Botanical Products Used for Premenstrual and Menopausal Symptoms
Catherine Ulbricht and Mary Giles

OVERVIEW
Symptoms related to menstruation and menopause are commonly reported by women living in Western countries. Surveys suggest most women experience at least mild premenstrual symptoms and in a minority (about 2.5%), symptoms are severe. Within 3 months of menopause, more than two thirds of women develop hot flashes and night sweats; 50% experience persistent symptoms for many years. Herbs and other plant-based supplements are popular for the treatment of both conditions. In particular, interest in the use of natural products for menopausal symptoms surged following the recent publication of studies identifying the risks of hormone replacement therapy. Although estrogen is very effective for the treatment of hot flashes and short term use is a reasonable option, many women are looking for safer therapies. Most natural products are used for the vaso-motor symptoms of menopause: hot flashes and night sweats. Some herbs, including Ginseng, St. Johns Wort and Valerian, are believed to improve other symptoms such as depressed mood and sleep disorders. These, however, will not be discussed in detail in this overview.

Although the body of literature evaluating natural products is growing, it remains difficult to draw firm conclusions about safety and effectiveness. Many of the available clinical trials do not meet current design standards (e.g., double-blind, randomized, placebo controlled). The inclusion of a placebo group is important in studies of premenstrual and menopausal symptoms because there is typically a 20-40% response to any therapy, including placebo. The length of studies may also be important.

For example, herbs may take longer than estrogen to relieve menopausal symptoms and a 12 week trial may not be sufficient to determine whether an herb is effective. Questions about the contents of botanical products further obscure the picture. The active components may not be known and optimal doses are often unclear. Standardization is not re-
quired and product content may vary from manufacturer to manufacturer, or even from batch to batch with one manufacturer. The effects of different brands may not be comparable. This issue summarizes the limited scientific evidence available for the natural products most often used for premenstrual and menopausal symptoms, including soy, black cohosh, red clover, flaxseed, ginkgo, fish oil, dong quai, evening primrose oil, chasteberry and wild yam. Dosing and safety information for these products is presented in Table 1.

Black Cohosh
Black cohosh is prepared from the dried roots of the perennial Cimicifuga racemosa. Traditionally, it was used by native Americans for gynecologic conditions as well as other, nongynecologic health problems. Black cohosh is widely available as a herbal supplement in tablet or capsule form. The commercial product Remifemin®, used in the majority of clinical studies, is an isopropyl alcohol extract standardized to contain 1 mg of 26-deoxyactein (also referred to as triterpene glycosides) per 20 mg tablet. The manufacturing process and dosing recommendations for Remifemin® have changed over the past 20 years, and doses used in different studies may not be comparable. A liquid formulation of Remifemin® prepared with a different extraction process was used in some studies.

Medicinal uses of black cohosh include the treatment of premenstrual syndrome and dysmenorrhea (painful menstruation). It is most popular as an alternative to hormonal therapy for the treatment of menopausal symptoms such as hot flashes, night sweats, palpitations, anxiety and depression.

The mechanism of action of black cohosh remains unclear and its effects on estrogen receptors and hormone levels (if any) have not been fully elucidated. Recent publications suggest that there may be no direct effects on estrogen receptors, although this is an area of ongoing controversy. One recent trial suggests black cohosh may have beneficial estrogenic effects in the brain (related to hot flash reduction), bone and vaginal tissue, without harmful estrogenic effects in the uterus.

Menopausal Symptoms: Several controlled trials evaluating black cohosh for up to six months have reported improvements in menopausal symptoms. At least 4 trials demonstrated a similar reduction in symptoms with black cohosh and estrogen therapy, such as 0.6 mg conjugated estrogens daily. Although these initial studies are suggestive, most were small and many suffered from methodological weaknesses. A recently updated overview by the National Center for Complementary and Alternative Medicine at the National Institutes of Health states “Although preliminary evidence is encouraging, the currently available data are not sufficient to support a recommendation on the use of black cohosh for menopausal symptoms.”

A recent review of the safety of black cohosh concluded that adverse effects are rare and mild. Short-term use appears safe in women with menopausal symptoms. Gastrointestinal upset and rash are the most frequently reported side effects. Black cohosh has not been well-studied beyond 6 months and long term safety remains unknown.

The potential estrogen-like effects of black cohosh continue to be debated, and caution is warranted in women with or at high risk for breast cancer and those with uterine cancer or endometriosis. Black cohosh should not be taken by pregnant or lactating women because its effects in these populations are unknown. Concurrent use of black cohosh and estrogen or tamoxifen, which has anti-estrogenic effects, has not been thoroughly studied and caution is advised. Black cohosh should also be used cautiously in women taking other herbs with possible estrogen-like effects, such as alfalfa, bloodroot, burdock, hops, kudzu, licorice, pomegranate, red clover, soy, thyme, white horehound, and yucca.

In nature, black cohosh contains small amounts of salicylic acid. It is not clear if salicylates are present in commercial black cohosh products in concentrations sufficient to have significant effects. Caution is advised in patients allergic to aspirin or other salicylates.

Black cohosh should not be confused with blue cohosh (Caulophyllum thalictroides), which contains potentially toxic chemicals. Both black cohosh and blue cohosh have been used by midwives in the United States to assist birth. There is one report of severe multi-organ damage in a child delivered with the aid of this combination. The herb pennyroyal (Hedeoma pulegioides L.) and black cohosh should not be used together, as there is a possibility of serious adverse effects and death.

Botanical Products Containing Phytoestrogens
Phytoestrogens are plant-based compounds structurally similar to estradiol. These compounds appear to stimulate estrogen receptors in some tissues and block the effects of estrogen in other tissues. Phytoestrogens have been identified in several medicinal plants, including soy, red clover and flaxseed. There are many types of phytoestrogens; three of the more widely studied are isoflavones, lignans and coumestans. Isoflavones are believed to reduce the signs and symptoms of menopause (such as hot flashes). Soybeans contain the two isoflavones with the most in vitro estrogenic activity, genistein and daidzein. Red clover is a source of four
isoflavones, genistein, daidzein, biochanin and formononetin. Lignans are found in flaxseed.

**Soy**

Soy is a member of the legume plant family (*Fabaceae*) and has been a dietary staple in Asian countries for at least 5,000 years. Large-scale soybean cultivation began in the United States during World War II. Currently, Midwestern U.S. growers produce approximately half of the world’s supply of soybeans, which are processed into food products, animal feed, oil, dietary supplements and nonedible products.

Dietary soy and isoflavone supplements derived from soy have been investigated as treatments for menopausal symptoms, specifically hot flashes and night sweats. Other potential benefits under study include reduced cholesterol levels, reduced bone loss in postmenopausal women, and reduction in the risks of breast and prostate cancer.

**Menopausal Symptoms:** A lifelong diet rich in soy foods may be related to the lower incidence of menopausal hot flashes reported by Asian women compared to women in Western countries. At least 14 randomized, placebo-controlled clinical trials have examined the effects of soy (consumed as a food, protein supplement, or isoflavone extract) on hot flashes. Most studies were fairly short, with treatment durations ranging from 6 to 24 weeks. Overall, the published evidence is variable and results are conflicting. Although some evidence suggests a benefit, better quality studies are needed to form a firm conclusion about efficacy.12,13

Soy is generally regarded as safe to consume as a food. Soy foods are usually considered safe during pregnancy or breast-feeding, although there is limited information available in this area. The risks of long term use are unknown, although traditional Asian dietary intake indicates the benign effect of soy foods.13 The safety of dietary supplements containing isoflavones or other soy extracts has not been established. These products appear to act at estrogen receptors and should not be assumed safe for women with estrogen-dependent cancers, most importantly breast cancer.3 Until more information is available about isoflavone supplements, foods are the safest source of soy-derived phytoestrogens.

**Red Clover**

Red clover (*Trifolium pratense*) is a legume which contains genistein and daidzein, the primary estrogenic isoflavones in soy, plus two additional isoflavones thought to have estrogenic activity: biochanin A and formononetin. Red clover supplements, prepared from the blossoms of the herb, are available as teas, tinctures, tablets, capsules, liquid extract, and extracts standardized to specific isoflavone contents. Traditionally, red clover has been used to treat asthma, pertussis, cancer, gout and dermatological conditions such as psoriasis and eczema.14,15 Currently, red clover supplements are marketed for the treatment of menopausal symptoms, as options to HRT, for the treatment of hyperlipidemia, and to prevent osteoporosis. Two commonly used supplements are Promensil®, containing an average of 41 mg isoflavones per tablet and Rimostil®, containing an average of 29 mg total isoflavones per tablet. (The products differ in the proportion of each isoflavone present.)

**Flaxseed**

Flaxseed and flaxseed oil come from the flax plant, which is also used to produce linen cloth. Flaxseed (not the oil) is a rich source of soluble fiber and the type of phytoestrogens called lignans. Flaxseed oil (also called linseed oil) is highly unsaturated and rich in alpha-linolenic acid, an omega-3 fatty acid similar to those found in fish oil. Health-related uses that have been studied include reduction of cholesterol levels (related to the unsaturated fat and fiber content), prevention of cardiovascular disease (related to omega-3 fatty acid content) and the prevention of hormone-sensitive cancers (related to the lignan content). Few studies evaluating these uses have been published and a benefit has not been established. As a source of soluble fiber, flaxseed may have laxative properties. However, large doses or inadequate fluid intake may precipitate bowel obstruction. Flaxseed (not flaxseed oil) has also been used to relieve cyclic breast pain and menopausal symptoms. The seed is typically ground or crushed and may be eaten plain,
Dong Quai, also known as Chinese Angelica, is prepared from the root of the perennial *Angelica sinensis*. The herb has been used for thousands of years in traditional Asian medicine. It remains one of the most popular plants in Chinese medicine and is used primarily for health conditions in women. Dong quai has been called “female ginseng,” based on its use for gynecologic disorders such as dysmenorrhea, pelvic pain, recovery from childbirth or illness, and fatigue/low vitality. In Chinese medicine, dong quai is most often used in combination with other herbs. It is available in combination products and as a single-ingredient tablet or capsule, typically containing 500-600 mg powdered root. Dong quai is also formulated as a tincture and a tea. There are no standard or well-studied doses of dong quai; a wide range of doses have been used traditionally and in Chinese research.

Recently, interest in dong quai has surged due to its proposed weak estrogen-like properties. However, it remains unclear if dong quai has the same effects on the body as estrogens, blocks the activity of estrogens, or has no significant hormonal effects. One small, well-designed trial in postmenopausal women trial found no short-term estrogen-like effects and no changes in blood estrogen levels. Additional research is necessary before a firm conclusion can be drawn about estrogen-like activity.

Dysmenorrhea (painful menstruation): There is no reliable scientific evidence for the use of dong quai in women with dysmenorrhea. Human studies evaluating this use have been reported in the Chinese medicine literature, but were generally of poor quality and evaluated dong quai in combination with other herbs. Animal studies examining the effects of dong quai on the uterus have had conflicting results; both relaxing and stimulatory effects have been reported.

**Dong quai**

Menstrual Migraine Headache: One small, 24 week study evaluated a combination of 60 mg soy isoflavones, 100 mg dong quai and 50 mg black cohosh daily as preventive therapy for menstrual-related migraine. A 50% reduction in the average frequency of migraine was demonstrated among women taking the study medication compared to those taking placebo. The effects of dong quai alone for this condition remain unclear.

Menopausal Symptoms: One well-designed clinical trial which evaluated the effects of dong quai on menopausal symptoms has been published. Seventy one women with menopausal symptoms received either dong quai or placebo for 24 weeks. This study found no difference between women taking dong quai and those taking placebo in the number of hot flashes or in the Kupperman Index (a commonly used measure of menopausal symptoms). However, this study evaluated dong quai alone and it is traditionally used in combination with several other herbs. In addition, the dong quai extract used, prepared by East Earth herbs, Inc. (4.5 milligrams per day, standardized to 0.5 milligrams per kilogram of ferulic acid), may not be manufactured in the same way as other dong quai products and may have different effects.

Because of the lack of high-quality studies and the wide variety of products and doses evaluated, no specific recommendations for the use of dong quai can be made.

**Ginkgo biloba**

The leaves of the *Ginkgo biloba* tree have been used medicinally for thousands of years and today, ginkgo is one of the top selling herbs in the United States. Ginkgo is used for the treatment of numerous conditions, several of which are under investigation. Available evidence suggests ginkgo may be effective in the management of intermittent claudication, Alzheimer’s/multi-infarct dementia, and cerebral insufficiency. One clinical trial has evaluated its use for premenstrual syndrome. Ginkgo leaf extract, the most commonly used form, is available in tablets, capsules and as a liquid. Most published...
<table>
<thead>
<tr>
<th>Herb and Use</th>
<th>Evidence Grade</th>
<th>Usual Dose</th>
<th>Side Effects</th>
<th>Potential Drug Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black Cohosh menopausal symptoms</td>
<td>B</td>
<td>20 mg twice (Remifemin®) daily</td>
<td>well tolerated with short term use; gastrointestinal upset and rash occur occasionally; poorly substantiated reports of hepatitis/hepatic failure; negative estrogenic effects, especially in hormone sensitive conditions&lt;sup&gt;1&lt;/sup&gt;, are a theoretical concern</td>
<td>estrogen products (HRT, OCs), phystrogen supplements, antihypertensive agents, antiplatelet/anticoagulant agents</td>
</tr>
<tr>
<td>Chasteberry PMS, breast pain</td>
<td>C</td>
<td>30-40 mg per day (aqueous extract)</td>
<td>well tolerated with short term use; gastrointestinal upset, nausea, itching and skin rash have been reported</td>
<td>unknown</td>
</tr>
<tr>
<td>Soy menopausal hot flashes</td>
<td>B</td>
<td>40-60 gm soy protein powder or 50-80 mg isoflavones daily</td>
<td>foods are well tolerated, protein powder may cause bloating, nausea, constipation; allergic reactions have been reported; negative estrogenic effects, especially in hormone sensitive conditions&lt;sup&gt;1&lt;/sup&gt;, are a theoretical concern</td>
<td>estrogen products (HRT, OCs), phystrogen supplements, tamoxifen, aromatase inhibitors, warfarin, panax ginseng</td>
</tr>
<tr>
<td>Fish Oil dysmenorrhea</td>
<td>C</td>
<td>no widely accepted dose</td>
<td>safety in medicinal doses unknown; may cause diarrhea, upset stomach, nausea, vomiting, loss of appetite, burping, bloating, photosensitivity (severe skin reactions); anticoagulant and antiplatelet effects have been reported; negative estrogenic effects, especially in hormone sensitive conditions&lt;sup&gt;1&lt;/sup&gt;, and carcinogenic potential are theoretical concerns</td>
<td>estrogen products (HRT, OCs), anticoagulants, antiplatelet agents, cholesterol lowering agents, antihypertensive agents</td>
</tr>
<tr>
<td>Ginkgo PMS</td>
<td>C</td>
<td>80-240 mg (50:1 standardized extract) daily</td>
<td>well tolerated with short term use; headache, nausea, upset stomach may occur; vomiting, diarrhea, stomatitis, proctitis, restlessless, dizziness, dermatologic allergic reactions, seizures, palpitations, ↓ blood pressure, and changes in insulin levels have been reported; serious bleeding has occurred rarely</td>
<td>donepezil, tacrine, anticonvulsants, antihypertensive agents, SSDs, hypoglycemic agents, sildenafil</td>
</tr>
<tr>
<td>Red Clover menopausal symptoms</td>
<td>C</td>
<td>40, 80, 160 mg (Promensil®) isoflavones daily</td>
<td>well tolerated; no reports of adverse effects for up to one year of use; an increased risk of bleeding and negative estrogenic effects, especially in hormone sensitive conditions&lt;sup&gt;1&lt;/sup&gt;, are theoretical concerns</td>
<td>estrogen products (HRT, OCs), phytoestrogen supplements, tamoxifen, antiplatelet agents, thyroid drugs</td>
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<td>Evening Primrose Oil breast pain PMS</td>
<td>C</td>
<td>2-4 grams daily (standardized 500 mg capsules)</td>
<td>well tolerated for up to one year of use; occasional headache, abdominal pain, nausea and loose stools; case reports of seizures</td>
<td>anticoagulants; antihypertensives and supplements with blood pressure lowering effects</td>
</tr>
<tr>
<td>Wild Yam menopausal symptoms</td>
<td>C</td>
<td>no widely accepted dose</td>
<td>information is limited; contact dermatitis and gastrointestinal upset (with higher doses) have been reported</td>
<td>estrogen products (HRT, OCs), phytoestrogen supplements, hypoglycemic agents</td>
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* Reported in human studies or anecdotally reported.  **Potential interaction based on the herb's mechanism of action(s); no well-substantiated cases of the interaction reported in the literature, however caution is advised.

<sup>1</sup>breast cancer, ovarian cancer, uterine cancer, endometriosis  <sup>1</sup>in vitro evidence only  <sup>3</sup>chlorpromazine, thiouridine, trifluoperazine, fluphenazine; Abbreviations: HRT: hormone replacement therapy, OCs: oral contraceptives, SSRIs: selective serotonin reuptake inhibitors, NSAIDs: nonsteroidal antiinflammatory drugs, CYP450: cytochrome P450
studies evaluated the standardized leaf extracts referred to as EGB 761 and L1 1370, which contain 24-25% ginkgo flavone glycosides and 6% terpenoids.

Premenstrual Syndrome (PMS): A double-blind, placebo controlled trial evaluated the effectiveness of ginkgo in relieving symptoms associated with premenstrual syndrome (PMS).29 Women with PMS between the ages of 18-45 years old were followed for two menstrual cycles. Each participant received either 80 mg twice daily of ginkgo extract (EGB 761) or placebo, starting on day 16 of the first cycle, until day 5 of the following cycle. The authors reported that ginkgo relieved PMS symptoms, particularly breast symptoms. However, outcomes were assessed subjectively by patients and clinicians, without the use of standardized scales. In addition, randomization was not described. Further study is warranted before a recommendation can be made for or against the use of ginkgo for symptoms associated with premenstrual syndrome.

Wild Yam
Wild yam (Dioscorea villosa and other Dioscorea species) grows throughout North and Central America and Asia. The dried root is ground and formulated as capsules and tablets. Wild yam extract is also commercially available in creams and tinctures. It has been hypothesized that wild yam possesses dehydroepiandrosterone (DHEA)-like properties and acts as a precursor to human sex hormones such as progesterone and estrogen. Based on this proposed mechanism, wild yam has been used to treat dysmenorrhea and menopausal symptoms (hot flashes and headaches). However, wild yam does not contain hormones or precursors that can be converted to hormones in the body. This misconception arose because a chemical extracted from wild yam, diosgenin, was used to manufacture progesterone, androgens, and cortisone in the 1960s. Diosgenin can be converted to progesterone in the laboratory, but not in the human body.30

Menstrual and Menopausal Symptoms: The use of wild yam as a treatment for dysmenorrhea, menstrual cramps or menopausal symptoms has not been well studied. One small clinical trial compared wild yam cream to a placebo cream for the treatment of menopausal symptoms and found no difference between the two creams.31 Manufacturers of a topical cream containing wild yam have claimed that the cream possesses progesterone-like effects and is a source of “natural hormones,” however, this is not supported by animal or human studies. Some commercial wild yam products have been adulterated with synthetic progesterone, which may be responsible for the reported steroidal effects. Synthetic progesterone (e.g., medroxyprogesterone) is effective in the treatment of hot flashes, but causes undesirable side effects including vaginal bleeding.2 Wild yam has also been marketed as a natural precursor of DHEA, which is unfounded in science. At this time, there is no scientific evidence to support the use of wild yam for menstrual or menopausal symptoms.

Chasteberry
Chasteberry, the fruit of the Chaste tree or shrub (Vitex agnus-castus), has been traditionally used to treat menstrual irregularities, infertility and acne, as well as to reduce the symptoms of premenstrual syndrome (PMS) and menopause. Preparations of the dried fruit are commercially available in tablet, capsule and liquid forms. The evidence accumulated to date suggests chasteberry inhibits prolactin secretion through dopaminergic activity, which may be the mechanism for some of its effects.

Menopausal & Menstrual Symptoms: Scientific evidence for the use of chasteberry in the treatment of menopausal symptoms is lacking. The results of numerous uncontrolled studies suggest chasteberry may reduce PMS symptoms. One recent placebo-controlled clinical trial evaluated chasteberry extract 20 mg daily (also called ZE 440 extract; supplied as tablets) for the treatment of PMS symptoms over 3 menstrual cycles.32 Several self-reported symptoms (irritability, mood alteration, anger, headache and breast fullness) improved significantly with chasteberry compared to placebo. There is also preliminary evidence suggesting chasteberry relieves cyclic breast pain (mastalgia).33 Although these results are promising, additional large, well-designed studies are necessary before a recommendation for use can be made. A recommended dose has not been established and studies have used a wide range of doses, as well as a variety of products.

Fish and Fish Oil Supplements
Fatty fish (e.g., mackerel, herring, salmon, tuna) and fish oil are rich sources of the omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). A third omega-3 fatty acid, alpha-linolenic acid (ALA), is present in flaxseed, canola oil, walnuts, and soybeans. ALA is converted to EPA and DHA in the body. These fatty acids are precursors for prostaglandins, thromboxanes, and leukotrienes which have antiinflammatory, antithrombotic, antiarrhythmic, and vasodilatory properties. It has been suggested that the antiinflammatory or prostaglandin-mediated effects linked with omega-3 fatty acids may play a role in the management of dysmenorrhea.

Menstrual Symptoms: Low dietary intake of marine omega-3 fatty acids has been associated with greater menstrual pain.34 Two small clinical trials have sug-
suggested that fish oil supplements (1080 mg EPA plus 720 mg DHA daily in one trial and 5 g fish oil daily in the other) significantly decrease menstrual discomfort.\textsuperscript{35,36} However, further research is needed to confirm these findings.

Some species of fish carry a high risk of environmental contamination, such as with methylmercury. The U.S. Environmental Protection Agency recommends that women who may become pregnant and pregnant or nursing women limit their fish intake to 12 oz a week and avoid certain fish altogether (mackerel, shark, swordfish, and tilefish). Fish oil supplements generally do not contain harmful contaminants.\textsuperscript{37}

**Evening Primrose Oil**

Evening primrose oil is made from the seeds of the herb *Oenothera biennis*. Sixty to 80\% of evening primrose oil is the essential fatty acid linoleic acid. Gamma linolenic acid (GLA), an omega-6 essential fatty acid synthesized from linoleic acid in the body, is also contained in the oil (8-14\%) and is considered the active ingredient. Evening primrose oil is commonly marketed for the treatment of premenstrual syndrome (PMS) and breast pain (i.e., mastalgia, mastodynia). It has also been used for a number of other conditions including hot flashes associated with menopause, skin disorders such as eczema and psoriasis, rheumatoid arthritis, diabetes, multiple sclerosis, obesity, asthma, Raynaud’s syndrome and chronic fatigue syndrome.\textsuperscript{38}

Linoleic acid and GLA are key precursors of an anti-inflammatory prostaglandin, prostaglandin E1 (PGE1). Deficiencies in GLA and PGE1 have been documented in some women with premenstrual syndrome and breast pain and may contribute to these disorders.\textsuperscript{39,40}

**Premenstrual Symptoms and Breast Pain:** One review of studies evaluating evening primrose oil for PMS determined that of ten clinical trials, only two were well designed.\textsuperscript{41} These two small trials evaluated evening primrose oil in women with PMS over 3-4 menstrual cycles and failed to find a significant reduction in symptoms compared to placebo.\textsuperscript{42,43} Other reviewers have also concluded that current evidence provides little if any support for evening primrose oil in the treatment of PMS symptoms.\textsuperscript{44} A beneficial response to the herb has been reported in women with cyclic breast pain (mastalgia) associated with the menstrual cycle.\textsuperscript{38} When compared to bromocriptine and danazol, two drugs commonly used for cyclic breast pain, evening primrose oil was as effective as bromocriptine (47\% response rate) but less effective than danazol (70\% response rate).\textsuperscript{45} Significant reductions in breast pain and tenderness have also been reported by other investigators.\textsuperscript{46} However, it isn’t clear that these positive studies were methodologically sound and a more recent randomized, controlled trial does not support their results. A 6 month evaluation of evening primrose oil found that the supplement did not reduce chronic mastalgia pain any more than placebo.\textsuperscript{47} Despite the lack of clear evidence, evening primrose oil is licensed for the treatment of non-cyclical breast pain in the United Kingdom and is considered a first line therapy in several European countries.\textsuperscript{38}

**Menopausal Symptoms:** Very few studies have investigated the use of evening primrose oil for menopausal symptoms. One small, 6-month trial concluded that evening primrose oil offers no benefit over placebo for the relief of vasomotor symptoms.\textsuperscript{48}

**Conclusion**

Many women are turning to phytoestrogens and other natural products for the relief of premenstrual and menopausal symptoms, although the risks and benefits have not been fully elucidated. Since phytoestrogens and hormone replacement therapy may have similar mechanisms for reducing menopausal symptoms, the risk of hormone-sensitive cancers and blood clots may be similar, eliminating a key reason for using options to estrogen -- it’s still unclear whether this is true or false. Patients with estrogen-sensitive diseases and those who take estrogen should use phytoestrogens cautiously.

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**Other Supplements**

A large number of herbals and other dietary supplements are promoted for the treatment of premenstrual symptoms, menopausal symptoms, or both. Use of the products mentioned below cannot be recommended because scientific evidence supporting effectiveness and/or safety is lacking.

**Botanicals with potential estrogenic activity:** kudzu (*Pueraria lobata*), alfalfa (*Medicago sativa*), licorice (*Glycyrrhiza glabra*) and hops (*Humulus lupulus*). Effects of these herbs on hormone-sensitive conditions such as breast, uterine, cervical or prostate cancer, and endometriosis are unknown.

**Vitamin E:** There is no reliable evidence that vitamin E reduces hot flashes in menopausal women. Two small clinical trials suggested vitamin E may reduce some symptoms of PMS.\textsuperscript{39,50}

**Centrally-acting natural products for nonvasomotor menopausal symptoms:** Valerian (*Valeriana officinalis*) can be effective for insomnia and St. John’s wort (*Hypericum perforatum*) can be effective for depression. However, there is no reliable evidence for benefit when these conditions are associated with menopause. Ginseng did not provide an overall benefit in the treatment of menopausal symptoms in one trial, although well-being and depression improved.\textsuperscript{41}

**Dr. Ulbricht and Dr. Giles report no financial interest in or other relationship with any commercial entity discussed in this issue.**
• What phytoestrogen supplement should I take to prevent hot flashes and other menopausal symptoms?

Plant estrogens, or phytoestrogens, have estrogen-like activity when taken in large quantities. They don’t provide a direct source of estrogen like hormone replacement therapy, but they are thought to provide some of the benefits of estrogen in relieving menopausal symptoms. Three that have been widely used are soybeans, red clover, and flaxseed.

Soy has been a staple of Asian diets for thousands of years and it has been suggested that soy foods (raw soy beans, tofu, or soy milk) and isoflavone supplements made from soy help relieve mild menopausal symptoms, specifically hot flashes and night sweats. While some scientific evidence supports the use of soy products for reducing hot flashes, more study is needed before a conclusion about effectiveness can be drawn. There isn’t sufficient evidence to know if isoflavone supplements are effective and safe long-term. Consuming soy-based foods (40-60 grams per day) is currently considered the safest source of phytoestrogens.

Red clover (Promensil®, Rimostil®) and flaxseed supplements are widely marketed for the relief of menopausal symptoms, although their use is controversial. Several clinical studies have not found red clover supplements beneficial for hot flashes or other menopausal symptoms. Flaxseed 40 grams daily relieved menopausal symptoms to a similar degree as conjugated estrogen in one small study. Further study is necessary to determine the benefits and risks before either supplement can be recommended.

• I plan on taking Remifemin® (black cohosh) if my menopausal symptoms worsen. Does it work?

Improved menopausal symptoms have been reported by several studies lasting up to 6 months. In some studies, improvements were similar to those seen with conjugated estrogens. Some experts support the short-term use of black cohosh (up to 6 months) to reduce menopausal symptoms, while others maintain that the available evidence isn’t adequate enough to recommend its use. Risks and benefits should be discussed with a healthcare provider before a decision is made.

• Are there major safety concerns with using phytoestrogen or other supplements with estrogen-like effects?

Since phytoestrogens, other supplements with estrogen-like effects, and hormone replacement therapy work similarly in the body, there may be similar risks. Women who have, or are at high risk for, estrogen-dependent cancers (most importantly breast cancer) and women who are pregnant or lactating should avoid these supplements. Women with other hormone sensitive conditions and those who take estrogen should use these supplements cautiously and only under the supervision of a healthcare provider.

• Which natural supplements are effective for premenstrual syndrome (PMS) symptoms?

Chasteberry has been shown to relieve PMS symptoms in a small number of studies. However, further study is necessary to confirm its beneficial effects. There is interest in fish oil and ginkgo as potential treatments, but the evidence is too limited to draw any conclusion about effectiveness. Evening primrose oil appears to provide little or no benefit for PMS symptoms. St John’s wort appears useful for mild depression linked with PMS; further study will likely define its role in PMS.

• Why are many studies of natural or botanical supplements not considered credible?

There are many reasons studies are considered “flawed” including poor design or setup of the study, failure to include enough patients, and failure to analyze the results with appropriate statistics. With respect to treatment for menopausal or premenstrual symptoms, there is a high “placebo-response”. Therefore, a positive response to any treatment (natural or conventional) may not represent a true beneficial effect.

Resources

• Natural Standard
  1 Broadway, 14th Floor
  Cambridge, MA 02142  (617) 758-4270
  http://www.naturalstandard.com

• Office of Dietary Supplements (ODS)
  National Institutes of Health
  6100 Executive Blvd. Room 3B01, MSC 7517
  Bethesda, MD 20814  (301) 435-2920

• National Center for Complementary and Alternative Medicine (NCCAM)
  P.O. Box 7923  (888) 644-6226
  http://nccam.nih.gov

• U.S. Pharmacopeia Dietary Supplement Verification Program
  12601 Twinbrook Parkway
  Rockville, MD 20852  (800) 227-8772 ext.8273
  http://www.uspverified.org

• The American College of Obstetricians and Gynecologists
  409 12th Street, SW
  P.O. Box 96920
  Washington, DC 20090  (202) 638-5577
  http://www.acog.org

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TEST QUESTIONS

Write your answers on the Credit Request/answer form provided or take the test online: www.rxconsultant.com

Questions are based on information provided in the text, tables and Frequently Asked Questions insert.

This program is valid through February, 2007.

1. Which of the following facts is particularly important to remember when evaluating natural products for premenstrual and menopausal symptoms?
   a. The same products from different manufacturers are not allowed to vary in content.
   b. There is a large placebo response.
   c. Natural products have been proven safer than conventional hormone replacement therapy (HRT).
   d. Clinical studies of natural products are well designed and provide reliable results.

2. Standardization of botanical products used as HRT alternatives is enforced by a government agency.
   a. true  
   b. false

3. Preliminary evidence suggests that black cohosh may have a benefit for which of the following symptoms?
   a. premenstrual tension
   b. memory loss
   c. menopausal symptoms
   d. bladder incontinence

4. Which of the following statements regarding phytoestrogens is true?
   a. Phytoestrogens bind to estrogen receptors only as agonists, exerting estrogen-like effects.
   b. Phytoestrogens are structurally identical to estradiol.
   c. The phytoestrogens that appear to have the most estrogenic activity are coumestans.
   d. Phytoestrogens appear to act like estrogen in some tissues and block estrogen effects in other tissues.

5. Which of the following botanical products has the most scientific evidence to support its use in the treatment of hot flashes related to menopause?
   a. chasteberry  
   b. soy  
   c. dong quai  
   d. ginkgo

6. What is the most concerning potential adverse effect of several botanical herbs (e.g., black cohosh, soy, red clover, flaxseed) used for menopausal symptoms?
   a. negative estrogenic effects
   b. breast pain
   c. GI upset
   d. headache

7. Promensil® is a red clover supplement that contains isoflavones.
   a. true  
   b. false

8. Which of the following supplements is associated with photosensitivity that may be severe?
   a. chasteberry  
   b. dong quai  
   c. fish oil  
   d. evening primrose oil

9. What property has been mistakenly attributed to wild yam and considered responsible for its proposed beneficial effects?
   a. high alpha-linolenic acid content
   b. estrogen and progestin-like effects
   c. inhibition of prolactin secretion
   d. high androgen content

10. Preliminary evidence suggests that chasteberry may have a benefit for which of the following?
    a. prevention of osteoporosis
    b. menopausal symptoms
    c. menstrual irregularities
    d. premenstrual syndrome

11. While not proven safe or effective for dysmenorrhea, why are fish oil supplements thought to be beneficial for this condition?
    a. fish oil contains isoflavones
    b. fish oil inhibits vaginal bleeding
    c. fish oil has antiinflammatory and prostaglandin-mediated effects
    d. the methylmercury found in fish oil supplements inhibits prolactin secretion

12. Which of the following is believed to be the “active” ingredient in evening primrose oil?
    a. lipoic acid
    b. ascorbic acid
    c. omega-3-fatty acids
    d. gamma-linolenic acid

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References


Documents dating back to 1988 that suggest a link between the use of Prozac® and violence have been forwarded to the FDA. The British Medical Journal received internal documents from an anonymous source indicating that Eli Lilly officials were aware that fluoxetine (Prozac®) caused behavioral problems, including agitation and panic attacks, in clinical trials. The documents in question apparently disappeared during a product liability suit in 1994. The FDA is currently reviewing the documents.

The FDA has issued a public health advisory concerning the use of NSAIDs including COX-2 inhibitors. The advisory was issued following the release of data from controlled clinical trials showing that COX-2 selective agents (Vioxx®, Celebrex®, and Bextra®) may be associated with an increased risk of serious cardiovascular events when used for a long period of time or in high risk settings. Long-term use of naproxen (up to 3 years) may also increase the risk of CV events. Consumers are advised to use NSAIDs in strict accordance with the label directions, and to consult healthcare providers if an NSAID is needed longer than 10 days.

**In The News**

**Does Size Matter with Oral Contraceptive Use?**

**Summary:** A case control study has found overweight and obese women who use oral contraceptives (OC) may have a higher risk of pregnancy than women who weigh less. Normal body-mass index (BMI) is 18.5 to 24.9. The research revealed that women with a BMI of >27.3 (~5’4” and 160 lbs) had a 60% greater risk of becoming pregnant while taking OCs. Women with a BMI of >32.2 had a 70% greater risk. There are several possible biologic explanations for the increased risk of pregnancy: Overweight women have higher basal metabolic rates, greater (induced) liver enzyme activity, and store more of the OC because those hormones are stored in fat. All of these factors decrease circulating blood levels of the OC hormones.

**Comment:** Researchers suggest that overweight women on the pill consider using a backup method of birth control. It may be prudent to avoid use of the 20 µg pill among overweight women. All women should be counseled on the importance of consistent use of the OC and how to manage missed doses.

*By Leslie Shimp, PharmD*

**Aspirin Underused By Adults With Diabetes**

**Summary:** The American Diabetes Association recommends daily aspirin for any high risk diabetic over 30 as an effective and inexpensive way to reduce the risk of heart attack. High risk patients include those with cardiovascular disease (CVD), and those with risk factors for CVD in addition to diabetes (family history of CVD, smoking, obesity, albuminuria, or dyslipidemia). A recent study analyzed data from surveys of over 8,000 diabetics. The data indicated that while aspirin use increased from 38% to 49% between 1997 and 2001, there was a distinct disparity between men and women, and that younger individuals used aspirin least. Only 65% of women with established CVD regularly used aspirin compared to 83% of men. In addition, only 40% of the diabetics who didn’t have evidence of CVD but were considered high risk because of smoking, hypertension or dyslipidemia regularly used aspirin.

**Comment:** Health professionals can help identify diabetic patients who are candidates for aspirin therapy and encourage this intervention.

*By James Chan, PharmD, PhD*