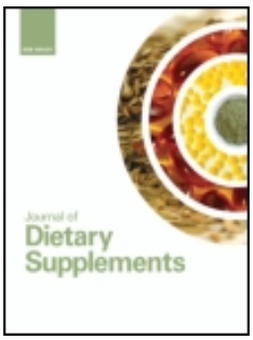

Journal of Dietary Supplements

ISSN: 1939-0211 (Print) 1939-022X (Online) Journal homepage: https://www.tandfonline.com/loi/ijds20

An Evidence-Based Systematic Review of Black cohosh (*Cimicifuga racemosa*, *Actaea racemosa*) by the Natural Standard Research Collaboration

Catherine Ulbricht & Regina C. Windsor

To cite this article: Catherine Ulbricht & Regina C. Windsor (2015) An Evidence-Based Systematic Review of Black cohosh (*Cimicifuga racemosa*, *Actaea racemosa*) by the Natural Standard Research Collaboration, Journal of Dietary Supplements, 12:3, 265-358, DOI: 10.3109/19390211.2014.946731

To link to this article: https://doi.org/10.3109/19390211.2014.946731

Published online: 25 Aug 2014.

Journal of Dietary Supplements, 12(3):265–358, 2015

Available online at www.informahealthcare.com/jds
DOI: 10.3109/19390211.2014.946731

informa
healthcare

ARTICLE

An Evidence-Based Systematic Review of Black cohosh (*Cimicifuga racemosa*, *Actaea racemosa*) by the Natural Standard Research Collaboration

Catherine Ulbricht, PharmD[1] & Regina C. Windsor, MPH[2*]

[1]*Massachusetts General Hospital,* [2]*Natural Standard Research Collaboration*

ABSTRACT. An evidence-based systematic review of black cohosh (*Cimicifuga racemosa*, *Actaea racemosa*) by the Natural Standard Research Collaboration consolidates the safety and efficacy data available in the scientific literature using a validated, reproducible grading rationale. This article includes written and statistical analysis of clinical trials, plus a compilation of expert opinion, folkloric precedent, history, pharmacology, kinetics/dynamics, interactions, adverse effects, toxicology, and dosing.

KEYWORDS. *Actaea racemosa*, adverse effects, black cohosh, *Cimicifuga racemosa*, dosing, evidence-based, interactions, pharmacodynamics, pharmacology, pharmacokinetics, systematic review

SYSTEMATIC AGGREGATION, ANALYSIS, AND REVIEW OF THE LITERATURE

Search Strategy

To prepare this Natural Standard review, electronic searches were conducted in several databases (including AMED, CANCERLIT, CINAHL, CISCOM, the Cochrane Library, EMBASE, HerbMed, International Pharmaceutical Abstracts, Medline, and NAPRALERT) from inception to February 2014. Search terms included the common name(s), scientific name(s), and all listed synonyms. Hand searches were conducted of 20 additional journals (not indexed in common databases), and of bibliographies from 50 selected secondary references. No restrictions were placed on language or quality of publications. Researchers in the field of complementary and alternative medicine (CAM) were consulted for access to additional references or ongoing research.

*Additional Natural Standard Research Collaboration contributors were involved in the production of this manuscript.

Address correspondence to: Catherine Ulbricht, PharmD, Massachusetts General Hospital, 55 Fruit St, Boston, MA 02114 AND Natural Standard Research Collaboration, 1 Davis Square, Somerville, MA, 02144. (E-mail: catherineulbricht@gmail.com).

Selection Criteria

All literature was collected pertaining to efficacy in humans (regardless of study design, quality, or language), dosing, precautions, adverse effects, use in pregnancy/lactation, interactions, alteration of laboratory assays, and mechanism of action (in vitro, animal research, human data). Standardized inclusion/exclusion criteria were utilized for selection.

Data Analysis

Data extraction and analysis were performed by healthcare professionals conducting clinical work and/or research at academic centers, using standardized instruments that pertained to each review section (defining inclusion/exclusion criteria and analytic techniques, including validated measures of study quality). Data were verified by a second reviewer.

Review Process

A blinded review was conducted by multidisciplinary research-clinical faculty at major academic centers with expertise in epidemiology and biostatistics, pharmacology, toxicology, complementary and alternative medicine (CAM) research, and clinical practice. In cases of editorial disagreement, a three-member panel of the Editorial Board addressed conflicts, and consulted experts when applicable. Authors of studies were contacted when clarification was required.

Natural Standard Systematic Review (www.naturalstandard.com) Copyright © 2014.

Synonyms/Common Names/Related Substances

- 5-HT(Bai et al., 2009) ligand, *Actaea macrotys*, *Actaea pachypoda*, *Actaea podocarpa*, *Actaea racemosa* L., *Actaea rubra*, actaealactone, actée à grappes (French), Amerikanisches Wanzenkraut (German), Appalachian bugbane, baneberry, BCE, black bugbane, black cohosh root extract Cr 99, black cohosh roots, black snakeroot, *Botrophis serpentaria*, bugbane, bugwort, caffeic acid, *Cimicifuga*, *Cimicifuga racemosa*, *Cimicifugae racemosae* rhizoma, Cimicifugawurzelstock (German), cimicifugic acid A, cimicifugic acid B, cimicifugic acid D, cimicifugic acid E, cimicifugic acid F, cimicifugic acid G, cohosh bugbane, CR, CR BNO 1055, CR extract, ferulic acid, fukinolic acid, herbe au punaise (French), ICR, isoferulic acid, isopropanolic black cohosh extract, isopropanolic extract, macrotys, *Macrotys actaeoides*, methyl caffeate, mountain bugbane, *N*-omega-methylserotonin, p-coumaric acid, phytoestrogen, protocatechualdehyde, protocatechuic acid, Ranunculaceae (family), rattle root, rattle snakeroot, rattle top, rattle weed, rattlesnake root, rattleweed, Remifemin®, rhizoma *Actaeae*, rich weed, richweed, schwarze Schlangenwurzel (German), snakeroot, solvlys, squaw root, squawroot, *Thalictrodes racemosa*, Traubensilberkerze (German), triterpene glycosides, Wanzenkraut, Ze 450.
- **Combination product examples**: GYNO-Plus (black cohosh and St. John's wort), PNC (pennyroyal, red raspberry, lobelia, blue cohosh, black cohosh, blessed thistle), Phyto-Female Complex (standardized extracts of black cohosh, dong quai, milk thistle, red clover, American ginseng, chaste-tree berry), and Reumalex®

(contains 35 mg of black cohosh, 100 mg of white willow bark, 25 mg of sarsaparilla (4:1), 17 mg of poplar bark (7:1), and 40 mg of guaiacum resin).

Note: Black cohosh (*Cimicifuga racemosa*) is not to be confused with blue cohosh (*Caulophyllum thalictroides*), which contains potentially cardiotoxic or vasoconstrictive chemicals. Black cohosh (*Cimicifuga racemosa*) is also not to be confused with *Cimicifuga foetida*, bugbane, fairy candles, or sheng ma; these are species from the same family (Ranunculaceae) with different therapeutic effects.

CLINICAL BOTTOM LINE/EFFECTIVENESS

Brief Background

- Black cohosh, a perennial plant from the buttercup family, is one of the best-selling supplements in the United States and is popular as an alternative to hormonal therapy in the treatment of menopausal (climacteric) symptoms such as hot flashes, mood disturbances, diaphoresis, palpitations, and vaginal dryness (Borrelli & Ernst, 2010; Donnelly, 2007; Kupferer, Dormire, & Becker, 2009; Mello, 2008; Roush, 2012; Shah & Agrawal, 2010; Shen & Stearns, 2009). With the exception of formononetin, extracts from black cohosh are not considered phytoestrogens (Villaseca, 2012). Several controlled trials and case series have reported black cohosh to improve menopausal symptoms for up to 1 year. Systematic reviews and meta-analyses report a mixed result for the effectiveness of black cohosh on climacteric symptoms. Black cohosh has been traditionally used for menstruation problems (Molla, Hidalgo-Mora, & Soteras, 2011; Roush, 2012).
- The mechanism of action of black cohosh remains unclear, and the effects on estrogen receptors or hormonal levels (if any) have not been fully elucidated. Studies suggest that there may be no direct effects on estrogen receptors, although this is an area of active controversy (Borrelli, Izzo, & Ernst, 2003; Burdette et al., 2003; Huntley & Ernst, 2003b; Jarry, Metten, Spengler, Christoffel, & Wuttke, 2003; Lupu et al., 2003; Mahady, 2003; Seidlova-Wuttke et al., 2003; Seidlova-Wuttke, Jarry, Becker, Christoffel, & Wuttke, 2003). Safety and efficacy data beyond one year are lacking, although reports suggest safety with short-term use, including in women experiencing menopausal symptoms for whom estrogen replacement therapy is contraindicated (Dog, Powell, & Weisman, 2003; Hernandez Munoz & Pluchino, 2003; Thacker, 2011). Use of black cohosh in high-risk populations (such as in women with a history of breast cancer) should be under the supervision of a licensed healthcare professional.
- Since the Women's Health Initiative Trial was halted early due to an excess risk of stroke and other adverse outcomes, millions fewer women are using prescription hormone replacement therapy. However, a 2005 survey showed a lack of appreciable increase in alternative therapies, including black cohosh (Kelly et al., 2005).
- Studies and reports of liver damage due to the use of black cohosh has led to the development of recommendations from several regulatory agencies to help promote safety and a better understanding of black cohosh (Becker, Letham, & Stoehr, 2009; Betz et al., 2009; Dunbar & Solga, 2007; Gori & Firenzuoli,

2007; Herbal Medicinal Products Committee, 2007; Mahady et al., 2008; Teschke, 2009b). A true causal relationship is considered questionable by several researchers in the field due to confounding factors (Mahady, Low Dog, Sarma, & Giancaspro, 2009; Mahady, Low Dog, Sarma, Giancaspro, & Griffiths, 2010; Teschke, 2009a, 2010; Teschke, Bahre, Fuchs, & Wolff, 2009; Teschke et al., 2009; Teschke & Schwarzenboeck, 2009; Teschke, Schwarzenboeck, Schmidt-Taenzer, Wolff, & Hennermann, 2011; Walji, Boon, Guns, Oneschuk, & Younus, 2007).

- A cross-sectional analysis of several herbal supplements, including black cohosh, reported that lead levels in the blood were higher in women that used the supplements studied vs. nonusers (Buettner et al., 2009).

Scientific Evidence

Arthritis pain	C
Bone density (postmenopausal women)	C
Breast cancer	C
Cognitive function (postmenopausal women)	C
Coronary heart disease (postmenopausal women)	C
Infertility	C
Menopausal symptoms	C
Migraine (menstrual)	C

Natural Standard Evidence-Based Validated Grading Rationale™

- Grades reflect the level of available scientific evidence in support of the efficacy of a given therapy for a specific indication.
- Expert opinion and historic/folkloric precedent are not included in this assessment, and are reflected in a separate section of each review ("Expert Opinion and Historic/Folkloric Precedent").
- Evidence of harm is considered separately; the below grades apply only to evidence of benefit.

Level of Evidence Grade	Criteria
A (strong scientific evidence)	Statistically significant evidence of benefit from >2 properly randomized trials (RCTs), OR evidence from one properly conducted RCT AND one properly conducted meta-analysis, OR evidence from multiple RCTs with a clear majority of the properly conducted trials showing statistically significant evidence of benefit AND with supporting evidence in basic science, animal studies, or theory.
B (good scientific evidence)	Statistically significant evidence of benefit from 1–2 properly randomized trials, OR evidence of benefit from >1 properly conducted meta-analysis OR evidence of benefit from >1 cohort/case–control/nonrandomized trials AND with supporting evidence in basic science, animal studies, or theory.
C (unclear or conflicting scientific evidence)	Evidence of benefit from >1 small RCT(s) without adequate size, power, statistical significance, or quality of design by objective criteria,* OR conflicting evidence from multiple RCTs without a clear majority of the properly conducted trials showing evidence of benefit or ineffectiveness, OR evidence of benefit from >1 cohort/case–control/nonrandomized trials AND without supporting evidence in basic science, animal studies, or theory, OR evidence of efficacy only from basic science, animal studies, or theory.

D (fair negative scientific evidence)	Statistically significant negative evidence (i.e., lack of evidence of benefit) from cohort/case–control/nonrandomized trials, AND evidence in basic science, animal studies, or theory suggesting a lack of benefit.
F (strong negative scientific evidence)	Statistically significant negative evidence (i.e., lack of evidence of benefit) from >1 properly randomized adequately powered trial(s) of high-quality design by objective criteria.*
Lack of evidence†	Unable to evaluate efficacy due to lack of adequate available human data.

*Objective criteria are derived from validated instruments for evaluating study quality, including the 5-point scale developed by Jadad et al., in which a score below 4 is considered to indicate lesser quality methodologically (Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, McQuay HJ. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Controlled Clinical Trials 1996; 17[1]:1–12).
†Listed separately in the "Historical or Theoretical Uses That Lack Sufficient Evidence" section.

Historical or Theoretical Uses That Lack Sufficient Evidence

- Abortifacient (Sakurai et al., 2004), allergies, antioxidant (Burdette et al., 2002; Kligler, 2003; Wojcikowski, Stevenson, Leach, Wohlmuth, & Gobe, 2007; Zhang, Khan, Willett, & Foran, 2003), antispasmodic (Shibata, Ikoma, Onoda, Sato, & Sakurai, 1980), antitussive, anxiety, aphrodisiac, appetite stimulant, asthma, astringent, back pain, breast cysts, breast enhancement (Fugh-Berman, 2003), bronchitis, cervical dysplasia, chorea, depression, diaphoretic, diarrhea, dyspareunia (pain with intercourse) (Willhite & OConnell, 2001), edema, endocarditis, endometriosis, estrogenic agent, fever, gallbladder disorders, gingivitis, HIV/AIDS, hot flashes (prostate cancer) (Moyad, 2002), hypertension (Hailemeskel, Lee, & Thomhe, 2000), inflammation (Kim et al., 2004), insect repellent, labor induction, leukorrhea, liver disease, malaise, malaria, mastitis, measles, menstrual disorders (Kligler, 2003; McKenna, Jones, Humphrey, & Hughes, 2001), myalgia, nephritis, nerve pain (Woo et al., 2004), neurovegetative complaints, pain (Kim et al., 2004), palpitations, pancreatitis, pertussis (whooping cough), polycystic ovarian syndrome, premenstrual syndrome (PMS), prostate cancer (Ng & Figg, 2003), pruritus, rectal prolapse, sleep disorders, snakebites, sore throat, thrombocytopenia, tinnitus, urinary disorders (Wojcikowski et al., 2007), uterine bleeding, uterine fibroids, uterine prolapse (Hunter, 1999), vaginal atrophy (Willhite & OConnell, 2001), vertigo, wrinkle prevention (facial rhytides) (Ehrlich, Rao, Pabby, & Goldman, 2006), yellow fever (Takahira et al., 1998).

Expert Opinion and Historic/Folkloric Precedent

- Black cohosh has been approved by the German expert panel, the Commission E, for premenstrual discomfort (weight gain, swelling, mood fluctuations, breast tenderness), dysmenorrhea, and perimenopausal symptoms, and it is a popular therapy in Europe for these uses.
- The North American Menopause Society (NAMS) recommends first considering lifestyle changes, alone or combined with a nonprescription remedy (such as dietary isoflavones, vitamin E, or black cohosh) for the relief of mild vasomotor symptoms. For moderate-to-severe menopause-related hot flashes, prescription systemic estrogen-containing products are the therapeutic standard (Neff, 2004).
- Native North Americans used the roots of black cohosh primarily for gynecologic conditions (lactation promotion, menstruation promotion, labor pain

relief), joint pains, analgesia, malaria, sore throat, and menopausal symptoms, including hot flashes, anxiety, and dysphoria (Jassim, 2011). The Cherokees used an alcoholic black cohosh extract to treat rheumatism, and black cohosh tea was used to treat colds, coughs, tuberculosis, fatigue, hives, and backache, and as a sedative for infants. The Iroquois used an infusion of the root as a galactagogue and to treat rheumatism. The northeastern Algonquians used black cohosh root to treat kidney trouble or "feeling all played out."

- Black cohosh has also been used for pain and inflammation in Korean folk medicine (Kim et al., 2004). According to secondary sources, other members of the genus *Cimicifuga* have been used in traditional Asian healing models as anti-inflammatory and analgesic agents as well. Black cohosh has been studied primarily in Germany over the past 40 years, with a standardized extract (Remifemin®) available since the 1950s. According to secondary sources, the onset of black cohosh's action is thought to start 2 weeks after beginning treatment.
- Several regulatory committees have released statements on the topic of liver damage due to black cohosh use. Australian and Canadian regulatory agencies and the European Union have all stated that there may be a "potential association" between black cohosh use and hepatotoxicity (Mahady et al., 2008). An Expert Committee of the U.S. Pharmacopeia (USP) analyzed 30 international adverse effects reports (AERs) of liver damage in black cohosh users. Black cohosh formulations and doses ranged widely, from 20 mg of extract to 1,500 mg of root, but all were within the recommended range. The AERs were rated with the Naranjo causality algorithm, which takes into account several perspectives: timing of substance use and adverse effect, existence of possible alternative causes, objective confirmation, and dechallenge/rechallenge (improvement of adverse effects when the substance is withdrawn and return of effects if it is reinstituted). The scoring system rates the likelihood of causation as doubtful/unlikely, possible, probable, or definitive/certain. Scores for each of the 30 AERs fell into the "possible" causation category. As a result, the USP committee recommended cautionary labeling for black cohosh products, including a statement to discontinue the product and consult a healthcare provider if the user has a liver disorder or develops symptoms of liver problems (abdominal pain, dark urine, or jaundice) (Mahady et al., 2008). In addition to the USP's recommendation that black cohosh may "possibly" cause liver damage, the Office of Dietary Supplements (National Institutes of Health) also suggests that black cohosh should be labeled with a cautionary statement (Betz et al., 2009; Gori & Firenzuoli, 2007; Teschke, 2009b). In 2007, the Therapeutics Goods Association of Australia released an update indicating that the association of liver toxicity with black cohosh consumption may be very rare.
- The U.S. Food and Drug Administration (FDA) does not list black cohosh on its Generally Recognized as Safe (GRAS) list.

Brief Safety Summary

- **Likely safe**: When used for up to one year in otherwise healthy, nonpregnant, nonlactating individuals (Bai et al., 2007; Dog et al., 2003; Geller et al., 2009; Hunter, 1999; Huntley & Ernst, 2003b; Kelley & Carroll, 2010;

Lehmann-Willenbrock & Riedel, 1988; Lieberman, 1998; Liske & Wstenberg, 1998; Maki et al., 2009; Nasr & Nafeh, 2009; Newton et al., 2006; Oktem et al., 2007; Palacio, Masri, & Mooradian, 2009; Pockaj et al., 2006; Raus, Brucker, Gorkow, & Wuttke, 2006; Shams et al., 2010; Uebelhack et al., 2006; Walji et al., 2007; Wong, Lim, Luo, & Wong, 2009; Zepelin et al., 2007). Long-term safety data are lacking (Thacker, 2011).

- Possibly safe: Black cohosh has been found to inhibit the growth of breast cancer cells in vitro (Nesselhut et al., 1993; Struck, Tegtmeier, & Harnischfeger, 1997) and has been well tolerated in breast cancer patients for 6 weeks when taken concomitantly with tamoxifen (Jacobson et al., 2001) and in breast cancer survivors with hot flashes (Hernandez Munoz & Pluchino, 2003).
- Possibly unsafe: When taken by individuals with a history of hormone-sensitive conditions, such as breast cancer, uterine cancer, or endometriosis, due to possible estrogenic effects and unknown risks (Einer-Jensen, Zhao, Andersen, & Kristoffersen, 1996; Liske & Wustenberg, 1998), although there is evidence that estrogenic properties, if any, may not be clinically relevant (Borrelli et al., 2003; Burdette et al., 2003; Hernandez Munoz & Pluchino, 2003; Huntley & Ernst, 2003b; Jarry et al., 2003; Lupu et al., 2003; Mahady, 2003; Seidlova-Wuttke et al., 2003; Seidlova-Wuttke et al., 2003). When taken as a labor-inducing agent concomitantly with blue cohosh (*Caulophyllum thalictroides*). There is a report of severe multiorgan hypoxic injury in a child delivered naturally (at home) with the aid of blue and black cohosh, who was not breathing at the time of birth; causality is unclear (Baillie & Rasmussen, 1997; Gunn & Wright, 1996; McFarlin, Gibson, ORear, & Harman, 1999). When used during lactation, due to possible estrogenic or antiestrogenic effects (Dugoua, Seely, Perri, Koren, & Mills, 2006). When used in patients with known seizure disorder, based on a case study (Shuster, 1996). When used in patients on antihypertensive medications, due to a risk of hypotension (Genazzani & Sorrentino, 1962; Hailemeskel et al., 2000; Roberts, 2010). When used in patients with a history of thromboembolic disease or stroke; although there is a lack of reports of these complications in the available literature, there may be a theoretical risk. When used in patients with liver disease, due to case reports of liver damage (Chitturi & Farrell, 2008; Chow, Teo, Ring, & Chen, 2008; Gori & Firenzuoli, 2007; Teschke, Schwarzenbock, & Hennermann, 2007). Safety reports by the USP suggest that black cohosh may cause liver damage (Mahady et al., 2008).
- Likely unsafe: When taken during pregnancy, due to possible emmenagogic (menstrual flow-stimulating) effects (particularly during the first two trimesters) (Dugoua et al., 2006). When used by patients with known allergy to black cohosh, its constituents, or to aspirin, other salicylates, or members of the Ranunculaceae (buttercup or crowfoot) family.

DOSING/TOXICOLOGY

General

- Doses may be based on those most commonly used in available trials, or on historical practice. However, with natural products it is often unclear what the

optimal doses are to balance efficacy and safety. Preparation of products may vary from manufacturer to manufacturer, and from batch to batch within one manufacturer. Because it is often unclear what the active component(s) of a product is, standardization may not be possible, and the clinical effects of different brands may not be comparable.

Standardization

- The dosage of black cohosh often is based on its content of triterpenes, calculated as 27-deoxyactein. The German product Remifemin®, used in the majority of clinical studies, contains an alcoholic extract of black cohosh rhizome standardized to contain 1 mg of 27-deoxyactein per 20 mg tablet (Pepping, 1999). The manufacturing process and dosing recommendations for Remifemin® have changed over the past 20 years, and doses used in different studies may not be comparable. A standardized liquid formulation of Remifemin® was used in some studies.
- A combination product called Phyto-Female Complex (SupHerb, Netanya, Israel) is a standardized extract of black cohosh, dong quai, milk thistle, red clover, American ginseng, and chaste-tree berry, which is prepared according to good manufacturing practice (GMP) standards (Rotem & Kaplan, 2007). Each capsule contains standardized extracts of black cohosh (*Cimicifuga racemosa*) root extract 100 mg (2.5 mg of triterpene glycoside, 2.5%), dong quai (Angelica sinensis) root extract 75 mg (7.5 mg of ligustilides, 1%), milk thistle (Silybum marianum) herb extract 75 mg (60 mg of silymarin, 80%), red clover (Trifolium pratense) flower extract 50 mg (4 mg of isoflavone, 8%), American ginseng (Panax quinquefolius) root extract 50 mg (12.5 mg of ginsenosides, 25%), and chaste-tree berry (Vitex agnus-castus) fruit extract 50 mg (2.5 mg of vitexin, 5%).
- Pharmaceutical-grade *Cimicifuga racemosa* (Lot BC191) extract was used in one study, without significant results on anxiety associated with menopause (Amsterdam et al., 2009). Products were analyzed by looking at four bioactive triterpene constituents (R-actein, 23-epi-26-deoxyactein, S-actein, and 26-deoxyactein) standardized to 5.6% of the active triterpene glycosides.
- Black cohosh standardized to contain 7.27 mg of triterpene glycosides has been studied (Geller et al., 2009; Maki et al., 2009).
- Some studied black cohosh products lacked information on the label as to where the product originated (Goda, 2008). Other products included the method to determine bioavailability (Overk et al., 2008; Pade & Stavchansky, 2008).

Dosing

Adult (age ≥18)

Oral.

- **General**: The British Herbal Compendium has recommended 40–200 mg of dried black cohosh rhizome daily in divided doses or 0.4–2 mL of a (1:10) 60% ethanol tincture of black cohosh daily, although traditional doses have been as high as 1 g three times daily. Powdered black cohosh root or tea 1–2 g three times daily also has been used.

- **Bone density (postmenopausal women)**: Women received two capsules of BNO 1055 rhizome extract, dried aqueous/ethanolic (58% v/v), of *Cimicifuga racemosa* consisting of 40 mg of herbal drug for 10 weeks, with a two-week run-in period (Wuttke, Gorkow, & Seidlova-Wuttke, 2006; Wuttke, Seidlova-Wuttke, & Gorkow, 2003). Women received 40 mg of *Cimicifuga racemosa* (CR BNO 1055) daily for 3 months on, three months off, then 3 months on again and discontinued it thereafter (Bebenek, Kemmler, von Stengel, Engelke, & Kalender, 2010). Women received 40 mg of Remifemin® daily for 3 months (Garcia-Perez, Pineda, Hermenegildo, Tarin, & Cano, 2009).
- Breast cancer (menopausal symptoms due to treatment): Black cohosh, as an isopropanolic extract, was administered to in women receiving tamoxifen at a dose of one to four 2.5 mg tablets for 6 months (Rostock et al., 2011). Women also received either black cohosh (CR BNO 1055, Menofem®/Klimadynon®, 20 mg daily) with their tamoxifen, or tamoxifen alone for 12 months in another study (Hernandez Munoz & Pluchino, 2003). In a case series, participants were administered one tablet of black cohosh (Remifemin®) twice daily for 6 months (Hirschberg et al., 2007; Lundstrom, Hirschberg, & Soderqvist, 2011). One capsule of 20 mg of black cohosh (comparable to Remifemin®) was given twice daily for 4 weeks (Pockaj et al., 2006).
- Cognitive function (postmenopausal women): Women received 128 mg of belowground parts of black cohosh, once daily in the evening for 12 months (Maki et al., 2009). The 128 mg of the belowground parts of black cohosh were standardized to 7.27 mg of triterpene glycosides.
- Coronary heart disease (postmenopausal women): Women received 40 mg of *Cimicifuga racemosa* (CR BNO 1055) daily for 3 months on, 3 months off, then 3 months on again and discontinued it thereafter (Bebenek et al., 2010).
- Infertility: In one trial, all women received 150 mg of clomiphene citrate daily on days 3–7 of their cycle. In addition, they either received 120 mg of *Cimicifuga racemosa* rhizome or 100 mcg daily of ethinyl estradiol on days 1–13 (Shahin, Ismail, & Shaaban, 2009). Another trial used *Cimicifuga racemosa* 120 mg daily on days 1–12 (Shahin, Ismail, Zahran, & Makhlouf, 2008). Human chorionic gonadotropin (HCG) injection was also used in these studies.
- Menopausal symptoms: For perimenopausal symptoms, studies have used two 20 mg Remifemin® tablets (corresponding to 1–2 mg of 27-deoxyactein) once or twice daily for up to 12 weeks (Bai et al., 2007; Nappi, Malavasi, Brundu, & Facchinetti, 2005; Vermes, Banhidy, & Acs, 2005). Other studies used one Remifemin® tablet (reported as 2.5 mg of isopropanolic extract of *Cimicifuga racemosa* corresponding to 20 mg of root stock) twice daily for 6–12 weeks (Bai et al., 2009; Hirschberg et al., 2007; Osmers et al., 2005). Forty mg of Remifemin® was also taken once daily for 12 weeks (Nappi et al., 2005). In a systematic review, Remifemin® was used at doses ranging from 40 drops twice daily to 8 mg–127 mg of the tablets daily for 12–24 weeks (Hanna, Day, ONeill, Patterson, & Lyons-Wall, 2005). Preparations of black cohosh other than the popularly used Remifemin® have been used as well, with mixed results. Studies using 40 mg or 127 mg of an isopropanolic extract of black cohosh daily for up to 6 months have reported similar effects on menopausal symptoms (Liske & Wstenberg, 1998; Spangler et al., 2007). Two capsules of CR BNO 1055

(Klimadynon®/Menofem®), providing a daily dose corresponding to 40 mg of black cohosh, have been studied for climacteric complaints, but their efficacy is unclear (Wuttke et al., 2003); in a separate study, this dose was studied for up to 1 year, and it was found to be safe, with marked reductions in hot flashes (Raus et al., 2006). Women also received 40 mg of CR BNO 1055 daily for 3 months on, 3 months off, then 3 months on again in another study (Bebenek et al., 2010). Remixin® (Mikro-Gen, Istanbul, Turkey) at a dose of 40 mg daily has been studied for 6 months for hot flashes and night sweats (Oktem et al., 2007). One capsule of black cohosh (6.5 mg of dried rhizome extract) daily for 12 weeks has been studied (Frei-Kleiner, Schaffner, Rahlfs, Bodmer, & Birkhauser, 2005). A titrated dose of black cohosh starting at 64 mg for 2 weeks titrated up to 128 mg by the fourth week has been studied (Amsterdam et al., 2009). In systematic review, various black cohosh formulations of 20–160 mg daily have been studied for up to 52 weeks (Hanna et al., 2005; Kelley & Carroll, 2010; Nedrow et al., 2006; Shams et al., 2010).

Children (age <18)

- Insufficient available evidence.

Toxicology

- In vitro, evidence of mutagenicity from an isopropanolic extract of black cohosh was lacking (Liske, 1998). In vitro, Hep-G2 cell growth was not shown to be inhibited by any black cohosh extracts (cimicifugic acids A and B, fukinolic acid, and triterpene glycosides) in concentrations as high as 50 mcg/mL. However, the extracts were shown to inhibit CYP isozymes that may contribute to adverse drug interactions with concomitant drug use (Huang et al., 2010).
- In animals, administration of high doses of black cohosh for up to 6 months lacked toxicity (Beuscher & Reichert, 1995), and specific organ toxicity was lacking in rats fed high doses (up to 5 g extract/kg) for 26 weeks (Korn, 1991). A difference in the onset and incidence of mammary tumors in MMTV-new mice was lacking when black cohosh was supplemented at a dose similar to 40 mg daily in humans (Davis et al., 2008).
- Black cohosh is an herbal extract that is often used as an alternative to estrogen-based replacement; however, black cohosh administered to mice with mammary tumors increased the rate of lung metastases (Davis et al., 2008, 2010).
- Anecdotally, overdose of black cohosh may cause headache, nausea, vomiting, dizziness, bradycardia, visual disturbances, and perspiration. A review of the literature reveals a lack of reports of toxicity in humans (McKenna et al., 2001).
- Several regulatory committees have released statements on the topic of liver damage due to black cohosh use. Australian and Canadian regulatory agencies and the European Union have all stated that there may be a "potential association" between black cohosh use and hepatotoxicity (Mahady et al., 2008). An Expert Committee of the U.S. Pharmacopeia (USP) analyzed 30 international adverse effects reports (AERs) of liver damage in black cohosh users. Black cohosh formulations and doses ranged widely, from 20 mg of extract to 1,500 mg of root, but all were within the suggested therapeutic range. The AERs were

rated with the Naranjo causality algorithm, which takes into account several perspectives: timing of substance use and adverse effect, existence of possible alternative causes, objective confirmation, and dechallenge/rechallenge (improvement of adverse effects when the substance is withdrawn and return of effects if it is reinstituted). The scoring system rates the likelihood of causation as doubtful/unlikely, possible, probable, or definitive/certain. Scores for each of the 30 AERs fell into the "possible" causation category. As a result, the USP committee recommended cautionary labeling for black cohosh products, including a statement to discontinue the product and consult a healthcare provider if the user has a liver disorder or develops symptoms of liver problems (abdominal pain, dark urine, or jaundice) (Mahady et al., 2008). In addition to the USP's recommendation that black cohosh may "possibly" cause liver damage, the Office of Dietary Supplements (National Institutes of Health) also suggests that black cohosh should be labeled with a cautionary statement (Betz et al., 2009; Gori & Firenzuoli, 2007; Teschke, 2009b). In 2007, the Therapeutics Goods Association of Australia released an update indicating that the association of liver toxicity with black cohosh consumption may be very rare.

- Case reports have indicated that in certain individuals, hepatic failure is possible (Cohen, OConnor, Hart, Merel, & Te, 2004; Joy, Joy, & Duane, 2008; Lontos, Jones, Angus, & Gow, 2003; Lynch, Folkers, & Hutson, 2006; Whiting, Clouston, & Kerlin, 2002). Although there are concerns about black cohosh's hepatotoxicity, the level of concern appears to be mixed, and proving causality may be difficult for several reasons, including confounding variables, methods of reporting, case reports vs. spontaneous reports, methods of detection of adverse drug reaction, and poor data quality of the reports (Mahady et al., 2009; Mahady et al., 2010; Teschke, 2009a, 2010; Teschke et al., 2009; Teschke et al., 2009; Teschke & Schwarzenboeck, 2009; Teschke et al., 2011; Walji et al., 2007). Some researchers believe that the scale used to detect causality may affect the results. Teschke et al. indicate that the Council for International Organizations of Medical Sciences liver-specific scale is preferred over the Naranjo scale, which is not organ specific (Teschke, Schmidt-Taenzer, & Wolff, 2011).
- A meta-analysis of five randomized, double-blind, controlled clinical trials of perimenopausal and postmenopausal women ($N = 1{,}117$) using isopropanolic black cohosh extracts at doses of 40–128 mg for 3–6 months did not report significant liver damage when aspartate aminotransferase and alanine aminotransferase were analyzed (Centre for Reviews and Dissemination, 2006; Naser et al., 2011; Shou, Li, & Liu, 2011). However, some analysts would like to see more data (Sarma, Giancaspro, Griffiths, & Dog, 2011). Human studies using one capsule of *Cimicifuga racemosa* 20 mg twice daily for 4 weeks to reduce hot flashes found minimal toxicity, which did not differ compared with placebo (Pockaj et al., 2006). Evidence of hepatotoxicity due to black cohosh supplementation was lacking in a randomized controlled trial of 89 women taking two capsules of black cohosh standardized to contain 7.27 mg of triterpene glycosides (Geller et al., 2009).
- A prospective longitudinal clinical study of 87 postmenopausal women that received 40 mg of a dry extract of *Cimicifuga racemosa* (Klimadyon) to treat

menopausal symptoms for 12 months did not report alterations in liver function tests or hepatic perfusion (Nasr & Nafeh, 2009).

- Computation approaches have been analyzed to try to determine the level of hepatobiliary toxicity that may be caused due to certain chemicals. Wang et al. conducted a computational analysis on several botanical extracts used in the treatment of menopause, including protocatechuic acid from black cohosh, to determine if the constituents had features that may contribute to hepatobiliary adverse effects (Wang, Dou, Cross, & Valerio, 2011). However, animal studies and human exposure have not been definitive (Beuscher & Reichert, 1995; Centre for Reviews and Dissemination, 2006; Cohen et al., 2004; Joy et al., 2008; Korn, 1991; Lontos et al., 2003; Lynch et al., 2006; Mahady et al., 2009; Mahady et al., 2010; Naser et al., 2011; Pockaj et al., 2006; Shou et al., 2011; Teschke, 2010; Teschke et al., 2009; Teschke et al., 2009; Teschke et al., 2011; Teschke, & Schwarzenboeck, 2009; Teschke et al., 2011; Walji et al., 2007; Whiting et al., 2002).
- Caution is advised when using herbal supplements, due to lack of strict regulation checking for contaminants. A cross-sectional analysis of several herbal supplements, including black cohosh, reported that lead levels in the blood were higher in women that used the supplements studied vs. nonusers (Buettner et al., 2009). However, in a laboratory study of the metal content in black cohosh and other dietary supplements, none of 47 metals tested were found in concentrations above the toxic levels or physiological limit levels for the daily doses specified by the products' labeling (Grippo, Hamilton, Hannigan, & Gurley, 2006).

ADVERSE EFFECTS/PRECAUTIONS/CONTRAINDICATIONS

Allergy

- Avoid with known allergy or hypersensitivity to black cohosh, its constituents, or other members of the Ranunculaceae (buttercup or crowfoot) family.
- According to secondary sources, native black cohosh contains small amounts of salicylic acid, but it is unclear how much (if any) is present in commercially available or standardized extracts. Caution is warranted in patients allergic to aspirin or other salicylates.
- An allergic skin reaction occurred in one of 40 patients taking Remixin® (40 mg per tablet, Mikro-Gen, Istanbul, Turkey) in an equivalence study. The reaction was minor and did not lead to withdrawal from the study (Oktem et al., 2007); allergic reactions were also reported in a small number of patients from a case study (Vermes et al., 2005).
- In an observational study of 6,141 patients, allergic conjunctivitis occurred in one patient who was administered either Remifemin® or Remifemin® Plus (unclear from which group this adverse effect came) (Briese, Stammwitz, Friede, & Henneicke-von Zepelin, 2007).

Adverse Effects

- General: Some reviews have reported black cohosh to be generally well tolerated in recommended doses for up to 1 year (Bai et al., 2007; Borrelli & Ernst, 2008; Dog et al., 2003; Geller et al., 2009; Hunter, 1999; Huntley & Ernst, 2003b; Kelley

& Carroll, 2010; Lehmann-Willenbrock & Riedel, 1988; Lieberman, 1998; Liske & Wstenberg, 1998; Maki et al., 2009; Nasr & Nafeh, 2009; Newton et al., 2006; Osmers et al., 2005, 2007; Palacio et al., 2009; Pockaj et al., 2006; Raus et al., 2006; Shams et al., 2010; Uebelhack et al., 2006; Walji et al., 2007; Wong et al., 2009; Zepelin et al., 2007), while others have determined that there is a lack of information regarding the safety of herbal preparations, such as black cohosh (Haimov-Kochman, Brzezinski, & Hochner-Celnikier, 2008). The most common adverse effects reported were gastrointestinal upset and rash (Huntley & Ernst, 2003b; Jassim, 2011). Tiredness (one out of 40) and irritability (one out of 40) have been reported after taking Remixin®; these were reported as minor and not significantly different from patients taking fluoxetine (Oktem et al., 2007). The potential effects of black cohosh on estrogen-sensitive conditions such as breast cancer, uterine cancer, or endometriosis are unclear. One woman reported vertigo, hypertension, and headache with black cohosh use, but the authors noted that changes in blood pressure and heart rate were lacking (Wuttke et al., 2006). In a systematic review of seven review articles and eight human trials, nausea, vomiting, rash, headache, dizziness, and one case of hepatotoxicity were reported (Wong et al., 2009).

- Cardiovascular: Arrhythmia of unspecified type was reported in one patient in a two-month placebo controlled trial of black cohosh ($N = 85$) (Jacobson et al., 2001). Anecdotally, high doses of black cohosh may cause bradycardia or cardiovascular depression. Reversible bradycardia was reported in one case involving a 59-year-old woman that began taking Remifemin® 2 weeks prior to her admission to the hospital emergency room due to episodes of syncope (McKenzie & Rahman, 2010). In a 1962 study, acteina, a constituent of black cohosh, was found to cause peripheral vasodilation in humans and was noted to elicit hypotension in animals (Genazzani & Sorrentino, 1962).
- Dermatologic: In a case report, a 56-year-old female patient had a case of cutaneous pseudolymphoma associated with Remifemin® (a standardized extract of black cohosh) (Meyer, Vogt, Obermann, Landthaler, & Karrer, 2007). Rare reports of mild skin complaints were reported with Remifemin® (Briese et al., 2007). Withdrawal of black cohosh resulted in regression and complete remission. In a case report, a 28-year-old woman ingested one ounce of pennyroyal oil and two cups of black cohosh tea as an abortifacient, vomited several times, and was admitted to the emergency department nauseous and diaphoretic (McCormick & Manoguerra, 1988). It is possible that these symptoms were due primarily to the pennyroyal oil ingestion. There is a report of cutaneous vasculitis in two patients taking an herbal supplement containing black cohosh (Ingraffea, Donohue, Wilkel, & Falanga, 2007).
- Endocrine: The estrogenic activity of black cohosh remains debated, and information on specific estrogenic constituents is lacking. It is unclear if black cohosh is safe in individuals with hormone-sensitive conditions such as breast cancer, uterine cancer, or endometriosis. Animal and in vitro research suggests that there may be a lack of direct effects on estrogen receptors, although this is an area of controversy (Borrelli et al., 2003; Burdette et al., 2003; Huntley & Ernst, 2003b; Jarry et al., 2003; Lupu et al., 2003; Mahady, 2003; Seidlova-Wuttke et al., 2003; Seidlova-Wuttke et al., 2003). Safety and efficacy data beyond 1 year are

lacking, although reports suggest the safety of short-term use, including in women experiencing menopausal symptoms for whom estrogen replacement therapy is contraindicated (Dog et al., 2003; Hernandez Munoz, & Pluchino, 2003). Breast tenderness and bleeding disturbances have been reported in a small number of women taking Remifemin® in a case study (Vermes et al., 2005). In a two-month trial in breast cancer survivors, endometrial hyperplasia was noted in one patient taking both black cohosh and tamoxifen (out of 42 subjects receiving black cohosh), and one instance each was noted of vaginal bleeding, weight gain, dilation and curettage, hysterectomy, and breast cancer recurrence (Jacobson et al., 2001). The influence of black cohosh alone or in combination with tamoxifen is unclear in these cases, although these complications were lacking among 43 nonblack cohosh subjects. Black cohosh was administered for 12 months in combination with tamoxifen to 136 breast cancer survivors for the prevention of hot flashes and was well tolerated, although long-term safety data are lacking (Hernandez Munoz & Pluchino, 2003). Black cohosh was administered with tamoxifen in 50 women for 6 months and was considered well tolerated (Rostock et al., 2011). In postmenopausal women, 3 months of therapy with *Cimicifuga racemosa* was shown to be well tolerated and did not result in a change in follicle-stimulating hormone, testosterone, or estradiol (Garcia-Perez et al., 2009). In animals and in vitro, initial reports of estrogen receptor-binding activity (Jarry, Harnischfeger, & Duker, 1985) stand in contrast with data suggesting no significant estrogen receptor-binding activity or estrogenic activities (Einer-Jensen et al., 1996; Liu et al., 2001; Liu, Yang, Zhu, & Huo, 2001; Zava, Dollbaum, & Blen, 1998). One in vitro study found no effects of black cohosh alone on estrogen receptors, but it reported that black cohosh antagonized proliferative effects on cells induced by estradiol (Zierau, Bodinet, Kolba, Wulf, & Vollmer, 2002). Several studies have aimed to assess estrogenic activity by measuring luteinizing hormone (LH), follicle-stimulating hormone (FSH), or prolactin levels (Duker, Kopanski, Jarry, & Wuttke, 1991; Jarry, & Harnischfeger, 1985). One study reported lower FSH levels (but not LH) in patients treated with black cohosh vs. placebo ($N = 110$), although the results are unclear, due to a lack of known baseline hormone levels in either group (Duker et al., 1991). Results from other trials have found no effects on these hormone levels after up to 6 months of black cohosh therapy (Jacobson et al., 2001; Lehmann-Willenbrock & Riedel, 1988; Liske, Wstenberg, & Boblitz, 2001; Wuttke et al., 2006). Administered to female infantile mice, premature onset of estrus could not be precipitated by black cohosh (Siess & Seybold, 1960). Estrogenic effects on vaginal epithelium were noted in one 3-month trial of black cohosh (Stoll, 1987), while another 6-month trial reported no effects on vaginal cytology (Liske & Wstenberg, 1998). Long-term safety data are lacking (Thacker, 2011). Use of black cohosh in high-risk populations (such as in women with a history of breast cancer) should be under the supervision of a licensed healthcare professional.

- Gastrointestinal: Mild gastrointestinal discomfort was found in 7% of a clinical sample of 629 women taking black cohosh (Stolze, 1982). Rare reports of mild gastrointestinal complaints have been reported with Remifemin® (Briese et al., 2007; Nappi et al., 2005; Vermes et al., 2005). Constipation was noted in one subject, as was indigestion in another subject taking both black cohosh and tamoxifen

in a placebo controlled trial (Jacobson et al., 2001). In a case report, a 28-year-old woman ingested one ounce of pennyroyal oil and two cups of black cohosh tea as an abortifacient, vomited several times, and was admitted to the emergency department nauseous and diaphoretic (McCormick, & Manoguerra, 1988). It is possible that these symptoms were due primarily to the pennyroyal oil ingestion. Anecdotally, high doses of black cohosh may cause nausea and vomiting. Dyspeptic problems (2 of 40) and constipation (2 of 40) have been reported after taking Remixin®; these were reported as minor and not significantly different from patients taking fluoxetine (Oktem et al., 2007). The most common adverse effects reported with the combination product GYNO-Plus® were gastrointestinal (12.8% (6/47) in the treatment group vs. 9.5% (4/42) in the placebo group). Gastrointestinal effects were severe enough to cause three patients to discontinue treatment.

- Hepatic: Although there are concerns about black cohosh's hepatotoxicity (Chitturi & Farrell, 2008; Chow et al., 2008; Gori & Firenzuoli, 2007; Mahady et al., 2008; Teschke et al., 2007), the data are inconclusive, according to Walji et al. (Walji et al., 2007). There are reported cases of hepatitis in patients taking herbal combinations containing black cohosh, including several cases of fulminant hepatic failure requiring transplantation (Cohen et al., 2004; Lontos et al., 2003; Lynch et al., 2006; Whiting et al., 2002). The specific role of black cohosh in these cases is unclear. In 2003, a case report was published of acute liver failure in a 52-year-old woman using an herbal combination for 3 months (for tinnitus) including black cohosh and several other herbs [a 200 mL bottle containing fluid extracts of black cohosh 20 mL, Nepeta hederacea (ground ivy) 80 mL, Hydrastis canadensis (goldenseal) 20 mL, Ginkgo biloba 40 mL, and Avena sativa (oat seed) 40 mL; concentration: 1 g/mL, except goldenseal (0.5 g/mL)]; the patient ingested 7.5 mL twice daily as needed, with an estimated 600 mL total taken over 3 months. A liver transplant was required. Laboratory analysis revealed no undeclared drugs in the preparation (which had been prepared by the patient's pharmacist). Notably, ground ivy contains very low concentrations of pulegone, a known hepatotoxin. Reversible mild hepatitis was reported in a 37-year-old woman that had been taking a supplement containing *Cimicifuga racemosa* for 18 months (Vannacci et al., 2009). Chronic hepatitis and submassive hepatic necrosis were reported in two cases of patients that took different supplements with black cohosh (Pierard et al., 2009). Autoimmune hepatitis was also reported in a case report (van de Meerendonk, van Hunsel, & van der Wiel, 2009). Liver failure was reported in a 51-year-old woman taking 20–40 mg of black cohosh twice daily on and off over a period of three years; it resulted in liver transplantation (Chow et al., 2008). A 44-year-old woman was reported to have reversible transient autoimmune hepatitis, bilateral lower leg edema, and coagulation activity after taking Remifemin® 5 mg daily for 3 weeks (Zimmermann, Witte, Voll, Strobel, & Frieser, 2010). In a systematic review, three studies linked black cohosh supplements with hepatotoxicity (Nedrow et al., 2006). Some authors feel that these cases have not been adequately substantiated, and given the widespread use of black cohosh and the paucity of other such reports, further investigation is merited (Naser & Liske, 2009; Thomsen & Schmidt, 2003). An Expert Committee of the U.S. Pharmacopeia (USP) analyzed 30 international adverse effects

reports (AERs) of liver damage in black cohosh users. Black cohosh formulations and doses ranged widely, from 20 mg of extract to 1,500 mg of root, but all were within the recommended range. The AERs were rated with the Naranjo causality algorithm, which takes into account several perspectives: timing of substance use and adverse effect, existence of possible alternative causes, objective confirmation, and dechallenge/rechallenge (improvement of adverse effects when the substance is withdrawn and return of effects if it is reinstituted). The scoring system rates the likelihood of causation as doubtful/unlikely, possible, probable, or definitive/certain. Scores for each of the 30 AERs fell into the "possible" causation category. As a result, the USP committee recommended cautionary labeling for black cohosh products, including a statement to discontinue the product and consult a healthcare provider if the user has a liver disorder or develops symptoms of liver problems (abdominal pain, dark urine, or jaundice) (Mahady et al., 2008). In a meta-analysis, adverse effects experienced by participants receiving black cohosh included connective tissue and musculoskeletal conditions (4–9.8%), infestation and infection (8.5–11.9%), and gastrointestinal symptoms (0.7–15%). In addition, breast complaints were reported in some studies. However, compared to the placebo groups, these adverse effects lacked increased frequency of occurrence.

- Genitourinary: In a clinical trial to assess the effects of black cohosh extract on endometrial tissue, 400 postmenopausal women took 40 mg of black cohosh extract daily for 52 weeks (Raus et al., 2006). Although the authors summarized that endometrial safety was proven due to lack of hyperplasia or more serious adverse endometrial outcomes, a few gynecologic organ-related adverse events were reported. In a randomized controlled trial in breast cancer survivors ($N = 85$), there was one case of endometrial hyperplasia, one case of vaginal bleeding, a hysterectomy, and a dilation and curettage (D&C) in patients taking black cohosh and tamoxifen; vaginal bleeding and endometrial hyperplasia have also been associated with tamoxifen use (Jacobson et al., 2001). Use of 40 mg of Remifemin® has been associated with vaginal bleeding, vaginal bleeding or spotting, breast pain, abdominal pain, and leukorrhea; however, the incidences were found to be significantly lower when compared to the tibolone group ($p < 0.0005$) (Bai et al., 2007). Edema was also reported in the Remifemin® group, with no significant difference compared to the tibolone group. Adverse effects were also reported to be significantly lower in the Remifemin® group when compared to tibolone in another study (Bai et al., 2009). According to secondary sources, large amounts of black cohosh have been associated with miscarriage, and black cohosh has been used traditionally as an abortifacient.
- Hematologic: It is unclear if black cohosh increases the risk of blood clots or stroke, and reports of these complications are lacking. It is unclear if black cohosh possesses a similar mechanism of action as estrogen and raloxifene, which have been associated with these complications. A 44-year-old woman was reported to have reversible transient autoimmune hepatitis, bilateral lower leg edema, and coagulation activity after taking Remifemin® 5 mg daily for 3 weeks (Zimmermann et al., 2010). There is a report of cutaneous vasculitis in two patients taking an herbal supplement containing black cohosh (Ingraffea et al., 2007). In a

clinical trial, a lack of changes in markers of coagulation has been reported (Wuttke et al., 2006).

- Musculoskeletal: In a case study, both clinical symptoms and biochemical parameters improved in a woman with severe asthenia and very high blood levels of creatine phosphokinase and lactate dehydrogenase after the discontinuation of black cohosh; due to the temporal relationship between the resolution of symptoms and discontinuation of black cohosh, the authors hypothesized that the black cohosh may have been the cause of the asthenia (Minciullo, 2009; Minciullo et al., 2006). One case study reported stiffness in the extremities in some patients (Vermes et al., 2005). In a study of 28 women, one woman receiving black cohosh discontinued the trial due to edema and arthralgia (Amsterdam et al., 2009). In a meta-analysis, adverse effects experienced by participants receiving black cohosh included connective tissue and musculoskeletal conditions (4–9.8%), infestation and infection (8.5–11.9%), and gastrointestinal symptoms (0.7–15%). In addition, breast complaints were reported in some studies. However, compared to the placebo groups, these adverse effects did not occur more frequently.
- Neurologic/CNS: Tonic-clonic seizures were reported in a 45-year-old woman who had been taking black cohosh, chaste-tree (Vitex agnus-castus) berries and seeds, and evening primrose oil (*Oenothera biennis*) for 4 months, and who also consumed alcohol (Shuster, 1996). The relative contribution of each agent is unclear. Anecdotally, high doses of black cohosh may cause frontal headaches, dizziness, diaphoresis, and visual disturbances.
- Psychiatric: According to secondary sources, black cohosh may cause dysphoria. However, dysphoria is a symptom associated with menopause. It is unclear whether black cohosh taken for the treatment of menopausal symptoms causes dysphoria or whether there is simply an association between the symptom and black cohosh.
- Other: A feeling of heaviness in the legs has been reported after black cohosh use, according to a secondary source. However, clinical research has used "heaviness in the legs" as a way to evaluate menopausal treatments, thus it is unclear whether heaviness in the legs is a side effect of black cohosh therapy or a symptom of menopause. Clinical research has not shown differences between patients taking black cohosh vs. placebo in self-reported diaries for the symptom of "heaviness in the legs" (Pockaj et al., 2004). Chest discomfort caused a patient to withdraw from a clinical trial using GYNO-Plus® (Chung et al., 2007), although the specifics are unclear.

Oncologic: It remains unclear if black cohosh possesses estrogenic activity that may affect hormone-sensitive cancers, such as some types of breast or uterine cancer. In a systematic review, one study linked black cohosh supplements to breast cancer metastasis in mice (Nedrow et al., 2006). Initial in vitro studies have reported black cohosh to possess inhibitory effects on estrogen-responsive cancer cell lines and breast cancer cells (Dixon-Shanies & Shaikh, 1999; Nesselhut et al., 1993; Struck et al., 1997). In a 2-month trial in breast cancer survivors, endometrial hyperplasia was noted in one patient taking both black cohosh and tamoxifen (out

of 42 subjects receiving black cohosh), and one instance each was noted of vaginal bleeding, weight gain, dilation and curettage, hysterectomy, and breast cancer recurrence (Jacobson et al., 2001). The influence of black cohosh alone or in combination with tamoxifen is unclear in these cases, although these complications were lacking among 43 non-black cohosh subjects. Black cohosh was administered for 12 months in combination with tamoxifen to 136 breast cancer survivors for the prevention of hot flashes and was well tolerated, although long-term safety data are lacking (Hernandez Munoz, & Pluchino, 2003). Black cohosh was administered with tamoxifen in 50 women for 6 months and was considered well tolerated (Rostock et al., 2011). Brasky et al. conducted a cohort study to assess the effects of specialty supplements, including black cohosh, on the risk of breast cancer ($N =$ 40,337) (Brasky, Lampe, Potter, Patterson, & White, 2010). Female members of the VITamines And Lifestyle (VITAL) cohort study aged 50–76 years were included in this study. The regular use of black cohosh lacked a statistically significant effect on the risk of for breast cancer.

Precautions/Warnings/Contraindications

- Use cautiously in individuals with a history of hormone-sensitive conditions, such as breast cancer, uterine cancer, or endometriosis, due to possible estrogenic effects and unknown risks (Einer-Jensen et al., 1996; Liske & Wustenberg, 1998), although there is evidence that estrogenic properties, if any, may not be clinically relevant (Borrelli et al., 2003; Burdette et al., 2003; Hernandez Munoz & Pluchino, 2003; Huntley & Ernst, 2003b; Jarry et al., 2003; Lupu et al., 2003; Mahady, 2003; Seidlova-Wuttke et al., 2003; Seidlova-Wuttke et al., 2003).
- Use cautiously as a labor-inducing agent concomitantly with blue cohosh (*Caulophyllum thalictroides*). There is a report of severe multiorgan hypoxic injury in a child delivered naturally (at home) with the aid of blue and black cohosh, who was not breathing at the time of birth; causality is unclear (Baillie & Rasmussen, 1997; Gunn & Wright, 1996; McFarlin et al., 1999).
- Use cautiously during lactation, due to possible estrogenic or antiestrogenic effects (Dugoua et al., 2006).
- Use cautiously in patients with known seizure disorder, based on a case study (Shuster, 1996).
- Use cautiously in patients on antihypertensive medications, due to a risk of hypotension (Genazzani & Sorrentino, 1962; Hailemeskel et al., 2000; Roberts, 2010).
- Use cautiously in patients with a history of thromboembolic disease or stroke. Although there is a lack of reports of these complications in the available literature, there may be a theoretical risk.
- Use cautiously in patients with liver disease, due to case reports of liver damage (Chitturi & Farrell, 2008; Chow et al., 2008; Gori & Firenzuoli, 2007; Mahady et al., 2008; Teschke et al., 2007).
- Avoid during pregnancy, due to possible emmenagogic (menstrual flow-stimulating) effects (particularly during the first two trimesters) (Dugoua et al., 2006).

- Avoid in patients with known allergy to black cohosh, its constituents, aspirin, other salicylates, or members of the Ranunculaceae (buttercup or crowfoot) family.

Pregnancy & Lactation

- Safety of black cohosh use during pregnancy has not been established and may be inadvisable due to purported effects on the uterus ("uterotonic" effects) and possible estrogenic properties.
- In a survey of 500 nurse-midwives in the United States, out of 172 respondents, 33% indicated that they use black cohosh to stimulate labor (McFarlin et al., 1999). There is one report of severe multiorgan hypoxic injury in a child delivered with the aid of both blue and black cohosh (*Caulophyllum thalictroides*) who was not breathing at the time of birth (Gunn & Wright, 1996). The child survived with permanent central nervous system damage. Notably, blue cohosh possesses a vasoconstrictive glycoside, which may have been responsible for the adverse effects. Although used internationally, few safety and efficacy data are available for homeopathic preparations of blue and black cohosh (Kistin & Newman, 2007).
- Black cohosh has been used as a galactagogue by Native American women, according to the U.S. National Library of Medicine Drugs and Lactation Database (LactMed) and a review (McKenna et al., 2001). There is insufficient evidence regarding use of black cohosh during lactation (Dennehy, 2006; Dennehy, Tsourounis, Bui, & King, 2010; Dugoua et al., 2006; Hardy, 2000; Mazaro-Costa, Andersen, Hachul, & Tufik, 2010; McKenna et al., 2001). According to the in vitro evidence available, black cohosh may have labor-inducing effects, hormonal effects, emmenagogue properties, and anovulatory effects; therefore, black cohosh should be avoided during pregnancy (Dugoua et al., 2006). Although no malformations have been reported, black cohosh should be used cautiously during the third trimester and for labor induction until clinical research has been conducted. Although the research on black cohosh use during lactation is poor, it may have estrogenic or antiestrogenic properties and should be used with caution.
- Tinctures may be ill advised during pregnancy, due to their high alcohol content, although the absolute quantity of alcohol ingested from tinctures at recommended doses is likely to be relatively small.

INTERACTIONS

Black cohosh/Drug Interactions

- Analgesics: According to traditional use, black cohosh may have additive effects with analgesics (Sakurai & Nagai, 1996).
- Anesthetics: The authors of a systematic review indicated that black cohosh may interact with anesthetics, according to the Clinical Practice Guideline of the Canadian Society of Obstetricians and Gynecologists (Roberts, 2010). According to traditional use, black cohosh may have additive effects with anesthetics (Sakurai & Nagai, 1996).

- Antiandrogens: In an in vitro study conducted on human prostate cancer cells with black cohosh extract, the extract killed hormone-responsive or hormone-unresponsive prostate cancer cells by induction of apoptosis and activation of caspases (Hostanska, Nisslein, Freudenstein, Reichling, & Saller, 2005). Another in vivo study in mice demonstrated inhibited PC3 prostate cancer tumor growth with black cohosh and other herbal extracts (Ng & Figg, 2003).
- Antiarthritics: In humans, Reumalex® has been reported to have significant improvements in arthritis pain (Mills, Jacoby, Chacksfield, & Willoughby, 1996).
- Anticoagulants and antiplatelets: The authors of a systematic review indicated that black cohosh may contain anticoagulant coumarins, although an effect on prothrombin times was lacking (Roberts, 2010). However, in a clinical trial of postmenopausal women, changes in markers of coagulation were lacking (Wuttke et al., 2006). Native black cohosh contains small amounts of salicylic acid and may potentiate the antiplatelet effects of other agents. It is unclear if therapeutic amounts of salicylates are present in commercial or processed black cohosh products.
- Antidepressant agents, selective serotonin reuptake inhibitors (SSRIs): Studies suggest that the mechanism of action of black cohosh may be centrally mediated, with possible action at the level of serotonin or dopamine receptors (Burdette et al., 2003; Jarry et al., 2003; Villaseca, 2012). A study in ovariectomized rats demonstrated strong binding to serotonin receptors 5-HT(1A), 5-HT(1D), and 5-HT(Bai et al., 2009) subtypes (Burdette et al., 2003).
- Antiestrogens: The estrogenic activity of black cohosh remains debated. Specific estrogenic constituents have not been identified, and it is unclear how (or if) black cohosh interacts with estrogens, estrogen receptors, and/or progestins. Publications suggest that there may be no direct effects on estrogen receptors, although this is an area of controversy (Borrelli et al., 2003; Burdette et al., 2003; Huntley & Ernst, 2003b; Jarry et al., 2003; Lupu et al., 2003; Mahady, 2003; Seidlova-Wuttke et al., 2003; Seidlova-Wuttke et al., 2003). In animals and in vitro, initial reports of estrogen receptor-binding activity (Jarry et al., 1985) stand in contrast with data suggesting a lack of significant estrogen receptor-binding activity or estrogenic activities (Einer-Jensen et al., 1996; Liu et al., 2001; Liu et al., 2001; Zava et al., 1998). One in vitro study found no effects of black cohosh alone on estrogen receptors, but it reported that black cohosh antagonized proliferative effects on cells induced by estradiol (Zierau et al., 2002). Several studies have aimed to assess estrogenic activity by measuring luteinizing hormone (LH), follicle-stimulating hormone (FSH), or prolactin levels (Duker et al., 1991; Jarry & Harnischfeger, 1985). One study reported lower FSH levels (but not LH) in patients treated with black cohosh vs. placebo ($N = 110$), although baseline hormone levels were not known in either group (Duker et al., 1991). Results from other trials have found no effects on these hormone levels after up to 6 months of black cohosh therapy (Jacobson et al., 2001; Lehmann-Willenbrock & Riedel, 1988; Liske et al., 2001). When administered to female infantile mice, black cohosh could not precipitate premature onset of estrus (Siess & Seybold, 1960). Estrogenic effects on vaginal epithelium were noted in one 3-month trial of black cohosh (Stoll, 1987), while a 6-month trial reported no effects on vaginal cytology (Liske & Wstenberg, 1998). In a systematic review, with relevance to cancer

patients, black cohosh also seemed to lack phytoestrogenic activity and may inhibit tumor growth (Walji et al., 2007).

- Antihistamines: In vitro, black cohosh extract showed inhibitory potential for histamine release (Kim et al., 2004).
- Antihypertensives: The authors of a systematic review mentioned that black cohosh may interact with antihypertensives, according to the Clinical Practice Guideline of the Canadian Society of Obstetricians and Gynecologists (Roberts, 2010). Due to theoretical hypotensive effects, black cohosh should be used cautiously with other hypotensive agents (Genazzani & Sorrentino, 1962; Hailemeskel et al., 2000). There have been reports of hypotension in animals, although human data are limited in this area; increased peripheral blood flow has been associated with black cohosh administration in a 1962 study (Genazzani & Sorrentino, 1962).
- Antiinflammatory agents: In animal research, a phytoestrogen compound containing genistein, daidzein, glycitein, black cohosh, Angelica, licorice, and Vitex agnus-castus lowered levels of proinflammatory cytokines and increased levels of TGF-beta (Marotta et al., 2006).
- Antilipemic agents: In a case report, black cohosh has been reported to interact with atorvastatin, resulting in an increase in liver enzymes, possibly due to inhibition of CYP3A4 (Patel & Derkits, 2007). In a clinical trial of black cohosh, changes in total, HDL, and LDL cholesterol were lacking in postmenopausal women, but an increase in triglycerides was reported (Wuttke et al., 2006). In women, *Cimicifuga racemosa* caused a statistically significant increase in high-density lipoprotein (HDL) cholesterol and a statistically significant decrease in low-density lipoprotein (LDL) cholesterol from baseline (Nappi et al., 2005). In human research, a combination of black cohosh (*Cimicifuga racemosa*) and St. John's wort (Hypericum perforatum) significantly increased HDL levels (Chung et al., 2007), although other studies have not found the same results (Spangler et al., 2007). In postmenopausal women, 3 months of therapy with *Cimicifuga racemosa* was reported to be well tolerated and did not alter the lipid profile (Garcia-Perez et al., 2009).
- Antineoplastic agents: In vitro, relatively low concentrations of actein or the methanol/water fraction of black cohosh caused synergistic inhibition of human breast cancer cell proliferation when combined with different classes of chemotherapy agents (Einbond et al., 2006). In vitro, black cohosh has been shown to inhibit the intestinal breast cancer resistant protein, which may lead to increased absorption of certain drugs (Tamaki, Satoh, Hori, Ohtani, & Sawada, 2010). However, black cohosh may not interact with all chemotherapy agents, according to an animal study using high doses of black cohosh with low doses of formestane (Nisslein & Freudenstein, 2007).
- Cytochrome P450-metabolized agents: Unlike that observed for rifampin and clarithromycin, midazolam pharmacokinetics was unaffected by black cohosh, and black cohosh did not appear to have a clinically relevant effect on CYP2D6 or CYP3A activity in vivo (Gurley et al., 2005, 2006). In a systematic review, the authors indicated that the effect of black cohosh on human cytochrome activity may be small (Roberts, 2010). However, another systematic review suggested that laboratory studies have shown that black cohosh may interact with CYP3A4

(Wong et al., 2009). In a clinical trial of 16 healthy volunteers, supplementation of black cohosh for 14 days did not demonstrate an effect on CYP2D6 (Gurley et al., 2008). In vitro, strong inhibition of all CYP isoenzymes was documented due to cimicifugic acids A and B and fukinolic acid at median inhibitory concentrations (IC50) of 1.8–12.6 mcM (Huang et al., 2010; Shi & Klotz, 2012). Triterpene glycosides were reported to be weakly active (IC50: 25–100 mcM). In addition, Hep-G2 cell growth was not shown to be inhibited by any black cohosh extracts (cimicifugic acids A and B, fukinolic acid, and triterpene glycosides in concentrations as high as 50 mcg/mL) (Huang et al., 2010). However, in vitro, seven black cohosh products were not shown to inhibit CYP3A4 in the human liver (Wanwimolruk, Wong, & Wanwimolruk, 2009). In vitro, methanolic extracts of black cohosh were shown to inhibit CYP2B6, (Ashar, Rice, & Sisson, 2008) 2C19, and (D)2C19 in human liver cells (Sevior et al., 2010). In vitro, black cohosh has been reported to lack an effect on CYP450-catalyzed 4-hydroxylation of estradiol in human mammary epithelial cells (Hemachandra et al., 2012). In mice, black cohosh at a dose of 500 mg/kg was reported to induce liver CYP3A11 sevenfold after 28 days of treatment (Pang, Cheng, Krausz, Guo, & Gonzalez, 2011; Shi & Klotz, 2012). This induction was reported to be both time and dose dependent. A change in the kidney and small intestine CYP3A11was lacking. In further research, mouse pregnane X receptor (PXR) was reported to be activated by black cohosh, but human PXR was not (Pang et al., 2011). In a case report, black cohosh has been reported to interact with atorvastatin, resulting in an increase in liver enzymes, possibly due to inhibition of CYP3A4 (Patel & Derkits, 2007).

- Disulfiram (Antabuse®): Tinctures may have high alcohol content and theoretically may elicit a disulfiram reaction.
- Dopamine agonists: Studies suggest that the mechanism of action of black cohosh may be centrally mediated, with possible action at the level of serotonin or dopamine receptors (Burdette et al., 2003; Jarry et al., 2003; Villaseca, 2012).
- Dopamine antagonists: Studies suggest that the mechanism of action of black cohosh may be centrally mediated, with possible action at the level of serotonin or dopamine receptors (Burdette et al., 2003; Jarry et al., 2003; Villaseca, 2012).
- Drugs that may lower seizure threshold: Tonic-clonic seizures have been reported in a 45-year-old woman who had been taking black cohosh, chaste-tree (berries and seeds), and primrose oil for four months, and who also consumed alcohol (Shuster, 1996). The relative contribution of each agent or risk of combination is unclear.
- Estrogens: The estrogenic activity of black cohosh remains debated. Specific estrogenic constituents have not been identified, and it is unclear how (or if) black cohosh interacts with estrogens, estrogen receptors, and/or progestins. Studies suggest that there may be no direct effects on estrogen receptors, although this is an area of active controversy (Borrelli et al., 2003; Burdette et al., 2003; Huntley & Ernst, 2003b; Jarry et al., 2003; Lupu et al., 2003; Mahady, 2003; Seidlova-Wuttke et al., 2003; Seidlova-Wuttke et al., 2003). Therefore, caution is warranted in individuals taking both black cohosh and estrogens, due to unknown effects, and interactions data in this area are lacking. In animals and in vitro, initial reports of estrogen receptor-binding activity (Jarry et al., 1985) stand in contrast with data suggesting no significant estrogen receptor-binding activity or

estrogenic activities (Einer-Jensen et al., 1996; Liu et al., 2001; Liu et al., 2001; Zava et al., 1998). One in vitro study found no effects of black cohosh alone on estrogen receptors, but it reported that black cohosh antagonized proliferative effects on cells induced by estradiol (Zierau et al., 2002). Several studies have aimed to assess estrogenic activity by measuring luteinizing hormone (LH), follicle-stimulating hormone (FSH), or prolactin levels (Duker et al., 1991; Jarry & Harnischfeger, 1985). One study reported lower FSH levels (but not LH) in patients treated with black cohosh vs. placebo ($N = 110$), although baseline hormone levels were not known in either group (Duker et al., 1991). Results from other trials have found no effects on these hormone levels after up to 6 months of black cohosh therapy (Jacobson et al., 2001; Lehmann-Willenbrock & Riedel, 1988; Liske et al., 2001). When administered to female infantile mice, black cohosh could not precipitate the premature onset of estrus (Siess & Seybold, 1960). Estrogenic effects on vaginal epithelium were noted in one 3-month trial of black cohosh (Stoll, 1987), while a 6-month trial reported no effects on vaginal cytology (Liske & Wstenberg, 1998). In a systematic review, with relevance to cancer patients, black cohosh also seemed to lack phytoestrogenic activity and may inhibit tumor growth (Walji et al., 2007).

- Ethanol: Tonic-clonic seizures have been reported in a 45-year-old woman who had been taking black cohosh, chaste-tree (berries and seeds), and primrose oil for four months, and who also consumed alcohol (Shuster, 1996). The relative contribution of each agent or risk of combination is unclear.
- Gastrointestinal agents: According to traditional use, black cohosh may have additive effects with gastrointestinal agents.
- Hepatotoxic agents: Several cases of liver damage have been reported following use of black cohosh (Chitturi & Farrell, 2008; Chow et al., 2008; Gori, & Firenzuoli, 2007; Mahady et al., 2008; Teschke et al., 2007). However, animal studies and human exposure have not been definitive (Beuscher & Reichert, 1995; Centre for Reviews and Dissemination, 2006; Cohen et al., 2004; Joy et al., 2008; Korn, 1991; Lontos et al., 2003; Lynch et al., 2006; Mahady et al., 2009; Mahady et al., 2010; Naser et al., 2011; Nasr & Nafeh, 2009; Pockaj et al., 2006; Shou et al., 2011; Teschke, 2010; Teschke et al., 2009; Teschke et al., 2009; Teschke et al., 2011; Teschke & Schwarzenboeck, 2009; Teschke et al., 2011; Walji et al., 2007; Whiting et al., 2002; Wuttke et al., 2006).
- Hormonal agents: The estrogenic activity of black cohosh remains debated. Specific estrogenic constituents have not been identified, and it is unclear how (or if) black cohosh interacts with estrogens, estrogen receptors, and/or progestins. Studies suggest that there may be a lack of direct effects on estrogen receptors, although this is an area of controversy (Borrelli et al., 2003; Burdette et al., 2003; Huntley & Ernst, 2003b; Jarry et al., 2003; Lupu et al., 2003; Mahady, 2003; Seidlova-Wuttke et al., 2003; Seidlova-Wuttke et al., 2003). Therefore, caution is warranted in individuals taking both black cohosh and estrogens, due to unknown effects, and interactions data in this area are lacking. In animals and in vitro, initial reports of estrogen receptor-binding activity (Jarry et al., 1985) stand in contrast with data suggesting no significant estrogen receptor-binding activity or estrogenic activities (Einer-Jensen et al., 1996; Liu et al., 2001; Liu et al., 2001; Zava et al., 1998). One in vitro study found no effects of black cohosh alone

on estrogen receptors, but it reported that black cohosh antagonized proliferative effects on cells induced by estradiol (Zierau et al., 2002). Several studies have aimed to assess estrogenic activity by measuring luteinizing hormone (LH), follicle-stimulating hormone (FSH), or prolactin levels (Duker et al., 1991; Jarry & Harnischfeger, 1985). One study reported lower FSH levels (but not LH) in patients treated with black cohosh vs. placebo ($N = 110$), although baseline hormone levels were not known in either group (Duker et al., 1991). Results from other trials have found no effects on these hormone levels after up to 6 months of black cohosh therapy (Jacobson et al., 2001; Lehmann-Willenbrock & Riedel, 1988; Liske et al., 2001). Administered to female infantile mice, premature onset of estrus could not be precipitated by black cohosh (Siess & Seybold, 1960). Estrogenic effects on vaginal epithelium were noted in one 3-month trial of black cohosh (Stoll, 1987), while a 6-month trial reported no effects on vaginal cytology (Liske & Wstenberg, 1998). In vitro, black cohosh has been reported to lack an effect on CYP450-catalyzed 4-hydroxylation of estradiol in human mammary epithelial cells (Hemachandra et al., 2012).

- Metronidazole (Flagyl®): A disulfiram reaction may occur when metronidazole and alcohol are used concomitantly. Due to the high alcohol content in some tinctures, this combination theoretically may cause such a reaction.
- Neurologic agents: In a clinical trial, the frequency of menstrual migraines was decreased with a combination of soy, dong quai, and black cohosh (Burke, Olson, & Cusack, 2002). Tonic-clonic seizures have been reported in a 45-year-old woman who had been taking black cohosh, chaste-tree (berries and seeds), and primrose oil for 4 months, and who also consumed alcohol (Shuster, 1996). The relative contribution of each agent or risk of combination is unclear.
- Oral agents: Extracts of black cohosh moderately (but significantly) inhibited estrone-3-sulfate uptake, which suggests that coadministration may decrease the absorption of orally administered substrates of organic anion-transporting polypeptide B, which is considered to be involved in the intestinal absorption of various drugs (Fuchikami et al., 2006). In vitro, black cohosh has been shown to inhibit the intestinal breast cancer-resistant protein, which may lead to increased absorption of certain drugs (Tamaki et al., 2010).
- Osteoporosis agents: In postmenopausal women, 3 months of therapy with *Cimicifuga racemosa* resulted in increased alkaline phosphatase and a decrease in the concentration of N-telopeptides in the urine (Garcia-Perez et al., 2009). In postmenopausal women, CR BNO 1055 was reported to increase osteoblast activity and decrease osteoclast activity (Wuttke et al., 2003). An increase in bone-specific collagen-1alpha1 was lacking with CR administration, and bone-specific alkaline phosphatase increased significantly with CR administration when compared to placebo after 12 weeks of treatment (Wuttke et al., 2006). According to animal and in vitro research, black cohosh may increase osteogenesis (Nisslein & Freudenstein, 2003; Seidlova-Wuttke et al., 2003; Viereck et al., 2005).
- Salicylate-containing agents (e.g., aspirin): Native black cohosh contains small amounts of salicylic acid, but it is unclear how much (if any) is present in commercially available or standardized extracts.
- Tamoxifen, raloxifene: Controversy surrounds the use of black cohosh in combination with tamoxifen (Hernandez Munoz & Pluchino, 2003; Jacobson et al.,

2001). The influence of black cohosh alone or in combination with tamoxifen is unclear in these cases. It is unclear if tamoxifen antagonized the effects of black cohosh or if hot flashes induced by tamoxifen are refractory to black cohosh therapy. The authors of a systematic review suggested that black cohosh may augment the antiproliferative effects of tamoxifen in clinical trials. However, some studies included in the review advised against using black cohosh during chemotherapy or radiotherapy (Roberts, 2010). In vitro research suggests possible additive antiproliferative effects of black cohosh and tamoxifen (Freudenstein & Bodinet, 1999; Zierau et al., 2002).

- Vasodilators: Laboratory research on cimicifugic acids C and D, and fukinolic acid in the rhizome of black cohosh has shown vasoactive effects (Noguchi et al., 1998).

Black cohosh/Herb/Supplement Interactions

- American pennyroyal: Pennyroyal (*Hedeoma pulegioides* L.) and black cohosh are sometimes taken together to induce abortion, although the use of these herbs together may increase toxicity and death. There is a case report of a 24-year-old woman who took 48–56% pennyroyal herb in an alcohol base and an unknown amount of black cohosh root for 2 weeks in an attempt to induce abortion (Anderson et al., 1996). Following a single subsequent dose of this combination, the patient died within 48 hours.
- Analgesics: According to traditional use, black cohosh may have additive effects with analgesics (Sakurai & Nagai, 1996).
- Anesthetics: The authors of a systematic review mentioned that black cohosh may interact with anesthetics, according to the Clinical Practice Guideline of the Canadian Society of Obstetricians and Gynecologists (Roberts, 2010). According to traditional use, black cohosh may have additive effects with anesthetics (Sakurai & Nagai, 1996).
- Antiandrogens: In an in vitro study conducted on human prostate cancer cells with black cohosh extract, the extract killed hormone-responsive or hormone-unresponsive prostate cancer cells by induction of apoptosis and activation of caspases (Hostanska et al., 2005). Another in vivo study in mice demonstrated inhibited PC3 prostate cancer tumor growth with black cohosh and other herbal extracts (Ng & Figg, 2003).
- Antiarthritics: In humans, Reumalex® has been reported to have significant improvements in arthritis pain (Mills et al., 1996).
- Anticoagulants and antiplatelets: In a systematic review, the authors of the review indicated that black cohosh may contain anticoagulant coumarins, although an effect on prothrombin times was lacking (Roberts, 2010). In a clinical trial of postmenopausal women, changes in markers of coagulation were lacking (Wuttke et al., 2006). Native black cohosh contains small amounts of salicylic acid and may potentiate the antiplatelet effects of other agents, such as ginkgo or garlic. It is unclear if therapeutic amounts of salicylates are present in commercial or processed black cohosh products.
- Antidepressants, selective serotonin reuptake inhibitors (SSRIs): Studies suggest that the mechanism of action of black cohosh may be centrally mediated,

with possible action at the level of serotonin or dopamine receptors (Burdette et al., 2003; Jarry et al., 2003; Villaseca, 2012). A study in ovariectomized rats demonstrated strong binding to serotonin receptors 5-HT(1A), 5-HT(1D), and 5-HT(Bai et al., 2009) subtypes (Burdette et al., 2003).

- Antihistamines: In vitro, black cohosh extract showed inhibitory potential for histamine release (Kim et al., 2004).
- Antihypertensives: The authors of a systematic review mentioned that black cohosh may interact with antihypertensives, according to the Clinical Practice Guideline of the Canadian Society of Obstetricians and Gynecologists (Roberts, 2010). Due to theoretical hypotensive effects, black cohosh should be used cautiously with other hypotensive agents (Genazzani & Sorrentino, 1962; Hailemeskel et al., 2000). There have been reports of hypotension in animals, although human data are limited in this area; increased peripheral blood flow was associated with black cohosh administration in a 1962 study (Genazzani & Sorrentino, 1962).
- Anti-inflammatory herbs and supplements: In animal research, a phytoestrogen compound containing genistein, daidzein, glycitein, black cohosh, Angelica, licorice, and Vitex agnus-castus lowered levels of proinflammatory cytokines and increased levels of TGF-beta (Marotta et al., 2006).
- Antilipemics: In a case report, black cohosh has been reported to interact with atorvastatin resulting in an increase in liver enzymes, possibly due to inhibition of CYP3A4 (Patel & Derkits, 2007). In a clinical trial of black cohosh, changes in total, HDL, and LDL cholesterol were lacking in postmenopausal women, but an increase in triglycerides was reported (Wuttke et al., 2006). In women, *Cimicifuga racemosa* caused a statistically significant increase in HDL cholesterol (51.6 ± 1.8 to 53.1 ± 1.7 mg/dL, respectively; $p = 0.04$) and a statistically significant decrease in LDL cholesterol (153.8 ± 39.0 to 146.1 ± 34.4 mg/dL, respectively; $p = 0.003$) from baseline (Nappi et al., 2005). In human research, it is unclear whether a combination of black cohosh (*Cimicifuga racemosa*) and St. John's wort (Hypericum perforatum) increased HDL levels (Chung et al., 2007) or leaves lipid levels unchanged (Spangler et al., 2007). In postmenopausal women, 3 months of therapy with *Cimicifuga racemosa* was reported to be well tolerated and did not cause a change in the lipid profile (Garcia-Perez et al., 2009).
- Antineoplastics: According to the authors of a systematic review, black cohosh may augment the antiproliferative effects of tamoxifen, based on clinical trials. However, some studies included in the review advised against using black cohosh during chemotherapy or radiotherapy (Roberts, 2010). In vitro, relatively low concentrations of actein or the methanol/water fraction of black cohosh caused synergistic inhibition of human breast cancer cell proliferation when combined with different classes of chemotherapy agents (Einbond et al., 2006). In vitro, black cohosh has been shown to inhibit the intestinal breast cancer-resistant protein, which may lead to increased absorption of certain drugs (Tamaki et al., 2010). However, black cohosh may not interact with all chemotherapy agents, according to an animal research using high doses of black cohosh with low doses of formestane (Nisslein & Freudenstein, 2007).
- Antioxidants: According to in vitro research, black cohosh may have antioxidant properties (Burdette et al., 2002; Jiang et al., 2005; Nuntanakorn et al., 2006).

- Blue cohosh (*Caulophyllum thalictroides*): Both black cohosh and blue cohosh (*Caulophyllum thalictroides*) are commonly used by nurse-midwives in the United States to assist birth (McFarlin et al., 1999). There is a report of severe multiorgan hypoxic injury in a child delivered with the aid of both blue and black cohosh, who was not breathing at the time of birth (Baillie & Rasmussen, 1997; Gunn & Wright, 1996; McFarlin et al., 1999). The child survived with permanent central nervous system damage. Notably, blue cohosh possesses a vasoconstrictive glycoside, which may have been responsible for the adverse effects. Although they are used internationally, few safety and efficacy data are available for homeopathic preparations of blue and black cohosh (Kistin & Newman, 2007).
- Chasteberry: Tonic-clonic seizures had been reported in a 45-year-old woman who had been taking black cohosh, chaste-tree (berries and seeds), and primrose oil for 4 months, and who also consumed alcohol (Shuster, 1996). The relative contribution of each agent or risk of combination is unclear.
- Cytochrome P450-metabolized herbs and supplements: In vivo, black cohosh did not appear to have a clinically relevant effect on CYP2D6 or CYP3A activity (Gurley et al., 2006; Gurley et al., 2005). The authors of a systematic review indicated that the effect of black cohosh on human cytochrome activity may be small (Roberts, 2010). However, another systematic review suggested that laboratory studies have shown that black cohosh may interact with CYP3A4 (Wong et al., 2009). In a clinical trial of 16 healthy volunteers, supplementation of black cohosh for 14 days did not demonstrate an effect on CYP2D6 (Gurley et al., 2008). In vitro, strong inhibition of all CYP isoenzymes was documented, due to cimicifugic acids A and B and fukinolic acid at median inhibitory concentrations (IC50) of 1.8–12.6 mcM (Huang et al., 2010; Shi & Klotz, 2012). Triterpene glycosides were reported to be weakly active (IC50: 25–100 mcM). In addition, Hep-G2 cell growth was not shown to be inhibited by any black cohosh extracts (cimicifugic acids A and B, fukinolic acid, and triterpene glycosides in concentrations as high as 50 mcg/mL) (Huang et al., 2010). However, in vitro, seven black cohosh products were not shown to inhibit CYP3A4 in human liver (Wanwimolruk et al., 2009). In vitro, methanolic extracts of black cohosh were shown to inhibit CYP2B6, (Ashar et al., 2008) 2C19, and (D)2C19 in human liver cells (Sevior et al., 2010). In vitro, black cohosh has been reported to lack an effect on CYP450-catalyzed 4-hydroxylation of estradiol in human mammary epithelial cells (Hemachandra et al., 2012). In mice, black cohosh at a dose of 500 mg/kg was reported to induce liver CYP3A11 sevenfold after 28 days of treatment (Pang et al., 2011; Shi & Klotz, 2012). This induction was reported to be both time and dose dependent. A change in the kidney and small intestine CYP3A11 was lacking. In further research, mouse pregnane X receptor (PXR) was reported to be activated by black cohosh, but human PXR was not (Pang et al., 2011). In a case report, black cohosh has been reported to interact with atorvastatin, resulting in an increase in liver enzymes, possibly due to inhibition of CYP3A4 (Patel & Derkits, 2007).
- Dopamine agonists: Studies suggest that the mechanism of action of black cohosh may be centrally mediated, with possible action at the level of serotonin or dopamine receptors (Burdette et al., 2003; Jarry et al., 2003; Villaseca, 2012).

- Dopamine antagonists: Studies suggest that the mechanism of action of black cohosh may be centrally mediated, with possible action at the level of serotonin or dopamine receptors (Burdette et al., 2003; Jarry et al., 2003; Villaseca, 2012).
- Evening primrose oil: Tonic-clonic seizures had been reported in a 45-year-old woman who had been taking black cohosh, chaste-tree (berries and seeds), and primrose oil for 4 months, and who also consumed alcohol (Shuster, 1996). The relative contribution of each agent or risk of combination is unclear.
- Gastrointestinal herbs and supplements: According to traditional use, black cohosh may have additive effects with gastrointestinal agents.
- Hepatotoxic agents: Several cases of liver damage have been reported following use of black cohosh (Chitturi & Farrell, 2008; Chow et al., 2008; Gori & Firenzuoli, 2007; Mahady et al., 2008; Teschke et al., 2007). However, animal studies and human exposure have not been definitive (Beuscher & Reichert, 1995; Centre for Reviews and Dissemination, 2006; Cohen et al., 2004; Joy et al., 2008; Korn, 1991; Lontos et al., 2003; Lynch et al., 2006; Mahady et al., 2009; Mahady et al., 2010; Naser et al., 2011; Nasr & Nafeh, 2009; Pockaj et al., 2006; Shou et al., 2011; Teschke, 2010; Teschke et al., 2009; Teschke et al., 2009; Teschke et al., 2011; Teschke & Schwarzenboeck, 2009; Teschke et al., 2011; Walji et al., 2007; Whiting et al., 2002; Wuttke et al., 2006).
- Herbs and supplements that lower seizure threshold: Tonic-clonic seizures had been reported in a 45-year-old woman who had been taking black cohosh, chaste-tree (berries and seeds), and primrose oil for 4 months, and who also consumed alcohol (Shuster, 1996). The relative contribution of each agent or risk of combination is unclear.
- Hormonal herbs and supplements: The estrogenic activity of black cohosh remains debated. Specific estrogenic constituents have not been identified, and it is unclear if black cohosh interacts with other estrogenic compounds, such as soy or evening primrose oil (*Oenothera biennis*). Publications suggest that there may be no direct effects on estrogen receptors, although this is an area of controversy (Borrelli et al., 2003; Burdette et al., 2003; Huntley & Ernst, 2003b; Jarry et al., 2003; Lupu et al., 2003; Mahady, 2003; Seidlova-Wuttke et al., 2003; Seidlova-Wuttke et al., 2003).
- Hormone replacement therapy: The estrogenic activity of black cohosh remains debated. Specific estrogenic constituents have not been identified, and it is unclear if black cohosh interacts with other estrogenic compounds, such as soy or evening primrose oil (*Oenothera biennis*). Publications suggest that there may be no direct effects on estrogen receptors, although this is an area of controversy (Borrelli et al., 2003; Burdette et al., 2003; Huntley & Ernst, 2003b; Jarry et al., 2003; Lupu et al., 2003; Mahady, 2003; Seidlova-Wuttke et al., 2003; Seidlova-Wuttke et al., 2003).
- Hypotensives: The authors of a systematic review mentioned that black cohosh may interact with antihypertensives, according to the Clinical Practice Guideline of the Canadian Society of Obstetricians and Gynecologists (Roberts, 2010). Due to theoretical hypotensive effects, black cohosh should be used cautiously with other hypotensive agents (Genazzani & Sorrentino, 1962; Hailemeskel et al., 2000). There have been reports of hypotension in animals, although human data

are limited in this area; increased peripheral blood flow has been associated with black cohosh administration in a 1962 study (Genazzani & Sorrentino, 1962).

- Neurologic herbs and supplements: In a clinical trial, the frequency of menstrual migraines was decreased with a combination of soy, dong quai, and black cohosh (Burke et al., 2002). Tonic-clonic seizures had been reported in a 45-year-old woman who had been taking black cohosh, chaste tree (berries and seeds), and primrose oil for 4 months, and who also consumed alcohol (Shuster, 1996). The relative contribution of each agent or risk of combination is unclear.
- Oral herbs and supplements: Extracts of black cohosh moderately (but significantly) inhibited estrone-3-sulfate uptake, which suggests that coadministration may decrease the absorption of orally administered substrates of organic anion-transporting polypeptide B, which is considered to be involved in the intestinal absorption of various drugs (Fuchikami et al., 2006). In vitro, black cohosh has been shown to inhibit the intestinal breast cancer-resistant protein, which may lead to increased absorption of certain drugs (Tamaki et al., 2010).
- Osteoporosis agents: In postmenopausal women, 3 months of therapy with *Cimicifuga racemosa* resulted in a significant increased alkaline phosphatase and a decrease in the concentration of N-telopeptides in the urine compared to placebo (Garcia-Perez et al., 2009). However, the mechanism to decrease bone remodeling is not known. In postmenopausal women, CR BNO 1055 was reported to increase osteoblast activity and decrease osteoclast activity (Wuttke et al., 2003). An increase of bone-specific collagen-1alpha1 was lacking with CR administration, and bone-specific alkaline phosphatase increased significantly with CR administration when compared to placebo after 12 weeks of treatment (Wuttke et al., 2006). According to in vitro and animal studies, black cohosh may increase osteogenesis (Nisslein & Freudenstein, 2003; Seidlova-Wuttke et al., 2003; Viereck et al., 2005).
- Phytoestrogens: The estrogenic activity of black cohosh remains debated. Specific estrogenic constituents have not been identified, and it is unclear if black cohosh interacts with other estrogenic compounds. Studies suggest that there may be no direct effects on estrogen receptors, although this is an area of active controversy (Borrelli et al., 2003; Burdette et al., 2003; Duker et al., 1991; Einer-Jensen et al., 1996; Huntley & Ernst, 2003b; Jacobson et al., 2001; Jarry & Harnischfeger, 1985; Jarry et al., 1985; Jarry et al., 2003; Lehmann-Willenbrock & Riedel, 1988; Liske & Wstenberg, 1998; Liske et al., 2001; Liu et al., 2001; Liu et al., 2001; Lupu et al., 2003; Mahady, 2003; Seidlova-Wuttke et al., 2003; Seidlova-Wuttke et al., 2003; Siess & Seybold, 1960; Stoll, 1987; Walji et al., 2007; Zava et al., 1998). Therefore, caution is warranted in subjects taking both black cohosh and herbs containing phytoestrogens, due to unknown effects, and interaction data in this area are lacking.
- Salicylate-containing herbs and supplements (e.g., willowbark): Native black cohosh contains small amounts of salicylic acid, but it is unclear how much (if any) is present in commercially available or standardized extracts.
- St. John's wort: According to an open observational study of 6,141 menopausal women, black cohosh combined with St. John's wort may alleviate climacteric mood symptoms more than black cohosh alone (Briese et al., 2007).

- Vasodilator herbs and supplements: Laboratory research on cimicifugic acids C and D and fukinolic acid in the rhizome of black cohosh has shown vasoactive effects (Noguchi et al., 1998).

Black cohosh/Food Interactions

- Insufficient available evidence.

Black Cohosh/Lab Interactions

- Allergy tests: In vitro, black cohosh extract showed inhibitory potential for histamine release (Kim et al., 2004).
- Bone markers: An isopropanolic extract of black cohosh has been shown to significantly diminish the urinary content of pyridinoline and deoxypyridinoline, specific markers for bone loss, and the morphometric correlates of bone loss associated with ovariectomy in rats (Nisslein & Freudenstein, 2003). In postmenopausal women, three months of therapy with *Cimicifuga racemosa* resulted in increased alkaline phosphatase and decreased concentration of N-telopeptides in the urine (Garcia-Perez et al., 2009). However, the mechanism to decrease bone remodeling is not known. In postmenopausal women, CR BNO 1055 was reported to increase osteoblast activity and decrease osteoclast activity (Wuttke et al., 2003). An increase of bone-specific collagen-1alpha1 was lacking with CR administration, and bone-specific alkaline phosphatase increased significantly with CR administration when compared to placebo after 12 weeks of treatment (Wuttke et al., 2006).
- Coagulation panel: In a systematic review, the authors indicated that black cohosh may contain anticoagulant coumarins, although an effect on prothrombin times was lacking (Roberts, 2010). In a clinical trial of postmenopausal women, changes in markers of coagulation were lacking (Wuttke et al., 2006). Native black cohosh contains small amounts of salicylic acid and may potentiate the antiplatelet effects of other agents. It is unclear if therapeutic amounts of salicylates are present in commercial or processed black cohosh products.
- Liver function tests: A prospective longitudinal clinical study of 87 postmenopausal women that received 40 mg of a dry extract of *Cimicifuga racemosa* (Klimadyon) to treat menopausal symptoms for 12 months did not report alterations in liver function tests or hepatic perfusion (Nasr & Nafeh, 2009).
- Serum glucose: In a randomized trial in 351 peri- or postmenopausal women, black cohosh lacked demonstrable effects on lipids, glucose, insulin, or fibrinogen (Spangler et al., 2007).
- Serum insulin: In a randomized trial in 351 peri- or postmenopausal women, black cohosh lacked demonstrable effects on lipids, glucose, insulin, or fibrinogen (Spangler et al., 2007).
- Serum levels of cytochrome P450-metabolized agents: In vivo, black cohosh did not appear to have a clinically relevant effect on CYP2D6 or CYP3A activity (Gurley et al., 2005, 2006). In a systematic review, the authors indicated that the effect of black cohosh on human cytochrome activity may be small (Roberts, 2010). However, another systematic review suggested that laboratory studies have shown that black cohosh may interact with CYP3A4 (Wong et al., 2009).

In a clinical trial of 16 healthy volunteers, supplementation of black cohosh for 14 days did not demonstrate an effect on CYP2D6 (Gurley et al., 2008). In vitro, strong inhibition of all CYP isoenzymes was documented, due to cimicifugic acids A and B and fukinolic acid at median inhibitory concentrations (IC50) of 1.8–12.6 mcM (Huang et al., 2010; Shi & Klotz, 2012). Triterpene glycosides were reported to be weakly active (IC50: 25–100 mcM). In addition, Hep-G2 cell growth was not shown to be inhibited by any black cohosh extracts (cimicifugic acids A and B, fukinolic acid, and triterpene glycosides in concentrations as high as 50 mcg/mL (Huang et al., 2010). However, in vitro seven black cohosh products were not shown to inhibit CYP3A4 in the human liver (Wanwimolruk et al., 2009). In vitro, methanolic extracts of black cohosh were shown to inhibit CYP2B6, (Ashar et al., 2008) 2C19, and (D)2C19 in human liver cells (Ashar et al., 2008). In vitro, black cohosh has been reported to lack an effect on CYP450-catalyzed 4-hydroxylation of estradiol in human mammary epithelial cells (Sevior et al., 2010). In mice, black cohosh at a dose of 500 mg/kg was reported to induce liver CYP3A11 sevenfold after 28 days of treatment (Pang et al., 2011; Shi & Klotz, 2012). This induction was reported to be both time and dose dependent. A change in the kidney and small intestine CYP3A11 was lacking. In further research, mouse pregnane X receptor (PXR) was reported to be activated by black cohosh, but human PXR was not (Pang et al., 2011). In a case report, black cohosh has been reported to interact with atorvastatin, resulting in an increase in liver enzymes, possibly due to inhibition of CYP3A4 (Patel & Derkits, 2007).

- Serum levels of oral agents: Extracts of black cohosh moderately (but significantly) inhibited estrone-3-sulfate uptake, which suggests that coadministration may decrease the absorption of orally administered substrates of organic anion-transporting polypeptide B, which is considered to be involved in the intestinal absorption of various drugs (Fuchikami et al., 2006). In vitro, black cohosh has been shown to inhibit the intestinal breast cancer-resistant protein, which may lead to increased absorption of certain drugs (Tamaki et al., 2010).
- Serum lipids: In human research, there is controversy about whether black cohosh alters serum lipid levels (Chung et al., 2007; Spangler et al., 2007). In postmenopausal women, 3 months of therapy with *Cimicifuga racemosa* was reported to be well tolerated and did not show a change in lipid profile (Garcia-Perez et al., 2009). In a clinical trial of black cohosh, changes in total, HDL, and LDL cholesterol were lacking in postmenopausal women, but an increase in triglycerides was reported (Wuttke et al., 2006). In women, *Cimicifuga racemosa* caused a statistically significant increase in HDL cholesterol and a statistically significant decrease in LDL cholesterol from baseline (Nappi et al., 2005).

Black Cohosh/Nutrient Depletion:

- Lipids: In human research, there is controversy about whether black cohosh alters serum lipid levels (Chung et al., 2007; Spangler et al., 2007). In postmenopausal women, 3 months of therapy with *Cimicifuga racemosa* was reported to be well tolerated and did not show a change in lipid profile (Garcia-Perez et al., 2009). In a clinical trial of black cohosh, changes in total, HDL, and LDL cholesterol were lacking in postmenopausal women, but an increase in triglycerides

was reported (Wuttke et al., 2006). In women, *Cimicifuga racemosa* caused a statistically significant increase in HDL cholesterol and a statistically significant decrease in LDL cholesterol from baseline (Nappi et al., 2005).

MECHANISM OF ACTION

Pharmacology

- Constituents: Constituents of black cohosh with proposed or demonstrated pharmacological activity include triterpene glycosides (23-epi-26-deoxyactein, actein, 27-deoxyactein, cimicifugoside A, cimicifugoside M, and cimiracemosides A-H) (Chen et al., 2007; Einbond et al., 2004, 2006, 2009; Fugh-Berman and Ernst, 2001; He, Zheng, Kim, Rogers, & Zheng, 2000; Huang et al., 2010; Onorato & Henion, 2001; Shao et al., 2000; Struck et al., 1997; van Breemen et al., 2010; Wang, Sakurai, Shih, & Lee, 2005), cyclolanostanol xylosides (Koeda, Aoki, Sakurai, & Nagai, 1995), formononetin (Kennelly et al., 2002), hydroxytyrosol (Johnson & van Breemen, 2003), actaeaeposcide (Wende, Mugge, Thurow, Schopke, & Lindequist, 2001), phenylpropanoids (cimiracemate A, cimiracemate B) (Burdette et al., 2002; Chen, Fabricant, Pauli, Fong, & Farnsworth, 2005), organic acids (caffeic acid, cimicifugic acid A, cimicifugic acid B, cimicifugic acid E, cimicifugic acid F, cinnamic acid ester dehydrocimicifugic A, dehydrocimicifugic acid B, dihydroxyphenyl lactic acid, ferulic acid, fukinolic acid, isoferulic acid, methyl caffeate acid, and salicylic acid) (Burdette et al., 2002; Hostanska, Nisslein, Freudenstein, Reichling, & Saller, 2004; Huang et al., 2010; Johnson & van Breemen, 2003; Li, Sun, Liang, Fitzloff, & van Breemen, 2003), phenols (Hostanska et al., 2004), quinoid metabolites of caffeic acid, cimiracemate B, fukiic acid, and hydroxytyrosol (Johnson and van Breemen, 2003). *Actaea racemosa* specifically contains lignans [e.g., actaealactone and 5-HT(Bai et al., 2009) ligand, N-omega-methylserotonin], phenylpropanoid ester derivatives (e.g., cimicifugic acid), polyphenols (0.36–2.92% (w/w) in dried root and rhizome), protocatechuic acid, protocatechualdehyde, *p*-coumaric acid, caffeic acid, methyl caffeate, ferulic acid, ferulate-1-methyl ester, isoferulic acid, 1-isoferuloyl-beta-D-glucopyranoside, and cimicifugic acids A, B, and D–F (Godecke et al., 2009; Nuntanakorn et al., 2006, 2007; Wang, Dou, Cross, & Valerio, 2011). Methods of extracting active ingredients from black cohosh have been described (Godecke et al., 2009; Hamburger, 2007).
- Antibacterial effects: In vitro, ethanolic extracts of *Cimicifuga racemosa* had weak or no antimicrobial activity against Neisseria gonorrhea (Cybulska et al., 2011).
- Anticlimacteric effects: In vitro, black cohosh was found to be consistent with a human mu-opiate receptor (hMOR) agonist, with an EC50 of 68.8 ± 7.7 mcg/mL, which may explain its purported beneficial role in alleviating menopausal symptoms (Rhyu et al., 2006).
- Anticoagulation effects: Native black cohosh contains small amounts of salicylic acid, but it is unclear how much (if any) is present in commercially available or standardized extracts. A popular combination product, Reumalex®, contains black cohosh, white willow bark, sarsaparilla, poplar bark, and guaiacum resin.

Notably, several constituents contain salicylates, and it has been estimated that each Reumalex® tablet may include up to 10–20 mg of salicylates. In a clinical trial of postmenopausal women, changes in markers of coagulation were lacking (Wuttke et al., 2006). In a randomized trial of 351 peri- or postmenopausal women, black cohosh lacked demonstrable effects on fibrinogen (Spangler et al., 2007).

- Antidiabetic effects: In a randomized trial in 351 peri- or postmenopausal women, black cohosh lacked demonstrable effects on glucose or insulin (Spangler et al., 2007).
- Antihistamine effects: In vivo oral administration of black cohosh extract inhibited the anti-IgE-induced passive cutaneous anaphylaxis reaction (Kim et al., 2004). Black cohosh extract also showed inhibitory potential on histamine release.
- Antiinflammatory effects: In vitro, *Cimicifuga racemosa* extract lacked an effect on human endothelial cells' serum interleukin (IL)-6 levels or prostacyclin production (Pineda et al., 2009). Ovariectomized Wistar rats administered a phytoestrogen compound (genistein, daidzein, glycitein, black cohosh, Angelica, licorice, and Vitex agnus-castus) orally showed a significantly lower level of proinflammatory cytokines and a higher level of TGF-beta (Marotta et al., 2006). The constituent isoferulic acid has also been reported to have antiinflammatory effects and may decrease muscular spasm (Shibata et al., 1980). Furthermore, salicylic acid is found in small quantities in black cohosh, and it is presumed that the salicylic acid contributes to the antiinflammatory and analgesic properties of black cohosh. In vitro research on human primary blood macrophages using cimiracemate A, a rhizome extract constituent from *Cimicifuga racemosa*, at lipopolysaccharide (LPS) concentrations of 1 ng/mL and 10 ng/mL, was found to suppress LPS-induced tumor necrosis factor (TNF)-alpha production by 47 $\pm$ 19% and 58 $\pm$ 30%, respectively (Yang, Chik, Li, Cheung, & Lau, 2009). The authors of the study hypothesized that the antiinflammatory activity may be due to the effects on transcription factor nuclear factor-kappaB and a signaling mitogen-activated protein kinase. *Cimicifuga racemosa* root extract, predominantly isoferulic acid, was shown to produce a time- and concentration-dependent decrease in the LPS-induced release of IL-6 and TNF-alpha at concentrations of 3–6 mcg/mcL (Schmid et al., 2009). Interferon-gamma release was also blocked almost completely. *Cimicifuga racemosa* root extracts were also shown to stimulate IL-8 secretion. However, isoferulic acid was not shown to be the active constituent for IL-8 secretion.
- Antilipemic effects: In rats, triterpene glycoside actein, at a dose of 35.7 mg/kg for six and 24 hr, was reported to elicit multiple alterations in gene expression in the liver (Einbond et al., 2009). Genes involved with biosynthesis of fatty acids and cholesterol were altered in a time-dependent manner. Cholesterol content and free fatty acids were reduced 0.6-fold in the liver by acetin at 24 hours. In women, *Cimicifuga racemosa* caused a statistically significant increase in HDL cholesterol (51.6 $\pm$ 1.8 to 53.1 $\pm$ 1.7 mg/dL, respectively; $p = 0.04$) and a statistically significant decrease in LDL cholesterol (153.8 $\pm$ 39.0 to 146.1 $\pm$ 34.4 mg/dL, respectively; $p = 0.003$) from baseline (Nappi et al., 2005). In a double-blind randomized, placebo controlled, study in 89 peri- or postmenopausal women

experiencing climacteric symptoms, a combination of black cohosh (*Cimicifuga racemosa*) and St. John's wort (Hypericum perforatum) significantly increased HDL levels (from 58.32 ± 11.64 to 59.74 ± 10.54; $p = 0.04$) compared to the control (from 60.20 ± 16.37 to 56.63 ± 12.67) (Chung et al., 2007). However, in a randomized trial in 351 peri- or postmenopausal women, black cohosh lacked demonstrable effects on lipids, glucose, insulin, or fibrinogen (Spangler et al., 2007).

- Antineoplastic effects: In systematic review, there was laboratory evidence of the antiproliferative properties of black cohosh, but a lack of confirmation from clinical studies for a protective role in cancer prevention (Walji et al., 2007). In vitro studies have reported black cohosh to possess inhibitory effects on estrogen-responsive cancer cell lines or breast cancer cells (Dixon-Shanies & Shaikh, 1999; Einbond et al., 2004, 2008; Hostanska, Nisslein, Freudenstein, Reichling, & Saller, 2007; Nesselhut et al., 1993; Struck et al., 1997). Furthermore, in a cell line study, relatively low concentrations of actein or the methanol/water fraction of black cohosh may cause synergistic inhibition of human breast cancer cell proliferation when combined with different classes of chemotherapy agents (Einbond et al., 2006). Acetein may activate genes that respond to DNA damage and unfolded protein responses, and enhance apoptosis and repressed cell-cycle genes (Einbond et al., 2007a, 2007b). Actaealactone and cimicifugic acid may also have a small stimulating effect on the growth of breast cancer cell proliferation (Nuntanakorn et al., 2006). In an in vitro study conducted on human prostate cancer cells with black cohosh extract, the extract killed hormone-responsive or hormone-unresponsive prostate cancer cells by induction of apoptosis and activation of caspases (Hostanska et al., 2005). Another in vivo study in mice demonstrated inhibited PC3 prostate cancer tumor growth with black cohosh and other herbal extracts (Ng & Figg, 2003). The mechanism behind tumor inhibition appeared to be antiangiogenic by decreasing intratumoral microvessel density. In vitro, black cohosh has been shown to inhibit the intestinal breast cancer-resistant protein, which may lead to increased absorption of certain drugs (Tamaki et al., 2010). In rats, triterpene glycoside actein, at a dose of 35.7 mg/kg for six and 24 hr, was reported to elicit multiple alterations in gene expression in the liver (Einbond et al., 2009). Genes involved with the p53 pathway as well as ID3 and CCND1 were altered in a time-dependent manner. Actein was also shown to decrease the growth of human HepG2 liver cancer cells.
- Antioxidant effects: Extracts of black cohosh have protected against induced DNA damage through scavenging of reactive oxygen species in vitro (Burdette et al., 2002). A sample of black cohosh collected in 1919 was compared with those of a modern collection of *Actaea racemosa* and showed that both extracts had similar antioxidant activity (Jiang et al., 2005). According to laboratory research, the constituents, actaealactone, cimicifugic acid, and fukinolic acid, may display antioxidant activity in the 1,1-diphenyl-2-picrylhydrazyl (DPPH) free-radical assay, with IC50 values of 26 and 37 mcM, respectively (Nuntanakorn et al., 2006, 2007).
- Bone metabolism effects: An isopropanolic extract of black cohosh has been shown to significantly diminish the urinary content of pyridinoline and deoxypyridinoline, specific markers for bone loss, and the morphometric correlates

of bone loss associated with ovariectomy in rats (Nisslein & Freudenstein, 2003). Ovariectomized rats treated with *Cimicifuga racemosa* extract had slightly stimulated gene expression of IGF-I, collagen-lalphal, osteoprotegerin, and osteocalcin (all osteoblast products), and of tartrate-resistant acid phophatase (TRAP, an osteoclast product) in the metaphysic of the femur (Seidlova-Wuttke et al., 2003). In an in vitro study, an isopropanolic extract (iCR) from the rhizomes of black cohosh stimulated osteoblastic osteoprotegerin protein secretion three- to fivefold as early as 12 hr without affecting receptor activator for nuclear factor-kappaB ligand (RANKL) expression (Viereck et al., 2005). In postmenopausal women, 3 months of therapy with *Cimicifuga racemosa* resulted in increased alkaline phosphatase and decrease the concentration of N-telopeptides in the urine (Garcia-Perez et al., 2009). However, the mechanism to decrease bone remodeling is unknown. In postmenopausal women, CR BNO 1055 was reported to increase osteoblast activity and decrease osteoclast activity (Wuttke et al., 2003). An increase of bone-specific collagen-1alpha1 was lacking with CR administration, and bone-specific alkaline phosphatase increased significantly with CR administration when compared to placebo after 12 weeks of treatment (Wuttke et al., 2006).

- CNS effects: Animal and in vitro research suggests that the mechanism of action of black cohosh may be centrally mediated, with possible action at the level of serotonin or dopamine receptors (Burdette et al., 2003; Jarry et al., 2003; Villaseca, 2012). A study in ovariectomized rats demonstrated strong binding to serotonin receptors 5-HT(1A), 5-HT(1D), and 5-HT(Bai et al., 2009) subtypes (Burdette et al., 2003).
- Cytochrome P450 (CYP) effects: In vitro, strong inhibition of all CYP isoenzymes was documented, due to cimicifugic acids A and B and fukinolic acid at median inhibitory concentrations (IC50) of 1.8–12.6 mcM (Huang et al., 2010; Shi & Klotz, 2012). Triterpene glycosides were reported to be weakly active (IC50: 25–100 mcM). In addition, Hep-G2 cell growth was not shown to be inhibited by any black cohosh extracts (cimicifugic acids A and B, fukinolic acid, and triterpene glycosides in concentrations as high as 50 mcg/mL (Huang et al., 2010). However, seven black cohosh products were not shown to inhibit CYP3A4 in human liver cells (Wanwimolruk et al., 2009). In vitro, methanolic extracts of black cohosh were shown to inhibit CYP2B6, (Ashar et al., 2008) 2C19, and (D)2C19 in human liver cells (Sevior et al., 2010). In vitro, black cohosh has been reported to have no effect on CYP450-catalyzed 4-hydroxylation of estradiol in human mammary epithelial cells (Hemachandra et al., 2012). In mice, black cohosh, at a dose of 500 mg/kg, was reported to induce liver CYP3A11 sevenfold after 28 days of treatment (Pang et al., 2011; Shi & Klotz, 2012). This induction was reported to be both time and dose dependent. A change in the kidney and small intestine CYP3A11 was lacking. In further research, mouse pregnane X receptor (PXR) was reported to be activated by black cohosh, but human PXR was not shown (Pang et al., 2011). In a clinical trial of 12 healthy volunteers (six women), black cohosh daily for 28 days had a statistically significant inhibition of CYP2D6 (difference: −0.046; 95% CI: −0.085 to −0.007), but the magnitude of the effect (approximately 7%) did not appear to be clinically relevant (Gurley et al., 2005; Shord, Shah, & Lukose, 2009). In another trial by the

same authors, healthy volunteers taking black cohosh 80 mg daily for 14 days did not experience a clinically relevant effect on their CYP3A activity (Gurley et al., 2006). In a clinical trial of 16 healthy volunteers, supplementation of black cohosh for 14 days did not demonstrate an effect on CYP2D6 (Gurley et al., 2008). In a case report, black cohosh has been reported to interact with atorvastatin, resulting in an increase in liver enzymes, possibly due to inhibition of CYP3A4 (Patel & Derkits, 2007).

- Endocrine effects: According to secondary sources, cimicifugoside contained in black cohosh is believed to affect hypothalamus-pituitary function. In a randomized trial in 351 peri- or postmenopausal women, black cohosh lacked demonstrable effects on glucose or insulin (Spangler et al., 2007).
- Estrogenic effects: It is unclear which constituents of black cohosh, if any, possesses estrogenic properties. In animals and in vitro, initial reports of estrogen receptor-binding activity (Jarry et al., 1985; Liu et al., 2001) stand in contrast with data suggesting no significant estrogen receptor-binding activity or estrogenic activities (Beck, Unterrieder, Krenn, Kubelka, & Jungbauer, 2003; Borrelli et al., 2003; Einer-Jensen et al., 1996; Liu et al., 2001; Liu et al., 2001; Lupu et al., 2003; Mahady, 2003; Nisslein & Freudenstein, 2004; Oerter Klein, Janfaza, Wong, & Chang, 2003; Onorato & Henion, 2001; Zava et al., 1998; Zhang et al., 2003). Two in vitro studies found no effects of black cohosh alone on estrogen receptors but reported that black cohosh antagonized proliferative effects on cells induced by estradiol (Zierau et al., 2002). A similar in vitro study on estrogen-sensitive breast cancer cells (MCF-7) reported that isopropanolic black cohosh extract did not stimulate MCF-7 growth and exerted inhibitory effects on cellular proliferation, indicating strong estrogen-antagonist effects (Bodinet & Freudenstein, 2004). The proliferation-inhibiting effect of tamoxifen has been enhanced by black cohosh extract (Zierau et al., 2002). Several studies have aimed to assess estrogen activity by measuring luteinizing hormone (LH), follicle-stimulating hormone (FSH), or prolactin levels (Duker et al., 1991; Jarry & Harnischfeger, 1985). One study reported lower FSH levels (but not LH) in patients treated with black cohosh versus placebo ($N = 110$), although baseline hormone levels were not known in either group (Duker et al., 1991). Results from other trials have found a lack of effects on these hormone levels after up to 6 months of black cohosh therapy (Jacobson et al., 2001; Lehmann-Willenbrock & Riedel, 1988; Liske et al., 2001). When administered to female infantile mice, black cohosh could not precipitate the premature onset of estrus (Siess & Seybold, 1960). Estrogenic effects on vaginal epithelium were noted in one 3-month trial of black cohosh (Stoll, 1987), while a 6-month trial reported no effects on vaginal cytology (Liske & Wstenberg, 1998). *Cimicifuga racemosa* ethanolic extract Ze 450 may inhibit cell proliferation and show antiestrogenic activity (Garita-Hernandez et al., 2006). The *Cimicifuga racemosa* extract bound to the progesterone receptor B1 but did not show progestin-like activity in the T-47D cell line. In an in vitro study using healthy breast tissue of pre- and postmenopausal women, incubation in vitro with black cohosh extract decreased local estrogen formation (Stute et al., 2007). In vitro, black cohosh has been reported to lack an effect on CYP450-catalyzed 4-hydroxylation of estradiol in human mammary epithelial cells (Hemachandra et al., 2012).

- Gastrointestinal effects: In an in vitro study, black cohosh extracts moderately (but significantly) inhibited estrone-3-sulfate (a typical organic anion-transporting polypeptide B (OATP-B) substrate) uptake, by 47.2% ($p < 0.05$) (Fuchikami et al., 2006). As OAT-B is involved in the intestinal absorption of various drugs, black cohosh may decrease the absorption of orally administered substrates of OATP-B.
- Neuropharmacologic effects: Black cohosh has been shown to exhibit an action on the central endogenous opioid system in postmenopausal women, as evidenced by suppression of mean luteinizing hormone pulse frequency following opioid receptor blockade (Reame et al., 2008). In vitro, black cohosh was found to be consistent with a human mu-opiate receptor (hMOR) agonist, with an EC50 of 68.8 ± 7.7 mcg/mL, which may explain its purported beneficial role in alleviating menopausal symptoms (Rhyu et al., 2006).
- Vascular effects: In a 1962 study, acteina, a constituent of black cohosh, was found to cause peripheral vasodilation and has been noted to elicit hypotension in animals (Genazzani & Sorrentino, 1962). Additional supporting data in humans are lacking. Laboratory research on cimicifugic acids C and D and fukinolic acid in the rhizome of black cohosh has shown vasoactive effects (Noguchi et al., 1998).
- Other: Cimicifugoside from Cimicifuga simplex has been found to inhibit cellular thymidine-3H uptake, and to act as a selective inhibitor of nucleoside transport into mammalian cells (Hemmi, Kitame, & Ishida, 1979; Hemmi, Kusano, & Ishida, 1980; Takahira et al., 1998).

Pharmacodynamics/Kinetics

- Absorption: In a clinical trial, oral black cohosh administration for 14 days did not significantly affect digoxin's area under the serum concentration time curves from 0–3 hours [AUC(0–3)], AUC(0–24), C_{max}, apparent oral clearance of digoxin (CL/F), and elimination half-life (Gurley et al., 2006). Digoxin is a known *p*-glycoprotein (P-gp) substrate, which suggests that black cohosh is not a potent modulator of P-gp in vivo.
- Distribution: In menopausal women, a 75% ethanol extract of 23-epi-26-deoxyactein at doses of 1.4, 2.8, and 5.6 mg showed a proportionate increase in the area under the curve with all three doses (Gurley et al., 2006).
- Metabolism: Phase I or phase II metabolites were lacking in menopausal women receiving a 75% ethanol extract of 23-epi-26-deoxyactein at doses of 1.4, 2.8, and 5.6 mg (van Breemen et al., 2010). In vitro, methanolic extracts of black cohosh were shown to inhibit CYP2B6, (Ashar et al., 2008) 2C19, and (D)2C19 in human liver cells (Sevior et al., 2010). In vitro, black cohosh has been reported to have no effect on CYP450-catalyzed 4-hydroxylation of estradiol in human mammary epithelial cells (Sevior et al., 2010). In mice, black cohosh, at a dose of 500 mg/kg, was reported to induce liver CYP3A11 sevenfold after 28 days of treatment (Pang et al., 2011; Shi & Klotz, 2012). This induction was reported to be both time and dose dependent. A change in the kidney and small intestine CYP3A11 was lacking. In further research, mouse pregnane X receptor (PXR) was reported to be activated by black cohosh, but human PXR was not (Pang et al., 2011). In vitro, strong inhibition of all CYP isoenzymes was documented due to cimicifugic acids

A and B and fukinolic acid at median inhibitory concentrations (IC50) of 1.8–12.6 mcM (Huang et al., 2010; Shi & Klotz, 2012). Triterpene glycosides were reported to be weakly active (IC50: 25–100 mcM). In addition, Hep-G2 cell growth was not shown to be inhibited by any black cohosh extracts, cimicifugic acids A and B, fukinolic acid, and triterpene glycosides, in concentrations as high as 50 mcg/mL (Huang et al., 2010). However, in vitro, seven black cohosh products were not shown to inhibit CYP3A4 in human liver (Wanwimolruk et al., 2009). In a clinical trial of 16 healthy volunteers, supplementation of black cohosh for 14 days did not demonstrate an effect on CYP2D6 (Gurley et al., 2008). In a clinical trial of 12 healthy volunteers (six women), black cohosh daily for 28 days had a statistically significant inhibition of CYP2D6 (difference: −0.046; 95% CI: −0.085 to −0.007), but the magnitude of the effect (approximately 7%) did not appear to be clinically relevant (Gurley et al., 2005; Shord et al., 2009). In another trial by the same authors, healthy volunteers taking black cohosh 80 mg daily for 14 days did not have a clinically relevant effect on their CYP3A activity (Gurley et al., 2006). Black cohosh as > 5% total triterpene glycosides in 50% ethanol was shown to inhibit 3-*O*-glucuronidation of estradiol in a concentration-dependent manner in human liver microsomes (Mohamed, Tseng, & Frye, 2010). Black cohosh was also shown to inhibit UDP-glucuronosyltransferase-1A4 and mycophenolic acid-7-*O*-glucuronide (Mohamed & Frye, 2011).

- Excretion: In menopausal women, a 75% ethanol extract of 23-epi-26-deoxyactein at doses of 1.4, 2.8, and 5.6 mg was reported to have a half-life of approximately 2 hr for all strengths (van Breemen et al., 2010). Twenty-four hours after administration, <0.01% was present in the urine. In rats treated with 35.7 mg/kg of actein for 6–24 hr, serum actein was reported to peak at 6 hr at a level of 2.4 mcg/mL (Einbond et al., 2009).

HISTORY

- Black cohosh is native to eastern North America (McKenna et al., 2001). Native American and Chinese herbalists have traditionally used black cohosh for a variety of ailments and as an insect repellent.
- According to secondary sources, black cohosh is known as macrotys to Eclectic physicians and was first described in the literature in 1696 in Leonard Plukenet's Phytographia. It became one of the most popular Eclectic remedies around 1850 and was frequently used as a uterine tonic to ease labor.
- According to secondary sources, in the 19th Century, black cohosh was used by medical practitioners for a variety of rheumatic disorders and dysmenorrhea, and to induce labor. John King, an Eclectic physician of obstetrics and gynecology in the 1800s, was a strong proponent of medicinal use of this herb. A popular product sold in the United States in the late 1800s for menstrual cramps was Lydia E. Pinkham's Vegetable Compound, which contained black cohosh and alcohol.
- Black cohosh has been widely used in Germany since the 1950s, principally for disorders associated with menopause and menstruation.
- A 2008 survey reported that more than one-third of medical-resident respondents were unaware of the reasons for use of black cohosh (Ashar et al., 2008).

EVIDENCE TABLE

Condition Treated	Study Type	Author, Year	*N*	Statistically Significant Results?	Quality of Study: 0–2 = poor 3–4 = good 5 = excellent	Magnitude of Benefit (how strong is the effect?)	Absolute Risk Reduction	# of Patients Needed to Treat for One Outcome	Comments
Bone density (postmenopausal women)	Randomized controlled trial	Wuttke et al., 2006	62	Yes	4	Small	NA	NA	Follow-up of Wuttke et al., 2003 assessing secondary outcome measures
Bone density (postmenopausal women)	Randomized controlled trial	Wuttke et al., 2003	62	Yes	4	Small	NA	NA	CR BNO 1055 (daily dose corresponding to 40 mg of herbal drug), 0.6 mg of conjugated estrogens, or matching placebo, for three months
Bone density (postmenopausal women)	Randomized controlled trial	Bebenek, 2010	128	No	3	NA	NA	NA	CR BNO 1055 studied with exercise, but lack of benefit due to supplementation
Breast cancer	Systematic review	Roberts, 2010	20 trials	Yes	NA	NA	NA	NA	Review of safety and efficacy with mixed results
Breast cancer	Systematic review	Walji, 2007	Five trials	No	NA	None	NA	NA	Lack of evidence from clinical trials to support black cohosh use in cancer prevention or reducing climacteric symptoms in breast cancer patients
Breast cancer	Systematic review	Antoine, 2007	No trials	NA	NA	NA	NA	NA	The authors were unable to find studies reporting the safety of black cohosh in breast cancer patients
Breast cancer	Randomized controlled trial	Pockaj, 2006	132	No	4	None	NA	NA	One capsule of *Cimicifuga racemosa* 20 mg twice daily for four weeks
Breast cancer	Randomized controlled trial	Jacobson, 2001	85	NA	3	NA	NA	NA	No improvement in hot flashes in breast cancer survivors from black cohosh vs. placebo. 69% of subjects took tamoxifen. 19% dropped out
Cognitive function (postmenopausal women)	Randomized controlled trial	Maki, 2009	70	No	5	NA	NA	NA	Randomized, placebo controlled, double-blind trial of black cohosh without significant results
Coronary heart disease (postmenopausal women)	Randomized controlled trial	Bebenek, 2010	128	No	3	NA	NA	NA	CR BNO 1055 studied with exercise, but there was a lack of benefit due to supplementation
Infertility	Randomized controlled trial	Shahin, 2009	134	No	4	NA	NA	NA	Patients received both clomiphene citrate and *Cimicifuga racemosa*, without a change in pregnancy rate
Infertility	Randomized controlled trial	Shahin, 2008	118	Yes	3	Large	14	6	Patients received both clomiphene citrate and *Cimicifuga racemosa*, with a significant increase in pregnancy
Menopausal symptoms	Meta-analysis	Shams, 2010	Nine trials	Yes	NA	Small	NA	NA	Meta-analysis of two studies evaluating effects of black cohosh alone, with an 11% rate difference in vasomotor symptoms

(Continued on next page)

(Continued)

Condition Treated	Study Type	Author, Year	*N*	Statistically Significant Results?	Quality of Study: 0–2 = poor 3–4 = good 5 = excellent	Magnitude of Benefit (how strong is the effect?)	Absolute Risk Reduction	# of Patients Needed to Treat for One Outcome	Comments
Menopausal symptoms	Systematic review	Guttuso, 2012	51 trials: six studies of black cohosh	Yes	NA	NA	NA	NA	Systematic review, with one trial reporting significant reduction in hot flashes
Menopausal symptoms	Systematic review	Kelley, 2010	Nine trials	Yes	NA	Small	NA	NA	Systematic review with mixed results
Menopausal symptoms	Systematic review	Mazaro-Costa, 2010	Six trials	No	NA	NA	NA	NA	Brief review of sexual dysfunction and anxiety in menopause
Menopausal symptoms	Systematic review	Palacio, 2009	15 RCT, one Open-label	Yes	NA	NA	NA	NA	Black cohosh analyzed in combination and compared to placebo or medications with known efficacy mixed results
Menopausal symptoms	Systematic review	Wong, 2009	Seven review articles; eight clinical trials	No	NA	NA	NA	NA	A trend toward improvement in menopausal symptoms was reported
Menopausal symptoms	Systematic review	Borrelli, 2008, 2002, 2001	Six trials	No	NA	NA	NA	NA	Evidence from these RCTs does not consistently demonstrate an effect of black cohosh on menopausal symptoms
Menopausal symptoms	Systematic review	Loprizini, 2008	10 trials	No	NA	NA	NA	NA	Hot flashes are not substantially decreased by black cohosh
Menopausal symptoms	Systematic review	Nedrow, 2006	Four trials	Yes	NA	NA	NA	NA	Systematic review with mixed results on vasomotor symptoms
Menopausal symptoms	Systematic review	Hanna, 2005	Seven trials	Yes	NA	NA	NA	NA	Controlled and uncontrolled trials were reviewed, with mixed results
Menopausal symptoms	Systematic review	Low Dog, 2005	Five Trials	Yes	NA	NA	NA	NA	Studies with methodological weakness and inconsistent results
Menopausal symptoms	Systematic review	Huntley, 2003	Four trials	NA	NA	NA	NA	NA	Poor methodology
Menopausal symptoms	Systematic review	Kronenberg, 2002	4	NA	NA	NA	NA	NA	Summarized study findings but did not critique studies
Menopausal symptoms	Randomized controlled trial	Amsterdam, 2009	28	No	5	NA	NA	NA	Randomized, placebo controlled, double-blind trial of black cohosh, without significant results
Menopausal symptoms	Randomized controlled trial	Geller, 2009	89	No	5	NA	NA	NA	Randomized controlled trial reported higher vasomotor symptoms in black cohosh group vs. placebo
Menopausal symptoms	Randomized controlled trial	Newton, 2006	351	No	5	None	NA	NA	Black cohosh 160 mg daily for one year compared to hormone treatment, placebo, and a multiherb formula
Menopausal symptoms	Randomized controlled trial	Osmers, 2005	304	Yes	5	Large	NA	NA	One Remifemin® tablet twice daily for 12 weeks. The effect size was 0.03–0.05 Menopause Rating Scale units, which is similar to contemporary hormone replacement therapy study results (0.036)
Menopausal symptoms	Equivalence trial	Bai, 2007	244	No	4	Medium	NA	NA	Effect of Remifemin® vs. tibolone on climacteric symptoms in menopausal women. Remifemin® was not inferior to tibolone, with fewer adverse effects

Menopausal symptoms	Randomized controlled trial	Pockaj, 2006	132	No	4	None	NA	NA	One capsule of *Cimicifuga racemosa* 20 mg twice daily for 4 weeks
Menopausal symptoms	Randomized controlled trial	Wuttke et al., 2003	62	Yes	4	Small	NA	NA	CR BNO 1055 (daily dose corresponding to 40 mg of herbal drug), 0.6 mg of conjugated estrogens, or matching placebo, for 3 months
Menopausal symptoms	Randomized controlled trial	Stoll, 1987	80	Yes	4	Medium	NA	NA	8 mg of Remifemin® (black cohosh) vs. conjugated estrogens or placebo for 12 weeks. Black cohosh was superior to placebo and equal to estrogens on the Kupperman Index, HAM-A, and vaginal epithelial proliferation; hot flashes were reduced more vs. estrogens
Menopausal symptoms	Randomized controlled trial	Bebenek, 2010	128	No	3	NA	NA	NA	CR BNO 1055 was studied with exercise, but there was no benefit due to supplementation
Menopausal symptoms	Randomized controlled trial	Bai, 2009	180	No	3	NA	NA	NA	Comparison trial of Remifemin® and tibolone, with Remifemin® being equivalent to tibolone
Menopausal symptoms	Randomized controlled trial	Frei-Kleiner, 2005	129	No	3	NA	NA	NA	Significance reported in subgroup analysis
Menopausal symptoms	Randomized equivalence trial	Nappi, 2005	64	Yes	3	Small	NA	NA	Significant decrease in hot flashes compared to baseline
Menopausal symptoms	Randomized controlled trial	Liske, 2002	150	No	3	NA	NA	NA	Peri- and postmenopausal women were treated with two different doses (39 mg and 127.3 mg) of a unique *C. racemosa* preparation over a 24-week period. No systemic estrogenic effect found
Menopausal symptoms	Equivalence trial	Oktem, 2007	120	Yes, for menopausal symptoms except depression	2	Medium	NA	NA	Effect of fluoxetine or black cohosh on women with postmenopausal symptoms
Menopausal symptoms	Equivalence trial	Lehmann-Willenbrock, 1988	60	NA	1	Medium	NA	NA	Black cohosh vs. three hormone replacement therapies for 6 months in hysterectomy patients. Equal improvements in all groups on the Kupperman Index. Sample size may have been inadequate

Explanation of Columns in Natural Standard Evidence Table

1	2	3	4	5	6	7	8	9	10
Condition	Study design	Author, *N* year		Statistically significant?	Quality of study 0–2 = poor 3–4 = good 5 = excellent	Magnitude of benefit	Absolute risk reduction	Number needed to treat	Comments

Condition

- Refers to the medical condition or disease targeted by a therapy.

Study Design

Common types include:

- Randomized controlled trial (RCT): An experimental trial in which participants are assigned randomly to receive either an intervention being tested or placebo. Note that Natural Standard defines RCTs as being placebo-controlled, while studies using active controls are classified as equivalence trials (see below). In RCTs, participants and researchers are often blinded (i.e., unaware of group assignments), although unblinded and quasi-blinded RCTs are also often performed. True random allocation to trial arms, proper blinding, and sufficient sample size are the basis for an adequate RCT.
- Equivalence trial: An RCT which compares two active agents. Equivalence trials often compare new treatments to usual (standard) care, and may not include a placebo arm.
- Before and after comparison: A study that reports only the change in outcome in each group of a study, and does not report between-group comparisons. This is a common error in studies that claim to be RCTs.
- Case series: A description of a group of patients with a condition, treatment, or outcome (e.g., 20 patients with migraine headache underwent acupuncture and 17 reported feeling better afterwards). Case series are considered weak evidence of efficacy.
- Case–control study: A study in which patients with a certain outcome are selected and compared to similar patients (without the outcome) to see if certain risk factors/predictors are more common in patients with that outcome. This study design is not common in the complementary & alternative medicine literature.
- Cohort study: A study which assembles a group of patients with certain baseline characteristics (for example, use of a drug), and follows them forward in time for outcomes. This study design is not common in the complementary & alternative medicine literature.
- Meta-analysis: A pooling of multiple trials to increase statistical power (often used to pool data from a number of RCTs with small sample sizes, none which demonstrates significance alone but in aggregate can achieve significance). Multiple difficulties are encountered when designing/reviewing these analyses; in

particular, outcomes measures or therapies may differ from study to study, hindering direct comparison.
- Review: An author's description of his or her opinion based on personal, non-systematic review of the evidence.
- Systematic review: A review conducted according to pre-specified criteria in an attempt to limit bias from the investigators. Systematic reviews often include a meta-analysis of data from the included studies.

Author, Year

- Identifies the study being described in a row of the table.

N

- The total number of subjects included in a study (treatment group plus placebo group). Some studies recruit a larger number of subjects initially, but do not use them all because they do not meet the study's entry criteria. In this case, it is the second, smaller number that qualifies as *N*. *N* includes all subjects that are part of a study at the start date, even if they drop out, are lost to follow-up, or are deemed unsuitable for analysis by the authors. Trials with a large number of drop-outs that are not included in the analysis are considered to be weaker evidence for efficacy. For systematic reviews, the number of studies included is reported. For meta-analyses, the number of total subjects included in the analysis or the number of studies may be reported.

Statistically significant?

- Results are noted as being statistically significant if a study's authors report statistical significance, or if quantitative evidence of significance is present (such as *p* values). *P* = pending verification.

Quality of Study

- A numerical score between 0–5 is assigned as a rough measure of study design/reporting quality (0 being weakest and 5 being strongest). This number is based on a well-established, validated scale developed by Jadad et al. (Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials (RCTs): is blinding necessary? Controlled Clinical Trials 1996;17[1]:1–12). This calculation does not account for all study elements that may be used to assess quality (other aspects of study design/reporting are addressed in the "Evidence Discussion" sections of reviews).
- A Jadad score is calculated using the seven items in the table below. The first five items are indications of good quality, and each counts as one point toward an overall quality score. The final two items indicate poor quality, and a point is subtracted for each if its criteria are met. The range of possible scores is 0 to 5.

Jadad Score Calculation

Item	Score
Was the study described as randomized (this includes words such as randomly, random, and randomization)?	0/1
Was the method used to generate the sequence of randomization described and appropriate (table of random numbers, computer-generated, etc.)?	0/1
Was the study described as double blind?	0/1
Was the method of double blinding described and appropriate (identical placebo, active placebo, dummy, etc.)?	0/1
Was there a description of withdrawals and dropouts?	0/1
Deduct one point if the method used to generate the sequence of randomization was described and it was inappropriate (patients were allocated alternately, or according to date of birth, hospital number, etc.).	0/−1
Deduct one point if the study was described as double blind but the method of blinding was inappropriate (e.g., comparison of tablet vs. injection with no double dummy).	0/−1

Magnitude of Benefit

- This summarizes how strong a benefit is: small, medium, large, or none. If results are not statistically significant "NA" for "not applicable" is entered. In order to be consistent in defining small, medium, and large benefits across different studies and reviews, Natural Standard defines the magnitude of benefit in terms of the standard deviation (SD) of the outcome measure. Specifically, the benefit is considered:
  - Large: if >1 SD
  - Medium: if 0.5 to 0.9 SD
  - Small: if 0.2 to 0.4 SD
- In many cases, studies do not report the standard deviation of change of the outcome measure. However, the change in the standard deviation of the outcome measure (also known as effect size) can be calculated, and is derived by subtracting the mean (or mean difference) in the placebo/control group from the mean (or mean difference) in the treatment group, and dividing that quantity by the pooled standard deviation [Effect size = (Mean Treatment−Mean Placebo)/SDp].

Absolute Risk Reduction

- This describes the difference between the percent of people in the control/placebo group experiencing a specific outcome (control event rate), and the percent of people in the experimental/therapy group experiencing that same outcome (experimental event rate). Mathematically, Absolute risk reduction (ARR) equals experimental event rate minus control event rate. ARR is better able to discriminate between large and small treatment effects than relative risk reduction (RRR), a calculation that is often cited in studies [(control event rate – experimental event rate)/control event rate]. Many studies do not include adequate data to calculate the ARR, in which cases "NA" is entered into this column. P = pending verification.

Number Needed to Treat

- This is the number of patients who would need to use the therapy under investigation, for the period of time described in the study, in order for one person to experience the specified benefit. It is calculated by dividing the Absolute Risk Reduction into 1 (1/ARR). P = pending verification.

Comments

- When appropriate, this brief section may comment on design flaws (inadequately described subjects, lack of blinding, brief follow-up, not intention-to treat, etc.), notable study design elements (crossover, etc.), dosing, and/or specifics of study group/subgroups (age, gender, etc.). More detailed description of studies is found in the "Evidence Discussion" section that follows the "Evidence Table" in Natural Standard reviews.

EVIDENCE DISCUSSION

Arthritis pain

- Summary: A literature review revealed a lack of high-quality studies of black cohosh monotherapy for symptoms of rheumatoid arthritis or osteoarthritis. Native black cohosh does contain small amounts of salicylates, although it is unclear if these are present in therapeutic amounts in commercial preparations. Clinical research on a combination product containing black cohosh and several other salicylate-containing herbs for rheumatoid arthritis or osteoarthritis found small improvements in pain scores, but no improvement in joint function or a decrease in self-medication with analgesics.
- Select combination studies (not included in the Evidence Table): Long et al. conducted a systematic review of herbal medicines for the treatment of osteoarthritis (Long, Soeken, & Ernst, 2001). Ernst et al. also conducted a systematic review on the treatment of osteoarthritis with herbal medicines (Ernst & Chrubasik, 2000). One trial with black cohosh in combination was found by each review (Mills et al., 1996); it is reviewed fully below, and it was also noted in the Centre for Reviews and Dissemination (Centre for Reviews and Dissemination, 2006).
- Mills et al. conducted a randomized, double-blind, placebo controlled trial to assess the efficacy of a fixed black cohosh combination product in 82 male and female patients with rheumatoid arthritis or osteoarthritis (Mills et al., 1996). Patients taking salicylates or antiinflammatory agents were excluded from this study. Two Reumalex® tablets or matching placebo (calcium phosphate) were administered to subjects over a 2-month period. Each Reumalex® tablet contained 35 mg of black cohosh, 100 mg of white willow bark, 25 mg of sarsaparilla (4:1), 17 mg of poplar bark (7:1), and 40 mg of guaiacum resin. Notably, several constituents contain salicylates, and it has been estimated that each Reumalex® tablet may include up to 10–20 mg of salicylates. The authors report that 72 patients completed the study in compliance, but eight dropouts were described, and causality is unclear [treatment group: dyspeptic symptoms (Cimicifuga racemosa, 2003), diarrhea (Cimicifuga racemosa, 2003), severe headaches (Cimicifuga racemosa, 2003), reasons unrelated to the study (Cimicifuga racemosa, 2003); placebo

group: headache and digestive complaints (Cimicifuga racemosa, 2003), angina (Cimicifuga racemosa, 2003), anxiety (Cimicifuga racemosa, 2003), stomach cramps (Cimicifuga racemosa, 2003)]. Outcome measures included scores on the validated Arthritis Impact Measurement Scales Health Status Questionnaire (AIMS-2). Small, significant improvements in pain were noted in the Reumalex® group vs. the placebo group ($p < 0.05$), although there were no other significant differences between groups, including measures of joint function and use of over-the-counter analgesics. Based on the AIMS-2 data, the effect size for Reumalex® is medium (0.53). These results cannot be extrapolated to any of the constituents alone.

Bone Density (postmenopausal women)

- Summary: Extracts of black cohosh have been studied in vitro and in vivo, with results suggesting that black cohosh may be able to prevent the resorption of bone (Garcia-Perez et al., 2009; Nisslein & Freudenstein, 2003; Seidlova-Wuttke et al., 2003; Viereck et al., 2005). However, an exact mechanism is unknown. In three trials of postmenopausal women, the results of black cohosh therapy have been mixed. Further research is warranted.
- Evidence: Wuttke et al. conducted a follow-up of the Wuttke et al., 2003 randomized, double-blind, placebo controlled trial ($N = 97$) (Cimicifuga racemosa, 2003). This review discussed the secondary outcomes. Further information may be found in the Wuttke et al., 2003 review. One woman reported vertigo, hypertension, and headache in the *Cimicifuga racemosa* (CR) group, but the authors noted that changes in blood pressure and heart rate were lacking. Secondary outcome measures reviewed in this study included markers of bone turnover, lipids, sex hormone-binding globulin, vaginal cytology, and routine laboratory parameters. Outcome measures were reviewed at baseline and then weeks 4, 8, and 12. Black cohosh did not demonstrate a change in immunoreactive E2, serum follicle-stimulating hormone, luteinizing hormone, total cholesterol, HDL or LDL cholesterol, international normalized ratio (INR), activated thromboplastin time, hepatic enzymes, or body weight. A slight increase was reported in sex hormone-binding globulin and serum triglycerides due to CR. An increase of bone-specific collagen-1alpha1 was lacking with CR administration. Bone-specific alkaline phosphatase increased significantly with CR administration when compared to placebo after 12 weeks of treatment. A significant change in vaginal cells was lacking with CR use. This was a well-conducted follow-up. Further research is warranted to confirm the results.
- Wuttke et al. conducted a double-blind, randomized, multicenter study to assess the effects of the *Cimicifuga racemosa* preparation CR BNO 1055 (Klimadynon®/Menofem®) on climacteric complaints, bone metabolism, and endometrium (Wuttke et al., 2003). Postmenopausal women, aged 40–60 years and with body mass indices of <30 and amenorrhea for at least 6 months, were included in this study. Ninety-seven patients were randomized and formed the intent-to-treat collective. Subjects received either two capsules of CR BNO 1055 (daily dose corresponding to 40 mg of herbal drug), 0.6 mg of conjugated estrogens (Oestrofeminal®), or matching placebo for 3 months. Two patients dropped

out prematurely and 35 patients were excluded from analysis because of protocol violations. Thus, statistical analysis was performed on 62 patients. Menopausal symptoms were assessed by a change from baseline to endpoint after 12 weeks of treatment in the Menopause Rating Scale and subjective reports in a diary. The authors reported that CR BNO 1055 was equipotent to conjugated estrogens and superior to placebo in reducing climacteric complaints. A significant increase on vaginal thickness was lacking with CR use. CR was reported to be as effective as estrogen for MRS scores when compared to placebo. CR was reported to decrease osteoclast activity and increase osteoblast activity. This study was properly randomized using a randomly permuted block design. However, the method of blinding the practitioners was not described. Further research is warranted.

- Bebeneck et al. conducted a randomized controlled trial of *Cimicifuga racemosa* (CR BNO 1055) in early postmenopausal women on bone density, 10-year coronary heart disease risk, and menopausal symptoms ($N = 128$) (Bebenek et al., 2010). German women 48–55 years old were included in the study. Women were excluded if they were taking medications that may affect the results (contraceptives and glucocorticoids), had other diseases or history of coronary heart disease, had an athletic history, or were not in the time frame of 1–3 years after menopause. Women were assigned to three different groups: exercise program plus CR supplementation 40 mg daily, exercise, or wellness control, all for 12 months. However, women received the CR supplement for 3 months on, 3 months off, then 3 months on again and discontinued it thereafter. Calcium and vitamin D was administered to all groups. Allergies, adverse effects, and toxic effects were not discussed. Dropouts were discussed. However, dropouts due to side effects of the CR supplement were not noted. The primary outcomes were bone mineral density and Wilson's 10-year coronary heart disease risk. Secondary endpoints were menopausal symptoms and body composition. Outcome measures were taken at baseline and 12 months. A significant difference in outcome measures due to CR supplementation was lacking. The trial did not clearly state if it was double-blinded. The placebo was not identical to the CR supplement, but based on a survey, the authors believed that blinding was successful. The supplement was administered for 3 months on and then off, which may not have been a long enough time period to demonstrate CR's effects. Also, the effects of CR may have been noted if outcome measures were monitored more frequently. However, 3 months of supplementation was compliant with the manufacturer's instructions. The study was also limited to German women, which may decrease external validity. Further research is warranted.
- Studies of lesser design strength (not included in the Evidence Table): Garcia-Perez et al. conducted a prospective controlled trial on menopausal women for 3 months to assess the effects of *Cimicifuga racemosa* on bone markers ($N = 82$) (Garcia-Perez et al., 2009). Women were excluded if they had recent bone fractures, were smokers, drank alcohol, were immobile, or took medication that altered calcium metabolism. Women were treated with 40 mg of Remifemin® daily for 3 months. The authors did not report any withdrawals from the study due to adverse effects. Three months of therapy with *Cimicifuga racemosa* resulted in a significant increase in alkaline phosphatase and decrease in the concentration

of N-telopeptides in the urine compared to placebo. However, the mechanism to decrease bone remodeling is unknown.

Breast Cancer

- Summary: Several in vitro studies have reported that black cohosh may possess inhibitory effects on estrogen-responsive cancer cell lines or breast cancer cells (Dixon-Shanies & Shaikh, 1999; Einbond et al., 2004; Nesselhut et al., 1993; Struck et al., 1997). According to animal research, a proposed mechanism of action behind tumor inhibition may be antiangiogenic effects by means of decreasing intratumoral microvessel density (Ng & Figg, 2003). Three retrospective studies analyzed the effect of black cohosh on breast cancer risk, although the results are mixed. Clinical trials and meta-analyses report mixed results on the effects of black cohosh on menopausal symptoms due to breast cancer treatments. Wuttke et al. suggested that the difference in the results may be due to product variability and dosage (Wuttke & Seidlova-Wuttke, 2012). Future research is warranted in this area.
- Systematic reviews: Roberts et al. conducted a systematic review to assess the safety and efficacy of herbal products in the treatment of hot flashes for women with a history of breast cancer (Roberts, 2010). The effects of phytoestrogens, Chinese herbs, combination herbs, evening primrose oil, dong quai, ginseng, wild yam extracts, and St. John's wort were assessed in this review but are excluded from this summary focusing on black cohosh. Twenty references assessing the effects of black cohosh in humans were included in this review (Booth et al., 2004; Borrelli & Ernst, 2008a, 2008b; Bruno & Feeney, 2006; Geller et al., 2009; Hernandez Munoz & Pluchino, 2003; Jacobson et al., 2001; Kronenberg & Fugh-Berman, 2002; Mahady et al., 2009; Mahady et al., 2008; Nash & Desindes, 2006; Newton et al., 2006; Osmers et al., 2005; Pockaj et al., 2006; Rebbeck et al., 2007; Richardson, 2008; Teschke et al., 2009; Walji et al., 2007). The authors pooled relevant trial results and systematic reviews from MEDLINE, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), PsycINFO, Allied and Complementary Medicine (AMED), and the National Center for Complementary and Alternative Medicine (NCCAM) databases. In addition, the references from the pooled studies were reviewed for additional relevant trials. References were included in the review if they involved perimenopausal or postmenopausal women with or without previous breast cancer history. Information regarding dosing, frequency and duration of treatment, and standardization was lacking. Two studies included in the review found that black cohosh had a stimulating effect on the vagina, although this effect was lacking in other studies. In addition, the authors suggested that black cohosh may affect liver function or cause liver damage, although the evidence is equivocal. According to the review, black cohosh may theoretically be converted to electrophilic quinones, which are carcinogenic, although this effect was lacking, according to assessment of urinary metabolites. Clinical studies have shown that black cohosh may have a chemotherapeutic effect and reduce the risk of breast cancer development. However, according to the 2006 Canadian Consensus Conference on Menopause, the use of this supplement is contraindicated for use by women with

estrogen-dependent tumors. Information on dropouts was lacking. According to the authors of the review, black cohosh may augment the antiproliferative effects of tamoxifen, according to clinical trials. However, some studies included in the review advised against using black cohosh during chemotherapy or radiotherapy. In addition, the authors of the review mentioned that black cohosh may interact with anesthetics, antihypertensives, and sedatives, according to the Clinical Practice Guideline of the Canadian Society of Obstetricians and Gynecologists, although other studies have indicated that the effect of black cohosh on human cytochrome activity may be small. Finally, the authors stated that black cohosh may contain anticoagulant coumarins, although an effect on prothrombin times was lacking. The primary endpoint was a positive benefit for hot flashes. According to one review included in this systematic review, black cohosh relieved the frequency of hot flashes in one of three double-blind, randomized controlled trials. According to results from two clinical trials, the effect of black cohosh on hot flashes in women taking tamoxifen is unclear. In addition, the effect of black cohosh on women with or without a history of breast cancer or tamoxifen use is unclear. The authors concluded that efficacy results for black cohosh in treating hot flashes were conflicting. Limitations of the studies assessed in the review include the short duration of the research, lack of long-term safety information, lack of data in women with breast cancer, and lack of study homogeneity comparisons. In addition, the review was limited by a lack of information regarding dosing ranges, as well as frequency and duration of treatment.

- Walji et al. conducted a systematic review of breast and prostate cancer clinical and preclinical studies to assess the effect of black cohosh on breast cancer (Walji et al., 2007). Databases, including MEDLINE, PubMed, Science Citation Index Expanded, Expanded Academic ASAP @ Scholars Portal, Plant Science, Biological Sciences, Applications of Hamlet Tools to Embedded Medical Instruments Design (AHMED; Alternative Medicine), CINAHL, and Embase, were searched from inception through February 2007. Five clinical studies (Hernandez Munoz & Pluchino, 2003; Jacobson et al., 2001; Pockaj et al., 2004, 2006; Rebbeck et al., 2007) and 21 preclinical studies were included, along with case reports, animal studies, and in vitro assessments of black cohosh's safety. The authors found that eligible studies showed conflicting evidence for black cohosh's ability to reduce climacteric symptoms in breast cancer patients. However, there is preliminary evidence that black cohosh may have antiproliferative effects. Based on the adverse effects found in cancer studies, black cohosh seems relatively safe, and according to the authors, significant adverse effects were not identified with black cohosh use. The authors concluded that black cohosh is not a phytoestrogen and that there is a lack of supportive evidence describing a causal relationship between black cohosh and hepatotoxicity. Although laboratory studies indicate that black cohosh may have antiproliferative properties, there is little evidence from clinical trials to support its use in cancer prevention.
- Antoine et al. conducted a systematic review to analyze the safety of drugs and herbs used to alleviate menopausal symptoms, other than hormone replacement therapy, in breast cancer patients (Antoine, Liebens, Carly, Pastijn, & Rozenberg, 2007). Search terms included tibolone, serotonin reuptake inhibitors, clonidine, veralipride, gabapentin, black cohosh, and phytoestrogens in breast cancer

patients. The authors were unable to find studies reporting the safety of black cohosh in breast cancer patients.

- Randomized controlled trials: Pockaj et al. conducted a double-blind, randomized, crossover clinical trial to assess the use of black cohosh in the treatment of hot flashes in women (Pockaj et al., 2006). Prospective patients were women with a history of breast cancer, an increased risk of breast cancer, or a preference to not take estrogen due to the risk of breast cancer. Patients did not have any malignant disease. All patients had 14 or more hot flashes per week for at least 1 month. One hundred thirty-two subjects were given one capsule of 20 mg of black cohosh (comparable to Remifemin®) or placebo twice daily for 4 weeks before crossover. Patients completed a daily hot flash diary and measured hot flashes by assigning points (1–4 on a scale of mild to very severe) to each hot flash based on severity and then adding the points for a given time period. The primary outcome was the average intrapatient hot flash score difference between the baseline measurements and the last week of each treatment. Toxicity was minimal and not different by treatment group. One subject dropped out of the study before receiving any medications. One hundred seven patients completed the first 5 weeks of diary entries, and 99 patients completed all 9 weeks of the study. Patients receiving black cohosh reported a mean decrease in hot flash score of 15% (CI: 2–29%) compared with a 31% decrease (CI: 18–44%) for patients on placebo ($p = 0.1$). Mean hot flash frequency was reduced 17% on black cohosh and 26% on placebo ($p = 0.36$). Patient treatment preferences were measured after completion of both treatment periods by ascertaining which treatment period, if any, the patient preferred. Thirty-two percent of patients preferred the black cohosh treatment, 37% preferred the placebo, and 31% did not prefer either treatment. The trial failed to provide any evidence that black cohosh reduced hot flashes more than the placebo. Although the study was very well designed, the statistical analysis was unclear, as the values in the abstract of the article were not the same as the values in the body of the article (as reported here) for seemingly the same outcomes. Lack of effect may be due to small sample size.
- Jacobson et al. conducted a RCT to assess the effects of black cohosh for 60 days on menopausal symptoms in 85 breast cancer patients (Jacobson et al., 2001). Primary outcomes were menopausal symptoms, including hot flash frequency, follicle-stimulating hormone (FSH) levels, and luteinizing hormone (LH) levels. Of 85 patients, 59 were on tamoxifen and 26 were not on tamoxifen. Subjects were randomized to the black cohosh treatment group ($N = 42$) and the placebo control ($N = 43$); 69 subjects completed all stages of the trial. Both groups reported a decrease in the number and intensity of menopausal symptoms and hot flashes, but the difference was not statistically significant. FSH and LH levels did not differ between the two groups. One weakness of this study is the study length, which was shorter than most black cohosh trials. Also, a large number of the subjects, but not all, were concurrently taking tamoxifen, which is known to cause hot flashes. The study also did not use a standardized index to evaluate menopausal symptoms, which would have simplified between-group comparisons.
- Studies of lesser design strength (not included in the Evidence Table): Hernandez et al. investigated the use of black cohosh for the prevention of hot flashes in women survivors of breast cancer taking tamoxifen (Hernandez Munoz &

Pluchino, 2003). In this randomized, open-label controlled trial, 136 women, aged 36–52, received either black cohosh (CR BNO 1055, Menofem®/Klimadynon®, 20 mg daily) with their tamoxifen, or tamoxifen alone. After 12 months, 24.4% of black cohosh subjects experienced hot flashes, compared to 73.9% in the tamoxifen-only group ($p < 0.01$). These results are promising, although the introduction of bias due to the open-label design is possible. Long-term follow-up of disease-free interval was not conducted; therefore, the safety of black cohosh in breast cancer patients was not established.

- Brasky et al. conducted a cohort study to assess the effects of specialty supplements, including black cohosh, on the risk of breast cancer ($N = 35{,}016$) (Brasky et al., 2010). Female members of the VITamins And Lifestyle (VITAL) cohort study, aged 50–76 years, were included in this study. All participants resided in the western portion of Washington State that is covered by the Surveillance, Epidemiology, and End Results (SEER) cancer registry. Women were excluded from the study if they had a history of breast cancer or in situ breast cancer, as well as if they avoided reporting cancer history at baseline. Women who were premenopausal, lacked menopausal status, or had breast sarcoma, phyllodes, or lymphoma histologies were also excluded. The investigators chose to avoid querying about dosing. However, the investigators asked about regular use of specialty supplements, which was defined as the use of at least one supplement daily for at least one year, over a 10-year period prior to baseline. The mean follow-up time was six years. Information on standardization interactions, allergies, adverse effects, and toxic effects was lacking. Of the 168,953 questionnaires mailed, 40,337 were deemed eligible for inclusion in the analysis. Outcome measures included in the incidence of breast cancer diagnoses between November 2000 and December 2007, as well as the alleviation of climacteric symptoms. Overall, for all supplements included in the analysis, an association between use of specialty supplements and relief of climacteric symptoms was lacking (HR = 1.01; 95% CI: 0.80–1.27). In particular, the regular use of black cohosh lacked a statistically significant effect on climacteric symptoms (HR = 1.17; 95% CI: 0.75–1.82), as well as on the risk of for breast cancer. According to the investigators, this study is limited by a lack of information regarding supplement dosage, a lack of updated exposure information after baseline, and the low prevalence of usage of some specialty supplements, including black cohosh, which contributed to a lack of power. In addition, 23.9% of the questionnaires mailed were deemed eligible for inclusion in the analysis.
- Rostock et al. conducted a prospective observational study of 50 women with breast cancer undergoing tamoxifen treatment with climacteric complaints (Rostock et al., 2011). All women had undergone surgery, 87% had undergone radiation, and 50% had received chemotherapy. Black cohosh, as an isopropanolic extract, was administered to every patient at a dose of one to four 2.5 mg tablets daily for six months. Tolerability of black cohosh was reported as good or very good by 90% of the patients. The menopause rating scale was used at one, three, and six months to assess effects of black cohosh. A significant reduction in total menopause rating scale was reported (from 17.6 at baseline to 13.6). A change in sweating, hot flashes, sleep disturbances, and anxiety was reported. However,

a change in musculoskeletal and urogenital complaints was lacking. Further research is warranted.

- Obi et al. conducted a case-control study to examine the risk of postmenopausal breast cancer with the use of herbal supplements for climacteric disorders (Obi et al., 2009). Postmenopausal German women aged 50–74 were included in the study. Physical activity and dietary habits were also reviewed. Black cohosh as Remifemin® or Remifemin® Plus was reported to be the most frequently used supplement. An inverse association was reported with Remifemin® or Remifemin® Plus use and breast cancer (OR = 0.80; 95% CI: 0.62–1.003). This result was reported to be independent of estrogen or progesterone receptor status. However, other Cimicifuga products did not report similar results. Limitations of this trial include limited external validity due to the studies being limited to German women. Further study is warranted.
- Rebbeck et al. conducted a retrospective case-control study to assess the effects of hormone-related supplements (HRS), including black cohosh, to evaluate the association of breast cancer risk (Rebbeck et al., 2007). Subjects were included if they were residents in the Philadelphia, PA, area and were living in the area at the time of diagnosis; were of African-American or European-American descent; were 50–79 years old; were newly diagnosed with breast cancer between July 1, 1999, and June 30, 2002; had a household telephone; lived in a noninstitutional setting; spoke English; and lacked cognitive, language, or speech impairment. Controls fit a similar profile but had never been diagnosed with breast cancer. Of the 1,214 eligible cases of breast cancer, 949 were interviewed and 1,524 controls were interviewed. All participants were interviewed over the telephone regarding family history of breast, endometrial, or uterine cancer; contraceptive history; fertility history; menstrual and menopausal history; medical history; gynecologic history; and use of exogenous hormones and medications. Participants were asked if they had taken up to five specific herbs or supplements (e.g., Biest, black cohosh, DHEA, etc.) at least three times per week for a month or more. Use of HRS varied significantly by race, with African-American women being more likely than European-American women to use any herbal preparation (19.2% vs. 14.7%, $p = 0.003$) as well as specific preparations such as black cohosh (5.4% vs. 2.0%, $p = 0.003$). Use of black cohosh had a significant breast cancer protective effect (adjusted odds ratio = 0.39, 95% CI: 0.22–0.70). This association was similar among women who reported use of either black cohosh or Remifemin® (an herbal preparation derived from black cohosh; adjusted odds ratio = 0.47, 95% CI: 0.27–0.82). Although the selection of prospective subjects was very well conducted, the study was retrospective, which may have biased results.
- In a pharmacoepidemiologic observational retrospective cohort study (mean overall observation time of 3.6 years), Zepelin et al. found that patients taking an isopropanolic *Cimicifuga racemosa* extract ($N = 1{,}102$) had a longer disease-free survival period than those who did not take black cohosh ($N = 17{,}759$) (Zepelin et al., 2007).
- Lundström et al. conducted a reexamination of results from an open-label case series study (Hirschberg et al., 2007) to reassess the effects of black cohosh on mammographic breast density in postmenopausal women ($N = 64$)

(Lundstrom et al., 2011). The reexamined results from this case series study were compared with reexamined results from a double-blind, randomized controlled trial that assessed the effects of combined hormone therapy (estradiol and norethisterone acetate) ($N = 43$), tibolone ($N = 49$), or placebo ($N = 53$) on breast density (Lundstrom et al., 2002). In the previously conducted studies, postmenopausal women aged 50–70 years, who had a body mass index (BMI) of 20 = 30 kg/m^2, were included if they had their last menstrual bleed at least 1 year before enrollment or they had follicle-stimulating hormone levels >40 mIU/L and estradiol levels <20 pg/mL. Women were excluded from both studies if they had used hormone therapy within 3 months of study enrollment, as well as if they presented with hypertension, hyperlipidemia, diabetes mellitus type 1 or type 2, or breast disease. In the case series study, participants were administered one tablet of black cohosh (Remifemin®) twice daily for 6 months. In the double-blind study, participants were administered placebo, 2.5 mg of tibolone (Livial®), or Kliogest®, which contained 2 mg of estradiol and 1 mg of norethisterone (E2/NETA group), once daily for 6 months. Each tablet of black cohosh (Remifemin®) provided 0.018–0.026 mL of liquid extract (40% isopropanol) from the rootstock of black cohosh, which is equivalent to 20 mg of herbal drug. Information on allergies, adverse effects, toxic effects, dropouts, and interactions was lacking. The primary outcome measure involved the digitization of previously obtained mammographic data of the craniocaudal projection of the left breast in order to quantify breast density using a computer-assisted program. Previously, the data had been classified using visual quantification scales. Compared to baseline, breast density increased significantly in participants receiving E2/NETA (14.3%; $p < 0.001$) and tibolone (2.3%; $p < 0.001$) after 6 months of treatment. However, statistically significant increase in breast density was lacking for the black cohosh (0%) and placebo (0%) groups. Compared to the other 3 groups, the increase in breast density for the E2/NETA group was statistically significant ($p < 0.001$). Twenty-four of 43 women treated with E2/NETA and one of the 49 women treated with tibolone showed a >10% increase in breast density. For all participants treated with black cohosh or placebo, a >10% increase in breast density was lacking. According to the authors, the results from this study may be limited by the fact that the mammograms evaluated were from two different studies, which could be a source of bias. In addition, this study lacked an adequate description of blinding or randomization, which may have allowed for the introduction of bias or confounding variables. Furthermore, information on allergies, adverse effects, interactions, and dropouts was lacking. Lastly, the studies with tibolone and black cohosh were supported by manufacturers of these products, which is a potential conflict of interest and source of bias.

Cognitive Function (postmenopausal women)

- Summary: The affect of black cohosh on cognitive function has not been well studied. In one randomized, double-blind controlled trial, a significant effect was lacking (Maki et al., 2009). Further studies are warranted.
- Evidence: Maki et al. conducted a phase II, double-blind, randomized controlled trial to assess the effects of red clover, black cohosh, or combined hormone

therapy on cognitive function ($N = 70$) (Maki et al., 2009). Subjects were enrolled from a parent trial. Women were included in the parent trial if they had their last menstrual period 6 months to 10 years prior to recruitment, they reported experiencing hot flashes at least 35 times weekly for at least 2 weeks, and their uterus and ovaries were intact. Participants were excluded from the original parent trial for (Cimicifuga racemosa, 2003) concurrent use of other menopausal therapies; (Amsterdam et al., 2009) smoking; (Anderson et al., 1996) presenting with conditions for which hormone therapy is contraindicated, such as heart disease, hypertension, diabetes, blood clots, or abnormal vaginal bleeding or mammograms; (Antoine et al., 2007) use of antidepressants, selective estrogen receptor modifiers (SERMS), or bisphosphonates; and (Ashar et al., 2008) presenting with any major systemic illness. For this particular study, participants were excluded for being diagnosed with an Axis I psychiatric disorder, presenting with a condition or using medication that affects cognitive function, speaking a language other than English as their first language, or taking part in another clinical trial (other than the parent trial) within the previous 30 days. Subjects received 120 mg of red clover aerial parts, 128 mg of belowground parts of black cohosh, and 0.625 mg of conjugated equine estrogens (CEE) with 2.5 mg of medroxyprogesterone acetate (MPA), or placebo once daily in the evening for 12 months. The 128 mg of the belowground parts of black cohosh was standardized to 7.27 mg of triterpene glycosides. Information regarding allergies, adverse effects, or toxic effects was lacking. One participant was excluded from the study due to noncompliance with treatment. Two participants from the parent study had withdrawn and were not included in the follow-up study. One woman fell asleep during posttreatment and was excluded from data analysis. In addition, one woman in the red clover treatment group withdrew after 92 days, but her data were included in the results. Therefore, the final sample size was 66 participants. Information regarding interactions was lacking. Primary outcome measures included verbal memory based on the California Verbal Learning Test (CVLT-Modified-28) and the Logical Memory Subtest of the Wechsler Memory Scale-Revised (WMS-R/LM-R-30). Secondary outcome measures included short-term figural memory based on the Benton Visual Retention Test (BVRT), visuospatial ability based on the Modified Card Rotations Test, verbal fluency based on the Letter Fluency Test, attention and working memory based on the Digit Span Forward and Backward Test, auditory attention based on the Modified Brief Test of Attention (BTA), visuoperceptual speed based on the Finding As Test, and verbal intelligence based on the Primary Mental Abilities Vocabulary (PMA) test, the Memory Functioning Questionnaire (MFQ), and the Positive and Negative Affect Scale (PANAS). In addition, hot flash frequency was recorded. Compared to placebo, treatment with black cohosh lacked a statistically significant effect on all primary ($p > 0.28$) and secondary outcomes ($p > 0.15$). Objective hot flashes decreased by 17% in the black cohosh group compared to 0% in the placebo group. This effect was statistically significant ($p < 0.001$), but lower than either of the other two treatment groups. According to the authors, black cohosh lacked a statistically significant effect on all cognitive outcome measures. Overall, the trial was well designed. However, limitations of this study may include the small sample size.

Coronary Heart Disease (postmenopausal women)

- Summary: Data are mixed on whether black cohosh has an effect on lipid profiles in humans (Chung et al., 2007; Garcia-Perez et al., 2009; Spangler et al., 2007; Wuttke et al., 2006). Arrhythmia and reversible bradycardia have been reported in two patients in clinical trials (Jacobson et al., 2001; McKenzie & Rahman, 2010). In a 1962 study, acteina, a constituent of black cohosh, was found to cause peripheral vasodilation in humans and was noted to elicit hypotension in animals (Genazzani & Sorrentino, 1962). Additional supporting data in humans are lacking. Further trials are warranted.
- Evidence: Bebenek et al. conducted a randomized, blinded, controlled trial of *Cimicifuga racemosa* (CR BNO 1055) in early postmenopausal women on bone density, 10-year coronary heart disease risk, and menopausal symptoms ($N = 128$) (Bebenek et al., 2010). German women 48–55 years old were included in the study. Women were excluded if they were taking medications that may affect the results (contraceptives and glucocorticoids), had other diseases or history of coronary heart disease, had an athletic history, or were not in the time frame of 1–3 years after menopause. Women were assigned to three different groups: exercise program plus CR supplementation 40 mg daily, exercise, or wellness control for 12 months. However, women received the CR supplement for 3 months on, 3 months off, then 3 months on again and discontinued it thereafter. Calcium and vitamin D was administered to all groups. Allergies, adverse effects, toxic effects were not discussed. Dropouts were discussed. However, dropouts due to side effects of the CR supplement were not noted. The primary outcomes were bone mineral density and Wilson's 10-year coronary heart disease risk. Secondary endpoints were menopausal symptoms and body composition. Outcome measures were taken at baseline and 12 months. A significant difference in outcome measures was lacking due to CR supplementation. The trial did not clearly state if it was double-blinded. The placebo was not identical to the CR supplement, but based on a survey, the authors believed that blinding was successful. The supplement was administered for 3 months on and then off, which may not have been a long enough time period to demonstrate CR's effects. Also, affects of CR may have been noted if outcome measures were monitored more frequently. However, 3 months of supplementation was compliant with the manufacturer's instructions. The study was also limited to German women, which may decrease its external validity. Further research is warranted.

Infertility

- Summary: Two randomized controlled trials of the addition of black cohosh to clomiphene citrate have been conducted, with mixed results. Additional high-quality clinical studies are needed before a conclusion can be made.
- Evidence: Shahin et al. conducted a randomized controlled trial of *Cimicifuga racemosa* and clomiphene citrate compared to ethinyl estradiol and clomiphene in infertile women with clomiphene failure ($N = 134$) (Shahin et al., 2009).Women included in the study were under 35 years of age, with primary or secondary infertility for one year and five unsuccessful clomiphene stimulation cycles. Women with a serum follicle-stimulating hormone level greater than 10

IU/mL on day 3 were excluded. All women received 150 mg of clomiphene citrate daily on days 3–7 of their cycle. In addition, they either received 120 mg of *Cimicifuga racemosa* rhizome or 100 mcg of ethinyl estradiol daily on days 1–13. Side effects, allergies, and toxic effects were not discussed. Withdrawals due to side effects were not noted by the authors. The primary outcome was pregnancy. A significant difference was lacking between the groups in the number of pregnancies. However, the authors noted that significant differences in days until human chorionic gonadotropin (HCG), endometrial thickness, serum estradiol on day of HCG, and serum progesterone were shown when the black cohosh group and ethinyl estradiol groups were compared. However, these were not primary outcomes. The authors noted that double-blinding was not possible due to "limitations in preparing identical drugs." Further studies are warranted with additional primary outcomes to assess the affect of black cohosh on infertility.

- Shahin et al. conducted a randomized controlled trial to investigate the role of oral phytoestrogens in improving pregnancy rate and cycle outcomes when used with clomiphene citrate (Shahin et al., 2008). Patients with unexplained infertility and recurrent clomiphene citrate induction failure, were randomly divided into two groups: group I ($N = 60$) and group II ($N = 59$). Both groups received clomiphene citrate 150 mg daily (days 3–7). Group I received an additional oral phytoestrogen (*Cimicifuga racemosa*) 120 mg daily on days 1–12. Human chorionic gonadotropin (HCG) injection (10,000 IU intramuscularly) was given, and timed intercourse was recommended when a leading follicle exceeded 17 mm and serum estradiol exceeded 200 pg/mL. There was a nonsignificant shortening of induction cycles in group I. Estradiol and LH concentrations were higher in group I compared with group II. Endometrial thickness, serum progesterone, and clinical pregnancy rate were significantly higher in group I (8.9 ± 1.4 mm vs. 7.5 ± 1.3 mm, $p < 0.001$; 13.3 ± 3.1 ng/mL vs. 9.3 ± 2.0 ng/mL, $p < 0.01$; 36.7% vs. 13.6%, $p < 0.01$, respectively).

Menopausal Symptoms

- Summary: Black cohosh is popular as an alternative to prescription hormonal therapy in the treatment of climacteric symptoms, such as hot flashes, mood disturbances, diaphoresis, palpitations, and vaginal dryness, due to conditions including menopause, breast cancer, and prostate cancer (Carroll, 2006; Gingrich & Fogel, 2003; Kanadys, Leszczynska-Gorzelak, & Oleszczuk, 2008; Kupferer et al., 2009; Low Dog, 2005; Maclennan, 2009; McBane, 2008; McKenna et al., 2001; Pinkerton, Stovall, & Kightlinger, 2009; Richardson, 2008; Rock & DeMichele, 2003; Umland, 2008; Zierau et al., 2002). Several controlled trials and case series have reported black cohosh to improve menopause-like symptoms for up to one year. Although these initial studies are suggestive, they have been small in number and have universally suffered from methodological weaknesses (Cheema, Coomarasamy, & El Toukhy, 2007). In addition, higher-quality trials indicate that black cohosh has little or no effect on menopausal symptoms. Most trials have utilized a standardized measurement scale to assess menopausal symptoms called the Kupperman Index. The mechanism of action of black cohosh remains unclear, and effects on estrogen receptors or hormonal levels have not been

demonstrated. In fact, some studies refute the idea that black cohosh is a phytoestrogen. Safety and efficacy data beyond one year are lacking. Due to the conflicting studies in this area, black cohosh may or may not affect menopausal symptoms. A well-designed, long-term, three-arm (black cohosh vs. standard therapy vs. placebo) evaluation of efficacy and safety is warranted.

- Meta-analysis: Shams et al. conducted a meta-analysis and systematic review of nine randomized controlled trials (Chung et al., 2007; Frei-Kleiner et al., 2005; Newton et al., 2006; Osmers et al., 2005; Rotem & Kaplan, 2007; Sammartino et al., 2006; Uebelhack et al., 2006; Verhoeven et al., 2005; Wuttke et al., 2003) to assess the effect of black cohosh on vasomotor symptoms associated with menopause (Shams et al., 2010). Using the phrases black cohosh and menopause, *Actaea racemosa* and menopause, and *Cimicifuga racemosa* and menopause, randomized controlled studies published in English from 1950 to 2008 were pooled from the Cochrane Library, PubMed, and Embase databases. In addition, the reference lists of the pooled articles were reviewed for other relevant studies. All included studies assessed the effects of black cohosh in postmenopausal women, used trial designs that involved a placebo group, and included frequency of vasomotor symptoms as an outcome measure. Studies were excluded from the review if they examined only women with a history of breast cancer. If the same study was published in multiple reports, the most recent report was cited in the review, but earlier publications were reviewed for information regarding study design or criteria used for including or excluding participants. In the studies that assessed the effects of black cohosh alone, participants were administered 160 mg of black cohosh, 42 mg of crude Cimicifuga racemosa, 40 mg of *Cimicifuga racemosa* rootstock, or 20 mg of *Actaea racemosa* herbal agent daily. Treatment was administered for 12 weeks to 12 months. Information regarding standardization was lacking. Adverse effects experienced by participants receiving black cohosh included connective tissue and musculoskeletal conditions (4–9.8%), infestation and infection (8.5–11.9%), and gastrointestinal symptoms (0.7–15%). In addition, breast complaints were reported in some studies. However, compared to the placebo groups, these adverse effects lacked increased frequency of occurrence. Information regarding toxic effects, dropouts, and interactions was lacking. Outcome measures included the rate difference of menopausal vasomotor symptom improvement compared to the placebo group. Two of the nine studies lacked data that could be used to calculate the rate difference for vasomotor symptom improvement. According to results from the remaining seven trials, treatment with black cohosh had a 24% rate difference for improvement of vasomotor symptoms compared to placebo (95% CI: 18–29%). Based on the random-effects model, this rate difference was increased to 26% (95% CI: 11–40%). However, five of these trials used combination treatment in which black cohosh and another herbal product were used. For these five studies, the combined estimate of the rate difference was 41% (95% CI: 20–62%). For the two studies that assessed the effects of black cohosh only, treatment with black cohosh resulted in an 11% rate difference in vasomotor symptom improvement compared to placebo (95% CI: 1–20%). The authors concluded that black cohosh may be effective in decreasing the rate of vasomotor symptoms associated with menopause, and that the use of this agent may be more effective when used in combination with other

natural products. Limitations of this review include strict selection of English-only literature, small number of trials reviewed, and the use of varied treatment interventions. The abstract was also reviewed (Shams et al., 2010).

- Systematic review: Guttuso conducted a systematic review of 51 randomized controlled trials to evaluate effective and clinically meaningful nonhormonal therapies for hot flashes ($N = 51$) (Guttuso, 2012). Six of these trials included black cohosh (Frei-Kleiner et al., 2005; Jacobson et al., 2001; Newton et al., 2006; Rotem & Kaplan, 2007; van der Sluijs, Bensoussan, Chang, & Baber, 2009; Verhoeven et al., 2005). Included studies were double-blind, randomized controlled trials assessing a nonhormonal compound for at least 8 weeks compared to placebo. Subjects in included studies used a daily diary to assess hot flash activity, and both menopausal and drug-induced hot flash studies were included. Excluded studies had placebo effects $\leq$10% due to concerns on the study's methodology and data comparability. Reviewed studies used 42–350 mg of black cohosh. Three studies used combination products including black cohosh: Verhoeven et al. (Verhoeven et al., 2005) used 100 mg of black cohosh, 50 mg of isoflavones, and 1,500 mg of evening primrose oil; van derSluijs et al. (van der Sluijs et al., 2009) used 350 mg of black cohosh in addition to Chinese herbs; and Rotem et al. (Rotem & Kaplan, 2007) used 100 mg of black cohosh, 50 mg of red clover, and other herbs in the treatment group. Treatments were given daily for 8–16 weeks. Information on standardization, adverse effects, allergies, toxic effects, dropouts, and interactions was lacking. The author intended to identify studies with statistically significant reductions in hot flashes. Of the six studies using black cohosh, one showed a clinically meaningful benefit (treatment effect: 3.25, $p = 0.026$). Evaluation of the six black cohosh studies showed that one study (Newton et al., 2006) showed significant benefits. The inconsistent results of black cohosh studies prevented the authors from making conclusions on the use of black cohosh to treat hot flashes. The thorough inclusion and exclusion criteria ensured that high-quality studies were used in this review.
- Kelly et al. conducted a systematic review of over-the-counter alternatives for hot flashes in women (Kelley & Carroll, 2010). PubMed, International Pharmaceutical Abstracts, and MEDLINE were searched for hot flash combined with multiple supplements, including black cohosh. Human trials using single ingredients and published in English were selected. Nine trials on black cohosh were reviewed (Bai et al., 2007; Frei-Kleiner et al., 2005; Nappi et al., 2005; Newton et al., 2006; Oktem et al., 2007; Pockaj et al., 2006; Pockaj et al., 2004; Vermes et al., 2005; Wuttke et al., 2003). Black cohosh 40–160 mg was administered daily for up to 52 weeks. The authors of the study considered black cohosh to be well tolerated, with few adverse effects reported. Efficacy of black cohosh was reported as being seen in 4–12 weeks. A significant decrease in hot flashes was reported in two prospective observational trials (Pockaj et al., 2004; Vermes et al., 2005). A significant decrease in the MRS was reported in one randomized controlled trial (Wuttke et al., 2003). Hot flashes and night sweats were also reported to decrease significantly when compared with fluoxetine in a randomized controlled trial (Oktem et al., 2007). Other significant results were lacking. This study illustrates the mixed results of the use of black cohosh for menopausal symptoms.

- Mazaro-Costa et al. conducted a systematic review to identify medicinal plants for female sexual dysfunction (Mazaro-Costa et al., 2010). A PubMed search was conducted including in vitro studies, animal models, clinical trials, and preclinical trials in both men and women involving plants. This summary will only review clinical trials on black cohosh. Six studies involving black cohosh were reviewed (Amsterdam et al., 2009; Julia Molla, Garcia-Sanchez, Romeu Sarri, & Perez-lopez, 2009; van der Sluijs et al., 2009; Wuttke et al., 2006; Wuttke et al., 2003). One of the studies was a randomized, placebo controlled trial using black cohosh in an herbal mixture of eight plants, including a standardization of 2.5% triterpene glycosides calculated as 27-deoxyactein. The study included 93 menopausal women aged 45–65 that received the mixture for 16 weeks but failed to show a significant difference in symptoms. Improvement in vaginal dryness and sexual disorders was noted in one controlled study, but it lacked significance when compared to estrogens. However, further information on the study is lacking. The authors noted that a German study showed an increase in the number of vaginal cells that was reported to be significant; however, further information is lacking on this study as well. Another study used a health-related quality of life scale, including the sexuality domain, but further information is lacking. The last trial analyzed the antianxiolitic effect of black cohosh on menopausal women, but further information is lacking. This systematic review is brief regarding the amount of information on the effects of black cohosh on sexual dysfunction. Additional high-quality clinical studies are needed before a conclusion can be made.
- Palacio et al. conducted a systematic review on the effect of black cohosh on women experiencing climacteric symptoms (Palacio et al., 2009). The authors conducted a PubMed search for randomized controlled trials involving adults written in English. The search was conducted on November 1, 2007, with two search terms: black cohosh and menopause. Seventeen articles were found; however, 12 were included in the review due to "relevance." Reviews of alternative therapies were also analyzed, and four additional studies were included. However, three German studies were not available for direct review, but the information for those studies was taken from the review (Jacobson et al., 2001; Lehmann-Willenbrock & Riedel, 1988; Stoll, 1987; Warnecke, 1985). The studies included had Jadad scores of 2–5. Varying doses of black cohosh ranging from 4 mg to 200 mg administered once or twice daily were studied. Three of the studies examined the effects of black cohosh in combination with other supplements (Newton et al., 2006; Rotem & Kaplan, 2007; Sammartino et al., 2006). Remifemin® was studied in four of the trials (Bai et al., 2007; Jacobson et al., 2001; Kronenberg & Fugh-Berman, 2002; Lehmann-Willenbrock & Riedel, 1988; Nappi et al., 2005; Osmers et al., 2005; Warnecke, 1985). Two studies evaluated the use of black cohosh with St. John's wort (Chung et al., 2007; Uebelhack et al., 2006). Duration of the trials ranged from 60 days to 1 year. A significant difference in adverse effects or allergies due to black cohosh was lacking in any study. The main adverse effects reported were gastrointestinal issues in the black cohosh and St. John's wort group, but it is difficult to determine if they were due to the black cohosh alone (Chung et al., 2007; Uebelhack et al., 2006). Dropouts were reported for each study, but none were significant. Drug interactions were not discussed in the review. Several outcome measures were evaluated, including hot flashes,

night sweats, number of awakenings at night, and scores for the Menopause Rating Scale (MRS), Kupperman Index (KI), Wiklund Menopause Symptoms Scale, Hamilton Depression and Anxiety Rating Scales, Symptom Rating Test, Greene Climacteric Scale, Vaginal Maturation Index, Clinical Global Impression scale, Self-Assessment Depression Scale, and Back Depression Inventory (BDI). Of the 12 studies, nine compared black cohosh to placebo (Frei-Kleiner et al., 2005; Jacobson et al., 2001; Newton et al., 2006; Osmers et al., 2005; Pockaj et al., 2006; Rotem & Kaplan, 2007; Sammartino et al., 2006; Stoll, 1987; Wuttke et al., 2003). Remifemin® was shown to significantly improve multiple outcomes in two studies (Kronenberg & Fugh-Berman, 2002; Osmers et al., 2005; Stoll, 1987). In two studies, hot flashes, night sweats, and mean KI scores were reported to be significantly lower (Rotem & Kaplan, 2007; Sammartino et al., 2006). However, black cohosh was used in combination in these trials. St. John's wort with black cohosh was compared to placebo in two studies, with significant improvement indicated (Chung et al., 2007; Uebelhack et al., 2006). Five studies compared black cohosh with medications with known efficacy, including fluoxetine, diazepam, and hormones (Bai et al., 2007; Lehmann-Willenbrock, & Riedel, 1988; Nappi et al., 2005; Oktem et al., 2007; Warnecke, 1985). Remixin was reported to significantly improve mean KI scores and hot flash when compared to fluoxetine (Oktem et al., 2007). However, mean BDI score improvement was significant in the fluoxetine group. Three trials that compared black cohosh to estrogen therapy did not report a significant difference between the two treatments (Bai et al., 2007; Lehmann-Willenbrock & Riedel, 1988; Nappi et al., 2005). The study evaluating Remifemin® vs. diazepam or estrogens did not report data to evaluate the claims of "greatest improvement" due to Remifemin® (Warnecke, 1985). Also, this study was open label. The actual effect of black cohosh is unclear. Further research with randomized controlled trials is warranted.

- Wong et al. conducted a systematic review to examine the efficacy and safety of complementary and alternative therapy for menopausal symptoms (Wong et al., 2009). Inclusion criteria included trials conducted in humans with complementary medicine used for the relief of menopausal symptoms. Exclusion criteria were studies published in languages except English or animal studies. Seven review articles (Cimicifuga racemosa, 2003; Cheema et al., 2007; Geller & Studee, 2006; Huntley & Ernst, 2003a; Kang, Ansbacher, & Hammoud, 2002; Low Dog, Powell, & Weisman, 2003; McBane, 2008) and eight human clinical trials (Frei-Kleiner et al., 2005; Jacobson et al., 2001; Newton et al., 2006; Osmers et al., 2005; Pockaj et al., 2006; Uebelhack et al., 2006; Verhoeven et al., 2005; Wuttke et al., 2003) that discussed black cohosh were included. Clonidine, gabapentin, selective serotonin reuptake inhibitors (SSRIs), ginseng, hormone replacement therapy (HRT), red clover, dong quai, evening primrose oil, soy (isoflavones), behavioral interventions, and acupuncture were also reviewed but have been excluded from this summary focusing on black cohosh. One trial used Remifemin®, which contains 20 mg of black cohosh at an unknown frequency. Specific doses and frequencies used in other included trials were lacking. Study durations ranged from 12 weeks to 12 months. Information on standardization was lacking. The adverse effects reported in this review included nausea and vomiting, rash, headache, dizziness, and one case of hepatotoxicity. Information on toxic effects and dropout

rates was lacking. Laboratory studies have shown that black cohosh may interact with CYP34A. Specific outcome measures for black cohosh studies were lacking. A meta-analysis comparing black cohosh with placebo showed results trending toward a decrease in hot flashes, but only for mild-to-moderate symptoms. One 12-week study revealed improvement in the frequency and intensity of hot flashes as well as in mood, sleep disorders, sexual disorders, and sweating. The Herbal Alternatives for Menopause Trial (HALT) compared black cohosh to both placebo and estrogen replacement and suggested that black cohosh lacked efficacy in decreasing vasomotor symptoms. A limitation of this review was a lack of information on the methodology and details beyond the results of the included studies.

- Borrelli et al. conducted a systematic review to evaluate the clinical evidence for or against the efficacy of black cohosh in alleviating menopausal symptoms (Borrelli et al., 2001; Borrelli & Ernst, 2002, 2008b). The 2008 update is described here. Five computerized databases (MEDLINE, Embase, AMED, Phytobase, and the Cochrane Library) were searched to identify all clinical data that provided evidence on the efficacy of *C. racemosa*. Bibliographies of the articles were scanned for further relevant publications. Only double-blind, RCTs were included in the evaluation of efficacy. No language restrictions were imposed. Trials were excluded if they did not focus on menopausal problems, included women suffering from medically induced menopause, did not use black cohosh monopreparations, or did not use placebo or a standard drug treatment for the control group. Six studies with a total of 1,112 peri- and postmenopausal women met the inclusion criteria. The evidence from these RCTs did not consistently demonstrate an effect of black cohosh on menopausal symptoms; however, a beneficial effect of black cohosh on perimenopausal women cannot be excluded. The efficacy of black cohosh as a treatment for menopausal symptoms is uncertain, and further rigorous trials seem warranted.
- Borrelli et al. conducted a systematic review of computerized literature databases (MEDLINE, Embase, AMED, CISCON, and the Cochrane Library) to review the effect of black cohosh on menopausal symptoms (Borrelli et al., 2001; Borrelli & Ernst, 2002). All randomized controlled trials and animal and in vitro experiments were reviewed. There were no restrictions on language. The authors stated that there was no convincing evidence to demonstrate the efficacy of black cohosh on menopausal symptoms, primarily due to poor-quality positive trials and one higher-quality trial that found no effect. The authors stated that earlier positive results may have been due to the placebo effect.
- Loprizini et al. conducted a review of hot flash studies conducted over the past two decades at the Mayo Clinic and in the North Central Cancer Treatment Group (Loprinzi et al., 2008). Ten randomized, controlled (eight placebo controlled), double-blind clinical trials were conducted involving a total of 1,581 women, as were three placebo controlled, double-blind clinical trials involving a total of 329 men. In addition, 14 pilot trials (with more than 325 participants to date) were included. Data from the pilot trials have given direction for substances that ought to be further explored in more definitive studies. In men, randomized studies demonstrated that hot flashes are markedly decreased by low doses of megestrol acetate, moderately decreased by gabapentin, and not

substantially decreased by clonidine. Results from the randomized trials in women demonstrated that hot flashes are markedly decreased by relatively low doses of progestational agents (megestrol acetate and medroxyprogesterone acetate), moderately decreased by venlafaxine, mildly to moderately decreased by fluoxetine, mildly decreased by clonidine, and not substantially decreased by vitamin E, a soy phytoestrogen product, or black cohosh.

- Nedrow et al. conducted a systematic review of 70 randomized controlled trials to assess the effect of various alternative therapies on menopausal symptoms (Nedrow et al., 2006). The effects of biologically based therapies; mind-body therapies; manipulative, body-based, and energy therapies; and whole medical system approaches are included in this review but are excluded from this summary focusing on black cohosh. Four trials assessed the effects of black cohosh (Hernandez Munoz & Pluchino, 2003; Jacobson et al., 2001; Osmers et al., 2005; Wuttke et al., 2003). The authors searched MEDLINE, PsycINFO, the Cochrane Library database, MANTIS, and AMED for full-text articles, systematic reviews, meta-analyses, references, expert statements, and websites published in English between 1966 and 2005. Included studies reported one or more menopausal symptoms. Studies were excluded if they investigated nonmenopausal women or animals. Participants in most of the black cohosh studies were administered one tablet containing 20 mg of black cohosh twice daily. In one study, participants were administered 2.5 mg of isopropanolic extract of black cohosh. The duration of black cohosh treatment was 9–12 weeks. Information on standardization, allergies, and adverse effects was lacking. Three studies linked black cohosh supplements with hepatotoxicity. One study linked black cohosh supplements to breast cancer metastasis in mice. Information on dropouts and interactions was lacking. Primary outcome measures included a variety of symptoms reported on the Kupperman Index and Greene Climacteric Scale (hot flash frequency and severity, sleep disturbance, vaginal dryness, vaginal bleeding, urinary frequency or incontinence, depression, anxiety, sexual dysfunction, cognitive function, paresthesias, nervousness, vertigo, weakness, arthralgia, myalgia, headache, palpitations, and formication). One study found a reduction in sweating for black cohosh supplements vs. placebo ($p = 0.04$). Two studies found a statistically significant reduction in hot flash frequency for black cohosh vs. placebo ($p < 0.01$ for one of these studies). This improvement was lacking from the other two studies, but the authors of the review attributed this lack of effect to concurrent use of tamoxifen. One study showed improvement in vasomotor symptoms for the black cohosh group, but this improvement was lacking in the other three studies. Participants, ethnic groups, therapeutic modalities, and standardization of therapies varied considerably. Data regarding dropouts, blinding, identification of studies with negative results but sufficient power, and statistical analysis of relevant outcomes were lacking. Exclusion of articles unavailable in English or a full-text format may reduce the comprehensiveness of the manuscript. The study was also reviewed by the Centre for Reviews and Dissemination (Centre for Reviews and Dissemination, 2006).
- Hanna et al. conducted a systematic review on the effectiveness on nonprescription medications on acute menopausal symptoms (Hanna et al., 2005). Only trials on black cohosh will be discussed here. PubMed, MEDLINE, ProQuest, and

the Cochrane Controlled Trials Registered were searched for relevant studies from 1940 to March 2004. Multiple keywords, including black cohosh, were used. Nonrandomized and uncontrolled trials were included if conducted in healthy women with menopausal symptoms. Seven trials were examined (Daiber, 1983; Lehmann-Willenbrock & Riedel, 1988; Liske et al., 2002; Stoll, 1987; Vorberg, 1984; Warnecke, 1985; Wuttke et al., 2003). Two of the seven trials were randomized, placebo controlled, double-blind, parallel trials. The rest of the trials were uncontrolled, and only one was randomized and double-blind. Remifemin® was used in six of the seven trials at doses ranging from 40 drops twice daily to 8 mg-127 mg daily of the tablets. A 40 mg daily black cohosh extract was used in the other study. The duration of the trials was 12–24 weeks. Outcome measures included hot flashes, night sweats, and multiple menopausal scales that measure menopausal symptoms. A significant decrease in the Kupperman Menopausal Index was reported in both randomized placebo controlled trials. A significant increase in proliferation of vaginal epithelial cells was also reported in one study. The uncontrolled trials using Remifemin® also reported significant increases in compared with baseline. The review included noncontrolled trials that may make the results inconclusive. Also, the studies were conducted on German and Polish women, which may decrease the external validity. Further studies are warranted. This study was also reviewed by the Centre for Reviews and Dissemination (Centre for Reviews and Dissemination, 2006).

- Low Dog conducted a review of botanical dietary supplements used to treat menopausal symptoms (Low Dog, 2005). The author searched the Cochrane Library and MEDLINE databases (January 1966 to October 2004) for multiple terms, including menopause, hot flashes, and phytoestrogen, and specific types of herbs used to treat menopausal symptoms (black cohosh, dong quai, etc.). Studies were included if they were controlled trials that used an oral herb administered for at least 6 weeks to peri- or postmenopausal women with hot flashes; dietary interventions (e.g., soy) were not included. Of the 13 published trials that used black cohosh, five met the criteria and were included. Three studies used Remifemin®, which reduced Kupperman Index ratings in two of the studies (Lehmann-Willenbrock & Riedel, 1988; Warnecke, 1985) and increased the proliferation of vaginal epithelium in two studies (Stoll, 1987; Warnecke, 1985). One study used an unspecified source of black cohosh and showed that black cohosh did not affect hot flashes compared to the placebo but did significantly decrease sweating (Jacobson et al., 2001). The final study used MenoFem® and showed a statistically significant reduction in the Menopause Rating Scale score, but no effect on hot flashes (Wuttke et al., 2003). Low Dog noted that all of the trials included in this review have methodological weaknesses that may introduce bias, including attrition bias (Stoll, 1987); small sample size, lack of placebo arm, and lack of blinding (Lehmann-Willenbrock, & Riedel, 1988); lack of analytical details in the article (Warnecke, 1985); inconsistencies in results (Wuttke et al., 2003); and the inclusion of women taking tamoxifen, a hot flash-inducing medication (Jacobson et al., 2001). The review seems well conducted and raises important concerns about the quality of menopausal symptom studies.
- Huntley et al. conducted a systematic review of computerized literature databases (MEDLINE, Embase, PhytoDoc, and the Cochrane Library) from

their inception to June 2001 to review the effect of plant-based products, including black cohosh, on menopausal symptoms (Huntley & Ernst, 2003a). Of the 23 RCTs that met the author's criteria, four investigated black cohosh. The authors stated that the evidence for black cohosh is limited by poor methodology.

- Kronenberg and Fugh-Berman conducted a systematic review of complementary and alternative therapies used to treat menopausal symptoms (Kronenberg & Fugh-Berman, 2002). The authors searched MEDLINE from January 1966 to December 2002, AMED from January 1985 to December 2000, and their own files. Although many terms related to menopause, its symptoms, and alternative therapies were searched, specific herb names, e.g., black cohosh, were not used as search terms. The search yielded four of the five studies (Jacobson et al., 2001; Lehmann-Willenbrock & Riedel, 1988; Stoll, 1987; Warnecke, 1985) covered by the Low Dog study (Low Dog, 2005). The evaluation of the studies seems cursory and summarizes the studies findings instead of critiquing them.
- Randomized controlled trials: Amsterdam et al. conducted a randomized, placebo controlled, double-blind, parallel-group study of the tolerability and efficacy of black cohosh extract for the treatment of anxiety disorder associated with menopause ($N = 28$) (Amsterdam et al., 2009). Subjects were eligible for the study if they were women who were at least 12 months postmenopausal, had a hysterectomy with FSH of at least 40 mIU/mL, or were perimenopausal (amenorrhea lasting 2–11 months in the previous year). Perimenopausal women had to be 40 years or age or older and have no other cause for their amenorrhea. Subjects were excluded from the study if they were diagnosed with bipolar disorder, major depressive disorder, panic disorder, obsessive-compulsive disorder, phobic disorder, acute stress disorder, posttraumatic stress disorder, schizophrenia, substance-induced anxiety disorder, dementia, or dependence/substance abuse disorder in the previous three months. Patients were also excluded if they had a history of endometrial hyperplasia, abnormal mammogram result, serum thyrotropin level of 5 kIU/mL or higher, malignancy, an unstable medical condition, hepatic disease, renal disease, endometrial cancer, undiagnosed uterine bleeding, an abnormal gynecologic exam, rapidly growing uterine leiomyomata, or known allergy to black cohosh. Patients were not allowed to use prescription antianxiety medications, antidepressants, sedatives, mood stabilizers, oral or topical estrogen or phytoestrogen, or other complementary and alternative medicine (CAM) remedies. Patients were randomly assigned to black cohosh 32 mg capsules ($N = 15$) or a rice flour placebo capsule ($N = 13$). Patients were started on two capsules daily (either 64 mg of black cohosh or two placebo capsules) for 2 weeks and titrated up to four capsules daily (either 128 mg of black cohosh or four placebo capsules) by the fourth week. If patients experienced adverse effects, the dose could be lowered to a minimum of one capsule daily. Data were recorded at baseline and weeks 2, 4, 8, and 12. The study drugs used were standardized, pharmaceutical-grade *Cimicifuga racemosa* (Lot BC191) extract and placebo (rice flour). The University of Pennsylvania Investigational Drug Service prepared all study products. Products were analyzed looking at four bioactive triterpene constituents via high-pressure liquid chromatography: R-actein, 23-epi-26-deoxyactein, S-actein, and 26-deoxyactein standardized to 5.6% of the active triterpene glycosides. One patient on black cohosh discontinued treatment

due to edema and arthralgia. Fourteen adverse events with black cohosh and eight with placebo were considered possible, probable, or definite. These events included two occurrences each of light-headedness and difficulty falling asleep, as well as one occurrence each of dry mouth, diaphoresis, pain, edema, gastrointestinal bloating, diarrhea, cramping, vaginal bleeding, waking in the middle of the night, and increased anxiety. A significant difference for adverse events between the treatment groups was lacking. Information on toxic effects and interactions was lacking. Six patients failed the initial screen and withdrew participation consent, one patient in each treatment group withdrew consent to participate after randomization, two patients in each treatment group were lost at follow-up, and one patient discontinued due to adverse effects. The primary outcome was change over time in total Hamilton Anxiety Rating Scale (HAM-A) scores. Secondary outcomes were the change in Beck Anxiety Inventory (BAI) score, total Green Climacteric Scale (GCS) and GCS subscale scores, and Psychological General Well-Being Index (PGWBI) ratings. Seventy-five percent of patients completed all study visits. Reduction in the total GCS scores was statistically significant, favoring placebo, and a modestly greater reduction on the GCS psychological subscale, favoring placebo. Statistically significant differences for all other outcomes were lacking. The authors found statistical significance in one of their outcome measures. Limitations of this study included a small population and low power. Further studies are needed to better understand the effects of black cohosh on anxiety in postmenopausal women.

- Geller et al. conducted a randomized, double-blind study in women to assess the safety and efficacy of black cohosh, red clover, and hormone therapy for the management of vasomotor menopausal symptoms over 12 months ($N = 89$) (Geller et al., 2009). Included subjects were perimenopausal or postmenopausal women with an intact uterus experiencing 35 or more vasomotor symptoms per week in the 2 weeks before study enrollment, amenorrhea for more than 6 months but less than 10 years, and an FSH level >40 mIU/mL as well as no contraindication to hormone replacement therapy. Patients were excluded if they had a previous hysterectomy or fewer than 35 vasomotor symptoms per week; if their last menstrual period was more than 10 years ago; if they had a positive pregnancy test or were breastfeeding; if they had a BMI >38 kg/m^2, abnormal vaginal bleeding, an abnormal transvaginal ultrasound (>7 mm thickness), an abnormal endometrial biopsy or mammogram, blood pressure >165/>95 mmHg, or current use of estrogen, progestin, SERM, St. John's wort, bisphosphonates, or dietary phytoestrogens; if they participated in another trial within 30 days of enrollment; or if they had more than five drinks per week, smoked, or were vegan. Other exclusion criteria were having history of the following: endometrial hyperplasia or neoplasia, cancers of the breast or reproductive tract, myocardial infarction or stroke, severe recurrent depression or psychiatric disturbance, cerebrovascular accident, severe varicose veins, sickle cell anemia, alcohol or drug abuse, migraine associated with hormone use, deep vein thrombosis, thrombophlebitis or thromboembolic disorder, or diabetes. Subjects in the black cohosh group were given 128 mg of black cohosh as two 64 mg capsules containing an ethanolic extract of belowground parts. Subjects in the red clover group were given 398 mg of red clover as an ethanolic extract of aerial parts. Subjects in the hormone

replacement therapy group were given 2.5 mg of medroxyprogesterone acetate and 0.625 mg of conjugated equine estrogens. All therapies were given daily for 12 months. Two capsules of black cohosh were standardized to contain 7.27 mg of triterpene glycosides. Two capsules of red clover were standardized to contain 120 mg of isoflavones. All study capsules were identical in appearance, taste, and smell. Serious adverse events from black cohosh were lacking. Significant differences between groups for other side effects were lacking. Evidence of hepatotoxicity due to black cohosh supplementation was lacking. One subject in the black cohosh group was lost to follow-up, and eight women terminated the study early: one from the placebo group (due to life changes), four from the hormone replacement group (due to two subjects experiencing adverse events, one subject relocating, and one dropping out due to life changes), one from the black cohosh group (due to lack of efficacy), and two from the red clover group (due to lack of efficacy). All dropouts were included in the intent-to-treat analysis. Information on interactions was lacking. The primary outcome measure was to assess the efficacy of black cohosh for the relief of vasomotor symptoms as measured by the subject in a diary. Relief of vasomotor symptoms was measured by the decrease in hot flashes and night sweats, hot flashes alone, and intensity of hot flashes compared with placebo. Secondary outcome measures were safety and measurement of relief of somatic symptoms, mood changes, sexual dysfunction, and health-related quality of life. Statistically significant differences were found in the black cohosh group compared to placebo at six and nine months, with the black cohosh group showing higher vasomotor symptom intensity than placebo [difference in mean reduction (SD) at 6 months: -0.71 (0.26) ($p = 0.008$), nine months: −0.66 (0.27) ($p = 0.02$)]. Statistically significant differences in all other primary and secondary outcomes were lacking. This well-designed study had a thorough description of inclusion and exclusion criteria as well as appropriate blinding and standardization of herbal products used. A safety analysis found that hepatotoxicity from black cohosh was lacking. Shulman et al. analyzed why Geller et al. did not report a benefit (Shulman, Banuvar, Fong, & Farnsworth, 2011).

- Newton et al. conducted a randomized, double-blinded trial to assess the effect of herbal medicines on menopausal symptoms in menopausal and postmenopausal women (Newton et al., 2006). The 351 subjects were 45–55 years old and had at least two episodes of hot flashes or night sweats daily. About one half of the subjects were menopausal and the other half were postmenopausal. Subjects were randomized to receive 160 mg of black cohosh, 200 mg of a multiherb formula (black cohosh, alfalfa, boron, chaste-tree, dong quai, false unicorn, licorice, oats, pomegranate, and Siberian ginseng), the multiherb formula with an increased intake of soy, hormone therapy (conjugated equine estrogen), or placebo, daily for one year. The black cohosh supplement was standardized as 2.5% triterpene glycosides and 70% ethanol. There were no statistical differences between the treatment groups and placebo for adverse effects, which included gastrointestinal symptoms, nausea and vomiting, fatigue, asthenia, malaise, headaches, or migraines. Twenty-six subjects dropped out and were well described. No interactions were described. The main outcome measure was the reduction of menopausal symptoms, specifically frequency and intensity of vasomotor

symptoms daily and the total Wiklund Menopause Symptom Scale score. There were no statistically significant differences in the Wiklund scores overall at 3, 6, or 12 months for any of the groups. The average adjusted difference for hormone therapy compared with placebo was −4.55 (95% CI: −6.51 to −22.59) vasomotor symptoms daily at 3 months ($p < 0.001$) and −4.06 (95% CI: −5.93 to −2.19) vasomotor symptoms daily for the average over all the follow-up time points ($p < 0.001$). Although the study was of very high quality, it may not be applicable to all women, as the enrolled subjects were highly selected (351 subjects enrolled of 3,443 who responded). Also the subjects were predominantly highly educated and white, with an average of six vasomotor symptoms daily. As most menopausal and postmenopausal women have much less frequent symptoms, they may or may not benefit from this study's findings. Also, the placebo group experienced a 30% reduction of symptoms during the 12-month follow-up period, which indicates that either menopausal symptoms are greatly influenced by the placebo effect or may resolve themselves independently of any treatment.

- Osmers et al. conducted a randomized, multicenter, placebo controlled, double-blind clinical trial to assess the efficacy and tolerability of an isopropanolic black cohosh extract in the treatment of climacteric complaints in 304 patients (Osmers et al., 2005). Postmenopausal women aged ≥45 with amenorrhea ≥12 months or with FSH ≥50 IU/L for 6 or more months were included in this study. Subjects were randomly allocated to receive one blinded Remifemin® tablet (2.5 mg of isopropanolic extract of *Cimicifuga racemosa* corresponding to 20 mg of rootstock) or matching placebo twice daily for 12 weeks. There was a 4-week washout period before study entry for hormone replacement therapy and a 1-week washout for nonhormonal climacteric drugs or herbs, antiepileptics, hypnotics, sedatives, and antidepressants. The authors reported numerous side effects, but none were significantly different from the placebo group. Of 304 patients randomized, 16 were excluded from intention-to-treat (ITT) analysis based on inclusion criteria violation (eight in the treatment group, 10 in the placebo group). ITT analysis was performed on 143 patients in the treatment group [including dropouts due to adverse effects (Bai et al., 2009), insufficient efficacy (Bai et al., 2009), withdrawal of consent (Cimicifuga racemosa, 2003), and noncompliance (Anderson et al., 1996)] and 141 patients in the placebo group [including dropouts due to adverse effects (Ashar et al., 2008), insufficient efficacy (Betz et al., 2009), marked protocol violation (Amsterdam et al., 2009), withdrawal of consent (Amsterdam et al., 2009), and noncompliance (Amsterdam et al., 2009)]. The primary outcome measure was the change from baseline on the Menopause Rating Scale; secondary measures included changes in its subscores and safety variables. Patient groups did not differ in baseline characteristics. The isopropanolic black cohosh extract was more effective than placebo ($p < 0.001$), depending on time from symptom onset ($p = 0.014$) and follicle-stimulating hormone level ($p = 0.011$). The effect size was 0.03–0.05 Menopause Rating Scale units, which is similar to contemporary hormone replacement therapy study results (0.036 Menopause Rating Scale units). Women in the early climacteric phase benefited more than women in the late phase. There were no relevant group differences in adverse events, laboratory findings, or tolerability. Use of black cohosh did not elevate liver enzyme activity in peripheral blood. This was

a well-designed study with adequate blinding, randomization, and power calculations for study size. Ross reviewed this trial (Ross, 2012).

- Bai et al. conducted a randomized, double-blind, controlled equivalence study in China to assess the effect of Remifemin® (an isopropanolic extract of black cohosh) on climacteric symptoms (Bai et al., 2007). A total of 244 menopausal patients (40–60 years old) with a Kupperman Menopausal Index scores ≥15 were randomized into two groups. In a double-dummy design, subjects were administered either two 20 mg Remifemin® tablets plus one tibolone-matching placebo ($N = 122$) or one 2.5 mg tibolone (Zi Zhu Awei®) tablet with two Remifemin®-matching placebos ($N = 122$) daily for 12 weeks. The primary outcome was the benefit-risk balance, which was assessed by a combination of the Mann-Whitney values (MWV) of the Kupperman Index (MWV >0.5 shows superiority; MWV >0.36 shows noninferiority) and the frequency of adverse effects. Two hundred eighteen subjects (89.3%) completed the trial, with 26 withdrawing from the trial early. Three hundred ninety-two adverse events occurred in 154 out of 243 analyzed subjects, of which 139 adverse events occurred in 64 (52.9%) subjects taking Remifemin® and 253 adverse events occurred in 90 (73.8%) subjects in the tibolone group. The Kupperman Index decreased in both the Remifemin® group (from 24.7 ± 6.1 to 11.2 ± 6.2 and 7.7 ± 5.8) and the tibolone groups (from 24.7 ± 6.1 to 11.2 ± 7.2 and 7.5 ± 6.8) at weeks 4 and 12, respectively. The authors concluded that Remifemin® was noninferior to tibolone and had significantly fewer adverse effects than tibolone ($p < 0.0001$).
- Pockaj et al. conducted a double-blind, randomized, crossover clinical trial to assess the use of black cohosh in the treatment of hot flashes in women (Pockaj et al., 2006). Prospective patients were women with a history of breast cancer, an increased risk of breast cancer, or a preference to not take estrogen due to the risk of breast cancer. Patients did not have any malignant disease. All patients had 14 or more hot flashes per week for at least one month. One hundred thirty-two subjects were given one capsule of 20 mg of black cohosh (comparable to Remifemin®) or placebo twice daily for 4 weeks before crossover. Patients completed a daily hot flash diary and measured hot flashes by assigning points (on a scale of 1–4 for mild to very severe) to each hot flash based on severity and then adding the points for a given time period. The primary outcome was the average intrapatient hot flash score difference between the baseline measurements and the last week of each treatment. Toxicity was minimal and not different by treatment group. One subject dropped out of the study before receiving any medications. One hundred seven patients completed the first 5 weeks of diary entries, and 99 patients completed all nine weeks of the study. Patients receiving black cohosh reported a mean decrease in hot flash score of 15% (95% CI: 2–29%) compared with a 31% decrease (95% CI: 18–44%) for patients on placebo ($p = 0.1$). Mean hot flash frequency was reduced 17% on black cohosh and 26% on placebo ($p = 0.36$). Patient treatment preferences were measured after completion of both treatment periods by ascertaining which treatment period, if any, the patient preferred. Thirty-two percent of patients preferred the black cohosh treatment, 37% preferred the placebo, and 31% did not prefer either treatment. The trial failed to provide any evidence that black cohosh reduced hot flashes more than the placebo. Although the study was very well designed, the statistical

analysis is unclear, as the values in the abstract of the article are not the same as the values in the body of the article (as reported here) for seemingly the same outcomes. Lack of effect may be due to the small sample size.

- Wuttke et al. conducted a double-blind, randomized, multicenter study to assess the effects of the *Cimicifuga racemosa* preparation CR BNO 1055 (Klimadynon®/Menofem®) on climacteric complaints, bone metabolism, and endometrium (Wuttke et al., 2003). Postmenopausal women, 40–60 years old with body mass indices of <30 and amenorrhea for at least 6 months, were included in this study. Ninety-seven patients were randomized and formed the intent-to-treat collective. Subjects received either two capsules of CR BNO 1055 (daily dose corresponding to 40 mg of herbal drug), 0.6 mg of conjugated estrogens (Oestrofeminal®), or matching placebo for 3 months. Two patients dropped out prematurely, and 35 patients were excluded from analysis because of protocol violations. Thus, statistical analysis was performed on 62 patients. Menopausal symptoms were assessed by a change from baseline to endpoint after 12 weeks of treatment in the Menopause Rating Scale and subjective reports in a diary. The authors reported that CR BNO 1055 was equipotent to conjugated estrogens and superior to placebo in reducing climacteric complaints. A significant increase on vaginal thickness was lacking with CR use. CR was reported to be as effective as estrogen for MRS scores when compared to placebo. CR was reported to decrease osteoclast activity and increase osteoblast activity. This study was properly randomized using a randomly permuted block design. However, method of blinding the practitioners was not described. Further research is warranted.
- Stoll et al. conducted a randomized controlled trial that compared 4 mg of black cohosh extract (Remifemin®) taken twice daily vs. 0.625 mg of conjugated estrogens vs. placebo in 80 women with menopausal symptoms (Stoll, 1987). Outcome measures included Kupperman Index scores, anxiety as measured by the Hamilton Anxiety Scale (HAM-A), and proliferation of vaginal epithelium. After 12 weeks, all measures were significantly improved in the black cohosh group vs. placebo, with reported equivalence to conjugated estrogens. In a separate measure of the frequency of hot flashes, improvement in the black cohosh group was superior to estrogens or placebo, with a mean reduction in the black cohosh group from 4.9 to 0.7 hot flashes daily vs. 5.2 to 3.2 in the estrogen group (which was similar to placebo). Despite methodological weaknesses of this study, including incomplete descriptions of baseline patient characteristics, blinding, and randomization, the three-arm design and use of multiple outcome measures add strength to the results.
- Bebenek et al. conducted a randomized, blinded, controlled trial of *Cimicifuga racemosa* (CR BNO 1055) in early postmenopausal women on bone density, 10-year coronary heart disease risk, and menopausal symptoms ($N = 128$) (Bebenek et al., 2010). German women 48–55 years old were included in the study. Women were excluded if they were taking medications that may affect the results (contraceptives and glucocorticoids), had other diseases or a history of coronary heart disease or athletics, or were not in the time frame of 1–3 years after menopause. Women were assigned to three different groups: exercise program plus CR supplementation 40 mg daily, exercise, or wellness control for 12 months. However, women received the CR supplement for 3 months on, 3 months off, then

3 months on again, and discontinued it thereafter. Calcium and vitamin D was administered to all groups. Allergies, adverse effects, and toxic effects were not discussed. Dropouts were discussed. However, dropouts due to side effects of the CR supplement were not noted. The primary outcomes were bone mineral density and Wilson's 10-year coronary heart disease risk. Secondary endpoints were menopausal symptoms and body composition. Outcome measures were taken at baseline and 12 months. A significant difference in outcome measures was lacking due to CR supplementation. The trial did not clearly state if it was double-blinded. The placebo was not identical to the CR supplement, but based on a survey, the authors believed that blinding was successful. The supplement was administered for 3 months on and then off, which may not have been a long enough time period to demonstrate CR's effects. Also, the effects of CR may have been noted if outcome measures were monitored more frequently. However, 3 months of supplementation was compliant with the manufacturer's instructions. The study was also limited to German women, which may decrease its external validity. Further research is warranted.

- Bai et al. conducted a multicenter, randomized, double-blind study to assess the safety and efficacy of Remifemin® compared to tibolone for climacteric symptoms ($N = 180$) (Bai et al., 2009). Women aged 40–60 years were included in the trial. Further inclusion and exclusion criteria are pending translation. The Remifemin® group received 20 mg twice daily for 12 weeks. The primary outcome measure was change in Kupperman Menopausal Index total scores from baseline. Adverse effects and laboratory tests were monitored at 4 and 12 weeks to assess safety. A significant difference in total Kupperman Menopausal Index scores between the Remifemin® group and tibolone was lacking. Adverse effects were significantly lower in the Remifemin® group when compared to tibolone.
- Frei-Kleiner et al. conducted a randomized, placebo controlled, double-blind, multicenter, parallel-group study to assess the effect of black cohosh for the treatment of hot flashes in 129 pre- or postmenopausal women (Frei-Kleiner et al., 2005). Patients 45–60 years old who suffered from three or more hot flashes daily were randomized to receive one capsule of black cohosh (6.5 mg of dried rhizome extract) or a matched placebo capsule daily for 12 weeks. Prevalence and intensity of the adverse events did not differ in the two groups. Of the original 129 patients, five were excluded due to protocol violations, and two were not treated. Thus, 122 patients were included in the intention-to-treat population, of which 15 patients discontinued the study prematurely, but details were not discussed. The primary outcomes were weekly weighted scores of hot flashes and the Kupperman Index, and the secondary outcome was the Menopause Rating Scale. The primary efficacy analysis showed no superiority of black cohosh extract compared to placebo. However, in the subgroup of patients with a Kupperman Index score ≥ 20, a significant superiority regarding this index was demonstrated ($p < 0.018$). A decrease in Kupperman Index scores of 47% and 21% was observed in the black cohosh and placebo group, respectively. The weekly weighted scores of hot flashes ($p < 0.052$) and the Menopause Rating Scale ($p < 0.009$) showed similar results. The authors suggested that black cohosh may be effective in subpopulations, but not in a general intent-to-treat the population as a whole.

- Nappi et al. conducted a randomized equivalence trial to evaluate the efficacy of an isopropanolic aqueous extract of *Cimicifuga racemosa* (CR) vs. low-dose transdermal estradiol (TTSE2) in the treatment of menopausal symptoms ($N = 64$) (Nappi et al., 2005). The trial enrolled 64 subjects, aged 45–55 years, with a body mass index range of 19–27 kg/m^2. The inclusion criteria were menopausal symptoms for at least 6 months, a follicle-stimulating hormone (FSH) level >30 mIU/L, occurrence of five or more hot flashes daily, and an endometrium less than 5 mm thick. Exclusion criteria included the previous use of hormone therapy and presenting with conditions or using other therapies for which hormone therapy is contraindicated. Using a computer-generated numbers list, the subjects were randomized to receive doses of 40 mg of isopropanolic aqueous CR extract (Remifemin®, OmeoPiacenza, Italy) or 25 mcg of TTSE2 (Estraderm®, Novartis Farma, Italy) and 10 mg of dihydrogesterone (Dufaston®, Solvay, Italy). Isopropanolic aqueous CR extract was taken once daily for 3 months. TTSE2 was taken once weekly for 3 months, and dihydrogesterone was added daily for the last 12 days of the 3-month treatment period with TTSE2. Information regarding standardization was lacking with respect to the natural product preparation. One patient in the CR extracts group reported nausea. Information regarding toxic effects and interactions was lacking. One subject in the CR extract group dropped out of the study after 2 months due to nausea. In addition, four participants from the CR group and five participants from the low-dose TTSE2 group were excluded from the study after refusing to give a follow-up blood sample. Outcome measures included frequency of hot flashes and a Greene scale assessment of vasomotor symptoms. The Symptom Rating Test (SRT), blood sampling, and assessment of endometrial thickness were conducted at the end of the 3-month treatment period. Compared to baseline, both treatment groups showed a statistically significant reduction in the number of daily hot flashes ($p < 0.001$) and Greene scores ($p < 0.001$) after 1 month of therapy. These improvements remained throughout the 3 months of the study, but statistically significant between-group differences were lacking. Compared to baseline, treatment with CR resulted in statistically significant decreases in anxiety ($p < 0.001$) and depression ($p < 0.001$), but a statistically significant between-group difference compared to the TTSE2 group was lacking. A statistically significant effect of CR on urogenital symptoms was lacking. Compared to baseline, CR caused a statistically significant increase in HDL cholesterol (51.6 ± 1.8 to 53.1 ± 1.7 mg/dL, respectively; $p = 0.04$) and a statistically significant decrease in LDL cholesterol (153.8 ± 39.0 to 146.1 ± 34.4 mg/dL, respectively; $p = 0.003$). A statistically significant effect on other aspects of lipid profile, liver function, hormones, and endometrial thickness was lacking for the CR group. Limitations of this study include small population size, subjective primary outcome measures, and lack of blinding.
- Liske et al. sought to confirm the efficacy and safety of the currently recognized dose of *Cimicifuga racemosa* rhizome (40 mg daily) and to evaluate a higher dose and its associated physiological effects (Liske et al., 2002). The study was a randomized, controlled, double-blinded, parallel-group study of 150 peri- and postmenopausal women treated with two different doses (39 mg and 127.3 mg) of a unique *C. racemosa* preparation over a 24-week period. Efficacy and tolerability

were determined by the Kupperman Menopausal Index, Self-Rating Depression Scale (SDS), a global assessment of tolerability, adverse events, routine hematology, and biochemical tests. Both peri- and postmenopausal patients tolerated the treatment well, and menopausal symptoms decreased regardless of dose (responder rate: 70% and 72%, respectively). The lack of change in vaginal cytology measures indicates a nonestrogenic effect of the tested extract in this organ. Likewise, the lack of significant changes in the levels of gynecologically relevant hormones does not indicate an overall estrogenic effect. The higher dose did not exert a significantly greater effect on any endpoint. Thus, the currently recognized standard dose of the isopropanolic aqueous *C. racemosa* extract should be preferred over the higher dose. Although this report suggests equal efficacy of the two doses of black cohosh, the lack of placebo weakens the results; benefits over time due to the natural history of menopausal symptoms to fluctuate cannot be ruled out as causative. Although no power calculation was conducted, the sample size was likely adequate to detect between-group differences.

- Oktem et al. conducted a randomized equivalence study to assess the effect of fluoxetine or black cohosh on 120 women with postmenopausal symptoms (Oktem et al., 2007). Women were included if they had at least one year of amenorrhea and FSH levels >40 mIU/mL. Subjects received either fluoxetine (Prozac® 20 mg per tablet; Lilly, Indianapolis, IN; $N = 60$) or black cohosh (Remixin®, 40 mg per tablet, Mikro-Gen, Istanbul, Turkey; $N = 60$) for 6 months. Fluoxetine is not U.S. Food and Drug Administration (FDA) approved for menopausal symptoms. However, a number of studies have been conducted investigating the use of antidepressants for the reduction of hot flashes. The primary endpoints for this study were assessed by the modified Kupperman Index and monthly hot flash scores using daily diaries, and patients were examined in months 1, 2, 3, and 6. Additionally, Beck's Depression Scale and a RAND-36 Quality of Life Questionnaire were used. There were seven adverse effects noted in the black cohosh group: dyspeptic problems (two out of 40), constipation (two out of 40), tiredness (one out of 40), allergic skin reactions (one out of 40), and irritability (one out of 40). Of the reported adverse effects, black cohosh had statistically fewer effects than fluoxetine ($p < 0.001$). At month 3, the black cohosh group had significantly lower Kupperman Index scores compared to the fluoxetine group ($p = 0.02$), but the fluoxetine group had significantly decreased Beck's Depression Scale scores compared to the black cohosh group ($p = 0.01$). At the sixth month, both groups showed reduced hot flashes and night sweats when compared to baseline, but when comparing black cohosh vs. fluoxetine, black cohosh had a hot flash score that was reduced by 85%, whereas the fluoxetine group's score was reduced by 62% ($p < 0.001$). A significant difference was not observed between groups in quality in life. This study was limited by its lack of description of blinding; it also had a high number of dropouts ($N = 40$, 33%).
- Lehmann-Willenbrock and Riedel conducted a 6-month randomized, nonblinded study that randomized 60 women younger than 40 years old who had undergone hysterectomy (but were left with at least one ovary) to receive either black cohosh (two tablets of 20 mg of Remifemin® twice daily), estriol (1 mg daily), conjugated estrogens (1.25 mg once daily), or an estrogen–progestin combination (one tablet of unclear dosage daily) (Lehmann-Willenbrock &

Riedel, 1988). Notably, subjects were not cancer patients, and they had undergone hysterectomy for nonmalignant conditions. Subjects were all experiencing menopausal symptoms prior to the study. Outcome measures included a modified Kupperman Index (a sum score of menopausal symptoms), as well as serum LH and FSH levels. Assessment at 1, 2, 3, and 6 months found improvements on the Kupperman Index to be comparable in all groups. The Kupperman Index score was noted to decrease in all groups by at least 50% vs. baseline (more in the conjugated estrogen and estrogen–progestin groups, without statistical significance). FSH and LH levels decreased in all hormonal replacement groups, but not in the black cohosh group. These results are compromised by the lack of a placebo group, poor description of baseline patient characteristics, and unclear procedures for blinding or randomization. The small sample size despite multiple subgroups, without a power calculation to determine adequate sample size, leaves open the possibility that results are due to lack of statistical power, rather than true equivalence of therapies.

- Studies of lesser design strength (not included in the Evidence Table): Julia Molla et al. conducted a prospective observation study in postmenopausal Spanish women to assess the effects of *Cimicifuga racemosa* on health-related quality of life ($N = 122$) (Julia Molla et al., 2009). Women aged 45–59 years that were considered overweight but otherwise healthy were included in the trial. *Cimicifuga racemosa* was administered at a dose of 20 mg twice daily for 3 months. Adverse effects were not discussed in the study. All participants completed the trial. The primary outcome measure was the Cervantes health-related quality of life scale. This scale includes 31 items, answered as a self-questionnaire, in four categories. The four categories were menopause and health, psychical domain, sexuality, and couple relationship. Women were also broken into three age groups; 45–49, 50–54, and 55–59. Significant results were seen in total Cervantes global scale ($p < 0.001$). Significant results were also reported for the menopause and health domain and the psychic domain for all age groups ($p < 0.001$). A significant result was reported for total sexuality domain (<0.5), but not when the age groups were analyzed individually. Significant results were lacking for the couple relationship domain.
- Briese et al. conducted a controlled, open-label observational study to assess the effect of Remifemin® Plus vs. Remifemin® on menopausal symptoms in 6,141 female patients (Briese et al., 2007). Women with menopausal symptoms were included, but patients taking any of the study medication during the previous 6 months or hormone therapy during the previous 4 weeks were excluded. The doses for the study medications were one tablet of Remifemin® twice daily or 1–2 tablets of Remifemin® Plus daily. Dosing and treatment was left to the discretion of the treating physician; both tablet and solution forms were administered. Remifemin® contains black cohosh, and Remifemin® Plus contains black cohosh plus St. John's wort. One case of allergic rhinitis occurred. Rare reports of mild gastrointestinal complaints, skin complaints, and a case of bleeding of a uterine myomatosis were also reported. A total of 768 subjects dropped out or were terminated from the study (13%). Primary outcomes were the Menopause Rating Scale (MRS) and the PSYCHE score at month 3 evaluated by ANCOVA.

Follow-up was conducted at 6 months and optionally at 12 months. The authors reported significant ($p < 0.001$) improvement in symptoms compared to the baseline for both groups [from 0.37 (adjusted) to 0.25 (95% CI: 0.24–0.25) and 0.23 (95% CI: 0.22–0.23), respectively]. This improvement was maintained at months 6 and 12. This study is limited by a lack of randomization, placebo group, and blinding. The ability of individual physicians to recommend therapies introduces possible bias into the results, making conclusions about efficacy difficult to determine. During the study, 331 subjects changed treatment. Additional research using a placebo group would be helpful.

- Raus et al. conducted a prospective, open-label, multinational, multicenter study to investigate endometrial safety by assessment of endometrial biopsy samples and the tolerability and efficacy of the special Actaea or *Cimicifuga racemosa* extract (CR BNO 1055, Klimadynon®/Menofem®, Bionorica AG, Newmarkt, Germany) (Raus et al., 2006). Four hundred postmenopausal women with symptoms related to estrogen deficiency were enrolled. Treatment duration (daily dose corresponding to 40 mg of herbal drug) was 52 weeks. The study medication was manufactured according to good manufacturing practice, although the authors noted that each tablet (batch no. 2471502) contained variable (1.66–2.86 mg) amounts of native extract. To determine the probability of endometrial hyperplasia and more serious adverse endometrial outcome, the point estimator and upper limit of 95% CI were calculated. Descriptive statistics were used to assess the secondary endpoints. Endometrial safety has been proven because no case of hyperplasia or more serious adverse endometrial outcome occurred (point estimate: 0.0; upper limit of 95% CI: 0.011). Endometrial thickness, which was measured by endovaginal ultrasonography, did not show an increase. The number and intensity of hot flashes were markedly decreased. The dropout rate was less than 10%. The overall tolerability was good. The lack of endometrial proliferation and improvement of climacteric complaints as well as a few gynecologic organ-related adverse events were reported for the first time after a treatment period of one year. Although this study shows the possible safety of extract CR BNO 1055, no randomization or blinding was used in this study to give support to any effectiveness found.
- Vermes et al. conducted a case studying 2,016 women with moderate-intensity menopausal symptoms to evaluate the effectiveness of *Cimicifuga racemosa* on the subjective symptoms of menopause (Vermes et al., 2005). All participants took two Remifemin® tablets daily without food for 12 weeks and were asked not to make any lifestyle changes during the study period. The primary outcome measure was Kupperman Index score, an assessment of 10 menopausal symptoms (hot flashes, night sweats, insomnia, anxiety, depression, vertigo, lack of concentration, arthralgia/myalgia, headache, and palpitation) where each symptom is rated with a score of 0 to 3 (0 = no symptom, 3 = severe symptom). The total menopause index was calculated at the end of each 4-week period. Of the 2,016 questionnaires returned, 1,876 were complete and eligible for evaluation. Total Kupperman Index scores decreased by 8.12 points (29%) in the first 4 weeks. Scores decreased by an additional 5.56 points (27.9%) in the second 4 weeks and 3.96 points in the last four weeks, for a total of 17.64 points over 12 weeks of treatment. *Cimicifuga racemosa* had the highest efficacy in decreasing the

severity of hot flashes, producing a decrease of 6.32 points in the weighted score. Night sweats decreased 2.86 weighted points. Insomnia decreased 2.27 points, and anxiety decreased 2.0 points, both of which were noted as being significant ($p < 0.001$). Palpitations decreased 0.84 points, depression decreased 0.72 points, and headache decreased 0.69 points. Vertigo, lack of concentration, and myalgia decreased <0.5 points. The authors discussed several limitations to their study. For example, this was not a placebo controlled trial, to allow for comparative analysis. The authors reported that *Cimicifuga racemosa* showed great drug tolerability, according to the patients, and demonstrated few adverse effects.

- Pockaj et al. conducted a pilot study of 21 women to estimate the effectiveness of black cohosh to reduce hot flashes (Pockaj et al., 2004). Women who reported significant hot flashes (≥14 per week) were enrolled. Black cohosh was given in the form of the commercial product Remifemin®. The first week was a no-treatment baseline period, and therapy was given for the subsequent 4 weeks. Hot flash data were collected by daily questionnaires during baseline and treatment weeks. Adverse effects were recorded. Twenty-one women completed the study. Their mean age was 56 years (range: 38–80). Thirteen patients had a history of breast cancer. Six patients were taking tamoxifen or raloxifene. Patients reported an average of 8.3 hot flashes daily during the baseline week. The reduction in mean daily hot flash frequency was 50% (95% CI: 34–65%), while weekly hot flash scores were reduced 56% (95% CI: 40–71%) at completion of the study. Overall, patients reported less trouble with sleeping, less fatigue, and less abnormal sweating. No patients stopped therapy because of adverse effects. Black cohosh appeared to reduce hot flashes and had a low toxicity. The efficacy found in this trial seems to be more than would be expected by a placebo effect (20–30% hot flash reduction in previous trials). The authors concluded that further evaluation of this black cohosh preparation with a phase III randomized trial is indicated.
- In a published conference abstract, Liske and Wüstenberg reported a comparison of two doses of an isopropanolic extract of black cohosh (Liske & Wstenberg, 1998). Menopausal women ($N = 152$, aged 43–60 years) were randomized to receive either 40 mg or 127 mg of black cohosh daily for 6 months. Improvements on the Kupperman Index were reported after 2 weeks in both groups. After 6 months, the groups were found to have similar results on the Kupperman Index (with 90% of subjects in both groups improving), without changes in either group in levels of LH, FSH, or prolactin, and without changes in vaginal epithelial proliferation. As a published conference abstract, the descriptions of methodology were limited.
- Petho conducted a controlled pilot study and an open study to assess the effects of black cohosh supplementation (Remifemin®) on menopausal symptoms in patients undergoing parenteral therapy due to severe symptoms (Petho, 1987). In the pilot study, all 26 patients received the first Gynodian injection at the beginning of therapy and a second injection 4 weeks later. Additional injections were given as needed for the next 4 months. Thirteen of the subjects were given two tablets of Remifemin® twice daily. This group received fewer Gynodian injections with longer intervals between the injections. In the 6-month open study, the 50 subjects were pretreated with one or two Gynodian® injections. All

patients were requested to try Remifemin®, but to feel free to return to the doctor for additional injections. By the end of the study, 21 of the patients received one Gynodian® injection (one patient received two). During the first 2 months, six injections were given. From month 2 to month 4, nine injections were given. From month 4 through month 6, eight injections were given. Twenty-eight of the subjects did not receive any injections. The Kupperman Menopausal Index significantly decreased, from 17.6 after the first injection to 9.2 after 6 months ($p < 0.001$). There were no side effects associated with Remifemin®, and there were no dropouts. Weaknesses of the study include a lack of blinding, randomization, and control.

- In a nonblinded study of 60 women with menopausal symptoms, Warnecke compared black cohosh (40 drops of Remifemin® liquid twice daily, standardized to 27-deoxyactein) vs. 0.625 mg of conjugated estrogens daily vs. 2 mg of the benzodiazepine diazepam daily (Warnecke, 1985). Outcome measures included the Kupperman Menopausal Index, the Hamilton Anxiety Scale (HAM-A), the Clinical Global Impressions (CGI) scale, and a patient self-assessment scale for depression. After 12 weeks, statistically significant improvements were noted in both groups in Kupperman, HAM-A, and self-assessment scores, without differences between groups. Nonsignificant improvements were noted in CGI scores in both groups. Although this is suggestive, the lack of placebo group or blinding allows for the influence of bias and confounders. The results may reflect the natural history of menopausal symptoms, rather than the benefits of therapy.
- In a case series, 40 drops of Remifemin® (standardized to 27-deoxyactein) was administered daily for 6–8 weeks to 629 women with menopausal symptoms (Stolze, 1982). Primary outcome measures included diaphoresis, hot flashes, headache, palpitations, and anxiety. After 4 weeks, 80% of subjects were reported to have experienced symptomatic relief. Although this is suggestive, this study is limited by the lack of a control group. The observed improvements may therefore reflect the natural history of menopausal symptoms to fluctuate, or may have been confounded by a "placebo effect" (rather than effects of black cohosh).
- Two case series with similar designs have been reported from gynecology practices (Daiber, 1983; Vorberg, 1984). In combination, 86 cases were presented of women treated with Remifemin® liquid, 40 drops twice daily for approximately 3 months. Improvements were reported in Kupperman Menopausal Index scores, and in Clinical Global Impressions (CGI) scores. Although this is suggestive, the short duration and lack of controls weakens these results.
- Select combination studies (not included in the Evidence Table): Sun et al. conducted a study to determine the efficacy of a morning and evening menopause formula (the morning capsule contained Panax ginseng, black cohosh, soy, and green tea extracts; the evening capsule contained black cohosh, soy, kava, hops, and valerian extracts) for relieving menopausal symptoms such as hot flashes and sleep disturbances (Li et al., 2003). Seventy-two healthy postmenopausal women, 45–65 years of age, were asked to take the menopause formula orally, one capsule of the morning formula every morning and one capsule of the evening formula every evening for two months. The Greene Climacteric Scale (GCS) and the Pittsburgh Sleep Quality Index (PSQI) were used to determine the efficacy.

Morning and evening menopause formulas significantly reduced the number of hot flashes. The reduction in the number of hot flashes was observed as early as at the end of the second week. At the end of the second week, the number of hot flashes was reduced by 47%. The morning and evening menopause formulas also significantly reduced the GCS total and subscale scores. At the end of the eighth week, the vasomotor, anxiety, and depression scores of GCS were reduced by 50%, 56%, and 32%, respectively. Furthermore, the morning and evening menopause formulas significantly reduced global PSQI score and scores in five components (sleep quality, sleep latency, sleep duration, sleep disturbance, and daytime dysfunction), by 18–46%. The authors concluded that the morning and evening menopausal formulas are safe and effective for relieving menopausal symptoms, including hot flashes and sleep disturbances. However, because a combination product was used in this study, the effects of black cohosh alone are unclear.

- Boblitz et al. conducted a double-blind, randomized, placebo controlled trial of Remifemin® Plus, a fixed combination of St. John's wort (Hypericum perforatum) and black cohosh (Boblitz et al., 2000). In this study, 179 patients with complaints associated with menopause were treated with two capsules given together once daily of either Remifemin® Plus or placebo. The Kupperman Index of those ingesting Remifemin® Plus decreased from 31.4 to 18.7 compared with a decrease in the placebo group from 30.3 to 22.3 ($p < 0.001$). Psychological parameters also significantly improved in the Remifemin® Plus group. However, it is not possible to separate the possible effects of black cohosh from St. John's wort, which has been found to improve symptoms of mild-to-moderate depression and may exert influence on Kupperman measures. As a published conference abstract, this report included limited descriptions of baseline patient characteristics and methods.
- Chung et al. conducted a double-blind randomized, placebo controlled study to assess the effect of black cohosh (*Cimicifuga racemosa*) and St. John's wort (Hypericum perforatum) on climacteric symptoms (Chung et al., 2007). Peri- or postmenopausal women experiencing climacteric symptoms were included in this study; women with breast cancer, undiagnosed uterine bleeding, cardiovascular or cerebrovascular diseases, or other diseases that might cause hot flashes were excluded. A total of 89 Korean subjects were randomized to receive one 264 mg tablet of GYNO-Plus® (Jin-Yang Pharm., Seoul, Korea), which contained St. John's wort and black cohosh extract, or a matched placebo for 12 weeks. Of the original 89 subjects, 42 subjects in the GYNO-Plus® group and 35 subjects in the placebo group completed the study. Five patients dropped out in the treatment group (three for gastrointestinal troubles, one for chest discomfort, and one for personal reasons), and seven patients discontinued in the placebo group (two for gastrointestinal troubles, one for generalized ache, and five for personal reasons). The most common adverse effects were gastrointestinal complaints (12.8% in the treatment group, six out of 47, vs. 9.5% in the placebo group, four out of 42). The primary outcome was climacteric symptoms assessed using the Kupperman Index. Additional outcomes included vaginal maturation indices, and serum estradiol, FSH, LH, total cholesterol, HDL cholesterol, LDL cholesterol, and triglyceride levels, which were all measured at baseline, 4 weeks, and 12 weeks.

The Kupperman Index scores were significantly lower at weeks 4 and 12 in the GYNO-Plus® group, compared to the placebo group (week 4: 12.46 ± 6.96 vs. 19.63 ± 11.09, $p = 0.002$; week 12: 6.37 ± 4.16 vs. 17.14 ± 11.61, $p < 0.001$). HDL levels also significantly increased in the treatment group (from 58.32 ± 11.64 to 59.74 ± 10.54; $p = 0.04$) compared to the control (from 60.20 ± 16.37 to 56.63 ± 12.67). Power calculations were conducted. Additional research investigating individual herbs alone would help ascertain the effectiveness of this preparation.

- Rotem et al. conducted a randomized, double-blind, placebo controlled trial to assess the effects of Phyto-Female Complex on menopausal symptoms (Rotem & Kaplan, 2007). Fifty healthy pre- and postmenopausal women who had FSH levels >30 mcg/mL and amenorrhea for at least six months were randomized to receive Phyto-Female Complex (SupHerb, Netanya, Israel) or a matched placebo orally twice daily for three months. Phyto-Female Complex is a standardized extract of black cohosh, dong quai, milk thistle, red clover, American ginseng, and chaste-tree berry, which is prepared according to good manufacturing practice (GMP) standards. Six women were withdrawn from the study due to missing data, and nine withdrew due to lack of compliance or desire to voluntarily discontinue participation. Primary outcomes of menopausal symptoms were measured using a structured questionnaire on the frequency and intensity of menopausal symptoms (administered weekly), biochemical tests, breast check, and transvaginal ultrasonography. The Phyto-Female Complex group reported a 25% reduction in hot flashes and 23% reduction in night sweats compared with the placebo group (8% and 15%, respectively) starting at week 2 ($p = 0.044$ and $p = 0.037$). Improvements in menopausal symptoms increased over time in the Phyto-Female Complex group; by three months, there was a 73% decrease in hot flashes (35% in placebo group; $p = 0.026$) and a 69% reduction of night sweats (29% in placebo group; $p = 0.027$), accompanied by a decrease in their intensity and a significant benefit in terms of sleep quality. In 47% of Phyto-Female Complex subjects, hot flashes completely stopped, compared with 19% in the placebo group. No changes were noted on vaginal ultrasonography, estradiol levels, follicle-stimulating hormone levels, liver enzymes, or thyroid-stimulating hormone levels in either group. This study had a large (30%) dropout rate, and randomization was not fully described. Additional research using black cohosh alone would help elucidate its role in reducing menopausal symptoms.
- Uebelhack et al. conducted a randomized, double-blind, placebo controlled study to investigate the efficacy of a fixed combination of black cohosh (*Cimicifuga racemosa*) and St. John's wort (Hypericum perforatum) extracts in 301 women 45–60 years old with climacteric complaints with a pronounced psychological component (Uebelhack et al., 2006). Subjects had to have climacteric complaints for at least 3 months, no treatment for the symptoms for 2 months, a Menopause Rating Scale score of 0.4 or more in at least three areas, a Hamilton Depression Rating Scale Total Score of 15–23 points, and a Hamilton Depression Rating Scale item 1 of two points or more. Exclusion criteria included any treatment for climacteric symptoms, treatment with antiepileptics, psycholeptics, or psychoanaleptics in the previous 12 weeks, severe diseases, a risk of suicide, or a score of two or more on the Hamilton Depression Rating scale item 3. The primary outcome measure was a decrease of the overall Menopause Rating Scale

score. Treatment subjects ($N = 151$) took two tablets orally twice daily (weeks 1–8) and one tablet orally twice daily to week 16. Each tablet contained black cohosh extract standardized to 1 mg of triterpene glycosides and St. John's wort extract standardized to 0.25 mg of total hypericin. The placebo ($N = 150$) group followed the same schedule but received placebo medication. A total of 14 subjects dropped out of the study (explanations given). The authors presented the intent-to-treat statistics. The mean (± standard deviation) Menopause Rating Scale score decreased 50% (0.46 ± 0.13 to 0.23 ± 0.13) in the treatment group and 19.6% (0.46 ± 0.14 to 0.37 ± 0.15) in the placebo group. The Hamilton Depression Rating Scale total score decreased 41.8% in the treatment group (18.9 ± 2.2 to 11.0 ± 3.8 points) and 12.7% in the placebo group (18.9 ± 2.1 to 16.5 ± 4.3). The treatment was significantly ($p < 0.001$) superior to placebo in both measures. There were no relevant group differences regarding adverse events, laboratory values, or tolerability. The authors reported that this fixed combination of black cohosh and St. John's wort is superior to placebo in alleviating climacteric complaints, including the related psychological component. However, this study used a combination product, and it is difficult to determine the effects of black cohosh alone in alleviating symptoms.

- Van Der Sluijs et al. conducted a randomized, double-blind, placebo controlled trial on the effects of an herbal formula containing *Cimicifuga racemosa* on quality of life and vasomotor symptoms in postmenopausal women ($N = 93$) (van der Sluijs et al., 2009). Women aged 45–65 were included in the trial if they reported five or more vasomotor symptoms per week and were otherwise healthy. Women received a mix of eight chines herbs, including *Cimicifuga racemosa* at a dose of 350 mg. Doses were administered twice daily, two hours after a meal or 30 minutes prior, for 16 weeks. The *Cimicifuga racemosa* was standardized to contain 2.5% triterpene glycosides as 27-deoxyactein. Headaches and gastrointestinal upset were the most frequently reported adverse effects in the treatment group. Liver and kidney tests did not report any abnormal values. The primary outcome measures were hot flashes. Secondary outcome was improvement in quality of life. Liver and kidney function, blood counts, and estradiol and follicle-stimulating hormone levels were also monitored. Significant results were lacking for the primary outcome or secondary outcome measures. Further trials using black cohosh alone are warranted.
- Verhoven et al. conducted a randomized, placebo controlled, double-blind trial on the effects of *Actaea racemosa* Linneaus and isoflavone on vasomotor symptoms in postmenopausal women ($N = 124$) (Verhoeven et al., 2005). Women aged 45–65 that experienced at least 35 hot flashes per week but were otherwise healthy were included in the trial. Women using other medications or supplements were allowed a 6-week washout period. Women received 125 mg of soy, 1,500 mg of evening primrose oil, 200 mg of calcium, 1.25 mcg of vitamin D, 10 IU of vitamin E, and 100 mg of *Actaea racemosa* Linneaus standardized to 8 mg of deoxyacetein daily in two capsules twice daily, after morning and evening meals, for 12 weeks. One woman in the supplement group withdrew due to weight gain and edema. Liver and kidney function was not altered. A difference in adverse effects between the groups was lacking. The primary outcome was change in

climacteric symptoms as determined by Kupperman Index (KI) after 12 weeks. Secondary out comes were KI scores after 6 weeks, the frequency and severity of hot flashes, quality of life, and Greene Climacteric Scale scores. A significant difference between groups was lacking. This was a well-designed trial. However, the lack of difference cannot be attributed to black cohosh alone. Further studies are warranted.

Migraine

- Summary: According to Burke et al., approximately 30% of women afflicted with migraine have migraines associated with menstruation (Burke et al., 2002). These migraines are often refractory to treatment. Evidence suggests that estrogen and progestin fluctuations may influence menstrual migraine. Phytoestrogens have demonstrated estrogenic effects in some tissues, but they do not stimulate the endometrium, suggesting a decreased risk with long-term use. One study using a combination treatment including black cohosh found the combination effective, although the effects cannot be attributed to black cohosh alone. Additional research is warranted in this area.
- Select combination studies (not included in the Evidence Table): Burke et al. conducted a randomized, placebo controlled study to assess the efficacy of a phytoestrogen combination in the prophylactic treatment of menstrual migraine (Burke et al., 2002). Forty-nine patients were randomized to receive either placebo, or a daily combination of 60 mg soy isoflavones, 100 mg of dong quai, and 50 mg of black cohosh, with each component standardized to its primary alkaloid. Patients received study medication for 24 weeks. Average frequency of menstrually associated migraine attacks during weeks 9–24 was reduced from 10.3 ± 2.4 (mean $\pm$ s.e.m.) in placebo-treated patients to 4.7 ± 1.8 ($p < 0.01$) in patients treated with the phytoestrogen preparation. The effects cannot be attributed to black cohosh alone.

BRANDS USED IN CLINICAL TRIALS/THIRD-PARTY TESTING

- Reumalex® (Mills et al., 1996).
- Remifemin® (originally manufactured by Schaper & Brümmer; now manufactured and distributed by GlaxoSmithKline) (Pockaj et al., 2004; Vermes et al., 2005).
- Remixin® (Mikro-Gen, Istanbul, Turkey) (Oktem et al., 2007).
- CR BNO 1055 (Menofem®/Klimadynon®) (Wuttke et al., 2003).
- Other trade names: Biophylin®, Black Cohosh liquid extract (Bio-pro), Black Cohosh Root Powder (Global Botanical), CimiPure®, Cimisan®, Femilla N®, Klimadyon®, Ligvites®, MenoFem®, Vegetex®.
- Combination products: Black Cohosh CX, Cimicifuga-Amyda-Shell Decoction, Estroven, FC with Dong Quai, GNC Menopause Formula, Natrol, Nature's Herbs, Qingwei san, Remifemin® Plus (black cohosh plus St. John's wort), Reumalex® (35 mg of black cohosh, 100 mg of white willow bark, 25 mg of sarsaparilla [4:1], 17 mg of poplar bark [7:1], and 40 mg of guaiacum resin), GYNO-Plus (black cohosh and St. John's wort), Phyto-Female Complex

(standardized extracts of black cohosh, dong quai, milk thistle, red clover, American ginseng, and chaste-tree berry).

Declaration of interest: The authors report no conflict of interest. The authors alone are responsible for the content and writing of this paper.

REFERENCES

Amsterdam JD, Yao Y, Mao JJ, Soeller I, Rockwell K, Shults J. Randomized, double-blind, placebo-controlled trial of *Cimicifuga racemosa* (black cohosh) in women with anxiety disorder due to menopause. J Clin Psychopharmacol. 2009;29(5):478–483.

Anderson IB, Mullen WH, Meeker JE, Khojasteh Bakht SC, Oishi S, Nelson SD, Blanc PD. Pennyroyal toxicity: measurement of toxic metabolite levels in two cases and review of the literature. Ann Intern Med 1996;124(8):726–734.

Antoine C, Liebens F, Carly B, Pastijn A, Rozenberg S. Safety of alternative treatments for menopausal symptoms after breast cancer: a qualitative systematic review. Climacteric. 2007;10(1):23–26.

Ashar BH, Rice TN, Sisson SD. Medical residents' knowledge of dietary supplements. South. Med J 2008;101(10):996–1000.

Bai W, Henneicke-von Zepelin HH, Wang S, Zheng S, Liu J, Zhang Z, Geng L, Hu L, Jiao C, Liske E. Efficacy and tolerability of a medicinal product containing an isopropanolic black cohosh extract in Chinese women with menopausal symptoms: a randomized, double blind, parallel-controlled study versus tibolone. Maturitas 2007;58(1):31–41.

Baillie N. Rasmussen P. Black and blue cohosh in labour. N.Z Med J 1997;110(1036):20–21.

Bai WP, Wang SY, Liu JL, Geng L, Hu LN, Zhang ZL, Chen SL, Zheng SR. Efficacy and safety of remifemin compared to tibolone for controlling of perimenopausal symptoms. Zhonghua Fu Chan Ke. Za Zhi. 2009;44(8):597–600.

Bebenek M, Kemmler W., von Stengel S, Engelke K, Kalender WA. Effect of exercise and *Cimicifuga racemosa* (CR BNO 1055) on bone mineral density, 10-year coronary heart disease risk, and menopausal complaints: the randomized controlled Training and Cimicifuga racemosa Erlangen (TRACE) study. Menopause. 2010;17(4):791–800.

Becker E, Letham T, Stoehr JD. Is black cohosh a safe and effective substitute for hormone replacement therapy? JAAPA. 2009;22(9):54–55.

Beck V, Unterrieder E, Krenn L, Kubelka W, Jungbauer A. Comparison of hormonal activity (estrogen, androgen and progestin) of standardized plant extracts for large scale use in hormone replacement therapy. J Steroid Biochem Mol Biol 2003;84(2–3):259–268.

Betz JM, Anderson L Avigan MI Barnes J Farnsworth NR Gerden B Henderson L Kennelly EJ Koetter U Lessard S Dog TL McLaughlin M Naser B Osmers RG Pellicore LS Senior JR van Breemen RB Wuttke W Cardellina JH. Black cohosh: considerations of safety and benefit. Nutrition Today 2009;44(4):155–162.

Beuscher N, Reichert R. *Cimicifuga racemosa* L.—black cohosh. Zeit Phytother 1995;16:301–310.

Boblitz N, Schrader E, Henneicke-von Zepelin HH, et al. Benefit of a fixed drug combination containing St. John's wort and black cohosh for climacteric patients—results of a randomised clinical trial (poster presentation from 6th Annual Symposium on Complementary Health Care, Exeter, England, December 2–4, 1999). Focus Alt Comp Ther (FACT) 2000;5(1):85–86.

Bodinet C, Freudenstein J. Influence of marketed herbal menopause preparations on MCF-7 cell proliferation. Menopause. 2004;11(3):281–289.

Booth NL, Nikolic D, van Breemen RB, Geller SE, Banuvar S, Shulman LP, Farnsworth NR. Confusion regarding anticoagulant coumarins in dietary supplements. Clin Pharmacol. Ther 2004;76(6):511–516.

Borrelli F, Ernst E. *Cimicifuga racemosa*: a systematic review of its clinical efficacy. Eur J Clin Pharmacol 2002;58(4):235–241.

Borrelli F, Ernst E. Black cohosh (*Cimicifuga racemosa*): a systematic review of adverse events. Am J Obstet. Gynecol. 2008a;199(5):455–466.

Borrelli F, Ernst E. Black cohosh (*Cimicifuga racemosa*) for menopausal symptoms: a systematic review of its efficacy. Pharmacol. Res 2008b;58(1):8–14.

Borrelli F, Ernst E. Alternative and complementary therapies for the menopause. Maturitas 2010;66(4):333–343.

Borrelli F, Izzo AA, Ernst E. Pharmacological effects of *Cimicifuga racemosa*. Life Sci. 2003;73(10):1215–1229.

Borrelli F, Mascolo N, Russo A, et al. *Cimicifuga racemosa*: a systematic review of its clinical and pharmacological effects. 8th Annual Symposium on Complementary Health Care, 6th-8th December 2001 2001

Brasky TM, Lampe JW, Potter JD, Patterson RE, White E. Specialty supplements and breast cancer risk in the VITamins And Lifestyle (VITAL) Cohort. Cancer Epidemiol Biomarkers Prev. 2010;19(7):1696–1708.

Briese V, Stammwitz U, Friede M, Henneicke-von Zepelin HH. Black cohosh with or without St. John's wort for symptom-specific climacteric treatment—results of a large-scale, controlled, observational study. Maturitas 2007;57(4):405–414.

Bruno D, Feeney KJ. Management of postmenopausal symptoms in breast cancer survivors. Semin. Oncol. 2006;33(6):696–707.

Buettner C, Mukamal KJ, Gardiner P, Davis RB, Phillips RS, Mittleman MA. Herbal supplement use and blood lead levels of United States adults. J Gen. Intern. Med 2009;24(11):1175–1182.

Burdette JE, Chen SN, Lu ZZ, Xu H, White BE, Fabricant DS, Liu J, Fong HH, Farnsworth NR, Constantinou AI, van Breemen RB, Pezzuto JM, Bolton JL. Black cohosh (*Cimicifuga racemosa* L.) protects against menadione-induced DNA damage through scavenging of reactive oxygen species: bioassay-directed isolation and characterization of active principles. J Agric. Food Chem 2002;50(24):7022–7028.

Burdette JE, Liu J, Chen SN, Fabricant DS, Piersen CE, Barker EL, Pezzuto JM, Mesecar A, van Breemen RB, Farnsworth NR, Bolton JL. Black cohosh acts as a mixed competitive ligand and partial agonist of the serotonin receptor. J Agric. Food Chem. 2003;51(19):5661–5670.

Burke BE, Olson RD, Cusack BJ. Randomized, controlled trial of phytoestrogen in the prophylactic treatment of menstrual migraine. Biomed. Pharmacother. 2002;56(6):283–288.

Carroll DG. Nonhormonal therapies for hot flashes in menopause. Am Fam. Physician 2006;73(3):457–464.

Centre for Reviews and Dissemination. Complementary and alternative therapies for the management of menopause-related symptoms: a systematic evidence review (Structured abstract), Archives of Internal Medicine, 2006;166(14):1453–1465.

Cheema D, Coomarasamy A, El Toukhy T. Non-hormonal therapy of post-menopausal vasomotor symptoms: a structured evidence-based review. Arch Gynecol. Obstet 2007;276(5):463–469.

Chen SN, Fabricant DS, Pauli GF, Fong HH, Farnsworth NR. Synthesis of cimiracemate B, a phenylpropanoid found in *Cimicifuga racemosa*. Nat Prod Res 2005;19(3):287–290.

Chen SN, Lankin DC, Nikolic D, Fabricant DS, Lu ZZ, Ramirez B., van Breemen RB, Fong HH, Farnsworth NR, Pauli GF. Chlorination diversifies *Cimicifuga racemosa* triterpene glycosides. J Nat Prod 2007;70(6):1016–1023.

Chitturi S, Farrell GC. Hepatotoxic slimming aids and other herbal hepatotoxins. J Gastroenterol. Hepatol. 2008;23(3):366–373.

Chow EC, Teo M, Ring JA, Chen JW. Liver failure associated with the use of black cohosh for menopausal symptoms. Med J Aust 2008;188(7):420–422.

Chung DJ, Kim HY, Park KH, Jeong KA, Lee SK, Lee YI, Hur SE, Cho MS, Lee BS, Bai SW, Kim CM, Cho SH, Hwang JY, Park JH. Black cohosh and St. John's wort (GYNO-Plus) for climacteric symptoms. Yonsei Med J 2007;48(2):289–294.

Cimicifuga racemosa Monograph. Altern. Med Rev 2003;8(2):186–189.

Cohen SM, O'Connor AM, Hart J, Merel NH, Te HS. Autoimmune hepatitis associated with the use of black cohosh: a case study. Menopause. 2004;11(5):575–577.

Cybulska P, Thakur SD, Foster BC, Scott IM, Leduc RI, Arnason JT, Dillon JA. Extracts of Canadian first nations medicinal plants, used as natural products, inhibit neisseria

gonorrhoeae isolates with different antibiotic resistance profiles. Sex Transm. Dis 2011;38(7): 667–671.

Daiber W. Menopause symptoms: success without hormones. Arztl Praxis 1983;35:1946–1947.

Davis VL, Jayo MJ, Ho A, Kotlarczyk MP, Hardy ML, Foster WG, Hughes CL. Black cohosh increases metastatic mammary cancer in transgenic mice expressing c-erbB2. Cancer Res 2008;68(20):8377–8383.

Davis SR, Lijovic M, Fradkin P, Bradbury J, La China M, Schwarz M, Bell RJ. Use of complementary and alternative therapy by women in the first 2 years after diagnosis and treatment of invasive breast cancer. Menopause. 2010;17(5):1004–1009.

Dennehy CE. The use of herbs and dietary supplements in gynecology: an evidence-based review. J Midwifery Womens Health 2006;51(6):402–409.

Dennehy C, Tsourounis C, Bui L, King TL. The use of herbs by California midwives. J Obstet. Gynecol. Neonatal Nurs. 2010;39(6):684–693.

Dixon-Shanies D, Shaikh N. Growth inhibition of human breast cancer cells by herbs and phytoestrogens. Oncol Rep. 1999;6(6):1383–1387.

Dog TL, Powell KL, Weisman SM. Critical evaluation of the safety of *Cimicifuga racemosa* in menopause symptom relief. Menopause. 2003;10(4):299–313.

Donnelly GF. Herbal efficacy: the case of black cohosh. Holist. Nurs Pract 2007;21(3):103.

Dugoua JJ, Seely D, Perri D, Koren G, Mills E. Safety and efficacy of black cohosh (*Cimicifuga racemosa*) during pregnancy and lactation. Can J Clin Pharmacol 2006;13(3):e257–e261.

Duker EM, Kopanski L, Jarry H, Wuttke W. Effects of extracts from *Cimicifuga racemosa* on gonadotropin release in menopausal women and ovariectomized rats. Planta Med 1991;57(5):420–424.

Dunbar K, Solga SF. Black cohosh, safety, and public awareness. Liver Int. 2007;27(7):1017–1018.

Ehrlich M, Rao J, Pabby A, Goldman MP. Improvement in the appearance of wrinkles with topical transforming growth factor beta(1) and l-ascorbic acid. Dermatol. Surg 2006;32(5): 618–625.

Einbond LS, Shimizu M, Ma H, Wu HA, Goldsberry S, Sicular S, Panjikaran M, Genovese G, Cruz E. Actein inhibits the Na+-K+-ATPase and enhances the growth inhibitory effect of digitoxin on human breast cancer cells. Biochem. Biophys. Res Commun. 2008;375(4):608–613.

Einbond LS, Shimizu M, Nuntanakorn P, Seter C, Cheng R, Jiang B, Kronenberg F, Kennelly EJ, Weinstein IB. Actein and a fraction of black cohosh potentiate antiproliferative effects of chemotherapy agents on human breast cancer cells. Planta Med 2006;72(13):1200–1206.

Einbond LS, Shimizu M, Xiao D, Nuntanakorn P, Lim JT, Suzui M, Seter C, Pertel T, Kennelly EJ, Kronenberg F, Weinstein IB. Growth inhibitory activity of extracts and purified components of black cohosh on human breast cancer cells. Breast Cancer Res Treat. 2004;83(3):221–231.

Einbond LS, Soffritti M, Esposti DD, Park T, Cruz E, Su T, Wu HA, Wang X, Zhang YJ, Ham J, Goldberg IJ, Kronenberg F, Vladimirova A. Actein activates stress- and statin-associated responses and is bioavailable in Sprague-Dawley rats. Fundam. Clin Pharmacol. 2009;23(3):311–321.

Einbond LS, Su T, Wu HA, Friedman R, Wang X, Jiang B, Hagan T, Kennelly EJ, Kronenberg F, Weinstein IB. Gene expression analysis of the mechanisms whereby black cohosh inhibits human breast cancer cell growth. Anticancer Res 2007a;27(2):697–712.

Einbond LS, Su T, Wu HA, Friedman R, Wang X, Ramirez A, Kronenberg F, Weinstein IB. The growth inhibitory effect of actein on human breast cancer cells is associated with activation of stress response pathways. Int J Cancer 2007b;121(9):2073–2083.

Einer-Jensen N, Zhao J, Andersen KP, Kristoffersen K. Cimicifuga and Melbrosia lack oestrogenic effects in mice and rats. Maturitas 1996;25(2):149–153.

Ernst E, Chrubasik S. Phyto-anti-inflammatories. A systematic review of randomized, placebo-controlled, double-blind trials. Rheum. Dis Clin North Am 2000;26(1):13–27, vii.

Frei-Kleiner S, Schaffner W, Rahlfs VW, Bodmer Ch, Birkhauser M. *Cimicifuga racemosa* dried ethanolic extract in menopausal disorders: a double-blind placebo-controlled clinical trial. Maturitas 2005;51(4):397–404.

Freudenstein J, Bodinet C. *Influence of an isopropanolic aqueous extract of Cimicifuga racemosae rhizoma on the proliferation of MCF-7 cells*. 23rd International LOF-Symposium on Phytoestrogens, University of Ghent, Belgium (January 15, 1999).

Fuchikami H, Satoh H, Tsujimoto M, Ohdo S, Ohtani H, Sawada Y. Effects of herbal extracts on the function of human organic anion-transporting polypeptide OATP-B. Drug Metab Dispos. 2006;34(4):577–582.

Fugh-Berman A. "Bust enhancing" herbal products. Obstet. Gynecol. 2003;101(6):1345–1349.

Fugh-Berman A, Ernst E. Herb-drug interactions: review and assessment of report reliability. Br J Clin Pharmacol 2001;52(5):587–595.

Garcia-Perez MA, Pineda B, Hermenegildo C, Tarin JJ, Cano A. Isopropanolic *Cimicifuga racemosa* is favorable on bone markers but neutral on an osteoblastic cell line. Fertil. Steril. 2009;91(4 Suppl):1347–1350.

Garita-Hernandez M, Calzado MA, Caballero FJ, Macho A, Munoz E, Meier B, Brattstrom A, Fiebich BL, Appel K. The growth inhibitory activity of the *Cimicifuga racemosa* extract Ze 450 is mediated through estrogen and progesterone receptors-independent pathways. Planta Med 2006;72(4):317–323.

Geller SE, Shulman LP, van Breemen RB, Banuvar S, Zhou Y, Epstein G, Hedayat S, Nikolic D, Krause EC, Piersen CE, Bolton JL, Pauli GF, Farnsworth NR. Safety and efficacy of black cohosh and red clover for the management of vasomotor symptoms: a randomized controlled trial. Menopause. 2009;16(6):1156–1166.

Geller SE, Studee L. Contemporary alternatives to plant estrogens for menopause. Maturitas 2006;55 Suppl 1:S3–13.

Genazzani E, Sorrentino L. Vascular action of acteina: active constituent of *Actaea racemosa* L. Nature 1962;194(4828):544–545.

Gingrich PM, Fogel CI. Herbal therapy use by perimenopausal women. J Obstet. Gynecol. Neonatal Nurs. 2003;32(2):181–189.

Goda Y. Safety of health foods and importance of their origin. Yakugaku Zasshi 2008;128(6):837–838.

Godecke T, Nikolic D, Lankin DC, Chen SN, Powell SL, Dietz B, Bolton JL, van Breemen RB, Farnsworth NR, Pauli GF. Phytochemistry of cimicifugic acids and associated bases in *Cimicifuga racemosa* root extracts. Phytochem. Anal. 2009;20(2):120–133.

Gori L, Firenzuoli F. Is black cohosh a hepatotoxic medicinal herb? Forsch Komplement. Med (2006.) 2007;14(2):109–110.

Grippo AA, Hamilton B, Hannigan R, Gurley BJ. Metal content of ephedra-containing dietary supplements and select botanicals. Am J Health Syst. Pharm 2006;63(7):635–644.

Gunn TR, Wright IM. The use of black and blue cohosh in labour. N.Z Med J 1996;109(1032):410–411.

Gurley BJ, Barone GW, Williams DK, Carrier J, Breen P, Yates CR, Song PF, Hubbard MA, Tong Y, Cheboyina S. Effect of milk thistle (*Silybum marianum*) and black cohosh (*Cimicifuga racemosa*) supplementation on digoxin pharmacokinetics in humans. Drug Metab Dispos. 2006;34(1):69–74.

Gurley BJ, Gardner SF, Hubbard MA, Williams DK, Gentry WB, Khan IA, Shah A. In vivo effects of goldenseal, kava kava, black cohosh, and valerian on human cytochrome P450 1A2, 2D6, 2E1, and 3A4/5 phenotypes. Clin. Pharmacol. Ther. 2005;77(5):415–426.

Gurley B, Hubbard MA, Williams DK, Thaden J, Tong Y, Gentry WB, Breen P, Carrier DJ, Cheboyina S. Assessing the clinical significance of botanical supplementation on human cytochrome P450 3A activity: comparison of a milk thistle and black cohosh product to rifampin and clarithromycin. J Clin Pharmacol 2006;46(2):201–213.

Gurley BJ, Swain A, Hubbard MA, Williams DK, Barone G, Hartsfield F, Tong Y, Carrier DJ, Cheboyina S, Battu SK. Clinical assessment of CYP2D6-mediated herb-drug interactions in humans: effects of milk thistle, black cohosh, goldenseal, kava kava, St. John's wort, and Echinacea. Mol. Nutr Food Res 2008;52(7):755–763.

Guttuso T, Jr. Effective and clinically meaningful non-hormonal hot flash therapies. Maturitas 2012;72(1):6–12.

Hailemeskel B, Lee HJ, Thomhe H. Incidence of potential herb-drug interactions among herbal users. ASHP Midyear Clinical Meeting 2000;35:p-267e.

Haimov-Kochman R, Brzezinski A, Hochner-Celnikier D. Herbal remedies for menopausal symptoms: are we cautious enough? Eur. J Contracept. Reprod. Health Care 2008;13(2):133–137.

Hamburger M. New approaches in analyzing the pharmacological properties of herbal extracts. Proc. West Pharmacol. Soc 2007;50:156–161.

Hanna K, Day A O'Neill S Patterson C Lyons-Wall P. Does scientific evidence support the use of non-prescription supplements for treatment of acute menopausal symptoms such as hot flushes? Nutrition & Dietetics 2005;62(4):138–151.

Hardy ML. Herbs of special interest to women. J Am Pharm Assoc (Wash.) 2000;40(2):234–242.

Hemachandra LP, Madhubhani P, Chandrasena R, Esala P, Chen SN, Main M, Lankin DC, Scism RA, Dietz BM, Pauli GF, Thatcher GR, Bolton JL. Hops (*Humulus lupulus*) inhibits oxidative estrogen metabolism and estrogen-induced malignant transformation in human mammary epithelial cells (MCF-10A). Cancer Prev. Res (Phila) 2012;5(1):73–81.

Hemmi H, Kitame F, Ishida N, et al. Inhibition of thymidine transport into phytohemagglutinin-stimulated lymphocytes by triterpenoids from *Cimicifuga* species. J Pharm Dyn 1979;2:339–349.

Hemmi H, Kusano G, Ishida N. Selective inhibition of nucleoside transport into mouse lymphoma L- 5178Y cells by cimicfugoside. J Pharmacobiodyn. 1980;3(12):636–642.

Herbal Medicinal Products Committee. Assessment of case reports connected to herbal medicinal products containing cimicifugae racemosa rhizoma (black cohosh, root). 2007.

Hernandez Munoz G, Pluchino S. *Cimicifuga racemosa* for the treatment of hot flushes in women surviving breast cancer. Maturitas 2003;44 Suppl 1:S59–S65.

He K, Zheng B, Kim CH, Rogers L, Zheng Q. Direct analysis and identification of triterpene glycosides by LC/MS in black cohosh, *Cimicifuga racemosa*, and in several commercially available black cohosh products. Planta Med 2000;66(7):635–640.

Hirschberg AL, Edlund M, Svane G, Azavedo E, Skoog L, von Schoultz B. An isopropanolic extract of black cohosh does not increase mammographic breast density or breast cell proliferation in postmenopausal women. Menopause. 2007;14(1):89–96.

Hostanska K, Nisslein T, Freudenstein J, Reichling J, Saller R. Evaluation of cell death caused by triterpene glycosides and phenolic substances from *Cimicifuga racemosa* extract in human MCF-7 breast cancer cells. Biol Pharm Bull 2004;27(12):1970–1975.

Hostanska K, Nisslein T, Freudenstein J, Reichling J, Saller R. Apoptosis of human prostate androgen-dependent and -independent carcinoma cells induced by an isopropanolic extract of black cohosh involves degradation of cytokeratin (CK) 18. Anticancer Res 2005;25(1A):139–147.

Hostanska K, Nisslein T, Freudenstein J, Reichling J, Saller R. Inhibitory effect of an isopropanolic extract of black cohosh on the invasiveness of MDA-mB 231 human breast cancer cells. In Vivo 2007;21(2):349–355.

Huang Y, Jiang B, Nuntanakorn P, Kennelly EJ, Shord S, Lawal TO, Mahady GB. Fukinolic acid derivatives and triterpene glycosides from black cohosh inhibit CYP isozymes, but are not cytotoxic to Hep-G2 cells in vitro. Curr Drug Saf 2010;5(2):118–124.

Hunter A. *Cimicifuga racemosa*: pharmacology, clinical trials and clinical use. Eur J Herbal Med 1999;5(1):19–25.

Huntley AL, Ernst E. A systematic review of herbal medicinal products for the treatment of menopausal symptoms. Menopause. 2003a;10(5):465–476.

Huntley A, Ernst E. A systematic review of the safety of black cohosh. Menopause 2003b;10(1):58–64.

Ingraffea A, Donohue K, Wilkel C, Falanga V. Cutaneous vasculitis in two patients taking an herbal supplement containing black cohosh. J Am Acad Dermatol 2007;56(5 Suppl):S124-S126.

Jacobson JS, Troxel AB, Evans J, Klaus L, Vahdat L, Kinne D, Lo KM, Moore A, Rosenman PJ, Kaufman EL, Neugut AI, Grann VR. Randomized trial of black cohosh for the treatment of hot flashes among women with a history of breast cancer. J Clin Oncol 2001;19(10):2739–2745.

Jarry H, Harnischfeger G. Endocrine effects of constituents of *Cimicifuga racemosa*. 1. The effect on serum levels of pituitary hormones in ovariectomized rats. Planta Med 1985;51(1):46–49.

Jarry H, Harnischfeger G, Duker E. The endocrine effects of constituents of *Cimicifuga racemosa*. 2. In vitro binding of constituents to estrogen receptors. Planta Med 1985;51(4):316–319.

Jarry H, Metten M, Spengler B, Christoffel V, Wuttke W. In vitro effects of the *Cimicifuga racemosa* extract BNO 1055. Maturitas 2003;44 Suppl 1:S31–S38.

Jassim GA. Strategies for managing hot flashes. J Fam. Pract. 2011;60(6):333–339.

Jiang B, Yang H, Nuntanakorn P, Balick MJ, Kronenberg F, Kennelly EJ. The value of plant collections in ethnopharmacology: a case study of an 85-year-old black cohosh (*Actaea racemosa* L.) sample. J Ethnopharmacol. 2005;96(3):521–528.

Johnson BM, van Breemen RB. In vitro formation of quinoid metabolites of the dietary supplement *Cimicifuga racemosa* (black cohosh). Chem. Res Toxicol. 2003;16(7):838–846.

Joy D, Joy J, Duane P. Black cohosh: a cause of abnormal postmenopausal liver function tests. Climacteric. 2008;11(1):84–88.

Julia Molla MD, Garcia-Sanchez Y, Romeu Sarri A, Perez-lopez FR. *Cimicifuga racemosa* treatment and health related quality of life in post-menopausal Spanish women. Gynecol. Endocrinol. 2009;25(1):21–26.

Kanadys WM, Leszczynska-Gorzelak B, Oleszczuk J. Efficacy and safety of Black cohosh (*Actaea*/*Cimicifuga racemosa*) in the treatment of vasomotor symptoms—review of clinical trials. Ginekol. Pol. 2008;79(4):287–296.

Kang HJ, Ansbacher R, Hammoud MM. Use of alternative and complementary medicine in menopause. Int. J Gynaecol. Obstet. 2002;79(3):195–207.

Kelley KW, Carroll DG. Evaluating the evidence for over-the-counter alternatives for relief of hot flashes in menopausal women. J Am Pharm. Assoc. (2003.) 2010;50(5):e106-e115.

Kelly JP, Kaufman DW, Rosenberg L, Kelley K, Cooper SG, Mitchell AA. Use of postmenopausal hormone therapy since the Women's Health Initiative findings. Pharmacoepidemiol. Drug Saf 2005;14(12):837–842.

Kennelly EJ, Baggett S, Nuntanakorn P, Ososki AL, Mori SA, Duke J, Coleton M, Kronenberg F. Analysis of thirteen populations of black cohosh for formononetin. Phytomedicine 2002;9(5):461–467.

Kim CD, Lee WK, Lee MH, Cho HS, Lee YK, Roh SS. Inhibition of mast cell-dependent allergy reaction by extract of black cohosh (*Cimicifuga racemosa*). Immunopharmacol Immunotoxicol. 2004;26(2):299–308.

Kistin SJ, Newman AD. Induction of labor with homeopathy: a case report. J Midwifery Womens Health 2007;52(3):303–307.

Kligler B. Black cohosh. Am. Fam. Physician 2003;68(1):114–116.

Koeda M, Aoki Y, Sakurai N, Nagai M. Studies on the Chinese crude drug "shoma." IX. Three novel cyclolanostanol xylosides, cimicifugosides H-1, H-2 and H-5, from cimicifuga rhizome. Chem Pharm. Bull. (Tokyo) 1995;43(5):771–776.

Korn WD. *Six month oral toxicity study with remifemin-granulate in rats followed by an 8-week recovery period*, p 1. Hannover, Germany, International Bioresearch, 1991.

Kronenberg F, Fugh-Berman A. Complementary and alternative medicine for menopausal symptoms: a review of randomized, controlled trials. Ann Intern Med 2002;137(10):805–813.

Kupferer EM, Dormire SL, Becker H. Complementary and alternative medicine use for vasomotor symptoms among women who have discontinued hormone therapy. J Obstet. Gynecol. Neonatal Nurs. 2009;38(1):50–59.

Lehmann-Willenbrock E, Riedel HH. Clinical and endocrinologic studies of the treatment of ovarian insufficiency manifestations following hysterectomy with intact adnexa. Zentralbl. Gynakol. 1988;110(10):611–618.

Lieberman S. A review of the effectiveness of *Cimicifuga racemosa* (black cohosh) for the symptoms of menopause. J Womens Health 1998;7(5):525–529.

Liske E. Therapeutic efficacy and safety of *Cimicifuga racemosa* for gynecologic disorders. Adv. Ther 1998;15(1):45–53.

Liske E, Hanggi W, Henneicke-von Zepelin HH, Boblitz N, Wustenberg P, Rahlfs VW. Physiological investigation of a unique extract of black cohosh (*Cimicifugae racemosae* rhizoma): a

6-month clinical study demonstrates no systemic estrogenic effect. J Womens Health Gend. Based. Med 2002;11(2):163–174.

Liske E, Wustenberg P. Efficacy and safety of phytomedicines with particular references to *Cimicifuga racemosa*. J Med Assoc Thai 1998;Jan:s108.

Liske E, Wüstenberg P. Therapy of climacteric complaints with *Cimicifuga racemosa*: herbal medicine with clinically proven evidence [poster presentation]. Menopause 1998;5(4):250.

Liske E, Wüstenberg P, Boblitz N. Human-pharmacological investigations during treatment of climacteric complaints with *Cimicifuga racemosa* (Remifemin): No estrogen-like effects. ESCOP 2001;1:1.

Li W, Sun Y, Liang W, Fitzloff JF, van Breemen RB. Identification of caffeic acid derivatives in Actea racemosa (*Cimicifuga racemosa*, black cohosh) by liquid chromatography/tandem mass spectrometry. Rapid Commun. Mass Spectrom. 2003;17(9):978–982.

Liu J, Burdette JE, Xu H, Gu C., van Breemen RB, Bhat KP, Booth N, Constantinou AI, Pezzuto JM, Fong HH, Farnsworth NR, Bolton JL. Evaluation of estrogenic activity of plant extracts for the potential treatment of menopausal symptoms. J Agric Food Chem 2001;49(5):2472–2479.

Liu Z, Yang Z, Zhu M, Huo J. Estrogenicity of black cohosh (*Cimicifuga racemosa*) and its effect on estrogen receptor level in human breast cancer MCF-7 cells. Wei Sheng Yan. Jiu. 2001;30(2):77–80.

Long L, Soeken K, Ernst E. Herbal medicines for the treatment of osteoarthritis: a systematic review. Rheumatology. (Oxford) 2001;40(7):779–793.

Lontos S, Jones RM, Angus PW, Gow PJ. Acute liver failure associated with the use of herbal preparations containing black cohosh. Med J Aust. 2003;179(7):390–391.

Loprinzi CL, Barton DL, Sloan JA, Novotny PJ, Dakhil SR, Verdirame JD, Knutson WH, Kelaghan J, Christensen B. Mayo Clinic and North Central Cancer Treatment Group hot flash studies: a 20-year experience. Menopause. 2008;15(4 Pt 1):655–660.

Low Dog T. Menopause: a review of botanical dietary supplements. Am J Med 2005;118 Suppl 12B:98–108.

Low Dog T, Powell KL, Weisman SM. Critical evaluation of the safety of *Cimicifuga racemosa* in menopause symptom relief. Menopause. 2003;10(4):299–313.

Lundstrom E, Christow A, Kersemaekers W, Svane G, Azavedo E, Soderqvist G, Mol-Arts M, Barkfeldt J, von Schoultz B. Effects of tibolone and continuous combined hormone replacement therapy on mammographic breast density. Am J Obstet. Gynecol. 2002;186(4):717–722.

Lundstrom E, Hirschberg AL, Soderqvist G. Digitized assessment of mammographic breast density—effects of continuous combined hormone therapy, tibolone and black cohosh compared to placebo. Maturitas 2011;70(4):361–364.

Lupu R, Mehmi I, Atlas E, Tsai MS, Pisha E, Oketch-Rabah HA, Nuntanakorn P, Kennelly EJ, Kronenberg F. Black cohosh, a menopausal remedy, does not have estrogenic activity and does not promote breast cancer cell growth. Int J Oncol. 2003;23(5):1407–1412.

Lynch CR, Folkers ME, Hutson WR. Fulminant hepatic failure associated with the use of black cohosh: a case report. Liver Transpl. 2006;12(6):989–992.

Maclennan AH. Evidence-based review of therapies at the menopause. Int. J Evid. Based. Healthc. 2009;7(2):112–123.

Mahady GB. Is black cohosh estrogenic? Nutr. Rev 2003;61(5 Pt 1):183–186.

Mahady GB, Low Dog T, Barrett ML, Chavez ML, Gardiner P, Ko R, Marles RJ, Pellicore LS, Giancaspro GI, Sarma DN. United States Pharmacopeia review of the black cohosh case reports of hepatotoxicity. Menopause. 2008;15(4 Pt 1):628–638.

Mahady G, Low Dog T, Sarma DN, Giancaspro GI. Suspected black cohosh hepatotoxicity—causality assessment versus safety signal. Maturitas 2009;64(2):139–140.

Mahady G, Low Dog T, Sarma ND, Giancaspro GI, Griffiths J. The causal relationship between the use of black cohosh-containing products and hepatotoxicity. Menopause. 2010;17(5):1088–1089.

Maki PM, Rubin LH, Fornelli D, Drogos L, Banuvar S, Shulman LP, Geller SE. Effects of botanicals and combined hormone therapy on cognition in postmenopausal women. Menopause. 2009;16(6):1167–1177.

Marotta F, Mao GS, Liu T, Chui DH, Lorenzetti A, Xiao Y, Marandola P. Anti-inflammatory and neuroprotective effect of a phytoestrogen compound on rat microglia. Ann N Y. Acad Sci 2006;1089:276–281.

Mazaro-Costa R, Andersen ML, Hachul H, Tufik S. Medicinal plants as alternative treatments for female sexual dysfunction: utopian vision or possible treatment in climacteric women? J Sex Med 2010;7(11):3695–3714.

McBane SE. Easing vasomotor symptoms: Besides HRT, what works? JAAPA. 2008;21(4): 26–31.

McCormick M, Manoguerra A. Toxicity of pennyroyal oil: a case report and review [abstract]. Vet Human Toxicol 1988;30(4):347.

McFarlin BL, Gibson MH, O'Rear J, Harman P. A national survey of herbal preparation use by nurse-midwives for labor stimulation. Review of the literature and recommendations for practice. J Nurse Midwifery 1999;44(3):205–216.

McKenna DJ, Jones K, Humphrey S, Hughes K. Black cohosh: efficacy, safety, and use in clinical and preclinical applications. Altern Ther Health Med 2001;7(3):93–100.

McKenzie SC, Rahman A. Bradycardia in a patient taking black cohosh. Med J Aust. 2010;193(8):479–481.

Mello NK. Commentary on black cohosh for the treatment of menopausal symptoms. Menopause. 2008;15(5):819–820.

Meyer S, Vogt T, Obermann EC, Landthaler M, Karrer S. Cutaneous pseudolymphoma induced by *Cimicifuga racemosa*. Dermatology 2007;214(1):94–96.

Mills SY, Jacoby RK, Chacksfield M, Willoughby M. Effect of a proprietary herbal medicine on the relief of chronic arthritic pain: a double-blind study. Br J Rheumatol 1996;35(9):874–878.

Minciullo PL. Causative relationship between asthenia and the intake of black cohosh. Phytomedicine 2009;16(8):800.

Minciullo PL, Saija A, Patafi M, Marotta G, Ferlazzo B, Gangemi S. Muscle damage induced by black cohosh (*Cimicifuga racemosa*). Phytomedicine 2006;13(1–2):115–118.

Mohamed ME, Frye RF. Inhibitory effects of commonly used herbal extracts on UDP-glucuronosyltransferase 1A4, 1A6, and 1A9 enzyme activities. Drug Metab Dispos. 2011;39(9):1522–1528.

Mohamed MF, Tseng T, Frye RF. Inhibitory effects of commonly used herbal extracts on UGT1A1 enzyme activity. Xenobiotica 2010;40(10):663–669.

Molla MD, Hidalgo-Mora JJ, Soteras MG. Phytotherapy as alternative to hormone replacement therapy. Front Biosci (Schol. Ed) 2011;3:191–204.

Moyad MA. Complementary/alternative therapies for reducing hot flashes in prostate cancer patients: reevaluating the existing indirect data from studies of breast cancer and postmenopausal women. Urology 2002;59(4 Suppl 1):20–33.

Nappi RE, Malavasi B, Brundu B, Facchinetti F. Efficacy of *Cimicifuga racemosa* on climacteric complaints: a randomized study versus low-dose transdermal estradiol. Gynecol. Endocrinol. 2005;20(1):30–35.

Naser B, Liske E. Liver failure associated with the use of black cohosh for menopausal symptoms. Med J Aust. 2009;190(2):99.

Naser B, Schnitker J, Minkin MJ, de Arriba SG, Nolte KU, Osmers R. Suspected black cohosh hepatotoxicity: no evidence by meta-analysis of randomized controlled clinical trials for isopropanolic black cohosh extract. Menopause. 2011;18(4):366–375.

Nash LI, Desindes S. Canadian consensus conference on menopause 2006 update. J Obstet Gynaecol Can 2006;28:S69–74.

Nasr A, Nafeh H. Influence of black cohosh (*Cimicifuga racemosa*) use by postmenopausal women on total hepatic perfusion and liver functions. Fertil. Steril. 2009;92(5):1780–1782.

Nedrow A, Miller J, Walker M, Nygren P, Huffman LH, Nelson HD. Complementary and alternative therapies for the management of menopause-related symptoms: a systematic evidence review. Arch Intern. Med 2006;166(14):1453–1465.

Neff MJ. NAMS releases position statement on the treatment of vasomotor symptoms associated with menopause. Am Fam. Physician 2004;70(2):393–4, 396, 399.

Nesselhut T, Schellhase C, Dietrich R, et al. Investigations into the growth-inhibitive efficacy of phytopharmacopia with estrogen-like influences on mammary gland carcinoma cells (translated from German). Arch Gynecol Obstet 1993;254:817–818.

Newton KM, Reed SD, LaCroix AZ, Grothaus LC, Ehrlich K, Guiltinan J. Treatment of vasomotor symptoms of menopause with black cohosh, multibotanicals, soy, hormone therapy, or placebo: a randomized trial. Ann Intern Med 2006;145(12):869–879.

Ng SS, Figg WD. Antitumor activity of herbal supplements in human prostate cancer xenografts implanted in immunodeficient mice. Anticancer Res 2003;23(5A):3585–3590.

Nisslein T, Freudenstein J. Effects of an isopropanolic extract of *Cimicifuga racemosa* on urinary crosslinks and other parameters of bone quality in an ovariectomized rat model of osteoporosis. J Bone Miner. Metab 2003;21(6):370–376.

Nisslein T, Freudenstein J. Concomitant administration of an isopropanolic extract of black cohosh and tamoxifen in the in vivo tumor model of implanted RUCA-I rat endometrial adenocarcinoma cells. Toxicol. Lett. 2004;150(3):271–275.

Nisslein T, Freudenstein J. Coadministration of the aromatase inhibitor formestane and an isopropanolic extract of black cohosh in a rat model of chemically induced mammary carcinoma. Planta Med 2007;73(4):318–322.

Noguchi M, Nagai M, Koeda M, Nakayama S, Sakurai N, Takahira M, Kusano G. Vasoactive effects of cimicifugic acids C and D, and fukinolic acid in cimicifuga rhizome. Biol Pharm Bull 1998;21(11):1163–1168.

Nuntanakorn P, Jiang B, Einbond LS, Yang H, Kronenberg F, Weinstein IB, Kennelly EJ. Polyphenolic constituents of *Actaea racemosa*. J Nat Prod 2006;69(3):314–318.

Nuntanakorn P, Jiang B, Yang H, Cervantes-Cervantes M, Kronenberg F, Kennelly EJ. Analysis of polyphenolic compounds and radical scavenging activity of four American Actaea species. Phytochem. Anal. 2007;18(3):219–228.

Obi N, Chang-Claude J, Berger J, Braendle W, Slanger T, Schmidt M, Steindorf K, Ahrens W, Flesch-Janys D. The use of herbal preparations to alleviate climacteric disorders and risk of postmenopausal breast cancer in a German case-control study. Cancer Epidemiol Biomarkers Prev. 2009;18(8):2207–2213.

Oerter Klein K, Janfaza M, Wong JA, Chang RJ. Estrogen bioactivity in fo-ti and other herbs used for their estrogen-like effects as determined by a recombinant cell bioassay. J Clin Endocrinol. Metab 2003;88(9):4077–4079.

Oktem M, Eroglu D, Karahan HB, Taskintuna N, Kuscu E, Zeyneloglu HB. Black cohosh and fluoxetine in the treatment of postmenopausal symptoms: a prospective, randomized trial. Adv Ther 2007;24(2):448–461.

Onorato J, Henion JD. Evaluation of triterpene glycoside estrogenic activity using LC/MS and immunoaffinity extraction. Anal. Chem 2001;73(19):4704–4710.

Osmers R, Friede M, Liske E, Schnitker J, Freudenstein J, Henneicke-von Zepelin HH. Efficacy and safety of isopropanolic black cohosh extract for climacteric symptoms. Obstet. Gynecol 2005;105(5 Pt 1):1074–1083.

Overk CR, Yao P, Chen S, Deng S, Imai A, Main M, Schinkovitz A, Farnsworth NR, Pauli GF, Bolton JL. High-content screening and mechanism-based evaluation of estrogenic botanical extracts. Comb. Chem. High Throughput. Screen. 2008;11(4):283–293.

Pade D, Stavchansky S. Selection of bioavailability markers for herbal extracts based on in silico descriptors and their correlation to in vitro permeability. Mol. Pharm. 2008;5(4):665–671.

Palacio C, Masri G, Mooradian AD. Black cohosh for the management of menopausal symptoms : a systematic review of clinical trials. Drugs Aging 2009;26(1):23–36.

Pang X, Cheng J, Krausz KW, Guo DA, Gonzalez FJ. Pregnane X receptor-mediated induction of Cyp3a by black cohosh. Xenobiotica 2011;41(2):112–123.

Patel NM, Derkits RM. Possible increase in liver enzymes secondary to atorvastatin and black cohosh administration. J Pharm Pract 2007;20:341–346.

Pepping J. Black cohosh: *Cimicifuga racemosa*. Am J Health Syst. Pharm 1999;56(14):1400–1402.

Petho A. Climacteric complaints are often helped with black cohosh. Ärztliche Praxis 1987;47:1551–1553.

Pierard S, Coche JC, Lanthier P, Dekoninck X, Lanthier N, Rahier J, Geubel AP. Severe hepatitis associated with the use of black cohosh: a report of two cases and an advice for caution. Eur J Gastroenterol Hepatol. 2009;21(8):941–945.

Pineda B, Garcia-Perez MA, Vazquez F, Julia MD, Tarin JJ, Hermenegildo C, Cano A. No effect of *Cimicifuga racemosa* extract on serum interleukin-6 levels and prostacyclin production by human endothelial cells. Eur J Obstet. Gynecol. Reprod. Biol. 2009;144(1):93–94.

Pinkerton JV, Stovall DW, Kightlinger RS. Advances in the treatment of menopausal symptoms. Womens Health (Lond Engl.) 2009;5(4):361–384.

Pockaj BA, Gallagher JG, Loprinzi CL, Stella PJ, Barton DL, Sloan JA, Lavasseur BI, Rao RM, Fitch TR, Rowland KM, Novotny PJ, Flynn PJ, Richelson E, Fauq AH. Phase III double-blind, randomized, placebo-controlled crossover trial of black cohosh in the management of hot flashes: NCCTG Trial N01CC1. J Clin Oncol. 2006;24(18):2836–2841.

Pockaj BA, Loprinzi CL, Sloan JA, Novotny PJ, Barton DL, Hagenmaier A, Zhang H, Lambert GH, Reeser KA, Wisbey JA. Pilot evaluation of black cohosh for the treatment of hot flashes in women. Cancer Invest 2004;22(4):515–521.

Raus K, Brucker C, Gorkow C, Wuttke W. First-time proof of endometrial safety of the special black cohosh extract (Actaea or *Cimicifuga racemosa* extract) CR BNO 1055. Menopause. 2006;13(4):678–691.

Reame NE, Lukacs JL, Padmanabhan V, Eyvazzadeh AD, Smith YR, Zubieta JK. Black cohosh has central opioid activity in postmenopausal women: evidence from naloxone blockade and positron emission tomography neuroimaging. Menopause. 2008;15(5):832–840.

Rebbeck TR, Troxel AB, Norman S, Bunin GR, DeMichele A, Baumgarten M, Berlin M, Schinnar R, Strom BL. A retrospective case-control study of the use of hormone-related supplements and association with breast cancer. Int J Cancer 2007;120(7):1523–1528.

Rhyu MR, Lu J, Webster DE, Fabricant DS, Farnsworth NR, Wang ZJ. Black cohosh (*Actaea racemosa Cimicifuga racemosa*) behaves as a mixed competitive ligand and partial agonist at the human mu opiate receptor. J Agric. Food Chem 2006;54(26):9852–9857.

Richardson MK. Black cohosh. . .a cautionary tale! Menopause. 2008;15(4 Pt 1):583.

Roberts H. Safety of herbal medicinal products in women with breast cancer. Maturitas 2010;66(4):363–369.

Rock E, DeMichele A. Nutritional approaches to late toxicities of adjuvant chemotherapy in breast cancer survivors. J Nutr 2003;133(11 Suppl 1):3785S–3793S.

Ross SM. Menopause: a standardized isopropanolic black cohosh extract (remifemin) is found to be safe and effective for menopausal symptoms. Holist. Nurs. Pract. 2012;26(1):58–61.

Rostock M, Fischer J, Mumm A, Stammwitz U, Saller R, Bartsch HH. Black cohosh (*Cimicifuga racemosa*) in tamoxifen-treated breast cancer patients with climacteric complaints—a prospective observational study. Gynecol Endocrinol. 2011;27(10):844–848.

Rotem C, Kaplan B. Phyto-female complex for the relief of hot flushes, night sweats and quality of sleep: randomized, controlled, double-blind pilot study. Gynecol Endocrinol. 2007;23(2):117–122.

Roush K. Managing menopausal symptoms. Am J Nurs. 2012;112(6):28–35.

Sakurai N., Nagai M. Chemical constituents of original plants of Cimicifugae rhizoma in Chinese medicine. Yakugaku Zasshi 1996;116(11):850–865.

Sakurai N, Wu JH, Sashida Y, Mimaki Y, Nikaido T, Koike K, Itokawa H, Lee KH. Anti-AIDS agents. Part 57: Actein, an anti-HIV principle from the rhizome of *Cimicifuga racemosa* (black cohosh), and the anti-HIV activity of related saponins. Bioorg. Med Chem. Lett. 2004;14(5):1329–1332.

Sammartino A, Tommaselli GA, Gargano V., di Carlo C, Attianese W, Nappi C. Short-term effects of a combination of isoflavones, lignans and *Cimicifuga racemosa* on climacteric-related symptoms in postmenopausal women: a double-blind, randomized, placebo-controlled trial. Gynecol Endocrinol. 2006;22(11):646–650.

Sarma ND, Giancaspro GI, Griffiths J, Dog TL. Black cohosh. . .more data, please! Menopause. 2011;18(4):350–351.

Schmid D, Woehs F, Svoboda M, Thalhammer T, Chiba P, Moeslinger T. Aqueous extracts of *Cimicifuga racemosa* and phenolcarboxylic constituents inhibit production of

proinflammatory cytokines in LPS-stimulated human whole blood. Can J Physiol Pharmacol. 2009;87(11):963–972.

Seidlova-Wuttke D, Hesse O, Jarry H, Christoffel V, Spengler B, Becker T, Wuttke W. Evidence for selective estrogen receptor modulator activity in a black cohosh (*Cimicifuga racemosa*) extract: comparison with estradiol-17beta. Eur J Endocrinol. 2003;149(4):351–362.

Seidlova-Wuttke D, Jarry H, Becker T, Christoffel V, Wuttke W. Pharmacology of *Cimicifuga racemosa* extract BNO 1055 in rats: bone, fat and uterus. Maturitas 2003;44 Suppl 1:S39-S50.

Sevior DK, Hokkanen J, Tolonen A, Abass K, Tursas L, Pelkonen O, Ahokas JT. Rapid screening of commercially available herbal products for the inhibition of major human hepatic cytochrome P450 enzymes using the N-in-one cocktail. Xenobiotica 2010;40(4):245–254.

Shah D, Agrawal S. Vasomotor symptoms: viewpoint from the Indian subcontinent and management of a common menopausal problem. Semin. Reprod. Med 2010;28(5):388–395.

Shahin AY, Ismail AM, Shaaban OM. Supplementation of clomiphene citrate cycles with *Cimicifuga racemosa* or ethinyl oestradiol—a randomized trial. Reprod. Biomed. Online. 2009;19(4):501–507.

Shahin AY, Ismail AM, Zahran KM, Makhlouf AM. Adding phytoestrogens to clomiphene induction in unexplained infertility patients—a randomized trial. Reprod. Biomed. Online. 2008;16(4):580–588.

Shams T, Setia MS, Hemmings R, McCusker J, Sewitch M, Ciampi A. Efficacy of black cohosh-containing preparations on menopausal symptoms: a meta-analysis. Altern. Ther Health Med 2010;16(1):36–44.

Shao Y, Harris A, Wang M, Zhang H, Cordell GA, Bowman M, Lemmo E. Triterpene glycosides from *Cimicifuga racemosa*. J Nat Prod 2000;63(7):905–910.

Shen W, Stearns V. Treatment strategies for hot flushes. Expert. Opin. Pharmacother. 2009;10(7):1133–1144.

Shibata M, Ikoma M, Onoda M, Sato F, Sakurai N. Pharmacological studies on the Chinese crude drug "Shoma". III. Central depressant and antispasmodic actions of Cimicifuga rhizoma, Cimicifuga simplex Wormsk (author's transl). Yakugaku Zasshi 1980;100(11):1143–1150.

Shi S, Klotz U. Drug interactions with herbal medicines. Clin Pharmacokinet. 2012;51(2):77–104.

Shord SS, Shah K, Lukose A. Drug-botanical interactions: a review of the laboratory, animal, and human data for 8 common botanicals. Integr Cancer Ther 2009;8(3):208–227.

Shou C, Li J, Liu Z. Complementary and alternative medicine in the treatment of menopausal symptoms. Chin J Integr Med 2011;17(12):883–888.

Shulman LP, Banuvar S, Fong HH, Farnsworth NR. Discussion of a well-designed clinical trial which did not demonstrate effectiveness: UIC center for botanical dietary supplements research study of black cohosh and red clover. Fitoterapia 2011;82(1):88–91.

Shuster J. Heparin and thrombocytopenia. Black cohosh root? Chasteberry tree? Seizures! Hosp Pharm 1996;31:1553–1554.

Siess VM, Seybold G. Studies on the effects of Pulsatilla pratensis, *Cimicifuga racemosa* and Aristolochia clematitis on the estrus in infantile and castrated white mice. Arzneimittelforschung 1960;10:514–520.

Spangler L, Newton KM, Grothaus LC, Reed SD, Ehrlich K, LaCroix AZ. The effects of black cohosh therapies on lipids, fibrinogen, glucose and insulin. Maturitas 2007;57(2):195–204.

Stoll W. Phytotherapeutikum beeinflusst atrophisches Vaginal epithel. Doppelblindversuch Cimicifuga vs. Oestrogenpraeparat [Phytopharmaceutical influences on atrophic vaginal epithelium. Double-blind study on Cimicifuga vs. an estrogen preparation]. Therapeutickon 1987;1:23–32.

Stolze H. An alternative to treat menopausal complaints. Gynecologie 1982;1:14–16.

Struck D, Tegtmeier M, Harnischfeger G. Flavones in extracts of *Cimicifuga racemosa*. Planta Med 1997;63:289–290.

Stute P, Nisslein T, Gotte M, Kamischke A, Kiesel L, Klockenbusch W. Effects of black cohosh on estrogen biosynthesis in normal breast tissue in vitro. Maturitas 2007;57(4):382–391.

Takahira M, Kusano A, Shibano M, Kusano G, Koizumi K, Suzuki R, Kim HS, Wataya Y, Takahara M. Antimalarial activity and nucleoside transport inhibitory activity of the triterpenic constituents of Cimicifuga spp. Biol Pharm Bull 1998;21(8):823–828.

Tamaki H, Satoh H, Hori S, Ohtani H, Sawada Y. Inhibitory effects of herbal extracts on breast cancer resistance protein (BCRP) and structure-inhibitory potency relationship of isoflavonoids. Drug Metab Pharmacokinet. 2010;25(2):170–179.

Teschke R. Liver failure associated with the use of black cohosh for menopausal symptoms. Med J Aust. 2009a;190(2):99–100.

Teschke R. A U.S. review determined that black cohosh products should be labeled with a cautionary statement. Menopause. 2009b;16(1):214–215.

Teschke R. Black cohosh and suspected hepatotoxicity: inconsistencies, confounding variables, and prospective use of a diagnostic causality algorithm. A critical review. Menopause. 2010;17(2):426–440.

Teschke R, Bahre R, Fuchs J, Wolff A. Black cohosh hepatotoxicity: quantitative causality evaluation in nine suspected cases. Menopause. 2009;16(5):956–965.

Teschke R, Bahre R, Genthner A, Fuchs J, Schmidt-Taenzer W, Wolff A. Suspected black cohosh hepatotoxicity–challenges and pitfalls of causality assessment. Maturitas 2009;63(4):302–314.

Teschke R, Schmidt-Taenzer W, Wolff A. Spontaneous reports of assumed herbal hepatotoxicity by black cohosh: is the liver-unspecific Naranjo scale precise enough to ascertain causality? Pharmacoepidemiol. Drug Saf 2011;20(6):567–582.

Teschke R, Schwarzenbock A, Hennermann KH. Toxic liver disease due to drugs, herbs and dietary supplements: diagnostic approaches. Z. Gastroenterol. 2007;45(2):195–208.

Teschke R, Schwarzenboeck A. Suspected hepatotoxicity by *Cimicifugae racemosae* rhizoma (black cohosh, root): critical analysis and structured causality assessment. Phytomedicine 2009;16(1):72–84.

Teschke R, Schwarzenboeck A, Schmidt-Taenzer W, Wolff A, Hennermann KH. Herb induced liver injury presumably caused by black cohosh: a survey of initially purported cases and herbal quality specifications. Ann Hepatol. 2011;10(3):249–259.

Thacker HL. Assessing risks and benefits of nonhormonal treatments for vasomotor symptoms in perimenopausal and postmenopausal women. J Womens Health (Larchmt.) 2011;20(7):1007–1016.

Thomsen M, Schmidt M. Hepatotoxicity from *Cimicifuga racemosa*? Recent Australian case report not sufficiently substantiated. J Altern. Complement Med 2003;9(3):337–340.

Uebelhack R, Blohmer JU, Graubaum HJ, Busch R, Gruenwald J, Wernecke KD. Black cohosh and St. John's wort for climacteric complaints: a randomized trial. Obstet. Gynecol. 2006;107(2 Pt 1):247–255.

Umland EM. Treatment strategies for reducing the burden of menopause-associated vasomotor symptoms. J Manag. Care Pharm. 2008;14(3 Suppl):14–19.

van Breemen RB, Liang W, Banuvar S, Shulman LP, Pang Y, Tao Y, Nikolic D, Krock KM, Fabricant DS, Chen SN, Hedayat S, Bolton JL, Pauli GF, Piersen CE, Krause EC, Geller SE, Farnsworth NR. Pharmacokinetics of 23-epi-26-deoxyactein in women after oral administration of a standardized extract of black cohosh. Clin Pharmacol. Ther 2010;87(2):219–225.

van de Meerendonk HW, van Hunsel FP, van der Wiel HE. Autoimmune hepatitis induced by *Actaea racemosa*. Side effects of an herb extract. Ned. Tijdschr. Geneeskd. 2009;153(6):246–249.

van der Sluijs CP, Bensoussan A, Chang S, Baber R. A randomized placebo-controlled trial on the effectiveness of an herbal formula to alleviate menopausal vasomotor symptoms. Menopause. 2009;16(2):336–344.

Vannacci A, Lapi F, Gallo E, Vietri M, Toti M, Menniti-Ippolito F, Raschetti R, Firenzuoli F, Mugelli A. A case of hepatitis associated with long-term use of *Cimicifuga racemosa*. Altern. Ther Health Med 2009;15(3):62–63.

Verhoeven MO, van der Mooren MJ, van de Weijer PH, Verdegem PJ, van der Burgt LM, Kenemans P. Effect of a combination of isoflavones and *Actaea racemosa* Linnaeus on climacteric symptoms in healthy symptomatic perimenopausal women: a 12-week randomized, placebo-controlled, double-blind study. Menopause. 2005;12(4):412–420.

Vermes G, Banhidy F, Acs N. The effects of remifemin on subjective symptoms of menopause. Adv. Ther 2005;22(2):148–154.

Viereck V, Grundker C, Friess SC, Frosch KH, Raddatz D, Schoppet M, Nisslein T, Emons G, Hofbauer LC. Isopropanolic extract of black cohosh stimulates osteoprotegerin production by human osteoblasts. J Bone Miner. Res 2005;20(11):2036–2043.

Villaseca P. Non-estrogen conventional and phytochemical treatments for vasomotor symptoms: what needs to be known for practice. Climacteric. 2012;15(2):115–124.

Vorberg G. Treatment of menopause symptoms. ZFA 1984;60:626–629.

Walji R, Boon H, Guns E, Oneschuk D, Younus J. Black cohosh (*Cimicifuga racemosa* [L.] Nutt.): safety and efficacy for cancer patients. Support. Care Cancer 2007;15(8):913–921.

Wang YJ, Dou J, Cross KP, Valerio LG, Jr. Computational analysis for hepatic safety signals of constituents present in botanical extracts widely used by women in the United States for treatment of menopausal symptoms. Regul. Toxicol. Pharmacol. 2011;59(1):111–124.

Wang HK, Sakurai N, Shih CY, Lee KH. LC/TIS-MS fingerprint profiling of Cimicifuga species and analysis of 23-Epi-26-deoxyactein in *Cimicifuga racemosa* commercial products. J Agric. Food Chem 2005;53(5):1379–1386.

Wanwimolruk S, Wong K, Wanwimolruk P. Variable inhibitory effect of different brands of commercial herbal supplements on human cytochrome P-450 CYP3A4. Drug Metabol. Drug Interact. 2009;24(1):17–35.

Warnecke G. Using phyto-treatment to influence menopause symptoms. Med Welt 1985;36:871–874.

Wende K, Mugge C, Thurow K, Schopke T, Lindequist U. Actaeaepoxide 3-*O*-beta-D-xylopyranoside, a new cycloartane glycoside from the rhizomes of *Actaea racemosa* (*Cimicifuga racemosa*). J Nat Prod 2001;64(7):986–989.

Whiting PW, Clouston A, Kerlin P. Black cohosh and other herbal remedies associated with acute hepatitis. Med J Aust. 2002;177(8):440–443.

Willhite LA. O'Connell MB. Urogenital atrophy: prevention and treatment. Pharmacotherapy 2001;21(4):464–480.

Wojcikowski K, Stevenson L, Leach D, Wohlmuth H, Gobe G. Antioxidant capacity of 55 medicinal herbs traditionally used to treat the urinary system: a comparison using a sequential three-solvent extraction process. J Altern Complement Med 2007;13(1):103–109.

Wong VC, Lim CE, Luo X, Wong WS. Current alternative and complementary therapies used in menopause. Gynecol. Endocrinol. 2009;25(3):166–174.

Woo KC, Park YS, Jun DJ, Lim JO, Baek WY, Suh BS, Kim KT. Phytoestrogen cimicifugoside-mediated inhibition of catecholamine secretion by blocking nicotinic acetylcholine receptor in bovine adrenal chromaffin cells. J Pharmacol Exp Ther 2004;309(2):641–649.

Wuttke W, Gorkow C, Seidlova-Wuttke D. Effects of black cohosh (*Cimicifuga racemosa*) on bone turnover, vaginal mucosa, and various blood parameters in postmenopausal women: a double-blind, placebo-controlled, and conjugated estrogens-controlled study. Menopause. 2006;13(2):185–196.

Wuttke W, Seidlova-Wuttke D. News about Black cohosh. Maturitas 2012;71(2):92–93.

Wuttke W, Seidlova-Wuttke D, Gorkow C. The Cimicifuga preparation BNO 1055 vs. conjugated estrogens in a double-blind placebo-controlled study: effects on menopause symptoms and bone markers. Maturitas 2003;44 Suppl 1:S67–S77.

Yang CL, Chik SC, Li JC, Cheung BK, Lau AS. Identification of the bioactive constituent and its mechanisms of action in mediating the anti-inflammatory effects of black cohosh and related Cimicifuga species on human primary blood macrophages. J Med Chem 2009;52(21):6707–6715.

Zava DT, Dollbaum CM, Blen M. Estrogen and progestin bioactivity of foods, herbs, and spices. Proc Soc Exp Biol Med 1998;217(3):369–378.

Zepelin HH, Meden H, Kostev K, Schroder-Bernhardi D, Stammwitz U, Becher H. Isopropanolic black cohosh extract and recurrence-free survival after breast cancer. Int J Clin Pharmacol Ther 2007;45(3):143–154.

Zhang L, Khan IA, Willett KL, Foran CM. In vivo effects of black cohosh and genistein on estrogenic activity and lipid peroxidation in Japanese Medaka (*Oryzias latipes*). J Herb. Pharmacother. 2003;3(3):33–50.

Zierau O, Bodinet C, Kolba S, Wulf M, Vollmer G. Antiestrogenic activities of *Cimicifuga racemosa* extracts. J Steroid Biochem. Mol. Biol 2002;80(1):125–130.

Zimmermann R, Witte A, Voll RE, Strobel J, Frieser M. Coagulation activation and fluid retention associated with the use of black cohosh: a case study. Climacteric. 2010;13(2): 187–191.

Notice of Correction

Changes have been made to this article since its original online publication date of 25 August 2014.