Cohosh, Black

Species (Family)

Cimicifuga racemosa Nutt. (Ranunculaceae)

Synonym(s)

Actaea Racemosa Radix, Black Snakeroot, Cimicifuga, Macrotys Actaea

Part(s) Used

Rhizome, root

Pharmacopoeial and Other Monographs

BHC 1992[G6]
BHP 1996[G9]
BPC 1934[G10]
Complete German Commission E[G3]
Martindale 32nd edition[G43]
Mills and Bone[G50]
PDR for Herbal Medicines 2nd edition[G36]

Legal Category (Licensed Products)

GSL[G37]

Constituents[1,G6,G22,G41,G64]

Alkaloids Quinolizidine-type. *N*-Methylcytisine and other unidentified compounds.

Tannins Type unspecified. Tannic and gallic acids are usually associated with hydrolysable tannins.

Terpenoids Triterpene glycosides, principally the xylosides actein (aglycone: acetylacteol) and cimicifugoside (also known as cimigoside; aglycone: cimigenol),[2–8,G6] also 26-deoxycimicifugoside, cimiaceroside A, 27-deoxyactein),[9,10] cimiracemosides A–H,[9–11] and cimicifugosides H-3, H-4 and H-6.[12]

Other constituents Acetic acid, butyric acid, formic acid, hydroxycinnamic acid esters of fukiic and piscidic acids (fukinolic acid, cimicifugic acids A, B, E, F), caffeic acid, ferulic acid,[13] isoferulic acid, oleic acid, palmitic acid, salicylic acid, racemosin, formononetin,[3] phytosterols, cimicifugin 15–20%, acteina (resinous mixture) and volatile oil.

Food Use

In the USA, black cohosh is listed by the Food and Drugs Administration (FDA) as a 'Herb of Undefined Safety'.[G22] Black cohosh is not used in foods.

Herbal Use

Black cohosh is stated to possess antirheumatic, antitussive, sedative and emmenagogue properties. It has been used for intercostal myalgia, sciatica, whooping cough, chorea, tinnitus, dysmenorrhoea, uterine colic, and specifically for muscular rheumatism and rheumatoid arthritis.[G6,G7,G8,G32,G64] Modern use of black cohosh is focused on its use in treating peri- and postmenopausal symptoms.[1,14,G50]

Dosage

Dried rhizome/root 40–200 mg daily.[G6]

Liquid extract Ethanolic extracts equivalent to 40 mg dried rhizome/root daily.[G3,G50]

Tincture 0.4–2 mL (1 : 10 in 60% ethanol) daily.[G6]

Several clinical trials of black cohosh have used a standardised black cohosh extract (Remifemin; each 20 mg tablet contained 1 mg triterpene glycosides, calculated as 27-deoxyactein) 40 mg twice daily for up to 24 weeks.[15–17]

Pharmacological Actions

Several pharmacological activities, including hormonal, cardiovascular, circulatory and anti-inflammatory activities, have been documented for black cohosh and/or its constituents. The triterpene glycosides and flavonoids are considered to be the active components of black cohosh.[18,G56]

In vitro and animal studies

Hormonal activity A methanolic extract of the rhizome of black cohosh reduced the serum concentration of luteinising hormone (LH) in ovariectomised rats, and exhibited a binding affinity to oestrogen receptors in isolated rat uterus.[2] *In vivo*, the activity of the methanolic extract was significantly reduced following enzymatic hydrolysis of glucosides present.

Subsequent *in vitro* studies isolated three compounds with endocrine activity, including an isoflavone, formononetin. Formononetin was found to exhibit competitive oestrogen receptor activity, but did not cause a reduction in serum concentrations of LH.[2] Recent research found that formonenetin could not be detected in commercial preparations of black cohosh, although other flavonoids were present.[19]

In ovariectomised rats, administration of a lipophilic extract of black cohosh (140 mg by intraperitoneal injection for three days) led to a significant reduction in serum LH concentrations, compared with control ($p < 0.01$), whereas no effect was observed with a hydrophilic extract (216 mg intraperitoneally for three days).[16] Subsequent studies using fractions of the lipophilic extract demonstrated that constituents inhibited LH secretion and/or exhibited activity in an oestrogen receptor-binding assay.

In an *in vitro* study in oestrogen receptor-positive breast cancer cells, black cohosh extract did not stimulate cancer cell growth, i.e. it did not exhibit oestrogen-like effects, but at a concentration of 2.5 µg/mL led to a marked inhibition of breast cancer cell proliferation.[20]

Oestrogenic activity has been documented *in vitro* for fukinolic acid, a hydroxycinnamic acid ester of fukiic acid, in oestrogen-dependent MCF-7 cells (a breast cancer cell line).[13] Fukinolic acid at concentrations of 5×10^{-7} mol/L and 5×10^{-8} mol/L led to significantly increased cell proliferation (mean (standard deviation): +120 (6%) and +126 (5%), respectively), compared with control. These effects were reported to be equivalent to those of oestradiol at 10^{-10} mol/L. By contrast, in other *in vitro* studies, a methanol extract of black cohosh rhizomes and roots did not demonstrate oestrogenic activity in several assays, including binding affinity for oestrogen receptors α and β, stimulation of pS2 mRNA expression in S30 cells (S30 is a subclone of an oestrogen receptor-negative breast cancer cell line), and induction of alkaline phosphatase in an oestrogen receptor-positive endometrial adenocarcinoma cell line.[21]

Other activities Anti-inflammatory and analgesic activity for constituents of black cohosh has been documented following *in vitro* and *in vivo* studies (mice and rats).

In vitro, caffeic acid, fukinolic acid and cimicifugic acids A, B, E and F inhibited the activity of neutrophil elastase in a concentration-dependent manner.[22] (Raised plasma concentrations of neutrophil elastase are a typical feature of active inflammation. Neutrophil elastase contributes to the destruction of basement membranes during inflammation.) Caffeic acid inhibited the enzyme with an IC_{50} of 16 µg/mL (93 µmol/L), whereas fukinolic acid had an IC_{50} of 0.1 µg/mL (0.23 µmol/L), relative to controls. Of the cimicifugic acids, A and B were the strongest inhibitors of the enzyme, with IC_{50} values of 2.2 µmol/L and 11.4 µmol/L, respectively.

Compared with controls, a methanol extract, a butanol-soluble fraction and a water-soluble fraction obtained from *Cimicifuga* rhizome inhibited carrageenan-induced rat paw oedema by 73–76%, 80–84% and 46–54%, respectively, compared with controls, 30–120 minutes after injection of 0.1 mL carrageenan 1%.[23] The same fractions (100 mg/kg by intraperitoneal injection), compared with controls, demonstrated analgesic activity determined by significant reductions in acetic acid-induced writhing in mice, and the methanol extract and butanol-soluble fraction also displayed analgesic activity in a tail-flick test (demonstrated by increased latency time upon infrared light exposure). All three fractions (40 µg/mL) inhibited bradykinin and histamine receptor-mediated contractions of guinea-pig ileum, and all inhibited lipopolysaccharide-induced 6-keto prostaglandin $F_{1\alpha}$ ($PGF_{1\alpha}$) formation in macrophages. Incubation of macrophages with lipopolysaccharide and the water-soluble fraction 10 µg/mL almost completely blocked (99% inhibition) lipopolysaccharide-induced 6-keto-$PGF_{1\alpha}$ formation. Lipopolysaccharide-induced 6-keto-$PGF_{1\alpha}$ formation in macrophages is related to selective expression of cyclooxygenase
2 (COX-2). The inhibitory effects of fractions of *Cimicifuga* rhizome in this model, and their inhibitory effects on bradykinin and histamine receptor-mediated reactions are possible mechanisms for the observed anti-inflammatory and analgesic activities.

In vitro studies using rat aortic strips have investigated the vasoactive effects of constituents of *Cimicifuga* species.[24] Cimicifugic acid D and fukinolic acid (3×10^{-4} mol/L) caused a sustained relaxation of aortic strips precontracted with noradrenaline (norepinephrine) in preparations with or without endothelium. By contrast, cimicifugic acid C inversely caused a weak contraction, and fukiic acid and cimicifugic acids A, B and E showed no vasoactivity at the concentration tested.

A resinous component, termed acteina, has exhibited a hypotensive action in both unanaesthetised rabbits and anaesthetised cats. The effect in unanaesthetised dogs was found to be inconsistent.[25] An effective dose of acteina 1 mg/kg body weight was recorded, with maximum hypotension attained using 10 mg/kg. It was stated that acteina may act by an effect on the vasomotor centres.

Triterpene compounds in black cohosh have been shown to possess hypocholesterolaemic activity *in vivo*, and an inhibitory effect on phytohaemagglutin-induced proliferative response *in vitro*. These activities were thought to be linked to molecular characteristics between the identified triterpenes and intermediates in cholesterol biosynthesis.[26]

Triterpenoid constituents from several *Cimicifuga* species, including actein from *C. racemosa*, have been investigated for antimalarial activity against *Plasmodium falciparum in vitro*.[27] Cimicifugoside (isolated from *C. simplex*) and actein were among the compounds with potent antimalarial activity (EC_{50} 5.0 µmol/L and 10.0 µmol/L, respectively), although activity was 2- to 3-fold less than that of positive controls (quinine, chloroquine and pyrimethamine).

The root of a related species, *Cimicifuga dahurica*, has been reported to exhibit antibacterial activity towards Gram-positive (*Bacillus subtilis*, *Mycobacterium smegmatis*, *Staphylococcus aureus*), and Gram-negative (*Escherichia coli*, *Shigella flexneri*, *Shigella sonnei*) organisms.[28]

In ovariectomised rats, ethyl acetate-soluble fractions from the rhizome of the related species *Cimicifuga heracleifolia* and *C. foetida* administered orally at doses of 100 mg/kg/day for 42 days led to a significant increase in bone mineral density of the lumbar spine, compared with that in untreated ovariectomised control rats.[29]

Clinical studies

Clinical trials of extracts of black cohosh have investigated mainly its effects in women with peri- and/or postmenopausal symptoms.

Menopausal symptoms In a randomised, double-blind, placebo-controlled trial, 80 women (mean (standard deviation) age: 51.2 (3.1) years) with menopausal symptoms received standardised black cohosh extract (Remifemin; each 20-mg tablet contained 1 mg triterpene glycosides, calculated as 27-deoxyactein) 40 mg twice daily, conjugated oestrogens 0.625mg daily, or placebo, for 12 weeks.[15] At the end of the study, somatic and psychological symptoms, measured by the Kupperman Menopausal Index and the Hamilton Anxiety Scale, had improved significantly only in women who received black cohosh, compared with those who received oestrogen or placebo. Similarly, a significant increase in proliferation of vaginal epithelium was noted only in the black cohosh group. However, there is a view that the dose of oestrogen used in the study was too low to provide a useful comparison.

A randomised, double-blind, placebo-controlled trial involving 85 women with a history of breast cancer assessed the effects of black cohosh (no details of extract provided) one tablet twice daily for 60 days on the frequency and intensity of hot flushes.[30] Participants were stratified according to whether or not they were using tamoxifen. Both treatment and placebo groups reported decreases in the number and intensity of hot flushes, compared with baseline values. There were no statistically significant differences between the two groups, and subgroup analysis of tamoxifen users and non-users did not reveal any statistically significant differences. Changes in other parameters measured during the study (other menopausal symptoms, serum concentrations of follicle-stimulating hormone (FSH) and luteinising hormone (LH)) were also not statistically significant between groups.

In a placebo-controlled study involving 110 women with menopausal symptoms, black cohosh extract (Remifemin) two tablets daily for two months significantly reduced serum LH concentrations, compared with placebo ($p < 0.05$).[16] There was no significant difference between the two groups with respect to serum FSH concentrations.

Most other studies of black cohosh involving women with menopausal symptoms have an open and/or uncontrolled design and, therefore, do not provide an unbiased assessment of efficacy. Generally, these studies report significant improvements in menopausal symptoms, compared with baseline values, after at least four weeks' treatment. Some studies involved administration of black cohosh extract for up to 12 weeks. These studies have been summarised elsewhere.[1,18,G50] Details of two of these studies are provided below.

In an open study, 60 women with at least one intact ovary who had undergone hysterectomy and who were experiencing menopausal symptoms were randomised to receive oestriol (1 mg daily), conjugated oestrogens (1.25 mg daily), oestrogen–progestagen sequential therapy (dose not specified), or black cohosh extract (Remifemin) 40 mg twice daily, for 24 weeks.[17] At the end of the study, improvements in Kupperman Index scores were significantly lower, compared with baseline values, in all groups. There were no statistically significant differences between groups.

Another open, controlled study involving women with menopausal symptoms ($n = 60$) assessed the effects of black cohosh extract administered as a tincture (80 drops daily), compared with oestrogen (0.625 mg daily) or diazepam (2 mg daily), over a 12-week period.[31] Cytological responses (proliferation and maturation of vaginal epithelial cells) were

observed for participants in the black cohosh and oestrogen groups, but not in the diazepam group. For all three groups, improvements in neurovegetative and psychological symptoms (e.g. self-assessed depression) were reported.

Other conditions Black cohosh has been reported to cause peripheral vasodilatation and an increase in peripheral blood flow, following the administration of a resinous constituent, acteina (500 µg/kg body weight), to patients suffering from peripheral arterial disease.[25] The blood pressure of conscious individuals, both normotensive and hypertensive, was stated to be unaffected. The chemical composition of acteina is undefined.

In a randomised, double-blind trial, 82 patients with osteoarthritis or rheumatoid arthritis received a proprietary combination herbal preparation containing black cohosh 35 mg (other ingredients: white willow bark, guaiacum resin, sarsaparilla and poplar bark; Reumalex), or placebo, two tablets daily for two months.[32] At the end of the study, there was a small, but statistically significant improvement in pain symptoms (as assessed by the Arthritis Pain Scale) in the treatment group, compared with the placebo group ($p < 0.05$).

Side-effects, Toxicity

A review of the literature on black cohosh[18] describes a postmarketing surveillance study involving 629 women with menopausal symptoms who received standardised black cohosh extract as a tincture (80 drops daily) for 6–8 weeks.[33] Tolerability was rated as 'good' in 93% of patients; mild, transient gastrointestinal symptoms were noted in 7% of patients.

A randomised, double-blind, placebo-controlled trial involving 80 women with menopausal symptoms who received standardised black cohosh extract (Remifemin) 40 mg twice daily, conjugated oestrogens, or placebo, for 12 weeks reported that non-specific adverse events, such as headaches, not considered treatment-related occurred in all three groups.[15] Another controlled trial ($n = 60$) of the same extract reported that tolerability of black cohosh extract was 'good'.[17] In a randomised, double-blind trial involving 85 women with a history of breast cancer who received black cohosh (no details of extract provided) one tablet twice daily, or placebo, for 60 days, 10 adverse events occurred in the treatment group, compared with three in the placebo group.[30] Three events were considered serious (treatment group: hysterectomy, recurrence of breast cancer; placebo group: appendectomy) all of which occurred in women who were also receiving tamoxifen. Minor adverse events (including constipation, weight gain, cramping, indigestion, vaginal bleeding) were not thought to be treatment related.

Older reference texts state that overdose may produce symptoms of nausea, vomiting, dizziness, visual and nervous disturbances, together with reduced pulse rate and increased perspiration.[G22,G42,G49]

Contra-indications, Warnings

In vitro studies investigating the oestrogenic activity of extracts of black cohosh and their constituents report conflicting results (*see In vitro* and animal studies, Hormonal activity). Some studies have documented that certain constituents of black cohosh bind to oestrogen receptors,[2,16] and others have reported oestrogenic activity *in vitro* for fukinolic acid, a hydroxycinnamic acid ester of fukiic acid, in an oestrogen receptor-positive breast cancer cell line (MCF-7 cells).[13] These findings contrast with those of a previous *in vitro* study in oestrogen receptor-positive breast cancer cells, which reported that black cohosh extract did not stimulate cancer cell growth, i.e. it did not exhibit oestrogen-like effects, but at a concentration of 2.5 µg/mL led to a marked inhibition of breast cancer cell proliferation.[20]

There is a view that the therapeutic effects of black cohosh extract are not attributable to oestrogenic effects, and that there is clinical evidence, such as lack of vaginal cell proliferation, as well as *in vitro* evidence to support this view.[18] The German Commission E monograph states that there are no known contraindications to the use of black cohosh. Concern has been expressed that herbs with oestrogenic activity might stimulate breast cancer cell growth and oppose the effects of competitive oestrogen receptor antagonists, such as tamoxifen.[34] A randomised, double-blind, placebo-controlled trial involving 85 women with a history of breast cancer assessed the effects of black cohosh (no details of extract provided) on hot flushes (*see* Clinical studies, Menopausal symptoms).[30] Participants were stratified according to whether or not they were using tamoxifen. One woman receiving both black cohosh and tamoxifen experienced a recurrence of breast cancer, although it was reported that the woman had an increase in carcinoembryonic antigen when she entered the trial (this had not been reported to the referring physician).

Further study is required to establish whether black cohosh has oestrogenic activity. Herbal medicines with oestrogenic activity should be avoided in

women with oestrogen-dependent tumours, such as breast cancer.[G50]

Pregnancy and lactation *In vitro* studies using rat uterus have indicated that black cohosh binds to uterine oestrogen receptors. Black cohosh has been used traditionally to assist labour. However, as there are insufficient data on the use of black cohosh during pregnancy and also during lactation, it is contra-indicated during these periods.[G49,G50,G56]

There is an isolated report of a child born with no spontaneous breathing and who subsequently experienced brain hypoxia and seizures following the oral administration of black cohosh and blue cohosh by a midwife in an attempt to induce labour in a woman who had had an uneventful pregnancy.[35] The report has been criticised as it did not provide any further details of the dose or formulation of the herbs, and as the authors of the report make several assumptions about the clinical activity of the herbs on the basis of studies in animals.[36]

Pharmaceutical Comment

The chemistry of black cohosh is well studied, although most of the documented information concerns the triterpene constituents. Most of the reputed traditional uses of black cohosh are not supported by data from experimental or clinical studies. One exception is the use of black cohosh in rheumatism and rheumatoid arthritis – there are data from *in vitro* and *in vivo* studies in rodents which indicate that black cohosh extracts have anti-inflammatory activity.[22,23] Other pharmacological actions have been observed in both animals and humans which provide supporting data for the hormonal activity of the herb. However, there are conflicting reports on the oestrogenic activity of black cohosh. As it is known that there are at least two types of oestrogen receptor, there is a view that research relating to the oestrogenic effects of black cohosh needs to be considered against this background.[1]

Little is known about the toxicity of black cohosh and excessive use should be avoided. It has been stated that the duration of use should not exceed three months.[G56] Further study is required to determine whether black cohosh has oestrogenic activity before definitive statements about its use in women with oestrogen-dependent tumours can be made.

There is evidence from one published, randomised clinical trial to indicate that black cohosh extract is more effective than placebo in the treatment of menopausal symptoms. However, another randomised clinical trial involving women with a history of breast cancer who were experiencing menopausal symptoms found no effect for an unspecified black cohosh extract on the frequency and intensity of hot flushes. There are supporting data for the effects of black cohosh extracts on menopausal symptoms from open, uncontrolled studies and from postmarketing surveillance studies that assessed effectiveness as well as safety. However, further randomised clinical trials are required to establish the effects of black cohosh in women with menopausal symptoms. There is also a lack of information on the toxicity of black cohosh.

References

See also General References G3, G5, G6, G9, G22, G31, G32, G36, G41, G42, G43, G49, G50, G56 and G64.

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Cohosh, Blue

Species (Family)

Caulophyllum thalictroides (L.) Mich. (Berberidaceae)

Synonym(s)

Caulophyllum, Papoose Root, Squaw Root

Part(s) Used

Rhizome, root

Pharmacopoeial and Other Monographs

BHP 1983[G7]
PDR for Herbal Medicines 2nd edition[G36]

Legal Category (Licensed Products)

GSL[G37]

Constituents[G22,G41,G48,G64]

Alkaloids Quinolizidine and isoquinoline-types. Anagyrine, baptifoline, magnoflorine, methylcytisine (caulophylline). Other unidentified minor tertiary alkaloids.[1]

Saponins Caulosaponin and cauloside D yielding hederagenin on hydrolysis.[2]

Other constituents Citrullol, gum, resins, phosphoric acid, phytosterol and starch.

Other Caulophyllum species A related species, *C. robustum* Maxim., is rich in triterpene glycosides (caulosides A–G), most of which possess hederagenin as their aglycone.

Food Use

Blue cohosh is not used in foods.

Herbal Use

Blue cohosh is stated to possess antispasmodic, emmenagogue, uterine tonic and antirheumatic properties. Traditionally, it has been used for amenorrhoea, threatened miscarriage, false labour pains, dysmenorrhoea, rheumatic pains, and specifically for conditions associated with uterine atony.[G7,G64]

Dosage

Dried rhizome/root 0.3–1.0 g or by decoction three times daily.[G7]

Liquid extract 0.5–1.0 mL (1:1 in 70% alcohol) three times daily.[G7]

Pharmacological Actions

In vitro and animal studies

A blue cohosh extract exhibited stimulant properties on the isolated guinea-pig uterus, although subsequent *in vivo* studies in cats, dogs and rabbits demonstrated no uterine activity.[3] Antifertility actions documented in rats were reported to be caused by inhibition of ovulation[4] and by interruption of implantation.[5]

Smooth muscle stimulation has been documented for a crystalline glycoside constituent on the uterus (*in vitro*), the small intestine (*in vitro*), and the coronary blood vessels (*in vivo*) of various small mammals.[6] The glycoside was also reported to cause erythrolysis and to be of an irritant nature. An earlier study that used a crystalline glycoside identified as caulosaponin, reported a variety of actions including an oxytocic effect on the isolated rat uterus, constriction of coronary and carotid blood vessels, a toxic action on cardiac muscle, and a spasmogenic action on the isolated intestine.[6]

Methylcytisine is stated to have a nicotinic-like action, causing an elevation in blood pressure and stimulating both respiration and intestinal motility.[G60]

An alcoholic extract of the aerial parts of blue cohosh produced up to 55% inhibition of inflammation in the carrageenan rat paw test[7].

Side-effects, Toxicity

Powdered blue cohosh is stated to be irritant, especially to mucous membranes.[G51] The leaves and seeds are reported to contain methylcytisine and some glycosides that can cause severe stomach pains. Children have been poisoned by eating the bright blue bitter-tasting seeds.[G22] Caulosaponin is

reported to be cardiotoxic, causing constriction of coronary blood vessels, to produce intestinal spasms, and to possess oxytocic properties.[G60]

Contra-indications, Warnings

Blue cohosh may interfere with existing therapy for angina, and may irritate gastrointestinal conditions. Excessive doses may cause a rise in blood pressure, because of the methylcytisine constituent and give rise to other symptoms of nicotine poisoning.

Pregnancy and lactation Blue cohosh should not be taken in pregnancy; it is reputed to be an abortifacient and to affect the menstrual cycle.[G30] Some texts give conflicting advice. It has been documented that blue cohosh should be avoided by pregnant women,[G22] only be taken once labour has commenced,[G49] only taken in small doses during the first trimester of pregnancy,[G7] or only be used under expert supervision.[G42]

Pharmaceutical Comment

Limited data are available on the chemistry of blue cohosh. Documented pharmacological actions support some of the reputed traditional uses, although many of these are not suitable indications for self-medication. No evidence regarding antirheumatic properties was located, although anti-inflammatory action has been documented for the aerial plant parts. In view of the potential toxicity associated with blue cohosh, it should be used with caution.

References

See also General References G7, G10, G20, G22, G30, G31, G32, G36, G37, G41, G42, G48, G49, G51, G60 and G64.

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