
Is Black Cohosh Estrogenic?

Many women seek safe and effective alternative therapies for the treatment of menopausal symptoms. Black cohosh, a botanical product, is one such treatment. Its mechanism of action may involve estrogenic effects, but new data dispute the estrogenic theory and indicate that extracts of black cohosh do not bind to the estrogen receptor, up-regulate estrogen-dependent genes, or stimulate the growth of estrogen-dependent tumors in animal models.

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Approximately 55 to 75% of all women who reach menopause, either naturally or surgically, will experience unpleasant symptoms such as vasomotor changes (e.g., night sweats, hot flashes), vaginal dryness, mood and libido changes, bladder control problems, and memory loss.1 For many years, the gold standard for treating menopausal symptoms has been hormone replacement therapy (HRT) with estrogens alone or combined with progesterone. However, the recent Women’s Health Initiative safety report assessing HRT use in postmenopausal women with an average follow-up of 5.2 years...
found that the combination of estrogen and progesterin increased the risk of invasive breast cancer, heart disease, stroke, and pulmonary embolism. In addition, whereas HRT significantly reduces the incidence of vasomotor symptoms, long-term use (>10 years) is also associated with an increased risk of breast cancer in women with or without a history of breast cancer and endometrial cancers. With the concerns menopausal women have about the long-term risks of HRT, many have turned to botanical dietary supplements (BDS) for symptom relief.

Black cohosh is a BDS that is frequently recommended by health care practitioners for the treatment of menopausal symptoms, including hot flashes, depression, and sleep disturbances. Black cohosh (Actaea racemosa syn. Cimicifuga racemosa) is a Native American perennial plant. Alcohol extracts of the dried roots and rhizomes are used to prepare the commercial products that are available on the dietary supplement market. Review of the data from published clinical trials showed that a standardized black cohosh extract was more effective than placebo for the treatment hot flashes in healthy women. Although black cohosh products appear to be moderately effective for the treatment of menopausal symptoms, however, the mechanism of action is not well understood. Because menopausal symptoms are associated with an imbalance of sex hormones, some have suggested that black cohosh may have estrogenic effects. However, data from numerous in vitro and in vivo studies with estrogen receptor–positive breast cancer cell lines have been mixed.

The most recent publication by Freudenstein et al. does not support an estrogenic mechanism for black cohosh. The authors evaluated the safety of a standardized black cohosh extract (CR) in ovariectomized female rats to determine the effects of CR on estrogen receptor–positive mammary gland cells in animals with 7,12-dimethylbenz[a]anthracene (DMBA)–induced tumors. Outcomes variables measured included tumor development, hormone levels, and organ weights. The rats were treated with a single dose of DMBA (20 mg) in sesame oil and were palpitated weekly for tumor development. Upon identification of mammary tumors >5 mm in diameter (5–9 weeks after tumor induction), the animals underwent a bilateral ovariectomy. After 9 days, the tumors were measured again and the animals were randomized to the following treatment groups: (a) CR–vehicle control; (b) 0.714 mg/kg CR extract; (c) 7.14 mg/kg CR extract; (d) 71.4 mg/kg CR extract, and (e) 450 μg/kg mestranol (an estrogen used in Europe). The CR extract and CR control (vehicle solvent) were suspended in water at a concentration of 100 mg/mL immediately prior to intragastric administration. The daily dose was 10 mL/kg body weight and the treatment period was 6 weeks. There were no statistical differences between the groups in terms of tumor latency, number of tumor carriers, and the distribution of tumor size.

The results of this investigation demonstrated that mestranol-treated animals had significantly reduced body weight as compared with controls or the CR-treated animals. No weight changes were observed in either the controls or the CR-treated animals. Mammary tumor growth, which was significantly reduced after ovariectomy owing to the loss of estrogen, was significantly increased after treatment of the rats with mestranol compared with the CR-control or CR-treated animals. In the CR-treated groups there was a tendency for decreased growth of mammary tumors but this did not reach statistical significance. In the mestranol group, 86% of the animals showed malignant tumors; 50% of the animals in the control group showed malignant tumors, as did 50%, 64%, and 47% in the CR-treated groups. These results support previously published in vitro studies that assessed the effects of a standardized black cohosh extract (40% isopropyl alcohol extract CR) on estrogen receptor–positive breast cancer cell lines. The proliferation of human mammary carcinoma cells was not stimulated after treatment of the cells with concentrations of <2.5 μg/mL, and concentrations of ≥2.5 μg/mL caused a significant inhibition of cell proliferation.

Similar results were reported in an investigation using the estrogen receptor–positive human mammary cancer cell line, MCF-7. Treatment of this cell line with a standardized 40% isopropyl alcohol extract of CR, in concentrations ranging from 1 ng/mL to 100 μg/mL, produced a dose-dependent inhibition of cell proliferation. Augmentation of the antiproliferative effects of tamoxifen were also observed, suggesting antiestrogenic activity.

Two other in vitro studies also failed to demonstrate any growth-stimulating effects of black cohosh in breast cancer cell lines. One recent study assessed the effects of ethanol and isopropanol extracts of black cohosh on the proliferation of MCF-7 cells and gene expression. (MCF-7 is an estrogen-dependent human breast cancer cell line.) Estrogenic effects were not observed in proliferation assays, in the gene expression assays using an estradiol-inducible yeast assay, or in estrogen-inducible MVLN cells (MCF-7 cells transfected with vitellogenin-A2-promoter/luciferase reporter construct). (MVLN are a stably transfected MCF-7 cell line in which cell proliferation is stimulated by estrogens and inhibited by antiestrogens.) Conversely, in all three experimental systems, the extracts antagonized estradiol-induced effects. Estradiol-induced cell proliferation was inhibited by a dosage >1 μg/mL of the extract, and estradiol-induced gene expression was suppressed by concentrations of 100 to 1000 μg/mL of the black co-
hosh extracts. The study concluded that extracts from the rhizome of black cohosh contain compounds with antiestrogenic properties. Only one study contradicts the above results; in this study an undefined extract of black cohosh at a concentration of 4.75 μg/mL significantly (P < 0.01) enhanced the growth of MCF-7 cells in vitro and up-regulated the expression of the estrogen receptor (type not specified).

The study by Freudenstein et al. also demonstrated that mestranol treatment of ovariectomized rats increased prolactin, luteinizing hormone (LH), and follicle-stimulating hormone levels (P ≤0.001), whereas no changes were observed in the CR-treated groups. These data support results from a number of clinical trials, in which no changes in hormone levels in women treated with a standardized black cohosh extract were observed. Only one clinical study has reported a significant reduction in LH levels in women treated with a black cohosh extract compared with placebo. Methodology used in this investigation was questionable, however, as baseline measurements were never performed.

In the Freudenstein study, CR-treated animals presented with decreased uterine size and weight; mestranol-treated animals had hypotrophic uteri and significant increases in uterine weights. Conversely, an undefined extract of black cohosh reportedly increased uterine weights and significantly prolonged estrus in immature female mice treated with a dose of 300 mg/kg body weight for 14 days. However, the extract of black cohosh used in this study was not adequately defined and 300 mg/kg body weight represents approximately a 450-fold increase of the human therapeutic dose. One other investigation, also using an undefined black cohosh extract, as part of a standard liquid diet administered to ovariectomized female rats daily for three weeks, showed increased uterine weights and serum ceruloplasmin levels, but no changes were observed in uterine c-myc mRNA levels (which are increased by estrogen, thus indicating that black cohosh does not induce changes normally attributed to estrogen) or liver ceruloplasmin mRNA concentrations. Although the results of this investigation were clearly inconclusive, the authors suggested that black cohosh has estrogenic activity.

The apparent contradictory results among different studies of the estrogenic effect of black cohosh are unsettling. A plausible answer to the question of whether black cohosh is estrogentic may be found in analyses of the different types of black cohosh extracts used in these investigations, and/or possible misidentification of the plant material in question. Results from the University of Illinois at Chicago/National Institute of Health for Botanical Dietary Supplements Research in Women’s Health corroborate the results of the Freudenstein study in that the data do not support an estrogenic mechanism for black cohosh. Using standardized alcohol extracts prepared from authenticated black cohosh roots and rhizomes (identified by taxonomic specialists and DNA analysis), we have demonstrated that black cohosh extracts do not bind to purified ERα and ERβ, do not increase the activity of estrogen-dependent alkaline phosphatase in Ishikawa cells (an endometrial cancer cell line), and do not up-regulate the expression of the estrogen-sensitive pS2 (presenelin-2) or the progesterone receptor mRNA. The Freudenstein study also used a well defined standardized alcohol extract of black cohosh rhizomes and found no estrogenic effects. In the few conflicting publications in which estrogenic effects are claimed for black cohosh, however, there is neither adequate description of the plant materials used nor acceptable information on the preparation or chemistry of the extracts. Thus, it is impossible to determine what type of extract was used or if the correct plant species or plant part was used in the preparation of the extract. Adulteration and the lack of quality control are very serious problems in botanical research and are most likely responsible for the many inconsistencies in pharmacologic data (i.e., some studies report an estrogenic effect and some do not). A good example of this is the case of formononetin, an estrogenic isoflavone that was erroneously reported to be a constituent of black cohosh extracts and to be responsible for its estrogenic effects. Formononetin is a constituent of red clover (Trifolium pratense) and, to a lesser degree, soybean (Glycine max). Recently it been conclusively demonstrated that formononetin is not a constituent of black cohosh root or rhizomes, and this compound has not been found in commercial extracts of black cohosh. It is therefore possible that the older data from 19853 may have been the result of adulteration of the plant materials used in the preparation of the extract or misidentification of the compound formononetin.

Whereas some of the experimental data concerning black cohosh is contradictory, the most recent evidence does not support an estrogenic mechanism of action. These new data dispute the estrogenic theory and demonstrate that extracts of black cohosh do not bind to the estrogen receptor in vitro, up-regulate estrogen-dependent genes, or stimulate the growth of estrogen-dependent tumors in animal models. The investigations that...
previously suggested an estrogenic mechanism of action for black cohosh have used a poorly defined extract, which was not well characterized and may have been subject to adulteration. Further investigations of black cohosh should employ a standardized extract prepared from authenticated plant materials.

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