



APPALACHIAN PLANT MONOGRAPHS

Prepared by Tai Sophia Institute
For the Appalachian Center for Ethnobotanical Studies



Actaea racemosa
black cohosh

Black cohosh *Actaea racemosa* L.

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BLACK COHOSH - *Actaea racemosa* L.

1. Taxonomy

Actaea racemosa L.

Family: Ranunculaceae (buttercup family)

Common names: black cohosh, black snakeroot, tall bugbane, black 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).

Formerly: *Cimicifuga racemosa* (L.) Nutt., *Macrotys actaeoides* Raf.

2. Botany and distribution

A. racemosa, a perennial herb with a smooth erect stem, can attain a height of eight feet when in flower. The leaves are ternately compound and deeply toothed with a glossy dark green appearance, and often only one compound leaf per plant. Terminal leaflets are trilobed with 3 basal veins. When developing the petiole has a shallow sulcus (groove) which disappears as the petiole enlarges (Ramsey, 1987). Flowers are feathery and 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. Staminodes (sterile stamens sometimes referred to as petals) with deeply cleft apices are also present (Ramsey, 1987; Compton, Culham, & Jury, 1998). 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 an oval-shaped, follicle, with angular, glabrous seeds arranged in two rows. The rootstock consists of a thick, branching, black rhizome, marked with petiole scars, the underside covered with a mass of rootlets (Applequist, 2006).

Several other white flowering species of *Actaea* found in North America may be mistaken for *A. racemosa*. Red baneberry (*A. rubra* (Aiton) Willd.) can be distinguished from *A. racemosa* by its flowers, which are arranged in short clusters, its less-pointed leaves and its distinctly rigid clusters of red or sometimes white berries. *A. racemosa* can easily be confused with the woodland species *A. podocarpa* DC. (formerly *Cimicifuga americana* Michx.) known as mountain bugbane or yellow cohosh. 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, DeAngelis, & Chamberlain, 2006). Appalachian bugbane (*A. rubifolia* Kearney) has the fewest leaflets and largest terminal leaflet of the group (Ramsey, 1987) while the inflorescence is shorter and more branched than in *A. racemosa* (Heikens, 2003). Unlike *A. racemosa* the sulcus in the petioles of these species persists as the leaf matures (Ramsey, 1987). *A. pachypoda* Elliott, the white baneberry, is smaller in stature than *A. racemosa*, and its flowers have broad stigma lobes, while the fruit are distinctly white (Compton, Culham, & Jury, 1998).

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, 2006). Macroscopic images of *A. racemosa* and other species published in the *American Herbal Pharmacopeia* monograph (Upton, 2002) are presented in Appendix I. During the spring when only the vegetative parts are visible, *A. racemosa* may be confused with any number of related and unrelated woodland species. Using a combination of a diagnostic table, leaf images and a vegetative key, Ramsey (1988) distinguished the *Cimicifuga* and *Actaea* genera (as they were then classified) from five other genera.

A. racemosa is native to 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, & Matthews, 2011).

Part used

Dried rhizome and roots are harvested in the fall.

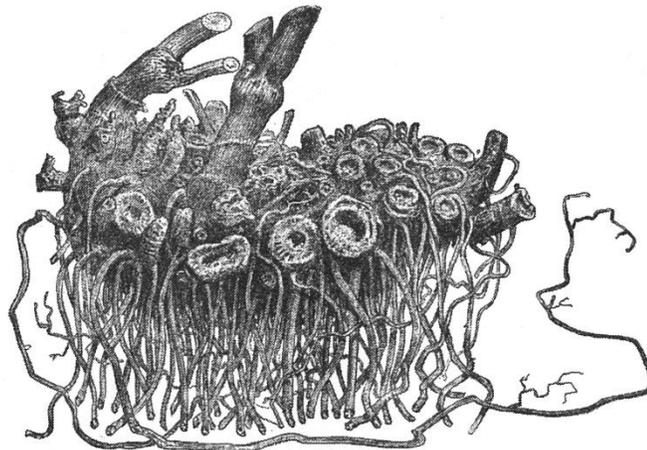


Figure 1. *A. racemosa* rhizome and roots. Reproduced from *Bulletin of the Lloyd Library* #30. By Lloyd, J.U & Lloyd, C.G. Cincinnati, OH 1931.

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 afflictions of the lungs (Millspaugh, 1974; Crellin & Philpott, 1990). Often, a tincture is 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). A root tea may be used to treat sore throat (Duke 1986).

Native American

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). Cherokee use the decoction for a range of conditions including backache, cough, insomnia and rheumatism (Duke 1986). 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, p. 622). Duke (1986) notes the Dakota, Penobscot and Winnebago have all used *A. racemosa* for snakebite and various ailments. 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), spasmodic afflictions, consumption, cough, neuralgia, ulcers, and scrofula (Brown, 1867). Wood (1896), states that the root and rhizome were used to treat small pox, 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 in American homes in the 1800s 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 *Physiomedical dispensatory* (1869), Cook claimed that *A. racemosa* had both soothing and stimulating qualities, whereby 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 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” (1905, p.65).

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” (p. 608) 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 (Petersen, 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 cerebro-spinal 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). 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).

Allopathic and practicing physicians

A. racemosa was included in the US Pharmacopoeia from 1820-1920 (Upton, 2002). The species was used for dropsy, rheumatism, “hysteria” and lung afflictions. It was 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 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 1800s *A. racemosa* was also used by some MDs for facilitation of childbirth, to the extent that clinical investigations were reportedly conducted (Westfall, 2001).

4. 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-deoxyacteïn and cimigenoside (Chen, Fabricant, Lu, Fong, & Farnsworth, 2002a; Chen, et al., 2002b; He, Zheng, Kim, Rogers, & Zheng, 2000; Jiang, Kronenberg, Nuntanakorn, Qiu, & Kennelly, 2006b).

Commercial extracts are usually standardized to 23-epi-26-deoxyacteïn, however detection of individual compounds is challenging due to low ultra-violet (UV) absorption (He et al., 2000; Cicek, Schwaiger, Stuppner, & Ellmerer, 2010). Various non-UV detection methods have been employed including 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 ^{13}C -NMR) (He et al., 2000; Chen et al., 2002b; Panossian, Danielyan, Mamikonyan, & Wilkman, 2004; Wang, Sakurai, Shih, & Lee, 2005; Jiang et al., 2006b). These systems are generally coupled with high performance liquid chromatography (HPLC) systems, and in one case high speed countercurrent chromatography (Cicek et al., 2010).

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, Yang, Nuntanakorn, Balick, Kronenberg, & Kennelly, 2005).

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 (acteïn and 27-deoxyacteïn) (Upton, 2002). This procedure has been further developed to detect 5% adulteration with other *Actaea* spp. (Ankli, Reich, & Steiner, 2009). AHP also published a HPLC method coupled with ELSD, which separates ten peaks and identifies eight triterpene glycosides (Upton, 2002) (Fig. 2). Recently new phytochemical fingerprinting methods to distinguish *A. racemosa* from other species have been developed. Wang and co-workers developed chromatogram fingerprints for seven *Actaea* spp. using 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). A method combining TLC with bioluminescence enabled ready detection of common *A. racemosa* contaminants (Verbitski, Gourdin, Ikenouye, McChesney, & Hildreth, 2008).

Using HR-LC-MS and 1/2D NMR analysis of *A. racemosa* roots and rhizomes collected in Virginia, Chen et al. (2007) detected a new peak eluting with triterpene glycosides; the peak was identified as a chlorine-containing derivative, and 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 (Chen et al., 2007).

The current European and US Pharmacopoeias both include TLC methods for detecting adulteration of *A. racemosa* with different *Cimicifuga* species. For comparisons of quality

standards for *A. racemosa* in the two pharmacopoeias see Table by Brinckmann presented in Appendix 2.

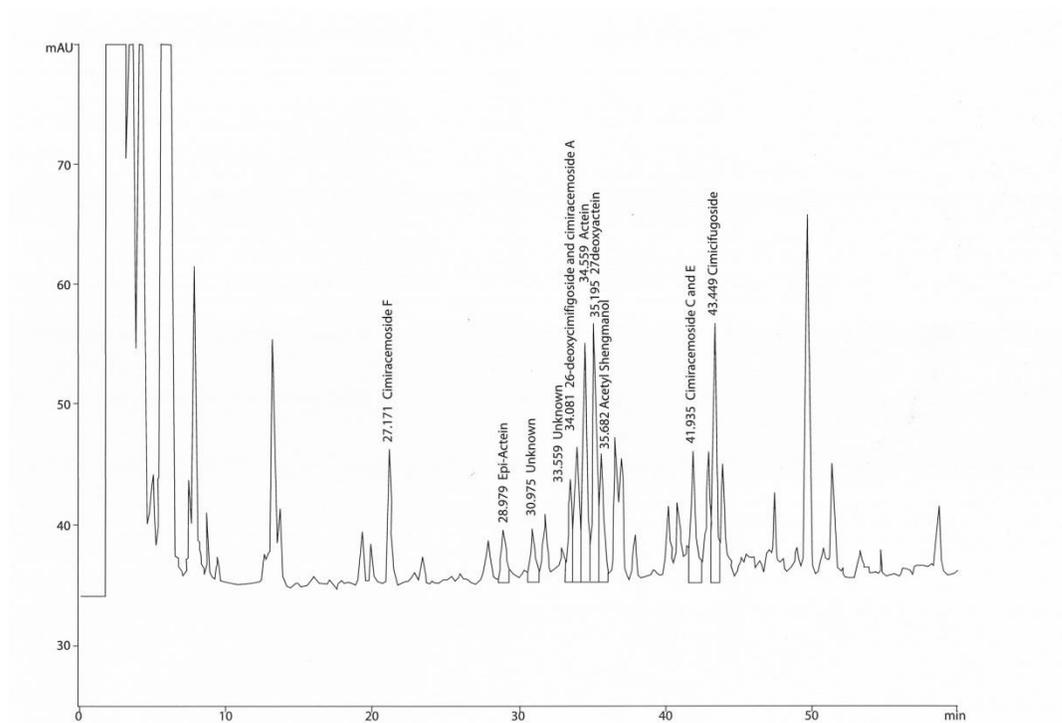


Figure 2. HPLC chromatogram of triterpene glycosides in *A. racemosa*. Reproduced with permission from Upton, (Ed) 2002, *American Herbal Pharmacopoeia*.

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., 2002c; Jiang et al., 2006b; Jiang, Lyles, Reynertson, Kronenberg, & Kennelly, 2008). The preferred analytical method for the phenolic compounds is HPLC coupled with photo diode-array (PDA) (Jiang et al., 2006b; Nuntanakorn, Jiang, Yang, Cervantes-Cervantes, Kronenberg, & Kenelly, 2007), although gas chromatography (GC-MS) has also been used to quantify isoferulic acid (Panossian, Danielyan, Mamikonyan, & Wikman, 2004). An HP-TLC 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 ether of sinapic acid, by ^1H NMR (Gödecke et al., 2009a).

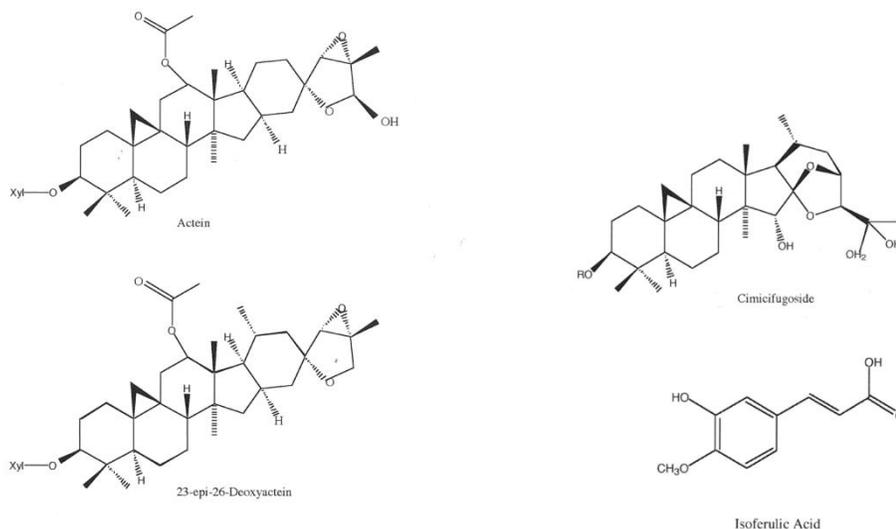


Figure 3. Primary constituents of *Actaea racemosa* L. Reproduced with permission from Upton (Ed.) 2002. *American Herbal Pharmacopoeia*.

Flavonoids

Reports of the presence of isoflavones formononetin and biochanan A and the flavanol 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 colleagues (2004) published a validated method for quantifying formononetin in *A. racemosa* using TLC-densitometry, claiming previous methods used had lacked the necessary sensitivity. Subsequently, other investigators have failed to replicate these findings despite using highly sensitive analytical procedures (Jiang et al., 2006a; Jiang et al., 2011). The consensus of these authors is that any estrogenic-like activity that may be associated with *A. racemosa* cannot be attributed to formononetin (Jiang et al., 2006a).

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 N^ω-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-*O*-glucoside (Gödecke et al., 2009b) (Fig. 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, Urban, Nuss, Gopalan, Stoltzfus, & Eisenstein, 2010).

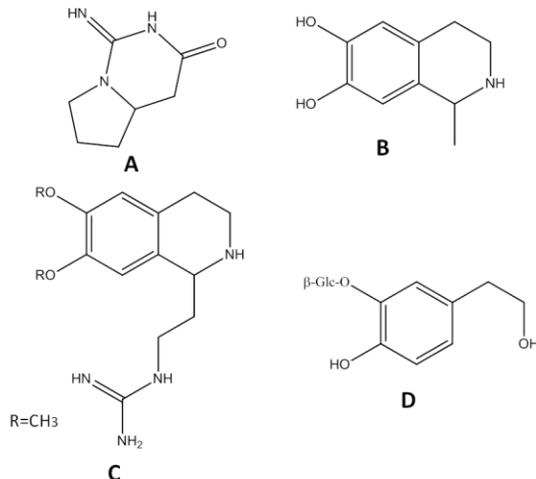


Figure 4. Alkaloids and dopamine derivatives from *A. racemosa*. A. cyclo-cimipronidine B. salsolinol C. dopargine D. hydroxytyrosol 3-O-glucoside. Adapted from Gödecke et al., 2009b.

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). AFLP fingerprinting has been applied to identify genetic diversity within and between geographic regions (Lueck, Cracker, & Motley, 2003). 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).

5. Pharmacology

Pharmacokinetics

Pharmacokinetics of *A. racemosa* triterpenoids were studied in a phase I clinical trial of healthy menopausal women given oral doses of a 75% ethanolic extract standardized to contain 3.64mg total triterpenes and 1.4mg of 23-epi-26-deoxyactein (van Breemen et al., 2010). 23-epi-26-deoxyactein was found to be readily absorbed into the bloodstream with a half-life of around 2 hours. It was also noted that urinary excretion of the compound was negligible, suggesting an alternative excretion pathway such as in bile and feces (van Breemen et al., 2010). Bioavailability of actein has been demonstrated in

Sprague-Dawley rats, achieving a peak concentration of 2.4 µg/mL after 6 hours (Einbond et al., 2009).

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, & 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 (ER α , ER β). 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, Thelen, Christoffel, Spengler, & Wuttke, 2005; 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, Tataryn, Frumar, Erlik, Lu, & Judd, 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; Jarry, Metten, Spengler, Christoffel, & Wuttke, 2003; Ruhlen, Sun, & Sauter, 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 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-HT_{1A} 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) neurons, 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 of *A. racemosa*, N^o-methylserotonin, 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., 2009b).

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 postmenopausal women (Chan, Lau, Jiang, Kennelly, Kronenberg, & Kung, 2008). One triterpenoid glycoside identified in *A. racemosa* – 25-acetylcimigenol xylopyranoside (ACCX), blocked *in vitro* osteoclastogenesis induced by cytokines such as tumor necrosis factor (TNF α), whilst also inhibiting pro-inflammatory signaling pathways NF- κ B and MAPK (Qiu et al., 2007).

Antioxidant effects

Both triterpene glycosides and phenolic constituents contribute to antioxidant activity in *A. racemosa* (Jiang et al., 2005b). 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 estrogen-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 et al., 2005b), confirming findings from earlier studies on immunodeficient mice (Ng & Wigg, 2003). Morphological changes in cell structure helped Hostanska 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). *In vivo* studies indicate bioavailability of actein sufficient for synergy with chemotherapeutic agents (Einbond et al., 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, although *in vivo* models are needed to confirm this activity.

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 extracts from this 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 patented 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 scale 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 Aging* 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 40 mg/day, at the bottom end of the dosage range recommended in the British Herbal Pharmacopoeia (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, Clouston, & Kerlin, (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*.

Histology studies on rat livers following gastric intubation with triterpene enriched (27%) *A. racemosa* extracts demonstrated hepatotoxic effects (Einbond et al., 2009),

while in studies with Wistar rats, each of which received 300mg/kg/day *A. racemosa* extract by gavage for 30 days, no adverse effects to liver morphology or hepatic function indices were observed (Mazzanti et al., 2008). Subsequent clinical studies have confirmed the lack of hepatotoxicity in healthy menopausal women (van Breemen et al., 2010), 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, Schnitker, Minkin, de Arriba, Nolte, & Osmers, 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 postmenopausal women following three months of regular ingestion (200 mg daily) (Spangler, Newton, Grothaus, Reed, Erlich, & LaCroix, 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).

Six triterpenoid glycosides of *A. racemosa* were shown *in vitro* to inhibit CYP3A4, the major cytochrome (CYP) P-450 enzyme associated with phase 1 drug metabolism (Tsukamoto et al., 2002). This finding was not confirmed in a clinical study of 19 healthy adults, where supplementation with a standardized *A. racemosa* extract for 14 days produced no significant change to serum levels of a known CYP3A substrate (Gurley et al., 2006a). In a separate study involving 12 healthy volunteers, *A. racemosa* induced changes to CYP phenotypic trait ratios indicating mild inhibition of CYP2D6 (Gurley et al., 2005). However a subsequent study with 16 healthy human adults failed to demonstrate significant inhibition of CYP2D6 (Gurley et al., 2008). In an investigation into possible interactions between *A. racemosa* extract and the drug digoxin in 16 human subjects, serum concentrations revealed no changes to the pharmacokinetics of digoxin following 14 days of supplementation. Given that digoxin is a known substrate for the P-glycoprotein (P-gp) transporter, the authors concluded there is little risk of P-gp mediated drug interactions with *A. racemosa* (Gurley et al., 2006b).

6. Modern Phytotherapy

Modern therapeutic use of *A. racemosa* reflects both clinical research and traditional use. 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) approved 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* L.).

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

ACTIONS	
Emmenagogue	Sedative
Antirheumatic	Anti-inflammatory
Spasmolytic	Expectorant
THERAPEUTIC INDICATIONS	
<p>Conditions associated with pain and inflammation: osteo- and rheumatoid arthritis, sciatica, neuralgias and ovarian pain.</p> <p>Symptoms associated with menopause and ovarian insufficiency: hot flashes, vertigo, heart palpitations, neurovegetative and emotional disorders</p> <p>Menstrual disorders: amenorrhea, dysmenorrhea, menorrhagia, pre-menstrual syndrome</p> <p>Respiratory disorders: whooping cough, asthma</p> <p>Nervous conditions: irritability, insomnia, headaches, tinnitus</p> <p>Hormonal imbalance: infertility, ovarian cysts, polycystic ovary syndrome</p>	

(Bradley, 1992; Mills & Bone, 2000; Hoffmann, 2003; Kraft & Hobbs, 2004).

Combinations

Black cohosh extracts can be combined with *Hypericum perforatum* for depression and neurovegetative disorders associated with the menopause.

Combined with blue cohosh (*Caulophyllum thalictroides*) in obstetrics historically and also in contemporary midwifery (Bergner, personal communication).

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 et al., 2005; Ruhlen et al., 2008). There are no reports of interactions with prescription drugs.

Preparation and dose

Dried rhizome and root. 40-200mg daily (Peirce, 1999; Bradley, 1992).

Tincture: 1:10. 0.4-2.0mL, three times daily (Bradley, 1992).

Extract: 1:3. 1.0 mL, 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).

7. Sustainability considerations

Ecological (RTE) status

In the United States and Canada, many wild plants have been researched and assigned an ecological status using the rare, threatened, endangered (RTE) classifications. At the federal, state, country and province levels each individual government agency has the authority to assign a status as well, and these are not always in consensus. The distribution of plants varies within its natural range, so while a particular species might be rare in a state at the extreme edges of its range, at the same time it might be abundant in another state where the habitat is most favorable. This produces some regional variability in conservation status which is complicated by the actual process of surveying populations (Brosi & Howell, 2010).

While some states assess, monitor and regulate their wild populations of plants and animals every 2-4 years, other states may reference 10 year old data or abstain from monitoring and regulation. The NatureServe Explorer (NatureServe, 2011) provides global, federal and state RTE status for *Actaea* (black cohosh) but these statuses are not always supported by the respective governments. Kansas, for example, has regulations prohibiting the listing of plants as threatened, endangered or rare beyond those cited in federal law (Mason, 2011) and as such, does not include any *Actaea* spp. since these are not rated as RTE by the US federal government (National Resource Conservation Service of the United States Department of Agriculture ([NCRS, USDA], 2011).

The NRCS of the USDA listed black cohosh (*A. racemosa* and *A. racemosa* var. *racemosa*) as endangered in the state of Illinois with a 2002 reference citation (NRCS, USDA, 2011). In the 2011 Checklist of endangered and threatened animals and plants of Illinois only one *Actaea* species, *A. rubifolia*, has an RTA status (threatened). These inconsistencies have serious implications for regulating and protecting medicinal plants.

This RTE status is not static, statuses change, legislature changes and governing agencies change. The data in this section and in the accompanying table is a snapshot to be used as a reference for anyone interested in marketing, growing or sustainability.

Legislation, state/local surveys and marketing references do not always use the most current botanical nomenclature and several closely related species may be harvested under a common local name (Lonner, 2007). Massachusetts refers to *Actaea racemosa* var. *racemosa* (formerly classified as *Cimifuga racemosa*) as *Actaea racemosa* (black cohosh) (Natural Heritage Endangered Species Program, 2010) while Illinois data identifies black cohosh as *Cimifuga rubrifolia* (Illinois Endangered Species Protection Board, 2011; Lyke, 2001). When researching legislation, permitting and restrictions, the utilization of both older and new nomenclature as well as common names may be needed to provide the most relevant information. The USDA NRCS website (2011) lists three species of *Actaea* (*A. pachypoda*, *A. rubra* and *A. spicata* ssp. *rubra*) with state protected status (Florida, New York, Indiana, Ohio and Rhode Island). New York lists *A. spicata* ssp. *rubra*, which is not a subspecies included on the NatureServe Explorer website (NatureServe, 2011) but was found as *A. rubra* ssp. *rubra* on the NRCS database.

Species found in the Appalachian region or collected in the Eastern United States are listed in the following RTE chart. Both the local and scientific names are listed along with the state or agency that has cited them (Table 2). Two names are listed where a resource lists both current and older scientific names; where only an older name is listed, this indicates the only name cited by that resource. Awareness of all the names used by wild-crafters, environmental protective agencies and governments may help to better track, meet and enforce existing regulations.

Table 2. Ecological status of *A. racemosa* and related species in the U.S. and Canada¹

Scientific Name	Common name	Ecological status by country/state/province	Reference
<i>A. pachypoda</i>	baneberry	Endangered - FL	(NRCS, USDA, 2011)
	baneberry, white baneberry, doll's eyes, necklace weed.	Endangered - FL	(Coile & Garland, 2003)
	white baneberry	G5 secure - global	(NatureServe, 2011)
		(S1): US-DE, FL, KS, NE, OK (S2): US-LA, & RI; Canada-PEI. (S3S4): US- IL. (S4): US-IA, NJ, NC & WV; Canada-NB, NS & QC. (S5): US-AL, CT, GA, KY, NY, VA; Canada- ON. (SNR unranked) US-AK, IN. (SNR): ME, MD, MA, MS,	(NatureServe, 2011)

		MO, NH, OH, PA, SC, TN, VT, WI; Canada - SK	
		Exploitably Vulnerable - NY	(NRCS, USDA, 2011)
		Exploitably Vulnerable - NY	(NY DEC, 2011)
<i>A. podocarpa</i> (<i>Cimifuga americana</i> Michx.)	mountain bugbane	G4 - Apparently vulnerable - global	(NatureServe, 2011)
		(S1) US-IL; (S2) US-MD; (S3) US-GA(?), PA, WV; (S4) US-NC, VA. (S5) US-KY. (SNR) US- SC, TN.	(NatureServe, 2011)
		Endangered - IL	(NRCS, USDA, 2011)
		No RTE Status - IL	(ILESPB, 2011)
		Rare - PA	(NRCS, USDA, 2011)
		S3 vulnerable - PA	(PNHP, 2005)
	Potentially threatened - PA	(PNHP, 2011)	
American bugbane	No RTE Status - IL ²	(ILESPB, 2011)	
<i>A. racemosa</i> (<i>Cimicifuga racemosa</i>)	black cohosh	G4 - global US:N4; Canada: N2	(NatureServe, 2011)
		(S1) US-IL, MA; (S1S2) US-MS; (S2) Canada- ON. (S3) US- IN; (S4) US- DE, GA, NY, NC, VA & WV; (S5) KY. (SH) IA, MI; (SNA) ME. (SNR) US-AL, AK, MD, CT, DC, OH, MO, NJ, PA, SC, TN.	(NatureServe, 2011)
		Endangered - IL, MA	(NRCS, USDA, 2011)
		No RTE Status - IL (2011)	(ILESPB, 2011)
		Endangered - MA- (2008)	(MA DFW, 2008)

<i>Actaea racemosa</i> var. <i>dissecta</i> (A. Gray) J.Compton (<i>Cimicifuga racemosa</i> var. <i>dissecta</i>)	black cohosh	G4 - Global	(NatureServe, 2011)
		(SNR) US- DE	(NatureServe, 2011)
		No RTE Status for any state	(NRCS, USDA, 2011)
<i>A. racemosa</i> var <i>racemosa</i> (L).	black cohosh	G4T4 - Global Apparently secure	(NatureServe, 2011)
		(S4) US- NY. (S5) US- NJ. (SNR) US - AL, AK, GA, CT, DE, IL, DC, IN, IA, KY, ME, MD, MA< MI, MS, MO, NC, OH, PA, SC, TN, VA, WV; Canada - ON.	(NatureServe, 2011)
	black bugbane	Endangered - IL, MA	(NRCS, USDA, 2011)
		No RTE Status - IL (2011)	(IESPB, 2011)
<i>A. rubifolia</i> (<i>Cimicifuga rubifolia</i>)	black cohosh	Threatened - IL	(NRCS, USDA, 2011)
		Threatened - IL	(ILESPB, 2011)
	Appalachian bugbane	G3 - Vulnerable Global	(NatureServe, 2011)
		(S1) US- IN; (S2) US- IL, KY, & VA; (S3) US- TN; (SH) US_AL	(NatureServe, 2011)
		Endangered -IN; Threatened - KY, TN	(NRCS, USDA, 2011)
		No RTE Status - IN	(IN DNR, 2007)
		KY (2011) Threatened	(KYSNPC, 2011)
		S3 - TN (rare and uncommon in the state 21-100 occurrences)	(TNHP, 2008)

<i>A. rubra</i>	red baneberry	G5- Global	(NatureServe, 2011)
		(S1) US - RI; (S2) US - IN, OH; (S2S4) US - PA; (S3) US - IL; (S3S4) Canada - YT; (S4) US-IA, MT, NB (?), WY. Canada-BC; (S5) US- NY. Canada - AL, MB, NB, NS, ON, PEI, QC, SK, NF; (SH) US- KS (SNR) US- AK, AZ, CA, CO, CT, ID, ME, MA, MI, MN, Navajo Nation, NV, NH, NJ, NM, ND, OR, SD, UT, VT, WA, WI. Canada- NT, Nunavut	(NatureServe, 2011)
		Strank-S2 (Imperiled in state)/ State - SR (rare) - IN	(IN DNR, 2007)
<i>A. rubra</i> ssp. <i>rubra</i>	red baneberry	G5T5 - Global	(NatureServe, 2011)
		(S2) US-NJ, (S3S4) Canada - LB; (S5) US-NY. Canada - NB, NF, NS, PEI, QC & SK; (SNR) US- AK, CT, IL, IN, IA, KS, ME, MA, MI, MN, MT, NB, NH, ND, OH, PA, RI, SD, VT, WI. Canada - AB, BC, MN, ON, YT, Nunavut	(NatureServe, 2011)
		The USDA plant database cross-references this citation as <i>A. rubra</i> (IN, OH, RI) and <i>A. spicata</i> ssp <i>rubra</i> (NY)	(NRCS, USDA, 2011)
<i>A.spicata</i> ssp. <i>rubra</i> (Aiton) Hultén	red baneberry	Exploitably Vulnerable - NY	(NY DEC, 2011)

1. Where a species has been listed by the USDA NRCS site with an RTE status for a state, that state's legislative status is included for reference. **Please note:** Governmental databases and legislature providing RTE status may utilize common, local or older biological names, the names in this table are accurate for the specific state, federal or provincial legislation cited, even though they may not use current botanical nomenclature.
2. Using data from 1999/2002 *A.podocarpa* American bugbane was listed by the USDA as endangered in Illinois (USDA, 2011)

According to Lonner (2007) there are several closely related species which are harvested as *A. racemosa* or black cohosh. *A. podocarpa* (yellow cohosh), which is not generally considered medicinal, has been harvested and sold as both *A. racemosa* var. *racemosa* (PNHP, 2005) and *A. racemosa* (Schlosser, 2002). Schlosser (2002) notes that yellow cohosh (*A. podocarpa*) has a leaf structure that is easily mistaken for black cohosh (*A. racemosa*). *C. rubifolia* or Appalachian bugbane is also commonly called black cohosh in Illinois and by the NRCS (2011), currently listed as threatened (Chester et al., 2009). In an online guide to wild-crafting, Drum (2011, para. 2) wrote "that most wild-crafters harvest herbs because they need the money, not because sick people need the herbs." Such monetarily-driven harvesters are more likely to collect whatever they can rather than take care to identify the correct species.

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 et al., 2011). Harvesting had occurred for three years with a two-year recovery period, during which time the 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 un-harvested plants. As most commercially sold *A. racemosa* is collected from wild populations, this raises serious questions of sustainability for this and other native species (Small et al., 2011; Schlosser, 2002).

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 for all species listed as endangered plant regulations. In Illinois a permit would be required to collect black cohosh as *A. rubifolia* but not for *A. racemosa*. The US Forest Service requires permits for collecting and had noted a gradual increase in requests over time (Lyke, 2002).

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 et al., 2011). Lyke (2002) noted that in 2001 the demand for black cohosh

was higher than the demand for goldenseal, especially in Europe and this has grown annually since then (AHPA, 2007). The annual tonnage for fresh plants and dried rhizome is presented in Table 3.

Table 3. Tonnage of cultivated and wild *A. racemosa* 1995-2005 (adapted from AHPA, 2007).

Year	Fresh Plants (lbs)		Dried rhizomes (lbs)	
	Wild	Cultivated	Wild	Cultivated
1997		----	227,002	0
1998	-----	----	725,984	35,430
1999	-----	-----	145,367	2,600
2000	-----	0	117,843	149
2001	1,414	0	177,681	6,521
2002	1,338	0	169,436	282
2003	818	175	318,143	410
2004	12,820	145	318,729	3,312
2005	10,072	0	136,370	6,930

Starting with *A. racemosa* harvests, the five-year high in 2003 was maintained at about 160 tons through 2004 but dropped back to 1999 - 2000 levels with 72 dried tons (cultivated and wild combined) reported for year 2005. The decision made in February of 2004 to stop the estrogen-only portion of the Women’s Health Initiative study and an increased interest in herbal alternatives might help account for the sustained harvest of *A. racemosa* for 2004. It is reasonable to suspect that excess inventory built up from the 2003 - 2004 years could have led to the tonnage drop of 88 tons in 2005 relative to 2004, though this information was not solicited in the AHPA survey and may not be the case. A summary of wholesale costs for *A. racemosa* rhizomes from selected distributors is presented in Appendix IV.

Adulteration

As interest in black cohosh grows, so does the presence of adulterants. Cumberland (2012) notes that in addition to *A. pachypoda*, *A. rubra* and *A. podocarpa*, woodland plants with similar foliage but dissimilar constituents such as *Caulophyllum*, *Astilbe* and *Aruncus* species have been identified as adulterants. Non-American species have also entered the market including *Actaea. cimifuga* L. (formerly *Cimifuga foetida*) or Chinese black cohosh, *A. dahurica* (Turcz. ex Fisch. & C.A.Mey.) Franch. and *A. heracleifolia* (Kom.) J.Compton (Cumberland, 2012).

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 (Blakley & 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; Blakley & Sturdivant, 1999).

Field production

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. Spacing of plants for commercial growers is estimated at 5 plants per square meter, which translates to 500 plants in a 100 square meter bed (Burkhart & Jacobson, 2009).

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. L., *Sanguinaria canadensis* L., and *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 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 and topped with plenty of leaf mulch (Greenfield & Davis, 2004).

Rhizomes may take a full year or more to produce an aboveground shoot (Tilford, 1998; Snow, 2006) but will gradually begin to produce offshoots (Snow, 2006) and grow to a marketable size in about 3-5 years (Greenfield & Davis, 2004; Burkhart & Jacobson, 2009).

Seeds

In the wild, *A. racemosa* seeds with varying germination rates 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: 70° Fahrenheit for two months, after planting and then 40° Fahrenheit for three months. Burkhart & Jacobson (2009) estimate that it takes about 4-6 years before a seed-sown crop is ready for harvest.

In vitro

While *in vitro* culture of *A. racemosa* is not yet in widespread commercial use, Massimino (2009) has provides some 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 and rhizomes 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 leaf spot, root rot and damping off (*Rhizoctonia solani* J.G. Kühn, 1858) 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

Burkhart & Jacobson (2009) advise that the costs required for forest cultivation mean that growers cannot compete with wild-harvested *A. racemosa*. In addition to site preparation, monitoring and protection, manual harvesting increases costs for all plants within a woodland environment (Greenfield & Davis, 2004). In addition, concerns regarding the questionable quality, identity and source of what is being sold as black cohosh are increasing (Cumberland, 2012) whether through wild-crafters or on Ebay (Burgess, 2011).

While wild plants are generally associated with greater potency, growers working with *Panax quinquefolius* have shown that consistency and reliability of product can have an important impact on marketability (Harrison et al, 2012, Burkhart & Jacobson, 2009). According to Harrison et al (2012), ginseng growers may invest as much as \$29,000 per acre and take ten years to break even. Growers interested in field cropping *A. racemosa* may expect a similar level of investment (Burkhart & Jacobson, 2009).

Another concern is environmental impact. Both forest cultivation and wild-crafting can impact on wild populations (Burkhart & Jacobson, 2009). This can potentially be offset by increased commercial and home production.

8. Summary and moving forward

Actaea racemosa is now on the leading edge of medicinal plant research for ecologists, botanists, phytochemists, pharmacologists, clinicians and geneticists. As data from clinical studies continue to demonstrate efficacy and safety, this inevitably leads to extra demand on the supply of raw materials that are still mainly derived from wild-crafted sources. Sustainable wild harvesting may be possible but studies to date have not supported this. Future funding should be targeted at pilot schemes for cultivating *A. racemosa* in both field and wild-simulated settings, and regional 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 purported influences on serum hormonal levels. There is a need for studies that focus on traditional uses including 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.

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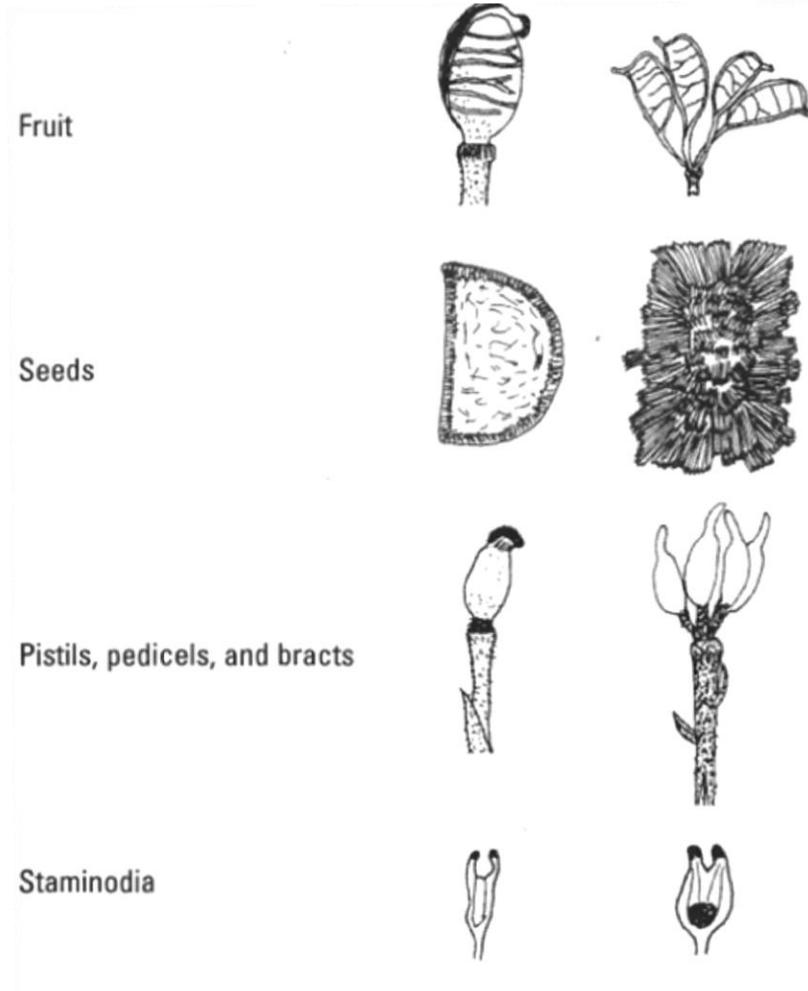
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Appendix I.

Macroscopic features of *A. racemosa* and other species. Reproduced with permission from Upton (ed.) 2002. *American Herbal Pharmacopoeia*.

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



Botanical features distinguishing *A. racemosa* (left) and *A. podocarpa* (right).



From left to right: Cut, dried *A. racemosa*; fresh roots and rhizome of *A. racemosa*; fresh roots and rhizome of *A. podocarpa*.

Appendix II.

Comparison of black cohosh rhizome pharmacopoeial quality standards. Reproduced with permission from Josef Brinckmann, (Personal Communication, 2012).

Standard	PhEur 7.5 2012	USP 35 2012
Identification Tests:	Macroscopic ID Test A	Macroscopic ID Test
	Microscopic ID Test B	Microscopic ID Test
	Thin-layer chromatography (TLC) ID Test C	Thin-layer chromatography (TLC) ID Test A
	TLC tests for detection of adulterations with <i>Cimicifuga americana</i> , <i>C. foetida</i> , <i>C. dahurica</i> and <i>C. heracleifolia</i>	TLC Tests B and C for detection of adulterations with <i>Cimicifuga foetida</i>
Loss on drying	NMT 12% (PhEur 2.2.32)	NMT 12.0% (USP <731>)
Foreign matter	NMT 5% (PhEur 2.8.2)	NMT 2.0% of foreign organic matter and NMT 5.0% of stem bases (USP <561>)
Total ash	NMT 10.0% (PhEur 2.4.16)	NMT 10.0% (USP <561>)
Acid insoluble ash	NMT 5.0% (PhEur 2.8.1)	NMT 4.0% (USP <561>)
Content	NLT 1.0% of triterpene glycosides, expressed as monoammonium glycyrrhizate (C ₄₂ H ₆₅ NO ₁₆ ; M _r 840) (dried drug) as determined by HPLC.	NLT 0.4% of triterpene glycosides, calculated as 23-epi-26-deoxyactein (C ₃₇ H ₅₆ O ₁₀) on the dried basis
Alcohol soluble extractives	No standard	NLT 8.0% (USP <561> Method II)
Microbial contamination (Note: PhEur limits are for herbal drugs that will be further prepared or processed with boiling water)	Total Aerobic Microbial Count: Acceptance criterion: 10 ⁷ /g; Maximum acceptable count: 50,000,000 /g Total Yeast and Mould Count: Acceptance criterion: 10 ⁵ /g; Maximum acceptable count: 500,000 /g <i>Escherichia coli</i> : Acceptance criterion: 10 ³ /g <i>Salmonella</i> : Absence (25 g)	Total aerobic microbial count NMT 10 ⁵ /g Combined molds & yeasts NMT 10 ³ /g Bile-tolerant Gram-negative bacteria NMT 10 ³ /g <i>Salmonella</i> species – absent <i>Escherichia coli</i> – absent
Pesticide Residues	Meets the requirements PhEur General Chapter 2.8.13	Meets the requirements of USP General Chapter <561>
Heavy Metals	NMT 1.0 ppm cadmium; NMT 5.0 ppm lead; NMT 0.1 ppm mercury	NMT 10 ppm (USP <231>)

Appendix III.

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

Name of Company	Country	Product
Anhui Minmetals Development Imp. & Exp. Co., Ltd.	China (Mainland)	black cohosh extract, Triterpenoid Saponins: 1.5% 2.5% 8% HPLC, 10:1, 20:1, 30:1
Xi'an Huarui Bio-Engineering Co., Ltd	China (Mainland)	<i>Cimicifuga racemosa</i> extract /black cohosh root /black cohosh/ black snakeroot/ <i>cimicifuga</i> / macrotys/CAS NO:84776-26-1

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 is 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 IV. Wholesale prices of *A. racemosa* from selected distributors. Reproduced with permission from Josef Brinckmann, (Brinckmann, 2010).

Note: In the U.S., many distributors sell in pound (lb) quantities rather than metric kilogram (kg) quantities. 1 kg = 2.2046 lb.

Wholesale distributors	Processed form	1-4 lb	5-9 lbs	10-24 lbs	25-49 lbs	50-99 lbs	>100 lbs
Good Hope Botanicals							
- Wild collected	Cut and sifted	\$13.90	\$12.51	\$11.82	\$10.43	Inquire	Inquire
Mountain Rose Herbs							
- Certified organic	Cut and sifted	\$19.50	\$17.55	\$16.58	\$15.60	\$13.65	\$11.70
- Certified organic	Powdered	\$22.00	\$19.80	\$18.70	\$17.60	\$15.40	\$13.20
Pacific Botanicals							
- Wild collected	Cut and sifted	\$11.90	\$10.60	\$10.60	\$10.00	\$10.00	\$9.20
- Wild collected	Powdered	\$13.50	\$12.50	\$12.50	\$10.50	\$10.50	\$9.70
San Francisco Herb & Natural Food Co.							
- Wild collected	Cut and sifted	\$12.50	\$11.88	\$11.25	\$10.63	Inquire	Inquire
- Wild collected	Powdered	\$12.75	\$12.11	\$11.48	\$10.87	Inquire	inquire
- Certified organic	Powdered	\$14.00	\$13.30	\$12.60	\$11.90	Inquire	Inquire

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>

San Francisco Herb & Natural Food Co. Wholesale Catalog 2010: <http://www.herbspicetea.com/SFPromo>.

Editor's Note: The American Botanical Council, publisher of HerbalEgram, 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 V. Additional resources for growing, monitoring and assessing black cohosh.

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