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Black Cohosh

By Adriane Fugh-Berman, MD, and Dennis V.C. Awang, PhD, FCIC

BLACK COHOSH [*CIMICIFUGA RACEMOSA* (L.) NUTT., SYN. *ACTAEA racemosa* L.] has become a popular treatment for hot flashes and other menopausal symptoms. A member of the buttercup family (Rananculaceae), black cohosh is a perennial woodlands plant, native to North America, that produces 1-1.5 m racemes bearing numerous small (1 cm) white or cream flowers, with prominent protruding stamens. Other names include black snakeroot, bugbane, bugwort, rattleroot, rattletop, and rattleweed. Insects avoid it, which accounts for some of its common names.

The rhizomes (underground stems) of black cohosh are used medicinally; small amounts of root occasionally survive harvesting. Traditionally used by North American Indians for rheumatism, kidney disorders, and malaise, black cohosh became extremely popular among "Eclectic" practitioners (alternative practitioners of the 19th century), who called black cohosh "macrotys" and prescribed it primarily for gynecological problems, including amenorrhea, menorrhagia, dysmenorrhea, endometritis, infertility, threatened abortion, and labor pains.[1]

Chemistry

Neither the identity of the plant's active constituents nor its precise mode of action is yet known. At least three classes of compounds have been proposed as active principles: triterpene glycosides; organic acids and esters; and flavonoids. Triterpene glycosides include principally the xylosides, actein, 27-deoxyactein,[2] 27-deoxyacetylacteol (these are actually 26-deoxyactein and 26-deoxyacetylacteol),[3] cimicifugoside (cimigoside),[2,4] cimicifugoside M,[2] cimiaceroside A, and others.[5] Eight cimiracemosides (A-H), triterpene arabinosides and xylosides, were isolated from a standardized extract of black cohosh;[6] however, the cineracemoside A of Shao et al is different from that of Bedir and Khan, which appears identical to cineracemoside F.[6] Recently, cimiracemosides I and J have been discovered (NR Farnsworth, personal communication).

The class of organic acids and esters includes the recently identified constituent, fukinolic acid (2E-caffeoylfukiic acid), which has

showed estrogenic activity in vitro in a breast cancer cell line and in vivo (increased uterine weight in rats). Hydroxycinnamic acid esters of fukiic and piscidic acids, cimicifugic acids A, B, E, and F, as well as ferulic, isoferulic, and caffeic acids, also were identified.[7] Salicylic acid also has been reported.[8] Flavonoids also are found in black cohosh. Formononetin, known to be a phytoestrogen, was reported in a methanol extract of the dried rhizome of *C. racemosa*,[9] but a more recent analysis of commercial ethanolic solutions and two extracts prepared from the dried rhizome (a 60% ethanol extract and a 40% isopropanol-water extract) failed to detect the isoflavone, although other flavonoids (unidentified) were claimed to be present.[10] Small amounts of the isoflavone biochanin A also have been identified in *C. racemosa* alcohol preparations.[11] Other black cohosh constituents reported include tannins and 15-20% cimicifugin (macrotin), an amorphous resinous substance, and a bitter principle, racemosin.[12]

Preparations and Dosages

Most clinical studies have been done with a commercial standardized black cohosh preparation, Remifemin®. Each tablet contains 20 mg of black cohosh extract, containing 1 mg triterpenes (calculated as 27-deoxyactein). The current recommended dose is 20 mg twice daily. However, both the formulation and dosage of Remifemin have changed during the past 40 years, so studies done with earlier versions of the product may not be applicable to the current version. Originally sold as a liquid ethanolic extract, the preparation form subsequently was changed to tablets containing an isopropanolic extract. The tablet dosage also has changed from 2 to 20 mg/tablet. Remifemin currently is distributed by GlaxoSmithKline.

Other preparation forms include teas or capsules of dried root/rhizome (commonly 40-200 mg dried root/rhizome/d, but some recommend dosages are as high as 1 g tid); liquid extract (1:2) 1.5-3.0 ml/d, or tincture (1:10, 60% ethyl alcohol) 0.4-2 ml/d; or alcohol extract equivalent to 40 mg root/rhizome/d.[13] A six-month dosing study of black cohosh extract (40 or 127 mg/d) found no difference between the two dosages in improving Kupperman index scores.[14] (The Kupperman index, used in many black cohosh studies, is an older scale of menopausal symptoms that does not include vaginal dryness but does include formication, the sensation of insects crawling under the skin.)

Placebo-Controlled Trials

Few controlled trials of black cohosh exist, and placebo-controlled trials are especially scarce.

A recent randomized, double-blind, placebo-controlled trial in breast cancer survivors age 18 years and older who were experiencing daily hot flashes found no effect of black cohosh on hot flashes but found a significant effect on excessive sweating.[15] Eighty-five women with breast cancer (59 on tamoxifen) took one tablet twice daily of placebo or black cohosh (the preparation is not identified further in the paper) for two months; outcome measures included hot flash frequency and intensity by diary, a menopausal symptom index (including excessive sweating, palpitations, headaches, poor sleep, depression, and irritability), and a visual analog scale of overall health and well-being. Sixty-nine subjects completed the study. The frequency and intensity of hot flashes decreased in both groups, with no significant difference between the groups. Other symptoms assessed improved in both groups; only excessive sweating decreased significantly more in the treatment group than in the placebo group. There was no difference between groups in other symptoms and scores on the global health and well-being scale were not affected in either group.

Two months is a relatively short period of time for a trial of herbs for hot flashes, which are notoriously placebo-responsive. Additionally, hot flashes caused by

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tamoxifen may be more difficult to treat than normal menopausal hot flashes.

Another randomized, double-blind, placebo-controlled trial in 80 menopausal women compared 4 mg Remifemin bid to placebo or 0.625 mg/d conjugated estrogens.[16] At 12 weeks, Kupperman index and Hamilton anxiety (HAM-A) scale scores were significantly lower in both treated groups compared to the placebo group. This is one of the few studies that assessed vaginal epithelium, and also one of the few that assessed hot flashes separately from other symptoms. Vaginal epithelium was significantly improved in the Remifemin group. Daily hot flashes decreased from 4.9 to 0.7 in the Remifemin group; from 5.2 to 3.2 in the estrogen group; and from 5.1 to 3.1 in the placebo group.

Treatment-Controlled Trials

A six-month study in 60 women who had undergone hysterectomy but maintained at least one ovary found black cohosh extract (Remifemin 4 tablets/d) comparable to three estrogen regimens: estriol (1 mg/d), conjugated estrogens (1.25 mg/d), or sequential therapy (estradiol 2 mg and norethisterone acetate 1 mg) on Kupperman index scores at 1, 2, 3, and 6 months.[17]

An open, randomized, three-month-long trial in 60 symptomatic women (80% postmenopausal) compared Remifemin liquid (40 drops bid) to conjugated estrogens (0.625 mg/d) or diazepam (2 mg/d).[18] All treatments improved the Kupperman index, a self-assessed depression scale, and the HAM-A scale.

Hormone Levels

Six months of treatment with 40 or 127 mg/d of Remifemin caused no changes in prolactin, estradiol, sex hormone-binding globulin, luteinizing hormone (LH), or follicle-stimulating hormone (FSH) in one study.[14] Other studies also have found that black cohosh does not affect LH or FSH.[15,17] One trial of 110 menopausal symptomatic women treated with 8 mg Remifemin/d for eight weeks found significantly lower mean LH (but not FSH) levels in the treated group compared with the control group.[19] However, the report does not indicate that baseline levels of hormones were drawn, so it is not clear that groups were comparable at trial initiation.

Vaginal Effects

One placebo-controlled, double-blind trial of black cohosh showed estrogenic changes in vaginal epithelium,[16] but another study of two Remifemin doses (40 or 127 mg/d) found that six months of treatment caused no changes in vaginal epithelium.[14]

Estrogenicity Studies

In vitro and in vivo estrogenicity studies have been mixed. Black cohosh increased uterine weights (an in vivo test of estrogenicity) in two studies of ovariectomized mice;[20,21] a third showed no estrogenic effects in mice given oral doses or rats given subcutaneously injected doses.[22]

A recent test of black cohosh in several in vitro estrogenicity assays showed no estrogenic activity.[23] Although four in vitro cell culture studies found that extracts of black cohosh did not stimulate breast cancer cell growth,[24-27] the most recent study found that black cohosh significantly increased breast cancer cell growth compared with control (the effect was equivalent to 17-beta-estradiol).[20]

A constituent of black cohosh, fukinolic acid, increased growth of MCF-7 breast cancer cells; again, the effect was similar to estradiol.[7]

Risks

Side effects of black cohosh include gastrointestinal discomfort or a frontal headache; nausea, dizziness, and bradycardia also have been attributed to black cohosh.[13]

The effects of black cohosh on endometrial or breast tissue stimulation have not been well delineated. No studies examining the uterine effects of black cohosh in humans have been completed. The recent Jacobson study of black cohosh in breast cancer survivors notes one case of endometrial hyperplasia, another of vaginal bleeding, a hysterectomy, and a D&C among black cohosh-treated women (all of whom also were taking tamoxifen). Certainly vaginal bleeding and endometrial hyperplasia have been associated with tamoxifen use, but no information is provided that would reassure the reader that black cohosh was not a contributor to the adverse event. Additionally, one case of arrhythmia (not otherwise defined, but classed as a "minor" adverse event) was reported in a black cohosh-treated patient who was not taking tamoxifen.

Adverse Birth Outcome

Black cohosh is used by midwives; it may be combined with the unrelated blue cohosh (*Caulophyllum thalictroides*) to prepare for labor or strengthen or restart contractions. There is a case report of neurological complications in a post-date baby after labor induction with a mixture of black cohosh and blue cohosh given during a home birth.[28] After an apparently normal labor, a 3,840 g female was born with no spontaneous breathing; mechanical ventilation was necessary, and hypoxic injury of the basal ganglia and parasagittal area was demonstrated by CT scan. At age 3 months the baby had lower limb spasticity and required nasogastric feeds.

Blue cohosh contains the vasoconstrictive and oxytocic glycoside caulosaponin and is more likely to be associated with this adverse event than black cohosh.

Conclusion

Black cohosh traditionally has not been used for long periods of time, and no published studies have followed women for more than six months. Although short-term use for hot flashes or other menopausal symptoms may be useful, long-term use (more than six months) should be avoided until studies of estrogenic effects in humans are completed. Women with breast cancer should be advised to avoid black cohosh until its effects on breast tissue have been better established. ❖

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Does Vitamin A Cause Birth Defects?

By Anthony R. Scialli, MD

VITAMIN A AND ITS PRECURSORS ARE POPULAR SUPplements, usually taken in the hope of preventing cancer or cardiovascular disease. Preformed vitamin A, retinol (also called vitamin A1 or vitamin A alcohol), is found only in animal products; vegetables and fruits contain provitamin A compounds called carotenoids, the most common of which is beta-carotene. Beta-carotene is cleaved in the liver to retinol. Although excessive ingestion of vitamin A can cause hypervitaminosis, excessive ingestion of dietary or supplemental beta-carotene results in deposition of beta-carotene in skin and other tissues rather than hypervitaminosis A. Vitamin A supplements, however, contain retinyl esters, which are readily converted to retinol. Retinol, whether derived from dietary or supplemental sources, is metabolized to retinal, the form important in vision, and to all-trans retinoic acid (also called retinoic acid). All-trans retinoic acid can isomerize to 13-cis retinoic acid (isotretinoin).

For many years, teratologists have used all-trans retinoic acid as a positive control in experimental animal studies on birth defects, and therapeutic use of isotretinoin (marketed as Accutane) has been associated with spontaneous abortion and a syndrome of birth defects when taken by pregnant women. In experimental animals, retinoids and vitamin A produce structural malformations involving the central nervous system, limbs, and cardiovascular system.[1-6] High-dose vitamin A treatment of pregnant rats produces behavioral abnormalities in offspring.[7] Very high doses of vitamin A are needed to produce developmental abnormalities; for example, in monkey experiments, doses of 20,000 IU/kg were required to produce an effect.[8] The comparable weight-adjusted dose in a pregnant woman would be 1.2 million IU, about 400 times the RDA.

Case reports document an association between high-dose supplemental vitamin A use by pregnant women and developmental abnormalities of the offspring.[5,9-14] Urinary tract anomalies (hydroureter) were seen with daily maternal ingestion of 25,000 and 40,000 IU of vitamin A[9,11] and central nervous system defects were seen with daily doses of 150,000 IU.[5,14] Malformations involving the face, palate, heart, and ears have been reported with maternal vitamin A ingestion in doses of 25,000 IU/d and more.[15,16] These abnormalities are similar to those reported after use of isotretinoin.

Mechanism of Action

The mechanism of abnormal embryo development with retinoid treatment is well characterized. As the neural folds elevate and fuse to form the neural tube, a separate population of cells just lateral to the folding tube, the neural crest cells, emerge and then migrate to positions elsewhere in the embryo, where they add to mesenchymal tissues. Neural crest cells contribute to some bony and connective tissue elements of the face, melanocytes, adrenal medulla, spinal and autonomic ganglia, and conotruncal portions of the heart. The abnormalities characteristic of isotretinoin embryopathy can be attributed to abnormal migration of neural crest cells of the cranial region of the embryo, and inhibition of neural crest cell migration has been documented in vitro and in experimental animals with retinoid exposure.

Clinical Studies

Epidemiologic studies have evaluated the association between cranial neural crest-related abnormalities in children and vitamin A intake during pregnancy. A widely reported study by Rothman et al in 1995 evaluated more than 22,000 women for vitamin A intake from food and supplements during pregnancy.[17] When maternal intake was estimated at greater than 10,000 IU/d, an increased prevalence of congenital anomalies was identified in infants. The prevalence ratio for all birth defects in the group exposed to more than 10,000 IU/d compared to the group exposed to 5000 IU/d or less was 2.4 (95% confidence interval [CI] 1.3-4.4). For the group of anomalies associated with abnormal craniofacial and cardiac development, the prevalence ratio was 4.8 (95% CI 2.2-10.5). A computer-smoothed curve fit to data from this study was consistent with a threshold for increased risk of congenital anomalies at 10,000 IU/d. The authors estimated from their data that pregnant women who ingest this amount of vitamin A have a 1-2% chance of having a baby with a birth defect attributable to the vitamin.

This study was criticized because some malformations attributed to abnormalities of cranial neural crest cell origin did not involve cranial neural crest-derived

structures. In addition, diverse single malformations identified among the offspring of the few women with high-dose exposure raise the possibility that the findings of the study were due to clustering, and that there is no actual causal relationship between lower doses of vitamin A and congenital malformations. In other words, a few babies exposed to high doses may have malformations by chance alone, but end up artifactually creating the high end of a presumed dose-response curve. The extrapolation of risk with low doses (in the range of 10,000 IU/d) is based on a dose-response curve that may have been unduly influenced by the clustering effect at high doses.[15,18]

Other epidemiological studies have failed to confirm the conclusions of the Rothman paper with regard to cranial neural crest-related abnormalities or, in one study, neural tube defects.[19-23] Supplement use by women in these studies typically involved vitamin A doses near 10,000 IU, although some exposures to higher doses were included. Dietary sources of vitamin A were not assessed and would be expected to add to the vitamin A intake of the women.

Perhaps the most important negative study, published by the European Network of Teratology Information, evaluated pregnancy outcome among women who called a Teratology Information Service with a concern about vitamin A ingestion of 10,000 IU/d or more prior to nine weeks of pregnancy; 394 of the women were followed for outcome information.[24] There was no increase in the incidence of congenital malformations among the 311 pregnancies evaluable for birth defects, compared to the offspring of 116 women who took vitamin A supplements after nine weeks of pregnancy or 679 women who had contacted the information service about an unrelated exposure judged not to be a pregnancy risk. Among 120 women who used more than 50,000 IU/d during early pregnancy, no congenital malformations were identified among their offspring.

A more recent study resurrects the question of whether supplementation at about 10,000 IU/d increases pregnancy risk. The Baltimore-Washington Heart Study, a large case-control study of possible risk factors associated with congenital heart disease, administered questionnaires to mothers of children with heart disease and a matched sample of children without birth defects.[25] The questionnaires involved many possible exposures and other risk factors, leaving open the likelihood that many associations could be identified by chance.

In spite of the multiple comparison problem, the vitamin A analysis may be more reliable, because it was based on an a priori hypothesis that makes biologic sense. The comparison made in this study was between mothers of children with two kinds of cardiac outflow tract abnormalities: those involving transposition of the great vessels, and those involving normal great vessels. Why would this difference be important? The great vessels, the aorta, and the pulmonary artery arise from the growth of a septum in the truncus arteriosis. This septum arises from conotruncal swellings, which receive a contribution from the neural crest. Thus, the distinction in this study may be between neural crest-related and neural crest-unrelated cardiac outflow tract abnormalities.

Vitamin A intake in the Baltimore-Washington Heart Study was evaluated by reported maternal food preferences for the year prior to conception. Supplement use also was recorded. The study found that intake of 10,000 IU/d from supplements, but not from food, was associated with an odds ratio of 9.2 (95% CI 4.0-21.2) with respect to cardiac outflow tract defects that included transposition of the great vessels. There was no significant association between vitamin A intake and outflow tract defects with normal great vessels. The lack of relationship of high intake of vitamin A from food is curious, and may have been due to errors from the use of food preference recall for the year prior to pregnancy. After all, dietary preferences may change during pregnancy, a fact acknowledged by the authors. Vitamin A from food may be less bioavailable than vitamin A from supplements; serum retinol levels have been shown to be increased more by ingestion of a supplement than by ingestion of liver with comparable vitamin A content.[26]

Conclusion

So how much vitamin A is safe? Prior to the Rothman study, it was believed, based on case reports, that women who were pregnant or might become pregnant should consume less than 25,000 IU/d.[5] Since the Rothman study, recommended vitamin A limits have decreased to less than 10,000 IU/d. Two small epidemiologic studies support the conclusion that less than 10,000 IU/d of vitamin A is not teratogenic.[27,28] In 1987, the Teratology Society recommended that the intake of supplemental vitamin A during pregnancy not exceed the RDA of 8,000 IU/d.[16] Since that time, the RDA has been lowered to 800 mcg/d of retinol (about 2,700 IU/d).[29] Manufacturers of prenatal vitamins have decreased the vitamin A content from 8,000 to 5,000 IU per dose and many have replaced some or all of the retinyl esters with beta-carotene. The evidence for an adverse effect of supplemental vitamin A in doses less than 10,000 IU is weak, but there is no reason to use high-dose supplementation during pregnancy.

Some nutritional advice, however, may be warranted too. An average portion of liver contains between four

and 12 times the RDA for vitamin A, and one nutritionist has suggested that the intake of liver and liver products (some sausages and patés) be limited to about 100 g (4 oz) per week during pregnancy.[30] The U.K. Department of Health has recommended that liver consumption be avoided entirely in early pregnancy.[31,32] Liver is an excellent source of nutrients (including B vitamins, iron, and vitamin D), and the bioavailability of vitamin A from liver may be less than that from supplements. There is concern that the U.K. warning might lead some women to avoid vitamin A-containing foods and thereby risk vitamin A deficiency during pregnancy.[32]

Alternative sources of retinol are full-fat dairy foods, egg yolks, and fatty fish (including herring, sardines, anchovies, salmon, mackerel, and bluefish). Other strategies include deriving most nutritional vitamin A from carotenoids in vegetables, and avoiding vitamin A supplements altogether.

Conflict of Interest Statement: *In the year after the Rothman study appeared, I was recruited by Hoffman-LaRoche, a manufacturer of vitamin A, to serve on a panel charged with considering the experimental and epidemiology data on the developmental effects of supplements. The meeting was held in Boston and included tickets to an absolutely superb performance by the Boston Symphony. Although this experience may be interpreted as having produced a biased point of view, as of this writing, Hoffman-LaRoche has not paid the honorarium that was promised, producing at least as strong a potential bias in the opposite direction, the Boston Symphony notwithstanding.* ❖

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CME Questions

19. In vitro, black cohosh:
a. stimulates growth of breast cancer cells.
b. has no effect on breast cancer cells.
c. has demonstrated mixed results on growth of breast cancer cells.

20. A recent study of black cohosh in breast cancer survivors found:
a. no effect on hot flashes.
b. beneficial effect on hot flashes.

21. Maternal ingestion of megadoses of vitamin A has been associated with which of the following birth defects?
a. Hydroureter
b. Central nervous system defects
c. Malformation of the face, palate, heart, and ears
d. All of the above

22. Vitamin A appears to be more bioavailable from:
a. dietary supplements.
b. food.

Clinical Abstracts

With Comments by Adriane Fugh-Berman, MD

Heat Helps Cramps

Source: Akin MD, et al. Continuous low-level topical heat in the treatment of dysmenorrhea. *Ob Gyn* 2001;97:43-49.

Design and Setting: A randomized placebo-controlled parallel-group study in four groups (apparently a 2x2 design).

Subjects: This study included 84 women (81 completed) with moderate or severe menstrual pain.

Treatment Dose/Route/Duration: Women were assigned to an active or placebo device plus an active or placebo oral medication. The active device treatment was a kidney bean-shaped thin, heated, disposable medical device that adheres to the inside of the underwear in the pelvic region and supplies heat at a constant temperature of 38.9° C over 180 cm^2 for 12 hours. The placebo device was an unheated patch. Patches were worn for 12 hours/d for two consecutive days. Active oral medication consisted of ibuprofen (400 mg tid) for two days.

Outcome Measures: Reduction in pain intensity score was calculated by taking differences from the patients' baseline scores. Reduction in pain intensity score was measured by analysis of covariance procedures; pain relief scores were obtained by one-way analysis of variance. Overall means were analyzed by nonparametric one-way analysis of variance methods using Cochran-Mantel-Haenszel tests for pain-intensity reduction and Wilcoxon rank-sum tests for pain-intensity relief.

Results: All three treated groups had significantly greater pain relief than the double-placebo group; the heated patch with ibuprofen was not more effective than ibuprofen alone. The time to pain relief was significantly shorter for the combination of heated patch and ibuprofen (median 1.5 hours) compared to unheated patch plus ibuprofen (median 2.79 hours).

Complete relief during the study was achieved by 35% of the double-placebo group; 68% in the double-active (heated patch plus ibuprofen) group; 70% in the group treated with heated patch plus placebo; and 55% in the group receiving unheated patch plus ibuprofen. Compared to double placebo, there was a significant benefit for both groups receiving the heated patch but not the ibuprofen-only group. Two patients in the heated patch group and one in the unheated patch group reported skin redness. Skin pinkness after 12 hours was reported by 42.5% (17/40) of patients in the heated patch group compared to 12.2% (5/41) of subjects in the placebo patch group (a significant difference). Skin color normalized by the next morning in all but two patients. All patients reported normal skin color at the final interview (day 3-7).

Funding: Procter & Gamble supplied study devices and materials. The first author is a contractual employee of Health Quest Therapy and Research Institute; four of five of the remaining authors are employees of Procter & Gamble.

Comments: Science validates a home remedy! Hot water bottles and heating pads are common home treatments for dysmenorrhea, but I've never seen a study on heat treatment of cramps until this one. Clearly the company that funded the study is preparing to market this disposable heat-generating device. It sounds like a good idea; the patch definitely sounds preferable to toting a hot water bottle to a business meeting. It is stated that the device is expected to cost about $3 per heat patch. A hot water bottle or heating pad, of course, would be cheaper.

This may be the first menses-related product that men might borrow—a discreet source of warmth to treat an aching back or shoulder may well cross gender lines. ❖