

## Levels of Evidence: Black Cohosh

**Normann Boblitz, MD**  
**Specialist for Internal Medicine**  
**Germany**

For centuries, extracts from the rootstock of *Cimicifuga racemosa* have been used in different dosages for treating various complaints. The traditional application range comprised rheumatic and neurological, but already gynecological disorders as well. Originally coming from North America, this plant was widely used by American Indians and white settlers.

At the end of the 19<sup>th</sup> and the beginning of the 20<sup>th</sup> century only a few pharmacological investigations had been carried out, but in the middle of the 20<sup>th</sup> century, especially in Germany, clinical investigation experience, at first mainly as empirical reports, was published. Several clinicians reported on their positive experience with approximately 1,000 patients who suffered from gynecological disorders. These comprised for instance juvenile menstrual disorders, pregnancy complaints, premenstrual syndrome, dysmenorrhea, bleeding disorders in the broader sense and in principle mainly climacteric, neurovegetative (hot flushes and sweating) and psychic symptoms (Földes, 1959; Schotten, 1958; Stefan, 1959; Stiehler, 1959; Brücker, 1960; Heizer, 1960; Starfinger, 1960; Görlich, 1962; Schildge, 1964).

In the 1980s, more studies followed that were designed and performed on a modern scientific basis as observational cohort studies (Stolze, 1982), non-controlled (Daiber, 1983; Vorberg, 1984) and controlled studies versus reference therapies such as psychopharmaceuticals and oestrogens (Warnecke, 1985; Lehmann-Willenbrock and Riedel, 1988) as well as versus placebo (Stoll, 1987) giving evidence for the efficacy of standardized extracts for climacteric symptoms (review: Boblitz et al., 2000). A recent

GCP-compliant, randomized and controlled study indicates equivalence of a dosage of 40 mg drug versus approx. 130 mg drug (Liske et al., 2000), showing clinically relevant effects already after a therapy phase of 2 - 4 weeks.

In summary, currently clinical data of empirical reports and open, randomized and controlled studies in approximately 2,600 patients treated with *Cimicifuga racemosa* rootstock are available. Both the efficacy for the treatment of climacteric neurovegetative and psychic complaints as well as good tolerability at the same time could be shown by means of commonly applied and validated scales (Kupperman Menopause Index, Hamilton Anxiety Scale, Self Depression Scale, Clinical Global Impression). This is, for example, confirmed by the positive monograph of the German Health Authorities of 1989; further international monographs, especially ESCOP and WHO, are in preparation. Formally, the evidence type for Black Cohosh corresponds to Level Ib, i.e. "Evidence obtained from at least one randomized controlled trial".

Further clinical studies are currently in progress. Additionally, the pharmacological research is of considerable interest, especially with regard to the mode of action, which can be of important clinical relevance.

While in the beginning an "oestrogen-like" effect was assumed (binding to the oestrogen-receptor, which was still known in an undifferentiated way at that time, vaginal-cytologic effects in the sense of an oestrogenic effect, proved efficacy comparable to that of oestrogen), preclinical and clinical data of the last 10 years have shown results deviating therefrom. In

clinical studies no changes of the endometrial thickness in the sense of oestrogenic effects (Nesselhut and Liske, 1999) and no changes of oestrogen-sensitive hormones and vaginal-cytologic parameters (Nesselhut and Liske, 1999; Liske et al., 2000) became evident. Preclinically, the majority of the investigations with oestrogen-receptor positive breast cancer cells show no stimulation of proliferation by *Cimicifuga racemosa* extracts (Nesselhut, 1993; Freudenstein and Bodinet, 1999; Dixon-Shanies and Shaik, 1999; Zava, 1998), with only one contrary observation (Löhning et al., 1998). Furthermore, in-vivo investigations with a rat-DMBA-breast cancer model did not reveal any tumor proliferating properties in the sense of oestrogen-agonistic effects for a Black Cohosh rootstock extract (Freudenstein et al., 2000), thus confirming the in vitro data. Recent investigations additionally showed oestrogen-agonistic effects on a molecular-biological level on bone, liver and aortal tissue and no effects on the uterus (Wuttke et al., 2000 a+b). The present concept regarding the mode of action of *Cimicifuga racemosa* is that of Selective Estrogen Receptor Modulation (SERM), i.e. simultaneous oestrogen-agonistic as well as non-oestrogen or oestrogen-antagonistic effects, depending on the corresponding target tissue. This phenomenon could be explained by the existence of at least two oestrogen receptors (a- and b-ER) with different tissue-dependent distribution patterns. In this context many herbal substances have a significantly increased affinity to the b-receptor (Kuiper et al., 1998). This concept is important and fascinating because of the possible but not yet evaluated clinical relevance of possible favourable effects on bone metabolism and cardiovascular system and at the same time the absence of undesired oestrogenic effects on sensitive critical organs.

In summary, extracts from the rootstock of Black Cohosh have proved efficacy and tolerability in the treatment of climacteric symptoms and are well established as an alternative for hormonal therapy. In connection with the mode of action, further favourable effects/extension of the indications are

currently being researched and appear encouraging for the future.

### References:

- Boblitz N, Liske E, Wüstenberg P. Traubensilberkerze – Wirksamkeit, Wirkung und Sicherheit von *Cimicifuga racemosa* in der Gynäkologie. Deutsche Apotheker Zeitung 2000;140:107-14.
- Brücker A. Beitrag zur Phytotherapie hormonaler Störungen der Frau. Med. Welt 1960;44:2331-3.
- Daiber W. Klimakterische Beschwerden: ohne Hormone zum Erfolg! Ärzt. Praxis 1983;35;65:1946-7.
- Dixon-Shanies D, Shaikh N. Growth inhibition of human breast cancer cells by herbs and phytoestrogens. Oncology Reports 1999;6:1383-7.
- Földes J. Die Wirkung eines Extraktes aus *Cimicifuga racemosa*. Ärztliche Forschung 1959;13;12:623-4.
- Freudenstein J, Bodinet C. Influence of an isopropanolic aqueous extract of *Cimicifugae racemosae* rhizoma on the proliferation of MCF 7 cells. Poster, 23. Int. LOF-Symposium „Phyto-Oestrogens“, Gent, January 1999.
- Freudenstein J, Dasenbrock C, Niblein T. Lack of Promotion of Estrogen Dependent Mammary Gland Tumors in vivo by an Isopropanolic Black cohosh Extract. Phytomedicine 2000;7;Supplement II:13,SL-14
- Görlich N. Behandlung ovarieller Störungen in der Allgemeinpraxis. Ärzt. Praxis 1962;14;34:1742-3.
- Heizer H. Kritisches zur *Cimicifuga*-Therapie bei hormonalen Störungen der Frau. Med. Klin. 1960;55;6:232-3.
- Kuiper GGJM, Lemmen JG, Carlsson B, Corton JC, Safe SH, van der Saag PT, van der Burg B, Gustafsson J-A. Interaction of Estrogenic Chemicals and Phytoestrogens with Estrogen Receptor  $\beta$ . Endocrinology 1998;139;10:4252-63.
- Liske E, Boblitz N, Henneicke-von Zepelin H.-H. Therapie klimakterischer Beschwerden mit *Cimicifuga racemosa* - Daten zur Wirkung und Wirksamkeit aus einer randomisierten kontrollierten Doppelblindstudie. In: Phytopharmaka VI, Rietbrock N, editor. Darmstadt: Steinkopff Verlag, 2000:247-57.
- Löhning A, Verspohl EJ, Winterhoff H. *Cimicifuga racemosa* in vitro findings using MCF 7 cells. Poster, Symposium der

Gesellschaft für Phytotherapie, Bonn, November 1998.

Nesselhut T, Liske E. Pharmacological measures in postmenopausal women with an isopropanolic aqueous extract of *Cimicifugae racemosae* rhizoma. 10<sup>th</sup> Annual Meeting of the North American Menopause Society (NAMS), September 23-25, 1999, New York (Abstract No. 99.012)

Nesselhut T, Schellhase C, Dietrich R, Kuhn W. Untersuchungen zur proliferativen Potenz von Phytopharmaka mit oestrogenähnlicher Wirkung bei Mammakarzinom-Zellen. Arch. Gynecol. Obstet. 1993;254:817-8.

Schildge E. Beitrag zur Behandlung von prämenstruellen und klimakterischen Verstimmungs- und Depressionszuständen. Ringelheimer Biologische Umschau 1964;19;2:18-22.

Schotten EW. Erfahrungen mit dem *Cimicifuga*-Präparat Remifeminâ. Landarzt 1958;34;11:353-4.

Starfinger W. Therapie mit Oestrogen-wirksamen Pflanzenextrakten. Med. Heute 1960;9;4:173-4.

Stefan H. Ein Beitrag zu den Erscheinungsformen und zur Therapie hormonal bedingter Biopathiesyndrome der Frau. Ringelheimer Biologische Umschau 1959;14;10:149-52;11:157-62.

Stiehler K. Über die Anwendung eines standardisierten

*Cimicifuga*-Auszuges in der Gynäkologie. Ärzt. Praxis 1959;11;26:916-7.

Stoll W. Phytotherapeutikum beeinflusst atrophisches Vaginalepithel. Doppelblindversuch Cimicifuga vs. Östrogenpräparat. Therapeutikon 1987;1:23-31.

Stolze H.: Der andere Weg, klimakterische Beschwerden zu behandeln. Gyne 3, 1 (1982):14 - 16.

Vorberg G. Therapie klimakterischer Beschwerden. Erfolgreiche hormonfreie Therapie mit Remifeminâ. Z. Allgemeinmed. 1984;60;13: 626-9.

Warnecke G. Beeinflussung klimakterischer Beschwerden durch ein Phytotherapeutikum. Med. Welt 1985;36:871-4.

Wuttke W, Jarry H, Heiden I, Seidlová-Wuttke D. Effects of *Cimicifuga racemosa* on estrogen-dependent tissues. Maturitas 2000;35;Supplement I:S34.

Wuttke W, Jarry H, Heiden I, Westphalen S, Seidlová-Wuttke D, Christoffel V. Selective estrigeb receotir nidzkatir (SERM) activity of the *Cimicifuga racemosa* extract BNO 1055: pharmacology and mechanisms of action. Phytomedicine 2000;7;Supplement II:12,SL-10.

Zava DT, Dollbaum CM, Blen M. Estrogen and Progestin Bioactivity of Foods, Herbs, and Spices. Proc. Soc. Exp. Biol. Med. 1998;217;3:369-78.

Normann Boblitz, MD  
Specialist for Internal Medicine,  
Hildesheimer Str. 77, 30169,  
Hanover,  
Germany.