This monograph was prepared by The Ottawa Integrative Cancer Centre (OICC), in collaboration with the Complementary Medicine Education and Outcomes (CAMEO) Research Program. It is part of a series of monographs being developed to share results of a review of the research evidence related to common therapies and products used within cancer patient care.

The following monograph is designed to summarize evidence-based research and does not advocate for or against the use of a particular therapy. Every effort is made to ensure the information included in this monograph is accurate at the time it is published.

Please note that this monograph does not include an exhaustive list of all potential adverse events; individuals may experience unique side effects. The information in this monograph should not be interpreted as medical advice nor should it replace the advice of a licensed health care provider. Prior to using a new therapy or product, always consult a licensed health care provider.

For the safe use of natural health products, please consider the following:

- Consult a licensed health care provider prior to using a natural health product and make a plan to monitor its effectiveness and any side effects. This is particularly important for pregnant or breast-feeding women and people with serious medical conditions.
    - To help prevent interactions with your prescribed medication, ensure your health care provider is aware of any drugs or natural health products you may be using. Make sure to note all natural health ingredients listed in compound products.
    - Read and follow all instructions on the product label.
- If purchasing natural health products in Canada, look for Health Canada approved products. Look for Natural Product Number (NPN) or Homeopathic Medicine Number (DIN-HM) on the label to identify licensed products. Avoid internet pharmacies, as the quality of products cannot be guaranteed and products might not be licensed for sale through Health Canada. For more information, visit http://www.hc-sc.gc.ca/dhp-mps/prodnatur/about-apropos/cons-eng.php

Please note: While the aim was to draw from the most extensive research, in some circumstances the information used was limited by the selection and caliber of available research studies. Full references are available in the corresponding full-length monographs found on the OICC website.

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BLACK COHOSH

Proper Name

Actea racemosa; Cimicifuga racemosa

Common Name

Black cohosh; Black snake root; Black bugbane
*Note: Black cohosh is **not** the same as Blue cohosh (Caulophyllum thalictroides)*

Proprietary Extracts

Remifemin; Klimadynon; CimiPure

Common Uses in Cancer Care

Management of hot flashes secondary to treatment with hormonal therapies or the early onset of menopause.

Route of Administration

Oral

Mechanism of Action

The mechanism of action of black cohosh is not well defined. Black cohosh does not appear to increase circulating estrogen levels or exert estrogenic effects on breast tissue, the endometrium, or vaginal tissue. Black cohosh may exert estrogenic effects on bone. Black cohosh may possess selective estrogen receptor modulating effects (1, 2). Alternately, black cohosh may act through serotonergic effects (3) and/or through modulation of the hypothalamic thermoregulatory centers (1, 2).

Clinical Evidence related to Effectiveness for Hot Flashes

Based on 1 cohort study, 2 uncontrolled trials, and 3 RCTs, there is mixed evidence regarding the efficacy of black cohosh in the management of hot flashes in breast cancer patients.

Of the RCTs, two showed reductions in hot flash score or Green Climacteric Scale (GCS) compared to baseline in the black cohosh group; however similar improvements were seen in the control groups also, so there was no statistically significant difference when black cohosh was compared to placebo (4, 5). In these studies, some of the women were also on tamoxifen, but these women were equally distributed between the black cohosh and the placebo groups.

One open label RCT assessing the effect of tamoxifen plus black cohosh compared to tamoxifen alone showed a large improvement in the black cohosh group, with 46% of women in the black cohosh group reporting no hot flashes, compared to 0% of women in the control group reporting no hot flashes (p value not reported) (6). However this was an unblinded study with higher risk of expectation bias.

Of 2 uncontrolled trials, both reported significant improvements in measures of hot flashes (hot flash score, hot flash severity, Menopause Rating Scale-II) compared to baseline (7, 8). In one of these studies all the patients were also receiving between 10-40mg tamoxifen (8), while in the other study 29% of patients were on either tamoxifen or an aromatase inhibitor (7).

One cohort study found no association between black cohosh use and quality of life (QOL) among breast cancer patients (9).

Clinical Evidence related to Risk of Breast Cancer

Based on a total of 3 observational studies, black cohosh does not appear to increase the risk of developing breast cancer. Two studies found no significant association between use of black cohosh by post-menopausal women and breast cancer, hazard ratio (HR) 1.17 (95%CI 0.75-1.82) and adjusted odds ratio (AOR) 0.80 (0.63-1.00) (10, 11). One study found a significant 53% reduction in risk of breast cancer among post-menopausal women, OR 0.47 (0.27-0.82) (12).

Clinical Evidence related to Risk of Recurrence

Based on 1 observational study, black cohosh does not appear to increase risk of breast cancer recurrence. This study reported a 25% decreased risk of breast cancer recurrence associated with use of Remifemin in women with recent breast cancer and breast cancer survivors, HR 0.75 (0.63-0.89) (13). A total of 35.8% of Remifemin users were also taking tamoxifen, while 24.0% of non-users were taking tamoxifen. It is possible that the decreased risk of recurrence was due to higher rate of tamoxifen use or to use of Remifemin; however it appears that at least Remifemin may not interfere with the effect of tamoxifen. More research is needed to support this.

Clinical Evidence related to Estrogenic Effects

Based on 12 RCTs and 5 uncontrolled trials conducted in women without breast cancer (with the exception of one study), black cohosh does not appear to affect circulating levels of estradiol (E2), progesterone, luteinizing hormone (LH), or follicle stimulating hormone (FSH); or exert estrogen-like effects on tissues of the reproductive system (breast, endometrium, vaginal tissue) (5, 14-29). The exception to this was in two RCTs of women with infertility undergoing Clomid therapy who had increased estrogen levels with black cohosh, however in this situation this was considered a therapeutic outcome (19, 20). Black cohosh may exert estrogen like effect in bone, increasing bone formation and decreased bone resorption (18, 24, 29).

Adverse Events and Side Effects

Among breast cancer patients, there was no difference in rates of adverse events between patients receiving black cohosh and the control group. AE that were reported were generally mild in severity. Isolated adverse events that were reported in one trial included: one case of breast cancer recurrence and one hysterectomy among patients who were taking black cohosh and tamoxifen, however causality could not be inferred (5). In 2 RCTS, minor AE were reported but not described except as being inconsistent (5, 6).

Based on a review by Flower et al. including 17 controlled trials conducted among otherwise healthy women, there is no difference in the rate of adverse events among black cohosh users compared to subjects in the control groups (30). Most commonly reported AE included gastrointestinal upset, anxiety, irritability, and mood changes, as well as headaches.

There have been 21 case reports of hepatotoxicity associated with use of black cohosh products, however a causal relationship has not been established (31). There was no evidence of liver toxicity or elevated liver enzymes in the studies included in our review or that by Flower et al., with the exception of 2 cases of increased GGT reported out of the 17 controlled trials and 487 participants (30). A meta analysis of 5 RCTs found no impact on ALT, AST, and GGT (32). Nonetheless, caution is warranted in patients with a pre-existing liver condition.

Interactions with other Therapies, including Drugs and Natural Health Products

Based on the 3 RCTs and 2 uncontrolled trials cited above, there is no evidence of increased adverse events related to co-administration of tamoxifen and black cohosh. One observational study suggests that black cohosh may not interact negatively with tamoxifen, however more studies in this area are needed to confirm this (13).

One study in humans found that a very large dose of black cohosh (>1000mg; 40mg is the therapeutic dose) inhibited by7% the enzyme CYP2D6, which is responsible for metabolizing tamoxifen to its active metabolite, endoxifen (33). The clinical relevance of this level of inhibition and this magnitude of dose is questionable but a theoretical possibility of interaction should be noted. Human trials co-administering black cohosh and tamoxifen in a clinical setting have not reported evidence of a negative interaction (see above).

Black cohosh does not appear to affect: CYP 1A2, CYP 2E1, CYP 3A4, CYP 3A5, or Pgp (33-36). The aromatase inhibitor anastrozole is primarily metabolized by CYP 3A4 (37).

Black cohosh does not appear to impact pharmacokinetics of digoxin in humans (36).

Cautions and Contraindications

Use with caution in patients with pre-existing liver conditions.

Dosing, frequency and length of treatment

40mg of a standardized extract daily for at least 3 months.

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