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Contemporary Alternatives to Plant Estrogens for Menopause

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Abstract

Objectives—Every year, millions of women begin the peri-menopause and may experience a number of symptoms related to this transition. Many women are reluctant to use exogenous hormone therapy for treatment of menopausal symptoms and are turning to botanical and dietary supplements (BDS) for relief. This paper reviews the literature on alternatives to plant estrogens for relief of menopausal symptoms.

Methods—The MEDLINE database was searched for clinical trials of non-estrogenic plant extracts for menopausal symptoms. To be included, studies had to include peri- or postmenopausal women as subjects. All clinical trials (randomized-controlled trials, open trials, and comparison group studies) were included for this review.

Results—Black Cohosh appears to be one of the most effective botanicals for relief of vasomotor symptoms, while St. John's wort can improve mood disorders related to the menopausal transition. Many other botanicals have limited evidence to demonstrate safety and efficacy for relief of symptoms related to menopause.

Conclusions—A growing body of evidence suggests that some botanicals and dietary supplements could result in improved clinical outcomes. Health care providers should discuss these issues with their patients so they can assist them in managing these alternative therapies through an evidence-based approach.

Keywords

Menopause; botanical supplements; dietary supplements

Introduction

Every year, millions of women begin the menopausal transition. By the year 2030, the World Health Organization estimates 1.2 billion women will be age 50 or over, which nearly triples the number of women in that age bracket in 1990.[1] Women experience menopause differently across the world, in terms of their symptomology. [2–6] Women in the United States (US), the United Kingdom (UK), and the United Arab Emirates report hot flashes as their most bothersome symptom of menopause, while women from Japan, India and Singapore report joint pain as their most common complaint. [2–4] In South America, women rated loss of libido

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as a major concern.[6] Even within a given country, such as the US, there are variations across racial/ethnic groups. For example, the most common menopause symptoms are vasomotor complaints among African Americans, psychosomatic problems among Caucasians, vaginal and urinary complaints among Hispanics, and forgetfulness among Japanese and Chinese women.[7]

Given the results of the Women's Health Initiative, many women are reluctant to use exogenous hormone therapy for treatment of menopausal symptoms and are turning to botanical and dietary supplements (BDS) for relief. [8,9] In most countries of the world, botanicals are not well regulated by federal agencies such as the US Food and Drug Administration (FDA). This fact results in considerable variability of content, standardization, dosage, and purity of available products. The European Food Safety Authority has only recently begun to address the issue of botanical safety and purity regulation for its member states.[10] By contrast, dietary supplements have been scrutinized for safety and efficacy by the Commission E in Germany for two decades.[11]

Women throughout the world have been using plant extracts for hundreds of years to treat uterine disorders, menstrual complaints, pregnancy and childbirth, all apparently without toxic effects, although rigorous long term safety trials are rare.[12,13] In the US and Britain, surveys show that 80% of peri and post menopausal women are current or former users of dietary supplements, and 60–70% of users cited the belief that these supplements are good for one's health. Most women report using such treatments largely because they find these alternatives to traditional medicine more congruent with their values, beliefs, and lifestyles, and they believe that use of these herbal products is natural and safe and cannot hurt them.[14–17]

While use of BDS may be widespread among menopausal women, almost three-quarters of users do not tell their providers about use of these products.[14,15] This lack of communication between clinicians and their patients creates problems since BDS products can interact with traditional medications. Even if conventional practitioners were aware of their patients' use of BDS, most have received little if any training related to BDS and they seldom ask their patients about use of alternative therapies.[18–21] However, many providers are open to learning more about these modalities and are interested in additional training, predominantly because of growing patient awareness and use.[22]

This paper reviews the scientific literature on botanicals and dietary supplements related to efficacy and safety, focusing primarily on alternatives to plant estrogens, for menopause.

Methodology

A multi-step strategy was used to find relevant articles for this paper. First, the MEDLINE database was searched (from 1966 to August, 2005) using terms related to botanical and dietary supplements and menopausal symptoms. The following terms were used in the search strategy: dietary supplements, plant extracts, black cohosh, medicinal plants, hot flashes, menopause, middle aged, and women. After a list of potential articles was created, all of these articles were reviewed. Next, the bibliographies of all clinical trials (randomized and open trials), other research studies, and review articles were searched for relevant studies. Finally, abstracts from the North American Menopause Society were searched by hand.

Studies were eligible for inclusion if study subjects were peri- or postmenopausal women and were related to menopausal or postmenopausal symptoms such as vasomotor complaints and somatic and psychological issues including mood, sleep, anxiety, depression and memory problems. Randomized, placebo-controlled trials were used when available, although open trials and comparison group studies were also used to gain as much information as possible. More detail on study design for each trial is outlined in the tables.

Results

Black Cohosh *(Cimicifuga racemosa)*

Black cohosh is a perennial plant native to North America and a member of the buttercup family.[23] Black cohosh contains triterpine glycosides, flavonoids, aromatic acids, and other constituents; however, the exact mechanism of action has been unclear.[24] Black cohosh was presumed to have estrogenic activity, however, recent studies show no effect on serum hormone levels (e.g., luteinizing hormone (LH), follicle stimulating hormone (FSH), prolactin, sex hormone binding globulin (SHBG), and estradiol).[25] Several animal studies using black cohosh extracts have found no estrogenic increases in uterine weight or stimulation of vaginal and breast tissue.[26–28] However, one study found evidence of estrogenic activity in the urogenital tract of mice. [29] Recent data, in fact, has demonstrated that black cohosh acts on serotonin receptors which may be the mechanism for relief of hot flashes and improvement in mood.[30, 31]

Much of the research on black cohosh has been conducted in Germany since the 1940's. The German health authorities (Commission E) have approved the use of 40 mg/day of black cohosh for 6 months for relief of menopausal symptoms.[32] There have been several clinical trials conducted related to vasomotor symptoms and most have shown positive results for reduction of hot flashes, although the methodology in some of these studies was weak and many were sponsored by the manufacturers.[33–36] Table 1 [32,37–49] summarizes clinical trials that have been performed on black cohosh. Overall, these studies show very promising results for relief of menopausal symptoms, primarily hot flashes and mood swings. However, a recent RCT, "The herbal alternatives for menopause study (HALT)," conducted in the US and as yet unpublished, reported at the North American Menopause Society that use of 160 mg of black cohosh daily showed no improvement over placebo for relief of hot flashes. (personal communication)

Black cohosh has been reported to have a positive safety profile when used for up to 6 months; however, in Germany, many women use this herbal remedy for longer periods of time with physician oversight. The most commonly reported side effects are mild gastric complaints, which tend to dissipate over time although high doses may cause headaches, vomiting, and dizziness. Black cohosh is also contraindicated in pregnancy and lactating women largely due to lack of safety data for the fetus and newborn.[32]

There have been no documented cases of drug interactions.[50] Of recent concern are a few case reports of liver failure in women using black cohosh.[51–53] It is not clear what the contribution of black cohosh was, if any, in these cases. Many questions remain about the composition and purity of the products used and the multiple co-morbidities as well as the concomitant medications of the women using black cohosh. The US National Institute of Health (NIH) has recently released their findings from a workshop on the safety of black cohosh in clinical trials. They concluded that "at this time there is no known mechanism with biological plausibility that explains any hepatotoxic activity of black cohosh." They also note that millions of women have taken black cohosh with very few adverse events reported, although they do suggest the monitoring of liver functions during the study of black cohosh. [54] Based on the evidence available it cannot be concluded that black cohosh is a cause of liver toxicity.[25, 55,56]

A presentation at the American Association for Cancer Research meeting raised some concern about the increased metastases, but not incidence, of breast cancer in mice using black cohosh. [57] However, no peer reviewed paper has been published or plausible mechanism of action presented and the investigators themselves have noted that the histology component of the research is not complete. In fact, previous studies on both in vitro investigations with breast

cancer cells and in vivo data show no stimulation of estrogen-dependent mammary gland tumors with black cohosh.[25,27,34–36]

In fact, black cohosh has been suggested for relief of vasomotor symptoms for women with breast cancer who are on tamoxifen, largely because of its presumed serotonergic rather than estrogenic effect. Two recent studies of black cohosh for women on tamoxifen have shown a significant reduction in number and severity of hot flashes as compared to placebo as well as improvement in sleep, fatigue levels and abnormal sweating.[47,48] One short term two-month clinical trial found no difference in climacteric symptoms between the treatment and placebo groups but the black cohosh group had a significant decrease in sweating.[49]

There has been almost no research on black cohosh to study health conditions associated with aging such as heart disease, osteoporosis and fracture, although one study compared the effects of black cohosh, conjugated estrogens, and placebo on menopausal symptoms as well as bone markers. The investigators found that black cohosh had an equivalent effect to conjugated estrogens on significantly improving both menopausal symptoms and bone markers compared to placebo.[39]

In summary, black cohosh shows great promise for relief of menopausal symptoms, primarily for treatment of vasomotor symptoms and possibly mood, with an overall positive safety profile for at least six months and likely longer.

Other Commonly used botanicals

Many other botanicals are commonly used for menopause and menopause-related complaints including licorice root (*Glycyrrhiza glabra*), dong quai (*Angelica sinensis*), chastetree (*Vitex Agnus Castus*), wild yam (*Dioscorea villosa*), evening primrose (*Oenothera biennis*), Ginkgo (*Ginkgo biloba*), ginseng (*Panax ginseng*), kava (*Piper methysticum*), valerian (*Valeriana officinalis*), motherwort (*Leonurus cardiaca*), St. John's Wort (*Hypericum perforatum*). Chastetree, wild yam, and evening primrose are more commonly used for premenstrual syndrome (PMS) and early menopausal symptoms. Other botanicals such as ginkgo, motherwort, ginseng, valerian, kava, and St. John's wort are used primarily for sleep disturbances, nervousness, depression, mood swings, and memory loss. Most of these products have not been studied in the general population and not in menopausal women. As such, the findings related to sleep, anxiety, and mood cannot be extrapolated to the menopausal experience. There is also very little data available on the efficacy and safety of many of these compounds, either used alone or in combination with other herbs. Table 2 [58–69] summarizes the available data on the clinical trials that have been conducted on these botanicals for menopausal women in specific. Trials conducted on non-menopausal populations are discussed in the text.

Many of the botanicals listed above are used in combination with other extracts, in the form of a multibotanical, of which there is even less data for efficacy and safety. For example, licorice is not often used on its own, but as part of a multibotanical remedy for menopause. Since it is thought that doses of as little as 500mg/day for 7 days is associated with congestive heart failure and most menopausal remedies contain about 150–225 mg of licorice a day, it is important to be aware of the amount of licorice root menopausal patients are consuming.[70]

Dong quai *(Angelica sinensis)*

Dong quai is one of the most commonly prescribed Chinese herbs for problems unique to women. [71] Despite the fact that it is known as a "female tonic" and is used by herbalists across the world for a variety of menstrual problems (both abnormal menstruation and menopausal symptoms), little research as been done to show the safety and efficacy of dong

quai for menopausal symptoms. One study that compared dong quai to placebo for relief of hot flashes found no effect but also showed no stimulation of the endometrium for either group. [59] Another more recent study of a product containing dong quai and chamomile found a significant reductions in hot flashes.[58] There is debate as to whether there is any estrogenic activity in dong quai as human studies do not support any estrogenic mechanism of action. Taken alone, dong quai does not appear to be beneficial for menopausal symptoms; however, it is most commonly used in multibotanical formulations and is still considered to be a valuable female tonic by herbalists around the world.

Chastetree *(Vitex Agnus Castus)*

Chastetree/Vitex has been approved by German health authorities for PMS, breast tenderness, and irregularities in the menstrual cycle and is often recommended for women in early menopause experiencing irregular menstrual cycles.[72] The progesterone like effect of Vitex has been verified by endometrial biopsy, analysis of blood hormone levels, and examination of vaginal secretions.[73] The majority of research has been limited to PMS and breast tenderness and very little is known about the efficacy related to menopausal symptoms. The only study of Chastetree alone in peri-and postmenopausal women reported improvement in mood and hot flashes, although the study had no placebo or comparison group.[60] Most often, when Chastetree is used for menopause it is in combination with black cohosh and other herbs.

Wild yam *(Dioscorea villosa)*

Wild yam has historically been used for menstrual cramps and postpartum pain. The only RCT of topical wild yam cream showed no difference in alleviation of menopausal symptoms or serum/salivary hormone levels compared to placebo.[61] Despite promotional claims, wild yam does not appear to convert to progesterone when taken internally or applied topically and although popular for menopause, there is no evidence of benefit.

Evening primrose (*Oenothera biennis*)

Evening primrose contains gamolenic acid which is believed to reduce vasomotor symptoms. [74] The only RCT of evening primrose for menopausal symptoms found no differences in the reduction of hot flashes between the placebo and evening primrose groups.[62]

Ginkgo *(Ginkgo biloba)*

Ginkgo biloba has been approved by the German Commission E for cerebral insufficiency, vertigo and tinnitus, and peripheral vascular disease.[72,75–77] Ginkgo works primarily by increasing blood flow to the brain, increasing uptake of glucose by brain cells and improving transmission of nerve signals. [75] A review of 40 clinical trials by Kleinen and Knipschild examined the effect of ginkgo on improved memory and cognition. The trials were all performed about 20 years ago, and few were of good quality (8 of 40). Seven of the 8 trials did show a positive effect of ginkgo over placebo for memory complaints and cognitive tests. [75]

A systematic review published in 2002, which included studies published until June of that year, found benefits for ginkgo over placebo in cognition, mood, and emotional function. There were no differences in adverse events between placebo and control groups.[78] The authors of this review did not do analyses for peri- or postmenopausal women alone.

There have been three recent studies that examined the effects of ginkgo in perimenopausal women. These studies are outlined in detail in Table 2. Two of the trials report limited positive effects of ginkgo over placebo for memory and cognitive functions.[63,64] Gingko can inhibit

platelet activating factor and therefore should not be used by patients on aspirin or warfarin. [79]

Ginseng *(Panax ginseng)*

Ginseng is known as a traditional "tonic" herb that is reported to help one cope with stress, and boost immunity. The German Commission E lists its uses as "a tonic for invigoration and fortification in times of fatigue and debility and for declining capacity for work and concentration".[72] Only two studies have been published examining the effects of ginseng in postmenopausal women (Table 2). Both showed no estrogenic effects, no improvement in vasomotor symptoms, but improvement in somatic complaints (fatigue, insomnia, and depression) and a favorable effect on depression and well-being health subscales compared with placebo.[66,67] There is no consensus, but ginseng does not appear to have estrogenic activity by in vitro assay or in vivo biological assay although it is contraindicated in presence of breast cancer.[80]

Kava *(Piper methysticum)*

Kava is a South Pacific herb used for treatment of anxiety and has shown significant improvement in irritability and insomnia compared with placebo in menopausal women.[68] However, because of the possible hepatotoxicity of the plant, the sale of kava has been banned in Canada, Australia, and several European countries. The exact mechanism of harm is not known but it may be that the stem peelings contain a toxic alkaloid. In response to reports of hepatotoxicity, the FDA, American Botanical Council, and various industry trade organizations have advised consumers of rare but potential risks of severe liver injury associated with the use of kava.[81] It is not recommended for those taking hepatotoxic medications, consuming excess alcohol, or with liver problems. It is best to avoid this botanical completely but if kava is used, it should be limited to 6–8 weeks and extreme caution should be exercised.

Motherwort *(Leonurus cardiaca)*

Motherwort is another botanical historically revered as a calmative agent for the heart, especially palpitations.[82] The German Commission E has approved its use for nervous cardiac disorders and as an adjuvant for thyroid hyperfunction.[72] It is also found in many menopausal formula and was typically combined with black cohosh as a "superior antispasmodic and nervine," however, contemporary research is lacking on efficacy and safety.

Valerian *(Valeriana officinalis)*

Valerian has been used for centuries by Greeks, Romans, Chinese, Europeans, and American Indians. In the 20th century, it has been approved by the German Commission E for "states of unrest and nervous sleep disturbances." [72] Three RCTs have been conducted that have shown improved subjective sleep quality, although none of the studies were conducted with menopausal women.[83–85] There have been no reported drug interactions; side effects, such as nausea, headache, dizziness, and upset stomach, have been reported in less than ten percent of subjects in RCTs.[86]

St. John's Wort *(Hypericum perforatum)*

St. John's wort is one of the most heavily studied botanicals for treatment of depression. The vast majority of studies have been conducted on non-menopausal populations. In thirty-seven out of thirty-nine clinical trials the herb has been shown to be superior to placebo or equivalent to antidepressant medications (61–75% improvement in mild-moderate depression) with minimal side effects as compared to some of the antidepressants.[87] Clinical trials of patients with mild to moderate depression have shown beneficial effects similar to standard antidepressants, although a recent meta-analysis of St. John's wort for depression found that

trials restricted to subjects with major depression found only minor improvements compared to placebo.[88] One non-placebo controlled clinical trial conducted in women experiencing climacteric symptoms found that 900 mg of St. Johns wort taken for 12 weeks, significantly improved psychological and psychosomatic symptoms and sexual well-being.[69]

St. John's wort is often combined with black cohosh for treatment of menopausal symptoms (hot flashes, irritability, minor depression, mood swings, and insomnia). A multi-center drug monitoring study of 911 pre, peri and postmenopausal women with psychological disorders demonstrated a synergistic effect of this combination of botanicals.[89]

The adverse herb-drug interactions are well documented. St. John's wort can interact with anticoagulants, cyclosporine, digoxin, and protease inhibitors used for HIV, specifically decreasing blood concentrations of these drugs. In addition, women using oral contraceptives have reported breakthrough bleeding and in some cases, unplanned pregnancies.[90]

Future Directions

Black cohosh appears to be the most effective herb for relief of menopausal symptoms, primarily hot flashes and possibly mood disorders. St. John's wort has been shown to improve mood disorders related to the menopausal transition and mild to moderate depressive symptoms. More research should be done in the menopausal population, especially for the combination of St. John's wort and black cohosh. The other botanicals discussed in this paper have limited evidence to demonstrate safety and efficacy for relief of symptoms related to menopause. These herbs should be studied separately and in combination with other botanicals they are commonly used with.

Although a growing body of evidence suggests that alternative therapy could result in improved clinical outcomes, more research on efficacy and safety is needed. In addition, health care providers should discuss these issues with their patients so they can assist them in managing these alternative therapies through an evidence-based approach that will promote good health.

References

1. World Menopause Day. [website] Lancaster, England: International Menopause Society. [accessed 2005 Dec 2] Available from: http://www.imsociety.org/pages/wmday.html
2. Dennerstein L, Lehert P. Women's sexual functioning, lifestyle, mid-age, and menopause in 12 European countries. Menopause 2004;11:778–85. [PubMed: 15543029]
3. Singh A, Kaur S, Walia I. A historical perspective on menopause and menopausal age. Bull Indian Inst Hist Med Hyderabad 2002;32:121–35. [PubMed: 15981376]
4. Rizk DE, Bener A, Ezimokhai M, Hassan MY, Micallef R. The age and symptomatology of natural menopause among United Arab Emirates women. Maturitas 1998;29:197–202. [PubMed: 9699190]
5. Chim H, Tan BH, Ang CC, Chew EM, Chong YS, Saw SM. The prevalence of menopausal symptoms in a community in Singapore. Maturitas 2002;41:275–82. [PubMed: 12034514]
6. Castelo-Branco C, Palacios S, Mostajo D, Tobar C, von Helde S. Menopausal transition in Movima women, a Bolivian Native-American. Maturitas 2005;51:380–5. [PubMed: 16039411]
7. Avis NE, Stellato R, Crawford S, et al. Is there a menopausal syndrome? Menopausal status and symptoms across racial/ethnic groups Soc Sci Med 2001;52:345–56.
8. Kolata, G. The New York Times. New York: 2002. "Race to fill the void in menopause drug market,"; p. p. 1
9. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. JAMA 2002;288:321–33. [PubMed: 12117397]
10. Botanicals and Botanical Preparations widely used as food supplements and related products: coherent and comprehensive risk assessment and consumer information approaches. [website] Brussels:

European Food Safety Authority; c 2004 [updated 2004 Sep 21; accessed 2005 Nov 14] Available from: http://www.efsa.eu.int/science/sc_commitee/sc_documents/616_en.html

11. Larsen LL, Berry JA. The regulation of dietary supplements. J Am Acad Nurse Pract 2003;15:410–4. [PubMed: 14560437]
12. Roemheld-Hamm B. Chasteberry. Am Fam Physician 2005;72:821–4. [PubMed: 16156340]
13. McKenna DJ, Jones K, Humphrey S, Hughes K. Black cohosh: efficacy, safety, and use in clinical and preclinical applications. Altern Ther Health Med 2001;7:93–100. [PubMed: 11347288]
14. Albertazzi P, Steel SA, Clifford E, Bottazzi M. Attitudes towards and use of dietary supplementation in a sample of postmenopausal women. Climacteric 2002;5:374–82. [PubMed: 12626217]
15. Mahady GB, Parrot J, Lee C, Yun GS, Dan A. Botanical dietary supplement use in peri- and postmenopausal women. Menopause 2003;10:65–72. [PubMed: 12544679]
16. Kass-Annese B. Alternative therapies for menopause. Clin Obstet Gynecol 2000;43:162–83. [PubMed: 10694998]
17. Goldstein MS, Glik D. Use of and satisfaction with homeopathy in a patient population. Altern Ther Health Med 1998;4:60–5. [PubMed: 9682513]
18. Schimpff SC. Complementary medicine. Curr Opin Oncol 1997;9:327–31. [PubMed: 9251882]
19. Lee MM, Lin SS, Wrensch MR, Adler SR, Eisenberg D. Alternative therapies used by women with breast cancer in four ethnic populations. J Natl Cancer Inst 2000;92:42–7. [PubMed: 10620632]
20. Seidl MM, Stewart DE. Alternative treatments for menopausal symptoms. Qualitative study of women's experiences. Can Fam Physician 1998;44:1271–6. [PubMed: 9640521]
21. The Landmark Report on Public Perceptions of Alternative Care. Landmark Healthcare. Landmark Healthcare; Sacramento, CA: 1997.
22. Geller SE, Studee L, Chandra G. Knowledge, Attitudes and Behaviors of Health Care Providers for Botanical and Dietary Supplement Use for Menopausal Health. Menopause 2005;12:49–55. [PubMed: 15668600]
23. Kligler B. Black cohosh. Am Fam Physician 2003;68:114–6. [PubMed: 12887117]
24. Cohosh Rhizome, Black. American Herbal Pharmacopoeia. Upton, R., editor. Santa Cruz, CA: 2002.
25. Dog TL, Powell KL, Weisman SM. Critical evaluation of the safety of Cimicifuga racemosa in menopause symptom relief. Menopause 2003;10:299–313. [PubMed: 12851513]
26. Einer-Jensen N, Zhao J, Andersen KP, Kristoffersen K. Cimicifuga and Melbrosia lack oestrogenic effects in mice and rats. Maturitas 1996;25:149–53. [PubMed: 8905606]
27. Freudenstein J, Dasenbrock C, Nisslein T. Lack of promotion of estrogen-dependent mammary gland tumors in vivo by an isopropanolic Cimicifuga racemosa extract. Cancer Res 2002;62:3448–52. [PubMed: 12067987]
28. Seidlova-Wuttke D, Jarry H, Becker T, Christoffel V, Wuttke W. Pharmacology of Cimicifuga racemosa extract BNO 1055 in rats: bone, fat and uterus. Maturitas 2003;44 (Suppl 1):S39–50. [PubMed: 12609558]
29. Liu ZP, Yu B, Huo JS, Lu CQ, Chen JS. Estrogenic effects of Cimicifuga racemosa (black cohosh) in mice and on estrogen receptors in MCF-7 cells. J Med Food 2001;4:171–178. [PubMed: 12639411]
30. Burdette JE, Liu J, Chen SN, et al. Black cohosh acts as a mixed competitive ligand and partial agonist of the serotonin receptor. J Agric Food Chem 2003;51:5661–70. [PubMed: 12952416]
31. Mahady GB. Is black cohosh estrogenic? Nutr Rev 2003;61:183–6. [PubMed: 12822708]
32. Cohosh, Black. The ABC Clinical Guide to Herbs. Blumenthal, M., editor. American Botanical Council; Austin, TX: 2002. p. 13-22.
33. Zava DT, Dollbaum CM, Blen M. Estrogen and progestin bioactivity of foods, herbs, and spices. Proc Soc Exp Biol Med 1998;217:369–78. [PubMed: 9492350]
34. Liu J, Burdette JE, Xu H, et al. Evaluation of estrogenic activity of plant extracts for the potential treatment of menopausal symptoms. J Agric Food Chem 2001;49:2472–9. [PubMed: 11368622]
35. Zierau O, Bodinet C, Kolba S, Wulf M, Vollmer G. Antiestrogenic activities of Cimicifuga racemosa extracts. J Steroid Biochem Mol Biol 2002;80:125–30. [PubMed: 11867271]
36. Bodinet C, Freudenstein J. Influence of Cimicifuga racemosa on the proliferation of estrogen receptor-positive human breast cancer cells. Breast Cancer Res Treat 2002;76:1–10. [PubMed: 12408370]

37. Osmers R, Friede M, Liske E, Schnitker J, Freudenstein J, Henneicke-von Zepelin HH. Efficacy and safety of isopropanolic black cohosh extract for climacteric symptoms. Obstet Gynecol 2005;105:1074–83. [PubMed: 15863547]
38. Frei-Kleiner S, Schaffner W, Rahlfs VW, Bodmer C, Birkhauser M. Cimicifuga racemosa dried ethanolic extract in menopausal disorders: a double-blind placebo-controlled clinical trial. Maturitas 2005;51:397–404. [PubMed: 16039414]
39. Wuttke W, Seidlova-Wuttke D, Gorkow C. The Cimicifuga preparation BNO 1055 vs. conjugated estrogens in a double-blind placebo-controlled study: effects on menopause symptoms and bone markers. Maturitas 2003;44 (Suppl 1):S67–77. [PubMed: 12609561]
40. Wuttke W, Raus K, Gorkow C. Efficacy and tolerability of the Black cohosh (Actea racemosa) ethanolic extract BNO 1055 on climacteric complaints: a double-blind, placebo- and conjugated estrogens-controlled study. Maturitas. this volume.
41. Duker EM, Kopanski L, Jarry H, Wuttke W. Effects of extracts from Cimicifuga racemosa on gonadotropin release in menopausal women and ovariectomized rats. Planta Med 1991;57:420–4. [PubMed: 1798794]
42. Nappi RE, Malavasi B, Brundu B, Facchinetti F. Efficacy of Cimicifuga racemosa on climacteric complaints: a randomized study versus low-dose transdermal estradiol. Gynecol Endocrinol 2005;20:30–5. [PubMed: 15969244]
43. Liske E, Hanggi W, Henneicke-von Zepelin HH, Boblitz N, Wustenberg P, Rahlfs VW. Physiological investigation of a unique extract of black cohosh (Cimicifugae racemosae rhizoma): a 6-month clinical study demonstrates no systemic estrogenic effect. J Womens Health Gend Based Med 2002;11:163–74. [PubMed: 11975864]
44. Lehmann-Willenbrock E, Riedel HH. Clinical and endocrinologic studies of the treatment of ovarian insufficiency manifestations following hysterectomy with intact adnexa [German]. Zentralbl Gynakol 1988;110:611–8. [PubMed: 2841818]
45. Raus K, Brucker C, Gorkow C, Wuttke W. First time proof of endometrial safety of the special Black cohosh extract (Actea racemosa or Cimicifuga racemosa extract) CR BNO 1055. Menopause. in press
46. Vermes G, Banhidy F, Acs N. The effects of remifemin on subjective symptoms of menopause. Adv Ther 2005;22:148–54. [PubMed: 16020404]
47. Pockaj BA, Loprinzi CL, Sloan JA, et al. Pilot evaluation of black cohosh for the treatment of hot flashes in women. Cancer Invest 2004;22:515–21. [PubMed: 15565808]
48. Hernandez Munoz G, Pluchino S. Cimicifuga racemosa for the treatment of hot flushes in women surviving breast cancer. Maturitas 2003;44 (Suppl 1):S59–65. [PubMed: 12609560]
49. Jacobson JS, Troxel AB, Evans J, et al. Randomized trial of black cohosh for the treatment of hot flashes among women with a history of breast cancer. J Clin Oncol 2001;19:2739–45. [PubMed: 11352967]
50. Pepping J. Black cohosh: Cimicifuga racemosa. Am J Health Syst Pharm 1999;56:1400–2. [PubMed: 10428447]
51. Lontos S, Jones RM, Angus PW, Gow PJ. Acute liver failure associated with the use of herbal preparations containing black cohosh. Med J Aust 2003;179:390–1. [PubMed: 14503910]
52. Whiting PW, Clouston A, Kerlin P. Black cohosh and other herbal remedies associated with acute hepatitis. Med J Aust 2002;177:440–3. [PubMed: 12381254]
53. Cohen SM, O'Connor AM, Hart J, Merel NH, Te HS. Autoimmune hepatitis associated with the use of black cohosh: a case study. Menopause 2004;11:575–77. [PubMed: 15356412]
54. NIH. “Workshop on the Safety of Black Cohosh in Clinical Studies”. National Center for Complementary and Alternative Medicine; NIH Office of Dietary Supplements; Washington, DC.: 2004.
55. Thomsen M, Schmidt M. Hepatotoxicity from Cimicifuga racemosa? Recent Australian case report not sufficiently substantiated. J Altern Complement Med 2003;9:337–40. [PubMed: 12816621]
56. Thomsen M, Vitetta L, Sali A, Schmidt M. Acute liver failure associated with the use of herbal preparations containing black cohosh. Med J Aust 2004;180:598–9. 99–600. [PubMed: 15175000]
57. Davis VL, Jayo MJ, Hardy ML, et al. Effects of black cohosh on mammary tumor development and progression in MMTV-neu transgenic mice. American Association of Cancer Research Proceedings 2003;44:R910.

58. Kupfersztain C, Rotem C, Fagot R, Kaplan B. The immediate effect of natural plant extract, Angelica sinensis and Matricaria chamomilla (Climex) for the treatment of hot flushes during menopause. A preliminary report Clin Exp Obstet Gynecol 2003;30:203–6.
59. Hirata JD, Swiersz LM, Zell B, Small R, Ettinger B. Does dong quai have estrogenic effects in postmenopausal women? A double-blind, placebo-controlled trial. Fertil Steril 1997;68:981–6. [PubMed: 9418683]
60. Lucks BC, Sorensen J, Veal L. Vitex agnus-castus essential oil and menopausal balance: a self-care survey. Complement Ther Nurs Midwifery 2002;8:148–54. [PubMed: 12353616]
61. Komesaroff PA, Black CV, Cable V, Sudhir K. Effects of wild yam extract on menopausal symptoms, lipids and sex hormones in healthy menopausal women. Climacteric 2001;4:144–50. [PubMed: 11428178]
62. Chenoy R, Hussain S, Tayob Y, O'Brien PM, Moss MY, Morse PF. Effect of oral gamolenic acid from evening primrose oil on menopausal flushing. BMJ 1994;308:501–3. [PubMed: 8136666]
63. Elsabagh S, Hartley DE, File SE. Limited cognitive benefits in Stage +2 postmenopausal women after 6 weeks of treatment with Ginkgo biloba. J Psychopharmacol 2005;19:173–81. [PubMed: 15728439]
64. Hartley DE, Heinze L, Elsabagh S, File SE. Effects on cognition and mood in postmenopausal women of 1-week treatment with Ginkgo biloba. Pharmacol Biochem Behav 2003;75:711–20. [PubMed: 12895689]
65. Hartley DE, Elsabagh S, File SE. Gincosan (a combination of Ginkgo biloba and Panax ginseng): the effects on mood and cognition of 6 and 12 weeks' treatment in post-menopausal women. Nutr Neurosci 2004;7:325–33. [PubMed: 15682929]
66. Tode T, Kikuchi Y, Hirata J, Kita T, Nakata H, Nagata I. Effect of Korean red ginseng on psychological functions in patients with severe climacteric syndromes. Int J Gynaecol Obstet 1999;67:169–74. [PubMed: 10659900]
67. Wiklund IK, Mattsson LA, Lindgren R, Limoni C. Effects of a standardized ginseng extract on quality of life and physiological parameters in symptomatic postmenopausal women: a double-blind, placebo-controlled trial. Swedish Alternative Medicine Group Int J Clin Pharmacol Res 1999;19:89–99.
68. Warnecke G. [Psychosomatic dysfunctions in the female climacteric. Clinical effectiveness and tolerance of Kava Extract WS 1490]. Fortschr Med 1991;109:119–22. [PubMed: 2029982]
69. Grube B, Walper A, Wheatley D. St. John's Wort extract: efficacy for menopausal symptoms of psychological origin. Adv Ther 1999;16:177–86. [PubMed: 10623319]
70. de Klerk GJ, Nieuwenhuis MG, Beutler JJ. Hypokalaemia and hypertension associated with use of liquorice flavoured chewing gum. BMJ 1997;314:731–2. [PubMed: 9116553]
71. Radix Angelicae Sinensis. WHO monographs on selected medicinal plants. WHO: Geneva, Switzerland; 2001.
72. Blumenthal, M. Herbal Medicine: Expanded Commision E Monographs. Newton, MA: Integrative Medicine Communications; 2003.
73. Brown, D. Quarterly Review of Natural Medicine. 1997. 1997 Spring. The use of Vitex agnus castus for hyperprolactinemia; p. 19-21.
74. McMillan TL, Mark S. Complementary and alternative medicine and physical activity for menopausal symptoms. JAMWA 2004;59:270–77. [PubMed: 16845756]
75. Kleijnen J, Knipschild P. Ginkgo biloba. Lancet 1992;340:1136–9. [PubMed: 1359218]
76. Rudofsky G. Effect of Ginkgo biloba extract in arterial occlusive disease. Randomized placebo controlled crossover study [German]. Fortschr Med 1987;105:397–400. [PubMed: 3301603]
77. Bauer U. 6-Month double-blind randomised clinical trial of Ginkgo biloba extract versus placebo in two parallel groups in patients suffering from peripheral arterial insufficiency. Arzneimittelforschung 1984;34:716–20. [PubMed: 6386008]
78. Birks J, Grimley EV, Van Dongen M. Ginkgo biloba for cognitive impairment and dementia. Cochrane Database Syst Rev 2002:CD003120. [PubMed: 12519586]
79. Fugh-Berman A. Herb-drug interactions. Lancet 2000;355:134–8. [PubMed: 10675182]
80. Amato P, Christophe S, Mellon PL. Estrogenic activity of herbs commonly used as remedies for menopausal symptoms. Menopause 2002;9:145–50. [PubMed: 11875334]

81. Blumenthal, M., editor. The ABC Clinical Guide to Herbs. Austin; TX: 2003.
82. Motherwort [website]. Science Views.com; c2003–04 [accessed 2005 Dec 01]. Available from: http://scienceviews.com/plants/motherwort.html
83. Balderer G, Borbely AA. Effect of valerian on human sleep. Psychopharmacology (Berl) 1985;87:406–9. [PubMed: 3936097]
84. Leathwood PD, Chauffard F. Aqueous extract of valerian reduces latency to fall asleep in man. Planta Med 1985:144–8.
85. Leathwood PD, Chauffard F, Heck E, Munoz-Box R. Aqueous extract of valerian root (Valeriana officinalis L.) improves sleep quality in man. Pharmacol Biochem Behav 1982;17:65–71. [PubMed: 7122669]
86. Valeriana officinalis. Alternative Medicine Review 2004;9:438–40. [PubMed: 15656716]
87. Linde K, Ramirez G, Mulrow CD, Pauls A, Weidenhammer W, Melchart D. St John's wort for depression--an overview and meta-analysis of randomised clinical trials. BMJ 1996;313:253–8. [PubMed: 8704532]
88. Linde K, Berner M, Egger M, Mulrow C. St John's wort for depression: meta-analysis of randomised controlled trials. Br J Psychiatry 2005;186:99–107. [PubMed: 15684231]
89. Liske E. Therapeutic efficacy and safety of Cimicifuga racemosa for gynecologic disorders. Adv Ther 1998;15:45–53. [PubMed: 10178637]
90. Zhou S, Chan E, Pan SQ, Huang M, Lee EJ. Pharmacokinetic interactions of drugs with St John's wort. J Psychopharmacol 2004;18:262–76. [PubMed: 15260917]

Table 1

Studies of Black Cohosh (*Cimifuga racemosa*)

Randomized, Placebo-controlled trials				
Reference	**Description of groups, drug name, and dosage**	**# of Participants**	**Duration**	**Results**
Osmers et al, 2005 [37]	Black cohosh: 40 mg Placebo	304 postmenopausal women	12 weeks	BC more effective than placebo in reducing score on the Menopause Rating Scale I
Frei-Kleiner et al, 2005 [38]	Black cohosh: 42 mg Placebo	122 menopausal women	12 weeks	In all women, no difference between BC and placebo. In women with KI ≥ 20, significant decrease of KI in BC compared to placebo
Wuttke et al, 2003 [39]	Black cohosh: 2 x 20 mg Conjugated estrogen (CE): 0.6 mg Placebo	62 postmenopausal women	3 months	Significant reduction in symptoms with BC compared to placebo, equivalent effect of CE.
Wuttke et al., 2006 [40]	Black cohosh: 2 x 20 mg Conjugated estrogen (CE): 0.6 mg Placebo	62 postemenopausal women (same patients as Wuttke et al., 2003)	3 months	Significant reduction of climacteric complaints as determined by a variety of instruments
Duker et al, 1991 [41]	Black cohosh: dosage not reported Placebo	110 women with menopausal complaints	8 weeks	Significant reduction in LH levels compared to placebo, no significant change in FSH was observed
Stoll, 1987 [32]	Black cohosh:: 80 mg E2: 0.625 mg Placebo	80 peri and postmenopausal women	12 weeks	Improved symptoms, decreased frequency of hot flashes, increased proliferation of vaginal epithelium with E2.
Geller, ongoing*	Black cohosh: 128 mg/day Red clover (RC): 120 mg/day HRT: Prempro ® Placebo	88 menopausal women planned, 41 randomized	1 year	No data yet, ongoing clinical trial.
Kronenberg, ongoing*	Black cohosh: 80 mg/day Placebo	unknown	l year	No data yet, ongoing clinical trial.
Newton et al, personal communication*	Black cohosh: 160 mg/day Multibotanical Multibotanical plus increased soy CEE 0.625 mg+2.5 mg MPA Placebo	351 peri and postmenopausal women	1 year	BC daily showed no improvement over placebo for relief of hot flashes
Randomized comparison group trials				
Reference	Description of groups, drug name, and dosage	# of Participants	Duration	Results
Nappi, 2005 [42]	Black cohosh: 40 mg/day Low-dose transdermal estradiol: 25 micrograms every 7 days	64 postmenopausal women	3 months	Both BC and estradiol significantly reduced the number of hot flashes per day and vasomotor symptoms.
Liske et al, 2002 [43]	Standard (S): 39 mg High (H): 127.9 mg dose of Black cohosh:	152 peri and postmenopausal women	24 weeks	Found decrease of KI for both groups, no difference between standard and high dose.
Lehmann-Willenbrock & Riedel, 1988 [44]	Estriol (E): 1 mg/day Conjugated estrogen (CE): 1.25 mg/day Estrogen-gestagen (EG): 1 tablet/day Trisequens Black cohosh: (R): 48–140 mg/day	60 women with hysterectomies and climacteric symptoms	6 months	BC produced a decline in KI no significant differences were observed among treatment groups.
Open trials				
Raus et al., in press [45]	Black cohosh 2 x 20 mg	375 postmenopausal women	12 months	Hot flushes decreased by more than 70%. No effects in endometrium, mammary gland, blood clotting factors or liver enzymes
Vermes, 2005 [46]	Black cohosh: dose not given	2016 Hungarian women	12 weeks	Average decrease in KI after 12 weeks was 17.64 points. Hot flash score decreased by 6.31 points

Randomized, Placebo-controlled trials				
Reference	**Description of groups, drug name, and dosage**	**# of Participants**	**Duration**	**Results**
Petho, 1987 [32]	Black cohosh: 48–140 mg/day	70 women changing from hormone injections to black cohosh.	6 months	After 2 months, significant improvement in mean menopausal index, 82% reported black cohosh preparation good or very good for relief of menopausal complaints
Warnecke, 1985 [32]	Black cohosh: 48–140 mg/day Conjugated estrogens: 0.6 mg/day Diazepam (D): 2 mg/day	60 women with menopausal complaints	12 weeks	BC and CE showed vaginal cytology changes, improvements in hot flashes and psychological symptoms in all three groups.
Vasomotor symptoms in breast cancer survivors				
Reference	Description of groups, drug name, and dosage	# of Participants	Duration	Results
Pockaj et al, 2004 [47]	Remifemin: dosage not reported (Open trial)	21 postmenopausal women, 13 w/ history of breast cancer	4 weeks	Significant reduction from baseline in hot flashes and improvement in sleeping, fatigue levels, and abnormal sweating.
Hernandez Munoz & Pluchino, 2003 [48]	Tamoxifen only: 20 mg/day Tamoxifen (20 mg) + black cohosh: 40 mg/day (Randomized open label trial)	136 breast cancer survivors, perimenopausal	6 months	Group taking combination therapy experienced significantly less severe hot flashes vs. group on tamoxifen only (24% vs. 74%)
Jacobson et al, 2001 [49]	Black cohosh: 40 mg/day Placebo stratified on tamoxifen use (RCT)	85 breast cancer survivors experiencing daily hot flashes	2 months	Black cohosh and placebo both reduced number and intensity of hot flashes during the study. There was no significant difference between BC and P.

* Geller study is at the University of Illinois at Chicago, Kronenberg study is at Columbia University, Newton study is at the University of Washington.

RCT=Randomized-controlled trial (double-blind, placebo controlled), BC=Black cohosh, KI=Kupperman Menopause index

Prempro=0.625 mg conjugated equine estrogen + 2.5 mg medroxyprogesterone acetate

Legend: RCT=randomized-controlled trial (double-blind, placebo controlled); CO=Double-blind, placebo-controlled, cross-over study

Table 2

Studies of Other Botanicals

Reference	Description of groups, drug name, and dosage	Study Design	# of Participants	Duration	Results
Kupfersztain et al, 2003 [58]	**Climex**: dong quai and chamomile **Placebo**	RCT	55 postmenopausal women	12 weeks	Climex group significantly decreased hot flashes compared to placebo. Alleviation of sleep disturbances.
Hirata et al, 1997 [59]	**Dong quai root**: 4.5 g. daily **Placebo**	RCT	71 postmenopausal women	24 weeks	Hot flash incidence decreased in dong quai group, compared to placebo, effect not significant.
Lucks, 2003 [60]	**Vitex agnus castus oil**: 2.5 ml transdermally	Open survey	52 peri- and postmenopausal women	3 months	33% reported major improvement in troublesome symptoms, most often emotional problems and hot flashes.
Komesaroff et al, 2001 [61]	**Wild yam cream** **Placebo**	CO	23 postmenopausal women	3 months	No changes in FSH, estradiol, progesterone, or hot flashes.
Chenoy et al, 1994 [62]	**Evening primrose oil**: 500 mg daily **Liquid paraffin**	RCT	56 women with 3 or more hot flashes a day	6 months	No differences in hot flash frequency between the two groups.
Elsabaugh et al, 2005 [63]	**Ginkgo Biloba:** 120 mg **Placebo**	RCT	87 postmenopausal women	6 weeks	Subjects divided into early (mean age 55) and late (mean age 61) stage of menopause. Only subjects in late stage menopause showed improvement in cognitive function after treatment with gingko.
Hartley et al, 2003 [64]	**Ginkgo Biloba:** 120 mg **Placebo**	RCT	31 postmenopausal women	1 week	Group treated with gingko did significantly better in a memory task after one week compared to placebo.
Hartley et al, 2004 [65]	**Gincosan**: Ginkgo biloba (120 mg) and ginseng (200 mg) **Placebo**	RCT	60 postmenopausal women	12 weeks	No significant effects of Gincosan on mood, anxiety, menopausal symptoms, sleepiness, or cognition.
Tode et al, 1999 [66]	**Korean red ginseng**: 6 g daily	Open trial	12 women with climacteric symptoms	30 days	Red ginseng improved fatigue, insomnia and depression. Cortisol/ DHEA-S ratio was significantly decreased.
Wiklund et al, 1999 [67]	**Ginseng**: 100 mg daily **Placebo**	Multicenter RCT	284 postmenopausal women	14 weeks	No benefit of ginseng over placebo in reduction of hot flashes.
Warnecke 1991 [68]	**Kava extract**: 100 mg, 3 X daily **Placebo**	RCT	40 women with climacteric symptoms	8 weeks	Significant improvement in Kupperman index and HAMA anxiety score.
Grube et al, 1999 [69]	**St. John's wort**: 900 mg daily	Open trial	111 women with climacteric symptoms	12 weeks	Significant improvement in psychological and

Reference	Description of groups, drug name, and dosage	Study Design	# of Participants	Duration	Results
					psychosomatic symptoms of menopause. Improvement in sexual well-being

RCT=Randomized-controlled trial (double-blind, placebo controlled); CO=Double-blind, placebo-controlled, cross-over study