Menopause

A Standardized Isopropanolic Black Cohosh Extract (Remifemin) Is Found to Be Safe and Effective for Menopausal Symptoms

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Black cohosh (*Actaea racemosa*; syn; *Cimicifuga racemosa*) is a perennial herb that belongs to the buttercup family (*Ranunculaceae*); it is characterized by a large, creeping rhizome, the source of its medicinal properties. The plant is native to eastern United States and Canada. It was first used medicinally by Native Americans who referred to it as "squaw root" for its traditional use as an effective herbal medicine in maintaining women's reproductive health. The Cherokees and Iroquois used black cohosh for relief of pain during menses and childbirth, as well as a mild sedative. Native Americans later introduced black cohosh to the European colonists. From 1820 to 1936, the rhizome was listed in the United States Pharmacopeia and in the National Formulary from 1936 to 1950; it was championed by the American Medical Association during the 1850s. Throughout the 19th century, black cohosh was an ingredient commonly found in patent medicines for treating menstrual difficulties and pain associated with childbirth. Lydia E. Pinkham's Vegetable Compound, a herbal formula made popular in the mid-19th century for female complaints, included black cohosh as one of its main ingredients, it is still available today. Although there was a decline in the use of black cohosh in the United States between 1950 and 1995, its use in Europe dramatically increased during this same period as a safe and effective alternative to hormone replacement therapy (HRT). Remifemin, a proprietary black cohosh extract, manufactured in Germany since the mid-1950s, has been prescribed for more than 50 years for the management of menopausal symptoms. Black cohosh is approved by the German government as a nonprescription drug for treatment of premenstrual discomfort, dysmenorrhoea, and menopausal symptoms.[1] In the United States, there has been a dramatic resurgence in the use of black cohosh for addressing menopausal symptoms, because of the negative side effects associated with HRT.

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ACTIVE CONSTITUENTS

The constituents of black cohosh root and rhizomes include triterpene glycosides, primarily actein, 27-deoxyactein, and cimicifugosides, and other constituents such as tannins, resin, fatty acids, starch, and sugars.[2,3] Although earlier reports showed that black cohosh contained the phytoestrogen flavonoid formononetin, more recent studies demonstrate that this chemical compound is not found in either the crude herb or standardized extracts.[4-6] It is suggested that initial reports of black cohosh containing

isoflavone ingredients were a result of contamination with a similar plant species.[7]

MECHANISM OF ACTION

The pharmacological action of black cohosh was originally thought to exert a phytoestrogenic effect (an estrogen-like action) by inhibiting luteinizing hormone secretion in menopausal women; however, recent scientific and clinical studies have refuted this activity.[8-10] At present, researchers have no clear definitive explanation regarding the efficacy of black cohosh in addressing menopausal symptoms.[8]

CLINICAL APPLICATIONS

The primary clinical applications of black cohosh include neurovegetative complaints associated with menopause, which include hot flashes, sleep disturbances, night sweats, irritability, nervousness, heart palpitations, vaginal atrophy, and depression.

RESEARCH IN REVIEW

Osmers R, Friede M, Liske E, et al Efficacy and safety of isopropanolic black cohosh extract for climacteric symptoms. *Obstet Gynecol*. 2005;105:1074-1083.[11]

HERBAL MEDICINE TEST EXTRACT

Remifemin, a proprietary standardized black cohosh extract is the most extensively used and thoroughly researched natural alternative to HRT. It is manufactured by Shaper & Brumer, Salzgitter, Germany, and distributed in the United States by Enzymatic Therapy, Inc. This proprietary standardized extract (Remifemin; *Actaea racemosa* standardized isopropanolic extract; www.remifemin.com) has been used successfully in Europe for over 50 years and has provided the most consistent clinical evidence for the treatment of common menopausal symptoms, such as hot flashes. The black cohosh formulation is standardized to contain 1 mg triterpene glycosides (27-deoxyactein) per tablet or 20 drops. The average dosage is 40 mg/d, in tablet or liquid format.

STUDY OBJECTIVE

To provide new evidence on the efficacy and safety of a proprietary standardized isopropanolic extract of black cohosh rootstock and rhizome (Remifemin; *Actaea racemosa*; syn; *Cimicifuga racemosa*) in the recommended daily dosage of 40 mg of the extract each day in comparison with placebo.

STUDY DESIGN

This study was a randomized, double-blind, placebo-controlled, multicenter study where subjects were recruited from 24 gynecologic private practices, located in Germany.

A total of 304 ($n = 304$) postmenopausal patients were randomly assigned to receive 1 of 2 treatments over a 12-week period. Group 1 ($n = 153$) received 1 Remifemin tablet (each tablet containing 2.5 mg isopropanolic extract of *Actaea racemosa* corresponding to 20 mg of root stock and rhizome) taken 2 times per day, and group 2 ($n = 151$) received the placebo tablet.

Strict parameter guidelines were closely followed to determine eligible test subjects. Clinical examinations and interviews were conducted prior to treatment and during weeks 4 and 12. The inclusion criteria consisted of postmenopausal women (12 months since last regular menses or 6 months since last regular menses plus follicle-stimulating hormone ≥ 50 U/L), a minimum age of 45 years, with climacteric symptom intensity as defined by the menopause rating scale (MRS) (an assessment tool consisting of 10 items that are each evaluated from 0 [*no complaints*] to 1 [*severe symptoms*] in increments of 0.1) and the response for inclusion was 0.4 or more in at least 3 items. The exclusion criteria were well defined and consisted of the following: body mass index $>$ 28 kg/m^2; diseases that could potentially interfere with the assessment of climacteric symptoms, cancer, drug, and alcohol abuse; and previous participation in a clinical study including the most recent 180 days. In addition, concomitant use of HRT was prohibited throughout the study, as well as nonhormonal climacteric agents, including homeopathic medicine and herbal supplements such as wild yam, soy, and red clover. Other medications that were excluded were sedatives, antidepressants, and antiepileptic drugs.

RESULTS

The primary result was the change from baseline on the MRS; secondary results included safety variables and changes in subscores. The changes in MRS included hot flashes (sweating, hot flashes, and sleep

disorders), psyche (nervousness, irritability, memory, and depression), soma (muscle, joint, and heart symptoms), and atrophy (vaginal dryness, sexual disorders, and urinary complaints).

The standardized isopropanolic extract of black cohosh (Remifemin) was significantly more effective than placebo in decreasing the MRS score ($P < .001$), with the greatest effect on early menopausal women. Four of 10 MRS subscores significantly decreased in the black cohosh group when compared to the placebo group: $P = .007$ (hot flashes), $P = .012$ (atrophy), $P = .019$ (psyche). The hot flush subscore demonstrated the most effective measure for the isopropanolic black cohosh extract's efficacy.

Adverse events in this clinical study were determined to be "mild and transient" and consistent with data of previous studies. Reported adverse effects included occasional gastrointestinal discomfort, with no significant difference in occurrence between the group taking black cohosh (32%) and the placebo group (31.1%). Researchers, in response to a few previous case reports that suggested a possible relationship between various black cohosh preparations (not Remifemin) and hepatotoxicity, evaluated a putative hepatotoxic potential of black cohosh, even though these case reports have since been reviewed and determined to lack evidence of causality.[12,13] Liver enzymes in both patient test groups were monitored throughout the study and showed no clinically relevant changes in hepatic enzymes. Safety reviews of black cohosh indicate that *Actaea racemosa* is safe, with adverse events that are rare, mild, and reversible.[14,15] However, as a cautionary measure, it may be beneficial to monitor liver function in patients who take oral doses of black cohosh.

CONTRAINDICATIONS

According to current literature, there are no known contraindications for using black cohosh (*Actaea racemosa*). Although there were earlier concerns about the possible phytoestrogenic activity (estrogen-like effect), and therefore the potential contraindication for use in women with estrogen-related breast cancer, present studies indicate that the mechanism of action of black cohosh is not estrogenic.[16] Although researchers have no clear definitive explanation regarding the efficacy of black cohosh in addressing menopausal symptoms, formononetin, the isoflavone thought to be an active estrogenic component of black cohosh in earlier studies, is not detected in the commercially available isopropanolic and ethanolic extracts such as Remifemin and is not a constituent of the dried root.[16,17] Women who are experiencing menopausal symptoms, who have either a family history or a personal history of estrogen-related cancers should seek the advice of their practitioners, before taking black cohosh.

PREGNANCY AND LACTATION

Black cohosh should not be used during pregnancy owing to its emmenagogue and uterine-stimulant effect, and it is not recommended during lactation.[18]

DRUG INTERACTIONS

There are no known drug interactions. However, concomitant use with HRT is not recommended.[16]

ADVERSE EFFECTS

On occasions, gastrointestinal tract discomfort has been reported. Overdose may cause headache, nausea, vomiting, impaired vision and circulation, and vertigo.[16]

SUMMARY

This randomized, double-blind, placebo-controlled, multicenter clinical study investigated the efficacy and various safety aspects of a standardized proprietary isopropanolic extract of black cohosh (Remifemin) in a population of 304 postmenopausal women who met strict parameter guidelines that determined the inclusion criteria. This clinical study confirmed previous results, which clearly indicate the efficacy and tolerability of this proprietary black cohosh extract (Remifemin) in addressing menopausal symptoms, particularly hot flashes.

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