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## Anti-breast cancer and estrogenic potential of *Actaea racemosa*

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### ABSTRACT

*Actaea racemosa* (black cohosh) is a smooth (glabrous) herbaceous perennial plant of the family Ranunculaceae. The aim of this study was to overview anti-breast cancer and estrogenic potential of *Actaea racemosa*. This review article was carried out by searching studies in PubMed, Medline, Web of Science, and IranMedex databases. Its anti-breast cancer activity is related to their triterpene glycoside composition. It is commonly used for its anti-breast cancer and anti-menopausal activity due to compounds that bind and activate serotonin receptors, and a derivative of serotonin with high affinity to serotonin receptors. Findings showed that compounds from *Cimicifuga* types may be useful in the prevention and treatment of human breast cancer. The results suggest caution for women using black cohosh, peculiarly for extensible periods of time. Regarding to estrogenic activity, although, Black cohosh reduced the GCS total score and all GCS subscale scores (vasomotor, psychiatric, physical, and sexual symptoms), it was reported not to be estrogenic. The results from this review are quite promising for the use of *Actaea racemosa* as an anti-breast cancer agent. Although, Black cohosh reduced the GCS total score and all GCS subscale scores (vasomotor, psychiatric, physical, and sexual symptoms), it was reported not to be estrogenic.

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**Keywords:** *Actaea racemosa, Phytochemicals, Therapeutic effects, Pharmacognosy, Alternative and complementary medicine*

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## INTRODUCTION

The history of herbal remedies in the treatment of many diseases dated back to ancient times [1-24]. *Actaea racemosa* (black cohosh or *Cimicifuga racemosa*) is a smooth (glabrous) herbaceous perennial plant of the family Ranunculaceae[25]. It is native to eastern North America from the extreme south of Ontario to central Georgia, and west to Missouri and Arkansas[26]. Its habitats is variety of woodland, and small woodland openings[26]. Black cohosh that produces large, compound leaves from an underground rhizome, reaching a height of about half meter[27].

The roots and rhizomes have long been used medicinally by Native Americans. Extracts from these plant materials are thought to possess anticancer[28, 29], analgesic and sedative[30], anti-estrogenic [30, 31] and inflammatory properties[32]. Today, black cohosh extracts are being studied as effective treatments for symptoms associated with menopause[33]. Native Americans used black cohosh to treat gynecological and other disorders[34], including sore throats, kidney problems[35], and depression[27], endometritis, amenorrhea, dysmenorrhea, menorrhagia, severe after-birth pains[36], and for increased breast milk production[37]. Black cohosh appeared to reduce hot flashes [25, 38]. Black cohosh have identified some beneficial effects on age-related disorders like osteoporosis [39]. Estrogen-like compounds had originally been implicated in effects of black cohosh extracts on vasomotor symptoms in menopausal women[40]. Physiological effects of black cohosh may be due to compounds that bind and activate serotonin receptors[41], and a derivative of serotonin with high affinity to serotonin receptors, *N* $\omega$ -methylserotonin, has been identified in black cohosh[42].

### *Chemical compounds*

Black cohosh contain numerous natural mixes with biological property[43]. triterpene glycosides (e.g. cycloartane), have been shown to reduce cytokine-induced bone loss (osteoporosis) by blocking osteoclastogenesis in in vitro and in vivo models[43]. 23-O-acetylshengmanol-3-O- $\beta$ -D-xylopyranoside, a cycloartane glycoside from *Actaea racemosa* [44], has been identified as a novel efficacious modulator of GABAA receptors with sedative activity in mice[45]

## RESULT

### *Breast cancer*

In vitro and in vivo impacts of actein on angiogenesis utilizing human microvascular endothelial cells and animal tumor-bearing was researched. Results showed that actein remarkably prohibited the proliferation, decreased the migration and motility of endothelial cells. This study confirmed the usage of actein for development of anti-angiogenic candidates for breast cancer[46].

The rhizomes of *C. foetida*, showed potential anti-cancer activity in multiple triple-negative breast cancer cell lines. The results suggest that KHF16 may restrain this kind of breast cancer through obstructing the NF- $\kappa$ B signaling pathway [47]. Anticancer

cycloartane triterpenoids from *Cimicifuga foetida* L. rhizome was examined. ADHC-AXpn significantly inhibited the growth of MCF-7 cells, induced mitochondrial apoptosis and cell-cycle arrest, and inhibited signaling pathway and phosphorylation[48].

The effects of estrogen and progesterone sequential therapies via *C. foetida* extract on the breasts of early postmenopausal women was investigated. findings showed that *C. foetida* extract at low doses did not raise the incidence of malign breast glands [49]. Therapeutic effect of *C. foetida* was evaluated. BNO-1055 reduce cellular uptake and incorporation of thymidine and BrdU in a dose-dependent manner and *tremendously* restrain cell growth after long-term exposure as a result of hindered nucleoside [50].

The possible estrogen receptor (ER) alpha effects of *Cimicifuga heracleifolia* var. *bifida* ethanol extract (C-Ex) was examined. The outcome suggested that C-Ex probably affect factors in ER signal transduction pathway[51]. In an animal study, the chemopreventive potential and action of the herb black cohosh was examined. results suggest that black cohosh may have chemopreventive potential for mammary carcinoma[52].

The antihormonal therapy of breast cancer patients with the antiestrogen tamoxifen often enforce or worsen menopausal complaints. As far as estrogen substitution is prohibited, herbal alternatives like extracts of black cohosh are often used. Black cohosh extract seems to be a reasonable treatment plan in tamoxifen treated breast cancer patients with mainly psychovegetative indication [53]. The antitumor potential of five cycloartane diterpenoids separated from *Cimicifuga* on the breast carcinoma cell line MCF7 was investigated. The results showed that compounds 2-5 have rather high antitumor influence on both MCF7 and R-MCF7 cells.

The chief role of apoptosis in cycloartane triterpenoids-induced cell death was confirmed. The findings of RT-PCR showed that compounds 2-5 augmented the expression of p53 and bax, which led to the loss of mitochondrial potential and then resulted in the activation of caspase-7. These findings concertedly demonstrated that compounds 2-5 induced apoptosis of MCF7 through p53-dependent mitochondrial pathway[54]. The effects of black cohosh on mammary tumorigenesis were described in the MMTV-neu mouse model due to its similarities to HER2 (+) breast cancer. The results suggest caution for women using black cohosh, peculiarly for extensible periods of time[55].

Hot flushes may also be a main complication for patients with a record of breast carcinoma, as they may result from cancer treatment. Opposing symptoms included gastrointestinal upsets, rashes, headaches, dizziness and mastalgia. Nevertheless, there are few cases of severe detrimental events[56].

A cytotoxic effect of black cohosh on both estrogen-sensitive and estrogen-insensitive breast cancer cells and a synergy with tamoxifen for inhibition of cancerous cell growth was shown[57]. The influence of BCE on circulating and breast-specific estrogenic markers was addressed. BCE had no effect on estrogenic markers in serum and no effect on pS2 or cellular morphology in nipple aspirate fluid. Triterpene content in commercially available black cohosh preparations varies. BCE standardized to 2.5% triterpenes relieved menopausal symptoms without systemic or breast-specific estrogenic effects[58].

The growth repressive effect of extracts and compounds from black cohosh and related *Cimicifuga* species on human breast carcinoma cells was evaluated. Results suggested that the growth inhibitory potent of black cohosh extracts appears to be related to their triterpene glycoside composition. findings showed that compounds from *Cimicifuga* types may be useful in the prevention and treatment of human breast cancer[59].

The influence of a lipophilic black cohosh rhizome extract and cycloartane-type triterpenoids on the estrogen receptor positive human breast cancer cell line MCF-7 was reported. No estrogenic but antiproliferative and proapoptotic gene regulation were shown for black cohosh in MCF-7 cells at the transcriptional level. The effects may be results of the activation of different pathways [60].

The safety and efficacy of black cohosh in patients with cancer was reviewed. The application of black cohosh appears to be secure in breast carcinoma patients without risk for liver disease, although more research is needed in this and other populations[61]. Alterations in gene expression induced by ethanolic extract therapy of black cohosh was reported. Since the Me OH extract activated genes that enhanced apoptosis and repressed cell cycle genes, it may be helpful in the prevention and therapy of breast carcinoma [62].

Non-steroidal as well as steroidal aromatase inhibitors are currently being discussed as substitute to tamoxifen in the first-line remedy of patients with hormone-dependent breast cancer. Naturally occurring symptoms like hot flashes and night sweats can be triggered or augmented by anti-hormonal drugs. Two low doses of formestane with a high dose of iCR, data do not raise concerns against combining aromatase suppressor with black cohosh[63].

The isopropanolic extract of black cohosh (iCR) b exert antiproliferative and apoptosis-inducing effects on estrogen receptor-positive MCF-7, as well as estrogen receptor-negative MDA-MB 231 human breast cancer cells. Thus, it is a secure factor in postmenopausal hormone alternative therapy with supplementary chemopreventive potential [64].

The influence of an isopropanolic *Cimicifuga racemosa* extract (iCR) on relapse-free living after breast cancer was researched. Adding the risk of breast carcinoma relapse for women having had iCR therapy, compared to women not treated with iCR is farfetched [65].

The growth repressive effects of specific breast carcinoma chemotherapy candidate in the triterpene glycosides existing in black cohosh was evaluated. Results indicate that relatively low concentrations of actein or the EtOAc fraction of black cohosh can cause synergetic suppression of human breast cancer cell multiplication when combined with different classes of chemotherapy candidates [66]. In a clinical trial study, no evidence that black cohosh reduced hot flashes more than the placebo was observed [67].

In a study, it illustrated that the cell death induced by iCR withstood a metabolic activation system. In addition, TTG and CAE compounds significantly contributed to its apoptotic action, CAE being the more potent suppressor of proliferation and apoptosis inducer [68].

### ***Anti-menopausal effect***

The clinical advantage and safety of black cohosh (*Cimicifuga racemosa* or *Actaea racemosa*) for treating menopausal symptoms in perimenopausal and postmenopausal women was evaluated. The uncertain quality of identified trials emphasize the need for improved reporting of study methodology, especially regarding allocation latency and the managing incomplete result[69].

In terms of safety, temporary side effects including vomiting, nausea, headaches, dizziness, mastalgia, and weight increase have been observed in clinical trials. A few cases of hepatotoxicity have been reported, but a direct association with the ingestion of

cimicifuga has not been demonstrated. The most recent result suggest that cimicifuga is not estrogenic[70]. The estrogenic property of black cohosh to examine its safety for those with, or at high risk of developing, breast cancer was assessed. The data displayed that Black cohosh extracts did not demonstrate estrogenic activity in any of these assay systems[29].

Both therapies demonstrated influence in relieving menopausal symptoms; however, isopropanolic black cohosh (Remifemin) seems to be a more appropriate choice in alleviating menopausal symptoms in women with uterine fibroid. Isopropanolic black cohosh seems to be a valid remedy choice in patients with uterine fibroids, as it provides sufficient relief from menopausal symptoms and prohibit growth of uterine fibroid size[71].

The effectiveness of black cohosh extract 40 mg/day for relieving moderate to serious menopausal indications and ameliorating quality of life in Thai women was evaluated. A black cohosh extract was not preferable to a placebo for soothing moderate to severe menopausal symptoms or boosting quality-of-life scores in Thai women[72].

The influence of Black cohosh (*Cimicifuga racemosa* L.) in curing early menopausal symptoms was evaluated. Black cohosh reduced the GCS total score and all GCS subscale scores (vasomotor, psychiatric, physical, and sexual symptoms) during 4 and 8 weeks of treatment[73].

The impact of black cohosh (*Cimicifuga racemosa*) on vasomotor symptoms in postmenopausal women was determined. data explained that black cohosh can be utilized as an effective replacement therapy in relieving menopausal vasomotor symptoms[74].

The influence and various safety aspects of a standardized proprietary isopropanolic extract of black cohosh (Remifemin) in postmenopausal women was studied. This study indicate the effect and tolerability of this proprietary black cohosh extract (Remifemin) in addressing menopausal symptoms, particularly hot flashes[75].

The safety and influence of black cohosh and red clover compared with placebo for the relief of menopausal vasomotor symptoms was evaluated. Black cohosh did not reduce the number of vasomotor symptoms. Safety monitoring indicated that chemically and biologically standardized extracts of black cohosh and red clover were secure during daily administration for 12 months[76].

## CONCLUSION

The results from this review are quite promising for the use of *Actaea racemosa* as an anti-breast cancer agent. Regarding to estrogenic activity, although, Black cohosh reduced the GCS total score and all GCS subscale scores (vasomotor, psychiatric, physical, and sexual symptoms), it was reported not to be estrogenic.

## CONFLICT OF INTERESTS

There are no conflicts of interest.

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