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Cimicifuga racemosa dried ethanolic extract in menopausal disorders: a double-blind placebo-controlled clinical trial

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Abstract

Objectives: To compare the efficacy and safety of the black cohosh root extract Cr 99 with placebo in women with climacteric complaints.
Methods: A multicenter, randomized, placebo-controlled, double-blind, parallel group study was conducted in 122 menopausal women (intention-to-treat population) with ≥3 hot flashes a day, treated over 12 weeks. Two main efficacy measures – weekly weighted score of hot flashes and Kupperman Index – and secondary efficacy variables, e.g. Menopause Rating Scale, were defined. Routine safety laboratory parameters and adverse events were documented.
Results: The primary efficacy analysis showed no superiority of the tested black cohosh extract compared to placebo. However, in the subgroup of patients with a Kupperman Index ≥ 20 a significant superiority regarding this index could be demonstrated ($P < 0.018$). A decrease 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. Prevalence and intensity of the adverse events did not differ in the two treatment groups.
Conclusions: The results indicate a superiority of the tested *Cimicifuga racemosa* extract compared to placebo in patients with menopausal disorders of at least moderate intensity according to a Kupperman Index ≥ 20, but not in the intention-to-treat population as a whole.

Keywords: *Cimicifuga racemosa* (black cohosh) extract; Menopausal disorders; Hot flashes; Kupperman Index; Menopause Rating Scale; Clinical pharmacology

1. Introduction

Due to the changing hormonal situation the menopausal transition period is associated with vasomotor, psychic and somatic disorders, particularly hot flashes, sweating, depressed mood, sleeping

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disorders and urogenital complaints. The symptoms are widespread with prevalences between 60% and 80% whereas duration and severity show a broad range.

In the last decades hormone replacement therapy (HRT) was a widely used and accepted medication for these climacteric disturbances. Numerous clinical studies have demonstrated efficacy and during short-term use safety. However, recent observational and randomized controlled trials suggest higher risks for long-term HRT use, particularly for combined estrogen-progestogen therapy started in the later postmenopause [1–5]. Newer findings show a growing evidence that HRT may increase the incidence of breast cancer, coronary heart disease and stroke in elderly women – whether the administration of unopposed estrogen increases breast cancer risk is doubtful. Thus, a significant number of women and physicians look for other treatment approaches [6,7]. Progressive interest in phytotherapy for relief of climacteric symptoms is seen during the past years and black cohosh root extracts (Cimicifugae racemosae rhizoma) are considered as an important treatment alternative [8–10].

Preclinical in vitro and in vivo tests suggest that these plant extracts exert tissue specific estrogenic effects [11–15]. They may show agonistic actions regarding central nervous system and bone, whereas regarding uterus and breast such actions are unlikely. Additionally, dopaminergic effects – mediated via D2 or D3 receptors – as well as serotonergic and progestogenic effects are proposed [16–19]. The data agree well with the observed improvement of vasomotor and psychic menopausal symptoms in several clinical studies [20–23]. Most of these, however, were poorly designed and do not fulfill actual GCP guidelines.

Thus, the aim of the study was to compare efficacy and safety of the black cohosh root extract Cr 99 with placebo in women with climacteric complaints following strict methodology.

2. Methods

2.1. Study design

The trial was conducted as a prospective, multicenter, randomized, placebo-controlled, double-blind, parallel group study in Switzerland according to GCP guidelines of the European Union, the International Conference on Harmonization and the Declaration of Helsinki. It was approved by the ethic committees of Aargau, Basel, Bern und Zürich.

The patients were randomized in the ratio of 2:1, i.e. the number of patients in the active group was double the size of the placebo group.

The trial was carried out at 12 private gynecological practices and two university menopause centers. The study participants were healthy female outpatients.

The study consisted of a 2-week run-in phase and a 12-week therapy phase. There were five assessments: at week −2 (screening), at week 0 (baseline), at week 4 and 8 and at week 12 (end of treatment).

2.2. Efficacy evaluation

Two main outcome measures were defined: hot flashes as cardinal symptom, i.e. a standardized composite score taking into account number and severity of the hot flashes – weekly weighted score – and Kupperman Index, a validated and internationally used climacteric symptom list [24]. Patients were asked to record number and severity of the hot flashes on a diary each day for the whole treatment period. The Kupperman Index was determined at each visit.

A secondary outcome measure was the Menopause Rating Scale, a recently developed self-assessment instrument [25]. Other secondary outcome measures were urogenital and ophthalmic symptoms, FSH serum level and karyopyknotic index. They were registered at each visit.

Clinical global impression of efficacy by physician and patient were evaluated at week 12.

2.3. Safety evaluation

Routine safety laboratory parameters – hemoglobin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, creatinine – were analysed at week −2 and 12.

Adverse events were documented under treatment at weeks 4, 8 and 12 and clinical global impression of tolerance was assessed at week 12.

2.4. Inclusion and exclusion criteria

Eligible to participate in the study were female patients in the peri- or early postmenopause with

climacteric disorders, aged 45–60 years, ≥3 hot flashes a day corresponding to ≥42 hot flashes during the run-in phase, ≥1 functioning ovary, normal gynecological examinations (endometrium, vagina and breast) and who gave written informed consent.

Exclusion criteria were history of breast or endometrium carcinoma, concomitant medication affecting menopausal complaints, e.g. psychopharmaca, alpha- and betablockers or ergotamine alkaloids (unless a well-controlled long-term therapy), use of HRT within the last month prior to screening visit, alcohol or drug abuse and other serious diseases or conditions interfering with the study objectives.

2.5. Study medication

One group received capsules of *Cimicifuga racemosa* extract (6.5 mg dried rhizome extract, drug/extract ratio 4.5–8.5:1 corresponding to 29–55 mg with an average of 42 mg crude drug, extraction solvent 60% ethanol v/v, excipients: silicium dioxide, lactose monohydrate, cellulose powder, magnesium stearate, talcum, corn starch) and the other group identically appearing placebo capsules (excipients: silicium dioxide, lactose monohydrate, magnesium stearate, talcum, corn starch).

The daily dose was one capsule. The treatment period lasted for 12 weeks.

The supplier of the study medication was Dr. Kolkmann and Partner GmbH Oldenburg Germany.

2.6. Study population

The intention-to-treat population included all enrolled patients who took test medication and had at least one efficacy assessment without serious protocol violations. The per-protocol population consisted of patients with neither serious nor major protocol violations.

The safety population included all patients who took test medication and had at least one contact with the investigator thereafter.

2.7. Statistical analysis

The calculated sample size was 70 in the *Cimicifuga racemosa* group and 35 in the placebo group on the basis of alpha = 0.025 (one-sided), beta = 0.1 and of detecting a large difference between groups corresponding to a Mann–Whitney estimator of 0.71. To compensate for dropouts a 15% higher sample size was chosen.

A directional test based on a multivariate generalization of the Wilcoxon–Mann–Whitney test by Wei and Lachin was applied for the primary efficacy analysis of the two main outcome measures, the weekly weighted score of hot flashes and the Kupperman Index, using the percentage change between end of treatment and baseline values of the intention-to-treat population [26]. The size of the difference between the groups was described with the Mann–Whitney estimator.

The secondary outcome measures were analysed with the same test procedure – interpreted in a descriptive manner.

In addition, subgroup analyses were performed for potentially prognostic variables such as menopausal status and intensity of the climacteric complaints by means of the weekly weighted score of hot flashes and the Kupperman Index. The Cochran–Mantel–Haenszel procedure was applied using the Cox–Mantel test for determination of odds ratios and confidence intervals.

The safety variables were analysed with the Wilcoxon–Mann–Whitney test for criteria of tolerance, the sign test and the shift tables for laboratory parameters.

3. Results

3.1. Study population

The study populations are shown in Table 1. Out of 127 treated patients, five patients were excluded from the intention-to-treat population because of serious protocol violations or a posteriori detected exclusion criteria. Fifteen patients discontinued the study

Table 1
Disposition of patients

Randomized patients	84/45[a]	129
Randomized and treated patients	83/44	127
Safety population	83/44	127
Intention-to-treat population (*ITT*)	*81/41*	*122* (*96*%)
Per-protocol population	68/36	104 (82%)
Drop outs – randomized and treated patients	8/7	15 (12%)
Drop outs – intention-to-treat population (ITT)	6/5	11 (9%)

[a] Verum/placebo.

Table 2
Patient characteristics at study entry (ITT population, verum $n = 81$, placebo $n = 41$)

	Cimicifuga racemosa	Placebo
Age (years)		
Mean ± S.D.	52.5 ± 3.7	52.2 ± 3.5
Median	53.0	52.0
Height (cm)		
Mean ± S.D.	164.9 ± 6.2	166.0 ± 5.2
Median	165.0	165.0
Body weight (kg)		
Mean ± S.D.	67.7 ± 12.9	66.6 ± 11.6
Median	67.0	65.0
FSH level (IU/L)		
Mean ± S.D.	83.3 ± 31.5	93.5 ± 32.0
Median	77.0	94.5
Duration of climacteric disorders (months)		
Mean ± S.D.	36.0 ± 37.9	37.9 ± 40.8
Median	24.0	28.0
Time between last menstruation and study entry (months)		
Mean ± S.D.	38.7 ± 50.5	37.3 ± 51.4
Median	21.8	18.0
Patients without/with hysterectomy (*n*, %)		
Without hysterectomy	68, 84.0	31, 75.6
With hysterectomy	13, 16.0	10, 24.4
Menopausal status (*n*, %)[a]		
Perimenopausal	28, 41.2	15, 48.4
Postmenopausal	40, 58.8	16, 51.6

[a] Patients without hysterectomy; missing verum group 13, placebo group 10.

prematurely. Table 2 lists demographic and diagnostic characteristics of the enrolled patients at study entry.

3.2. Efficacy results – primary efficacy analysis

In the primary efficacy analysis no superiority of the tested black cohosh extract compared to placebo could be demonstrated regarding the two simultaneously tested main efficacy variables.

The weekly weighted score of hot flashes showed a nearly parallel decrease of 37% in the black cohosh group and 30% in the placebo group. Concerning the Kupperman Index the results were similar. A 26% and 17% decrease was observed, respectively (Fig. 1). The global test (Wei-Lachin procedure) resulted in a Mann–Whitney estimator of 0.53 (97.5 % CI-LB = 0.44).

3.3. Efficacy results – subgroup analysis

The analysis of the subgroup of patients with a Kupperman Index ≥ 20, defined as climacteric complaints of at least moderate intensity, showed a significant superiority regarding this index ($P = 0.018$). A decrease of 47% was observed in the black cohosh group of 35 patients, whereas the reduction in the placebo group of 18 patients was 21% (Fig. 2). The weekly weighted scores of hot flashes decreased by 53% and 25% in the active and placebo group, respectively – with a trend towards significance ($P = 0.052$). Concerning the Menopause Rating Scale the active group showed again a significant superiority in comparison with the placebo group ($P = 0.009$). The score values decreased by 48% in the *Cimicifuga racemosa* group and by 14% in the placebo group. The univariate analysis of all outcome measures are shown in Fig. 3. The multivariate analysis thereof resulted in a superiority of the plant extract nearly reaching significance in this subgroup ($P = 0.053$). The results are summarized in Table 3.

The two assessment instruments – the Kupperman Index and the Menopause Rating Scale – correlated markedly and produced similar results ($r = 0.76$).

A further subgroup analysis by intensity of the menopausal disorders regarding the weekly weighted score of hot flashes showed no differences between active medication and placebo.

In the subgroup of perimenopausal patients (verum $n = 28$, placebo $n = 15$) the active preparation showed a superiority with a trend towards significance compared to placebo as assessed by the Kupperman Index ($P = 0.052$).

3.4. Safety results

There were no differences between the *Cimicifuga racemosa* group and the placebo group regarding adverse events or other safety assessments. Frequency – 17/83 patients (20%) in the plant extract group and 10/44 patients (23%) in the placebo group – and intensity of adverse events were comparable in the two groups. No relevant changes under active or placebo therapy were observed with respect to safety variables. In particular, the karyopyknotic index showed no proliferative effects on the vaginal epithelium.

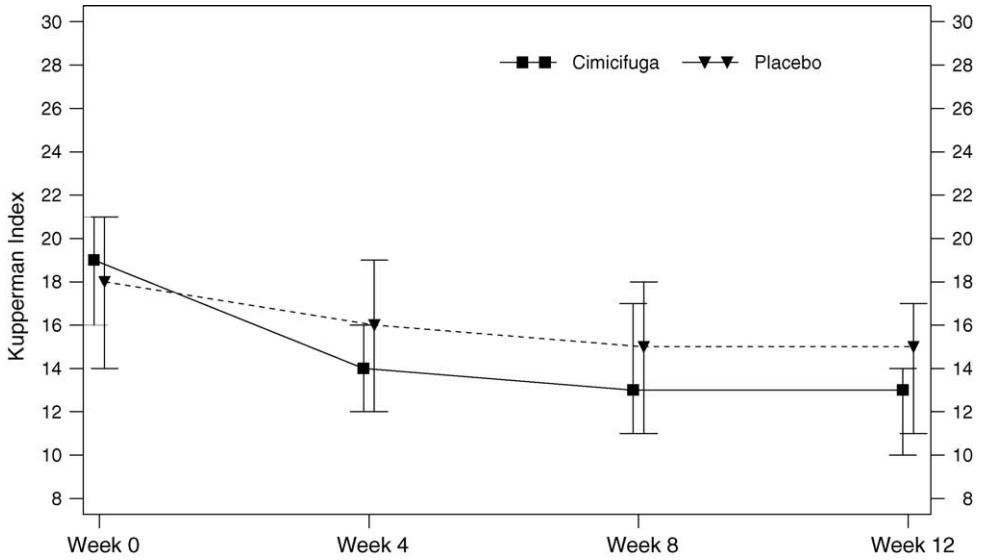

Fig. 1. Kupperman Index; ITT population (verum $n = 81$, placebo $n = 41$); medians and 95% confidence intervals.

4. Discussion

In the primary efficacy analysis no significant difference between the tested black cohosh extract and placebo could be demonstrated. The results, however, indicate a superiority of the active medication compared to placebo with respect to symptoms of menopausal disorders in patients with a Kupperman Index ≥ 20.

The *Cimicifuga racemosa* extract was significantly superior to placebo regarding the Kupperman Index and the Menopause Rating Scale in spite of the small

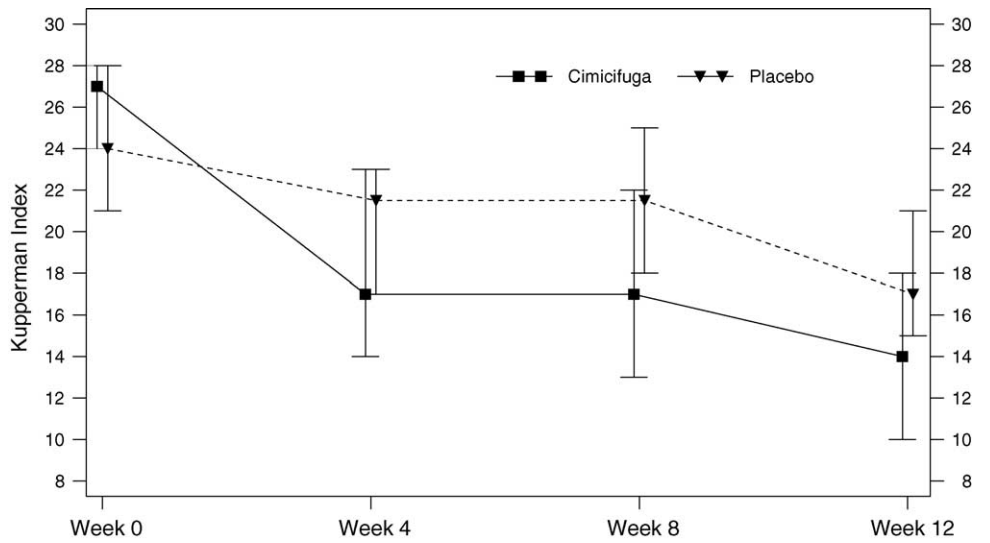

Fig. 2. Kupperman Index; subgroup Kupperman Index ≥ 20 (verum $n = 35$, placebo $n = 18$); medians and 95% confidence intervals.

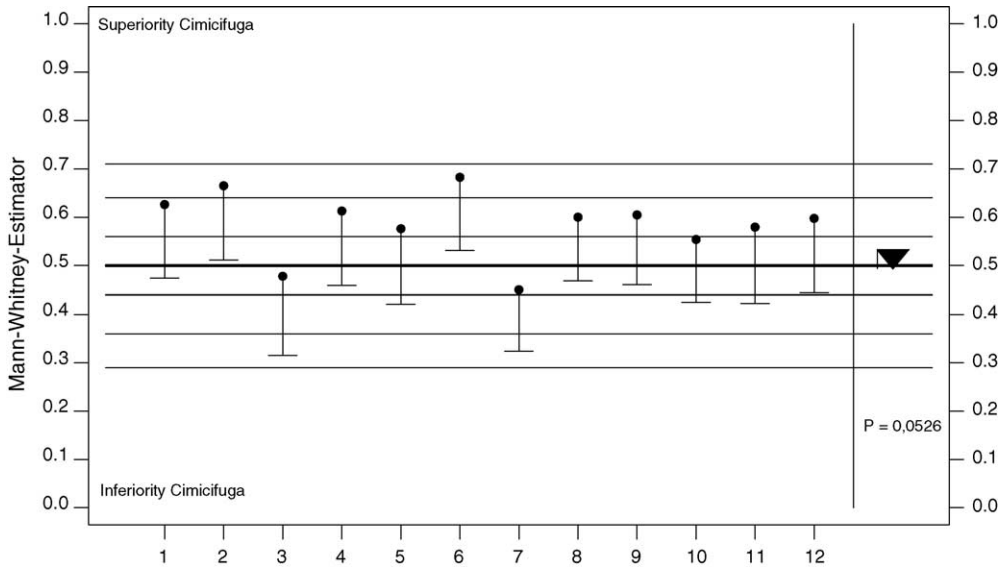

Fig. 3. Primary and secondary outcome measures; subgroup Kupperman Index ≥ 20 (verum $n = 35$, placebo $n = 18$); univariate Wilcoxon–Mann–Whitney tests and Wei-Lachin procedure, Mann–Whitney estimators and 97.5% confidence limits (one-sided). 1 Hot flashes (weekly weighted score), 2 Kupperman Index, 3 light hot flashes, 4 medium-sized hot flashes, 5 severe hot flashes, 6 Menopause Rating Scale, 7 urinary tract disorders, 8 vaginal dryness, 9 dyspareunia, 10 keratoconjunctivitis, 11 clinical global judgement (physician), 12 clinical global judgement (patient). Mann–Whitney estimator: 0.29/0.71 = large difference, 0.36/0.64 = medium-sized difference, 0.44/0.56 = small difference, 0.5 = no difference. Primary and secondary outcome measures: percentage change to baseline except hot flashes, urogenital and ophthalmic symptoms (difference to baseline), clinical global judgement (absolute values).

number of patients of 35 and 18, respectively, in the corresponding treatment groups. The Kupperman Index in the active group decreased by 13 index points, a reduction being described as clinically relevant [27].

This suggests that patients suffering from at least moderate complaints show a better therapeutic response than patients with mild symptoms. A comparable, yet uncontrolled study enrolling only patients with a Kupperman Index ≥ 20 supports this finding [22].

In perimenopausal patients – menstruating or amenorrhoeic < 1 year – but not in postmenopausal patients, the active preparation was superior to placebo with a trend towards significance as assessed again by the Kupperman Index. Animal experiments could serve as explanation [12,28]. A combination therapy of estrogen and *Cimicifuga racemosa* showed to be more effective than estrogen alone with respect to vaginal smear and LH excretion. These findings may correspond to the improvement of climacteric symptoms with *Cimicifuga racemosa* in perimenopausal patients still producing endogenous estradiol.

The Kupperman Index and the Menopause Rating Scale appear to cover the whole spectrum of climacteric complaints more adequately and to respond to treatment effects more sensitively than the weekly weighted score focussed solely on hot flashes and sweating. The two assessment instruments showed similar results. Thus, the newly established Menopause Rating Scale

Table 3
Mann-Whitney estimator, confidence interval – lower border (CI-LB) and *P* values; subgroup Kupperman Index ≥ 20 (verum $n = 35$, placebo $n = 18$)

Outcome measure	Mann-Whitney estimator	CI-LB	*P* value
Kupperman Index	0.67 (medium-sized superiority)	0.51	0.018
Menopause Rating Scale	0.68 (medium-sized superiority)	0.53	0.009
Global test – all outcome measures	0.53 (small superiority)	0.49	0.053

can be recommended for diagnostic procedures and efficacy evaluations in menopausal disorders as mentioned in other studies [25,29].

According to the analysed safety variables as well as according to frequency and intensity of the reported adverse events the 3-month treatment with the tested black cohosh extract may be regarded as safe for women with menopausal disorders. Long-term effects as to breast and endometrium have not yet been studied.

These results may help in the choice of assessment instruments (exploring a spectrum of menopausal symptoms not a unique item) and inclusion criteria (preferably perimenopausal patients with moderate to severe disorders) in future studies.

The findings with the applied black cohosh root extract cannot be extrapolated to other *Cimicifuga racemosa* preparations due to differences in plant material, extraction methods and standardizations based on an inadequate knowledge of the active principles.

In summary, the results indicate a superiority of the tested *Cimicifuga racemosa* extract compared with placebo in patients with at least moderate menopausal disorders, but not in the intention-to-treat population as a whole. The plant extract was well tolerated during the 3-month therapy.

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