the root of the plant *Angelica* (botanical

CLINICIAN CHECKLIST

- ✓ Document major symptoms and severity of symptoms.
- ✓ Ask patients kindly, but repeatedly, about all medication and supplement use, and check for drug-drug or drug-herb interactions before making recommendations.
- ✓ Give patients basic information about products, preferably in written documents such as handouts.
- ✓ Provide patients with clear warnings of the potential for adverse events with botanicals, especially if a woman insists on using an ineffective product or one with known risks.
- ✓ Include data on efficacy and safety for recommended treatment modalities by putting reprints or abstracts into the patient’s chart.
- ✓ Document informed consent discussion.
- ✓ Provide a list of quality products from reputable manufacturers, or refer the patient to the US Pharmacopeia Web site for a listing of verified products.
- ✓ Follow up with the patient at a reasonable interval, usually at 6 to 12 weeks, to assess compliance and satisfaction with the treatment plan.
- ✓ Maintain a list of qualified CAM and behavioral therapy providers in your area. (Complementary and alternative medicine departments at academic medical centers may provide lists of qualified prescreened specialists).
- ✓ Monitor and report adverse events through MedWatch or through your local poison control network.
- ✓ Advise women to look for products with the US Pharmacopeia Verified Mark.²⁸ The USP sets standards for the quality, purity, identity, and strength of medicines, food ingredients, and dietary supplements to ensure that the product:
 - Contains the ingredients listed on the label, in the declared potency and amounts
 - Does not contain harmful levels of specified contaminants
 - Will break down and release into the body within a specified amount of time
 - Has been made according to FDA current Good Manufacturing Practices (GMPs) using sanitary and well-controlled procedures.
- ✓ Another excellent source of information on supplement quality is available at www.ConsumerLab.com. This company performs independent testing at the manufacturers’ request and expense.
- ✓ Note that botanicals are more tightly regulated in Europe, and products from Germany, Switzerland, and the United Kingdom offer more consistent quality.

Evening primrose

Evening primrose (scientific name, *Oenothera biennis* L; family Onagraceae), also known as evening star and evening primrose oil (EPO), is commonly recommended for symptoms of premenstrual syndrome, not menopause. Five randomized trials of EPO for the treatment of premenstrual syndrome all had negative findings.³³ Similarly, there is no scientific rationale for the use of EPO for menopause-related hot flashes. One published study of EPO use in menopausal women found that hot flashes had a decline of -1.0 per day with EPO and -2.6 per day with placebo.³⁴

Ginseng (*Panax ginseng*)

American ginseng (white or yellow in color) and Asian ginseng (Korean or Chinese red ginseng) serve different purposes in herbal medicine. American ginseng is said to be cooling, while Asian ginseng is supposed to have a warming influence. American ginseng supposedly acts as an “adaptogen,” an agent that enhances the body’s ability to tolerate and acclimate to environmental challenges, physical and emotional stress, and illness. Korean/Chinese ginseng is said to be a stimulant, aphrodisiac, and digestive aid. Asian ginseng is supposedly anabolic and is used to enhance sexual function and as a tonic for frail elderly persons.³⁰

Siberian ginseng (scientific name, *Acanthopanax senticosus* or *Eleutherococcus senticosus*) is another product promoted as an adaptogenic “ginseng.” However, it is not a true ginseng but rather a member of a closely related family of plants, Araliaceae. *Eleutherococcus ginseng* has been used by the Soviet military and Olympic trainers to heighten athletic performance and stamina.³⁵

A ginseng panax extract was studied for treatment of menopausal

name, *Angelica polymorpha* Maxim var *sinesis* Oliv). In traditional Chinese medicine, dong quai is used as the female balancing agent, and it is described as “a warm herb that both circulates and nourishes blood, strengthening someone who is underweight, frail, anemic and chilly.”³⁰ Based on reports of uterine bleeding with use and uterotrophic effects observed in ovariectomized rats, dong quai is reputed to be estrogenic; how-

ever, studies in humans have failed to demonstrate any estrogenic activity.³¹

In a randomized controlled trial, Hirata et al studied 71 postmenopausal women treated with dong quai 4.5 g daily or placebo. After 24 weeks, there were no differences in the number of vasomotor flushes or in Kupperman index of menopausal symptoms. Levels of FSH, LH, and estradiol as well as vaginal maturation index and endometrial thickness were unchanged.³²



complaints in 384 postmenopausal women.³⁶ After 16 weeks, women taking the ginseng extract showed slightly better overall symptom relief, but the improvements were not statistically significant ($P < 0.1$). The benefits may have accrued from improvements in depression, well-being, and health scores. Ginseng had no effect on hot flushes, and there were no changes in FSH or estradiol levels, endometrial thickness, vaginal maturity index, or vaginal pH.³⁶

Ginseng may offer some benefits, but not for menopausal symptoms. It is generally well tolerated by most people, and it has documented effects on response to antibiotics and to flu vaccination in the elderly.³⁷

Maca

Maca (scientific name, *Lepidium meyenii* Walp; *L. peruvianum* Chacón), a traditional foodstuff from South America, is a cruciferous root grown exclusively in the central Peruvian Andes at high altitude. Characterized as “Peruvian ginseng,” it is recommended as a tonic and adaptogen and is used to enhance strength, stamina, athletic performance, and fertility; it is also used to improve anemia and for its aphrodisiac properties.^{38,39} Maca is also used to treat hormone imbalances and menstrual irregularities.

Maca’s mechanism of action is unknown. It contains a weak phyto-sterol, β -sitosterol, and methanolic and aqueous extracts of maca exhibit estrogenic activity in vitro. However, clinical studies have found no estrogenic effects. A proposed mechanism of action for maca is alteration of sex steroid receptor dynamics. Some studies investigating maca have found modest alteration in estrogen in perimenopausal women, but not in menopausal women.⁴⁰

There are no studies of maca for

the treatment of menopause in peer-reviewed journals. Efficacy of maca is uncertain. It is generally regarded as safe and is used as a food staple in South America.⁴¹

Rhubarb

Siberian rhubarb (scientific name, *Rheum rhaponticum*) contains 2 hydrostilbenes, rhapontigenin and desoxyrhapontigenin, that have very weak binding affinity for estrogen receptor- α (ER- α) but higher activity via estrogen receptor- β (ER- β). In vitro and in vivo studies support the hypothesis that rhubarb’s hydrostil-

Rhubarb extract ERr 731, S-equol, and genistein may offer some relief from vasomotor symptoms.

benes act as SERMs, providing mixed agonistic/antagonist activity.⁴²

A rhubarb extract product known as “rhaponticin” or “extract ERr 731” that has been available in Germany for more than 20 years was recently introduced in the United States (brand name, Phytoestrol). A randomized trial with this product versus placebo in 112 perimenopausal women found improvements in symptoms in the active arm within 1 week. No vaginal or uterine stimulation was seen, though the study period was short. A significant reduction was seen in all items on the menopause rating scale, hot flush number, and hot flush weekly weighted score.⁴³ In a follow-up study, the safety data gathered from a subset included 20 women followed for 96 weeks, and 23 followed for 48 weeks.⁴⁴ Few adverse events were reported.

In long-term toxicity studies of ERr 731 in beagle dogs, no abnormal

hematologic or metabolic trends were seen, even at high doses.⁴⁵

Counseling patients about botanicals and alternative medicine remedies

Rhubarb extract ERr 731, S-equol, and genistein may offer some relief from vasomotor symptoms. Soy foods do not appear to be effective. While there is a considerable body of research on both black cohosh and soy-based isoflavones, current evidence is insufficient to determine whether they have a place in the array of treatment options. They do appear to be safe. In some studies, these products have performed 15% to 30% better than placebo. Perhaps they are more effective in a specific patient population that has yet to be defined. Red clover, evening primrose oil, ginseng, wild yam, and vitamin E are ineffective.

Liver function tests should be performed prior to starting black cohosh.

Although most botanicals appear to be no better than placebo, they may be perceived as helpful. Some people hold attitudes that predispose them to prefer “natural” or holistic methods, even if such treatments are marginally effective. For these individuals, perception becomes reality. On the other hand, use of alternative medicine treatments, specifically herbal medicine, may be consistent with an individual’s cultural values and personal philosophy, and clearly also supports the individual’s desire for autonomy. Therefore, if a botanical product is safe and not exorbitantly expensive, it may be kinder to stop trying to dissuade someone who really wants to try that approach. In addition, it may be more palatable than continued pressure to use hormone therapy.

When patients choose to pursue CAM options, clinicians should record

how this decision was made. (See the “Clinician Checklist” on page S6.) Careful documentation of the pros, cons, risks, and benefits of CAM remedies will provide protections for the patient and for the health care provider. ■

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