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Physiological Investigation of a Unique Extract of Black Cohosh (*Cimicifugae racemosae rhizoma*): A 6-Month Clinical Study Demonstrates No Systemic Estrogenic Effect

E. LISKE, Ph.D.,¹ W. HÄNGGI, M.D.,² H.-H. HENNEICKE-VON ZEPELIN, Ph.D.,¹
N. BOBLITZ, M.D.,⁴ P. WÜSTENBERG, M.D.,¹ and V.W. RAHLFS, Ph.D., C.STAT.³

ABSTRACT

Objective: This study sought to confirm the efficacy and safety of the currently recognized dose of *Cimicifugae racemosae rhizoma* (40 mg/day) and to evaluate a higher dose and its associated physiological effects.

Methods: We conducted a controlled, randomized, double-blinded parallel group study of perimenopausal 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 Menopause Index, Self-Rating Depression Scale (SDS), a global assessment of tolerability, adverse events, routine hematology, and biochemical tests. To determine if the unique *C. racemosa* preparation exerts its effect through an estrogen-identical mode of action, we investigated vaginal cytology and gynecologically relevant hormones.

Results: Both perimenopausal 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 critical organ. Likewise, the lack of significant changes in the levels of gynecologically relevant hormones does not indicate an overall estrogenic effect.

Conclusions: The higher dose did not exert a significantly greater effect on any end point. Thus, the currently recognized standard dose of the isopropanolic aqueous *C. racemosa* extract should be preferred over the higher dose. Despite the absence of a placebo group, this study suggests that *C. racemosa* extract is associated with improvement in menopause symptoms without evidence of estrogenlike effects.

INTRODUCTION

HORMONE REPLACEMENT THERAPY (HRT) has been used successfully for decades to treat estrogen deficiency symptoms, such as vasomotor disturbances and genitourinary atrophy.¹ Al-

though HRT prevents postmenopausal osteoporosis and may offer protective effects against cardiovascular disease after prolonged treatment,² the possibility of side effects, including a transitory increased risk of heart disease at the start of treatment^{2,3} or various forms of cancer^{4,5}

¹Schaper & Brümmer GmbH & Co. KG, Salzgitter, Germany.

²Universitäts-Frauenklinik, Inselspital Bern, Switzerland.

³idv-Data Analysis and Study Planning, Gauting/Munich, Germany.

⁴Practice for Internal Medicine, Hannover, Germany.

has led doctors to disagree on the utility of HRT in all menopause patients. Studies suggest that HRT significantly increases the risk of breast cancer (by 20%–30% if taken for more than 5 years and by 50% in women over the age of 60 who have taken it for more than 5 years).^{5–7} In addition, other studies suggest that the use of estrogen increases the risk of ovarian cancer,⁸ and progestin combined with estrogen may increase the risk of breast cancer.⁷ The benefits associated with HRT use, particularly those related to prevention of osteoporosis, appear only after a 7–10-year period of use.⁹ This benefit may not be realized, as most users discontinue treatment within the first year,^{10–12} and 20%–30% of women for whom HRT is prescribed never begin treatment.¹³

Natural treatments of herbal origin are gradually gaining importance for the relief of acute menopausal symptoms because of their proven therapeutic efficacy and low risk of side effects.^{14,15} *Cimicifugae racemosae rhizoma* (also known as black cohosh, black snakeroot, and rattlesnake root) has a long tradition as a beneficial herbal remedy for joint, muscle, and nerve aches, rheumatism, and gynecological disorders.^{15,16} Since the late 1950s, the safe and effective use of *C. racemosa* in the treatment of menopausal symptoms¹⁷ and menstrual disorders,^{18–28} as well as premenstrual syndrome (PMS),^{19,26,28} has been widely reported in the scientific and medical literature. Clinical studies comparing *C. racemosa* with placebo²⁹ or conventional treatments (HRT/estrogen replacement therapy [ERT],^{29–31} psychotropic drugs³¹ and estriol³⁰) and clinical practice observations suggest positive experiences with *C. racemosa* in daily practice for menopausal complaints.

The German Commission E, set up by the German Federal Health Authorities to collect data and evaluate herbal remedies, published a monograph approving the use of *C. racemosa* crude drug (40 mg/day) as a nonprescription drug for premenstrual discomfort, dysmenorrhea, and menopause.¹⁶ The findings of this Commission are based largely on studies that have demonstrated that a unique extract, Remifemin®/Remifemin Menopause (Schaper & Brümmer GmbH & Co. KG, Salzgitter, Germany), is effective, in both tablet,^{29,30,33} and liquid^{31,34–36} form for the relief of menopausal symptoms.

The intention of our study was to confirm the safety and efficacy of the currently recognized 40

mg/day dose of *C. racemosa* and to evaluate a 3-fold higher dose with the specific aim of looking at the physiological effects induced by this isopropanolic aqueous *C. racemosa* extract. In light of the clinical studies and therapeutic support for the efficacy of *C. racemosa*, there has been controversy as to whether the compounds of the *C. racemosa* rootstock have an estrogen-identical profile as determined by the organ-specific agonistic effects seen with estradiol.^{16,29,31,32,37–41} To confirm the presence or absence of an estrogen-identical effect of the Remifemin *C. racemosa* extract, vaginal cytology and gynecologically relevant hormones were monitored.

MATERIALS AND METHODS

Study design

This study, conducted in accordance with the Good Clinical Practice (GCP) Guideline⁴² and the Helsinki Accord⁴³ and other European ethics commissions, was carried out at four gynecological clinics within the Polish medical academies, Szczecin, Warszawa, Gdansk, and Bydgoszcz, during 1995 and 1996. Written informed consent was obtained from all study participants. Quality was assured by GCP monitoring and an independent audit of all centers and study reports. In order to guarantee a balancing of treatments per trial center, patients were randomized to treatments using a random permuted block design (RANCODE by idv, Gauting, Germany). The double-blind, randomized, parallel group multicenter study of 150 perimenopausal and postmenopausal outpatients extended over a 12-week treatment period, with the majority of the patients enrolling in a continuation study to 24 weeks. The protocol-specified sample size ($n = 150$) was based on an ability to detect a 0.5 standardized difference ($\alpha = 0.05$: one sided; $\beta = 0.1$). Data were collected at time 0 (baseline), weeks 2, 4, 8, and 12 (main study months 0–3), and weeks 16, 20, and 24 (extension study months 4–6).

Study population

The study protocol inclusion criteria allowed perimenopausal and postmenopausal outpatients, aged 42–60, with a Kupperman Menopause Index score ≥ 20 (at least moderate severity). Exclusion criteria included serious gy-

neurological, internal, or psychiatric diseases or other states or conditions that could interfere with the study objectives. After receiving written and verbal instructions about type, importance, implications, and duration of the study and information about alternative therapies, all patients gave voluntary written consent to participate in the study. Of the 152 randomized patients, 149 participants were evaluated in the 12-week study intention-to-treat (ITT) population. One hundred twenty-three subjects completed the 12-week study without any major protocol violation and were included in the per-protocol (PP) data set. One hundred sixteen subjects continued into the extension study and were evaluated after 24 weeks.

Products for investigation

The study treatment consisted of an isopropanolic aqueous extract (40% v/v) from the rootstock of *C. racemosa* (Remifemin®). One group received the standard 39 mg crude drug per day dose, and the other received a high dose, 127.3 mg crude drug per day. Inactive ingredients were cellulose powder, potato starch, magnesium stearate, and peppermint oil. The study's double-blind design was maintained by ensuring that both doses were similar in taste, odor, and appearance blistered using opaque foil and indistinguishable to the patient and investigator. The preparations were produced according to good manufacturing practice (GMP) standards, and a certificate of analysis and description of the investigational product were filed with the study documentation (batch No. standard 504860; high 504740).

Efficacy/tolerability

The Kupperman Menopause Index, which has been used in many similar studies and is generally regarded as a valid, reliable, and responsive efficacy criterion,^{29–31,33–36,44} was the primary measure of efficacy. Useful categories for describing clinical relevance of the index are: >35 (severe complaints), 20–35 (moderate complaints), 15–19 (mild complaints), <15 quasinormal.^{29,45} A secondary efficacy criterion was the Self-Rating Depression Scale (SDS), which was validated previously as a measure of efficacy in another *C. racemosa* study.³¹ Values on the SDS scale between 41 and 47 indicate mild depression, and values below 41 indicate a normal state. A

clinical global impression of efficacy based on a 5-point rating scale was also determined. Safety was assessed using a global assessment of tolerability (5-point rating scale), number of adverse events, and routine hematology and biochemistry studies.

Physiological parameters

Evaluation of physiological effects was based on vaginal cytology measures and hormone level determinations. The vaginal cytology parameters were the degree of cell proliferation in the vaginal epithelium (according to Schmitt's graduation scale),⁴⁶ the karyopyknotic index (percentage of surface cells with completely pyknotic cell nuclei in relation to the nonpyknotic squamous epithelium cells found in the smear), and the eosinophilic index (ratio of eosinophilic/basophilic surface cells found in the smear). Levels of the following hormones were measured in serum: 17 β -estradiol (E₂), luteinizing hormone (LH), follicle-stimulating hormone (FSH), prolactin (PRL), and sex hormone-binding globulin (SHBG). Physiological parameter data were collected at weeks 0 (baseline), 4, 12, and 24.

Statistical analysis

This study was statistically designed and analyzed using internationally recognized standards and procedures in accordance with EU guidelines.^{42,47} The powerful directional test (test for stochastic ordered hypotheses) based on a multivariate generalization of the Wilcoxon-Mann-Whitney test by Wei and Lachin^{48,49} was the primary analysis procedure for testing for differences between groups ($\alpha = 0.05$). As a measure of statistical relevance, the two-sided univariate 95% confidence intervals (95% CI) of the Mann-Whitney value (MW) were evaluated for combined and local results. The primary analysis focused on the Kupperman Index at weeks 2, 4, and 8 using the null hypothesis H₀: MW \leq 0.5 and the alternative hypothesis H_A: MW > 0.5. This test allows for a simultaneous decision regarding superiority or equivalence⁵⁰ and provides data about the precision of the study. For the purpose of interpretation of efficacy data, a responder analysis was performed, counting all patients who, after treatment, had a Kupperman index score <15 (favorable therapeutic result).

In an effort to analyze all patients in this study, a supportive analysis was performed for all patients treated according to the protocol (PP). Pa-

tients who had missing values were included in the ITT population analysis only. Replacing missing values with the last-value-carried-forward (LVCF) method, as defined by Gillings and Koch,⁵¹ included all patients who had at least one observation after the start of treatment.

RESULTS

Patient characteristics

The number and disposition of the patient populations in this study are shown in Table 1. The dropout frequency was comparable in both groups. With the exception of the menopause state (perimenopause, postmenopause, $p = 0.239$), the two groups were comparable with respect to age, height and weight, and duration of complaints (Table 2). The two groups were also comparable with regard to previous treatment, bleeding anomalies, concomitant diseases, vital statistics, baseline efficacy criteria, clinical chemistry, urinalysis, and hematology. An analysis of the pill count data demonstrated a high level of compliance in both dose groups.

Efficacy and tolerability

Both the standard and high dose preparations of this unique *C. racemosa* extract exerted a substantial effect by decreasing (normalizing) the median value of the Kupperman Index. No indication for statistical superiority of the higher dose was observed in either the ITT (MW = 0.47, $p = 0.73$) or PP datasets. The lower boundary of the one-sided 95% CI of MW was 0.36. At baseline, ITT population patients had a Kupperman Index score of 30.5 in the standard dose group and 31 in the high-dose group. After 12 weeks of treatment, the median scores decreased to 8 and 7, respectively (Fig. 1). A responder analysis (score < 15) demonstrated that 70% (52 of 74) of the standard dose group and 72% (54 of 75) of the high-dose group were responders (95% CI: 59%–80% and 61%–82%, respectively). The SDS supports the Kupperman Index data, indicating that the median score decreased from 44.5 to 37 (standard dose) and from 44 to 36 (high dose). Thus, the decrease reflects an improvement in the state of menopausal depression. The global assessment of efficacy after 12 weeks showed that 78.4% of the standard dose group ($n = 74$) and 78.6% of the high-dose group ($n = 75$) reported

TABLE 1. OVERVIEW OF PATIENT FLOW

<i>Population size</i>	<i>Standard dose (39 mg/day)</i>	<i>High dose (127.3 mg/day)</i>	<i>Total</i>
Randomized	76	76	152
Dropouts (weeks 0–12)	9	10	19 ^a
Lack of efficacy	3	5	8
Adverse event	2	1	3
Protocol noncompliance	1	1	2
Administrative reason	0	1	1
Other	3	2	5
Not entering extension study	10	7	17
Regular, no reason	7	6	13
Administrative reason	1	1	2
Lack of efficacy	2	0	2
Dropouts (weeks 12–24)	3	2	5
Lack of efficacy	1	1	2
Administrative reason	1	0	1
Other	1	1	2
Datasets			
Safety	75	75	150
ITT	74 ^b	75 ^c	149
PP	61	62	123

^a4 of 19 patients terminated study after week 12 and thus are available for all data evaluations until that week.

^b2 patients failed to return after baseline visit.

^c1 patient excluded from ITT dataset because of drug discontinuation after 3 days of intake (reason: lack of efficacy).

TABLE 2. PATIENT DEMOGRAPHIC CHARACTERISTICS

Characteristic	Standard dose (39 mg/day)	High dose (127.3 mg/day)
Age, years		
Mean/SD	49.7/4.39	50.2/4.45
Median	48	49
Minimum/maximum	42/60	42/60
Weight, kg		
Mean/SD	66.6/10.73	67.6/9.72
Median	66	66
Minimum/maximum	45/99	50/90
Height, cm		
Mean/SD	162/4.97	163.1/5.86
Median	163	164
Minimum/maximum	151/175	150/176
Duration of complaints		
Up to 1 month	1	0
>1–6 months	11	10
>6–2 years	34	34
>2 years	28	31
Type of menopause		
Perimenopause	28	35
Early postmenopause (<2 years)	18	18
Late postmenopause (≥2 years)	28	22

an overall rating of “very good” or “good.” The remaining patients reported either a “moderate” (16.2% standard, 13.3% high) or “bad” (5.4% standard, 8% high) assessment of overall treatment efficacy. The differences between standard and high-dose groups for all efficacy criteria were not statistically significant. An analysis of menopause

subgroup by type (perimenopause or postmenopause) suggested a possible superiority of the high-dose preparation in the perimenopause group). However, this conclusion requires further investigation.

As with the efficacy data, the tolerability findings also appeared to be unaffected by dose. Over

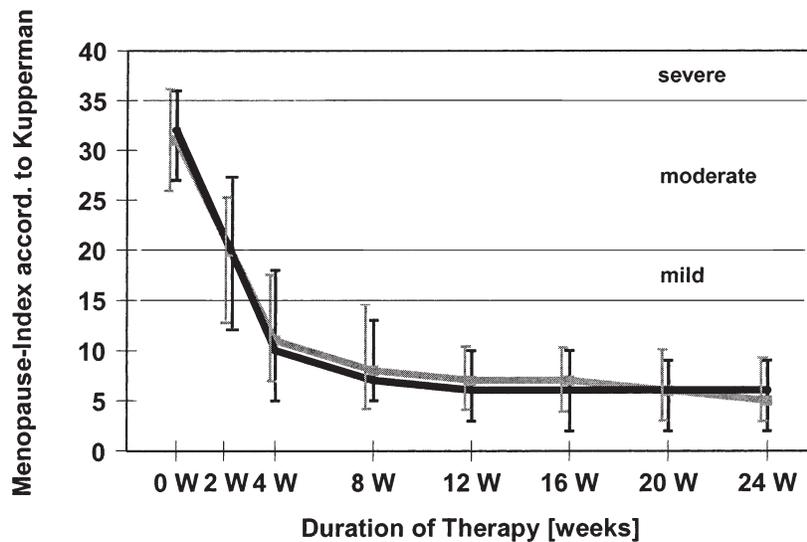


FIG. 1. Course of the Kupperman Menopause Index (ITT population, medians and quartiles) (Gray curve) *C. racemosa* standard dose (39 mg/day). (Black curve) *C. racemosa* high dose (127.3 mg/day). Scores between 15 and 20 indicate mild complaints, between 20 and 35 indicate moderate complaints, and >35 indicate severe menopausal complaints.

comparable treatment durations, both the standard and high-dose groups reported “good” or “very good” tolerability ratings (standard: 94.7% [71 of 74] at 12 weeks and 100% [57 of 57] at 24 weeks; high: 82% [69 of 75] at 12 weeks and 100% [59 of 59] at 24 weeks). Similarly, the prevalence rates of adverse events (AE) were statistically equal (MW = 0.5; CI: 0.44–0.54) in the two dose groups (1.8%–7% standard; 1.5%–8 % high). In the 12-week study, 19 adverse events (7 in standard dose group, 12 in high-dose group) occurred after ingestion of the study medication. However, there was no report of a definite causal relationship between the intake of the investigational product and an AE. These AE, most of which were mild or moderate, could be classified in the following organ classes: gastrointestinal, 5 (standard 1, high 4); CNS, 5 (standard 1, high 4); breast/genitals, 5 (standard 3, high 2); other, 4 (standard 2, high 2). Other reported complaints were joint aches and chest pain. One patient reported metrorrhagia, determined to be caused by an inactive endometrium. Neither treatment dose (standard or high) influenced biochemical or

hematological laboratory findings. During treatment weeks 12–24, no AE that were causally related to the tested products occurred.

Vaginal cytology

Statistical analyses of the ITT and PP groups suggest that the two doses of *C. racemosa* did not cause an alteration in the vaginal cytology measures during the initial 12-week study ($n = 149$) or the extended 24-week study ($n = 116$). If these doses of *C. racemosa* had exerted an estrogenic effect, cell proliferation would have reached degree 3–4 or degree 4, indicating a dominance of outer surface cells, with few parabasal or inner surface cells. Similarly, an estrogenic effect would have been expected to induce a karyopyknotic index similar to that of a mature woman during the ovulation phase (60%–90%),⁵² and an eosinophilic index between 45% and 65%.

After 24 weeks of therapy, most patients maintained a proliferation degree of 2 (only intermediary cells) or 2–3 (mostly intermediary cells and scattered surface cells). Some patients had a pro-

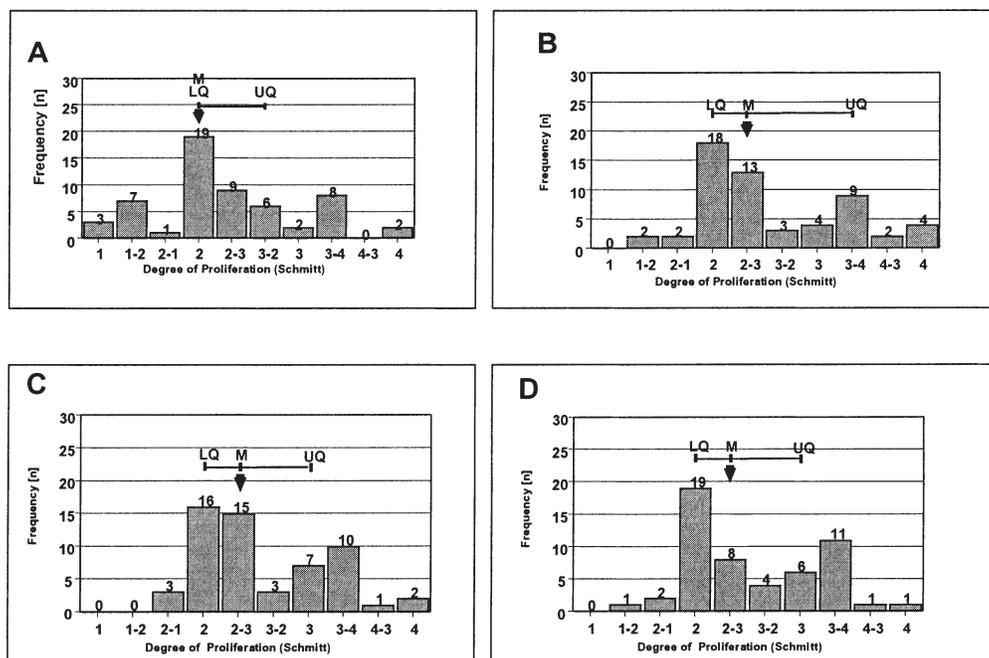


FIG. 2. Degree of vaginal cell proliferation. Frequency distribution for the intention-to-treat (ITT) population including perimenopausal and postmenopausal patients at baseline (A), 4 weeks (B), 12 weeks (C), and 24 weeks (D) after treatment with the standard dose (39 mg crude drug per day) of *C. racemosa*. Statistical measures are incorporated. M, median (arrow); LQ, lower quartile; UQ, upper quartile. Over the treatment period of 24 weeks, the center of distribution is associated with degree 2 (only intermediary cells) and degree 2–3 (mostly intermediary cells, individual inner surface cells). Degree 1 corresponds to the cellular appearance of only parabasal cells, and degree 4 corresponds with only external superficial cells.

liferation cell status of degree 3–2 (predominantly inner surface cells, single intermediary cells) throughout treatment. There was no significant change in the number of patients with proliferation degrees 3–4 or even higher (which would have indicated an estrogenic effect on this tissue). The frequency distribution of cell proliferation for the standard dose group is represented in Figure 2. The high-dose group reported statistically similar values for degree of proliferation. Within the perimenopause (standard: $n = 27$, high: $n = 33$) and postmenopause (standard: $n = 46$, high: $n = 37$) strata, data suggested a similar slight but insignificant increase in the degree of cell proliferation.

Both standard ($n = 57$) and high-dose ($n = 59$) treatment groups reported a slight but non-significant increase in the karyopyknotic index. The mean karyopyknotic index increased from 16% (range 0%–50%) at baseline to 24% (range 5%–60%) at 24 weeks and from 17% (range 0%–60%) to 22% (range 4%–60%), respectively, for the standard and high-dose treatment groups, representing nonclinically relevant findings.

Similarly, the eosinophilic index exhibited a slight but nonsignificant increase for both the standard and high-dose groups. The mean value

of the eosinophilic index in the standard dose group ($n = 57$) increased from 18% (range 0%–80%) at baseline to 25% (range 0%–60%) at 24 weeks. In the high-dose group ($n = 59$), the corresponding values of the eosinophilic index were 19% (range 0%–70%) at baseline and 23% (range 0%–70%) at 24 weeks.

Gynecologically relevant hormones

In both the perimenopausal and postmenopausal patients, no significant differences were observed in the levels of E_2 , LH, FSH, PRL, and SHBG (data not shown) after treatment with the standard or high dose of *C. racemosa*. For looking at the physiological effects of *C. racemosa*, we report the hormone levels for the postmenopausal group only (Fig. 3) because of the normal hormone variability in perimenopausal women.

DISCUSSION

Efficacy and tolerability

The objective of this study was to confirm the safety and efficacy of the recognized German

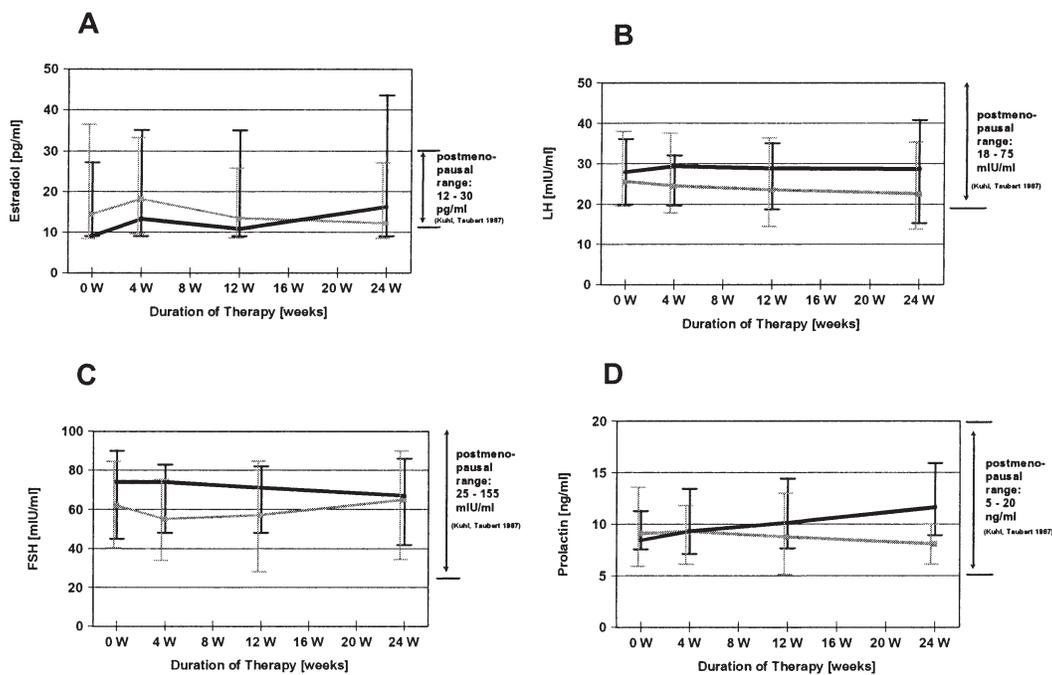


FIG. 3. Hormone levels in the postmenopause strata during treatment. Over the treatment period of 24 weeks, levels of E_2 (A), LH (B), FSH (C), and PRL (D) were measured for the two doses of *C. racemosa*. Standard dose: 39 mg crude drug per day (gray curves) ($n = 36-46$); high dose: 127.3 mg crude drug per day (black curves) ($n = 31-37$). The points represent the median values, with lower and upper quartiles for the ITT collective. The lines at right side indicate the normal range of hormone levels in postmenopausal women without medication.

Federal Health Authority's monograph-compliant dose (40 mg/day) of *C. racemosa* extract for the treatment of menopausal symptoms. The safety and efficacy of the standard dose were compared with those of a high dose to determine if differences in speed of onset or level of therapeutic effect could be observed. However, no dose-response effect could be demonstrated, suggesting a treatment ceiling effect that is attainable by the standard dose. Thus, the currently recommended 40 mg crude drug per day dose appears to be sufficient for the desired relief of menopausal symptoms.

Although this study did not include a placebo control group, excluding the possibility of an internal validation for the results, our findings are consistent with numerous other studies^{29–31,33–36} in which a substantial superiority of the isopropanolic *C. racemosa* extract over placebo was demonstrated with the standard dose.²⁹ With respect to the tolerability and safety of *C. racemosa*, our study is also consistent with the earlier clinical studies that reported only few adverse events and gastric complaints, even at higher doses than previously examined. These findings further support a clinically relevant treatment benefit of the *C. racemosa* preparation studied.

Our findings that patients show positive effects of treatment throughout the 24-week extended study, without adverse effects or laboratory changes indicative of toxic effects, suggest that this preparation can be safely used over at least a 24-week period. Furthermore, based on the lack of treatment differences between perimenopausal and postmenopausal women, these findings support the utility of *C. racemosa* treatment in menopausal women even if HRT is contraindicated.

Vaginal cytology

To determine if *C. racemosa* acts through an estrogenlike mechanism, this study looked at the vaginal epithelium, an exceptionally sensitive indicator of an estrogenic effect.⁵³ The degree of cell proliferation, the karyopyknotic index, and the eosinophilic index were monitored to evaluate whether *C. racemosa* exerts an estrogen-identical effect. The degree of proliferation was similar in both *C. racemosa* dose groups during the course of the treatment. Only intermediary cells or intermediary cells with individual inner surface cells were observed in the smear (proliferation degree 2 or 2–3). Neither dose group (standard

or high) reached a degree of proliferation indicating an estrogenic effect (proliferation degree 3–4 or 4) of *C. racemosa*. The same observations were made with respect to the eosinophilic and karyopyknotic indices, where no significant differences were observed between dose groups.

Based on the vaginal cytology data from this study, claims of an estrogen-identical effect of the *C. racemosa* extract^{16,29} cannot be substantiated. Our results are similar to those of Nesselhut and Liske,⁵⁴ who reported the absence of effects of *C. racemosa* on the female genital tract. In their study, postmenopausal patients had no change in endometrial thickness, monitored by transvaginal sonography, or in hormone levels (LH, FSH, PRL, E₂) following treatment with approximately 136 mg/day isopropanolic *C. racemosa* extract for 3 months. Animal experiments on the uterine growth of immature mice and proliferation of the vaginal epithelium of ovariectomized rats³⁷ also support the conclusion that this *C. racemosa* extract does not have an estrogenic effect.

Gynecologically relevant hormones

The endocrinological findings also support the absence of an estrogenic effect in patients treated with either the standard or high dose of the isopropanolic aqueous *C. racemosa* extract. During menopause, E₂ concentrations decrease,⁵³ causing an increase in FSH and LH levels.⁵⁵ In this study, because no relevant differences in E₂ levels during therapy could be found, there is no support for the theory that *C. racemosa* extracts influence endogenous estrogens. If *C. racemosa* followed an estrogenic pathway, we would expect LH and FSH levels to decrease because of the E₂-induced negative feedback mechanism. However, in the current study, the concentrations of both gonadotropins remained almost constant throughout the treatment period, thus suggesting the lack of an estrogenic effect. Data from a study of hysterectomized menopausal patients³⁰ correlates with our study data, suggesting that *C. racemosa* does not influence the LH and FSH serum concentrations.

In contradiction to our data, a clinical trial of menopausal women³² found that *C. racemosa* treatment reduced LH secretion while not influencing the FSH and PRL serum concentrations. Likewise, two studies of ovariectomized rats suggest that *C. racemosa* has an estrogenic effect, causing a reduction in LH concentration.^{38,39} The *in*

vitro binding study of *C. racemosa* (methanolic extract) shows that formononetin, an isoflavone (phytoestrogen) fraction, binds to estrogen receptors.³⁸ Although the *C. racemosa* extract in this binding study contained formononetin, recent pharmacological investigations demonstrate that the commercially available *C. racemosa* preparation used in the current study does not contain formononetin.^{40,56} The effects noted in this study, therefore, cannot be attributed to the presence of formononetin.

The presence or absence of formononetin may affect the clinical effects of *C. racemosa* extracts, and the specific method of extraction (i.e., isopropanolic vs. ethanolic and methanolic) or origin of the medicinal plant⁵⁷ may also influence efficacy and mechanisms of action. Such differences support the fact that clinical effects could be formulation dependent, suggesting that not all extracts of *C. racemosa* may provide similar efficacy and tolerability.

It has been reported that PRL levels fluctuate slightly during menopause.⁵³ In our study, PRL did not show any significant changes following standard or high-dose *C. racemosa* treatment. However, our data are in contrast to *in vitro* investigations of hypophyseal cell cultures, which suggest a decrease in basal PRL secretion and a thyrotropin-releasing hormone (TRH)-stimulated PRL secretion due to *C. racemosa*.⁵⁸ Furthermore, this *in vitro* study showed that the effects of *C. racemosa* could be reversed by treatment with haloperidol, suggesting that the extract follows a dopaminergic mechanism, the significance of which is unknown.⁵⁸ This hypothesis requires further investigation.

Levels of SHBG, which has a high affinity for estrogens and androgens, can fluctuate slightly during menopause because of the decreased levels of estrogen.⁵³ However, we did not find any significant changes in SHBG levels after either dose of *C. racemosa* extract.

Our cytology and hormone level findings that *C. racemosa* does not have an estrogen-agonistic effect are supported by studies that indicate that this extract does not induce an estrogenlike effect on vagina, uterus, or breast tissue.^{41,54,59,60} Although *C. racemosa* does not have an estrogenlike effect on the female reproductive organs, there are data that suggest it may exert an estrogenic effect on other tissues. Animal experiments have detected increased estrogen receptor-alpha expression in the preoptic region of the hypothala-

mus of ovariectomized rats treated with *C. racemosa*,³⁸ and an estrogenic effect of *C. racemosa* extract on bone tissue.⁵⁷ In contrast, estrogen antagonism has been demonstrated in studies of estrogen receptor-positive breast cancer cell lines (MDAMB 435 S,⁴¹ MCF-7⁵⁹), supporting the position that isopropanolic *C. racemosa* should not be contraindicated in patients with breast cancer.¹⁷

Despite earlier discussions in the literature, we cannot confirm that the mode of action of this isopropanolic aqueous extract in two different doses (39 mg crude drug daily and 127.3 mg crude drug daily) causes an overall estrogenic effect. If the *C. racemosa* extract did exert estrogenic effects, we would have expected to see an increase in vaginal proliferation and an increase in E₂ levels, causing a decrease in LH and FSH levels. Data from our study did not reveal any significant changes in the vaginal proliferation or gynecologically relevant hormone levels. Based on our results, it is clear that the mode of action of this isopropanolic aqueous extract differs from that of estrogen, possibly suggesting a tissue-selective mechanism.

CONCLUSIONS

This study is consistent with the findings of other reports on the efficacy and safety of the standard 40 mg/day dose of *C. racemosa*, as recommended in the 1989 German Federal Health Authority monograph,¹⁶ in spite of the absence of a control group. Furthermore, based on the vaginal cytology and gynecologically relevant hormone parameters of this GCP-compliant clinical study, we conclude that *C. racemosa* does not alter hormone levels or induce estrogenlike effects and supports other claims that there is no estrogenic effect of this isopropanolic aqueous *C. racemosa* extract on the female genital tract or breasts.^{54,60,61} Further investigation is necessary to evaluate the mechanism of action and to determine the possible favorable effects of *C. racemosa* on lipid metabolism and the cardiovascular and skeletal systems.

In the treatment of menopausal symptoms, it is important to consider the potential side effects of any treatment option. HRT/ERT can be associated with an increased risk of endometrial, ovarian, and breast cancers,^{8,61,62} specifically in women older than 55 and those who have used

HRT for >5 years.^{8,61} Thromboembolism and increased risk of heart disease also have been associated with initiation of HRT/ERT,^{2,3,63,64} further warranting the need for alternative treatments for patients at high risk for heart-related disorders. Based on these concerns, it has been recommended that patients with endometrial, ovarian, or breast cancer or at risk for heart disease consider alternative therapies for relief of menopausal symptoms.⁶² Safe alternative treatments are also valued for women who refuse HRT because of its inherent risks.

The findings of our study indicate that this *C. racemosa* formulation offers an alternative for menopausal complaints when HRT is either contraindicated or refused.

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Address reprint requests to:

Eckehard Liske, Ph.D.

Schaper & Brümmer GmbH & Co. KG

Bahnhofstrasse 35

D-38259 Salzgitter

Germany