Black Cohosh – *Actaea racemosa* L.

1. **Taxonomy**

*Actaea racemosa* L.

Family: Ranunculaceae (buttercup family)

Common names: Black cohosh, black snakeroot, tall bugbane, macrotys, battleweed, columbine-leaved leontice, cordate rattle top, false cohosh, papoose root. It has been called ‘squaw root’ though that name is normally reserved for blue cohosh (*Caulophyllum thalictroides* (L.) Michx.) (Lloyd & Lloyd, 1931).


2. **Botany and distribution**

*A. racemosa*, a perennial herb rising from a smooth erect stem, can attain a height of eight feet when in flower. The leaves are compound tripinnate and deeply toothed with a glossy dark green appearance – often only one compound leaf per plant. Flowers are feathery white in an elongated raceme that extends up to two feet, occurring through the summer. White petal-like sepals die back to reveal a ring of numerous creamy-white stamens with long slender filaments and white anthers, enclosing solitary pistils with broad stigmas and single ovary. The flowers are notable not only for their dramatic appearance but also for their bitter-sweet smell, which acts as an attractor to carrion eating pollinating flies (Blanchan, 1904). The fruit consist of oval-shaped follicles, the angular seeds arranged in two rows. The rootstock consists of a thick branching black rhizome, marked with scars, covered with a mass of rootlets.

The species is distinguished from the white baneberry (*A. alba* (L.) Mill.) whose flowers are arranged in short clusters, and the red baneberry (*A. spicata var. rubra* Aiton) which has less pointed leaves and distinctly rigid clusters of red berries. *A. racemosa* can easily be confused with the rare woodland species yellow cohosh *Cimicifuga americana* Michx (syn *Actaea podocarpa* DC) known as mountain bugbane, however the flowers of the latter species contain three or more ovaries maturing to papery follicles, the seeds covered in chaffy scales (Gleason & Cronquist 1991; Predny, De Angelis, & Chamberlain, 2006). In order to distinguish *A. racemosa* rhizomes and roots from other potentially contaminating species, the Missouri Botanical Garden published a microscopic profile showing substantial morphological differences (Applequist, 2003). Macroscopic images of *A. racemosa* and species published in the *American Herbal Pharmacopeia* monograph (Upton, 2002) are presented in Appendix I of this monograph.

*A. racemosa* is a plant of the north-eastern woodlands of North America. The center of distribution was said by Lloyd in 1931 to be the Ohio Valley, but stretching from Alabama in the south, Eastern Kansas in the west and north into Canada (Lloyd & Lloyd, 1931). While it may be locally abundant, the species has undergone some decline in recent decades due to habitat loss and over-harvesting (Small, Chamberlain, & Mathews, in press).
Part used
Dried rhizome and roots, harvested in the fall.

3. Traditional Uses

Traditional uses in Appalachia
*A. racemosa* is one of the most prevalent and widely used herbs in Appalachia. It has traditionally been used in “rheumatism” and disorders of menstruation (especially for delayed menses), slow parturition, dropsy and affections of the lungs. (Millspaugh,1974; Crellin & Philpott, 1990). Often, a tincture was prepared by soaking the root in alcohol to address rheumatic pains and coughs and occasionally to help a restless baby sleep (Howell, 2006). *A. racemosa* is currently an ingredient in a common liver formula to address “torpid liver” conditions, and to treat non-specific menstrual problems (Cavender, 2003). It is said to slow the pulse and soothe pain effectively, offering a mild sedative effect upon the nerves (Crellin & Philpott, 1990).

General traditional uses

Native American use
Native Americans found this to be a beneficial herb in all manner of pain management and inflammation. Clymer (1905) and Moerman (1998) state that Native American women utilized this herb for menstrual pain with cramping. It was also used in decoction to address pain associated with sore throats (when used as a gargle) and rheumatism (Wintermute & Palmer, 1905; Lloyd, 1911). Interestingly, *A. racemosa* was used in emergency medicine when treating snakebites, “for which purpose it [was] bruised and applied to the wound; and at the same time a little of the juice was to be taken internally” (Wood, 1896). A kettle containing a hot decoction of the roots was placed in a hole in the ground, and rheumatic limbs were placed over the steam in a way that brought great relief to the area (Lloyd & Lloyd, 1931).
Folklore & Home
Early American writers report that *A. racemosa* was used for a wide range of disorders including cholera, periodical convulsions, fits, epilepsy, nervous excitability, asthma, delirium tremens (alcohol withdrawal), and spasmodic afflictions, consumption, cough, neuralgia, ulcers, and scrofula (Brown, 1867). Wood (1896), states that the root and rhizome were used to treat smallpox, measles and scarlet fever. Pain management and rheumatic disorders were commonly treated with the herb. A tincture of the rhizome and root was used to treat inflammation of the nerves, rheumatism and old ulcers (Brown, 1867). It was also mentioned as having bug repelling properties when the leaves were applied topically, hence *Cimicifuga*, derived from “*cim*” - a bug, and “*fugo*” - to drive away (Brown, 1867).

Paralleling Native American use, *A. racemosa* was renowned as a women’s remedy associated with childbearing and the menstrual cycles. Brown (1867) states that it was valuable in treating amenorrhea, dysmenorrhea, leucorrhea, and other menstrual and uterine conditions - noting a particular affinity for the uterus.

Physiomedical
In his *Physiological dispensatory* Cook (1869) claimed that *A. racemosa* had both soothing and stimulating qualities, where it could reduce pain and spasm locally by soothing tissues, while also being used as an expectorant. Lyle (1897) observed that the form of preparation used significantly influenced clinical outcomes. For example syrup preparations of the roots act as alteratives for eruptive diseases and scrofula provided the dose is sufficiently high, whereas the equivalent dose of fluid extracts influence the central nervous system and can cause dizziness. Lyle also indicated *A. racemosa* for dysmenorrhea, amenorrhea, parturition, uterine cramping, and general imbalance of the menstrual function. Clymer (1905), a student of Lyle, gives specific indications for the use of *A. racemosa* as a women’s remedy for, “ovarian neuralgia, rheumatic dysmenorrhea, and convulsions as a result of nervous excitement, feeling heavy weight in the sacral and lumbar region, and hysterical spasms before or during menstrual period, melancholia and deep feeling of depression; dull aching headache”.

Eclectic
The Eclectics also regarded *A. racemosa* as primary remedy for menstrual irregularities. For dysmenorrhea, Scudder, (1883) indicated it “in cases of tardy, slow, irregular, scanty, or protracted menstruation”, while it was also employed in some cases of amenorrhea (Webster, 1893). *A. racemosa* was used widely in the Eclectic practice as a supporting herb for pain management, as it relieved irritation of the nerve centers that cause contraction of muscles, with specific influence at the nerve periphery” (Peterson, 1905). The leading Eclectic pharmacist John Uri Lloyd described *A. racemosa* as a ‘nervous sedative’ and relates various clinical successes in treating chorea, nervous headaches associated with congestion of the brain, “hysteria”, neuralgia, melancholia and delirium tremens (Lloyd & Lloyd, 1931). His colleague Hale described *A. racemosa* as a cerebrospinal remedy, indicated generally for neuralgias where the pain is aching and pressing, accompanied by restlessness and exhaustion It was also revered for treating menstrual pain, especially dragging pains in the lower back. (Lloyd & Lloyd, 1931).
Homoeopathic
Homoeopaths have also focused on the influence of A. racemosa on the cerebrospinal and muscular systems along with the female reproductive organs (Boericke, 1927). For menstrual disorders, it was used for amenorrhea, shooting pains and neuralgia in the ovaries, pain before menses and for profuse menstrual flow with irregular cycles. It was also indicated for rheumatic pain of the back and neck, and pain in the lumbar and sacral areas (Boericke, 1927).

Regulars (allopathic and practicing physicians)
A. racemosa was included in the US Pharmacopoeia from 1820-1936 (Westfall, 2001). The species was used for “dropsy,” rheumatism, “hysteria” and lung afflictions by some practitioners. It was also believed that A. racemosa had a sedative effect on the nervous system - lowering the pulse, soothing pain, and reducing irritability (Wood & Bache, 1858). Some practicing physicians found the use of A. racemosa extremely beneficial in addressing pain associated with nervous tension and spasms, as well as reducing arterial tension. Warren (1859) utilized this herb for people with epilepsy, nervous excitability, asthma, delirium tremens and other spasmodic affections, as well as in children with uncontrolled movements, and patients suffering from both chronic and acute rheumatism. A. racemosa was also used successfully in patients with depressed symptoms, as well as asthma, epilepsy and nervous excitability (Hodge, 1911). Hodge also used the herb for amenorrhea associated with “dull, aching pain” and for tonifying tissue states.

In the late 1800 A. racemosa was also used by some MDs for facilitation of childbirth, to the extent that clinical investigations were reportedly conducted (Westfall, 2001).

Scientific Research

Phytochemistry

Triterpenoids
A. racemosa contains over 40 highly oxygenated triterpene glycosides, all based on a cycloartane-type aglycone (Upton, 2002; He et al., 2006). The major triterpenes that have been reported are 23-epi-26-deoxyactein (formerly named 27-deoxyacetin), actein, cimiracemoside A, 20-deoxyactein and cimigenoside (S.-N. Chen et al., 2002; Chen, Fabricant, Lu, Fong, & Farnsworth, 2002; He, Zheng, Kim, Rogers, & Zheng, 2000; Jiang, Kronenberg, Nuntanakorn, Qiu, & Kennelly, 2006).

Commercial extracts are usually standardized to 23-epi-26-deoxyactein, however detection of individual compounds is challenging due to low ultra-violet (UV) absorption (He et al., 2000; Cicek, Schwaiger, Stuppner, & Ellmerer, 2010), and various non-UV detection methods have been employed. These include atmospheric pressure chemical ionization (APCI), infra-red (IR), evaporative light scattering detector (ELSD), mass spectrometry (MS), turbo ion spray (TIS)-MS, X-ray crystallization as well as nuclear magnetic resonance (1H and 13C-NMR) (He et al., 2000; Chen et al., 2002; Panossian, Danielyan, Mamikonyan, & Wikman, 2004; Wang, Sakurai, Shih, & Lee, 2005; Jiang et al., 2006). These systems are generally coupled with high performance liquid
chromatography (HPLC) systems, and in one case high speed countercurrent chromatography (Cicek, Schwaiger, Stuppner, & Ellmerer, 2010).

The American Herbal Pharmacopoeia (AHP) published a high performance thin layer chromatography (HPTLC) method developed by CAMAG of Switzerland for comparing batches of *A. racemosa* roots against known samples and two standards (actein and 27-deoxyactein) (Upton, 2002). This procedure has been further developed to detect 5% adulteration with other species of *Actaea* (Ankli, Reich, & Steiner, 2009). AHP also published a HPLC method coupled with ELSD, which effectively separates out ten peaks and identifies eight triterpene glycosides (Upton, 2002) – see Figure 2. Recently new phytochemical fingerprinting methods to distinguish *A. racemosa* from other species have been developed. Wang and co-workers (2005) developed chromatogram fingerprints for seven *Cimicifuga* (syn. *Actaea*) species using a liquid chromatography (LC)/TIS-MS (Wang et al., 2005). Using HPLC-PDA and LC-MS techniques, the chromone cimifugin (not found in *A. racemosa*) and triterpene cimiracemoside F were found to be effective distinguishing marker compounds for the species (Jiang, Ma, Motley, Kronenberg, & Kennelly, 2011).

Using an LC-MS method, samples from rhizomes collected in 1919 were found to have an almost identical profile of triterpene glycosides compared to a modern sample, demonstrating a high level of stability for these constituents (Jiang et al., 2005).

![Figure 2: HPLC chromatogram of triterpene glycosides in A. racemosa. Reproduced from Upton (Ed) 2002, American Herbal Pharmacopoeia.](image)
**Phenolic constituents**
The main phenolic constituents found in *A. racemosa* are caffeic acid and derivatives (hydroxycinnamic acids) including methyl caffeate, ferulic acid, isoferulic acid, fukinolic acid, cimicifugic acids, esters of piscidic acid, and four phenylpropanoid ester dimers known as cimiracemate A-D (Burdette et al., 2002; Chen et al., 2002; Jiang et al., 2006; Jiang, Lyles, Reynerton, Kronenberg, & Kennelly, 2008). The preferred analytical method for the phenolic compounds is HPLC coupled with photo diode-array (PDA) (Jiang et al., 2006; Nuntanakorn et al., 2007), although gas chromatography (GC-MS) has also been used to quantify isoferulic acid (Panossian, Danielyan, Mamikonyan, & Wikman, 2004). An HPTLC method developed by CAMAG for caffeic acid is available (Upton, 2002). The polyphenolic profile of *A. racemosa* has been used as a means of distinguishing it from other American species of *Actaea* (Nuntanakorn et al., 2007). More recently Gödecke and co-workers identified cimicifuga acid KS, the fukiic acid eater of sinapic acid, by $^1$H NMR (Gödecke et al., 2009).

**Flavonoids**
Reports of the presence of isoflavones formononetin and biochanan A and the flavonol kaempferol in *A. racemosa* are inconclusive (Upton, 2002). In an analysis of 13
populations of *A. racemosa* rhizomes, no isoflavones were detected (Kennelly et al., 2002). Despite this, Panossian and co-workers published a validated method for quantifying formononetin in *A. racemosa* using TLC-densitometry, claiming previous methods used had lacked the necessary sensitivity (Panossian et al., 2004). Subsequently other investigators have failed to replicate these findings despite using highly sensitive analytical procedures (Jiang, Kronenberg, Balick, & Kennelly, 2006; Jiang et al., 2011). The consensus of these authors is that any estrogen-like activity that may be associated with *A. racemosa* cannot be attributed to formononetin (Jiang et al., 2006).

**Alkaloids and amines**

In recent years a research group from the University of Illinois has identified a number of alkaloidal and biogenic amines in *A. racemosa*, inspired by an earlier study that demonstrated *A. racemosa* extracts acted on serotonin receptors rather than estrogen receptors (Burdette et al., 2003). Subsequently a methanolic extract of *A. racemosa* was fractionated and the polar compound Nó–methylserotonin was identified by liquid chromatography-mass spectrometry (LC-MS/MS) (Powell et al., 2008). This finding led to further analysis of polar fractions, which along with previously identified phenolic acids yielded guanidine alkaloids, dopamine derivatives salsolinol, dopargine and the nitrogen-free glycoside 3-hydroxytyrosol 3-<i>O</i>-glucoside (Gödecke et al., 2009) (see Figure 4). A genetic screening program investigating possible gene sequences involved with production of secondary metabolites in *A. racemosa*, led to the identification of genes involved in plant serotonin biosynthesis (Spiering et al., 2010).

![Figure 4. Guanidine alkaloids and dopamine derivatives from A. racemosa.](image)

**Figure 4.** Guanidine alkaloids and dopamine derivatives from *A. racemosa*. 1. cyclo-cimipronidine 2. cimipronidine methyl ester 3. cimipronidine 4. salsolinol 5. dopargine 6. guanidinobutyraldehyde (proposed intermediate) 7. hydroxytyrosol 3-<i>O</i>-glucoside. Reproduced from (Gödecke et al., 2009).
Other constituents
These include tannins, resins, fatty acids, starch and sugars (Upton, 2002).

DNA Fingerprinting
In addition to the current botanical and phytochemical methods available for species identification, biomolecular methods for detecting genetic differences between *Actaea* species have also been developed at the New York Botanical Gardens. Using amplified fragment length polymorphisms (AFLP) analysis, distinct DNA fingerprinting profiles were established for *A. racemosa*, *A. cordifolia* (DC.) Torr. & A. Gray, *A. podocarpa* and *A. pachypoda* Elliott, and the technique could be applied to both commercial rhizome pieces and capsules of *A. racemosa* but not to tea bags (Zerega, Mori, Lindqvist, Zheng, & Motley, 2002). Subsequently genetic screening of *A. racemosa* has revealed 70 unique genes thought to be involved in secondary metabolism, including two gene sequences linked to plant serotonin metabolism (Spiering et al., 2010).

Pharmacology

Pharmacokinetics
In a routine HPLC analysis (Chen, Lankin, Nikolic, et al., 2007) detected a new peak eluting with triterpene glycosides, which was identified as a chlorine containing derivative, named chlorodeoxycimigenol-3-O-β-D-xyloside. It was inconclusive as to whether this compound was an artifact of the analytical process, but the authors suggest potential for gastric *in vivo* conversion of *A. racemosa* saponins into chlorinated derivatives with altered properties (S.-N. Chen, Lankin, Nikolic, et al., 2007).

Pharmacodynamics
There have been relatively few investigations into the traditional uses of *A. racemosa*. Most studies have been focused on the effects on menopausal symptoms and on hormonal profiles - particularly estrogen. Many studies are based on the European proprietary isopropanolic extract Remifemin, standardized to contain minimum levels of triterpenoid glycosides (Braun & Cohen, 2010). Several reviews of experimental and clinical studies are available (Foster, 1999; Gruenwald, 1998; Upton, 2002; Kronenberg & Fugh-Berman 2002; Blumenthal, 2004; Viereck, Emons, & Wolfgang Wuttke, 2005; Borrelli & Ernst, 2008; Fabricant, Dentali, Krause, & Farnsworth, 2008) so the objective of this section is to summarize and update these reviews in addition to assessing research for *A. racemosa* not associated with menopause.

Hormonal modulation and related menopausal changes
While there is good clinical evidence in support of the use of *A. racemosa* for some symptoms of menopause (see below), there is to date no clearly established mechanism of action. Most studies have failed to find direct binding effects on the two primary classes of estrogen receptors (ERα, ERβ). However, there is evidence of selective effects on tissues such as bone, suggesting *A. racemosa* could act as a selective estrogen receptor modulator (SERM) (Upton, 2002; Jarry, Metten, Spengler, Christoffel, & Wuttke, 2003; Braun & Cohen, 2010). There is also evidence in both animal and human studies for inhibition of luteinizing hormone (LH) (Jarry, Harnsichfeger, & Duker, 1985; Düker, Kopanski, Jarry, & Wuttke, 1991) although this association is not universally accepted (Liske, 1998). There is clear clinical evidence for a correlation between raised LH levels
and hot flashes in postmenopausal women (Meldrum et al., 1980), thought to occur within the CNS (Düker et al., 1991).

Using a lipophilic fraction Bolle and co-workers demonstrated a SERM effect in vitro but not in vivo, and hypothesized the existence of an unidentified estrogen receptor that may be associated with modulation of inflammation (Bolle, Mastrangelo, Perrone, & Evandri, 2007). Other investigators have downplayed the significance of estrogen-like effects and focused on alternative mechanisms such as antioxidant, inhibition of inflammatory pathways, central nervous system effects and binding to other receptor types such as serotonergic, dopaminergic and opiate (Viereck et al., 2005; Hubertus Jarry et al., 2003; Ruhlen et al., 2008; Farnsworth & Mahady, 2009).

**Serotonergic activity**

Given the lack of a definitive pathway to support phytoestrogenic claims for *A. racemosa*, serotonin’s (5-HT) ability to partially reduce hot flashes became a subject of research interest. Burdette, Lui, Chen, Fabricant, & Piersen et al., (2003) set out to identify structural markers that could help explain its reported effects. They found that propanol extracts of *A. racemosa* demonstrated an inhibitory effect on 5-HT sub receptors 1A, 1D and 7. These subtypes are found in the hypothalamus, an area known for its thermoregulatory effects (Powell, et. al., 2008). The inhibition of a 5-HT1A receptor indicates a hypothermic effect that could show up as a decrease in vasomotor symptoms. There are specific 5-HT receptors that terminate directly onto the LH releasing hormone (LhRh), leading to inhibition of LH secretion from the pituitary gland. Hot flashes are characterized by low levels of estrogen and a rise in LH and follicle-stimulating hormone (FSH) levels (Burdette et al., 2003). *A. racemosa* selectively inhibits LH in vivo - Duker et al. (1991) discuss possible mechanisms for this effect.

Powell et al., (2008) identified a new constituent - Nó–methylserotonin - of *A. racemosa* that is believed to potentiate serotonergic factors relating to its regulatory effects of menopausal symptoms (see above). This compound has a high affinity in the 5-HT7 receptor-binding assay leading to increased 5-HT levels, which may in turn lead to mood changes that alleviate depression symptoms. Subsequent investigations into polar constituents of *A. racemosa* failed to detect other compounds with serotonergic activity (Gödecke et al., 2009).

**Osteoprotection**

The role of estrogen in bone mineral density has become a concern for post-menopausal women at risk for osteoporosis. Chan and co-workers observed the anabolic effects of *A. racemosa* extracts on bone nodule formation in osteoblasts, providing evidence for protective effects against bone mineral loss that is typically found in post menopausal women (Chan et al., 2008). One triterpenoid glycoside identified in *A. racemosa* – 25-acetylxicigenol xylopyranoside (ACCX), blocked in vitro osteoclastogenesis induced by cytokines such as tumor necrosis factor (TNFα), whilst also inhibiting pro-inflammatory signaling pathways NF-κB and MAPK (Qiu et al., 2007).
Antioxidant effects
Both triterpenes glycosides and phenolic constituents contribute to antioxidant activity in *A. racemosa* (Jiang, et al. 2005). Using bioassay-directed fractionation, nine phenolic compounds demonstrated antioxidant effects in the DPPH assay, and six of these (of which the most potent was methyl caffeate) reduced menadione-induced DNA damage in breast cancer cells (Burdette et al., 2002).

Cancer-related effects
Various laboratory studies indicate that *A. racemosa* extracts inhibit proliferation of both estrogen- positive and negative human breast cancer cells (Einbond et al., 2004; Hostanska, Nisslein, Freudenstein, Reichling, & Saller, 2004). In one study the extract not only slowed the growth of estrogen dependent tumors, it also inhibited the conversion of estrone sulphate to active estradiol (Rice, Amon, & Whitehead, 2007). Methanol extracts of *A. racemosa* as well as the triterpene constituent actein were found to activate genes that promote apoptosis of breast cancer cells (Einbond et al., 2007). Similar cytotoxic and apoptotic effects have been observed on both androgen dependent and independent prostate carcinoma cells (Hostanska, Nisslein, Freudenstein, Reichling, & Saller, 2005; Jarry, Thelen, Christoffel, Spengler, & Wuttke, 2005), confirming findings from earlier studies on immunodeficient mice (Ng & Wigg, 2003). Morphological changes in cell structure helped Hostanksa et al. (2005) recognize the apoptotic factor leading to cell death. In a recent anti-cancer screening program using malignant neuroblastoma cells, *A. racemosa* extracts were found to have moderate tumoricidal effects (Mazzio & Soliman, 2009). The combined results of these studies indicate *A. racemosa* is potentially a useful agent for inhibiting proliferation of breast, prostate and other cancer cells.

Clinical Studies
Over the last decade there has been an upsurge of public demand for alternatives to hormone replacement therapy (HRT), especially following the negative side effects that occurred during the Women’s Health Initiative (WHI) study, which was prematurely terminated (Viereck et al., 2005; Fabricant et al., 2008). Apart from isoflavone-containing leguminous species such as soybean, the most interest has centered around *A. racemosa*, leading in turn to a marked increase in sales of the species in Europe, the US and elsewhere (Blumenthal, 2004; Fabricant et al., 2008). In the *American Herbal Pharmacopoeia* *A. racemosa* monograph (Upton, 2002), 16 clinical studies on treatment of menopausal symptoms including hot flashes, vaginal thinning and depression were reviewed, dating from 1957 to 2001. All but two of these used the patent Remifemin extract. While the quality of the studies was variable, the reviewer’s overall conclusion was in support of the use of *A. racemosa* for menopausal symptoms (Upton, 2002). During the intervening years several new studies have been conducted. In a recent systemic review, 72 clinical studies relating to menopausal symptoms were identified, of which 25 were randomized trials (RCTs). Only six of these were deemed to meet the inclusion criteria (Borrelli & Ernst, 2008). The six RCTs represented a total of over 1,100 peri- and postmenopausal women, and all scored at least 3/5 points on the Jadad score, indicating a satisfactory level of blinding of participants and treatments. The authors concluded that *A. racemosa* reduced severity of symptoms of menopause as measured by
validated indices used in these studies, however it was uncertain as to whether the frequency of symptoms was reduced (Borrelli & Ernst, 2008). In contrast a systemic review in the journal Drugs and Ageing identified 16 eligible clinical trials for menopausal symptoms. Their conclusions were less positive, focusing mainly on the conflicting findings from the different studies as well as flaws in the methodology of many of them (Palacio, Masri, & Mooradian, 2009). Morgan (2011) noted that a number of the studies used extract dosages of 40mg/day, at the bottom end of the dosage range recommended in the British Herbal Compendium (see below).

**Safety issues and drug interactions**

Considering the thousands of women who have participated in clinical investigations of *A. racemosa*, there have been relatively few adverse events reported. There have, however, been a number of case reports in medical journals which have attracted much publicity. One report by Whiting et al. (2002) published in the Medical Journal of Australia described six case studies in which acute hepatitis and other adverse liver effects were linked to the use of *A. racemosa* preparations. This report was widely criticized at the time, on the basis of lack of verification of the herbal medicines used, insufficient exclusion of other possible causes and lack of any known hepatotoxicity or proposed mechanisms associated with this species (Thomsen, 2003). Despite this, with other cases of suspected hepatotoxicity having been reported, concerns continued to be expressed amongst scientists and regulators, leading to several investigations into potential for hepatotoxicity and the general safety of *A. racemosa*. Mazzanti et al. (2008) conducted studies with Wistar rats each of which received 300mg/kg/day *A. racemosa* extract for 30 days, after which they showed no adverse affects to liver morphology or hepatic function indices. Subsequent clinical studies have confirmed the lack of hepatotoxicity in healthy postmenopausal women (Nasr & Nafeh, 2009) and breast cancer patients (Walji, Boon, Guns, Oneschuk, & Younus, 2007), while a recent meta-analysis of five RCTs of peri- and postmenopausal women found no evidence of adverse effects on liver function (Naser et al., 2011). Despite these findings, regulators in some countries require labels warning of potential association between *A. racemosa* and hepatotoxicity, and recently the Dietary Supplement Information Expert Committee recommended a similar warning system be established in the USA (Mahady et al., 2008).

In other studies, no formation of potentially toxic phase I metabolites was observed in perimenopausal women taking *A. racemosa* (Johnson & van Breeman, 2003), and there were no adverse changes reported to lipid profiles, fibrinogen, glucose and insulin in 310 peri- and post menopausal women following three months of regular ingestion (200mg daily) (Spangler et al., 2007). In an assessment of 400 symptomatic postmenopausal women there was no evidence of endometrial proliferation or significant gynecologically related adverse events as assessed by biopsy method, and there was no increase in breast density observed after one year of treatment with *A. racemosa*. While liver enzymes were also unaffected there was an increase in total cholesterol and triglycerides (Raus, Brucker, Gorkow, & Wuttke, 2006).

An *in vivo* study involving 12 healthy volunteers sought to assess potential drug-interactions via phytochemical mediation on cytochrome P(CYP) -450 enzymes, with
four medicinal herbs including *A. racemosa*. Changes to CYP phenotypic trait ratios indicates that *A. racemosa* is a mild inhibitor of CYP2D6 (Gurley et al., 2005). In a separate study using bioassay-guided fractionation, six triterpenoid glycosides of *A. racemosa* were shown to inhibit CYP3A4, another major CYP-450 enzyme associated with phase 1 drug metabolism (Tsukamoto et al., 2002).

### 4. Modern Phytotherapy

Modern therapeutic use of *A. racemosa* reflects both clinical research and traditional indications. It is specifically indicated for drawing and muscular pains in the loins, back and thigh, pain across the shoulders and stiff neck. It has also been used for meningitis after the acute symptoms have passed (Harper-Shove 1952). Contemporary use emphasizes gynecological indications but broader application of *A. racemosa* is still found today. The German Commission E (Blumenthal, 1998) approves its use for “premenstrual discomfort, dysmenorrhea or climacteric [menopausal] neurovegetative ailments”. Romm (2010) suggests similar uses while adding the modern indication of osteoporosis as well as the traditional indications of ovarian pain, musculoskeletal pain and coughs.

Although *A. racemosa* is most commonly used to aid premenstrual and perimenopausal anxiety and depression, it has broader use as nervine amongst herbal practitioners (Upton 2002). For nervous system indications it is commonly combined with St. John’s wort (*Hypericum perforatum*).

**Table 1**: Modern phytotherapeutic uses of *A. racemosa*

<table>
<thead>
<tr>
<th>ACTIONS</th>
<th>THERAPEUTIC INDICATIONS</th>
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<tr>
<td>Emmenagogue</td>
<td>Conditions associated with pain and inflammation: osteo- and rheumatoid arthritis, sciatica, neuralgias and ovarian pain.</td>
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<tr>
<td>Antirheumatic</td>
<td>Symptoms associated with menopause and ovarian insufficiency: hot flashes, vertigo, heart palpitations, neurovegetative and emotional disorders</td>
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<tr>
<td>Spasmolytic</td>
<td>Menstrual disorders: amenorrhea, dysmenorrhea, menorrhagia, pre-menstrual syndrome</td>
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<tr>
<td>Expectorant</td>
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Respiratory disorders: whooping cough, asthma, tinnitus

Nervous conditions: irritability, insomnia, headaches

Hormonal imbalance: infertility, ovarian cysts, polycystic ovary syndrome


**Combinations**
May be combined with *Hypericum perforatum* for depression and neurovegetative disorders associated with the menopause

**Toxicity and contra-indications**
The *Botanical Safety Handbook* classifies *A. racemosa* as Class 2b, 2c – “Not to be used during pregnancy or while nursing” (McGuffin, Hobbs, Upton, & Goldberg, 1997). Commission E recommends that use be limited to six months (Blumenthal 1998), although this limitation is not linked to any known long-term safety concerns (Blumenthal, 2003). Occasional gastro-intestinal disturbances have been reported. It is contra-indicated during pregnancy and lactation (Bradley, 1992). Previous concerns about the potentiation of estrogen-dependent disorders such as breast cancer are no longer warranted, now that it is clearly established that any estrogenic effects *A. racemosa* does exert are quite selective (Liske, 1998; Blumenthal, 2003; Viereck, Emons, & Wuttke, 2005; Ruhlen, Sun, & Sauter, 2008). There are no reports of interactions with prescription drugs.

**Preparation and dose**
Dried rhizome and root. 40-200mg daily or by decoction
Tincture: 1:10. 0.4-2.0mL daily (Bradley 1992).
Extract: 1:3. 1mL, three times daily.

**Regulatory Status**
*A. racemosa* is regulated in the U.S.A. as a Dietary Supplement. In Canada it is regulated as a drug if a single dose is sufficiently high or as a “New Drug” for specific nontraditional use claims (Blumenthal, 2003).

**6. Sustainability considerations**

**Ecological status-RTE status**
While *A. racemosa* is not listed as endangered, threatened or rare in the US or Canada, a variety, *A. racemosa var. racemosa* (black bugbane) is listed as endangered for both Massachusetts and Illinois (USDA NRCS, 2011). *A. racemosa var. racemosa*, formerly classified as *Cimifuga racemosa* (L.) Nutt., is listed as *A. racemosa* and identified as black cohosh by Massachusetts (NHESP, 2010) and classified as *Cimifuga rubrifolia* Kearney and identified as black cohosh on the Illinois website (Illinois Endangered Species Protection Board, 2011). Another variety *A. racemosa var. dissecta* (A.Gray) J. Compton has only been documented in Delaware (USDA NRCS, 2011). Tennessee lists
C. rubrifolia as currently threatened using the common name Appalachian bugbane (Chester, Wofford, Estes & Bailey, 2009)

According to (Lonner, 2007) there are several closely related species which may be harvested as A. racemosa. This may be a result of a lack of consistent identification between state and US federal sites.

In a recent study examining the impact of wild harvesting A. racemosa, plant vigor and root size was significantly reduced in sites where 66% of the population had been harvested, compared to controls where no harvest took place (Small, Chamberlain & Matthews, in press). Harvesting had occurred for three years with a two-year recovery period, during which plants were measured but not harvested. Even at sites where only one-third of the populations were harvested, there was a notable decrease in the average size of unharvested plants. As almost all A. racemosa sold commercially is collected from wild populations, this raises serious questions of sustainability for this and possibly other native species (Small, Chamberlain & Matthews, in press).

Brinkmann (2010) notes that in 2002, CITES (Convention on International Trade in Endangered Species of Wild Flora and Fauna) considered adding A. racemosa to Appendix II but did not do so. United Plant Savers (2011) considers it an at-risk species. As of March 2006, the U.S. Fish and Wild Life Service withdrew active consideration to list the species, but it continues to monitor its status (Lonner 2007). Currently, The University of Massachusetts has implemented a diversity study of 26 naturally occurring populations in the state for the purpose of improving plant breeding and conservation (Univ. of Massachusetts, 2011).

**Harvesting & Collection regulations**

Permits are required in Massachusetts and Illinois according to endangered plant regulations.

**Market data - harvesting impact, tonnage surveys**

A. racemosa was number 8 of the 20 top-selling herbal dietary supplements in the USA for 2010, achieving sales of $US 9,303,047, an increase of 14.3% over the previous year (Blumenthal, Lindstrom, Lynch, & Rhea, 2011). The annual tonnage for fresh plants and dried rhizome is presented in Table 2.

**Table 2. Tonnage of cultivated and wild A. racemosa 1995-2005 (AHPA, 2007).**

<table>
<thead>
<tr>
<th>Year</th>
<th>Fresh Plants (lbs)</th>
<th>Dried rhizomes (lbs)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cultivated</td>
<td>Wild</td>
</tr>
<tr>
<td>1997</td>
<td>----</td>
<td>-----</td>
</tr>
<tr>
<td>1998</td>
<td>----</td>
<td>-----</td>
</tr>
<tr>
<td>1999</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td>2000</td>
<td>0</td>
<td>1,853</td>
</tr>
<tr>
<td>2001</td>
<td>0</td>
<td>1,414</td>
</tr>
</tbody>
</table>
## Cultivation

### Habitat
In the wild, *A. racemosa* can be found in moist soil in forest clearings high in organic material which provide a few hours of filtered sunlight each day (Tilford, 1998; Greenfield & Davis, 2004). In gardens, it prefers light shade, high humidity, and regular watering (Blakeley and Sturdivant, 1999; Bascom, 2002). *A. racemosa* has been known to grow with increased light if there is adequate moisture (Greenfield & Davis, 2004), however plants may not self-seed if there is too much sun (Cech, 2002).

A study by Lueck, et al. (2003) of *A. racemosa* genetics concluded that southern and northern populations vary in their ability to thrive in different locations, such that growers may need to test stock from both populations to find which is best for their land. Several sources suggest utilizing local stock (Lueck, 2003; Blakeley & Sturdivant, 1999).

### Field propagation
For field production, Greenfield & Davis (2004) recommend shade structures (wood lathe or polypropylene) over seven feet in height, with two ends open to the prevailing winds and soils with a pH range of 5 to 6.

### Wild-simulated & Woods-cultivated
For forest culture, select a site with good air and water drainage in an area shaded by tall trees, preferably hardwood; if there is clay or overly moist soil, raised beds are recommended (Greenfield & Davis, 2004). Other species found with *A. racemosa* include: *Podophyllum peltatum* L., *Trillium* spp., *Sanguinaria canadensis* L., *Panax quinquefolius* L. (Greenfield & Davis, 2004).

### Propagation
Rhizomes
Plant the rhizomes or rhizome pieces (with at least one bud) in the spring or fall (Blakeley & Sturdivant, 1999; Greenfield & Davis, 2004), burying them horizontally under about 2 inches soil pressed firmly around the root in a partially shaded location.
(Tilford, 1998). A single rhizome can be cut into smaller pieces, since a single rhizome may have as many as fifteen buds and it might produce fifteen potential *A. racemosa* plants. Greenfield and Davis (2004) also suggest that the long rootlets should be left on the parts to be planted. Plants should be spaced at least 18-24 inches from each other with the bud facing upright (Greenfield & Davis, 2004).

Mulch the plantings with plenty of natural leaf material. The rhizomes may take a full year or more to produce an above ground sprout (Tilford, 1998; Snow, 2006) but will gradually begin to produce offshoots (Snow, 2006) and becoming market-size in 5 years or so (Greenfield & Davis, 2004).

**Seeds**
In the wild, *A. racemosa* self-seeds with varying germination depending upon soil and environmental conditions. Mature seed can be harvested just as the pods begin to open in the fall and sown immediately (Greenfield & Davis, 2004). When using seedbeds, the seeds should be planted under two inches of soil and kept moist and shaded (Greenfield & Davis, 2004). Cech (2002) advises alternating temperatures under greenhouse conditions as a stratification strategy: seventy degrees F. for two months, after planting and then forty degrees F. for three months.

**In vitro**
While *in vitro* culture of *A. racemosa* is not yet in widespread commercial use, Massimo (2009) has detailed information and current research on the process. Considerations for *in vitro* propagation would include the importance of genetic diversity and the procuring of correct cultivars for habitats and climate zones (Lueck, 2003; Blakeley & Sturdivant 1999).

**Harvest**
Tilford (1998) suggests harvesting in the fall of the 4th or 5th year, while Blakeley & Sturdivant (1999) and Brinkmann (2010) suggest waiting until the fruit has ripened 3-5 years after planting. The medicinal properties and weight of the rhizomes are thought to be greatest in the autumn (Greenfield & Davis, 2004). Roots are usually air-dried whole (about one-third the fresh weight) and should not be kept longer than one year (Cech, 2002; Greenfield & Davis, 2004; Brinkmann, 2010). In the wild, Brinkmann (2010) suggests that no more than 20% of a stand should be removed at one time.

**Pests**
*A. racemosa* is susceptible to several leaf spots, root rot and damping off (*Rhizoctonia solani*) especially under crowded conditions. In the wild black cohosh is a common forage plant for deer, rabbits, slugs and snails (Greenfield & Davis, 2004).

**Costs and Considerations**
Plants within woodland settings must be harvested manually, which may affect cost (Greenfield & Davis, 2004).

7. **Summary and moving forward**
Actaea racemosa is now a leading edge species for medicinal plant research – by ecologists, botanists, phytochemists, pharmacologists, clinicians and geneticists. As data from clinical studies continues to demonstrate efficacy and safety, this inevitably leads to extra demand on the supply of raw materials – which are still mainly derived from wilcrafted sources. Sustainable wild harvesting may be possible but studies to date have not supported this idea. Future funding should be targeted at pilot schemes for cultivating A. racemosa in both field and wild-simulated settings, and regulatory bodies could set realistic targets for attaining increasing proportions of the annual crop from cultivated sources.

As noted above most therapeutic studies have focused on the effects of A. racemosa on menopausal symptoms and changes to hormonal profiles. There is a need for studies that focus on traditional uses – these could include menstrual cramps, rheumatic pain and/or neurological disorders. Scientific validation of traditional uses is an important step in promoting the credibility of herbal medicine practice.

8. References


Brown, O.P. (1867). The complete herbalist, or, the people their own physicians by the use of nature's remedies. Jersey City, NJ: O. Phelps Brown.


Webster, H.T. (1893). *Dynamic therapeutics; A work devoted to the theory and practice of specific medication, with special reference to the newer remedies, with clinical index, adapting it to the needs of the busy practitioner*. Oakland, CA: Herbert T. Webster.


Wood, G. (1896). Vitalogy, adapted for home and family use... Embracing food remedies for the cure and prevention of all diseases, Chicago, IL: I.N. Reed.

Appendix I.

Left: Cut, dried *A. racemosa*; Freshly harvested rhizome and roots of *A. racemosa* (centre) and *A. podocarpa* (right).

Botanical features distinguishing *A. racemosa* and *A. podocarpa*.

Appendix II.
Selection of companies from Google search for pharmaceutical black cohosh (June 15, 2011).

<table>
<thead>
<tr>
<th>Name of Company</th>
<th>Country</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anhui Minmetals Development Imp. &amp; Exp. Co., Ltd.</td>
<td>China (Mainland)</td>
<td>black cohosh extract, Triterpenoid Saponins: 1.5% 2.5% 8% HPLC, 10:1, 20:1, 30:1</td>
</tr>
<tr>
<td>Xi'an Huarui Bio-Engineering Co., Ltd</td>
<td>China (Mainland)</td>
<td>Cimicifuga racemosa extract /black cohosh root /black cohosh/ black snakeroot/ cimicifuga/ macrotys/CAS NO:84776-26-1</td>
</tr>
</tbody>
</table>
Changsha Sunfull Bio-Tech Co., Ltd.  China (Mainland)  Black Cohosh Extract 2.5% Triterpene
Shaanxi Zishan Technology Corporation Ltd.  China (Mainland)  Black cohosh Extract Triterpene Glycosides 5%-8%
Xian Avatar International Trade Co., Ltd.  China (Mainland)  Black Cohosh Plant Extract Powder
Xi'an Day Natural Tech Co., Ltd.  China (Mainland)  Black Cohosh P.E.

Pricing varied from $1-$12/kilogram for powdered extracts with these companies. It is also noteworthy that the genus and species are not always mentioned.

Accessed online at http://www.alibaba.com/countrysearch/CN/black-cohosh-extract-for-pharmaceutical_2.html?tracelog=24581_list_turnpage

Appendix III.
Pricing from selected distributors as republished in Herbalgram (Brinkmann, 2010)

<table>
<thead>
<tr>
<th>Wholesale distributors</th>
<th>Processed form</th>
<th>1-4 lb</th>
<th>5-9 lbs</th>
<th>10-24 lbs</th>
<th>25-49 lbs</th>
<th>50-99 lbs</th>
<th>&gt;100 lbs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good Hope Botanicals</td>
<td>Cut and sifted</td>
<td>$13.90</td>
<td>$12.51</td>
<td>$11.82</td>
<td>$10.42</td>
<td>Inquire</td>
<td>Inquire</td>
</tr>
<tr>
<td>Mountain Rose Herbs</td>
<td>Cut and sifted</td>
<td>$19.50</td>
<td>$17.55</td>
<td>$16.58</td>
<td>$15.60</td>
<td>$13.65</td>
<td>$11.70</td>
</tr>
<tr>
<td>Pacific Botanicals</td>
<td>Powdered</td>
<td>$22.00</td>
<td>$19.00</td>
<td>$16.70</td>
<td>$17.60</td>
<td>$15.40</td>
<td>$13.20</td>
</tr>
<tr>
<td>San Francisco Herb &amp; Natural Food Co.</td>
<td>Cut and sifted</td>
<td>$11.90</td>
<td>$10.60</td>
<td>$10.50</td>
<td>$10.00</td>
<td>$9.00</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Powdered</td>
<td>$13.50</td>
<td>$12.50</td>
<td>$12.50</td>
<td>$10.50</td>
<td>$9.70</td>
<td></td>
</tr>
</tbody>
</table>

**SOURCES:**
Good Hope Botanicals  http://www.goodhopebotanicals.com/herbs_spices.htm
Mountain Rose Herbs Wholesale: http://www.mountainroseherbs.com/wholesale.html
Pacific Botanicals Online Store: http://www.pacificbotanicals.com/store

*Editor's Note:* The American Botanical Council, publisher of HerbalGram, has republished for educational purposes only this pricing information as it was published in the original version of the ITC/MNS newsletter. The listing of suppliers' names should not be misinterpreted as an ABC recommendation or endorsement of these suppliers or the black cohosh raw materials.

Appendix IV.

Additional resources for growing, monitoring and assessing black cohosh.


Appendix V. Voucher specimens lodged at the Claude E. Phillips Herbarium, Delaware State University. Specimen on left – flowering raceme collected from the Green Farmacy Garden, Fulton MD on 7/20/11. Specimen on right collected from the Ohio Botanical Sanctuary, via Rutland Ohio, May 2011.