Therapeutic Efficacy and Safety of *Cimicifuga racemosa* for Gynecologic Disorders

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ABSTRACT

The reproducible quality of phytopharmaceuticals—herbal medicines—is an essential prerequisite for good efficacy and tolerability in the treatment of functional disorders. In clinical trials and scientific investigations, standardized assessments (ie, validated, internationally recognized and accepted scales) provide the basis for establishing clinical efficacy and tolerability. Extracts (ethanolic and isopropanolic aqueous, Remifemin®) of the rootstock of the herb *Cimicifuga racemosa* (black cohosh) are active ingredients developed for the treatment of gynecologic disorders, particularly climacteric symptoms. Drug-monitoring and clinical studies documenting experience with *C. racemosa* rootstock extracts comprise the database of this herbal treatment for menopausal symptoms (eg, hot flashes, profuse sweating, sleep disturbances, depressive moods). These studies show good therapeutic efficacy and tolerability profiles for *C. racemosa*. In addition, clinical and experimental investigations indicate that the rootstock of *C. racemosa* does not show hormone-like activity, as was originally postulated.

Keywords: *Cimicifuga racemosa;* black cohosh; herbal medicine; menopausal disorders; efficacy and tolerability studies

INTRODUCTION

Although hormone therapy is used most effectively for climacteric complaints, premenstrual syndrome, and dysmenorrhea, herbal medicines (also known as phytopharmaceuticals) are also recognized for their efficacy and safety. Commission E of the German Federal Health Authorities certified a favorable benefit:risk ratio for use of *Cimicifuga racemosa* rootstock extracts for "premenstrual and dysmenorrheic as well as climacteric neurovegetative complaints."[1] The benefit of *C. racemosa*

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in alleviating gynecologic symptoms is cited in several publications on herbal medicines.[2-11]

Considerable interest in herbal medicine has been a current trend in the North American market that shows no signs of abating.[12] This may be attributed to a renaissance in "natural living." Concerns about contraindications, risk factors, and adverse drug reactions of synthetic pharmaceuticals do not quite motivate compliance. Approximately one third of North Americans older than 18 years of age use herbal remedies for numerous illnesses; 53% are convinced of their therapeutic efficacy and 65% of their safety.[13] Women experiencing menopausal symptoms often search for alternatives to hormone-replacement therapy[14]; to date, herbal remedies have treated menopausal symptoms in 4% of these patients and premenstrual syndrome in 17%.[13] A natural way of treating menopausal symptoms—in particular, with the *C. racemosa* monodrug preparation Remifemin®*—has recently been discussed in the literature.[6,15-17]

The use of *C. racemosa* rootstock (black cohosh), which grows in the eastern United States and Canada, has a long tradition.[8,18] The shamans of North American Indian tribes and the colonists used black cohosh extracts for joint pain, myalgia, and neuralgia, as well as for climacteric symptoms, general gynecologic complaints, pain in childbirth, and rheumatism.[7,18] In traditional Chinese medicine, *Cimicifugae* rhizoma (rhizome of the *Cimicifuga* species) has been an anti-inflammatory,[19,20] analgesic, and antipyretic remedy.[20]

DATABASE SURVEY

A literature survey of reports published until July 1997 was performed from the DIMDI, MEDLINE, BIOSIS, Embase, STN, and Chemical Abstracts databases using the following key words: *Cimicifuga; C. racemosa; Actaea racemosa;* Traubensilberkerze; Traubensilberkerze Wurzelstock; black cohosh; rootstock; *Cimicifugae* rhizoma; rhizome, *Cimicifuga* root; clinical trials. The database for the Schaper & Brümmer *Cimicifuga* preparation Remifemin® (ethanolic [60% by volume, liquid] or isopropanolic [40% by volume, tablets] aqueous extracts), dating back to 1956, was also considered.[21]

CLINICAL DATA

Case Reports

Since the late 1950s, numerous case reports have been recorded from medical practices on the use of standardized *Cimicifuga* monodrug preparations (aqueous isopropanolic 40% and ethanolic 60% by volume) to treat various gynecologic disorders, such as the climacteric syndrome, menstrual disorders (amenorrhea, oligomenorrhea, dysmenorrhea, polymenorrhea), juvenile disorders, premenstrual syndrome, and complaints of pregnancy.[22-32]

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The literature describes the efficacy of *C. racemosa* extracts in approximately 1500 patients, citing distinct and clear improvements in the clinical picture and good to very good therapeutic responses. The tolerability of *C. racemosa* extracts is described as good and very good; only one report mentioned occasional gastric complaints.[23]

Over the years, favorable experiences with extracts of this medicinal plant were quantitatively assessed, particularly in clinical trials of climacteric disorders.

Drug-Monitoring Studies

In a multicenter drug-monitoring study of 704 individuals with climacteric complaints (data from 629 patients evaluated; mean age 51 years), women were treated with *C. racemosa* rootstock extract (ethanolic extract, 2 × 40 drops/d) for 6 to 8 weeks.[33] The neurovegetative (hot flashes, profuse sweating, headache, vertigo, heart palpitations, tinnitus) and psychological (nervousness, irritability, insomnia, depressive moods) symptoms improved in 80% of women after 4 weeks or disappeared after completion of therapy. In 93% of patients, tolerability was very good; mild and transitory concomitant symptoms (gastrointestinal complaints) were observed in only 7%.

Clinical Studies

In clinical studies with *C. racemosa,* patients with diagnosed climacteric complaints were enrolled according to defined inclusion and exclusion criteria. In the individual studies, these criteria were almost identical, so that a common basis for patient selection was achieved. Thus, patients were matched for age (range 42 to 60 years), height, weight, and body-mass index. As a rule, treatments lasted 3 and 6 months, and *C. racemosa* tablet or solution extracts were used.

Results were compared by means of internationally recognized therapeutic efficacy scales, such as the quantitative Kupperman Menopause Index.[34] In this instrument, menopausal complaints like hot flashes are assigned a higher numerical value (4) than milder concurrent symptoms (1 to 2). This value is multiplied by a numerical conversion factor assigned according to symptom severity (range 0 to 3: severe = 3, not present = 0). The resulting values are added, and the total score indicates the severity of the syndrome (severe, total score >35; moderate 20–35; mild 15–20). A favorable therapeutic result is represented by a total score below 15.

In the early 1980s, therapeutic efficacy was observed in two open, noncontrolled studies[35,36] (n = 36, mean age 51.6 ± 5 years, range 45 to 62; n = 50, mean age 53.3 ± 4.3 years, range 45 to 60) that used the Kupperman Index and the Clinical Global Impression Scale (CGI, evaluation of benefits and tolerability). Efficacy was seen after 4 weeks of treatment with ethanolic extract, 2 × 40 drops/d. After 12 weeks, therapeutic success was statistically significant ($P<.001$) and clinically relevant (CGI assessment: very much better). Evaluation of the Profile of Mood Scale (POMS, self-assessment of the severity of psychological symptoms) established very good therapeutic efficacy of the preparation.[36] In all cases, tolerability was described as good to very good; only 4 patients reported mild gastrointestinal problems at the beginning of therapy.[36]

In an open, controlled, randomized study with reference therapy[37] (n = 60, mean age 54 ± 4 years, range 45 to 60), 3 months' treatment with *C. racemosa* (ethanolic extract, 2 × 40 drops/d; n = 20), conjugated estrogens (0.625 mg/d; n = 20), or diazepam (2 mg/d; n = 20) showed equivalent efficacy in neurovegetative and psychological symptoms, with a statistically significant decrease ($P<.05$). This was seen in the values of the Kupperman Index, the Self-Evaluation Depression Scale (SDS, detection and quantified evaluation of a depression), and the Hamilton Anxiety Scale (HAMA, evaluation and quantification of psychological and somatic anxiety). All medications were assessed as equivalent by the CGI. Compliance was considered good, tolerability very good.

The therapeutic and clinically relevant efficacy of *C. racemosa* (isopropanolic extract, 2 × 2 tablets/d) for climacteric complaints was confirmed in a double-blind, randomized, placebo-controlled comparison with hormone therapy (conjugated estrogens 0.625 mg/d) (n = 80; mean age 51.2 ± 3.1 years, range 45 to 58).[38] For patients receiving *C. racemosa* (n = 30), scores on the Kupperman Index and the HAMA scale versus placebo (n = 20) showed clinical improvements after 4 weeks and were significant in less than 12 weeks ($P<.001$). At treatment end (12 weeks), the Kupperman Index mean score was 15 or less, indicating that no further therapy was required. Treatment with *C. racemosa* was superior in efficacy to that with conjugated estrogens after 3 months. Nonspecific adverse events (eg, headaches) not considered treatment related occurred in the three groups (including placebo).

Because the efficacy of *C. racemosa* extracts for neurovegetative climacteric complaints is comparable to that of hormones, an open, noncontrolled clinical study investigated whether a change from hormone-replacement therapy to *C. racemosa* (isopropanolic extract, 2 × 2 tablets/d) is possible in women with climacteric symptoms.[39] Over a 6-month period, 56% of patients (n = 50, mean age 49) who initially received a hormone combination (estradiolvalerate injection 4 mg and prasterone-nantate 200 mg) required no further hormone treatment when given *C. racemosa*. Only 44% requested one more hormone injection. The Kupperman Index score decreased to below 15 points ($P<.001$), indicating successful treatment. *C. racemosa* was very well tolerated. Thus, in many cases, hormone-replacement therapy may be switched to *C. racemosa* without problems and with equivalent success.

Surgical ovarian deficiencies also respond to *C. racemosa*.[40] In an open, controlled, randomized clinical study with hormone-replacement therapy in 60 women younger than 40 years of age, hormonal deficiencies with climacteric symptoms after hysterectomy (at least one adnexum remaining) were treated with *C. racemosa* (isopropanolic extract, 2 × 2 tablets/d; n = 15) or estriol (1 mg/d, n = 15), conjugated estrogens (1.25 mg/d, n = 15), or a hormone combination (estradiol 2 mg and norethisterone acetate 1 mg, n = 15). After 6 months, a clinically relevant and statistically significant decrease ($P = .01$) in symptoms was seen, verified by reductions in the modified Kupperman Index score (including an additional evaluation of trophic genital disorders). Differences between treatment groups were not significant at 4, 8, and 12 weeks ($P>.05$). Serum levels of luteinizing hormone and follicle-stimulating hormone, determined during treatment, did not change in any group ($P>.05$). Tolerability of *C. racemosa* therapy was very good.

CONSTITUENTS, SAFETY DATA, AND POSSIBLE EFFECTS OF *C. RACEMOSA*

Herbal extracts typically involve numerous constituents. Although the *C. racemosa* rootstock has not been completely analyzed, the triterpene glycosides are considered its decisive components:[41] Actein, cimicifugoside, 27-deoxyacetylacteol, isoferulic acid, salicylic acid, tannins, resins, fatty acids, starch, and fats[18] as well as biochanine[42] have also been identified in *C. racemosa* alcohol preparations.

Constituents of *C. racemosa* rootstock bind to estrogen receptors (source of tissue, rat uteri and pituitary glands[43,44]); however, they do not affect the luteinizing hormone level[21,40] and do not exhibit estrogen-like effects,[21] as postulated from earlier studies of luteinizing hormone suppression[45,46] and effect on functional vaginal parameters,[37,38] described elsewhere.[1] The isoflavone formononetin, which exhibits weak estrogen-like activity[47-49] and shows an affinity to estrogen receptors,[43,47-49] was thought to be an active substance in *C. racemosa*.[43] It has been shown recently, however, that commercially available (ethanolic and isopropanolic) *C. racemosa* preparations do not contain formononetin,[42,50] kaempferol,[50] or genistein.[42]

C. racemosa (isopropanolic aqueous extract) does not have estrogen-like effects in established estrogen-receptor–positive breast cancer cell lines whose growth is estrogen dependent.[51] In vitro, a concentration-dependent proliferation inhibition was observed for *C. racemosa* that may be interpreted as an estrogen-receptor blockade. In the presence of estradiol and *C. racemosa*, the estrogen-induced stimulatory effects may be inhibited by the herbal extract.[21,52] The combined inhibitory effects on breast cancer cells of tamoxifen and *C. racemosa* applied simultaneously were even higher than those of the individual substances.[21,52] Although contraindications are in debate, the present data for Remifemin®* indicate that it is suitable for use in patients with climacteric symptoms and a history of breast cancer.[16,17,52,53]

A recently published experimental investigation showed that *C. racemosa* (ethanolic extracts) did not exert an estrogenic effect on the vagina and uterus of ovariectomized rats and mice.[54]

In vitro *Salmonella* microsome assays (Ames test) showed no evidence of a mutagenic potential of *C. racemosa* (isopropanolic extract). Compared with the negative control, neither a dose-related doubling nor a biologically relevant increase in the mutant count with or without "S9-mix" (simulation of mammalian metabolic effects by homogenized mammalian liver together with cofactors) was observed.[18,21]

A 6-month oral toxicity study in female Wistar rats followed by an 8-week recovery period indicated no toxic potential of the isopropanolic *C. racemosa* preparation, even at a very high dose (up to 5000 mg of *Cimicifuga* granulate/kg body weight). No anomalies were noted in clinical, chemical, histopathologic, or macroscopic organ findings compared with the simultaneously treated control group (amount of inactive additives corresponded to the highest dose).[16-18,21] These results support unlimited application in humans.[55]

Cimicifugae rhizome is a component of two traditional Chinese medicines.[56,57] In teratology studies, up to 2000 mg/kg per day of these medicines was administered orally to female F344/DuCrj rats on days 7 to 17 of gestation. Neither teratogenic nor adverse effects were observed in the fetuses of rats receiving either medicine.

The mode(s) of action of *C. racemosae* rhizome observed in clinical trials cannot be explained with certainty. A likely assumption, however, is that the therapeutic efficacy, repeatedly confirmed and comparable to that of hormones, is not attributable to hormonal (estrogenic) effects.

Shengma (*Cimicifugae* rhizome) is a Chinese drug with central nervous system (CNS) activity. The CNS effects may be explained by results of receptor binding assays, which showed that water extracts of the rhizome act on serotonin (5-HT_{1A}) receptors,[58] and by animal experiments, which showed serotonin-blocking activities for the rhizome.[59] In the clinical studies already described, *C. racemosa* treatment improved climacteric and psychological symptoms, demonstrating a mild psychotropic effect.[36-38] The psychological symptoms of menopause may be managed with a combination of *C. racemosa* and *Hypericum perforatum* (St. John's wort, a CNS-active herb), as demonstrated by results of a multicenter drug-monitoring study in 911 pre-, peri-, and postmenopausal women with psychovegetative disorders.[60] Synergistic effects of this combination are indicated by these data.

The *Cimicifuga* rhizome has been shown to have anti-inflammatory,[19,20] analgesic,[20] and antipyretic effects.[20] In addition, an antiulcer triterpene glycoside racemoside was obtained from the rootstock of *C. racemosa*.[61] *Cimicifuga heracleifolia* Komarov and *Cimicifuga foetida* have demonstrated inhibition of bone resorption in tissue (bone-organ) culture[62] and an antiosteoporotic effect in ovariectomized rats.[63] In these studies, bone resorption was experimentally induced by parathyroid hormone.

CONCLUSION

No known contraindications or interactions with other active substances have been demonstrated for *C. racemosa* extracts.[1] Clinical and statistical data corroborate the therapeutic efficacy of *C. racemosa* for moderate to severe neurovegetative symptoms of the climacteric. Good tolerability and low risk of side effects have been confirmed repeatedly in case reports and clinical studies with *C. racemosa* ethanolic and isopropanolic aqueous extracts.* Experimental studies indicate no toxic, mutagenic, carcinogenic, or teratogenic properties of the rhizome. Extracts of this plant have to be considered as a safe and effective natural treatment for menopausal complaints such as hot flashes, profuse sweating, and sleep disturbances.

*To improve compliance and in response to the recent optimized standardized pharmaceutical extraction of the ethanolic and isopropanolic *C. racemosa* extracts (Remifemin®), the previous daily dosage of four (2×2) tablets or 80 (2×40) drops may be reduced to two (2×1) tablets or 40 (2×20) drops per day, corresponding to 40 mg of herbal drug daily.[1] Equivalence of therapeutic efficacy and safety has been demonstrated.[21]

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