

Remifemin® Study Compendium



Expertise in the treatment of
menopausal symptoms since 1956

Hormone-free phytotherapy with the
unique isopropanolic
Cimicifuga racemosa (iCR) special extract



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Black cohosh
Cimicifuga racemosa L. (Nutt.)
Actaea racemosa L.



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Menopausal complaints, due to hormonal changes in the female body, can arise during the climacteric. The climacteric includes three stages: premenopause, perimenopause and postmenopause. These are temporally related to the final menstruation known as the menopause. During this time the ovaries gradually decrease their production of estrogen and progesterone. This leads to an increased release of gonadotrophic hormones, i.e. luteinizing hormone (LH) and follicle stimulating hormone (FSH), from the pituitary gland. This hormonal change is considered responsible for numerous menopausal symptoms, including not only vasomotor and vaginal symptoms but also psychological symptoms. Some of the most notable symptoms are: hot flashes, sweating, vaginal dryness, sleep disorders, irritability, and nervousness. During this time more than 70% of affected women complain about more or less pronounced menopausal symptoms; about one third of the women suffer from mild, moderate, or severe symptoms.

In order to relieve menopausal symptoms, hormone therapy is still used in many cases today. However, there are phytotherapeutic alternatives, with clinically proven efficacy and safety, such as treatment with the isopropanolic extract from black cohosh root (iCR) in Remifemin®.

Black cohosh (*Cimicifuga racemosa* L. (Nutt.), *Actaea racemosa* L., CR) is a species from the family Ranunculaceae. It is indigenous to Northeastern America and Canada. The oldest known description goes back to 1680 and is from R. Morrison under the name "Christopheriana canadensis".²⁷ As early as 1729, some samples of this species were planted by John Bartram in the first botanical garden in America. In the 19th century, black cohosh, together with other American plants, was brought to Germany.

In 1753 black cohosh was first published under its first botanical name "*Actaea racemosa* L." in *Species Plantarum*,⁴⁴ and in 1818 Thomas Nuttall used "*Cimicifuga racemosa*", the common name today, to describe the plant.³¹ The genus name "*Cimicifuga*" is derived from Latin. The word "Cimex" means "bug". "Fugare" means "to banish" - thus "banishes bugs". This led to the common name bugbane. The subsequent epithet of the species name "*racemosa*" comes from "*Racemus*", which means cluster of grapes and refers to the arrangement of the blossoms.

Black cohosh has a centuries-old tradition as a medicinal plant. Long ago shamans from tribes native to North America used different parts of the plant in

their indigenous medicine for various indications. For example, exhaustion/burn-out, rheumatism, and bronchial catarrh were treated.¹² But the use in general gynecology was¹² and is one of the most important areas of application for black cohosh.

In a description of black cohosh for the American Medical Association in 1849, Frances Porcher wrote: "The root is used in the debility of females attendant upon uterine disorder, and, in its action, is thought to have a special affinity for this organ."³⁵

In 1989, in the corresponding monograph, the Commission E of the German health authority (BfArM), now the Federal Institute for Drugs and Medical Devices (BfArM), named premenstrual and dysmenorrheal as well as neurovegetative complaints induced by menopause as indications for extracts made from the rhizomes of *Cimicifuga racemosa*.¹⁹ The World Health Organization (WHO) also listed climacteric symptoms such as hot flushes, profuse sweating, sleeping disorders and nervous irritability in their 2002 monograph.⁴⁵ In addition, in 2011 monographs were published by the European Scientific Cooperative on Phytotherapy (ESCOP; climacteric symptoms) as well as the Committee for Herbal Medicinal Products (HMPC; menopausal complaints).^{9,10}

Over 90 years ago studies and records of the treatment of menopausal complaints with extracts from black cohosh already existed. Shortly after hormone therapy for menopausal complaints was introduced, the reduction of hormone therapy, at a minimum, was the focus of many publications.

The herbal medicine now known worldwide as Remifemin® was launched on the German market in 1956. Even back then the isopropanolic special extract from *Cimicifuga racemosa* (iCR) was already used. In 1990 the product range was extended with the combination drug Remifemin® plus, which included St. John's wort (*Hypericum perforatum*) in addition to the iCR special extract. The range was extended again in 2012 with the addition of Remifemin® mono with a practical single daily dose.

Directly after the introduction of Remifemin®, the first very positive comments were made by Günther and Tietze at a therapy congress in Karlsruhe in 1956.⁴¹ In addition in *Therapiewoche* 7 (1957), Tietze spoke positively about treatment with Remifemin® and reported good experience in the treatment of menopausal complaints.⁴¹ Up to that point in time, including a publication by E. Schildge³⁹ in 1964, there had already been reports on around 1800 patients treated with Remifemin®.

Therapeutic studies on efficacy and tolerability were performed quite frequently. From 1991 - 1997 alone, treatment data on around 2,800 women with menopausal complaints were compiled in studies where Remifemin® was used. Today, the Remifemin® products are the most frequently studied herbal preparations for the treatment of menopausal symptoms. This includes comparative studies with hormone therapy,^{2,28} dose comparisons,^{24,25} and studies that clearly demonstrate the superiority of the combination drug Remifemin® plus for predominantly psychological symptoms.^{5,6,23,42} A good overview is presented in a review article by Beer et al. 2013⁴ and in an update published in the *Zeitschrift für Phytotherapie* in 2015³. Both articles differentiate according to extract specification, pharmaceutical quality (proven within the context of a medicinal product approval), and indication as a medicinal product. Both articles include publications from 2000 - 2012 as well as 2012 - 2014. It was shown that the isopropanolic CR special extract (iCR) has level 1 evidence and meets the requirements for a grade A recommendation.

Furthermore, the safety of Remifemin® and Remifemin® plus was studied on both perimenopausal and postmenopausal women with climacteric complaints,

in women with breast cancer and co-medication with tamoxifen, and in natural menopause and menopause caused by an operation. Data from multiple clinical studies (controlled, randomized, double-blind) and observational studies have shown that Remifemin® and Remifemin® plus, with the iCR special extract, are effective and safe herbal medicines for the treatment of menopausal symptoms. They do not influence patients' hormone levels or induce undesired estrogen-like effects. Since the earlier assumption of an estrogen-like effect was clearly disproved, it is currently believed that *Cimicifuga racemosa* has a CNS-active mode of action. Remifemin® and Remifemin® plus offer a safe and effective alternative to the classic hormone therapy.

To date the iCR special extract has been studied in over 12,000 patients.⁷ With this compendium, we have compiled a current overview of the most important studies since 1997 for you.

The compendium is limited to this time period because the detailed ICH GCP Guideline E6 was published for implementation in January 1997 (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use = ICH, Good Clinical Practice = GCP). The guideline originated from a harmonization of the evaluation criteria, which are based on existing regulations on approving human medicinal products in the USA, Europa, and Japan. The guideline is known under the acronym CPMP/ICH/135/95. In the following, you will receive an impression of the most important studies, selected from the large scope of studies with Remifemin® preparations, on the topics efficacy and safety (also for breast and uterus as well as liver), mode of action, additional uses, and also the positive influence on the quality of life. If you are interested in further literature, you will find an extensive list of all Remifemin® and Remifemin® plus studies since 1997 in the appendix.

Clinical Studies



Double-blind study on efficacy and tolerability

Objective:

A comparative clinical study on the superior efficacy of Remifemin® for menopausal symptoms compared to a placebo.

Methods:

The severity of menopausal complaints, including hot flushes and psychological symptoms, were assessed according to the Menopause Rating Scale I (MRS I) at the beginning of the study as well as after weeks 4 and 12. The study took place over three months, and the reduction of symptoms was evaluated. Adverse events as well as the patients' compiled laboratory results (liver values, vital signs, body weight, and physical parameters) were analyzed. Twice a day the patients received either 1 tablet Remifemin® (20 mg drug = 2.5 mg extract) or a placebo.

Results:

The analysis of the MRS-score data showed a statistically significant superiority of Remifemin® compared to treatment with the placebo. In particular, this statistically significant and superior improvement could be shown for the menopause rating scale subscores hot flushes (MRS 1 - 3: hot flushes, sweating and sleep problems), psyche (MRS 4 - 6: depressive mood, anxiety, irritability, general decrease in performance and

impaired memory), and atrophy (MRS 7 - 9: sexual problems, bladder problems, and vaginal dryness). Relevant changes in other bodily parameters or laboratory results did not occur. Additionally, the test results of liver enzymes remained unchanged. Only six possible adverse events were documented; none were serious. The compliance of the verum group was 91.3%. A higher efficacy was shown in early postmenopausal patients compared to patients in late postmenopause. This could clearly be seen for the psychological symptoms. In patients in early postmenopause compared to patients in late postmenopause, psychological symptoms showed a significant improvement compared to the placebo group.

Conclusion:

In the early menopausal phase, patients have a slightly greater chance of improving menopausal symptoms by using Remifemin®. The preparation is most effective in the relief of hot flushes. The safety of the preparation was confirmed as well as a positive risk-benefit profile.

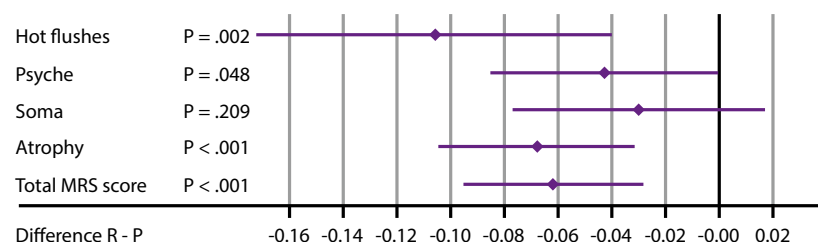


Fig. 1. Treatment difference and the 95% confidence limits of active medication (iCR) minus placebo based on MRS I and the subscores hot flushes, psyche, soma, and atrophy, determined for women in early menopause (assuming follicle-stimulating hormone = 20 U/L and 1 year of climacteric complaints). MRS = Menopause Rating Scale; R = active medication; P = placebo; iCR = isopropanolic extract of Cimicifuga racemosa. (Modified based on Osmer et al., 2005.)

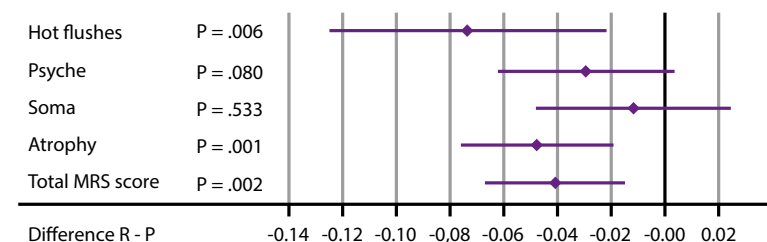


Fig. 2. Treatment differences and 95% confidence limits of active medication (iCR) minus placebo based on MRS I and the subscores hot flushes, psyche, soma, and atrophy, determined for women in late menopause (assuming follicle-stimulating hormone = 40 U/L and 3 years of climacteric complaints). MRS = Menopause Rating Scale; R = active medication; P = placebo; iCR = isopropanolic extract of Cimicifuga racemosa. (Modified based on Osmer et al., 2005.)

Study design:

Clinical, randomized, multicenter, placebo-controlled, double-blind study in 24 centers over 3 months.

Controls were conducted at the beginning as well as after weeks 4 and 12.

The efficacy against menopausal complaints was assessed using the Menopause Rating Scale (MRS I) and its subscores. Efficacy and safety were also determined based on the documentation of adverse events as well as the consideration of the patients' laboratory results (liver values, vital signs, body weight, physical parameters).

Study profile:

Female patients: 304 postmenopausal patients with menopausal symptoms (MRS ≥ 0.4 in at least 3 items), last period ≥ 12 months ago or ≥ 6 months ago + FSH ≥ 50 U/L, at least 45 years old. Average age 53 years.

Treatment: 153 patients: 2 x 1 tablet Remifemin® per day (20 mg drug = 2.5 mg extract/tablet).
151 patients: placebo.

Main results:

- Positive risk-benefit profile
- Significant improvement of hot flushes compared to placebo
- Significantly superior to placebo
- Highest efficacy for vasomotor symptoms
- No clinically relevant changes in laboratory results or other physical parameters
- No influence on liver enzyme levels
- No serious adverse events
- 91.3% compliance

Double-blind study on efficacy and safety for sleep disturbances

Objective:

To study the efficacy and the safety of an isopropanolic extract from *Cimicifuga racemosa* for sleep disturbances during postmenopause.

Methods:

42 women who had been suffering from problems sleeping for at least 1 month underwent a clinical interview. They underwent initial testing (blood glucose level, serum FSH, estradiol level, liver function, renal function, breast and pelvic ultrasounds) as well as testing for sleep disturbances via polysomnography. In addition, the women filled-out a PSQI questionnaire (sleep quality and sleep problems) and a MENQOL questionnaire (vasomotor, psychosocial, physical and sexual). Liver and renal values and ultrasound were tested again after 3 months. The patients underwent a 6-month therapy; they received either 1 tablet two times per day of an isopropanolic *Cimicifuga racemosa* extract (20 mg drug/tablet = 2.5 mg extract) or a placebo. At the end of the study, the patients were tested and interviewed again.

Results:

The compliance was 99% in the verum group and 98.2% in the placebo group. In the group of women who already suffered from vasomotor symptoms at the beginning of the study, the treatment with isopropanolic *Cimicifuga racemosa* extract led to a significant reduction in the MENQOL vasomotor score ($p = 0.015$) compared to the placebo. The psychosocial score sank in both groups with no differences

between the groups. Physical symptoms were reduced in both groups with a significant difference in favor of the isopropanolic extract group ($p = 0.041$). The scores for sexual items were not influenced in either therapy group. In the subjective PSQI, the isopropanolic extract demonstrated a medium effect, which was, however, indistinguishable from the placebo. The treatment with the isopropanolic extract showed a higher sleep efficiency (SE), a reduced wake time after sleep onset (WASO), and a lower arousal in the intra-group comparison with the objective polysomnography. The placebo group showed none of these effects, and the difference to the treated group was significant for SE and WASO. With *Cimicifuga* treatment, the percentage of women with low sleep efficiency was reduced from 70% to 50%, and the length of WASO was decreased by 15.8%. None of the safety parameters were influenced in either group. No adverse events occurred.

Conclusion:

Sleep disturbances during the early postmenopausal phase are effectively improved with *Cimicifuga racemosa*. Menopausal sleep problems can safely be treated with *Cimicifuga racemosa*.

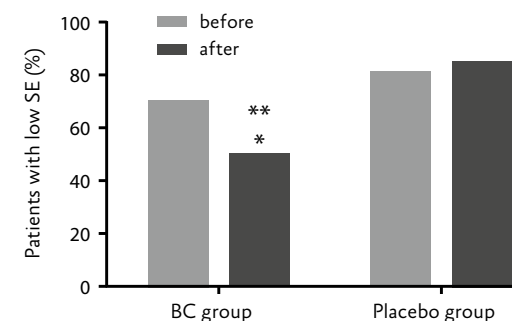


Fig. 3. Percent of participants with <85% sleep efficiency (SE) before and after the intervention in both groups. **, $p = 0.003$ compared to baseline; *, $p = 0.011$ compared to placebo group; BC = black cohosh. (Modified based on Jiang et al., 2015.)

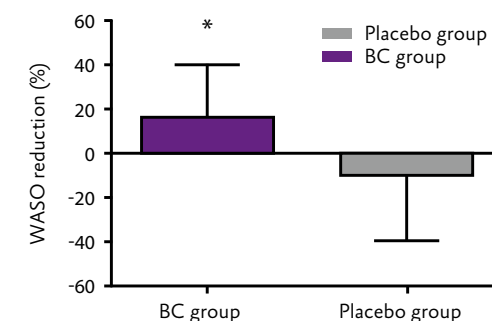


Fig. 4. Reduction of wake after sleep onset (WASO) compared to WASO baseline. Presented as average mean and standard deviation in both groups. *, $p = 0.005$ compared to placebo group; BC = black cohosh (Modified based on Jiang et al., 2015.).

Study design:

Randomized, placebo-controlled, double-blind study over 6 months in China.

Controls at the beginning and after 3 and 6 months.

The efficiency was determined subjectively based on the Pittsburgh Sleep Quality Index (PSQI with 24 items) and the Menopause-specific Quality of Life Questionnaire (MENQOL with 29 items) and objectively using polysomnography on two consecutive nights at the beginning and the end of the study. In addition, the estradiol and FSH levels were tested at the beginning and the end of the study. The safety was evaluated every 3 months using liver function, renal function, blood glucose level, and coagulation tests as well as breast and pelvic ultrasounds. Adverse events were documented.

Study profile:

Female patients: 42 postmenopausal patients with sleep problems for at least 1 month
 BMI ≤ 30 kg/m², 1 year \leq final period ≤ 5 years, FSH > 30 IU/l.
 45 - 60 years old.

Treatment: 20 patients: 2 x 1 tablet with isopropanolic extract from *Cimicifuga racemosa* per day (20 mg drug = 2.5 mg extract/tablet).
 22 patients: 2 x 1 placebo.

Main results:

- ▶ Improved sleep efficiency
- ▶ Reduction of the wake time after sleep onset
- ▶ No adverse events
- ▶ No influence on the hormone levels
- ▶ No influence on the breast or uterus
- ▶ No influence on liver or renal functions

Comparative clinical trial with low-dose estradiol

Objective:

Investigate the use of Remifemin® for menopausal symptoms compared to low-dose transdermal estradiol application (TTSE2).

Methods:

Daily, for the entire 3 months of the study, the patients documented the number of hot flashes they experienced in a diary. Further menopausal symptoms were recorded monthly using the Greene Scale (vasomotor, urogenital) and the Symptom Rating Test (anxiety, depression). During the patient's first visit, all medical and gynecological results were compiled, the thickness of the endometrium was measured using ultrasound, and menopausal symptoms were asked about in an interview. Blood was drawn to measure 17 β -estradiol, luteinizing hormone, follicle-stimulating hormone, prolactin and sex hormone-binding globulin, cortisol, lipoproteins (HDL, LDL), triglycerides, and liver function.

The evaluation of the diaries and the Greene Scale was done monthly whereas the Symptom Rating Test, the blood tests, and the ultrasound were redone and evaluated at the end of the 3-month therapy.

Results:

Starting the first month, Remifemin® was able to significantly reduce the number of hot flashes ($p = 0.001$) and the Greene Score for vasomotor symptoms ($p = 0.001$) as well as low-dose TTSE2. After 3 months, compared to the baseline, Remifemin® was as significantly effective as TTSE2 for anxiety ($p = 0.001$) and depression ($p = 0.001$). Remifemin® did not have any significant influence on the urogenital symptoms in this study. Liver function, hormone levels, and total cholesterol were not influenced by Remifemin®. Also, the thickness of the endometrium remained unchanged, and contrary to the application of TTSE2, no bleeding occurred.

Conclusion:

Remifemin® is equally as effective for the treatment of menopausal symptoms as low-dose estradiol (TTSE2) and, therefore, provides a reasonable and safe alternative.

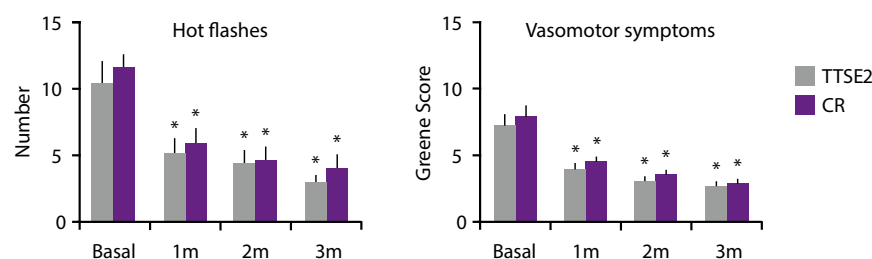


Fig. 5. Mean (\pm standard deviation) number of hot flashes per day, which were documented in a diary during the 3-month treatment, and the mean of the Greene Score for vasomotor symptoms, which were documented monthly. Postmenopausal women, who were treated with either *Cimicifuga racemosa* (CR) or low-dose transdermal estradiol (TTSE2) were assessed. The significance (*) is given in the text. (Modified based on Nappi et al. 2005.)

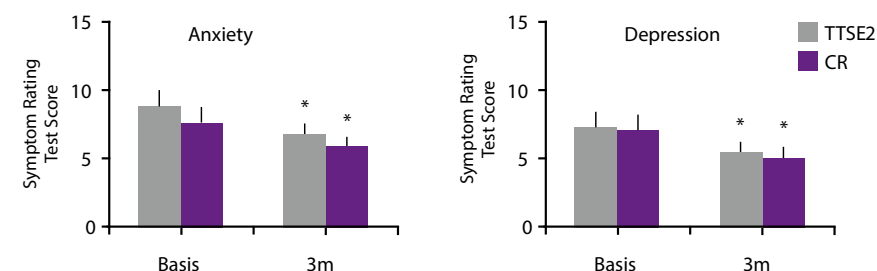


Fig. 6. Mean (\pm standard deviation) of the Symptom Rating Test scores for anxiety and depression measured before and after the 3-month treatment with either *Cimicifuga racemosa* (CR) or low-dose transdermal estradiol (TTSE2). The significance (*) is given in the text. (Modified based on Nappi et al. 2005.)

Study design:

Randomized, clinical study over 3 months.

Controls were conducted at the beginning and after 3 months. In addition, hot flashes and the Greene Scale were controlled monthly.

The efficacy for hot flashes was assessed using the patients' daily diaries. Other menopausal symptoms (vasomotor, urogenital, anxiety and depression) were queried using the Greene Scale and the Symptom Rating Test. Serum hormone level of 17 β -estradiol, luteinizing hormone, follicle-stimulating hormone, prolactin and sex hormone-binding globulin, cortisol, lipoproteins (HDL, LDL), triglyceride, and liver function as well as the status of the endometrium were monitored.

Study profile:

Female patients: 64 postmenopausal patients with at least 5 hot flashes per day, menopause for at least 6 months, FSH >30 mIU/l, and endometrium thickness <5 mm. 45 - 55 years old.

Treatment: 32 patients: 2 x 1 tablet Remifemin® per day (20 mg drug = 2.5 mg extract/tablet).
32 patients: 25 μ g TTSE2 every 7th day and dihydrogesterone 10 mg/day for the last 12 days.

Main results:

- ▶ Significant reduction of hot flashes
- ▶ Significant reduction of vasomotor symptoms, anxiety, and depression
- ▶ Improvement already after 4 weeks
- ▶ Equally as effective as a low-dose estradiol therapy
- ▶ Total cholesterol was not influenced
- ▶ No influence on triglycerides and liver function
- ▶ No influence on hormone levels
- ▶ No influence on endometrium

Clinical study on the efficacy for pronounced psychological symptoms

Objective:

To investigate the efficacy of the combination drug Remifemin® plus (*Cimicifuga racemosa* and *Hypericum perforatum*) for women with menopausal symptoms with pronounced psychological symptoms.

Methods:

293 patients were included; 150 patients were treated with Remifemin® plus and 143 with a placebo. The treatment lasted 16 weeks and was divided into an 8-week initial phase (2 x 2 tablets Remifemin® plus or placebo daily) and a maintenance dose for the last 8 weeks (2 x 1 tablet Remifemin® plus or placebo daily). During treatment the severity of the complaints was assessed using the Menopause Rating Scale (MRS I) at baseline and after weeks 8 and 16. The data obtained were subsequently divided among four factors according to Schneider et al.: hot flashes, atrophy, psyche, and somatic symptoms. These data were supported by using the Hamilton Depression Rating Scale (HAMD-17). The efficacy was assessed according to the Clinical Global Impression Scale CGI 3.1 and patient opinion. A pre-post comparison was then used to evaluate the improvement rates. Records of adverse events (AE) and patient opinion were collected for safety.

Results:

After just 8 weeks, the Remifemin® plus preparation was significantly superior to the placebo ($p < 0.001$) in all 10 points of the Menopause Rating Scale. Under treatment with the verum, the symptoms continued to decrease up to the third assessment. After 16 weeks, the total complaints had improved by 50% (from 0.46 to 0.23 points; placebo 19.6%) under treatment with Remifemin® plus. The factor hot flashes had improved by 53.4% and the factor psyche by 56.4%. Based on the Hamilton Depression Rating Scale, there was a distinct decrease in psychological complaints by 41.8% after 16 weeks (placebo 12.7%). There were no group differences regarding laboratory results, tolerability, and adverse events. Tolerability was 97%, and none of the adverse events were related or even possibly related to the medication.

Conclusion:

The combination drug Remifemin® plus is significantly superior to the placebo. In addition to menopausal symptoms, Remifemin® plus alleviates, in particular, the pronounced psychological component not only significantly but also clinically relevant. Remifemin® plus has a very good risk-benefit ratio, and its efficacy is comparable to a hormone therapy.

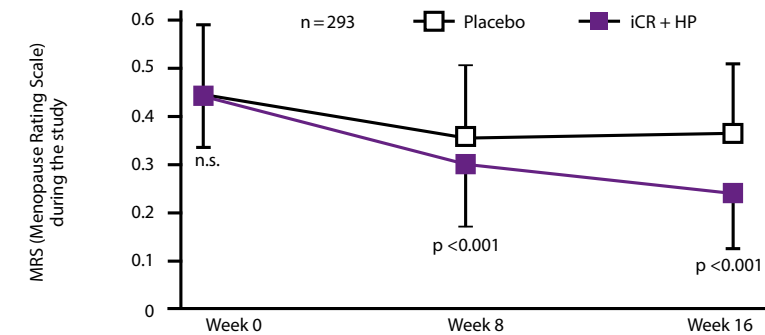


Fig. 7. Total complaints according to the Menopause Rating Scale. Mean \pm standard deviation of the verum group (iCR + HP) and placebo group during the study are presented as well as the multivariate statistical analysis of the 3 time points. (Modified based on Uebelhack et al. 2006.)

Study design:

Randomized, placebo-controlled, double-blind clinical study over 16 weeks.

Controls were conducted at the beginning as well as after weeks 8 and 16.

The menopausal complaints were assessed according to the Menopause Rating Scale (MRS I). The psychological component was based on the Hamilton Depression Rating Scale (HAMD-17). The efficacy was evaluated according to the Clinical Global Impression Scale CGI 3.1 as well as patient assessment; the safety was evaluated by means of documented adverse events and patient assessment.

Study profile:

Female patients: 293 patients with pronounced psychological components, symptoms for at least 3 months and at least 2 months without treatment, Menopause Rating Scale Score of ≥ 0.4 in at least 3 items, Hamilton Depression Rating Scale total score of 15 - 23 points with at least 2 points under item I *depressed mood*. 45 - 60 years \rightarrow average age 52.1 years.

Treatment: 151 patients: 2 x 2 tablet Remifemin® plus (22.5 - 41.25 mg Cimicifuga = 3.75 mg extract and 245 - 350 mg Hypericum = 70 mg extract/tablet) per day for 8 weeks then 2 x 1 tablet Remifemin® plus per day for 8 additional weeks.
143 patients: 2 x 2 placebo/day for 8 weeks then 2 x 1 placebo/day.

Main results:

- Significant superiority of Remifemin® plus compared to placebo already after 8 weeks
- 50.0% \rightarrow reduction of the total complaints in the Menopause Rating Scale
- 41.8% \rightarrow reduction of the psychological complaints according to the Hamilton Depression Rating Scale
- 78.8% \rightarrow good and very good efficacy according to CGI 3.1
- Very positive risk-benefit profile

Double-blind study on the risk-benefit ratio in Chinese women

Objective:

A double-blind study with Chinese women to test the risk-benefit ratio of Remifemin® versus tibolone for climacteric complaints.

Methods:

The female participants were thoroughly examined at the beginning of the study. Using ultrasound, endometrium thickness and condition of the breast were determined. A Pap smear was also done, and an interview was conducted concerning existing climacteric complaints. Follicle-stimulating hormone (FSH) and estrogen (E2) levels, standard hematology, and further biochemistry were determined; a urine sample was collected. At both control visits (4 and 12 weeks), adverse events were documented, severity of the climacteric complaints according to the Clinical Global Impression Scale (CGI 1) as well as change in status according to CGI 2 were determined, the Kupperman Menopause Index was noted, and vital signs and body weight were measured. Furthermore, after 12 weeks, the efficacy (CGI 3.1) was assessed, hematology and biochemistry were retested, and another ultrasound of the uterus was performed.

Results:

Already after 4 weeks of Remifemin® treatment, the Kupperman Menopause Index score was reduced from 24.7 at the beginning to 11.2 (tibolone: 11.2 points). After 12 weeks a score of 7.7 was determined (tibolone: 7.5 points). Also, the responder rate for the Kupperman Menopause Index and the reduction in the severity of the complaints were almost the same for both medications; a slight trend was shown for a

better responder rate for Remifemin®. The treatment success with Remifemin® was shown not to be statistically inferior to that of tibolone. When tolerance was considered, there was a similar picture for both treatment methods, but Remifemin® showed significantly fewer possible adverse events during the study in postmenopausal patients ($p < 0.0001$; 0 vaginal bleeding compared to 17 with tibolone) and did not have any influence on body weight. Remifemin® did not influence the endometrium, hematology, blood tests, and urine tests. The results of the Clinical Global Impression Scale (CGI 3.2) showed a significantly better responder rate for Remifemin® than for tibolone for adverse events (week 4: $p = 0.002$; week 12: $p = 0.033$).

Conclusion:

Remifemin® is remarkably effective in the treatment of climacteric complaints and is not inferior to tibolone. However, it has a significantly better risk-benefit balance and should clearly be preferred.

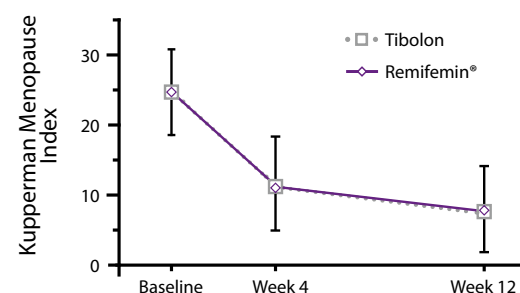


Fig. 8. Time response of the Kupperman Menopause Index for the entire group analysis. The mean \pm standard deviations are given. (Modified based on Bai et al. 2007.).

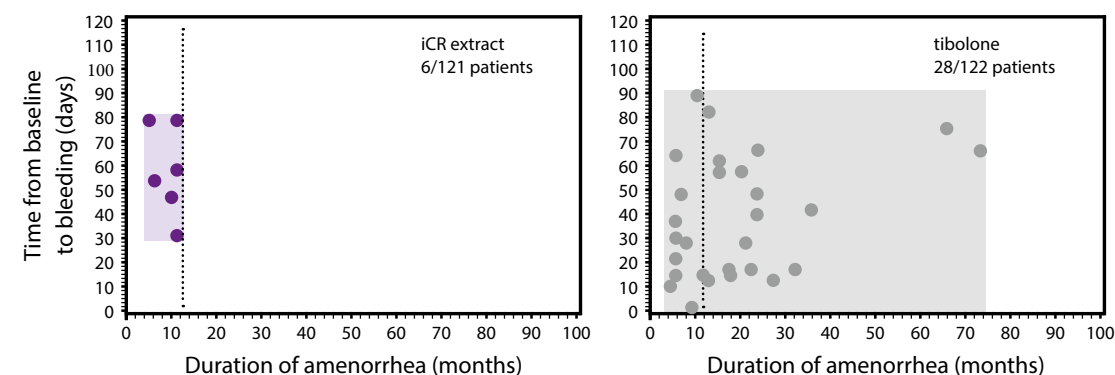


Fig. 9. Scatter plots of the correlation between the occurrences of adverse gynecological bleeding over the duration of amenorrhea before the start of therapy. (Modified based on Bai et al. 2007.).

Study design:

Randomized, tibolone-controlled, double-blind, clinical study in 5 centers in China over 3 months.

Controls were conducted at the beginning and after weeks 4 and 12.

Climacteric complaints were recorded according to the Kupperman Menopause Index. Severity and changes in status as well as efficacy were assessed using the Clinical Global Impression Scale (CGI). For safety, in addition to adverse events, endometrium thickness, vaginal cytology results, the condition of the breast, FSH and E2 values, standard hematology, additional biochemistry, and a urine sample were collected.

Study profile:

Female patients: 244 perimenopausal and postmenopausal patients with a Kupperman Menopause Index score of ≥ 15 , complaints for at least 4 weeks, final menstruation ≥ 5 months ago, if final menstruation was < 12 months than E2 level ≤ 30 pg/ml. 40 - 60 years old.

Treatment: 122 patients: 2 x 1 tablet Remifemin® per day (20 mg drug = 2.5 mg extract/tablet) + 1 x 1 placebo per day.
122 patients: 1 x 1 tibolone (2.5 mg) + 2 x 1 placebo per day.

Main results:

- ▶ Risk-benefit balance significantly superior to tibolone
- ▶ Significantly as effective as tibolone
- ▶ No vaginal bleeding in postmenopausal women with Remifemin® treatment
- ▶ No clinically relevant influence on the endometrium in perimenopausal and postmenopausal women
- ▶ No serious adverse events
- ▶ No changes in the blood, urine or liver tests
- ▶ Compliance very good in 95% of the patients

Clinical observational study on efficacy, safety and use patterns

Objective:

This clinical study was conducted to gain better insight into the use patterns as well as the efficacy and safety of treatment with Remifemin®/Remifemin® plus.

Methods:

Observation of patients took place between March 2002 and March 2004. For 6 or 12 months, the patients were treated with either the pure Cimicifuga drug (Remifemin®) or the combination drug with St. John's wort (Remifemin® plus); dosages were recommended by the doctor. A change in the dosage and the medication could be done at any time. Data collection was done at the beginning and after 3 and 6 months using the Menopause Rating Scale (MRS) and the corresponding subscores. A primary evaluation of the efficacy was already carried out after 3 months and analyzed on the basis of the changes in the subscore PSYCHE. All further changes (subscores and total score) were included as a secondary evaluation.

Results:

The patients, who were considered by their attending physicians as candidates for therapy with the combination drug Remifemin® plus, showed significantly higher baseline values in the subscore PSYCHE on the Menopause Rating Scale and a slight tendency towards more pronounced symptoms in general. With both forms of treatment, there was a marked reduction of the Menopause Rating Scale scores in

the overall symptoms with the strongest effects for vasomotor symptoms. In a comparison of the subscore PSYCHE for Remifemin® plus versus Remifemin®, Remifemin® plus was significantly superior after the first 3 months ($p < 0.001$). In addition to the assessment of efficacy, based on the improvement of symptoms (CGI 2), it was demonstrated that the largest effect in the reduction of symptoms was observed after 3 months; this also increased after 6 months for both drugs. It was also demonstrated that the therapeutic success for all symptoms was maintained over an extended period of 12 months. Further subgroup analyses showed that patients ($n = 286$) receiving antiestrogen therapy also profited from treatment with Remifemin®/Remifemin® plus as well as patients ($n = 486$) who had previously undergone a hormone therapy. Hardly any adverse events were reported (0.16%). The tolerability of both preparations was assessed as *good* and *very good* (>90%); compliance was rated at 97% *very good*.

Conclusion:

Remifemin® and Remifemin® plus can both be judged as effective and safe. In therapeutic practice, the pure Cimicifuga drug is used for predominately neurovegetative symptoms and the combination drug with St. John's wort is used for additional, pronounced, mood-influencing symptoms because of its superiority for such complaints.

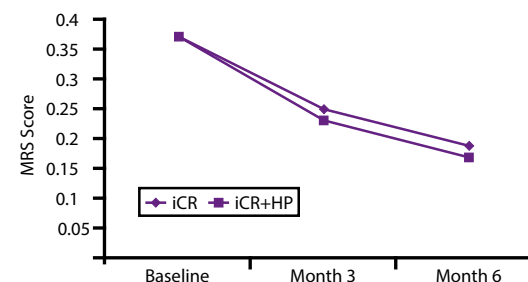


Fig. 10. Main efficacy variable MRS score PSYCHE at the beginning of treatment and after 3 and 6 months for both treatment groups. The mean scores adjusted for the multivariate model (covariates: baseline score, menopause status, antiestrogen therapy, hormone replacement therapy within the last 3 months, propensity score) are shown. The standard error is <0.01. HP = ethanolic *Hypericum perforatum* (St. John's wort) extract; iCR = isopropanolischer *Cimicifuga racemosa* (black cohosh) extract. (Modified based on Briesse et al. 2007.)

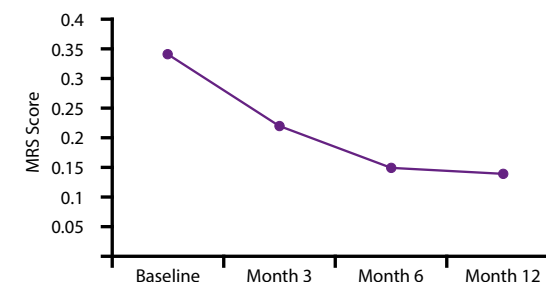


Fig. 11. Total MRS score at the beginning and after 3, 6, and 12 months for the patient subgroups, which were monitored for 12 months ($n = 736$). The standard error is <0.01. (Modified based on Briesse et al. 2007.)

Study design:

Perspective, controlled, open, clinical, observational study in 1,287 established gynecological offices over 6 months, optionally 12 months.

Controls were conducted at the beginning as well as after 3 and 6 months and eventually 12 months.

The efficacy and the change in symptoms were assessed using the Menopause Rating Scale (MRS) and corresponding subscores as well as the Clinical Global Impression Scale (CGI). Adverse events were documented.

Study profile:

Female patients: 6,141 menopausal patients.
Average age 52 years.

Treatment: 3,027 patients: 2,798 patients 2 x 1 tablet Remifemin® (20 mg drug = 2.5 mg extract/tablet) and 299 patients an equivalently dosed solution
3,114 patients: 2 x 1-2 tablets Remifemin® plus (3.75 mg extract + 70 mg extract from 245 - 350 *Hypericum perforatum*/tablet) depending on physician's assessment.

Main results:

- ▶ 50% *add-on* effect for the improvement of psychological symptoms with the use of Remifemin® plus
- ▶ >90% of the patients in both groups → tolerability *good* and *very good*
- ▶ Only 0.16% possibly related non-serious adverse events
- ▶ 97% compliance: *very good* for Remifemin® and Remifemin® plus
- ▶ Consistent efficacy after 6 - 12 months in both groups

Additional studies I

Clinical studies	Study design	Study profile	Treatment	Main results
Physiological investigation of a unique extract of black cohosh (<i>Cimicifuga racemosa rhizoma</i>): A 6-month clinical study demonstrates no systemic estrogenic effect Liske, et al., 2002 Journal of Women's Health & Gender-Based Medicine, 11 (2), 163–174. ²⁴	Controlled, randomized, double-blind study (GCP conform) 123 = 3 months 116 = 6 months	123 perimenopausal and postmenopausal patients 42 - 60 years (Menopause Index according to Kupperman ≥ 20)	n = 61 Remifemin®: 39 mg <i>Cimicifuga racemosa</i> daily or n = 62 Remifemin®: 127.3 mg <i>Cimicifuga racemosa</i> daily	<ul style="list-style-type: none"> ▶ 78.4 - 78.6% of the patients → good to very good efficacy ▶ Responder rate 70 - 72% ▶ 82 - 100% of the patients → tolerability good and very good ▶ No changes in vaginal cytology ▶ No influence on the hormone levels ▶ 40 mg/day is an optimal dose ▶ Compliance: high <p>Remifemin® did not have any influence on the patients' hormone levels, nor did it induce an estrogen-like effect. A daily dose of 40 mg Remifemin® is enough to offer a safe and effective alternative to classical hormone therapy for women where hormone therapy is contraindicated or for women who do not want it.</p>
Efficacy of Remifemin® for control of climacteric symptoms Li, et al., 2011 Prog Obstet Gynecol, 20 (6) 462–465. ²¹	Randomized, double-blind study 3 months	89 perimenopausal patients 40 - 55 years (menopause for at least 3 months, estradiol level <20 pg/ml, FSH-Level >40 IU/L, KMI Score ≥ 17 points)	n = 45 Remifemin®: 2 x 28 mg daily or n = 32 Placebo: 2 x daily	<ul style="list-style-type: none"> ▶ Significant decrease in the KMI score after 4 and 12 weeks ▶ Significant reduction of hot flashes ▶ No influence on the endometrium ▶ No influence on hormone levels, liver values or lipid profile <p>Remifemin® is an effective and safe option for women with climacteric complaints.</p>

The effects of Remifemin® on subjective symptoms of menopause Vermes, et al., 2005 Advances in Therapy, 22 (2), 148-154. ⁴³	Multicenter, open, prospective, observational study 3 months	2,016 menopausal patients in Hungary 40 - 65 years ((Menopause Index according to Kupperman ≥ 20 and a contraindication for (25.5%) or refusal of (74.5%) hormone therapy))	2 x 1 tablet Remifemin® per day	<ul style="list-style-type: none"> ▶ Already, noticeable success after 4 weeks of treatment ▶ Reduction of hot flashes from severe to mild/moderate ▶ Reduction of nightly sweating from severe to mild/moderate ▶ Significant improvement of sleeping problems and anxiety ▶ Tolerability very good <p>During a 12-week treatment with Remifemin®, the Kupperman Menopause Index score was effectively reduced by 17.64 points on average.</p>
Wirksamkeit und Sicherheit von Traubensilberkerze (<i>Cimicifuga racemosa</i> , Cimifemin®) bei Menopausebeschwerden: Therapiebeobachtung unter Praxisbedingungen Schmidt, et al., 2005 J Menopause, 12 (1), 27–32. ⁴⁰	Multicenter, open, prospective, observational study 3 months	502 patients with menopausal complaints 40 - 84 years	2 x 1 tablet Remifemin® per day	<ul style="list-style-type: none"> ▶ 77.5% of the patients → impressive reduction of sweating ▶ 71.6% of the patients → particularly efficient reduction of hot flashes ▶ 64.5% of the patients → reduction of sleep problems ▶ 60.6% of the patients → reduction of depressive moods ▶ 56.6% of the patients → reduction of nervousness ▶ 73.8% of the patients → positively impressed ▶ 69.8% of the patients → continued after the study ▶ Tolerability very good ▶ No adverse events <p>With Remifemin® treatment, a noticeable effect on all the symptoms was seen especially hot flashes. The good tolerability means a high user safety. The preparation is a good alternative for women for whom a hormone therapy is contraindicated..</p>

Cohort study on tumor-free survival time and recurrence rate in breast cancer

Objective:

The evaluation of the influence of Remifemin® or Remifemin® plus on the relapse-free, survival rate of female patients after breast cancer (hormone-receptor-positive tumors were also included).

Methods:

Anonymous data from the years 1992 - 2003 were retrieved from the "Disease Analyzer – Mediplus" databank (IMS Health, Frankfurt). The data included therapeutic observations from 1,278 general practitioner offices and 233 gynecologist offices in Germany. All the patients included had had breast cancer for the first time (47,795). Hormone-receptor-positive tumors were also included. For the diagnosis, both the ICD-9 code C50 and text entries were taken into account and were only considered as a positive diagnosis when at least 2 temporally independent entries existed. If there was only one entry or an entry was suspicious, the diagnosis was not considered as verified until an entry for the corresponding treatment was found. A relapse was presumed if a tumor or metastases reappeared. Two data groups were formed: patients who received Remifemin®/Remifemin® plus at least once in the time between the first diagnosis and relapse and those who did not receive this treatment.

Results:

The data from a total of 18,861 female patients were analyzed. 1,102 patients had been treated with Remi-

femin® or Remifemin® plus for an average of 590 days. 17,759 patients had not received Remifemin®/Remifemin® plus treatment and were viewed as the control group. The data as the whole were highly consistent. The average age for the first diagnosis was 61.4 years. This age varied between the groups and was 7.3 years younger in patients in the verum group. 38.5% of the patients in the Remifemin® group had been treated with tamoxifen; in the control group the number was 24%. A medium observation time of 3.6 years was defined (6 months to 11 years). In the entire patient collective as well as for the entire observation time period, an increased recurrence rate with treatment with Remifemin®/Remifemin® plus could not be determined. On the contrary, in a group analysis it was discovered that for Remifemin® or Remifemin® plus treatment the relapse rate was 17% lower than without this treatment for all age groups. 14% of the patients in the control group experienced a relapse after 2 years whereas this percentage was not reached by the Remifemin® users until 6.5 years.

Conclusion:

In no case did Remifemin® or Remifemin® plus treatment increase the risk of breast cancer recurrence, but rather it was actually reduced. The recurrence-free survival time was lengthened.

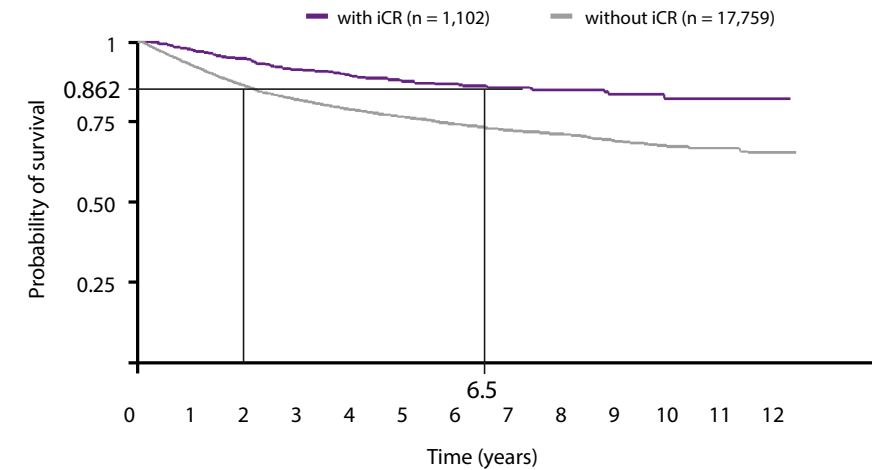


Fig. 12. Recurrence-free survival in years, stratified into the iCR treated group. iCR = isopropanolic *Cimicifuga racemosa* extract. (Modified based on Henneicke-von Zepelin et al. 2007.)

Study design:

Retrospective, databank-based, comparative cohort study with data from 1,278 general practitioner offices and 233 gynecologist offices.

Databank analysis was done with the "Disease Analyzer – Mediplus" databank. Correlations were determined using Spearman's rank correlation coefficient. The Kaplan Meier estimator was used for the descriptive analysis, and the non-inferiority of the treatment was determined with a survival time analysis.

Study profile:

Female patients: 18,861 patients with first time breast cancer, observation time period of at least 6 months, without primary metastatic tumors or other primary tumors before breast cancer.
Average age at first diagnosis 61.4 years.

Treatment: 1,102 patients: Remifemin® or Remifemin® plus.
17,759 patients: control group without treatment with *Cimicifuga racemosa*.

Main results:

- 17% → reduction of relapse risk for breast cancer
- Prolonged recurrence-free survival time

Meta-analysis of existing clinical studies on the influence of liver function

Objective:

To study the safety of Remifemin® and Remifemin® plus on liver function.

Methods:

This meta-analysis included published as well as unpublished data (from the manufacturer) from studies investigating the efficacy and safety of the use of drugs containing black cohosh on peri- and postmenopausal women. Only double-blind, randomized, controlled studies according to good clinical practice, where data on the liver function were recorded before and after treatment, were considered. The treatment period should have been 3 - 6 months. Studies that included patients who had previously had breast cancer were excluded. In particular, the specific liver function parameters were studied: aspartate aminotransferase (AST), alanine aminotransferase (ALT), and γ -glutamyltranspeptidase (γ -GT).

Results:

A total of 40 studies were identified from which 5 studies could be included in the meta-analysis. From a total of 1,117 women ages forty to sixty, 1,020 women had completed the studies (517 Remifemin®/Remifemin® plus, 503 control group); none of the reasons for the 88 dropouts were given as an adverse event

involving the liver. At the beginning, the liver parameters were homogeneous within the group distributions, and the data from the various studies were also balanced when compared with each other. It could be shown that the aspartate aminotransferase values remained in the normal range in 94.5% (465/492) of the patients in the Remifemin® group and in 95.1% of the patients in the reference group (450/473) after treatment. There was an abnormally high increase in AST values not only in 5.5% of the patients in the Remifemin® group (27/492) but also in 4.9% of the patients in the reference group (23/473). On the other hand, 62.2% of the patients treated with Remifemin®/Remifemin® plus (23/37) and 38.6% of the reference group (28/40) started with very high AST values, but after the study ended the values normalized. Examination of the alanine aminotransferase and γ -glutamyltranspeptidase values showed similarities. The liver function values, which were normal at the beginning, increased in seven cases (3 Remifemin®/Remifemin® plus, 4 control) during the course of the study. However, there was no causal relationship with *Cimicifuga racemosa*.

Conclusion:

Remifemin® has no adverse effects on the liver function.

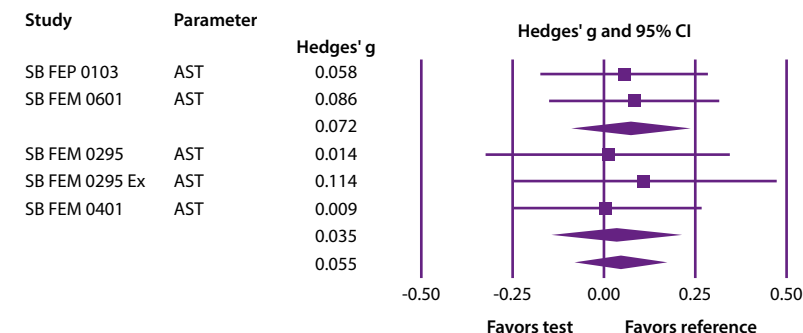


Fig. 13. Meta-analysis of the changes to baseline in double-blind, placebo-controlled and other studies. Aspartate aminotransferase (AST). (Modified based on Naser et al. 2011.)

Study design:

Meta-analysis of studies on the efficacy and safety of the use of the isopropanolic black cohosh extract on peri- and postmenopausal women.

Length of treatment: 3 - 6 months.

Controls were conducted at the beginning and end of the treatment at a minimum.

Only double-blind, randomized, controlled studies according to good clinical practice (GCP) were included if raw data on the liver function had been recorded and Remifemin®/Remifemin® plus were used as test drugs. In order to evaluate the safety, specific liver function parameters were analyzed, in particular: AST, ALT, and γ -GT.

Study profile:

Female patients: 1,117 peri- and postmenopausal patients.
 40 - 60 years old.
 1. n = 301 patients
 2. n = 152 patients
 3. n = 116 patients
 4. n = 244 patients
 5. n = 304 patients

Treatment:
 1. 64 - 128 mg Remifemin® plus vs. placebo (16 weeks)
 2. 40 mg vs. 128 mg Remifemin® (12 weeks)
 3. 40 mg vs. 128 mg Remifemin® (24 weeks)
 4. 40 mg Remifemin® vs. tibolone (12 weeks)
 5. 40 mg Remifemin® vs. placebo (12 weeks)

Main results:

- No negative influence on the aspartate aminotransferase values
- No negative influence on the alanine aminotransferase values
- No negative influence on the γ -glutamyltranspeptidase values
- No significant influence on liver function

Case-control study on alleviating menopausal symptoms and the risk of breast cancer

Objective:

To investigate the relationship between use patterns of herbal drugs and the incidence of breast cancer in postmenopausal women in a German population-based, case-control study.

Methods:

In the MARIE (Mamma Carcinoma Risk Factor Investigation) case-control study from August 2002 to September 2005, data received on 10,121 postmenopausal women from participating hospitals and the Hamburger Cancer Registry were analyzed. Each of the 3,464 patients included who had histologically confirmed primary invasive breast cancer or a carcinoma in situ were assigned to one of two controls (6,657). The risk factors for breast cancer were collected in personal interviews with emphasis on hormonal or herbal therapies. The herbal therapies were divided into seven main groups: Remifemin®/Remifemin® plus, other Cimicifuga preparations, St. John's wort, Vitex agnus castus, phytoestrogens, other preparations, and unknown preparations.

Results:

The average age in the control group was 63.2 years

and 63.3 years in the case group. 224 (6.7%) of the cases with invasive cancer and 669 (10.1%) of the controls said that they had used an herbal preparation. According to the active substance classification of the herbal preparations, Cimicifuga was the most commonly used herbal preparation, mainly Remifemin®/Remifemin® plus. Inverse correlations with invasive breast cancer were proven for Remifemin®/Remifemin® plus, chaste tree, other specified preparation, phytoestrogens as well as unknown preparations. If herbal preparations from any of the active substance classes had ever been used, then the risk of invasive breast cancer was reduced by approximately 26% and by 4% per year of use. It was observed that Remifemin®/Remifemin® plus were slightly inversely associated with invasive breast cancer while for the other Cimicifuga preparation no correlation was determined.

Conclusion:

The use of herbal preparations appears to protect postmenopausal women from invasive breast cancer, irrespective of other health related behaviors. Possible modes of action seem to be independent from the estrogen receptor mediated signaling pathway (i.e. cytotoxicity, apoptosis).

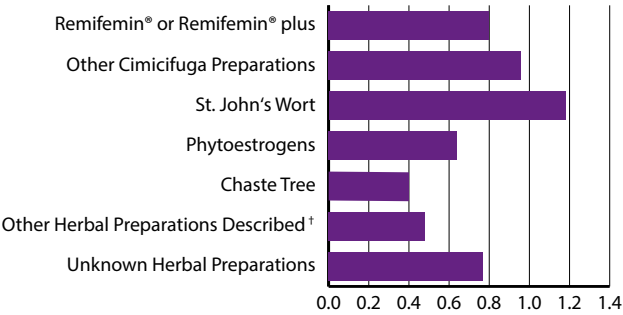


Fig. 14. Herbal preparations and invasive breast cancer (adjusted ORs; 95% confidence interval from logistic regression). Models are adjusted for the regions (Hamburg, Rhine-Neckar-Karlsruhe). Birth year (≤ 1934 , 1935 - 1939, 1940 - 1944, 1945 - 1949, ≥ 1950). Hormone use (never, previous, actual). Age at menopause (<47 , 47 - <52 , 52 - <56 , ≥ 56 years old, unknown). Age at menarche (<12 , 12 - 14, ≥ 15 years old, unknown). Number of pregnancies (≥ 28 th week: 0, 1, 2, ≥ 3). Ever breastfed (yes, no). Benign breast disease (yes, no, unknown). Number of mammograms (0, 1 - 4, 5 - 9, ≥ 10 , unknown). Familial breast cancer in first degree relatives (yes, no, unknown). Occupation- see Table 1 in original publication. Physical activity (quintiles based on distribution in the controls: 1st quintile = no physical activity; and category "unknown"). †Mainly includes Pulsatilla, Rheum raphaniticum. (Modified based on Obi et al. 2009.)

Study design:

Population-based, case-control study with data from hospitals in two regions in Germany ((Rhine-Neckar-Karlsruhe Region (RNK) and the city and state of Hamburg)) and the Hamburg Cancer Registry.

The data concerning risk factors for breast cancer were gathered in personal interviews. The main focus was placed on hormonal therapies (estrogen mono and combination therapies with progesterone, tibolone) and herbal therapies. Physical activity and nutritional habits were viewed as potential confounders for the efficacy of herbal preparations. The nutritional habits for the last 12 months were collected using a validated questionnaire.

Study profile:

Female patients: 3,919 postmenopausal patients, observation time period August 2002 to September 2005, with histologically confirmed primary invasive breast cancer or a carcinoma in situ.
Controls: 7,421 postmenopausal patients without this illness.
50 - 74 years old.

Treatment: Remifemin® (Cimicifuga) or Remifemin® plus (Cimicifuga, St. John's wort), other Cimicifuga preparations, St. John's wort, Vitex agnus castus, "phytoestrogens" (soy isoflavones, red clover), others (mainly Pulsatilla, Rheum raphaniticum) as well as unknown preparations. Women who used combined preparations or more than one preparations were placed in more than one preparation class.

Main results:

- Protective effects from invasive breast cancer
- Longer use improves risk reduction

Obi, et al., *The use of herbal preparations to alleviate climacteric disorders and risk of postmenopausal breast cancer in a German case-control study*. Cancer Epidemiol Biomarkers Prev, 18 (8), 2207-2213, (2009).³²

Prospective observational study on the efficacy in breast cancer patients treated with tamoxifen

Objective:

To test the efficacy of Remifemin® in patients with climacteric symptoms that are caused by tamoxifen treatment for breast cancer.

Methods:

Only women with menopausal complaints caused by breast cancer and treatment with tamoxifen were included in this study at the Tumor Biology Center in Freiburg. The women received 1 tablet Remifemin® twice a day (20 mg drug/tablet) for 4 weeks. Subsequently, it was possible to vary the medication from 1 - 4 tablets daily or change to Remifemin® plus. A tumor anamnesis and the Menopause Rating Scale (MRS II) were used as baseline documentation. The Menopause Rating Scale was also used after months 1, 3, and 6. The results were compared, and based on these data, the efficiency of treatment with Remifemin® was determined. In addition, adverse events, co-medication, compliance, concomitant illnesses, and the assessment of the efficacy and tolerability by the patients were compiled.

Results:

At the beginning of the study, hot flashes and sweating (severe) were the most pronounced symptoms followed by sleep problems as well as mental and physical complaints (moderate) and psychological symptoms (mild to moderate). There was a statistically significant reduction in the score of the Menopause Rating Scale (MRS II) from 17.6 to 13.6 during the observation period ($p = 0.001$). Likewise, the differences in the subscores vegetative symptoms and psychological symptoms were also statistically significant after 1, 3, and even 6 months ($p = 0.01$). After an average treatment period of 134 ± 60 days, 43 from 48 of the patients assessed the tolerability as *good* or *very good*; no adverse events were observed in connection with Remifemin®. There was also no recurrence of cancer.

Conclusion:

Remifemin® is a reasonable alternative for the treatment of women with prevalent psychovegetative climacteric symptoms during breast cancer treatment with tamoxifen.

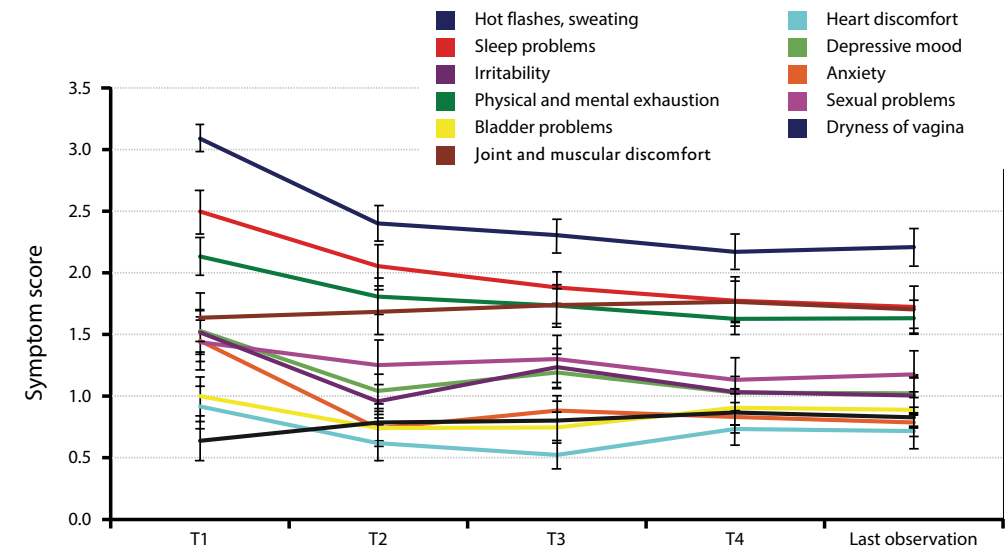


Fig. 15. Symptom scores according to MRS II (average \pm SD) with the use of black cohosh extract. T1 = day 1; T2 = day 28 ± 7 ; T3 = day 90 ± 14 ; T4 = day 180 ± 28 . (Modified based on Rostock et al. 2011.)

Study design:

Prospective observational study over 6 months.

Controls were conducted at the beginning as well as after months 1, 3, and 6.

The Menopause Rating Scale (MRS II, 11 symptoms, and 3 subscores; psychological complaints, urogenital complaints, and vegetative complaints) was used to assess the efficiency at the beginning of treatment and after months 1, 3, and 6. Adverse events, co-medication, compliance, and concomitant illnesses were compiled as well as the assessment of efficacy and tolerability by the patients. A tumor anamnesis was conducted.

Study profile:

Female patients: 50 breast cancer patients undergoing tamoxifen treatment, all had undergone an operation, 80% with additional radiation therapy, 50% with additional chemotherapy. Further criteria: at least 3 months without the application of a Cimicifuga product, no treatment with other anti-hormonal products except for tamoxifen, no concomitant radiation or chemotherapy, no participation in other studies. Average age 56 years old.

Treatment: 4 weeks 2 x 1 tablet Remifemin® per day (20 mg drug/tablet); after that a variation of the medication from 1 - 4 tablets Remifemin®/day was possible. ($n = 15 \rightarrow 80$ mg, $n = 3 \rightarrow 60$ mg, $n = 2 \rightarrow 20$ mg, $n = 4 \rightarrow$ Remifemin® plus).

Main results:

- Significant reduction of the MRS II scores after 1, 3, and 6 months
- Significant reduction of hot flashes, sweating, anxiety, and sleep problems
- 90% \rightarrow tolerability good and very good
- No adverse events connected to Remifemin®
- No recurrence of cancer

Rostock, et al., *Black cohosh (Cimicifuga racemosa) in tamoxifen-treated breast cancer patients with climacteric complaints – a prospective observational study*. Gynecol Endocrinol, 27 (10), 844-848, (2011).³⁸

Observational study on changes in breast tissue density and breast cell proliferation

Objective:

The aim of the present study was to investigate possible changes in breast tissue density and breast cell proliferation in healthy women going through natural menopausal with climacteric symptoms and taking Remifemin®.

Methods:

A mammogram, a vaginal ultrasound, and a fine-needle aspiration biopsy were performed on the patients 2 or 3 weeks before the start of therapy as well as 6 months later. In addition, blood serum tests for sex hormone-binding globulin (SHBG), insulin-like growth factors (IGF-1), cholesterol and triglycerides were performed; further vital signs were measured. After months 2 and 4, data for compliance and adverse events were also documented. Two weeks after the end of therapy, each patient was called by a midwife and asked about adverse events again.

Results:

At the beginning of treatment, breast tissue density was classified according to Wolfe. 29 of the patients

(44.6%) were P1 and 36 of the patients (55.4%) were P2. These values remained absolutely identical in each individual patient after 6 months of treatment with Remifemin®. Even by means of percent calculation of the breast tissue density, no increase in the breast tissue density could be found to indicate possible cancer development. There was even a reduction of tissue density by one category in one of the patients. The breast cells that had been taken from 35 patients (54%) via biopsy were subjected to an antibody reaction; these showed no change in the proliferation rate after 6 months. Also, the thickness of the endometrium as well as the vital signs and blood results were not influenced by the treatment.

Conclusion:

Remifemin® has no influence on breast tissue and is therefore much better suited in this regard than a hormone therapy and is at least as good as tibolone.

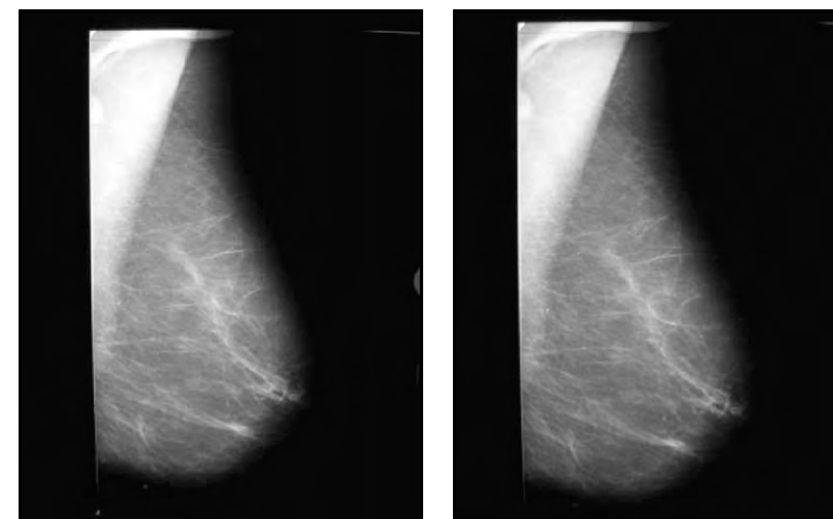


Fig. 16. The mammograms show the breast tissue density in a single women at the beginning (left) and after 6 months of therapy with isopropanolic black cohosh rootstock extract (right). (Modified based on Hirschberg et al. 2007.)

Study design:

Prospective, uncontrolled, open, clinical, observational study over 6 months.

Controls were conducted at the beginning and after 2, 4, and 6 months.

Breast tissue density and breast cell proliferation were monitored with mammograms and by sampling breast cells by performing a percutaneous fine-needle aspiration biopsy of the upper, outer quadrant of the left breast. The data from the mammograms were classified according to the Wolfe classification and grouped using a percentage scale. Ki-67/MIB-1 monoclonal antibodies were used to determine breast cell proliferation. Safety was monitored by recording adverse events (AE), with laboratory results ((sex hormone-binding globulin (SHBG), insulin-like growth factors (IGF-1), cholesterol and triglycerides)) and by measuring endometrium thickness using ultrasound.

Study profile:

Female patients: 74 postmenopausal patients, BMI 20 - 30 kg/m², final menstrual bleeding ≥12 months ago or FSH level ≥40 IU/L and estradiol level ≤20 pg/ml, hormone therapy ≤3 months ago, 50 - 70 years old.

Treatment: 2 x 1 tablet Remifemin® per day (20 mg drug/tablet = 2.5 mg extract)

Main results:

- ▶ No influence on breast tissue density
- ▶ No influence on breast cell proliferation
- ▶ No serious adverse events
- ▶ No influence on endometrium thickness
- ▶ No influence on laboratory results or vital signs

Reanalysis of changes in breast tissue density

Objective:

To quantify, within the context of this present reanalysis, possible changes in breast tissue density during continuous combination therapy with hormones, tibolone, Remifemin®, and placebo with the help of digitalized mammographic data from women with climacteric complaints during natural menopause.

Methods:

In two studies, postmenopausal patients were included according to the same criteria but treated with different medications. The influence on breast tissue density during treatment with estradiol 2 mg/norethisterone acetate 1 mg (E2/NETA) (n = 43) was compared to tibolone 2.5 mg (Livial®) (n = 49) or placebo (n = 53) in the first study. In the second study, patients were treated with 2 x 1 tablet Remifemin® (2 x 20 mg, n = 64). Mammograms of the outer upper quadrant of the left breast were done at baseline and 6 months after the start of therapy in both studies. In this reanalysis, these data were analyzed with computer assistance and compared.

Results:

All patients included in the trials had an average age of 57 years for each treatment group. Also, there were

no significant group differences with respect to other parameters, including breast tissue density. During treatment with E2/NETA and tibolone, the density increased by 14.3% (p < 0.001) and 2.3% (p < 0.001) on average and, thus, significantly. The breast tissue density remained unchanged during treatment with Remifemin® and placebo. The increase under the combination therapy E2/NETA was therefore the most pronounced. With this treatment model, 24 from 43 patients had a 10% increase in breast tissue density, and 6 patients even had a 30% increase. Only one patient had a 10% increase with tibolone; 9 patients had a 5 - 9% increase. No increase could be measured for any of the women being treated with Remifemin® or the placebo (0%).

Conclusion:

Remifemin® has no influence on the mammographic breast tissue density whereas the density was significantly increased with the standard E2/NETA treatment.

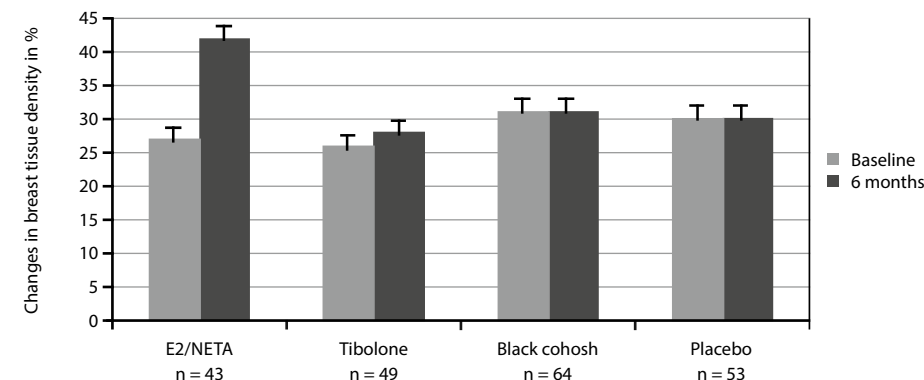


Fig. 17. Changes in breast density during various treatments. Mean and standard error for the mammographic breast tissue density at the beginning and after 6 months in the 4 treatment groups. The breast tissue density increased significantly with E2/NETA and tibolone (p < 0.001, accordingly) but not with black cohosh or placebo. (Modified based on Lundström et al. 2011.)

Study design:

Meta-analysis of two observational, clinical studies over 6 months.

Controls were conducted at the beginning and after 6 months.

Breast tissue density was examined using mammography and included a cranio-caudal projection of the left breast. All the images were digitalized; the tissue density was analyzed according to the Wolfe scale with the computerized program Cumulus (Sierra plus, Systems Corporation, Medical Imaging, Herndon, VA).

Study profile:

Female patients: 209 postmenopausal patients, BMI = 20 - 30 kg/m², final menstruation ≥ 12 months ago or FSH ≥ 40 IU/L, and estradiol level ≤ 20 pg/ml, hormone therapy ≤ 3 months ago. 50 - 70 years old.

Treatment: 43 = E2 2 mg/NETA 1 mg (Kliogest®)
49 = tibolone 2.5 mg (Livial®)
53 = placebo 1 x daily
64 = 2 x 1 Remifemin® tablets (20 mg = 2.5 mg extract/tablet)

Main results:

► No influence on breast tissue dens



Parallel group study to exclude possible interactions

Objective:

To test for possible interactions of an ethanolic St. John's wort extract (Esbericum®, 60 mg = 0.88 mg hyperforin) with cytochrome P450 (CYP) enzymes CYP3A4, CYP1A2, CYP2C9 as well as p-glycoproteins using corresponding substrates: alprazolam, caffeine, tolbutamide and digoxin.

Methods:

2 studies were conducted, each with 28 healthy participants. On days 2 to 10 in each study, 12 participants were given a placebo (2 x 2 capsules daily) and 16 participants were given Esbericum® (2 x 2 capsules daily). On day 11, only 1 x 2 capsules were given respectively. In addition, the participants in Study A received alprazolam (Tafil®, 1 mg) and caffeine (Coffeinum purum®, 100 mg) on days 1 and 11. The participants in Study B received tolbutamide (Orabet®, 500 mg) on days 1 and 11 and digoxin (Digoren®) with 0.75 mg on days -2 and -1 as well as 0.25 mg on days 1 and 11. The drug concentration in the blood plasma was measured on days 1 and 11 right before co-medication as well as 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, and 24 hours thereafter. Separate blood samples were drawn on days 1, 4, 7, and 11 to test hypericin, pseudohypericin and hyperforin levels. Vital signs and adverse events were documented on days 1, 4, 7, 11, 12, and after the study.

Results:

The bioavailability values determined for alprazolam varied only slightly between the placebo group and the St. John's wort group. The calculations used to determine an eventual influence of St. John's wort did not show any significance differences between the groups. The values were only reduced by 3.3%. The differences in the bioavailability values of caffeine and paraxanthine were only marginally statistically significant between the placebo and St. John's wort groups and were decreased by 11%. Only the tolbutamide values reached a statistical significance between the groups and only a 6.8% decrease of the values. The digoxin medication was not significantly influenced and had an 11.8% reduction compared to day 1 before medication. The slight decrease in bioavailability with St. John's wort application is, however, interpreted as a natural fluctuation, and it is unlikely caused by co-medication. No participant experienced adverse events. Also, the general laboratory results and the vital signs were not influenced.

Conclusion:

A daily dose of 240 mg of the St. John's wort extract demonstrated no relevant influence on the chosen co-medication: alprazolam (CYP3A4), caffeine (CYP1A2), tolbutamide (CYP2C9), and digoxin (p-glycoprotein). Therefore, an interaction is not expected.

Study design (A + B):

Randomized, monocentric, placebo-controlled, study containing 2 parallel groups (A and B) for 11 days.

Controls on days 1 and 11.

Interactions were investigated using pharmacokinetic tests for the drug concentration in blood plasma. Hypericin, pseudohypericin, and hyperforin levels were also tested in the participants' blood. General laboratory tests and vital signs were also used to investigate the safety in addition to the documentation of adverse events.

Study profile:

Test persons:	56 healthy participants; non-smokers; no more than moderate alcohol, xanthine, and quinine consume; no abnormalities in drug testing or heart function (EEG). 18 - 55 years old.
Treatment A	(n = 28): n = 12 → 2 x 2 placebo (days 2 to 10), 1 x 2 placebo (day 11) + a single dose of alprazolam (Tafil®, 1 mg) and caffeine (Coffeinum purum®, 100 mg) on days 1 and 11. n = 16 → 2 x 2 Esbericum® capsules (60 mg = 0.25 mg total hypericin and 0.88 mg hyperforin) on days 2 to 10, 1 x 2 capsules (day 11) + a single dose of alprazolam (Tafil®, 1 mg) and caffeine (Coffeinum purum®, 100 mg) on days 1 and 11.
Treatment B	(n = 28): n = 12 → 2 x 2 placebo (days 2 to 10), 1 x 2 placebo (day 11) + a single dose of tolbutamide (Orabet®, 500 mg) and multiple doses digoxin (Digoren®) with 0.75 mg on days -2 and -1 as well as 0.25 mg on days 1 and 11. n = 16 → 2 x 2 Esbericum® capsules (60 mg = 0.25 mg total hypericin and 0.88 mg hyperforin) on days 2 to 10, 1 x 2 capsules (day 11) + a single dose of tolbutamide (Orabet®, 500 mg) and multiple doses of digoxin (Digoren®) with 0.75 mg on days -2 and -1 as well as 0.25 mg on days 1 and 11.

Main results:

- ▶ No changes in the overall laboratory results and vital signs
- ▶ No adverse events
- ▶ No influence on cytochromes CYP3A4, CYP1A2, and CYP2C9 as well as p-glycoproteins
- ▶ No interactions observed

Phase 1 study on the effect on photosensitivity

Objective:

To investigate the effect of an ethanolic St. John's wort extract (Esbericum®) on dermal photosensitivity.

Methods:

The volunteers received 2 x 3 Esbericum® capsules (60 mg/capsule) daily. Two days before therapy started and on day 14 of therapy, the skin of the volunteers was treated with solar irradiation (Dermalight® erythema tester 285 - 350 nm) in order to conduct a before and after (MEDpre and MEDpost) comparison of possible irritations. The possible photoreaction and skin irritation symptoms were classified 24 hours after irradiation using a validated rating scale.

Results:

The values determined on days -2 and 14 showed an average difference in pre-post MED of 2.3 mJ/cm²; this correlates to a non-significant reduction of 8.25%. This corresponds to a non-relevant increase of dermal photosensitivity.

Conclusion:

A daily dose of 2 x 3 capsules of the St. John's wort extract used (360 mg) does not demonstrate a relative effect on the minimal erythema dose (MED) and thus on the dermal photosensitivity.

Study design:

Open, phase 1 study for 14 days.

Solar stimulation of the skin on days -2 and 14. Each control was done 24 hours after irradiation.

The photosensitivity was determined based on the comparison of the minimal erythema dose (MED) before treatment and after 2 weeks of treatment.

Study profile:

Volunteers: 20 healthy, male and female participants

Treatment: 2 x 3 capsules Esbericum® per day (60 mg/capsule)

Main results:

- ▶ No relevant influence on the minimal erythema dose (MED)
- ▶ No relevant influence on photosensitivity

Observational study on efficacy and safety after an operation for early endometrial cancer

Objective:

To investigate the efficacy and safety of treatment with Remifemin® for menopausal symptoms in patients after an operation for early endometrial cancer.

Methods:

In this study, 60 female patients with early endometrial cancer and menopausal symptoms after an operation were divided into two groups. One group received treatment with 2 x 1 tablet Remifemin® daily for 24 weeks. The second group served as the control group and received no treatment. Both groups were monitored for 12 months. In order to measure the effectiveness of the treatment, the Menopause Indexes according to Kupperman were applied. Treatment safety was evaluated based on bone density, cancer recurrence rate, deaths, and kidney and liver functions of the patients.

Results:

After 24 weeks of treatment with Remifemin®, a significant reduction of the Menopause Index scores

according to Kupperman was observed (from 26 ± 7 to 9 ± 4 points). In comparison, the scores in the control group did not change significantly (from 25 ± 8 to 21 ± 5 points). Bone density in the verum group also increased significantly whereas this effect did not occur in the control group. No adverse events happened in the treatment group. During the “follow-up” year, one person died in each group. In the control group, there was one recurrence.

Conclusion:

Remifemin® can improve menopausal symptoms occurring after an operation for early endometrial cancer without increasing the relapse rate.

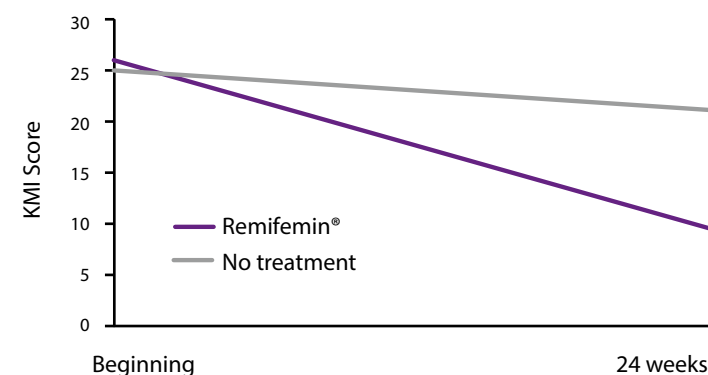


Fig. 18. Changes in the Menopause Index according to Kupperman during the study. Remifemin®: $p < 0.05$; no treatment: $p > 0.05$. (Modified based on Li et al., 2012.)

Study design:

Observational study over 12 months.

Controls were conducted at the beginning and after 6 months.

The measurement of efficiency was done based on a comparison of the Kupperman Menopause Indexes (KMI). Safety evaluation included monitoring of bone density, cancer recurrence rate, deaths, and kidney and liver functions.

Study profile:

Female patients: 60 menopausal patients after an operation for early endometrium cancer.
KMI ≥ 15 .
Average age 55.

Volunteers: Verum group: 2 x 1 tablet Remifemin® (20 mg drug/tablet) for 24 weeks.
Control group: no medication.

Main results:

- ▶ No influence on the recurrence rate for early endometrial cancer
- ▶ Significant improvement of the KMI scores
- ▶ No adverse events
- ▶ Significant increase in bone density

Double-blind study to examine the effect on uterine fibroids vs. tibolone in Chinese women

Objective:

To examine the safety of Remifemin® treatment vs. tibolone with uterine fibroids.

Methods:

In the study "Efficacy and tolerability of a medicinal product containing an isopropanolic black cohosh extract in Chinese women with menopausal symptoms: A randomized, double-blind, parallel-controlled study versus tibolone"² published in 2007, Bai and colleagues investigated the risk-benefit ratio of Remifemin® vs. tibolone. During this study, ultrasound images of the uterus were made and various other tests were conducted. A subgroup was formed from a total of 244 patients. This subgroup included 62 patients who had had at least one uterine fibroid prior to the first study. In the first study, 34 of the patients had received treatment with Remifemin® and 28 with tibolone. The female participants had undergone thorough gynecological and physical examinations at the beginning and at each check-up. (See pages 20 – 21.)² In the present study, all the ultrasound data from these 62 patients were reanalyzed. The measurements of the single, largest, ellipsoid myoma (cranio-caudal, transverse, and anteroposterior), determined by transvaginal ultrasound, were evaluated before and after 3 months of treatment with either tibolone or Remifemin®. The changes in the mean diameter, the geometric mean diameter, and the volume of the single largest myoma were calculated as percentages.

Results:

In the group treated with Remifemin®, the mean volume of the single, largest myoma decreased from 1,787 mm³ to 1,086 mm³ (-30.3%) in 70.1% of the patients. The mean diameter and the geometric mean diameter of the single largest myoma decreased significantly (each $p = 0.006$). In the tibolone group, the change in the volume of the single largest myoma from 1,063 mm³ to 1,096 mm³ could only be detected in 35.7% of the patients. Thus, on average, the volume of the single largest myoma in the tibolone group increased by +4.7%. The data for the mean diameter and the geometric mean diameter of the single largest myoma were not significant.

Conclusion:

Remifemin® offers an effective treatment for menopausal symptoms for patients with uterine fibroids. Compared to tibolone, it inhibits the growth of myomas.

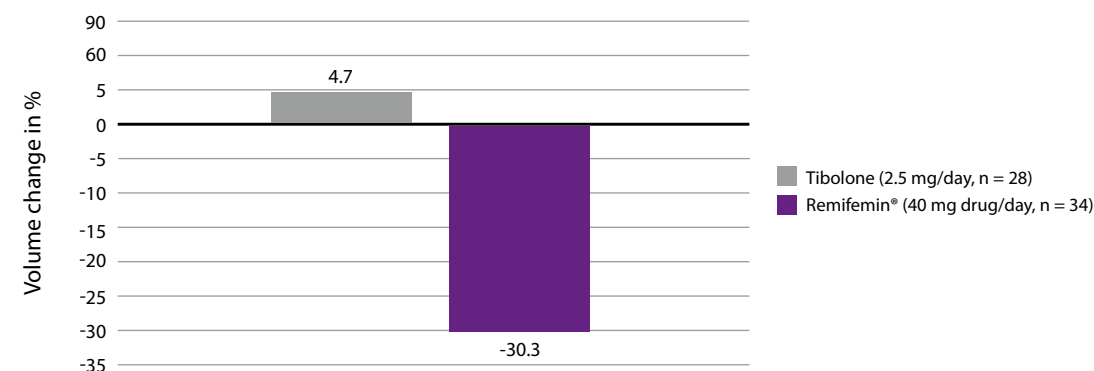


Fig. 19. Mean of the volume change of the largest myoma in each patient during treatment. (Modified based on Xi et al., 2014.)

Study design:

Randomized, tibolone-controlled, double-blind, clinical study in 5 centers in China over 3 months.

Controls were conducted at the beginning as well as after weeks 4 and 12.

In the present subgroup analysis, the size of the uterine fibroids, determined using transvaginal ultrasound, were evaluated in detail.

Study profile:

Female patients: 62 from 244 peri- and postmenopausal patients with a Kupperman Menopause Index of ≥ 15 , symptoms for at least 4 weeks, last menstruation ≥ 5 months ago, if last menstruation < 12 months ago than E2 levels ≤ 30 pg/ml. 40 - 60 years old.

Treatment: 34 patients = 2 x 1 tablet Remifemin® (20 mg = 2.5 mg extract/tablet) + 1 placebo per day.
28 patients = 1 x 1 tibolone (2.5 mg) + 2 placebo per day.

Main results:

- ▶ Significant decrease in the mean volume of the myoma (-30.3%)
- ▶ Significant reduction of the mean diameter of the myoma (-25.6%)
- ▶ Significant reduction of the geometric mean diameter of the myoma (-26.6%)
- ▶ Responder rate 70.1%

Xi, et al., *Effect of Isopropanolic Cimicifuga racemosa extract on uterine fibroids in comparison with Tibolone among patients of a recent randomized, double blind, parallel-controlled study in Chinese women with menopausal symptoms*. Evid Based Complement Alternat Med, 2014: 717686, (2014).⁴⁶

Clinical study on the changes in bone formation parameters

Objective:

To explore the influence of Remifemin® on bone biochemical markers. In addition, using a cell line, the serum from patients treated with Remifemin® was tested for its potential to stimulate cell function and to influence the expression of 3 genes for bone formation.

Methods:

The study included 82 women. 45 patients received 40 mg of Remifemin® per day and 37 patients received no treatment. Compliance was checked using diary data. At the beginning of the study and after 3 months, blood and urine samples were collected. General biochemical parameters were tested, including alkaline phosphatase (ALP), lipid profile, level of intact parathyroid hormone, follicle-stimulating hormone (FSH), estradiol, and testosterone as well as creatinine levels, calcium, and n-telopeptides of type I collagen (NTx). Additionally, bone mineral density testing was done on the lumbar vertebrae L2-L4 and the neck of the femur. The mouse cell line MC3T3-E1 was incubated together with the blood serum. Then the alkaline phosphate activity and the protein content in the supernatant were determined. In order to guarantee that mature osteoblasts were used, additional cells were treated with β -glycerophosphate (10 mM) and ascorbic acid (50 μ g/ml) to induce differentiation. By means of a polymerase chain reaction, the expression of the 3 genes (Runx2, ALP, and osteocalcin) associated with osteoblast differentiation and function was quantified.

Results:

Patients treated with Remifemin® showed a significantly reduced level of the indicator for bone resorption (NTx) and a higher level of the indicator for bone formation in their serum (ALP). The analytical parameters, including lipid profile and sex hormones (FSH, testosterone, estradiol), were not influenced by the treatment. Based on the cell culture tests, no differences could be found in the effects of the sera from treated and untreated patients on the activity of the alkaline phosphatase or gene expression.

Conclusion:

Remifemin® is well tolerated and has a positive influence on biochemical changes that can be associated with a small protective effect for bones.

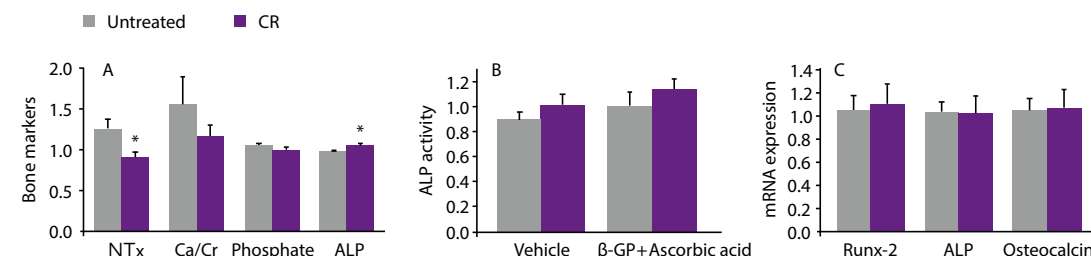


Fig. 20. The *Cimicifuga racemosa* effects on bones depicted as changes in female bone markers (A) or changes in the cell activity and the gene expression (B and C) in the osteoblastic cell line MC3T3-E1. Presented as mean \pm standard error and depicted in relationship to the corresponding baseline values. Gray columns: untreated control group. Purple columns: treatment with *Cimicifuga racemosa*. NTx: N-telopeptides of type I collagen, Ca/Cr: calcium-creatinine in proportion, ALP: alkaline phosphatase, β -GP: β -glycerophosphate, Runx2: Runt-related transcription factor 2. * $p < 0.05$ comparison of both groups. (Modified based on García-Pérez et al., 2009.)

Study design:

Prospective, clinical study over 3 months as well as an in vitro study with the mouse osteoblast cell line MC3T3-E1.

Controls were conducted at the beginning and end of the study.

The overall state of health was determined with general and gynecological check-ups as well as a blood count. Blood and urine samples were collected at the beginning and end of the study. General biochemical parameters were tested in the blood serum including ALP, a complete lipid profile, the level of intact parathyroid hormone, FSH, estradiol, and testosterone. Urine samples were tested for creatinine levels, calcium, and NTx. Bone mineral density was tested on the lumbar vertebrae (L2-L4) and the neck of the femur. The influence of the extract on osteoblast function was investigated using the mouse cell line MC3T3-E1. Alkaline phosphate activity and protein content were evaluated. The quantification of the expression of the 3 genes (Runx2, ALP, and osteocalcin) for osteoblast differentiation and function was done via RT-PCR.

Study profile:

Female patients: 82 patients with natural or surgical menopause, amenorrhea ≥ 1 year
FSH level ≥ 40 IU/L, non-smoker, no alcohol consumption, generally healthy.
Average age 55 years old.

Treatment: 45 patients: 40 mg/day Remifemin®.
37 patients: untreated control group.

Cell culture: MC3T3-E1 mouse osteoblast cells: incubated with blood serum from treated (Remifemin®) and untreated patients.

Controls: β -glycerophosphate (10 mM) and ascorbic acid (50 μ g/ml).

Main results:

- Treatment well tolerated
- Positive influence on the bones
- No influence on the hormone levels and lipid values

Ambulant study on the central opioid activity of Remifemin®

Objective:

To investigate if Remifemin® treatment has an effect on the endogenous opioid system of postmenopausal women.

Methods:

At the beginning of the study, 2 ml blood samples were drawn from seven patients via a venous catheter every 10 minutes from 3 pm to 7 am the next day. Additionally, a 90-minute PET scan was done. The motoric activity during sleep was recorded by an actigraph for 16 hours. The patients took Remifemin® for 3 months (40 mg drug/day). Between weeks 11 and 12, blood was collected and a PET scan was done similar to the first time. However, this time saline solution (0.9%, 20ml/h, week 11) or naloxone solution (1mg/m²/h, week 12) was injected in the other arm for 8 hours (3 pm to 11 pm). Naloxone is an opioid antagonist and is used to reverse an opioid induce depression of the central nervous system. The concentration of luteinizing hormones (LH) was tested in all blood samples.

Results:

On average the patients were 53.2 years old and had not menstruated for an average of 3.7 years. The spon-

taneous LH secretion parameters were not influenced by Remifemin®; this rules out estrogenic activity by Remifemin® on the hypothalamic-pituitary-ovarian axis. During the additional treatment with naloxone, a prolongation of the interphase (by almost 90 minutes) and a significant suppression of the secretion phase as well as an increase in the prolactin level were observed, especially at night, compared to the administration of saline. This also indicates a lack of estrogenic activity. In addition, a significantly increased availability of μ -opioid receptor binding potential was detected in the brain regions for cognitive and emotional processes. Significant reductions were also identified in the regions involved in responses to sensory stimuli with an emotional component. These regions are also active in thermoregulatory reactions and hot flushes. Thus, there are bi-directional differences which vary within the brain regions.

Conclusion:

Remifemin® has no effect on the spontaneous pulsatility of the luteinizing hormone or the estrogen concentration. However, neuropharmacological effects were proven.

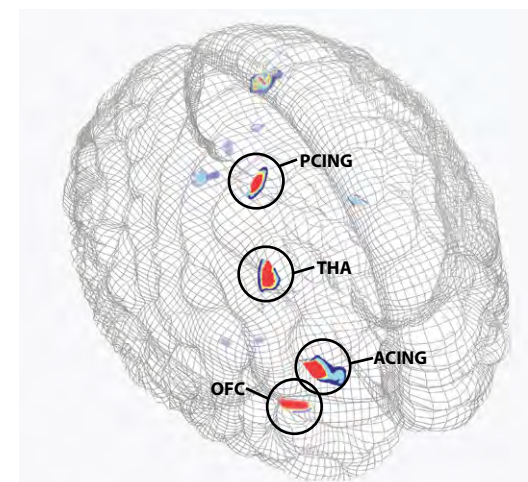


Fig. 21. Brain regions that showed an increase of μ -opioid receptor binding potential after treatment with black cohosh, presented as a three-dimensional image. Standardized Z-scores of the statistical significance are depicted with a pseudocolor scale. The red regions show the most significant differences. ACING, anterior cingulate cortex; OFC, orbitofrontal cortex; PCING, posterior cingulate cortex; THA, thalamus. (Modified based on Reame et al. 2008.)

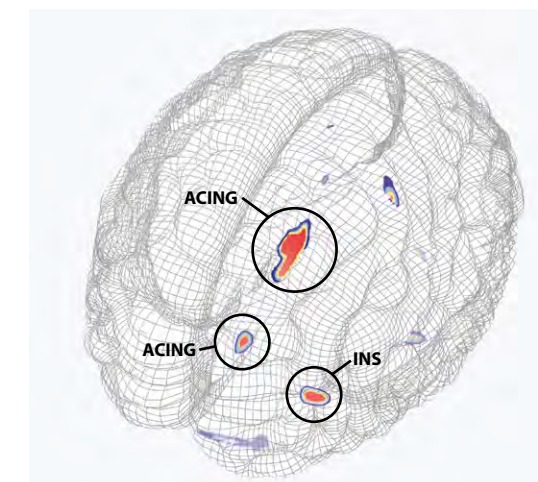


Fig. 22. Brain regions that showed a reduction of μ -opioid receptor binding potential after treatment with black cohosh, presented as a three-dimensional image. Standardized Z-scores of the statistical significance are depicted with a pseudocolor scale. The red regions show the most significant differences. The most noticeable reductions were seen in the anterior insular cortex and cingulate cortex. ACING, anterior cingulate cortex; INS, insular cortex. (Modified based on Reame et al. 2008.)

Study design:

Ambulant study over 3 months.

Controls were conducted at the beginning and the end of treatment.

Regional changes in the binding behavior of μ -opioid receptors were assessed using modern molecular neuroimaging techniques. The neurotransmitter system was evaluated with positron emission tomography (PET). Blood was drawn to measure LH (pulsatility), FSH, E2 and progesterone levels. Actigraphy was used to monitor sleep.

Study profile:

Female patients: 7 postmenopausal patients (right handed) with amenorrhea for at least 12 months, FSH >40 IU/L, and estradiol level <20 pg/ml, hormone therapy at least \leq 6 months ago, and with menopausal symptoms. Average age 53.2 years.

Treatment: 2 x 1 tablet Remifemin® per day (20 mg drug/tablet).

Main results:

- Significantly increased availability of μ -opioid receptor binding potential in brain regions for cognitive and emotional processes
- Significant reduction in regions that are involved in reactions to sensory stimuli with emotional components, thermoregulatory reactions, and hot flashes

Observational study to examine the combined treatment with paroxetine

Objective

The efficacy and safety of a combined therapy with Remifemin® and paroxetine for patients with perimenopausal depression was investigated within the framework of this study.

Methods:

During this study, 120 patients with postmenopausal depression were treated with either 2 x 1 tablet Remifemin® and 1 x 1 tablet paroxetine (20 mg) daily (n = 60) or only 1 x 1 tablet paroxetine (20 mg) daily (n = 60). In order to characterize the efficacy of the treatment with regard to menopausal symptoms, the Kupperman Menopause Index (KMI) was used. For the psychological symptoms, the Hamilton Depression Rating Scale (HAMD) was applied. Blood, urine, electrocardiography, liver function, kidney function, and blood pressure were monitored. All the data were compared before and after the treatment in order to assess undesired effects.

Results:

An 88.3% improvement of the HAMD was determined after 2 months of treatment with Remifemin® + paroxetine; the treatment with only paroxetine achieved 78.3%. The therapeutic efficacy regarding menopausal symptoms was significantly better (p <0.05) in the combined therapy group. Likewise, after 8 weeks a significantly superior (p <0.01) KMI score of 9.89 ± 3.76 was achieved compared to 15.75 ± 5.84 in the single therapy. No significant differences between the groups were found when looking at the blood, urine, electrocardiography, liver, and kidney results as well as blood pressure.

Conclusion:

A combination of Remifemin® with paroxetine for perimenopausal depression may increase the efficiency of the single therapy with paroxetine and is well accepted.

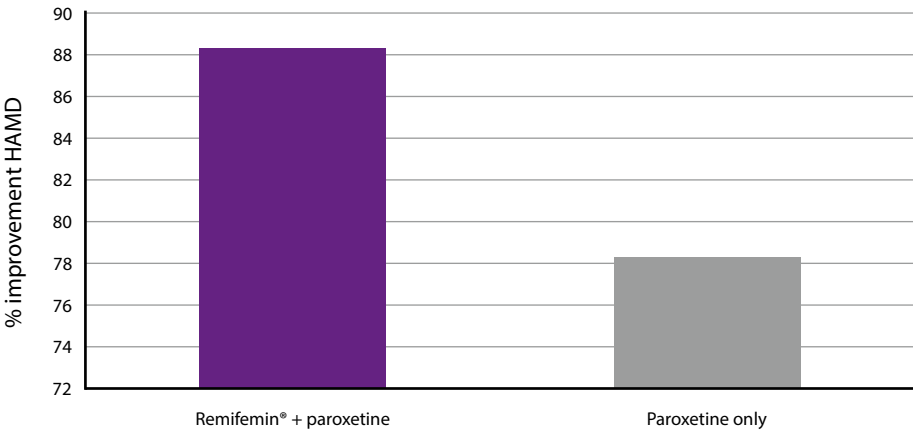


Fig. 23. Improvement of the perimenopausal depression in the Hamilton Depression Rating Scale (HAMD). Shown as percentage of change after 2 months of treatment. p <0.05. (Modified based on Huang et al. 2013.)

Study design:

Observational study over 2 months.

Controls were conducted at the beginning and after 2 months.

Efficiency was evaluated by comparing the Menopause Indexes according to Kupperman (KMI) as well as the Hamilton Depression Rating Scale (HAMD). Safety was assessed by monitoring blood and urine results, electrocardiography, liver and kidney functions, and blood pressure.

Study profile:

Females patients: 120 perimenopausal patients with depression.

Treatment: 60 patients 1 x 1 tablet paroxetine (20 mg) daily.
60 patients 1 x 1 tablet paroxetine (20 mg) daily plus 2 x 1 tablet Remifemin® (20 mg drug/tablet).

Main results:

- ▶ Significant improvement of the KMI with the combined therapy
- ▶ Improvement of the HAMD by 88.3% with the combined therapy
- ▶ Good acceptance

Huang, et al., *Clinical Study of combined treatment of Remifemin and Paroxetine for perimenopausal depression*. Zhonghua Yi Xue Za Zhi, 93 (8), 600-602, (2013).¹⁵

Observational study on the efficacy in women with an increased BMI

Objective:

To study the effect of Remifemin® administration in Spanish patients with increased BMI (representative of the Spanish population).

Methods:

122 women with increased BMI and postmenopausal hot flashes (mild to severe) were included in the study; the women had had amenorrhea for at least 1 year and had not undergone any gynecological operation in the last 6 months. The women were ages 45 - 59 years old. The women were divided into three groups according to age. At the beginning of the study, each patient filled-out a questionnaire with the Cervantes Health-related Quality of Life Scale (HRQoL). For 3 months the volunteers received 40 mg Remifemin® per day as 2 x 1 tablet. At the end of 3 months, they were asked to fill-out the questionnaire again. The differences in the evaluations were then statistically analyzed.

Results:

All patients had an increased BMI. The majority of the patients were 50 - 54 years old; the other groups were grouped by ages 45 - 49 years old and 55 - 59 years old. There were no significant group differences regarding weight, size, BMI, and blood pressure. Also, to this effect, none were caused by treatment with Remifemin®. However, after 3 months, Remifemin® treatment demonstrated a significant improvement in the general quality of life in all age groups ($p < 0.001$). In the individual groups as well as in the group as a whole, significant positive effects were shown in the domains *menopause and health* and *psyche* ($p < 0.001$). In addition, there was a significant improvement in the scores for the domain *sexuality* ($p < 0.001$) for the entire group, but this could not be transferred to the individual age groups. No significant change was demonstrated in the domain *relationship*.

Conclusion:

Treatment with Remifemin® increased the quality of life in all four domains (*menopause and health*, *psyche*, *sexuality*, and *relationship*). It is an effective treatment method for postmenopausal symptoms for women with increased body weight.

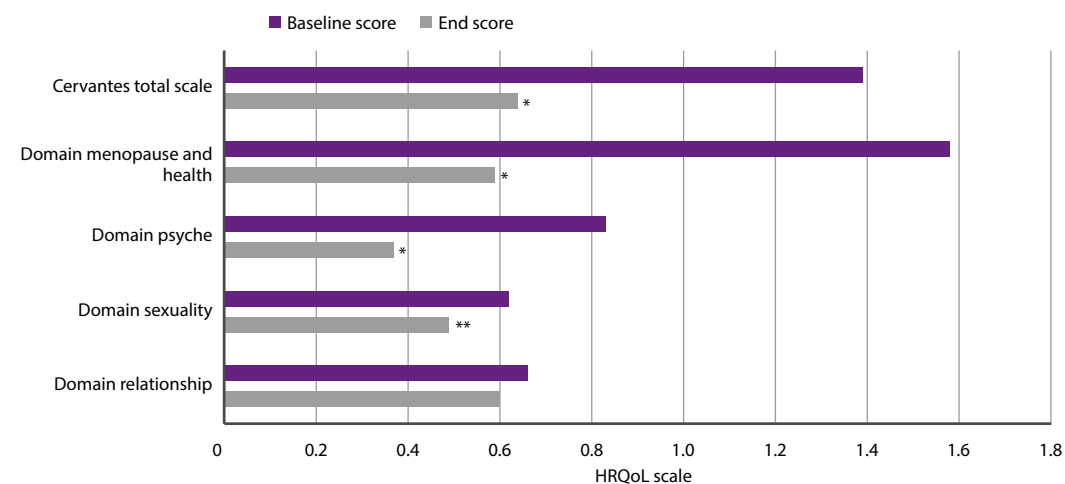


Fig. 24. Mean of the global and the four domains of the Cervantes scale (before and after Remifemin® treatment). The mean \pm standard mistake of the group values are presented (* $p < 0.001$ compared to baseline score, ** $p < 0.05$ compared to baseline score). (Modified based on Julia Mollá et al. 2009.)

Study design:

Prospective, observational study over 3 months.

Controls were conducted at the beginning and at the end.

Quality of life was determined using the self-evaluation scale Cervantes Health-related Quality of Life Scale (HRQoL) with 31 items (each scored with 0 - 5) in four domains: *menopause and health* (15 items), *psyche* (9 items), *sexuality* (4 items) and *relationship* (3 items). Weight, size, BMI, and blood pressure were measured.

Study profile:

Female patients: 122 postmenopausal patients with an increased body-mass-index, generally healthy, at least 12 months amenorrhea, mild to severe hot flashes, no gynecological operation in the last 6 months. 45 - 59 years old.

Treatment: 2 x 1 tablet Remifemin® (20 mg drug/tablet)

Main results:

- No influence on body weight
- Improved quality of life in the domains *menopause and health*, *psyche*, *sexuality*, and *relationship*
- Also an effective treatment method for women with increased body weight

Additional studies II

Clinical study	Study design	Study profile	Treatment	Main results
Pilot evaluation of black cohosh for the treatment of hot flashes in women Pockaj, et al., 2004 Cancer Investigation, 22, (4), 515–521. ³⁴	Open observational study 4 weeks	21 patients - with previous breast cancer - with a high risk for breast cancer - refuse to have estrogen therapy Average age 56 years old (Over 18 years old, ≥ 14 hot flashes per week for at least 1 month, life expectancy at least 6 months, no previous antineoplastic chemotherapy or therapy with androgens, estrogens, clonidine, progestational agents or Bellerigal-S for at least 4 weeks prior. No antidepressants for at least one year.) 13 had had breast cancer in the past, 6 had also been taking tamoxifen or raloxifene for at least a month.	2 x 1 tablet Remifemin® per day	<ul style="list-style-type: none"> ▶ 50% → reduction of the number of daily hot flashes after 5 weeks ▶ 22% → reduction in the severity of the hot flashes ▶ 56% → reduction in the number of weekly hot flashes ▶ Reduction of other climacteric symptoms (sleep problems, tiredness) ▶ No therapy dropouts <p>A signification reduction of excessive sweating during menopausal hot flashes was demonstrated while taking Remifemin®. In an in vitro yeast assay, it was shown that no estrogenic-like activity could be proven.</p>
Pharmacological measures in postmenopausal women with an isopropanolic aqueous extract of <i>Cimicifugae racemosa</i> rhizoma Nesselhut, et al., 1999 Menopause, 6 (4), 331. ³⁰	Non-interventional study Average duration 98 days	28 postmenopausal patients with menopausal complaints Average age 56.4 years old	136 mg Remifemin® per day	<ul style="list-style-type: none"> ▶ No clinically relevant increase in the thickness of the endometrium ▶ No negative influence on the vaginal cells ▶ No estrogenic effects on LH, FSH, prolactin, or E2 ▶ 80% of the patients → good to very good efficiency <p>The Remifemin® preparation that was taken demonstrated no estrogenic effect on the vaginal cell tissue and the hormone levels of LH, FSH, prolactin, and E2.</p>

A retrospective case-control study of the use of hormone-related supplements and association with breast cancer Rebbeck, et al., 2007 Int J Cancer, 120, 1523–1528. ³⁷	Population-based case study	949 patients with breast cancer 1,524 controls without breast cancer 50-79 years old (Patients with African or European heritage, breast cancer stages I, II, or III)	Remifemin® (n = 13) or other commercial drugs or preparations, also dong quai (Angelica sinensis), red clover or ginseng extracts as well as non-standardized preparations with the same contents or other plants, combination drugs, steroid hormone DHEA, or other natural isoflavones, etc. n = 56 2 x 1 tablet Remifemin® per day n = 60 1 x 1 tibolone (2.5 mg) per day	<ul style="list-style-type: none"> ▶ Significant breast cancer protective effects ▶ No significant interactions with tamoxifen or raloxifene <p>Remifemin® has a significant breast cancer protective effect.</p>
Efficacy and safety of Remifemin® on peri-menopausal symptoms induced by post-operative GnRH-a therapy for endometriosis: A randomized study versus Tibolone Chen, et al., 2014 Medical Science Monitor 20, 1950–1957. ⁸	Randomized, prospective, tibolone-controlled, clinical study 12 weeks	116 patients with endometriosis and GnRH-a injection	n = 56 2 x 1 tablet Remifemin® per day n = 60 1 x 1 tibolone (2.5 mg) per day	<ul style="list-style-type: none"> ▶ Reduction of the menopausal symptoms caused by GnRH-a therapy ▶ Equally as effective as tibolone ▶ Fewer adverse events than with tibolone ▶ No estrogenic effects ▶ No negative influence on liver or renal functions or the lipid profile <p>Compared with tibolone, Remifemin® was equally effective for perimenopausal symptoms that were triggered by GnRH-a therapy and demonstrated a better safety profile because there were no estrogen-like effects.</p>

References

1 Arold, et al., *No relevant interaction with alprazolam, caffeine, tolbutamide, and digoxin by treatment with a low-hyperforin St John's wort extract*. *Planta Med*, 71 (4), 331-337, (2005).

2 Bai, et al., *Efficacy and tolerability of a medicinal product containing an isopropanolic black cohosh extract in Chinese women with menopausal symptoms: A randomized, double blind, parallel-controlled study versus tibolone*. *Maturitas*, 58 (1), 31-41, (2007).

3 Beer, *Cimicifuga racemosa bei klimakterische Beschwerden - Aktuelle Daten bestätigen Wirksamkeit und Sicherheit*. *Zeitschrift für Phytotherapie*, 36 (01), 10-17, (2015).

4 Beer, et al., *Differentiated evaluation of extract-specific evidence on Cimicifuga racemosa's efficacy and safety for climacteric complaints*. *Evid Based Complement Alternat Med*, 2013, 860602, (2013).

5 Blohmer, et al., *Behandlung vorwiegend psychisch orientierter, klimakterischer Beschwerden mit der fixen Kombination eines Traubensilberkerzen- und eines Johanniskrautextraktes (Remifemin plus)*. *Journal für Menopause*, 1, 34-37, (2006).

6 Briesse, et al., *Black cohosh with or without St. John's wort for symptom-specific climacteric treatment - Results of a large-scale, controlled, observational study*. *Maturitas*, 57 (4), 405-414, (2007).

7 Castelo-Branco, *Cimicifuga racemosa for non-hormonal treatment on climateric complaints – an overview*. *Climacteric*, 19 (Suppl 1), (2016).

8 Chen, et al., *Efficacy and safety of remifemin on peri-menopausal symptoms induced by post-operative GnRH-a therapy for endometriosis: A randomized study versus tibolone*. *Med Sci Monit*, 20, 1950-1957, (2014).

9 European Medicines Agency, et al., *Community herbal monograph on Cimicifuga racemosa (L.) Nutt*. EMA/HMPC/600717/2007 Corr.1, 1-6, (2011).

10 European Scientific Cooperative on Phytotherapy (ESCOP), *Cimicifugae rhizoma – Black cohosh*. 1-26, (2011).

11 Garcia-Perez, et al., *Isopropanolic Cimicifuga racemosa is favorable on bone markers but neutral on an osteoblastic cell line*. *Fertil Steril*, 91 (Suppl 4), 1347-1350, (2009).

12 Goodenough, *Dr. Goodenough's home cures and herbal remedies*. Avenel Books, (1904).

13 Henneicke-von Zepelin, et al., *Isopropanolic black cohosh extract and recurrence-free survival after breast cancer*. *Int J Clin Pharmacol Ther*, 45 (3), 143-154, (2007).

14 Hirschberg, et al., *An isopropanolic extract of black cohosh does not increase mammographic breast density or breast cell proliferation in postmenopausal women*. *Menopause*, 14 (1), 89-96, (2007).

15 Huang, et al., [Clinical study of combined treatment of remifemin and paroxetine for perimenopausal depression]. *Zhonghua Yi Xue Za Zhi*, 93 (8), 600-602, (2013).

16 Jacobson, et al., *Randomized trial of black cohosh for the treatment of hot flashes among women with a history of breast cancer*. *J Clin Oncol*, 19 (10), 2739-2745, (2001).

17 Jiang, et al., *Black cohosh improves objective sleep in postmenopausal women with sleep disturbance*. *Climacteric*, 18 (4), 559-567, (2015).

18 Juliá Mollá, et al., *Cimicifuga racemosa treatment and health related quality of life in post-menopausal Spanish women*. *Gynecol Endocrinol*, 25 (1), 21-26, (2009).

19 Kommission E, *Monograph on Cimicifuga racemosa (L.) Nutt*. (1989).

20 Köppel, et al., *Investigation of the effect on photosensitivity following repeated oral dosing of Hypericum extract in 20 healthy male and female volunteers*. *Tagung Phytopharmaka und Phytotherapie, Zeitschrift für Phytotherapie*, 29 (Suppl 1), 26, (2008).

21 Li, et al., *Efficacy of remifemin for control of climacteric symptoms*. *Prog Obstet Gynecol*, 20 (6), 462-465, (2011).

22 Li, et al., *Cimicifuga racemosa for treatment of menopausal symptoms in patients with early endometrial cancer after operation*. *Academic Journal of Second Military Medical University*, 33 (5), 562-564, (2012).

23 Liske, *Klimakterium: Phytokombination lindert psychovegetative Leiden. [Phytokombination alleviates psycho-vegetative disorders]*. *TW Gynäkologie*, 10, 172-175, (1997).

24 Liske, et al., *Physiological investigation of a unique extract of black cohosh (Cimicifugae racemosae rhizoma): A 6-month clinical study demonstrates no systemic estrogenic effect*. *J Womens Health Gend Based Med*, 11 (2), 163-174, (2002).

25 Liske, et al., *Therapy of climacteric complaints with Cimicifuga racemosa: Herbal medicine with clinically proven evidence*. *Ninth annual meeting of NAMS, Menopause*, 5 (4), 250, (1998).

26 Lundström, et al., *Digitized assessment of mammographic breast density - Effects of continuous combined hormone therapy, tibolone and black cohosh compared to placebo*. *Maturitas*, 70 (4), 361-364, (2011).

27 Morrison, *Plantarum historiae universalis oxoniensis II — Oxonii*. (1680).

28 Nappi, et al., *Efficacy of Cimicifuga racemosa on climacteric complaints: A randomized study versus low-dose transdermal estradiol*. *Gynecol Endocrinol*, 20 (1), 30-35, (2005).

29 Naser, et al., *Suspected black cohosh hepatotoxicity: no evidence by meta-analysis of randomized controlled clinical trials for isopropanolic black cohosh extract*. *Menopause*, 18 (4), 366-375, (2011).

30 Nesselhut, et al., *Pharmacological measures in postmenopausal women with an isopropanolic aqueous extract of Cimicifuga racemosa rhizoma*. *10th annual meeting of NAMS, Menopause*, 6 (4), 331, (1999).

31 Nuttall, *The genera of North American plants, and a catalogue of the species, to the year 1817*. D. Heartt, (1818).

32 Obi, et al., *The use of herbal preparations to alleviate climacteric disorders and risk of postmenopausal breast cancer in a German case-control study*. *Cancer Epidemiol Biomarkers Prev*, 18 (8), 2207-2213, (2009).

33 Osmer, et al., *Efficacy and safety of isopropanolic black cohosh extract for climacteric symptoms*. *Obstet Gynecol*, 105 (5, part 1), 1074-1083, (2005).

34 Pockaj, et al., *Pilot evaluation of black cohosh for the treatment of hot flashes in women*. *Cancer Invest*, 22 (4), 515-521, (2004).

35 Porcher, *Report on the indigenous medicinal plants of South Carolina*. American Medical Association, (1849).

36 Reame, et al., *Black cohosh has central opioid activity in postmenopausal women: evidence from naloxone blockade and positron emission tomography neuroimaging*. *Menopause*, 15 (5), 832-840, (2008).

37 Rebbeck, et al., *A retrospective case-control study of the use of hormone-related supplements and association with breast cancer*. *Int J Cancer*, 120 (7), 1523-1528, (2007).

38 Rostock, et al., *Black cohosh (Cimicifuga racemosa) in tamoxifen-treated breast cancer patients with climacteric complaints – a prospective observational study*. *Gynecological Endocrinology*, 27 (10), 844-848, (2011).

39 Schildge, *Beitrag zur Behandlung von prämenstruellen und klimakterischen Verstimmungs- und Depressionszuständen*. *Ringelheimer Biologische Umschau*, 19 (2), 18-22, (1964).

40 Schmidt, et al., *Wirksamkeit und Sicherheit von Traubensilberkerze (Cimicifuga racemosa, Cimifemin®) bei Menopause-beschwerden: Therapiebeobachtung unter Praxisbedingungen*. *Journal für Menopause*, 1, 27-32, (2005).

41 Tietze, *Jetziger Stand der Hormontherapie gynäkologischer Störungen*. *Therapiewoche*, 7 (14-15), 471-476, (1957).

42 Uebelhack, et al., *Black cohosh and St. John's wort for climacteric complaints: A randomized trial*. *Obstet Gynecol*, 107 (2 Pt 1), 247-255, (2006).

43 Vermes, et al., *The effects of remifemin® on subjective symptoms of menopause*. *Adv Ther*, 22 (2), 148-154, (2005).

44 von Linné, *Species plantarum, exhibentes plantas rite cognitae, ad genera relatas, cum differentiis specificis, nominibus trivialibus, synonymis selectis, locis natalibus, secundum systema sexuale digestas*. Lars Salvius, (1953).

45 World Health Organization, *Rhizoma Cimicifugae racemosae*. WHO Monographs on Selected medicinal plants, 55-65, (2002).

46 Xi, et al., *Effect of isopropanolic Cimicifuga racemosa extract on uterine fibroids in comparison with tibolone among patients of a recent randomized, double blind, parallel-controlled study in Chinese women with menopausal symptoms*. *Evid Based Complement Alternat Med*, 2014 (Article ID 717686), (2014).

47 Yilin, et al., *Efficacy of remifemin for control of climacteric symptoms*. *Progress in Obstetrics and Gynecology*, 20 (6), 462-465, (2011).

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Appendix – Complete list of literature since 1997

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- Bai, et al., *Efficacy and tolerability of a medicinal product containing an isopropanolic black cohosh extract in Chinese women with menopausal symptoms: A randomized, double blind, parallel-controlled study versus tibolone*. *Maturitas*, 58 (1), 31-41, (2007).
- Beck, et al., *Comparison of hormonal activity (estrogen, androgen and progestin) of standardized plant extracts for large scale use in hormone replacement therapy*. *The Journal of Steroid Biochemistry and Molecular Biology*, 84 (2-3), 259-268, (2003).
- Blohmer, et al., *Behandlung vorwiegend psychisch orientierter, klimakterischer Beschwerden mit der fixen Kombination eines Traubensilberkerzen- und eines Johanniskrautextraktes (Remifemin plus)*. *Journal für Menopause*, 1 34-37, (2006).
- Bodinet, et al., *Influence of Cimicifuga racemosa on the proliferation of estrogen receptor-positive human breast cancer cells*. *Breast Cancer Res Treat*, 76 (1), 1-10, (2002).
- Bodinet, et al., *Influence of marketed herbal menopause preparations on MCF-7 cell proliferation*. *Menopause*, 11 (3), 281-289, (2004).
- Briese, et al., *Clinical efficacy and drug safety of herbal remedies in the treatment of climacteric complaints*. 5th international symposium on women's health and menopause, Italien, Florenz, (2004).
- Briese, et al., *Black cohosh with or without St. John's wort for symptom-specific climacteric treatment - Results of a large-scale, controlled, observational study*. *Maturitas*, 57 (4), 405-414, (2007).
- Chen, et al., *Efficacy and safety of remifemin on peri-menopausal symptoms induced by post-operative GnRH-a therapy for endometriosis: A randomized study versus tibolone*. *Med Sci Monit*, 20 1950-1957, (2014).
- Cui, et al., *Effects of remifemin treatment on bone integrity and remodeling in rats with ovariectomy-induced osteoporosis*. *PLoS One*, 8 (12), e82815, (2013).
- Da, et al., *A comparison of the effects of estrogen and Cimicifuga racemosa on the lacrimal gland and submandibular gland in ovariectomized rats*. *PLoS One*, 10 (3), e0121470, (2015).
- Freudenstein, et al., *Influence of an isopropanolic aqueous extract of Cimicifugae racemosae rhizoma on the proliferation of MCF-7 cells*. 23rd International LOF-Symposium on Phyto-Oestrogens Gent, Belgium, Workshop of the Society for Medicinal Plant Research, (1999).
- Freudenstein, et al., *Lack of promotion of estrogen-dependent mammary gland tumors in vivo by an isopropanolic Cimicifuga racemosa extract*. *Cancer Res*, 62 (12), 3448-3452, (2002).
- García-Pérez, et al., *Isopropanolic Cimicifuga racemosa is favorable on bone markers but neutral on an osteoblastic cell line*. *Fertil Steril*, 91 (Suppl 4), 1347-1350, (2009).
- García de Arriba, et al., *Neuroprotective effects of Cimicifuga racemosa may be able to prevent age-related neurodegeneration*. *Phytokongress 2013: Phytotherapie im Spannungsfeld zwischen Forschung und Praxis*, Deutschland, Leipzig, (2013).
- García de Arriba, et al., *Isopropanolic Cimicifuga extract modulates brain activity; Electropharmacogram from various brain areas in freely moving rats (Tele-Stereo-EEG)*. 10th european congress on menopause and andropause (EMAS), Italien, Madrid, *Maturitas*, 82 318, (2015).
- García de Arriba, et al., *Pharmacologic rationale for beneficial effects of Vitex agnus castus on infertility and outcomes in Polycystic Ovary Syndrome (PCOS)*. 15th world congress on menopause (IMS), Tschechien, Prag, (2016).
- García de Arriba, et al., *Neuroprotective strategies of Cimicifuga racemosa (CR): Update*. 15th world congress on menopause (IMS), Tschechien, Prag, (2016).
- García de Arriba, et al., *Cimicifuga racemosa for treatment of vasomotor symptoms: Update of mode of action*. 15th world congress on menopause (IMS), Tschechien, Prag, (2016).
- Henneicke- von Zepelin, et al., *Pharmakoepidemiologische Kohortenstudie zur Anwendung von Remifemin®/ Remifemin® plus bei Patientinnen mit Mammakarzinom einschließlich Hormonrezeptor-positiver Tumore*. Kongreß der Deutschen Menopause Gesellschaft, Münster, *Menopause*, 12 (2), 18-19, (2005).
- Henneicke-von Zepelin, *60 years of Cimicifuga racemosa medicinal products*. *Wiener Medizinische Wochenschrift*, 167 (7), 147-159, (2017).
- Henneicke-von Zepelin, et al., *Isopropanolic black cohosh extract and recurrence-free survival after breast cancer*. *Int J Clin Pharmacol Ther*, 45 (3), 143-154, (2007).
- Hirschberg, et al., *An isopropanolic extract of black cohosh does not increase mammographic breast density or breast cell proliferation in postmenopausal women*. *Menopause*, 14 (1), 89-96, (2007).
- Hostanska, et al., *Cimicifuga racemosa extract inhibits proliferation of estrogen receptor-positive and negative human breast carcinoma cell lines by induction of apoptosis*. *Breast Cancer Res Treat*, 84 (2), 151-160, (2004).
- Hostanska, et al., *Evaluation of cell death caused by triterpene glycosides and phenolic substances from Cimicifuga racemosa extract in human MCF-7 breast cancer cells*. *Biol Pharm Bull*, 27 (12), 1970-1975, (2004).
- Hostanska, et al., *Inhibitory effect of an isopropanolic extract of black cohosh on the invasiveness of MDA-MB 231 human breast cancer cells*. *In Vivo*, 21 (2), 349-355, (2007).
- Huang, et al., *[Clinical study of combined treatment of remifemin and paroxetine for perimenopausal depression]*. *Zhonghua Yi Xue Za Zhi*, 93 (8), 600-602, (2013).
- Hui, et al., *Effects of black cohosh and estrogen on the hypothalamic nuclei of ovariectomized rats at different temperatures*. *J Ethnopharmacol*, 142 (3), 769-775, (2012).
- Jacobson, et al., *Randomized trial of black cohosh for the treatment of hot flashes among women with a history of breast cancer*. *J Clin Oncol*, 19 (10), 2739-2745, (2001).
- Jiang, et al., *Black cohosh improves objective sleep in postmenopausal women with sleep disturbance*. *Climacteric*, 18 (4), 559-567, (2015).
- Juliá Mollá, et al., *Cimicifuga racemosa treatment and health related quality of life in post-menopausal Spanish women*. *Gynecol Endocrinol*, 25 (1), 21-26, (2009).
- Kennelly, et al., *Analysis of thirteen populations of black cohosh for formononetin*. *Phytomedicine*, 9 (5), 461-467, (2002).
- Köppel, et al., *Investigation of the effect on photosensitivity following repeated oral dosing of Hypericum extract in 20 healthy male and female volunteers*. *Tagung Phytopharmaka und Phytotherapie, Zeitschrift für Phytotherapie*, 29 (Suppl 1), 26, (2008).
- Kretzschmar, et al., *No estrogen-like effects of an isopropanolic extract of Rhizoma Cimicifugae racemosae on uterus and vena cava of rats after 17 day treatment*. *J Steroid Biochem Mol Biol*, 97 (3), 271-277, (2005).
- Li, et al., *Cimicifuga racemosa for treatment of menopausal symptoms in patients with early endometrial cancer after operation*. *Academic Journal of Second Military Medical University*, 33 (5), 562-564, (2012).
- Liske, *Klimakterium: Phytokombination lindert psychovegetative Leiden. [Phytocombination alleviates psychovegetative disorders]*. *TW Gynäkologie*, 10 172-175, (1997).
- Liske, et al., *Physiological investigation of a unique extract of black cohosh (Cimicifugae racemosae rhizoma): A 6-month clinical study demonstrates no systemic estrogenic effect*. *J Womens Health Gend Based Med*, 11 (2), 163-174, (2002).
- Liske, et al., *Therapy of climacteric complaints with Cimicifuga racemosa: Herbal medicine with clinically proven evidence*. Ninth annual meeting of NAMS Menopause, 5 (4), 250, (1998).
- Lundström, et al., *Digitized assessment of mammographic breast density – Effects of continuous combined hormone therapy, tibolone and black cohosh compared to placebo*. *Maturitas*, 70 (4), 361-364, (2011).
- Ma, et al., *Effects of an isopropanolic-aqueous black cohosh extract on central body temperature of ovariectomized rats*. *J Ethnopharmacol*, 138 (1), 156-161, (2011).
- Ma, et al., *[Effects of Remifemin on Expression of 5-HT1AR and 5-HT2AR in Preoptic Area of Hypothalamus of Ovariectomized Rats]*. *Journal of International Obstetrics and Gynecology*, 38 (2), 148-154, (2011).
- Muhammad, et al., *Estrogen receptor modulatory effects of germinated brown rice bioactives in the uterus of rats through the regulation of estrogen-induced genes*. *Drug Design, Development and Therapy*, 7 1409-1420, (2013).

Muhammad, et al., *Upregulation of genes related to bone formation by γ -amino butyric acid and γ -oryzanol in germinated brown rice is via the activation of GABAB-receptors and reduction of serum IL-6 in rats*. Clinical Interventions in Aging, 8 1259-1271, (2013).

Nappi, et al., *Efficacy of Cimicifuga racemosa on climacteric complaints: A randomized study versus low-dose transdermal estradiol*. Gynecol Endocrinol, 20 (1), 30-35, (2005).

Naser, et al., *Suspected black cohosh hepatotoxicity: no evidence by meta-analysis of randomized controlled clinical trials for isopropanolic black cohosh extract*. Menopause, 18 (4), 366-375, (2011).

Nesselhut, et al., *Pharmacological measures in postmenopausal women with an isopropanolic aqueous extract of Cimicifuga racemosa rhizoma*. 10th annual meeting of NAMS, Menopause, 6 (4), 331, (1999).

Nisslein, et al., *Effects of Black Cohosh on urinary bone markers and femoral density in an OVX-rat model*. IOF World Congress on Osteoporosis, Chicago, USA, 11 504, (2000).

Nisslein, et al., *Effects of black cohosh on bone marrow cytology and epiphyseal bone architecture*. IOF World Congress on Osteoporosis, Lissabon, Portugal, 13 P148MO, (2002).

Nisslein, et al., *Prepubertal treatment with black cohosh attenuates pathogenicity in the DMBA rat model of mammary carcinoma*. Climacteric, 5 (Suppl1), 139-140, (2002).

Nisslein, et al., *Effects of an isopropanolic extract of Cimicifuga racemosa on urinary crosslinks and other parameters of bone quality in an ovariectomized rat model of osteoporosis*. J Bone Miner Metab, 21 (6), 370-376, (2003).

Nisslein, et al., *Long term treatment of uterine carcinoma prone dark agouti rats with a standardized isopropanolic extract of Cimicifuga racemosa*. GA-Tagung, (2003).

Nisslein, et al., *Synergistic effects of Black Cohosh and Tamoxifen in an animal model of mammary carcinoma*. Maturitas, 44 (Suppl 2), 83-166, (2003).

Nisslein, et al., *Concomitant administration of an isopropanolic extract of black cohosh and tamoxifen in the in vivo tumor model of implanted RUCA-I rat endometrial adenocarcinoma cells*. Toxicol Lett, 150 (3), 271-275, (2004).

Nisslein, et al., *Long term treatment of ovariectomized rats with black cohosh: Site specific effects and calcium balance*. IOF World Congress on Osteoporosis, Rio de Janeiro, Brasil, 15 P348MO, (2004).

Nisslein, et al., *Coadministration of the aromatase inhibitor formestane and an isopropanolic extract of black cohosh in a rat model of chemically induced mammary carcinoma*. Planta Med, 73 (4), 318-322, (2007).

Nisslein, et al., *Urodynamische Effekte eines isopropanolischen Extraktes der Traubensilberkerze (iCR) [Urodynamic effects of an isopropanolic extract of Black cohosh]*. J Menopause, 1 27-28, (2006).

Nisslein, et al., *Apoptoseinduktion durch Triterpenglykoside und Zimtsäureester aus einem Extrakt von Actaea racemosa in menschlichen Brustkrebszellen*. Journal für Menopause, 13 (1), 24-26, (2006).

Nisslein, et al., *In vitro binding of an isopropanolic extract of black cohosh to selected central nervous receptors*. 53rd annual congress of GA, Italien, Florenz, (2005).

Obi, et al., *The use of herbal preparations to alleviate climacteric disorders and risk of postmenopausal breast cancer in a German case-control study*. Cancer Epidemiol Biomarkers Prev, 18 (8), 2207-2213, (2009).

Omer-Adam, et al., *Quantification of characteristic marker substances and evaluation of their effects on MCF-7 cell proliferation*. 7th Joint Meeting of GA, AFERP, ASP, (2008).

Osmer, *Wirksamkeit und Verträglichkeit eines isopropanolischen Extraktes aus dem Wurzelstock der Traubensilberkerze*. Phytopharmaka und Phytotherapie 2004 – Forschung und Praxis, Deutschland, Berlin, Phytopharmaka und Phytotherapie 2004 - Forschung und Praxis, (2004).

Osmer, et al., *Efficacy and safety of isopropanolic black cohosh extract for climacteric symptoms*. Obstet Gynecol, 105 (5, part 1), 1074-1083, (2005).

Pockaj, et al., *Pilot evaluation of black cohosh for the treatment of hot flashes in women*. Cancer Invest, 22 (4), 515-521, (2004).

Reame, et al., *Black cohosh has central opioid activity in postmenopausal women: evidence from naloxone blockade and positron emission tomography neuroimaging*. Menopause, 15 (5), 832-840, (2008).

Rebbbeck, et al., *A retrospective case-control study of the use of hormone-related supplements and association with breast cancer*. Int J Cancer, 120 (7), 1523-1528, (2007).

Rostock, et al., *Black cohosh (Cimicifuga racemosa) in tamoxifen-treated breast cancer patients with climacteric complaints - a prospective observational study*. Gynecological Endocrinology, 27 (10), 844-848, (2011).

Schmidt, et al., *Wirksamkeit und Sicherheit von Traubensilberkerze (Cimicifuga racemosa, Cimifemin®) bei Menopausebeschwerden: Therapiebeobachtung unter Praxisbedingungen*. Journal für Menopause, 1, 27-32, (2005).

Shalan, et al., *Noni leaf and black tea enhance bone regeneration in estrogen-deficient rats*. Nutrition, 33, 42-51, (2017).

Struck, et al., *Flavones in extracts of Cimicifuga racemosa*. Planta Med, 63 (3), 289, (1997).

Stute, *Zentrale Wirkung von Cimicifuga racemosa (Prof. Petra Stute erhält NATUM-Forschungspreis)*. Gynäkologie und Geburtshilfe, 20 (6), 54-55, (2015).

Stute, et al., *Effect of black cohosh on estrogen biosynthesis in hippocampus of non-human primates ex vivo in vitro and in human neuroblastoma cells in vitro*. 25th annual meeting of NAMS, Washington, DC, (2014).

Stute, et al., *Effects of black cohosh on estrogen biosynthesis in hippocampus of non-human primates ex vivo in vitro and in human neuroblastoma cells in vitro*. Clinical Phytoscience, 2 (1), 1-8, (2016).

Stute, et al., *The impact of testosterone, tibolone and black cohosh on purified mammary and placental 17 beta-hydroxysteroid dehydrogenase type 1*. J Enzyme Inhib Med Chem, 30 (3), 448-457, (2015).

Stute, et al., *Effects of black cohosh on estrogen biosynthesis in normal breast tissue in vitro*. Maturitas, 57 (4), 382-391, (2007).

Sun, et al., *Black cohosh improves vaginal atrophy in postmenopausal women*. Academic Journal of Second Military Medical University, 32 (3), 339-341, (2012).

Uebelhack, et al., *Black cohosh and St. John's wort for climacteric complaints: A randomized trial*. Obstet Gynecol, 107 (2 Pt 1), 247-255, (2006).

Vermes, et al., *The effects of remifemin® on subjective symptoms of menopause*. Adv Ther, 22 (2), 148-154, (2005).

Viereck, et al., *Ein isopropanolischer Extrakt der Traubensilberkerze (iCR) stimuliert die Expression von Osteoprotegerin in primären humanen Osteoblasten*. Journal für Menopause, 13 (1), 18-21, (2006).

Vollmer, et al., *Estrogenic/Antiestrogenic activities of Cimicifuga racemosa extract*. 10th word congress on the menopause, Climacteric, 5, 106, (2002).

Wang, et al., *Effects of estradiol valerate and remifemin on norepinephrine signaling in the brain of ovariectomized rats*. Neuroendocrinology, 101 (2), 120-132, (2015).

Wang, et al., *Estradiol Valerate and Remifemin ameliorate ovariectomy-induced decrease in a serotonin dorsal raphe-preoptic hypothalamus pathway in rats*. Annals of Anatomy, 208, 31-39, (2016).

Xi, et al., *Effect of isopropanolic Cimicifuga racemosa extract on uterine fibroids in comparison with tibolone among patients of a recent randomized, double blind, parallel-controlled study in Chinese women with menopausal symptoms*. Evid Based Complement Alternat Med, 2014 (Article ID 717686), (2014).

Yilin, et al., *Efficacy of remifemin for control of climacteric symptoms*. Progress in Obstetrics and Gynecology, 20 (6), 462-465, (2011).

Zierau, et al., *Antiestrogenic activities of Cimicifuga racemosa extracts*. The Journal of Steroid Biochemistry and Molecular Biology, 80 (1), 125-130, (2002).

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The following is a translation of the German product information. This information is only valid for Germany. Regulatory information may possibly vary in other countries.

Remifemin®, **Active substance:** dried extract from Cimicifuga rootstock. **Composition:** 1 tablet contains 2.5 mg dried extract from Cimicifuga rootstock (6 - 11 : 1). Extraction solvent: propan-2-ol (40 % v/v). Excipients: cellulose powder, potato starch, lactose monohydrate, magnesium stearate. **Therapeutic indications:** psychic and neurovegetative menopausal complaints such as hot flushes, sweating, and sleeping disorders. **Contraindications:** hypersensitivity to Cimicifuga rhizome or to any of the excipients. **Undesirable effects:** rare gastrointestinal disorders (dyspepsia, diarrhea), allergic skin reactions (urticaria, pruritus, skin rash), facial edema and peripheral edema, weight gain, increase in transaminases. Very rare reports of liver injury during the use of medicines containing Cimicifuga rootstock. (No causal relationship has been proven.) **Warnings:** contains lactose. Refer to the package leaflet. Date 11/14

Remifemin® mono, **Active substance:** dried extract from Cimicifuga rootstock. **Composition:** 1 tablet contains 5 mg dried extract from Cimicifuga rootstock (6 - 11 : 1). Extraction solvent: propan-2-ol (40 % v/v). Excipients: cellulose powder, potato starch, lactose monohydrate, magnesium stearate (vegetable). **Therapeutic indications:** psychic and neurovegetative menopausal complaints such as hot flushes, sweating, and sleeping disorders. **Contraindications:** hypersensitivity to Cimicifuga rhizome or to any of the excipients. **Undesirable effects:** rare gastroin- testinal disorders (dyspepsia, diarrhea), allergic skin reactions (urticaria, pruritus, skin rash), facial edema and peripheral edema, weight gain, increase in transaminases. Very rare reports of liver injury during the use of medicines containing Cimicifuga rootstock. (No causal relationship has been proven.) **Warnings:** contains lactose. Refer to the package leaflet. Date 6/16

Remifemin® plus, **Composition:** 1 coated tablet contains: active substances: Hyperici herb. extr. sicc. (dry extract from St. John's wort) corresponding to a total hypericin (standardized) = 0.25 mg; Cimicifugae rhiz. extr. sicc. (dry extract from black cohosh rhizomes) corresponding to triterpene glycosides calculated as 27-doxyactein (standardized) = 1.0 mg. Excipients: microcrystalline cellulose, glyceryl alconate, glyceryl behenate, potato starch, lactose, macrogol, magnesium stearate, methylhydroxypropyl cellulose, colloidal anhydrous silica, talc, colorants E 132 & E 172. **Therapeutic indications:** menopausal symptoms such as hot flashes, sweating, depressive moods and psychovegetative disorders such as dejection, inner tension, irritability, lack of concent- ration, sleeplessness, anxiety, and/or nervous restlessness; premenstrual psychovegetative complaints. **Contraindications:** Remifemin® plus may not be used by patients who are being treated with medicines that contain the following drugs or drugs in one of the following substance groups: Immunosuppressants (ciclosporin, tacrolimus for internal use), anti-HIV medications (protease inhibitors such as indinavir and fosamprenavir), cytostatics (such as irinotecan), anticoagulants (warfarin). In addition, Remifemin® plus may not be taken when hypersensitive to black cohosh rhizomes, St. John's wort or to any of the excipients. **Undesirable effects:** rare gastrointestinal disorders (dyspepsia, diarrhea), allergic skin reactions (urticaria, pruritus, skin rash). Frequency not known: cases of liver damage while using medicines containing black cohosh, increased liver count (transaminases), facial or peripheral edema, weight gain, sunburn-like reaction of the skin, especially in people with light skin after intensive exposure to ultraviolet light without sufficient sun protection, tiredness or restlessness. **Warnings:** contains lactose. Refer to the package leaflet. Date 1/17

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„CR medicinal products approved for climacteric complaints have a positive benefit–risk ratio – iCR special extract provides the best evidence with LOE 1 and GR A with > 11,000 examined patients.“

(Translation)

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