Black Cohosh

Actaea racemosa L. (syn. *Cimicifuga racemosa* [L.] Nutt.)

[Fam. *Ranunculaceae*]

Overview

Black cohosh is indigenous to the eastern U.S. and Canada, with a long and widely recognized medicinal tradition. Native Americans and early colonists used black cohosh root to treat conditions including general malaise, malaria, rheumatism, abnormalities in kidney function, sore throat, menstrual irregularities, and childbirth. In Chinese medicine, rhizomes of many different species have been traditionally used to treat inflammation, fever, headache, pain, sore throat, and chills. Black cohosh has been used in Europe for more than 40 years to treat symptoms associated with menopause. In 1996, nearly 10 million retail units of a standardized ethanolic and isopropanolic extract were sold monthly in Germany, Australia, and the U.S. The herb has become increasingly popular as a dietary supplement in the U.S., with retail sales in mainstream markets in 2000 ranking 14th of all herbals. Currently, black cohosh root is approved to treat premenstrual discomfort, dysmenorrhea, and neurovegetative complaints associated with menopause by the German Commission E.

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Primary Uses

- Neurovegetative complaints associated with menopause, including hot flashes, heart palpitations, nervousness, irritability, sleep disturbances, tinnitus, vertigo, perspiration, depression
- Premenstrual discomfort
- Dysmenorrhea

Other Potential Uses

- Surgical ovarian deficiencies

Pharmacological Actions

Estrogenic activity (with alcoholic fractions) inhibits LH secretion but not FSH secretion in menopausal women; proliferates vaginal epithelium. However, other studies have refuted estrogen-like activity and further research needs to be conducted to determine the mechanism of action.

Dosage and Administration

The German Commission E Monograph recommends a maximum treatment duration of six months. In Germany, prescriptions for hormone replacement therapy (HRT) are limited to a six-month duration in order to ensure that women return to their healthcare providers for general check-ups. In the case of black cohosh, the Commission E has based its limitations of therapy with black cohosh on the same criteria as used for HRT.

Black cohosh (crude drug): 40 mg–80 mg (or oral dose equivalent) per day.

Dried rhizome and root: 40–200 mg.

Decoction: 240 ml boiling water poured onto 40–200 mg black cohosh (crude drug), simmered for 10–15 minutes.

Fluid extract: 1:1 (*g/ml*) 90% alcohol, 0.3–1.0 ml, or 0.3–2.0 ml, or 5–30 drops.

Tincture: 1:10 (*g/ml*) 40–60% alcohol, 0.4–2.0 ml, or 2–4 ml, or 40 drops twice daily.

Extract: 40%–60% ethanolic or isopropyl alcohol extracts of the rhizome with monitoring of active compounds (triterpene glycosides) corresponding to 40 mg of black cohosh daily.

Contraindications

None known. Since black cohosh is considered to be a phytoestrogen, it was originally contraindicated in patients with a history of breast cancer. However, recent studies suggest that this contraindication needs to be reevaluated.

Pregnancy and Lactation: Not recommended during pregnancy due to its emmenagogue and uterine-stimulant effect (based on empirical observations). Not recommended during lactation (based on empirical observations).

Adverse Effects

Occasional gastrointestinal discomfort has been reported. Vertigo, headache, nausea, vomiting, impaired vision, and impaired circulation have been reported in cases of overdose.

Drug Interactions

None known.

Clinical Review

Of 10 clinical studies, including a total of 1,371 participants, nine of these studies demonstrated positive effects for menopausal symptoms. Numerous clinical trials with varied methods and designs have been conducted on the standardized isopropanolic/ethanolic extract of black cohosh root, Remifemin®, from 1981 to the present. Five of the studies were open-label, and evaluated the effectiveness of the extract as a monotherapy for the treatment of menopausal complaints. Two studies compared black cohosh extract to conventional hormonal therapy in the treatment of complaints associated with menopause or hormonal deficiencies in ovariectomized/hysterectomized patients. One open-label, randomized, controlled study compared the efficacy of three different black cohosh therapies to conjugated estrogens and diazepam for menopausal problems. One R, DB study compared two dosages of Remifemin® for the treatment of menopausal symptoms. A decrease in the Kupperman-Menopause Index (KPI) was reported in five clinical studies on black cohosh extract.

Black Cohosh

Actaea racemosa L. (syn. *Cimicifuga racemosa* [L.] Nutt.)
[Fam. *Ranunculaceae*]

Overview

Black cohosh, a plant commonly found in the eastern U.S. and Canada, was a botanical remedy of Native Americans. It has been used in Europe for over 40 years. Today, black cohosh root is approved by the German government as a treatment for premenstrual discomfort, painful menstruation, and menopausal symptoms.

Uses

Menopausal complaints including hot flashes, heart palpitations, nervousness, irritability, sleep disturbances, ringing in the ears (tinnitus), whirling sense or dizziness (vertigo), perspiration, and depression; premenstrual discomfort; painful menstruation.

Dosage

The German Commission E Monograph recommends taking black cohosh for a period of six months, after which a check-up with your healthcare practitioner is advised before resuming further use.

AVERAGE RECOMMENDED DOSE: 40mg–80mg (or oral dose equivalent) of black cohosh per day (available in tablet and liquid form).

DRIED RHIZOME AND ROOT: 40–200 mg.

DECOCTION: Pour 240 ml boiling water onto 40–200 mg black cohosh root, simmer for 10–15 minutes.

FLUID EXTRACT: 1:1 (*g/ml*) 90% alcohol, 0.3–1.0 ml, 0.3–2.0 ml, 5–30 drops.

TINCTURE: 1:10 (*g/ml*) 40–60% alcohol, 0.4–2.0 ml, 2-4 ml, 40 drops twice daily.

Contraindications

None known.

PREGNANCY AND LACTATION: Patients who are pregnant and/or lactating should not use black cohosh. It is not recommended during pregnancy because it may promote menstrual flow or stimulate the uterus. Black cohosh is not recommended during breast-feeding.

Adverse Effects

Occasional gastrointestinal discomfort has been reported. Overdose may cause vertigo, headache, nausea, vomiting, impaired vision, and impaired circulation.

Drug Interactions

None known. Minimal side effects were noted when standardized black cohosh extracts and estrogen-replacement therapy were taken at the same time.

Comments

When using a dietary supplement, purchase it from a reliable source. For best results, use the same brand of product throughout the period of treatment. As with all medications and dietary supplements, please inform your healthcare provider of all herbs and medications you are taking. Interactions may occur between medications and herbs or even among different herbs when taken at the same time. Treat your herbal supplement as you would any type of medication by taking it as directed, storing it as advised on the label, and keeping it out of the reach of children and pets. Consult your healthcare provider with any questions.

AMERICAN BOTANICAL COUNCIL

Black Cohosh

Actaea racemosa L. (syn. *Cimicifuga racemosa* [L.] Nutt.)

[Fam. *Ranunculaceae*]

Overview

Black cohosh is indigenous to the eastern U.S. and Canada, with a long and widely recognized medicinal tradition (Blumenthal *et al*., 2000; Liske, 1998). Native Americans and early colonists used black cohosh root to treat conditions including general malaise, malaria, rheumatism, abnormalities in kidney function, sore throat, menstrual irregularities, and childbirth (Blumenthal *et al.*, 2000; Boon and Smith, 1999; Liske, 1998). In Chinese medicine, rhizomes of many different species have been traditionally used to treat inflammation, fever, headache, pain, sore throat, and chills (Foster, 1999; Liske, 1998). Black cohosh has been used in Europe for more than 40 years to treat symptoms associated with menopause (Foster, 1999). In 1996, nearly 10 million retail units of a standardized ethanolic and isopropanolic extract were sold monthly in Germany, Australia, and the U.S. (Blumenthal *et al*., 2000; Pizzorno and Murray, 1999). The herb has become increasingly popular as a dietary supplement in the U.S., with retail sales in mainstream markets in 2000 ranking 14th of all herbals (Blumenthal, 2001). Currently, black cohosh root is approved as a nonprescription drug to treat premenstrual discomfort, dysmennorhea, and neurovegetative complaints associated with menopause by the German Commission E (Blumenthal *et al* 1998; Liske, 1998).

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Description

Crude preparations of black cohosh consist of the dried rhizome and roots of *Actaea racemosa* L. (syn. *Cimicifuga racemosa* [L.]) (Foster, 1999; McGuffin *et al*., 2000) [Fam. *Ranunculaceae*], harvested in the fall (Blumenthal *et al*., 2000; Bradley, 1992). Some commercial extracts have been standardized based upon triterpene glycoside content (Liske, 1998; McKenna, 1998). Remifemin®, a German standardized oral formulation used in all of the black cohosh clinical studies published through 2000, contains 20 mg of black cohosh extract standardized to 1 mg triterpene glycosides (calculated as 27-deoxyactein) per tablet or twenty drops (Blumenthal *et al*., 2000; Liske, 1998; McKenna, 1998).

Primary Uses

Gynecology

- Menopause: Neurovegetative complaints associated with menopause, including hot flashes, heart palpitations, nervousness, irritability, sleep disturbances, tinnitus, vertigo, perspiration, and depression (Liske and Wüstenberg, 1998; Düker *et al*., 1991; Lehmann-Willenbrock and Riedel, 1988; Blumenthal *et al*., 1998; Bratman and Kroll, 1999; Pethö, 1987; Stoll, 1987; Warnecke, 1985; Vorberg, 1984; Daiber 1983; Stolze 1982)
- Premenstrual discomfort (Blumenthal *et al*., 1998; Bratman and Kroll, 1999)
- Dysmenorrhea (Blumenthal *et al*., 1998; Bratman and Kroll, 1999)

Other Potential Uses

- Treatment of surgical ovarian deficiencies (Lehmann-Willenbrock and Riedel, 1988; Liske, 1998)

Dosage

In clinical studies before 1996, the dose was 2x2 tablets/day, or 2x40 drops/day, which is equivalent to 48–140 mg of black cohosh extract per day (Foster, 1999; Liske, 1998). A recent clinical trial comparing two different dosages of Remifemin® (40 mg vs. 127 mg daily), for six months, in 152 women with menopausal complaints, found similar safety and efficacy profiles for both doses (Liske and Wüstenberg, 1998). Based upon the results of this trial, a recommended dose equivalent to 40 mg of black cohosh (dried root) daily is currently recommended (Liske, 1998). Nevertheless, the dosage in most of the clinical trials shown in the table below is 80 mg daily of the extract (the doses in the studies using liquid preparation form at 40 drops twice daily are equivalent to 80 mg daily).

Internal

Crude Preparations

DRIED RHIZOME AND ROOT: 40–200 mg (Bradley, 1992).

DECOCTION: 240 ml boiling water poured onto 40–200 mg black cohosh (cut, dried root) and simmered for 10–15 minutes (Bradley, 1992).

FLUID EXTRACT: 1:1 (*g/ml*) 90% alcohol, 0.3–1.0 ml (Karnick, 1994); 0.3–2.0 ml (Newall *et al*., 1996); 5–30 drops (Lust, 1974).

TINCTURE: 1:10 (*g/ml*) 40–60% alcohol, 0.4–2.0 ml (Bradley, 1992); 2–4 ml (Newall *et al*., 1996; Wren, 1988), 40 drops are taken twice daily (Hunter, 1999; Warnecke, 1985).

Standardized Preparations

EXTRACT: 40%–60% ethanolic or isopropyl alcohol extracts of the rhizome with monitoring of active compounds (triterpene glycosides) (Liske, 1998; Liske and Wüstenberg, 1998), corresponding to 40 mg of black cohosh daily (Blumenthal *et al*., 1998).

DURATION OF ADMINISTRATION

The German Commission E monograph recommends a maximum treatment duration of six months (Blumenthal *et al.*, 1998). Some authors have suggested that this is due to a lack of clinical trials longer than six months published at the time the monograph was compiled (Bratman and Kroll, 1999; McKenna, 1998). According to Professor H. Schilcher, vice-president of the Commission E, the reason for this limitation is predicated on the Commission's desire to ensure that women return to their healthcare provider for periodic examinations at six-month intervals. The limitation is not based on any concerns about the long-term safety of black cohosh. Based on a long history (33 years) of black cohosh use in Germany at the time the monograph was written in 1989, and on the herb's general safety in long-term use (including data from clinical experience, post-marketing studies, and market data on daily doses prescribed, adverse events reports, etc.), the Commission E considered allowing unlimited duration of use of black cohosh without concern for safety. However, in Germany, prescriptions for hormone replacement therapy (HRT) are limited to a six-month duration in order to ensure that women return to their healthcare provider for general checkups; in the case of black cohosh, the Commission E treated it with the same limitations as HRT (Schilcher, 2001). The relative safety of black cohosh in long-term use is also supported by pharmacological and clinical research. In a six-month chronic toxicity study, followed by an eight-week recovery period, up to 1,800 mg/kg body weight, or roughly 90 times the therapeutic dose, of black cohosh granulate was administered to rats, and no detectable anomalies or toxic effects were observed (Korn, 1991). Although this study may support long-term use of black cohosh (Pizzorno and Murray, 1999), studies of carcinogens in rats must typically be two years long to equate to long-term use in humans (Cott, 2000). Ames tests (*in vitro Salmonella* microsomal assays) performed on isopropanolic extracts showed no evidence of mutagenicity (Bratman and Kroll, 1999; Liske, 1998). Although long-term studies may be warranted to satisfy current standards in toxicology, these findings suggest that black cohosh may be considered relatively safe for long-term therapy (Liske, 1998; Pizzorno and Murray, 1999).

CHEMISTRY

Constituents of black cohosh root and rhizome include triterpene glycosides: actein, cimicifugoside, cimigoside, 27-deoxyactein, deoxyacetylacteol, and racemoside (Bradley, 1992; Bratman and Kroll, 1999; McKenna, 1998; Newall *et al*., 1996). Eight new triterpene glycosides named cimiracemosides A-H have been identified (Shao *et al.*, 2000). Some references state that it also contains isoflavones including formononetin (Bradley, 1992; Jarry *et al*., 1985; Pizzorno and Murray, 1999). NOTE: Although Jarry and coworkers reported the isolation of formononetin from a methanolic extract in 1985, more recent studies of Remifemin® (an isopropyl/ethanolic extract) along with five other commercial preparations failed to identify appreciable levels of the flavonoids (Liske, 1998; Liske and Wüstenberg, 1998; Foster, 1999; Stuck *et al.*, 1997). A recent review suggests black cohosh does not contain isoflavones (Hagels *et al*., 2000). Constituents of black cohosh root and rhizomes also include the aromatic acids, isoferulic acid and salicylic acid (Bradley, 1992; Newall *et al*., 1996; Pizzorno and Murray, 1999) and other constituents including tannins, resin, phytosterols, fatty acids, starch, and sugars (Bradley, 1992; Foster, 1999; Newall *et al*., 1996).

PHARMACOLOGICAL ACTIONS

Studies refuting the estrogenic activity of black cohosh:

Human

A good-clinical-practices-compliance study (40 mg vs. 127 mg daily) in postmenopausal women yielded no estrogen-like LH or FSH suppression. In addition, endogenous estradiol, sex hormone-binding globulin (SHBG), and prolactin levels remain unaffected (Liske *et al.*, 1998; Liske and Wüstenberg, 1998). Estrogenic changes in vaginal cytological parameters (e.g., degree of vaginal proliferation) were not observed (Liske *et al.*, 1998; Liske and Wüstenberg, 1998). No increase in thickness of the endometrium, no changes in vaginal cell status, and no changes in the hormone values of LH, FSH, prolactin, estradiol were observed before and after a black cohosh treatment (Nesselhut and Liske, 1999).

Animal

No estrogen-like uterine effects or changes in vaginal cytology were detected in animal experiments using an ethanolic extract (Einer-Jensen *et al*., 1996). In rats with artificially (DMBA) induced breast tumors, it was demonstrated that different doses of an isopropanolic black cohosh extract (1x, 10x, 100x human therapeutic dose) did not cause stimulation of mammary tumors compared to the placebo group. Estrogen substitution with mestranol resulted in a progression of the tumors. No estrogenic-agonistic effects on prolactin, LH, FSH, or on the uterine tissue were seen (Freudenstein *et al.*, 2000). Pyridinoline and deoxypyridinoline as markers of bone metabolism in rats declined significantly under black cohosh administration (isopropanolic extract) compared to the control, suggesting potential benefits in retarding bone loss (Nisslein and Freudenstein, 2000).

In vitro

Formononetin, the isoflavone thought to be an active estrogenic component of black cohosh in earlier studies (Jarry *et al.*, 1985; Jarry and Harnischfeger, 1985), is not detected in the commercially available isopropanolic and ethanolic extract (Struck *et al.*, 1997) and is not a constituent of the dried root (Hagels *et al*., 2000). An isopropanolic/alcoholic extract inhibits the proliferation of estrogen-receptor positive (ER+) human breast cancer cell lines (MDA MB 435S) (Nesselhut *et al*., 1993). Investigations show that an isopropanolic-aqueous extract does not stimulate the proliferation of ER+ human breast cancer cell lines (MCF-7), but the extract does produce a dose-dependent inhibition of DNA synthesis, an antagonization of estradiol activity, and a synergistic increase in the anti-proliferative effect of tamoxifen (Freudenstein and Bodinet, 1999). An ethanolic black cohosh extract inhibited growth of T-47D human breast cancer cells (Dixon-Shanies and Shaikh, 1999).

Studies supporting the estrogenic activity of black cohosh:

Human

Earlier research showed that black cohosh improves neurovegetative symptoms (hot flashes, increased perspiration, headache, vertigo, heart palpitations, tinnitus) and psychological complaints

(nervousness, irritability, sleep disturbances, depressive mood) associated with menopause or hormonal deficiencies experienced by hysterectomized/ovariectomized patients (Stolze, 1982; Daiber, 1983; Vorberg, 1984; Warnecke, 1985; Stoll, 1987; Pethö, 1987; Lehmann-Willenbrock and Reidel, 1988; Lieberman, 1998; Liske, 1998; Liske and Wüstenberg, 1998); proliferation of vaginal epithelium (Stoll, 1987). Three alcoholic fractions produced endocrine effects that inhibit luteinizing hormone (LH) secretion, but not follicle-stimulating hormone (FSH) secretion, in menopausal women. The authors hypothesize that this is an estrogen-like effect (Düker *et al.*, 1991).

In vitro

A methanolic extract demonstrated endocrine activity in an *in vitro* estrogen-receptor assay. The three fractions identified were believed to compete with estradiol for binding sites on estrogen receptors (Jarry *et al.*, 1985).

Mechanism of Action

Although estrogen-like effects, such as LH suppression, have been proposed as the primary mechanism of action in alleviating the symptoms of menopause, results of recent animal investigations and clinical studies indicate that the mode of action is not identical with estrogen. On the contrary, estrogen-agonistic and estrogen-antagonistic effects on different target organs indicate a tissue selectivity for black cohosh ingredients (Boblitz *et al*., 2000). Although some studies suggest black cohosh has an estrogen-like effect based on its observed LH- suppressive activity, a definite mechanism of action has not been established (Düker *et al.*, 1991). A recent animal study failed to detect estrogen-like uterine effects or changes in vaginal cytology with black cohosh administration. Thus, the authors concluded that LH suppression was associated with neurotransmitter interference instead of estrogenic activity (Einer-Jensen *et al.*, 1996). Similarly, another study comparing two different dosages of Remifemin® (40 mg vs. 127 mg daily) showed no effect on hormonal levels of LH, FSH, SHBG, prolactin, or estradiol, or on vaginal cytological parameters; however, menopausal symptoms were clearly alleviated (Liske *et al.*, 1998; Liske and Wüstenberg, 1998). Although the authors cannot definitively explain the mechanism responsible for the efficacy of black cohosh in the treatment of menopausal complaints, they agree that Remifemin® does not exert a hormonal (estrogenic) effect (Liske *et al*., 1998; Liske and Wüstenberg, 1998).

Contraindications

None known (Blumenthal *et al*., 1998; Pizzorno and Murray, 1999).

Note: Despite earlier concerns about the possible estrogenicity of black cohosh, and thus a possible contraindication for women with estrogen-positive breast cancer, as explained in the Pharmacology and Mechanism of Action sections above and in the discussion below, it is clearly established that black cohosh is not estrogenic. Thus, no such contraindication is warranted.

According to an *in vitro* study, the use of an isopropanolic aqueous extract of black cohosh reportedly inhibited the proliferation of estrogen-receptor positive (ER+) human breast cancer cells and, although still debated, the present data indicate that black cohosh does not increase the risk of developing breast cancer (Nesselhut *et al*., 1993). Another *in vitro* study reported that Remifemin® extract did not stimulate the proliferation of ER+ human breast cancer cells (Freudenstein and Bodinet, 1999). In addition, the extract inhibited DNA synthesis in a dose-dependent manner, antagonized the estrogenic activity of estradiol, and enhanced the anti-proliferative effect of tamoxifen (Freudenstein and Bodinet, 1999). In rats with artificially (DMBA) induced breast tumors, it could be demonstrated that different doses of an isopropanolic black cohosh extract (1x, 10x, 100x human therapeutic dose) did not cause any stimulation of mammary tumors compared to the placebo group. Estrogen substitution with mestranol resulted in a progression of the tumors. No estrogenic-agonistic effects on prolactin, LH, or FSH, or on uterine tissue were seen (Freudenstein *et al*., 2000).

Pregnancy and Lactation: Not recommended during pregnancy due to its emmenagogue and uterine-stimulant effect (based on empirical observations) (Brinker, 2001; McGuffin *et al*., 1997). Not recommended during lactation (based on empirical observations) (Brinker, 2001; McGuffin *et al*., 1997).

Adverse Effects

Occasional gastrointestinal discomfort has been reported (Blumenthal *et al.*, 1998; Foster, 1999; McGuffin *et al*., 1997). Vertigo, headache, nausea, vomiting, impaired vision, and impaired circulation have been reported with overdose (Foster, 1999; McGuffin *et al*., 1997).

Drug Interactions

None known (Blumenthal *et al*., 1998; Brinker, 2001), including in cases of simultaneous administration of standardized black cohosh extracts and estrogen-replacement therapy (McKenna, 1998; Pethö, 1987; Warnecke, 1985).

American Herbal Products Association (AHPA) Safety Rating

Class 2b: Not to be used during pregnancy.

Class 2c: Not to be used while nursing (McGuffin *et al.*, 1997).

Regulatory Status

Canada: Regulated as a drug if single dose is sufficiently high or as a potential "New Drug" for specific nontraditional use claims (HPB, 1993). Included in the Drugs Directorate "List of Herbs Unacceptable as Non-medicinal Ingredients in Oral Use Products" (Health Canada 1995a). When identified as a Traditional Herbal Medicine (THM) or as a homeopathic drug, black cohosh is regulated as a nonprescription over-the-counter (OTC) drug requiring premarket authorization and assignment of a drug identification number (DIN) (Health Canada, 1995b; Health Canada, 2001; WHO, 1998).

France: Traditional medicine.

Germany: Fresh or dried rhizome with attached roots is an approved nonprescription drug for oral use in the German Commission E Monographs (Blumenthal *et al.*, 1998). The fresh rhizome and roots for preparation of hydro-alcoholic mother tincture and liquid dilutions are an official drug of the *German Homeopathic Pharmacopoeia* (GHP, 1993). No monograph in the *German Pharmacopoeia* (DAB).

Italy: No information available.

Sweden: Classified as a natural remedy; intended for self-medication; require advance application for marketing authorization. A monograph for the product Remifemin® is published in the Medical Products Agency (MPA) "Authorised Natural Remedies" (MPA, 1999, 2001; WHO, 1998).

SWITZERLAND: Approved as single-ingredient Herbal Medicine and as a component of multiple-ingredient Homeopathic Medicines, both classified by the *Interkantonale Kontrollstelle für Heilmittel* (IKS) as List D medicinal products with sales limited to pharmacies and drugstores, without prescription (Morant and Ruppanner, 2001; WHO, 1998).

U.K.: OTC herbal medicine specified in the *General Sale List*, Schedule 1 (medicinal products requiring a full product license), Table A (for internal or external use); 200 mg maximum single dose and maximum daily dose (GSL, 1990).

U.S.: Dietary supplement (USC, 1994). The homeopathic mother tincture 1:10 (*w/v*), 55% (*v/v*), of fresh or dried black cohosh root, is a Class C OTC drug of the *Homeopathic Pharmacopoeia of the United States* (HPUS, 1990).

CLINICAL REVIEW

Ten clinical studies are outlined in the following table, "Clinical Studies on Black Cohosh," including a total of 1,371 participants. Nine of these studies demonstrated positive effects for menopausal symptoms. Numerous clinical trials with varied methods and designs have been conducted on the standardized isopropanolic/ethanolic extract of black cohosh root, Remifemin®, from 1981 to the present. Five of the studies were open-label, and evaluated the effectiveness of the extract as a monotherapy for the treatment of menopausal complaints (Pethö, 1987; Warnecke, 1985; Vorberg, 1984; Daiber, 1983; Stolze, 1982). Two studies, a randomized, double-blind (R,DB) study (Liske *et al*., 1998), and a randomized study (Lehmann-Willenbrock and Reidel, 1988) compared black cohosh extract to conventional hormonal therapy in the treatment of complaints associated with menopause or hormonal deficiencies in ovariectomized/hysterectomized patients. One open-label, randomized, controlled study compared the efficacy of three different black cohosh therapies to conjugated estrogens and diazepam for menopausal problems (Warnecke, 1985). One R, DB study compared two dosages of Remifemin® for the treatment of menopausal symptoms (Liske *et al*., 1998). A decrease in the Kupperman-Menopause Index (KPI) was reported in five clinical studies on black cohosh extract (Liske *et al*., 1998; Lehmann-Willenbrock and Reidel, 1988; Stoll, 1987; Vorberg, 1984; Daiber, 1983).

BRANDED PRODUCTS

Remifemin®: GlaxoSmithKline / One Franklin Plaza / Philadelphia, PA 19102 / U.S. / Tel.: (800) 366-8900. One tablet contains black cohosh extract corresponding to 20 mg of crude drug standardized to 1% 27-deoxyacteine.

Remifemin®: GlaxoSmithKline. Twenty drops correspond to 20 mg of crude drug. This product is no longer available.

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Clinical Studies on Black Cohosh (*Actaea racemosa* L., syn. *Cimicifuga racemosa*)

Gynecology

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Jacobson *et al.*, 2001	Menopausal symptoms: Hot flashes in women with history of breast cancer	R, DB, PC n=69 (randomized based on current tamoxifen use)	2 months	One, 20 mg tablet, 2 x daily with meals	Remifemin®	Although both treatment and placebo groups self-reported declines in number and intensity of hot flashes, black cohosh was not found to be statistically more harmful or beneficial than placebo in treating menopausal symptoms. Sweating was the only symptom that did show significantly greater improvement over placebo in the black cohosh group (p=0.4). Subset analysis showing effects on patients taking tamoxifen was not reported.
Liske and Wüstenberg, 1998	Menopause complaints	R, DB n=152 (women ages 43–60 with climacteric complaints)	6 months	40 mg/day (crude drug) vs. 127 mg/day (crude drug)	Remifemin®	Decrease in the Kupperman-Menopause Index (KPI) (values ~31 at the beginning) was observable after 2 weeks of Remifemin® therapy. Similar results in safety and efficacy were observed for both dosages. After 6 months, a positive response (KPI<15) was seen in ~90% of patients. No detectable changes were seen in hormone levels of LH, FSH, SHBG, prolactin, or estradiol. Remifemin® did not influence vaginal cytological parameters (degree of proliferation). The authors concluded that Remifemin may act as a selective estrogen receptor modulator ("Phyto-SERM") (no statistics presented).
Düker *et al.*, 1991	FSH and LH levels during menopause	PC n=110 female patients with menopausal-complaints who have received no hormonal therapy for at least 6 months (mean age=52)	2 months	8mg/day extract vs. placebo	Remifemin® tablet vs. placebo	Remifemin® showed an estrogen-like mode of action with selective LH suppression in menopausal women. No significant change in FSH was observed. Mean LH levels significantly reduced compared to placebo ($p<0.05$).
Lehmann-Willenbrock and Riedel, 1988	Menopause complaints	R, Cm n=60 randomized into 4 treatment groups (Estriol, conjugated estrogen, estrogen gestation, black cohosh)	6 months	1 mg tablet/day Ovestin® or 1.25 mg tablet/day Presomen® or 1 tablet/day Trisequens® or 48–140 mg/day Remi-femin®	Ovestin®, Estriol alone; Presomen®, conjugated estrogens; Trisequens®, combined estrogen-gestagen theapy; Remifemin® tablet	Remifemin® extract was shown to produce a decline in modified KPI and improvement of complaints associated with postoperative ovarian function deficiencies. No significant differences were noted among treatment groups. No differences in LH or FSH levels were observed.
Pethö, 1987	Menopause complaints	O n=50 (female patients converting from hormone injections to black cohosh over 6 months)	6 months	48–140 mg/day	Remifemin® tablet	Hormone replacement therapy (Gynodian, injection) may be switched to black cohosh extract with equivalent success. Of the patients, 82% reported black cohosh preparation good or very good; 56% of patients did not require additional hormone injections. No side effects were noted. Significant improvement in mean menopausal index after 2 months ($p<0.001$).

KEY: C – controlled, **CC** – case-control, **CH** – cohort, **CI** – confidence interval, **Cm** – comparison, **CO** – crossover, **CS** – cross-sectional, **DB** – double-blind, **E** – epidemiological, **LC** – longitudinal cohort, **MA** – meta-analysis, **MC** – multi-center, **n** – number of patients, **O** – open, **OB** – observational, **OL** – open label, **OR** – odds ratio, **P** – prospective, **PB** – patient-blind, **PC** – placebo-controlled, **PG** – parallel group, **PS** – pilot study, **R** – randomized, **RC** – reference-controlled, **RCS** – retrospective cross-sectional, **RS** - retrospective, **S** – surveillance, **SB** – single-blind, **SC** – single-center, **U** – uncontrolled, **UP** – unpublished, **VC** – vehicle-controlled.

Clinical Studies on Black Cohosh (*Actaea racemosa* L., syn. *Cimicifuga racemosa*)(cont.)

Gynecology (cont.)

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Stoll, 1987	Menopause complaints	R, DB, PC, Cm n=80 female patients (ages 46 to 56)	12 weeks	48–140 mg/day or 0.625 mg CE/day + 3 placebo tablets/ day on days 1–21, then 2 placebo tablets 2x/day on days 22–28 or 2 placebo tablets 2x/day	Remifemin® tablet or conjugated estrogens (CE) or placebo	Patients treated with Remifemin® showed significant increase in proliferation status of vaginal epithelium compared to those patients treated with estrogens or placebo ($p<0.001$) and significant improvements in somatic and psychological parameters ($p<0.001$) (measured by KPI and HAMA scales). The number of hot flashes dropped from average of 4.9 daily to < 1 in black cohosh group; estrogen group, dropped from 5.2 to 3.2 average daily; and placebo dropped from 5.1 to 3.1 average daily occurrences. Improvements in vaginal lining were so significant, author suggests that black cohosh extract is suited as a remedy of first choice to treat menopausal symptoms, particularly if HRT is contraindicated or not desired by patient. Significant improvement of proliferation of vaginal epithelium with Remifemin®, compared to other groups ($p<0.001$).
Warnecke, 1985	Menopause complaints	O, C, Cm n=60 female patients with menopausal complaints (average age 54 years)	12 weeks	48–140 mg/day or 0.6 mg/day or 2 mg/day	Remifemin® drops or Conjugated estrogens or diazepam	Patients showed similar cytological responses (measured by proliferation and maturation of vaginal epithelial cells) to Remifemin® and estrogens. Patients receiving diazepam had no observable cytological changes. Comparable improvements in neurovegetative and psychological symptoms (measured by Self-Assessment Depression scale, Hamilton Anxiety scale (HAMA), and Clinical Global Impressions scale) were seen in all 3 treatment groups.
Vorberg, 1984	Menopause complaints	O n=50 menopausal women (39 patients showed contraindications to HRT, and 11 refused hormone treatment)	12 weeks	48–140 mg/day	Remifemin® drops	Improvements in psychological symptoms, KPI ($p<0.001$), Profile of Mood States (POMS) ($p<0.001$), and Clinical Global Assessment scale (CGI) ($p<0.001$) were all significant to highly significant in treatment group. No serious side effects were observed. Only mild gastrointestinal disturbances, which did not require discontinuation of treatment, were observed.
Daiber, 1983	Menopause complaints	O n=36 menopausal women; hormone replacement therapy was refused or contraindicated for these subjects (ages 45–62 years)	12 weeks	48–140 mg/day	Remifemin® drops	Highly significant decreases in KPI were observed, as was improvement in psychological symptoms including decreases in weariness and despondency, and increases in motivation and positive mood. A positive response in the CGI scale was also observed. No side effects or incompatibility reactions were observed during the 12 weeks of administration. Reduction of hot flashes ($p<0.001$), nervousness ($p<0.001$), depressive psychosis ($p<0.01$).
Stolze, 1982	Menopause complaints	O, MC n=704 female patients, 629 evaluated (mean age 51 years)	6 to 8 weeks	48–140 mg/day	Remifemin® drops	Significant improvements in neurovegetative complaints and psychological disturbances were experienced by 3 of 4 patients after 4 weeks of Remifemin® therapy. After 6 to 8 weeks, 40–50% of patients experienced complete relief from symptoms and another 30–40% of patients reported marked improvement in symptoms. The Remifemin® was well-tolerated, with no discontinuation of therapy. Only 7% of patients reported mild, transitory nonspecific complaints. In 72% of cases, physicians observed advantages of Remifemin® over previous hormonal treatment. In 54.3% of the cases, physicians stated advantages of Remifemin® compared to previous treatment with psychoactive drugs. No statistics provided.

KEY: **C** – controlled, **CC** – case-control, **CH** – cohort, **CI** – confidence interval, **Cm** – comparison, **CO** – crossover, **CS** – cross-sectional, **DB** – double-blind, **E** – epidemiological, **LC** – longitudinal cohort, **MA** – meta-analysis, **MC** – multi-center, **n** – number of patients, **O** – open, **OB** – observational, **OL** – open label, **OR** – odds ratio, **P** – prospective, **PB** – patient-blind, **PC** – placebo-controlled, **PG** – parallel group, **PS** – pilot study, **R** – randomized, **RC** – reference-controlled, **RCS** – retrospective cross-sectional, **RS** - retrospective, **S** – surveillance, **SB** – single-blind, **SC** – single-center, **U** – uncontrolled, **UP** – unpublished, **VC** – vehicle-controlled.