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File: ■ Black Cohosh (*Actaea racemosa* syn. *Cimicifuga racemosa*)
■ Menopause
■ Safety and Efficacy

HC 111358-494

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RE: Differentiated Evaluation of Black Cohosh's Efficacy and Safety

Beer A-M, Neff A. Differentiated evaluation of extract-specific evidence on *Cimicifuga racemosa*'s efficacy and safety for climacteric complaints. *Evid Based Complement Alternat Med*. 2013;2013:860602. doi: 10.1155/2013/860602.

Safe and effective alternatives to hormone replacement therapy (HRT) for the treatment of climacteric complaints are needed. Reviews of the efficacy and safety of black cohosh (*Actaea racemosa* syn. *Cimicifuga racemosa*) have shown heterogeneous conclusions. The authors hypothesize that this inconsistency is attributed to reviews including all types of black cohosh preparations without regard to distinctions in manufacturer, harvest, cultivation, type of extract, pharmaceutical quality, or indication. The purpose of this systematic review was to evaluate the literature based on types of extract, pharmaceutical quality, and indication.

Medline, Biosis, Embase, Embase Alert, and PubMed databases were searched from 2000 to 2012. The following search terms were used: *Cimicifuga racemosa*, Traubensilberkerze, black cohosh, *Actaea racemosa*, clinical trial, clinical study, klinische Studie, Review, meta-analysis, Meta Analyse, efficacy, Wirksamkeit, side effect, Nebenwirkung, adverse reaction, adverse drug, adverse event, adverse effect, ADR, UAW, interaction, Interaktion, Wechselwirkung, safety, Sicherheit, toxicity, Toxizität, intoxication, Intoxikation, poison, breast, Brust, mamma, uterin, uterus, Gebärmutter, tumor, tumour, cancer, hormon, estrogen, Östrogen, Leber, liver, hepat, case report, and Fallstudie. Inclusion criteria were as follows: women with neurovegetative and/or psychic climacteric complaints treated with the investigated phytopharmaceutical for ≥ 3 months; all types of studies; any treatment duration; monotherapy or combination therapy (not more than two active ingredients in the combined preparation); and comparison with placebo, hormone preparations/tibolone, fluoxetine, and different dosages of the study preparation. Exclusion criteria were as follows: preclinical studies, mode of action studies, not the registered indication of *Cimicifuga racemosa*, reviews, general surveys, comments, discussions, conference presentations, individual case reports, and published in a language other than English or German.

The results of this review are reflecting the type of extract as well as the regulatory status.

Efficacy
A total of 105 efficacy references were located, and 19 full publications from 18 trials met the inclusion criteria. The efficacy studies included 10,284 patients treated for climacteric complaints with black cohosh, with 98.5% (10,121 patients in 15 clinical studies) treated with a registered medicinal product. The most widely studied black cohosh preparations were special isopropanolic *Cimicifuga racemosa* extract (iCR, Remifemin®; Schaper & Brümmer GmbH & Co.; Salzgitter, Germany; distributed by Enzymatic Therapy; Green Bay, Wisconsin), with 9,391 patients treated with iCR (9 original publications from 9 studies), and BNO 1055 (Klimadynon®/Menofem®; Bionorica AG; Neumarkt, Germany), with a total of 420 patients (2 studies, 3 publications) treated. The authors separated the studies by regulatory status (i.e., marketing authorization: iCR and BNO 1055 are registered as medicinal products in several countries).

The efficacy of the iCR extract "has been proven" by 4 randomized, controlled studies with a Grade of Recommendation A (=confirmatory evidence), and is further supported by 2 controlled and 3 uncontrolled studies (=exploratory evidence) with proof of efficacy as the primary objective. Together, the studies of iCR as monotherapy and in combination with St. John's wort (SJW; *Hypericum perforatum*) show that black cohosh was efficacious.

The efficacy of BNO 1055 was demonstrated in a randomized controlled study with only 62 patients and supported by an uncontrolled study of 400 women (both Grade of Recommendation B = exploratory evidence).

In contrast, according to the authors, for the 3 studies of black cohosh extracts produced in the United States, products were not registered as medicinal products and not controlled by regulatory drug approval procedure; 2 studies were randomized controlled design and concluded that black cohosh was not effective, and 1 study was open-label, uncontrolled and showed efficacy. The authors conclude that evidence for efficacy depends on the regulatory status of the black cohosh product (Table 1 and Table 2).

Table 1: Studies with Evidence for Efficacy (n = 18)

Evidence for Efficacy	**Registered Product**	**Not a Registered Product**
Yes	15 studies	1 study
No	0	2 studies

Table 2: Evidence for Efficacy of Studies Rated as Having Confirmatory Methodology* (n = 7)

Evidence for Efficacy	**Registered Product**	**Not a Registered Product**
Yes	5 studies	0 study
No	0	2 studies

*The highest level of quality

Safety
A total of 134 safety references were located. Twenty-eight met the inclusion criteria for general safety, 14 met the inclusion criteria for safety on estrogen-sensitive organs (breast and uterus), and 8 met the inclusion criteria for safety in the liver. The safety was

evaluated in 13,492 users of black cohosh, with 11,961 (88.6%) users receiving a registered medicinal product.

For general safety, regardless of the regulatory status, the studies showed that black cohosh had good to very good tolerability. Overall, there were no clinically relevant changes in hormones (estradiol, follicle-stimulating hormone, and luteinizing hormone). A study including a total of > 9,900 patients showed that there was no increase in breast cancer risk. There may be a slight reduction in the risk of breast cancer recurrence in patients using the isopropanolic extract iCR. The authors conclude that black cohosh extract does not have estrogenic effects, which is contrary to decades-old thinking that black cohosh has adverse effects on estrogen-sensitive organs.

Clinical studies do not report any clinically relevant changes in liver function tests. Also, no liver damage was clinically observed as an adverse event. In contrast, there are individual case reports that suspect black cohosh hepatotoxicity. In 2006, the first analysis showed, that in 4 of 42 cases known worldwide, the causality was assessed as possible or probable. Those 4 cases have been reassessed. The difficulty is that there are several algorithms to evaluate causality and depending on which one is used, the reassessment of those 4 cases changes from possible causality to no causality. The authors point out that the subjects of those 4 cases were taking food supplements containing black cohosh and not medicinal quality products. Impurities and adulterations (such as using cheaper Asian *Cimicifuga* species) have been found in food supplement grade products.

The authors conclude, "For several products without marketing authorization and therefore without quality approval by regulatory authorities, quality deficiencies may be the reason for the deviating results regarding efficacy. Short descriptions of product quality cannot replace extensive product specifications of drug registration dossiers." The authors state that the pharmaceutical quality of an herbal extract is (only) granted by the regulatory status as medicinal product. Conversely, does this mean that herbal products without official quality approval do not meet quality standards? In general, the pharmaceutical quality of an herbal product is documented by a quality management system associated with quality assurance documents. Therefore, it is questionable if herbal products not quality-approved by regulatory authorities do not fulfill the criteria of a "good pharmaceutical quality herbal product." No doubt, the pharmaceutical quality of a product is a prerequisite for reliable data; however, one has to assume that other factors involved in clinical research may contribute to "negative" results regarding efficacy or, at least, facilitate them.

—Heather S. Oliff, PhD

Referenced article can be found at www.hindawi.com/journals/ecam/2013/860602.

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