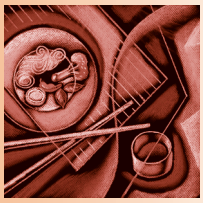

Black Cohosh

Considerations of Safety and Benefit

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Black cohosh, *Actaea racemosa* L (syn. *Cimicifuga racemosa* [L] Nutt), has enjoyed a rapid rise in popular use for the amelioration or alleviation of menopausal symptoms. At the same time, the last decade has witnessed a significant expansion of research on the chemistry, pharmacology, and clinical efficacy and safety of this botanical species. As a consequence of the growing body of data on black cohosh, together with the appearance of reports implicating this botanical in cases of liver damage, the Office of Dietary Supplements (National Institutes of Health) convened a workshop on the current state of knowledge for black cohosh (Gaithersburg, Maryland; June 2007); this review is based on that workshop. Based on the information presented and the ensuing discussions, several recommendations are proposed to facilitate better understanding and management of the safety of this botanical in the context of clinical trials. Nutr Today. 2009;44(4):155–162

Introduction

Black cohosh is a perennial plant belonging to the family Ranunculaceae, with the scientific name of *Actaea racemosa* L, a common synonym for which is *Cimicifuga racemosa* (L) Nutt. In 1998, the genus *Actaea* was revised to subsume or include the genera *Cimicifuga* and *Souliea*; thus, the genus now contains 28 species.[1,2] Of these, 8 are found in North America, 19 in Asia, and 1 in Europe.

Actaea racemosa is indigenous to North America, where it was used by Native Americans principally for musculoskeletal pain and also for fever, cough, pneumonia, sluggish labor, and menstrual irregularities.[3] Black cohosh was adopted by early European settlers as a female tonic and was widely used into the early 20th century, with official entries in the US Pharmacopeia until 1926. In the United States, it is now found most frequently in dietary supplement and herbalist formulations for menopause, premenstrual syndrome, menstrual cramping, preparation for childbirth, and, to a lesser extent, in products for rheumatoid arthritis and mild depression. The German Commission E (1989) has approved extracts from the rootstock of black cohosh for use in premenstrual discomfort and dysmenorrhea or climacteric (menopausal) neurovegetative symptoms. The World Health Organization (WHO, 2002) and the European Scientific Cooperative on Phytotherapy (2003) have also listed black cohosh for menopausal symptoms.

The body of evidence regarding black cohosh has continued to grow, and concerns have recently developed over the safety of black cohosh products. On November 22, 2004, the National Center for Complementary and Alternative Medicine (NCCAM), National Institutes of Health (NIH), in collaboration with the NIH Office of Dietary Supplements (ODS), convened a small workshop to discuss issues related to the safety of black cohosh.[4] Other participants included the Office of Research on Women's Health, NIH; the National Cancer Institute; the National Institute on Aging; the US Food and Drug Administration; the American Herbal Products Association; and the Center for Science in the Public Interest. The original meeting was called in response to 5 case reports associating black cohosh with hepatotoxicity and an abstract[5] referencing data from a murine model of breast cancer that raised questions about the safety of black cohosh. The focus on safety

was necessitated by the fact that NCCAM, ODS, and other institutes and centers at the NIH support clinical studies on black cohosh and that an important responsibility of the NIH is the safety of research subjects.

In the 3 years that have passed since the initial workshop, numerous preclinical and clinical articles have been published on the safety and efficacy of black cohosh. Furthermore, there have been several dozen additional reports of hepatotoxicity associated with use of products containing black cohosh, as well as a number of publications on the effect of black cohosh on breast health. As a consequence of the additional case reports involving the liver, new cautionary statements were mandated for black cohosh product labels by a number of national regulatory agencies. The ODS (NIH) convened a second workshop in June 2007 to (*a*) gain a better understanding of the reports of hepatotoxicity of black cohosh in human beings and (*b*) discuss steps that investigators might take to continue to protect participants in clinical studies of black cohosh.

Chemistry of Black Cohosh—A Question of Marker Compounds

Because black cohosh has only recently been brought into cultivation, it is difficult to meet escalating world demand, and much of this botanical is still collected from the wild, where species identification depends on the skill, knowledge, experience, and honesty of the collector and where mistakes might be made. This situation might also tempt a less scrupulous supplier to substitute related but possibly ineffective and potentially harmful species for *A racemosa*.

The chemistry of black cohosh (*A racemosa*) has been studied since 1962, with a substantial increase in such investigations in the last decade. Triterpene glycosides (~62) and polyphenols (~30) are the most frequently encountered compounds. Most triterpene aglycones are cycloartanes, whereas the polyphenolics are quite diverse, including isoferulic and salicylic acids, tannins, and others. In contrast, only 1 alkaloid, cimipronidine, has been reported from black cohosh.[6] The phytochemistry of other species of *Actaea* has not been investigated as thoroughly as has that of *A racemosa*.

Comparative analyses of 4 American species—*A racemosa*, *Actaea podocarpa*, *Actaea pachypoda*, and *Actaea rubra*—have been conducted, and major qualitative and quantitative differences in both the polyphenol and triterpene constituent profiles in these species have been observed. However, only the species *A podocarpa* has thus far been shown to contain distinctive compounds, the podocarpasides. Unfortunately, this comparative study also revealed that 26-deoxy-23-epi-actein, commonly called 27-deoxyactein and frequently used as a marker compound for standardization[7] of extracts and commercial products in the United States, was also present in the 4 American species examined and all Asian species in commerce. Therefore, it is not a meaningful or appropriate marker compound for identification of *A racemosa*. Currently, cimiracemoside C seems to be a better marker for *A racemosa*, whereas cimicifugin and its glycoside might best serve as indicators for the Asian species.

It would seem that using analytical profiles, that is, high-performance liquid chromatography (HPLC) fingerprinting, of black cohosh raw material ingredients or products might be the most expedient and effective method for evaluating these raw materials and products and ensuring their identity, authenticity, and lack of adulteration by other species.[8–11] In an experiment to test the utility of such analytical profiles, an HPLC analysis of 11 commercial black cohosh products in the United States indicated that 3 of them contained undeclared Asian species of *Actaea* and 1 was an undeclared mixture of Asian and American species; thus, more than one-third of products examined in this small marketplace review were misbranded or adulterated.[12]

Clinical Evidence of Efficacy

At least 47 human trials of some sort have been conducted on black cohosh formulations since 1957, with increasing emphasis on randomized, double-blind, placebo-controlled or comparative trials. Most trials (n = 29) used Remifemin, an isopropanolic black cohosh extract, but there are no consistent statements in the published trial reports about standardization of the test articles or interventions, and the manufacturer has not been responsive to inquiries in this regard. The likely explanation for this is that, according to the general monograph "Extracts" in the European Pharmacopoeia, extracts in Europe can only be described as standardized when the constituents responsible for the therapeutic activity are known, when specific constituents are generally accepted as contributing to the therapeutic activity, or where they are relevant to the safety of the product. The European Pharmacopoeia defines other types of extract where the therapeutically active constituent is not known, but descriptions of the phytochemical content of such extracts are not mandatory. The lack of any such phytochemical description is problematic when trying to evaluate existing literature and may hinder future research on black cohosh and, potentially, other botanicals. The NCCAM will only support studies that provide adequate information on test article composition.[13]

In 3 of 4 recent clinical trials of black cohosh for relief of menopausal symptoms,[14–16] each with a duration of

12 weeks, black cohosh was superior to placebo and equivalent to conjugated equine estrogen and topical estradiol. The fourth trial ran for a full year (Herbal Alternatives for Menopause study, 2006)[17] and showed no differences among the 4 treatment arms and placebo, except that hormone therapy did reduce vasomotor symptoms significantly. In a recently published randomized, double-blind, placebo-controlled study, the isopropanolic black cohosh extract was as effective as tibolone in the reduction of neurovegetative and psychological symptoms.[18]

Another work, led by the Wang group in the University of Illinois at Chicago Botanical Research Center, indicated that a 75% ethanol extract of black cohosh acts as a mixed competitive ligand for the human μ opiate receptor (pain), but at fairly high concentrations not likely to be achieved in the bloodstream after ingestion of recommended doses of black cohosh.[19] Similarly, other workers at the same center found that black cohosh extract inhibits the 5-HT7 receptor in the serotonin pathway and tracked this activity to the phenolic constituents but subsequently found these compounds to be only marginally bioavailable.[20] Jarry et al[21] have determined that black cohosh upregulates the gene for tyrosine hydroxylase, suggesting an involvement of dopamine in hot flashes. In following this hypothesis, their group confirmed a dopaminergic effect by black cohosh, and a non–sexual-steroid central nervous system activity via opioid receptors has been shown in symptomatic postmenopausal women.[22,23] There is still much to do in sorting out the pharmacology and mechanisms of action of black cohosh.

Safety—The Paramount Issue

There have been 2 areas of concern about black cohosh—its impact on breast tissue and on the liver. While the hepatotoxicity issue has arisen more recently, both concerns have been the subject of considerable discussion and investigation.

Breast

Because black cohosh is used primarily for relief of menopausal symptoms, it has long been thought to have estrogenic activity, raising concerns about the potential impact of the botanical in patients with breast and other cancers. An illuminating study demonstrated estrogen-like cell proliferation at a low *Cimicifuga* extract concentration but anti–estrogen-like inhibition of cell proliferation at high extract concentrations in human breast cancer cells (MCF7).[24] However, subsequent studies have dispelled that concern. In 1 study, the proliferation of EMT6 mouse breast cancer cells was not altered by 3 different preparations of black cohosh, nor was the response of the EMT6 cells to radiation or cisplatin; however, black cohosh did increase the toxicity of adriamycin and docetaxel (Taxotere) toward those cancer cells.[25] There are 9 other recent preclinical investigations that showed no effects of black cohosh on breast tissue.[26–34]

Several studies have demonstrated that black cohosh is, in fact, not estrogenic.[35–37] The University of Illinois at Chicago group showed that black cohosh roots and rhizomes do not contain any compounds that serve as ligands for the estrogen receptors ER-α or ER-β or have the ability to induce alkaline phosphatases, pS2, or progestin receptors.[38] In addition, black cohosh exhibited no estrogenic activity in vivo in ovariectomized mice.[39] Furthermore, 2 studies of women given black cohosh have shown no endometrial stimulation or thickening;[40,41] whereas another clinical study involving postmenopausal women who received an isopropanolic extract of black cohosh also found no evidence of increased mammographic (breast tissue) density.[42]

Liver

Following a first case report[43] in 2002 of the potential association of a black cohosh product with hepatotoxicity in Australia, additional reports began to appear, some as case reports in the medical literature, others as spontaneous notification to national authorities and the manufacturers of black cohosh products. The true number of such reports may be unclear because of duplication.

- The Herbal Medicines Product Committee[44] of the European Medicines Agency reviewed 44 case reports of liver damage "related" to black cohosh: 31 from the European Union (EU), 5 from non-EU countries, and 8 from the published literature. Overall, 18 were considered sufficiently documented; of these, only 3 were considered to represent a possible relationship between black cohosh and liver damage, and 2 more were judged to have a probable relationship. Because the documentation in the latter 5 cases was not complete, a hepatologist carried out a more thorough qualitative/quantitative causality assessment of these files. No relationship between black cohosh and hepatotoxicity could be found in 4 of the 5 cases, and the remaining case was judged as unlikely to be due to black cohosh.[45] The Federal Institute for Drugs and Medical Devices in Germany has examined, in detail, these same 44 case reports, plus 2 additional literature reports, and reached the same conclusions. In one of the "probable causality" cases, a very high dose of black cohosh was used, more than 10-fold the usually recommended dose.[46] It is also notable that this

case seems to have been inaccurately reported. The publication[46] contained a statement that "the patient did not drink alcohol or use drugs and was not taking any medications including other herbal medications, acetaminophen, or nonsteroidal anti-inflammatory drugs." Later, the female patient attested under oath that she regularly drank wine and had used drugs that are known to influence the liver (Nebraska judgment of September 8, 2006). In a follow-up article regarding the same case, the authors have now published an erratum,[47] clarifying that the patient admitted to consuming alcohol and taking other medications at the time of her initial presentation of liver failure; the authors expressed regret about the omission of this information from the original case report.

- The Medical Products Agency in Sweden has received a total of 7 adverse event reports involving hepatotoxicity associated with Remifemin and none for Klimadynon, the only approved black cohosh products in Sweden. A detailed review by a hepatologist found that 4 of the 7 cases were possible associations, but 3 of those were confounded by use of other drugs associated with adverse effects on the liver (eg, ketoprofen, levothyroxine, lamotrigine, tramadol, paracetamol). At least 6 of these cases are duplicates of those already included in the European Medicines Agency assessment report, wherein none of them were assessed to have a possible or probable association.
- In the United Kingdom, the Medicines and Healthcare Products Regulatory Agency has received a total of 26 reports of liver problems. Cases range in severity from abnormal liver function to hepatitis; 1 patient required a liver transplant. As standard causality methods do not transpose well to spontaneous case reports, specific causality categories were not assigned. However, all cases have undergone detailed analysis and consideration by the United Kingdom's expert advisory committees, which resulted in detailed warnings being added to both licensed and unlicensed products containing black cohosh. The Medicines and Healthcare Products Regulatory Agency continues to monitor for cases of hepatotoxicity suspected to be associated with black cohosh.
- The Office of Complementary Medicine, Therapeutic Goods Administration, in Australia reviewed 16 adverse event reports of hepatic injury with concomitant black cohosh received between 2002 and 2006. Although sufficient data were not available to draw conclusions about mechanism of liver toxicity, dose-response relationship, or linkage to a particular product, 3 of the cases were serious, all requiring liver transplants. One patient died. These latter cases prompted a mandate for the use of very strong, detailed warning labels on black cohosh products in Australia.
- The WHO's Uppsala Monitoring Centre (WHO-UMC) in Sweden receives the national spontaneous suspected adverse drug reaction case reports from more than 80 countries (including all of those mentioned above). (The information presented is not homogeneous at least with respect to origin or likelihood that the pharmaceutical product caused the adverse reaction. The information does not represent the opinion of the World Health Organization.) By May 2007, the WHO-UMC had received 43 reports of 66 liver adverse events for black cohosh from 6 countries. Duplication of reports can sometimes occur in the system when a country submits follow-up information to the WHO-UMC. Exclusion of likely duplicates gave a total of 40 case reports of liver adverse events associated with black cohosh (36 reports for monopreparations and 4 reports for multiherb preparations containing black cohosh as an ingredient). The WHO-UMC uses a quantitative method to detect possible signals of safety concerns within the database; an information component value is calculated, which is a measure of disproportionality or unexpectedness within the database. A positive information component value means that the drug–adverse drug response combination (eg, black cohosh–liver adverse events) occurs more frequently than is expected, against the background of the rest of the database. Retrospective analyses indicated that there has been an association between black cohosh and liver adverse drug responses since 2001 (this analysis includes 3 duplicate reports, as these were unconfirmed duplicates at the time of the analysis). Quantitative analysis can also be undertaken for specific liver adverse event terms: for example, black cohosh has been associated with "abnormal hepatic function" since the fourth quarter of 2004 and with "hepatic failure" since the fourth quarter of 2006. Once a signal has been detected using quantitative analysis, the WHO-UMC and its team of expert reviewers carry out a manual assessment of the case reports received (not reported here because of similarities with work described above). This may include undertaking a formal causality assessment for individual cases, although this has usually been done by the pharmacovigilance center in the country that originally received the report.
- Health Canada has received 4 reports of hepatic injury associated with use of black cohosh, all of them regarded as serious medical cases. A causality assessment found 3 to be possible and the remaining 1 to be probable. The product used in the probable case has been identified, and samples of the actual manufacturer's lot in question have been obtained and analyzed by HPLC–mass spectrometry fingerprinting. That analysis revealed that authentic black cohosh (*A racemosa*) was not present in the product and suggested that an

undeclared *Actaea* sp was used in its place.[48] These findings more than amply illustrate the critical importance of rigorously verifying the identity of raw botanical materials before manufacturing finished products.

In contrast to these adverse event reports, it is noteworthy that all the reported clinical trials and other human studies of black cohosh involved a total of more than 3,000 subjects; of these, about 1,200 were given black cohosh, but only about one-third of those were monitored directly for liver function. Nonetheless, there was not a single report of serious liver problems in any of these trials. There were 2 cases of mildly elevated liver enzymes, but these were judged as clinically insignificant by the investigators. This disparity between clinical studies and general population use may be due to several factors:

- Not all the clinical trials monitored liver function or did not adequately report data on adverse events occurring during trials.
- No serious liver-related illnesses were observed or reported in trials; however, the duration of the trials may have been too short for any deleterious effect on the liver to be manifested or observed.
- The test articles, formulation, and dose were well defined, controlled, and limited to a small number of commercial products.
- Liver damage while taking black cohosh might be caused by other factors, such as alcohol consumption or comedication with other potentially liver toxic drugs, actions that are usually excluded or controlled in clinical trials.
- Liver damage from black cohosh may be idiosyncratic, affecting only a very small percentage of the general population, too small to be detected in a population sampling of only ~3,000 subjects. Calculations of adverse event occurrence rates for black cohosh range from 1 in 14,000 to 1 in 100,000, both well below the accepted background rate of liver disease of unknown etiology, that is, autoimmune hepatitis, ~24 in 100,000 per year.[49]
- Liver damage may be caused by constituents of the wrong plant part or different species of *Actaea*, substituted for *A racemosa* roots and rhizomes in some black cohosh products.

Recommendations

1. There needs to be better compliance by attending healthcare professionals with existing nomenclature guidelines for reporting adverse events, in general (Medical Dictionary for Regulatory Affairs and WHO—Adverse Reactions Terminology), and for adverse events associated with herbal medicines, in particular.[50]
2. Regulatory and monitoring agencies should communicate more closely about adverse event reports on botanicals, sharing all data and analyses in a timely way. Agencies with oversight of phytomedicines, natural health products, and botanical supplements may need to establish the same communications channels that prescription and over-the-counter pharmaceutical oversight agencies have. For example, in the EU, the national authorities regulating herbal medicinal products do communicate through Herbal Medicines Product Committee.
3. Further research should be encouraged in the area of monitoring adverse event reports related to herbal products. Although the NIH has established a network of 5 clinical centers and a data coordinating center to conduct studies over the next 3 years of patients who have suffered severe liver injury because of prescription and over-the-counter medications, nutritional supplements, alternative medicines, and herbals,[51] there remains an urgent need to gather, organize, and investigate instances of suspected adverse events related to botanicals.
4. Additional research on black cohosh should be conducted, with emphasis on

a. clinical benefit and safety;
b. a possible mechanism of liver toxicity and identification of the causal agents in *A racemosa* and/or adulterating species;
c. establishment of appropriate marker compounds for species identification in the genus *Actaea*, where possible;
d. refining and completing HPLC fingerprinting of all *Actaea* species for use in raw material verification and finished product authentication; and
e. mechanism of action studies on black cohosh and its chemical constituents.

5. For clinical trials of black cohosh products,

a. informed consent forms should be standardized to include a note that liver problems have been "possibly" associated with use of products containing black cohosh;
b. monitoring of liver function should be mandatory before, during, and at follow-up of any clinical trials; and
c. a thorough evaluation, for example, a meta-analysis, of liver function data from published studies with black cohosh should be performed.

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Calendar

Obesity Summit 2009

September 9–11, 2009

Cleveland, Ohio
For more information, go to:
http://www.clevelandclinicmeded.com/live/promo/2009/obesity09.asp

3rd International EuroFIR Congress European Food Composition
Data for Better Diet, Nutrition, and Food Quality

September 8–10, 2009

Vienna, Austria
For more information, go to: www.eurofir.net/vienna

World Congress on Fats and Oils and the 28th International Society for Fat Research Congress

September 27–30, 2009

Sydney, Australia
For more information, go to:
http://www.isfsydney2009.com

50th Annual Meeting of the American College of Nutrition

October 1–4, 2009

Lake Buena Vista, Orlando, Florida
For more information, go to:
www.americancollegeofnutrition.org

19th International Congress of Nutrition

October 4–9, 2009

Bangkok, Thailand
For more information, go to: www.icn2009.com/

6th Biennial World Congress on Men's Health and Gender

October 9–11, 2009

Vienna, Austria
For more information, go to: www.wcmh.info

11th Symposium of the International Diabetes Epidemiology Group

October 15–18, 2009

Le Château Frontenac, Québec City, Canada
For more information, go to:
http://www.uchsc.edu/misc/diabetes/IDEG/idegmtgs.html

American Dietetic Association Food and Nutrition Conference

October 17–20, 2009

Denver, Colorado
For more information, go to:
www.eatright.org

American Public Health Association 137th Annual Meeting

November 7–11, 2009

Philadelphia, Pennsylvania
For more information, go to:
www.apha.org/meetings

The First International Vitamin Conference

May 19–21, 2010

Copenhagen, Denmark
For more information, go to: http://www.vitamin2010.dk