Black Cohosh: An Alternative Therapy for Menopause?

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**ABSTRACT**

Due to the long-term health risks now associated with hormone replacement therapy, many menopausal women are actively seeking alternative treatments. One such alternative is black cohosh (Actaea racemosa, syn. Cimicifuga racemosa), which has been used in the United States for the treatment of gynecologic complaints for more than 100 years. Review of the published clinical data suggests that black cohosh may be useful for the treatment of menopausal symptoms, such as hot flashes, profuse sweating, insomnia, and anxiety. Results from the most recently published trial, however, indicate that black cohosh is not effective for the treatment of menopausal symptoms in breast cancer survivors being treated with tamoxifen. Because the overall quality of the published clinical trials is low, two new randomized, double-blind, placebo-controlled clinical trials are currently underway in the United States. To date, only one standardized black cohosh extract has been tested clinically; the current recommended dose is 40–80 mg per day. At least 4–12 weeks of treatment may be required before any therapeutic benefits may be apparent. Adverse reactions such as nausea, vomiting, headaches, dizziness, mastalgia, and weight gain have been observed in clinical trials. No drug interactions are reported in the medical literature. The estrogenic effects of black cohosh are controversial, and the more recent data indicate that black cohosh extracts may have an anti-estrogenic activity. Owing to potential effects on sex hormones, however, black cohosh should not be administered to children or during pregnancy and lactation.

**KEY WORDS:** black cohosh, estrogenic, menopause, hot flashes, clinical trials

**INTRODUCTION**

Natural menopause, defined as the cessation of menstruation, is retrospectively determined following 12 months of amenorrhea during the midlife period;¹ surgical menopause, on the other hand, is defined as cessation of menses because of removal of both ovaries, with or without removal of the uterus.² During menopause, between 55–75% of women will experience vasomotor symptoms (hot flashes) or other symptoms such as depression, mood swings, sleep disorders, vaginal dryness, and joint pain.³ Approximately 25–30% of women will seek treatment from their healthcare provider for the adverse effects of menopause,⁴ and many use hormone replacement therapy (HRT) for the treatment of menopausal symptoms.⁴

Numerous studies have demonstrated the short- and long-term benefits of HRT; these include the relief of menopausal symptoms such as hot flashes and insomnia,⁵⁶ and possible reductions in the risk of cardiovascular disease, osteoporosis, and Alzheimer's disease.⁵⁷ A significant number of women never seek treatment, or will refuse/discontinue HRT owing to the perceived risks, medical contraindications, or a general reluctance to use "unnatural" exogenous hormones.⁸ The concern regarding HRT and breast cancer appears justified; a
small but significant increase in breast cancer, coronary heart disease, and stroke was observed among long-term estrogen users. Many women are now actively seeking alternative approaches—including botanical dietary supplements such as black cohosh—to manage their menopausal symptoms.

Black cohosh, known scientifically as Actaea racemosa L. (syn. Cimicifuga racemosa (L) Nutt, Ranunculaceae), is a coarse perennial woodland herb with large compound leaves and a thick, knotted rhizome (root) system. The plant is native to North America, with a distribution from southern Canada to Georgia. There are numerous common names for this plant, including black snakeroot, black root, bugbane, rattle root, rattle top, rattle squawroot, snake root, and rattleweed. Black cohosh rhizomes and roots were routinely used as medicine by Native Americans (i.e., Penobscot, Winnebago, and Dakota) for the treatment of coughs, colds, constipation, fatigue, and rheumatism, as well as to increase breast milk production. In 1832, Dr. John King, an eclectic physician, began using a tincture of black cohosh rhizome for the treatment of pain and inflammation associated with endometriosis, rheumatism, neuralgia, and dysmenorrhea. From 1840 to 1946, a fluid extract of black cohosh was listed in the U.S. National Formulary. Currently, black cohosh products are marketed in the United States as herbal remedies for the treatment of menopausal symptoms and are regulated as dietary supplements.

STANDARDIZATION AND QUALITY ISSUES

The characteristic chemical constituents of the roots and rhizomes of black cohosh include cycloartenol-type triterpenoids, such as actein, 23-epi-27-deoxyactein, and cimicifugoside, as well as cinnamic acid derivatives (i.e., ferulic acid, isoferulic acid, and piscidic and fukiic acid esters). Although the estrogenic isoflavone, formononetin (Figure 2), is reportedly a chemical constituent of black cohosh, its presence was not detected in alcoholic extracts of the root/rhizome. Formononetin is a constituent of red clover (Trifolium pratense), and to a lesser extent, soybean (Glycine max); its presence in a black cohosh extract may have been due to improper taxonomic identification of the starting plant material or to adulteration with plant parts other than the roots and rhizomes.

Today, standardized extracts and other commercial products of black cohosh are prepared from the dried rhizomes and roots of the plant. Remifemin® (SBC-R) is a commercially available black cohosh product that is a dried 40% isopropanol extract (although a 60% ethanol is also used as a solvent) of the roots and rhizomes. The extract is standardized to contain 1 mg of triterpenes (Figure 1) calculated as 27-deoxyactein (now known as 26-deoxyactein) per 20 mg of extract. This is the only commercial black cohosh extract to be tested clinically for safety and efficacy thus far.

REVIEW OF THE CLINICAL EVIDENCE

Prior to 1970, at least 14 studies were published regarding black cohosh; these detailed case reports and clinical investigations of black cohosh for various gynecologic ailments. Since 1982, at least 11 clinical trials have assessed the efficacy of a standardized formulation of black cohosh (40% isopropanol alcohol or a 60% ethanol extract of the roots and rhizomes, SBC-R, commercially known as Remifemin®) for the symptomatic treatment of climacteric symptoms such as anxiety, hot flushes, profuse sweating, insomnia, and vaginal atrophy. Of the 11 trials, six were randomized controlled or comparison trials, and the other five were uncontrolled studies. Many of the trials have methodological flaws, including lack of placebo groups, no randomization, lack of double blinding, small sample size, and usage of different doses. Stoll conducted a 12-week randomized, double-blind, placebo-controlled trial that compared the efficacy of a SBC-R extract with that of conjugated estrogens or placebo for the treatment of climacteric symptoms and vaginal atrophy. Eighty women between the ages of 45–58 were treated with 8 mg per day of the extract (which corresponds to 48–140 mg of the dried herb), 0.625 mg per day of conjugated estrogens, or a placebo. Outcomes were measured using the Kupperman Index (KI) for climacteric symptoms, the Hamilton Anxiety Rating Scale (HAMA), and the vaginal maturity index. At the end of the 12-week treatment period, all groups showed improvements. In the group treated with black cohosh, however, a significant decrease in climacteric symptoms was observed by a reduction in the KI...
from 34 to 14 \((P < 0.001)\), which indicates an improvement in vasomotor symptoms. There was also a significant decrease in the HAMA \((P < 0.001)\), which indicates a reduction in anxiety, and a significant improvement in the proliferative status of the vaginal epithelium \((P < 0.01)\), which indicates a possible estrogenic effect. Minor adverse events were reported in the group that was treated with the extract, including headache, weight gain, mastalgia, and leg heaviness. The major criticism of this study was the lack of effect of the low-dose estrogen \((0.625 \text{ mg})\), which was reported to be less effective than placebo.  

A randomized comparison trial assessed the efficacy of black cohosh for the treatment of climacteric symptoms in 60 women under the age of 40 who had undergone a hysterectomy but retained one ovary. \(^{20}\) The women were treated with estriol (1 mg/day), conjugated estrogens (1.25 mg/day), an estrogen-progesterone sequence therapy (2 mg estradiol and 1 mg norethindrone acetate), or the SBC-R extract (8 mg/day corresponding with 49–140 mg of dried herb) for six months. The results of each treatment were determined at 4, 8, 12, and 24 weeks, and outcomes were measured using a modified KI, as well as the serum concentrations of follicle stimulating hormone (FSH) and luteinizing hormone (LH). The results showed a statistically significant decrease in climacteric symptoms in all treatment groups \((P < 0.01)\), as measured by reductions in a modified KI. Conjugated estrogens or estrogen-progesterone combinations appeared to be slightly more effective than the black cohosh extract; however, the difference between the three treatment groups was not statistically significant. Serum levels of LH and FSH did not change in any of the treatment groups. \(^{20}\) The major flaw of this trial was the lack of a placebo group, and the lack of change in FSH or LH levels in those patients treated with estrogen or the estrogen/progesterone combination.

A controlled comparison trial, which involved 60 women between ages 45–60, compared the efficacy of the SBC-R extract with the efficacy of conjugated estrogens or diazepam for the treatment of climacteric symptoms. \(^{26}\) The outcomes measured included a modified KI index comprised of the following symptoms: hot flashes, nocturnal sweating, nervousness, headache, and palpitations. Assessment of the vaginal epithelium proliferation was also performed. Psychological symptoms were measured using the HAMA and self-assessment depression scale (SDS). The patients were treated with 80 drops (1 mL equivalent to 1 mg) of a 60% ethanol extract of black cohosh, 0.625 mg conjugated estrogens, or 2 mg diazepam daily for a period of 12 weeks. Unfortunately, no placebo group was included. All three forms of therapy reduced the modified KI, HAMA, and SDS. A reduction in atrophic changes in the vaginal mucosa was also observed in the groups treated with black cohosh or conjugated estrogens. \(^{26}\)

A randomized, double-blind, placebo-controlled clinical trial by Jacobson et al. assessed the efficacy

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**Figure 1.** Cycloartenol-type triterpenes extracted from the rhizome of black cohosh.
of Remifemin® in breast cancer survivors. Twenty-nine women, who were diagnosed with breast cancer and had completed their primary treatment (types not indicated), were randomly assigned to black cohosh or to a placebo, stratified on tamoxifen use. At baseline, patients completed a questionnaire about menopausal symptoms. In addition, before starting treatment, as well as at 30 and 60 days into treatment, the women kept a four-day hot flash diary. At the final visit, they completed another menopausal symptom questionnaire. FSH and LH levels were measured in a subset of patients at the first and final visits. Of the 85 patients enrolled in the study (59 on tamoxifen, 26 not on tamoxifen), 42 (29 using tamoxifen) were assigned to treatment (40 mg of black cohosh extract/day) and 43 (30 using tamoxifen) were assigned to placebo; 69 completed all three hot flash diaries. Both the treatment and the placebo groups reported declines in number and intensity of hot flashes, but the differences between the groups were not statistically significant. The treatment/no tamoxifen group (n = 9) experienced a continued decline in hot flash intensity; however, owing to the small number of women in this group, this change was not statistically significant. Changes in blood levels of FSH and LH also did not differ between the two groups. The only symptom that showed a significant (P = 0.04) difference was sweating. The major limitations of this study include the small sample size, the high dropout rate (18.8%), the short treatment period (two months), and the low dose of black cohosh (40 mg/day as opposed to 80 mg/day used in the other trials). In addition, because the mechanism of black cohosh is not understood, the confounding effects of tamoxifen, an estrogen agonist/antagonist, may have influenced the results.

A randomized, double-blind clinical trial involving 152 women with climacteric symptoms compared the effects of two different doses of Remifemin (40% isopropyl alcohol extract, corresponding to 39 mg drug vs. 127 mg drug/day) over three or six months. A decrease in the KI (beginning value 31) was observed after two weeks in both treatment groups. Both dosage levels had similar therapeutic safety and efficacy. After six months of treatment, the number of responders (KI ≤ 15) was approximately 90%. No effects on the levels of LH, FSH, sex hormone-binding globulin, prolactin, estradiol, or vaginal cytology were observed. Unfortunately, no placebo or comparison drug were used in this investigation.

Whereas the value of uncontrolled trials is very limited owing to the high placebo response, some of the investigations did provide statistical analysis of the data, and are included for the sake of completeness. In an uncontrolled clinical trial involving 50 women with climacteric complaints, oral administration of a black cohosh extract (Remifemin®, 80 mg/day) reduced moderate symptoms to “requiring no therapy” after 12 weeks of treatment. In another uncontrolled trial, 36 women with climacteric symptoms were treated with a 60% ethanol extract of black cohosh (80 mg/day) for 12 weeks. A statistically significant (P < 0.001) decrease in the average values of the KI was reported, and an increase in the Clinical Global Impressions scale was observed. In an open study, 50 women with climacteric symptoms, who had previously been treated with intramuscular injections of estradiol valerate (4 mg) and prasteronenantate (200 mg, every for six weeks), were alternatively treated with a SBC-R extract (80 mg/day for six months). The therapeutic results were rated as “good” to “very good” in 41 of the patients. Twenty-eight patients (56%) required no further injections, 21 patients (44%) required one injection in six months, and one patient required two injections. The KI decreased to below 15 points (P < 0.001), indicating alleviation of symptoms. An open multicenter drug-monitoring study of 629 patients with meno-
pausal symptoms assessed the efficacy of SBC-R extract at a dose of 80 mg daily for eight weeks of treatment.24 Symptoms such as hot flashes, profuse sweating, headache, vertigo, nervousness, and depression were improved in more than 80% of all cases after six to eight weeks of treatment with the extract.24

Case reports with a total of 833 women have described the use of Remifemin® for the treatment of climacteric symptoms, as well as the treatment of menstrual disorders such as primary or secondary amenorrhea and premenstrual disorders.29–33 Due to the limited value of such reports, the details are not described.

In addition to climacteric symptoms, one clinical trial specifically assessed the effect of a standardized extract of black cohosh on gonadotropin secretion. A placebo-controlled clinical trial involving 110 women with climacteric symptoms assessed the effect of the SBC-R extract on serum levels of LH and FSH.19 The women were treated with the extract (8 mg/day) or a placebo for two months. Blood samples were taken after treatment and the concentrations of LH and FSH in the serum were determined by radioimmunoassay. Whereas a significant reduction in serum LH levels (P < 0.05) was seen in the group receiving treatment compared with the group receiving placebo, no difference in serum FSH levels was observed between the treatment and placebo groups.19

MECHANISM OF ACTION

The mechanism by which black cohosh reduces hot flashes is not well understood, and there are conflicting reports in the literature with regard to its possible estrogenic effects. Data from clinical trials are contradictory. In one study, treatment with the SBC-R extract led to a significant reduction in LH levels as compared with placebo; however, the methodology of this study is questionable because baseline measurements were not performed.19 In other clinical investigations, there was no effect observed on serum hormone concentrations in women treated with the SBC-R extract.20,23,27 The effects of this extract on the proliferation of vaginal tissue or the endometrium are also contradictory.21,25

To date, in vitro and in vivo studies assessing the effects of black cohosh on estrogen receptor-posit
MCF-7 cancer cells or increase uterine weight after oral administration of the extract to female mice for four days. In yet another study, treatment of breast cancer cells with the SBC-R extract did not stimulate cell proliferation, but instead prevented estradiol-induced cell proliferation (>1 μg/mL) indicating anti-estrogenic effects. Finally, a recent investigation of the SBC-R extract found no tumor-promoting effects in female rats with estrogen-dependent tumors. Thus, the most recently published studies do not support an estrogenic mechanism for black cohosh, and alternative mechanisms of action are currently under investigation.

CONCLUSION

Black cohosh (Cimicifuga racemosa) has been used as an herbal remedy by women for more than 100 years and is currently advocated as an alternative therapy for menopausal symptoms. A review of the clinical trial data suggests that treatment with a standardized black cohosh extract may be of some benefit for the relief of hot flashes. It is important to remember that all the trials cited in this review used a standardized black cohosh extract (Remifemin®) at a dose corresponding to 40–80 mg daily. As with many other botanicals, however, the methodology used in all the published clinical trials is flawed, and even the most recent trial had significant limitations. Data from longer, more rigorous clinical trials performed with well-defined extracts of botanically authenticated plant materials are needed. There are currently two randomized, double-blind, placebo-controlled trials underway, both of which are funded by the National Institutes of Health. One study is being performed at Columbia University in New York, and the other at the Center for Botanical Dietary Supplements Research in Women’s Health at the University of Illinois at Chicago.

The most recent investigations do not support an estrogen-receptor mediated theory as a plausible mechanism of action of black cohosh. Alternate mechanisms of action have been proposed, such as a dopaminergic or serotonergic effects, and pharmacologic investigations in these areas are currently underway.

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