Journal of Ethnopharmacology 141 (2012) 775–779

Contents lists available at SciVerse ScienceDirect

Journal of Ethnopharmacology

journal homepage: www.elsevier.com/locate/jethpharm

Review

Black cohosh: Coming full circle?

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ARTICLE INFO

Article history:
Received 7 February 2012
Received in revised form 28 March 2012
Accepted 29 March 2012
Available online 6 April 2012

Keywords:
Analgesic
Antinociceptive
Black cohosh
Actaea racemosa
Premenstrual syndrome (PMS)
Reproductive pharmacology
Triterpenoids
Traditional medicine Northern America

ABSTRACT

Ethnopharmacological relevance: Black cohosh (*Actaea racemosa* L.), Ranunculaceae, thrives in temperate climates east of the Mississippi River in the USA. It is economically important to the Appalachian region where it is wild harvested, but it has resisted most efforts at deliberate cultivation. Black cohosh has been used for many centuries both in Europe and in the US (by indigenous people and subsequent Caucasian medical practitioners), most notably for indications of premenstrual syndrome (PMS), menstrual pain and cramping.
Aim of the study: To highlight black cohosh as an example in which disregard for the ethnobotanical and ethnopharmacologic usages of a plant has perhaps hindered modern scientific attempts to understand the mechanism of action of its bioactive phytochemicals, and ascribe cause to effect.
Results: Research on its mode of action has historically focused on its presumed hormonal (phytoestrogenic) activity, but very recent work suggests that it may in fact be acting as an antinociceptive agent. Re-examination of some of the writings of 19th and 20th century physicians and folk literature suggests that this mode of action may have been overlooked in modern experimentalists' in vitro and animal studies and in the very few well conducted human trials to date.
Conclusions: The common folk perception of this plant as a "remedy for female problems" may thus require revision, as it may possess more general analgesic properties. In the broader context, ethnopharmacologic indications for other herbal remedies must be revisited in light of the explosion in understanding of mechanisms of action of small molecule effectors of which actein and cimicifugoside (from black cohosh) are only two examples.

Contents

1. Introduction

Black cohosh (*Actaea racemosa* L.), a member of the Ranunculaceae family, is an herbaceous plant native to the eastern United States. It has a long and varied history of medicinal use in both traditional and allopathic medicine. In modern times, its most notable clinical application has been in the role of anti-climacteric agent to reduce the frequency and severity of hot flashes in menopausal women.

Abbreviations: CE, catecholestrogen; CYP, cytochrome P450; GST, glutathione-*S*-transferase; NMS, *N*-ω-methylserotonin; NE, norepinephrine; PMS, premenstrual syndrome; NQO1, NAD(P)H:quinone oxidoreductase 1; TRPV, transient receptor potential vanilloid.

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0378-8741/$ – see front matter © 2012 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.jep.2012.03.050

Over the last century, much serious scientific research has occupied itself with clinical and mechanistic studies focused on the role of specific compounds present in plants such as black cohosh for specific indications. The discovery of the beneficial role of a large number of phytochemicals that are now items of commerce has resulted from these endeavors (e.g. morphine (analgesic), artemisinin (anti-malarial), scopolamine (anti-cholinergic), curcumin (anti-neoplastic), and salicylate (anti-inflammatory)). When viewed with this parochial lens, the field of vision regarding these plants has become narrowed and, by necessity, self-limiting.

This "single drug—single target" philosophy has so guided (and misguided) much of the research, such that the context within which many of these phytochemicals and even their synthetic or semi-synthetic derivatives are viewed has had limited scope. It has only been with the recent advent of high-throughput screening and the "-omics" revolution that unanticipated uses for some of these compounds are being discovered, and much of this is driven by pharmaceutical companies' lack of an efficient (productive and cost-effective) synthetic pipeline.

It is against this backdrop that black cohosh has been regarded in modern times as an herb with compounds that are effective for the amelioration of menopausal symptoms such as hot flashes. However, we suggest that perhaps this view should be broadened in light of new understandings that modern techniques have brought into focus about the mechanism(s) by which this long understood traditional use indication may function.

2. Botanical history and ethnobotanical use

Black cohosh was first described in 1705 in botanist Leonard Plukenet's *Phytographia* as *Christopheriana facie, Herba spicata, ex Provincia Floridana* (Hutton et al., 1809; Ewan, 1969). The herb was later designated *Actaea racemosa* L. in Linnaeus' seminal work, *Species Plantarum* (Foster, 1999). Nearly 150 years of circular taxonomical debate generated a succession of name changes that included *Cimicifuga serpentaria*, *Cimicifuga racemosa*, and *Macrotys*, an adulteration of an earlier classification, *Macrotrys* (Foster, 1999). In 1999, black cohosh was reclassified as *Actaea*, based on analysis of the species' nuclear ribosomal DNA (Compton et al., 1998). The etymology of the herb's familiar name is not known; however, the first usage of "cohosh" is found in the writings of botanist Constantine Rafinesque in the early 1800s (Rafinesque, 1828, 1836). Anecdotally, cohosh is believed to be an Algonquian word for "pregnancy" (Gladstar and Hirsch, 2000).

Historically, black cohosh has been alternately characterized in terms of its appearance, "conspicuously handsome"(Felter, 1922); odor, "like smoke from smoldering twigs and leaves"(King and Wintermute, 1892); or taste, "sweet, earthy" (Gladstar and Hirsch, 2000). Others have anthropomorphized the plant, associating its physical characteristics with its putative targets of action, claiming the unfurled tips of its leaves resemble a fetus; its racemes mimic the human spine; and its massed, fibrous root mirror a morose, disconsolate disposition (Gladstar and Hirsch, 2000). North American indigenous people's treatment of the herb was somewhat more pragmatic, however, referring to it simply as "squaw root," a descriptor more in keeping with its preferential application as a treatment for gynecological conditions such as pain associated with premenstrual syndrome (PMS), pain during childbirth, and menopausal complaints, including migraine (Lighthall, 1883).

Black cohosh was adopted by early settlers to North America and has had a long tradition of use among medical practitioners in the United States and Europe. The American Eclectics, a sect of late 19th and early 20th century physicians whose treatment philosophy was based chiefly on botanical remedies, adopted black cohosh into their repertoire of "Specific Medicines," potent extractions of the bioactive components of a resinous compound derived from the plant's rhizomes (Wilder, 1901; Felter, 1922). Attempts to separate the compound into its constituent parts revealed the individual components lacked the efficacy of the original resin, described poetically as a "complex mixture of bodies" (Felter, 1922).

John Uri Lloyd, a renowned Eclectic pharmacist, ethnobotanist, and herbalist, documented the sources, techniques, and uses for the suite of drugs available to early 20th century practitioners (Felter, 1922). Lloyd's meticulous and indisputable scientific approach gained him the respect of all the schools of medicine of his day. His Specific Medicine Macrotys was a potent tincture derived by macerating the fresh root in a 50% alcohol solution for ten days; the recommended dose was 1–30 drops or "minims." A minim, a now-obsolete apothecary's measure, was equal to one grain, or 65 mg of the crude drug (Cook, 1869; Felter, 1922). Alternatively, the herb was dispensed in the form of an infusion produced by steeping the powdered dried root in very hot but not boiling water.

In 1922, Eclectic physician Harvey Wickes Felter wrote a series of monographs describing the medicinal plants commonly employed by his colleagues. His *Treatise on Macrotys* revealed that the Eclectics prescribed black cohosh for relief from a variety of ailments and diseases associated with gynecological disorders and pain-related conditions (Felter, 1922). In describing the pharmacodynamics of the plant's bioactive compounds, Felter reported that small doses induced a state of relaxation, stimulated the appetite, and elicited diaphoresis. When employed as a diaphoretic, a pronounced odor of the plant was detectable in the patient's perspiration. Large doses produced impaired vision, vertigo, nausea, vomiting, and, in the case of overdose, hypotensive shock (Blair, 1917).

Interestingly, black cohosh was appreciated as both an abortifacient and as a treatment for incipient puerperal insanity, a severe form of postpartum depression (Ellingwood and Lloyd, 1919; Felter, 1922). While the herb was used extensively for gynecological disorders, it is noteworthy that the majority of its documented uses emphasized its analgesic qualities for both men and women. In 1848 black cohosh was acclaimed by the American Medical Association for its superior sedative qualities (Gladstar and Hirsch, 2000). More recently, in the latter part of the 20th century, black cohosh gained popularity as a remedy for the hot flashes associated with menopause (Rhyu et al., 2006). Paradoxically, folk and ethnomedical accounts of the usage of black cohosh praised the herb's diaphoretic qualities: it elicits the very symptoms it purportedly prevents such as flushing and perspiring during hot flashes (Shanafelt et al., 2002).

Natural stands of black cohosh are threatened not only by habitat destruction but also by excessive wild harvest above and beyond its natural replacement rate due to the increasing global demand for this plant. Although efforts are being made to develop tissue culture micropropagation protocols (Lata et al., 2002), these techniques do not appear to have gained widespread acceptance, nor is the controlled cultivation of black cohosh necessarily going to alleviate the pressure on wild populations. Wild-harvested plant materials supply nearly all commercial sales of black cohosh, with plant materials from Appalachian forests in the eastern United States providing millions of kilograms of roots and rhizomes (Small et al., 2011). Thus, if the demand for this plant keeps growing, strategies for sustainable harvesting (i.e. low harvest intensities and minimum recovery periods) must be better developed and disseminated. If indications for black cohosh become better supported by clinical trials, as with other wild-harvested herbs, demand could soon outstrip supply of authentic material. The sale of inferior or improperly identified plant material then becomes even more of a danger than it is currently.

3. Role as an anti-climacteric

The data supporting the efficacy of black cohosh in preventing or reducing the frequency and severity of hot flashes have not been invariant. Several randomized, double blind, placebo controlled clinical trials found no significant improvement in vasomotor symptoms in menopausal women (Liske et al., 2002; Newton et al., 2006; Pockaj et al., 2006; Geller et al., 2009; Maki et al., 2009). However, other well-designed studies found the converse to be true (Frei-Kleiner et al., 2005; Raus et al., 2006; Wuttke et al., 2006; Bai et al., 2007). A strong placebo effect was seen in many of these trials, leading researchers to question the putative efficacy of the herb in relieving hot flashes (Shanafelt et al., 2002).

The mechanisms underlying the etiology of hot flashes are complex. Whereas it has long been postulated that decreased estrogen levels associated with menopause produce hot flashes, it is now widely understood that estrogen *withdrawal* during menopause induces hypothalamic thermoregulatory center dysfunction, precipitating a heat loss response and the characteristic symptoms of hot flashes: vasodilation, profuse perspiration, palpitations, and anxiety (Shanafelt et al., 2002). The body's thermoregulatory zone, a homeostatically maintained temperature range, is governed by hypothalamic input; increases in core body temperature of 0.01 °C above this zone can trigger a hot flash (Casper and Yen, 1985; Freedman, 2001). A complex interplay of catecholamines, steroid hormones, endogenous opioids, and their respective neuroendocrinal pathways provides multiple mechanisms for thermoregulatory center dysfunction (Casper and Yen, 1985; Kronenberg and Downey, 1987; Rosenberg and Larsen, 1991).

Norepinephrine (NE), a catecholamine released from the noradrenergic neurons of the brain's locus ceruleus, is thought to be a key player in the etiology of hot flashes (Casper and Yen, 1985; Kronenberg and Downey, 1987; Rosenberg and Larsen, 1991). Catecholestrogen (CE), a metabolite of estrogen, and endogenous opioids typically keeps NE activity in check but in menopause, CE and opioid levels decrease, ablating their inhibitory effects on NE. Without adequate control, NE becomes a "smoking gun," reducing the set point of the thermoregulatory zone and triggering a heat loss response—the hot flash (Casper and Yen, 1985; Kronenberg and Downey, 1987; Rosenberg and Larsen, 1991; Freedman, 2001).

Whereas hot flashes are somewhat acute, subsiding after estrogen levels are depleted, other conditions associated with modulating estrogen levels can be considered chronic. For this reason, several chronic pain syndromes such as fibromyalgia, temporomandibular pain, and arthralgia are more frequently diagnosed in women than in men (Unruh, 1996; Macfarlane et al., 2002; Magliano, 2010). One theory regarding this association asserts that estradiol, the most abundant of the estrogens, participates in antinociceptive pathways through its actions on endogenous opioid receptors (Smith et al., 2006). The μ-opioid receptors, in particular, are highly efficacious mediators of pain (Zubieta et al., 2001). When women were given a pain challenge during a high-estradiol state, μ-opioid receptors demonstrated increased binding potential and the women reported a less intense pain experience. When the same challenge was given during a low-estradiol state, binding potential was impaired and the pain experience was heightened (Smith et al., 2006).

Interestingly, black cohosh serves as an agonist and competitive ligand for the μ-opioid receptor (Rhyu et al., 2006). Its affinity for the receptor may elucidate the herb's beneficial role in ameliorating symptoms associated with estrogen withdrawal during menopause. The relationship between estrogen, the endogenous opioid system, and black cohosh was explored recently in a novel study utilizing molecular neuroimaging to gauge μ-opioid receptor binding of the herb's bioactive components. Positron electron tomography imaging of the brains of postmenopausal women treated with black cohosh revealed significant increases in the binding potential of μ-opioid receptors in the nucleus accumbens, an area associated with the placebo effect (Reame et al., 2008). Increased binding potential was also evinced in the hypothalamus, the region associated with thermoregulatory dysfunction, but this increase did not achieve statistical significance (Reame et al., 2008). Although the objective of this small pilot study was to further elucidate the connection between black cohosh and hot flashes, it serendipitously provided insights into the herb's sustained reputation as an analgesic.

4. Phytochemistry: efficacy and toxicity

Phytochemical studies have identified more than 50 secondary metabolites in black cohosh, including chromones (primarily phenylpropanoid derivatives of hydroxycinnamic acid), flavonoids, simple alkaloids, and polyphenolic fukiic acid esters. These compounds and their purported biological effects have been thoroughly and comprehensively covered in a number of recent reviews (Chen et al., 2002; Li and Yu, 2006; Jarry et al., 2007). Whether black cohosh contains the isoflavone formononetin is still under debate (Jarry and Harnischfeger, 1985; Panossian et al., 2004; Jiang et al., 2006). The principal bioactive constituents of black cohosh are *N*-ω-methylserotonin and the triterpene glycosides actein, 23-epi-26-deoxyactein, and cimicifugoside (Bedir and Khan, 2000, 2001; Shao et al., 2000; Wende et al., 2001; Chen et al., 2002; Watanabe et al., 2002; Powell et al., 2008).

N-ω-methylserotonin (NMS) is a metabolite of the mammalian and plant hormone, serotonin. It has been suggested that in humans, serotonin participates in thermoregulation through its influence on the release of various neurotransmitters, including norepinephrine (Hedlund and Sutcliffe, 2004). Alternatively, the hot flash may be modulated by serotonergic inhibition of hypothalamic mediation of vasomotor symptoms (Horiuchi et al., 2008). NMS demonstrates an affinity for serotonin receptors 5-HT1A and 5-HT7, providing a possible mechanism by which black cohosh ameliorates hot flashes (Burdette et al., 2003; Hedlund and Sutcliffe, 2004; Powell et al., 2008). Interestingly, NMS is present in black cohosh in micromolar concentrations and genetic analysis of the plant revealed that expression of genes encoding for enzymes instrumental in serotonin biosynthesis is negligible and inconsistent (Spiering et al., 2011).

Triterpenes are steroid precursors present in humans and plants. They demonstrate a complex pattern of pharmacokinetics, serving as both substrates and inhibitors for cytochromes CYP 2D6; inhibitors of CYP3A4, CYP1A2, and CYP2C19; and potent inducers but not substrates of phase II enzymes glutathione-*S*-transferase (GST) and NAD(P)H:quinone oxidoreductase 1 (NQO1) (Gurley et al., 2005; Yates et al., 2006). As such, the principle triterpenes in black cohosh do not appear to undergo biotransformation in the gut. Rather, in light of the relatively small amounts present in the systemic circulation or urine following ingestion, it has been suggested that the intact parent compound is taken up in the enterohepatic circulation and excreted in bile (van Breemen et al., 2010).

The catalog of putative beneficial effects attributed to the triterpenes is extensive and includes anti-HIV, anti-carcinogenic, anti-inflammatory, anti-diabetic, anti-malarial, anti-inflammatory, anti-atherosclerotic, and anti-osteoporotic properties, among others (Bortalanza et al., 2002; Watanabe et al., 2002; Jarry et al., 2005; Wuttke et al., 2006; QueffÈlec et al., 2008; Ramalhete et al., 2010; Liang et al., 2011; Ravikumar et al., 2011; Tang et al., 2011). Their role as analgesics is very strongly supported by an

abundance of rodent studies. Examples of the analgesic qualities of triterpenes include their binding to TRPV1, a vanilloid receptor, to combat both acute and visceral pain (Oliveira et al., 2005; Cui et al., 2006); opioid and serotonergic system effects to combat visceral, neurogenic and inflammatory pain, and amelioration of mustard-oil induced visceral hyperalgesia (Maia et al., 2006a,b).

While the body of evidence supporting the efficacy of black cohosh has increased, concerns regarding its safety have similarly increased. Recent reports of the economic adulteration of commercial black cohosh preparations have prompted concerns regarding possible black cohosh-induced hepatotoxicity (Mahady et al., 2008; Jiang et al., 2011). However, assessment of suspected liver toxicity cases revealed insufficient data to implicate black cohosh as a hepatotoxin (Teschke et al., 2009a,b). In addition, a recent meta-analysis of several well-designed clinical trials of black cohosh efficacy demonstrated that pure black cohosh did not induce liver damage. Where hepatotoxicity was present, causality could not be assigned because there was insufficient evidence to indicate whether hepatotoxicity was induced by an adulterated version of black cohosh, concomitant drug or herbal supplement use, or antecedent liver disease (Naser et al., 2011).

5. Perspective and conclusions

Consider this somewhat parallel and perhaps better known example of indigenous wisdom without (yet) a clear-cut mandate that specific phytochemicals are responsible: In addition to the triterpenes oleanolic acid and ursolic acid, the popular Brazilian beverage maté contains several other phytochemicals, including quercetin, matein, chlorogenic acid, and saponins. These compounds synergistically coalesce to deliver a phytochemical cocktail that, in addition to relieving pain, purportedly reduces risk of atherosclerosis, cancer, diabetes, and neurodegenerative diseases (Puangpraphant and de Mejia, 2009). This is not newsworthy to those who consume maté on a regular basis; it has been "good medicine" to many generations of Brazilians and their Amazonian ancestors (Heck and de Mejia, 2007). Thus, traditional medicinal applications of various indigenous herbal remedies may appear at first glance to include lengthy and indiscriminant laundry lists of effects. The fact that there may be a sound basis for some or many of these indications is anathema to Western medicine practitioners in the absence of mechanistic or clinical trial support. Although that is perhaps how it should be, a myopic focus on single mechanisms, derived from recent (historically speaking) identification of "the target," may distract us from proper critical evaluation of a panoply of putative targets.

The ethnobotanical and historical uses of black cohosh should similarly be scrutinized for the inherent wisdom they hold. Centuries before actein, 23-epi-26-deoxyactein and cimicifugoside were identified, early practitioners believed the rhizomes of this plant contained a "complex mixture of bodies"(Felter, 1922), that could relieve pain. Future research will be hindered if the ancient wisdom is ignored and the synergy of the plant matrix is overlooked. A small number of studies in the Western medicine tradition have now begun to consider the link between black cohosh and pain, acknowledging what has been known for a long time. More rigorous work is needed for this plant medicine to truly come full circle.

Acknowledgments

The authors gratefully acknowledge funding from the Lewis B. and Dorothy Cullman Foundation (JWF), and the Harry D. Kruse Publication Award in Human Nutrition (TLJ).

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