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File: ■ Black Cohosh (*Actaea racemosa* syn. *Cimicifuga racemosa*)
■ Ethnopharmacological Research

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RE: Black Cohosh Review: A Lesson in Ethnopharmacological Research

Johnson TL, Fahey JW. Black cohosh: coming full circle? *J Ethnopharmacol*. June 2012;141(3):775-779.

Black cohosh (BC; *Actaea racemosa* syn. *Cimicifuga racemosa*) is an herbaceous plant indigenous to the eastern United States which has a long and varied history of medicinal use by Native Americans, European settlers, and allopathic physicians. In modern times, BC is most commonly used in the alleviation of menopausal symptoms[1] and research initiatives have largely been focused on elucidating the "active ingredients" and their "mechanism(s) of action" in ameliorating hot flashes. The body of BC research exemplifies the current scientific approach to ethnopharmacological research; the discovery and isolation of bioactive compounds from whole plant material. The authors posit that this reductionist approach is very limited and blinds researchers to the wisdom embodied in traditional knowledge. This brief review of BC ethnopharmacology connects its traditional use as an analgesic with recent research.

BC was traditionally used by Native Americans to treat a range of female reproductive ailments (amenorrhea, dysmenorrhea, ovarian disorders, and childbirth pain). However, it was also used as a tonic (to treat fatigue and for blood purification), diuretic, cold and cough treatment, sedative, and an analgesic. Early European settlers readily adopted BC into their pharmacopoeia, and by the 1800s it had become a mainstay treatment. In addition to the traditional applications described above, Eclectic physicians prescribed BC for muscular pain, false pains, irregular pains, and sore throat; as a stomachic, cardiotonic, an expectorant, and diaphoretic; and to induce relaxation, promote childbirth, and stimulate appetite. Both men and women were prescribed BC as an analgesic for a wide range of ailments.

There have been many studies on the use of BC for the treatment of hot flashes, but the results to date are conflicted. In addition, large placebo effects were observed in some trials, further confounding estimates of BC efficacy in treating menopausal symptoms.

It is thought that estrogen withdrawal during menopause causes hypothalamic thermoregulatory center dysfunction, which results in the typical hot flash symptoms. Catechol estrogen (CE; an estrogen metabolite) and endogenous opioids which normally

keep norepinephrine (NE) activity in check decrease during menopause and NE activity increases, resulting in thermoregulatory dysfunction. Although hot flashes usually subside after estrogen is depleted, several other conditions associated with estrogen modulation persist; consequently, chronic pain conditions, such as fibromyalgia and arthralgia, are more common in women than in men.

It is theorized that estradiol acts on endogenous opioid receptors, especially μ-opioid receptors, which are highly effective mediators of pain. Women given a pain challenge during a high-estradiol state showed increased μ-opioid receptor binding and reported less intense pain, whereas the same challenge during low-estradiol states produced lower μ-opioid receptor binding and more intense pain. It has been reported that BC is a ligand and agonist of the μ-opioid receptor, suggesting a possible mechanism for its efficacy in the treatment of hot flashes and as an analgesic. A pilot brain-imaging study found that BC increased the binding potential of μ-opioid receptors in the nucleus accumbens brain region, which is associated with placebo effect, and in the hypothalamus, which mediates thermoregulatory function.

The most significant BC bioactives related to the treatment of hot flashes are reported to be the triterpene glycosides actein, 23-epi-26-deoxyactein, and cimicifugoside. Nω-methylserotonin (NMS), a metabolite of serotonin, has affinity for the serotonin receptors 5-hydroxytryptamine 1A (5-HT1A) and 5-HT7, suggesting possible serotonergic mechanisms for alleviating hot flashes by influencing levels of neurotransmitters such as NE, or inhibiting hypothalamic-mediated thermoregulatory function. However, a recent study reported that NMS is only present in micromolar concentrations in BC, and gene expression of the required NMS biosynthetic enzymes is negligible.

Triterpenes are steroid precursors that have complex pharmacokinetics affecting a number of enzyme systems. These compounds exert a broad range of pharmacological activities, including analgesic, antiatherosclerotic, anticarcinogenic, anti-inflammatory, antidiabetic, antimalarial, and antiosteoporotic effects. The analgesic effects of triterpenoids are especially well documented and involve a variety of mechanisms, including vanilloid, opioid, and serotonergic receptors that affect acute, visceral, neurogenic, and inflammatory pain.

BC is commonly wild harvested for commercial consumption, and wild stands are becoming increasingly threatened by habitat destruction, overharvesting, and growing market demand. Agroforestry, field, and tissue culture propagation has not yet reached levels sufficient to relieve the pressure on wild populations. There are concerns that increasing market demand will result in increased adulteration of the commercial supply of BC.

The safety of BC has been investigated mainly in the context of liver toxicity due to adulteration of commercial material. A 2011 meta-analysis found that pure BC did not induce liver damage, and causality in suspected hepatotoxicity cases could not be assigned to BC due to insufficient evidence as to whether the toxicity was induced by adulterated BC, concomitant drug or supplement use, or antecedent liver disease.

In summary, the authors point out that Western researchers typically view the multiple traditional applications of herbal medicines as "lengthy and indiscriminant laundry lists of effects" and dismiss the idea that there may be sound scientific bases for many of these uses. There is a tendency to not only focus exclusively on pharmacological activity

supported by mechanistic and/or clinical evidence, but also to further reduce investigations to a myopic concentration on eliciting "the active ingredient" and its singular mechanism of action.

This review cautions that the reductionist approach effectively blinds scientists to the investigative leads inherent in the many pharmacological activities indicated by traditional use. Specifically in the case of BC, the authors assert that research progress will be hindered if scientists continue to ignore the wealth of traditional knowledge indicating multiple mechanisms and the extant evidence of the synergistic effects of its plant constituents. They suggest that future researchers should broaden their perspective to encompass the prominent traditional use of BC as an analgesic, its demonstrated effect on neurotransmitter and μ-opioid receptors, and the growing body of scientific evidence linking BC and pain relief.

—Amy C. Keller, PhD

Reference

[1]Blumenthal M, Goldberg A, Brinckmann J, eds. *Herbal Medicine: Expanded Commission E Monographs*. Austin, TX: American Botanical Council; Newton, MA: Integrative Medicine Communications; 2000.

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