

BLACK COHOSH

Practical management of adverse effects and drug interactions

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Black cohosh (*Cimicifuga racemosa* [L.] Nutt.) was traditionally used for joint pain, gynecologic disorders, and relief of labour pain.¹ Its Latin name, literally meaning bug repellent, points to its early use. Black cohosh should not be confused with blue cohosh (*Caulophyllum thalictroides*), which has significantly different pharmacologic action, uses, and clinical toxicity.

Today, black cohosh is commonly used in the treatment and management of menopausal symptoms. Using its root or rhizome, black cohosh can be administered as tablets, dried rhizome, a tincture, powdered root, or tea.¹ Alcoholic tinctures or extracts of the herb's rhizome have been most commonly studied and appear to have the greatest pharmacologic effect.²

Uses

Black cohosh has been studied in multiple randomized controlled trials (RCT) for the treatment of menopausal symptoms. The most recent update of the Canadian consensus guidelines on menopause states that black cohosh may be used for the short-term treatment of mild vasomotor symptoms (e.g., hot flashes and night sweats), recognizing that long-term safety data are lacking.³ The North American Menopause Society also recommends the use of a trial of black cohosh if lifestyle modifications are insufficient to manage mild symptoms.⁴ Most of the studies with black cohosh are of rela-

tively short follow-up, therefore use for longer than 6 months cannot be recommended.¹

For use in osteoarthritis, there is one published RCT.⁵ However, the product used in this trial contained several other herbals (such as willow bark) that could have an independent effect on osteoarthritic symptoms.

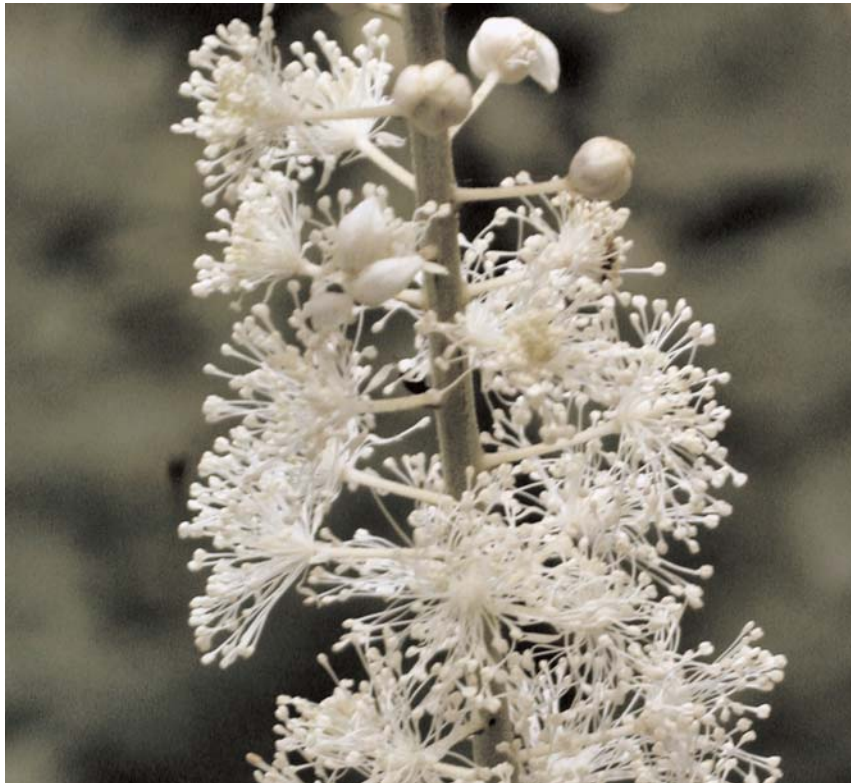
Other uses that have not been well studied include bronchitis, depression, edema, hypertension, polycystic ovarian syndrome, premenstrual syndrome, and uterine bleeding.¹

Safety

Adverse effects

Adverse effects associated with black cohosh are rare.⁶ Patients in clinical trials report few adverse effects associated with black cohosh.⁷ The most commonly reported effects are gastrointestinal-related complaints (in less than 10% of patients) and rash.² Other adverse effects that have been reported include headache, hypotension, dizziness, and nausea; these are associated with higher doses of black cohosh.^{1,2}

There are published case reports linking black cohosh use to acute liver failure.⁸⁻¹⁰ In 2 cases, the patients required liver transplantation.⁸⁻¹⁰ The salicylate and alkaloid components of black cohosh are suspected to be the potential cause of liver damage.¹⁰ There is one published case report of seizures in a 45-year-old woman taking black cohosh.¹¹ Not



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all of the case reports did a product analysis to determine if contaminants or adulterants were the potential cause of the adverse event. In one of the case reports of liver failure, product analysis did not reveal any contaminants.⁹

There is controversy with regard to use of black cohosh in women with a history of breast cancer. The mechanism of action of black cohosh is unknown and recent data suggest that there may be no estrogenic or hormonal effects, and black cohosh may ultimately have anti-estrogenic effects (selective estrogen receptor modulator effects).¹²⁻¹⁴ It has been studied for use in women with a history of breast cancer.^{15,16} In one RCT, black cohosh was used to treat hot flashes in women who had completed their primary treatment for breast cancer.¹⁵ There was no significant difference in the treatment (black cohosh) and placebo groups with regards to hot flashes. In terms of adverse effects, there were no significant differences between the two groups. Patients were only followed for 2 months. The authors conclude that their study cannot provide evidence for either benefit or harm.

In a second study investigating the use of black cohosh in the treatment of hot flashes in women

post-breast cancer treatment, also taking tamoxifen, black cohosh was found to significantly reduce symptoms.¹⁶ This study was an open-label, randomized trial that followed patients for 12 months. No significant adverse events were noted in either group. These studies were small, had methodologic flaws and limited follow-up. In addition, in vitro or animal model studies have shown conflicting results regarding the estrogen-receptor effects of black cohosh.¹⁷ Further study in this area is required to definitively determine the safety of black cohosh in women with breast cancer. There is also a lack of evidence regarding the long-term effect of black cohosh on vaginal cytology, notably endometrial hyperplasia.²

Drug interactions

Due to its hypothesized estrogenic effects, black cohosh may interact with hormone replacement therapy, oral contraceptives, and tamoxifen. Given that the estrogenic effects of black cohosh have not been fully elucidated, it is unclear how its administration could affect therapy with other estrogenic compounds.

There is limited evidence that black cohosh may enhance the effects of antihypertensive agents and

cause peripheral vasodilation.¹⁸ There are no published case reports of serious adverse events associated with concomitant use of black cohosh and antihypertensives.

Black cohosh contains relatively small amounts of salicylic acid, and theoretically it may potentiate the effects of anticoagulant drugs.¹ Therefore this herb should be avoided in people with a salicylate allergy.

In vivo studies show that black cohosh is not a potent modulator of p-glycoprotein, a common pathway for drug interactions.¹⁹ Black cohosh is thought to be a weak inhibitor of CYP2D6, however, the clinical implications of this are considered insignificant.

Precautions/contraindications

Patients taking antihypertensive drugs should be cautioned regarding concomitant use. Patients with a history of liver disease should be cautioned against use, given the potential for liver failure.

As mentioned above, patients with a personal

history or family history of breast cancer should discuss use of black cohosh with their physician.

Due to black cohosh's potential to stimulate uterine contraction, it is not recommended for use by pregnant women.¹

Pharmaceutical care

Black cohosh is safely tolerated in most women for the short-term treatment of mild vasomotor symptoms associated with menopause. Patients should be counselled on the most commonly occurring adverse events, notably GI upset and rash. Patients taking antihypertensives should be warned about the potential hypotensive effect; they can be counselled on monitoring their blood pressure when initiating black cohosh therapy. Women with a history of breast cancer should be advised to discuss black cohosh use with their physician. Adverse events and drug interactions should be immediately reported to the Natural Health Products Directorate of Health Canada. ■

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References

1. Natural Standard Monograph. Black cohosh. *Natural Standard* 2006. Available: www.naturalstandard.com (accessed May 2006).
2. Low Dog T, Powell KL, Weisman SM. Critical evaluation of the safety of *Cimicifuga racemosa* in menopause symptom relief. *Menopause* 2003;10:299-313.
3. Belisle S, Blake J, Basson R, et al. Canadian consensus conference on menopause, 2006 update. *J Obstet Gynaecol Can* 2006 Feb;28(2 Suppl 1):S7-S94.
4. North American Menopause Society. Treatment of menopause-associated vasomotor symptoms: position statement of The North American Menopause Society. *Menopause* 2004;11:11-33.
5. Mills SY, Jacoby RK, Chacksfield M, Willoughby M. Effect of a proprietary herbal medicine on the relief of chronic arthritic pain: a double-blind study. *Br J Rheumatol* 1996;35:874-8.
6. Huntley AL, Ernst E. A systematic review of safety of black cohosh. *Menopause* 2003;10:58-64.
7. Low Dog T. Menopause: a review of botanical dietary supplements. *Am J Med* 2005;118:98S-108S.
8. Whiting PW, Clouston A, Kerlin P. *Med J Aust* 2002;177:440-3.
9. Levitsky J, Alli TA, Wiscarver J, Sorrell MF. Fulminant liver failure associated with the use of black cohosh. *Dig Dis Sci* 2005;50:538-9.
10. Lontos S, Jones RM, Angus PW, Gow PJ. Acute liver failure associated with the use of herbal preparations containing black cohosh. *Med J Aust* 2003;179:390-1.
11. Shuster J. Heparin and thrombocytopenia. Black cohosh root?

- Chasteberry tree? Seizures! *Hosp Pharm* 1996;31:1553-4.
12. Liu J, Burdette JE, Xu H, et al. Evaluation of estrogenic activity of plant extracts for the potential treatment of menopausal symptoms. *J Agric Food Chem* 2001;49:2472-9.
13. Borrelli F, Izzo AA, Ernst E. Pharmacological effects of *Cimicifuga racemosa*. *Life Sci* 2003;73:1215-29.
14. Einer-Jensen N, Zhao J, Andersen KP, Kristoffersen K. Cimicifuga and Melbrosia lack oestrogenic effects in mice and rats. *Maturitas* 1996;25:149-53.
15. Jacobson JS, Troxel AB, Evans J, et al. Randomized trial of black cohosh for the treatment of hot flashes among women with a history of breast cancer. *J Clin Oncol* 2001;19:2739-45.
16. Hernandez Munoz G, Pluchino S. *Cimicifuga racemosa* for the treatment of hot flushes in women surviving breast cancer. *Maturitas* 2003;44 Suppl 1:S59-65.
17. Mahady GB, Fabricant D, Chadwick LR, Dietz B. Black cohosh: an alternative therapy for menopause? *Nutr Clin Care* 2002;5:283-9.
18. Boon H, Smith M. *The complete natural medicine guide to the 50 most common medicinal herbs*. Hilderley B, editor. 2nd edition. Canada: Robert Rose Inc.; 2004.
19. Gurley B, Hubbard MA, Williams DK, et al. Assessing the clinical significance of botanical supplementation on human cytochrome P450 3A activity: comparison of a milk thistle and black cohosh product to rifampin and clarithromycin. *J Clin Pharmacol* 2006;46:201-13.