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REVIEW

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ABSTRACT

A systematic literature search revealed 35 clinical studies and one meta-analysis comprising 43,759
women, of which 13,096 were treated with isopropanolic *Cimicifuga racemosa* extract (iCR). Compared
to placebo, iCR was significantly superior for treating neurovegetative and psychological menopausal
symptoms, with a standardized mean difference of −0.694 in favor of iCR ($p < 0.0001$). Effect sizes
were larger when higher dosages of iCR as monotherapy or in combination with St. John's wort
(*Hypericum perforatum* [HP]) were given (−1.020 and −0.999, respectively), suggesting a dose-depend-
ency. For psychological symptoms, the iCR+HP combination was superior to iCR monotherapy.
Efficacy of iCR was comparable to low-dose transdermal estradiol or tibolone. Yet, due to its better tol-
erability, iCR had a significantly better benefit–risk profile than tibolone. Treatment with iCR/iCR+HP
was well tolerated with few minor adverse events, with a frequency comparable to placebo. The clin-
ical data did not reveal any evidence of hepatotoxicity. Hormone levels remained unchanged and
estrogen-sensitive tissues (e.g. breast, endometrium) were unaffected by iCR treatment. As benefits
clearly outweigh risks, iCR/iCR+HP should be recommended as an evidence-based treatment option
for natural climacteric symptoms. With its good safety profile in general and at estrogen-sensitive
organs, iCR as a non-hormonal herbal therapy can also be used in patients with hormone-dependent
diseases who suffer from iatrogenic climacteric symptoms.

Introduction

Up to 80% of climacteric women, especially those suffering
from hot flushes, use complementary and alternative medi-
cine, mainly without informing their health-care providers[1–5].
This highlights not only patients' wishes but also a need for
evidence-based information on the efficacy and safety of
these treatments.

One of the most popular herbal remedies is *Cimicifuga
racemosa* (CR) syn. *Actaea racemosa* (black cohosh). CR has
been used by Native Americans and eclectic physicians as a
gynecological remedy and for rheumatism and other condi-
tions. The earliest literature references date back to the
seventeenth century[6]. The first allopathic herbal medicinal
product (HMP) containing CR rootstock extract was intro-
duced in Germany in 1956 and has been extensively studied
since[7]. In Germany, where HMPs are authorized medicines
under strict regulatory control requiring state-of-the-art proof

of efficacy, safety, and pharmaceutical quality, gynecologists
rate CR treatment as well-known and effective for climacteric
symptoms[8]. In many other countries, CR products are mar-
keted as food supplements (FS). FS are not as rigorously con-
trolled as HMPs and run the risk of adulteration and
contamination. Frequently, FS claiming to consist of authen-
tic North American CR have contained completely different
Asian *Cimicifuga* species[9]. While FS often have little or no sci-
entific evidence behind them, they are regarded as comple-
mentary and alternative medicine. On the other hand, (CR)
HMPs are evidence-based rational phytopharmaceuticals and
should be treated as such[10].

In 2011, and again in 2018, the European Medicines
Agency issued an official monograph with a positive
benefit–risk ratio for CR HMPs for the treatment of climac-
teric symptoms[11,12]. A Cochrane review doubted CR's super-
iority versus placebo for menopausal symptoms[13] but was
internationally criticized soon after. Apart from a failure to

identify all appropriate randomized controlled trials (RCTs) and an incorrect exclusion of positive results, the review's main shortcoming was a missing differentiation between the extracts used[14]. The new meta-analysis showed CR to be significantly superior to placebo for menopausal symptoms[14].

Unlike synthetic drugs, the active ingredient of phytopharmaceuticals is not a single substance but the whole plant extract. Herbal extracts contain a multitude of different constituents and – even if derived from the same plant – their composition varies depending on many factors (e.g. cultivation, harvesting conditions, extraction process, extractant, and standardization) that may lead to different effects and efficacies[15]. Therefore, study results gained with a specific extract cannot be transferred one-to-one to different extracts of this herb. For phytopharmaceuticals there are no genuine generics as with synthetic drugs. Consequently, when analyzing scientific data, it is crucial to differentiate between HMPs and non-HMPs/FS and between different extracts. The first differentiated evaluation of extract-specific evidence on CR's efficacy and safety was performed by Beer and Neff in 2013[16]. Their analysis of publications from 2000 to 2012 came to the conclusion that only HMPs, but not FS/non-HMPs, of CR demonstrated evidence for their efficacy. Best evidence was provided by the isopropanolic CR extract (iCR); the only extract tested in several thousand women and the only extract that provided confirmatory Level 1 evidence and Grade of Recommendation A[16]. These results were confirmed by an additional analysis of newer studies published from 2012 to 2014[17].

This review's purpose is to give a current update and overview of all placebo-controlled clinical data (irrespective of publication date) and additional data from clinical studies with iCR during a broader time span ranging from the establishment of the EU Guideline on Good Clinical Practice E6 in 1997 until January 2020. Furthermore, for the first time, all placebo-controlled data gained with iCR are pooled in a meta-analysis. Efficacy and safety results are analyzed in detail and discussed in order to enable health-care providers to advise patients who refuse or have contraindications to hormone therapy for climacteric symptoms.

Methods

MEDLINE, EMBASE, EMBASE Alert, BIOSIS, and PubMed were searched for clinical studies with iCR (irrespective of design) and meta-analyses thereof, published from 1997 to January 2020, as a basis for our review. Furthermore, all available randomized placebo-controlled data, irrespective of publication date, were collected as a basis for our meta-analysis. The database search was complemented by a manual search in the authors' library and an additional search in ClinicalTrials.gov and the EU Clinical Trials Register.

Inclusion criteria were medical use of iCR, efficacy for neurovegetative and psychological climacteric symptoms, additional clinical benefits, occurrence and frequency of adverse events, and influence on liver, hormones, and estrogen-sensitive organs. No restrictions regarding patients' ages, menopausal status, and treatment duration were made.

Patient-relevant endpoints were reduction of neurovegetative and psychological climacteric symptoms (e.g. scales for climacteric symptoms, symptom frequency and intensity, and objective symptom measurement), additional clinical benefits, and frequency and severity of adverse events, including influence on estrogen-sensitive organs or laboratory parameters.

Studies were sorted according to their quality and the RCTs regarding their control group (placebo, active comparator). The placebo-controlled RCTs were pooled in the meta-analysis and independently assessed for risk of bias with the revised Cochrane RoB 2 tool (2019) by three authors (M.G., H.H.H.-v.Z., and S.P.). Disagreements were discussed until a consensus was reached. The meta-analysis was performed using SAS version 9.4 under the fixed-effect size model. For studies that did not directly report the standardized group difference and the corresponding confidence interval, these parameters were deduced either from the published means, standard deviations, and sample size N or from the published means, sample size N, and p-values.

Results

The search revealed one meta-analysis[18] and 35 clinical studies[19–53], including 16 RCTs[19–31,50,52,53], that met the inclusion criteria. Altogether, 43,759 patients were included in the studies; 13,096 of the patients were treated with iCR. A detailed overview of populations, interventions, and results for each study is presented in Table S1.

Efficacy for natural menopausal symptoms

Placebo-controlled, double-blind RCTs

The first RCT demonstrated that iCR was superior to placebo in improving the Kupperman Menopause Index (KMI) and the Hamilton Anxiety Rating Scale[19] scores for all assessment points (4, 8, and 12 weeks; $p < 0.001$). In the iCR group, the average symptom intensity decreased from 'moderate' at baseline to 'mild' at study termination, showing a good therapeutic result. In the placebo group, it decreased but still remained 'moderate'.

Significantly greater improvements in the total Menopause Rating Scale (MRS) scores were found in patients taking iCR for 3 months compared to placebo ($p < 0.001$)[22]. Efficacy was best for vasomotor symptoms (hot flushes, sweating, and sleep disorders). With 0.03–0.05 MRS units, the effect size was similar to that of 0.6 mg conjugated estrogens in a previous study and clinically relevant. The therapeutic benefit was highest in patients who were treated in the early climacteric phase.

In iCR-treated patients, significantly higher reductions in climacteric symptom severity (total KMI and hot flush scores) were seen after 4 weeks ($p < 0.05$ for KMI, $p = 0.041$ for hot flushes) and 12 weeks ($p < 0.001$ for KMI, $p = 0.021$ for hot flushes) compared to placebo[26]. iCR noticeably decreased both scores from baseline to study termination (KMI, 26.46 ± 10.46 to 6.37 ± 4.16; hot flushes, 7.52 ± 2.37 to 1.52 ± 1.97).

Polysomnography, conducted to objectively measure sleep disturbances in a 6-month trial, showed that patients using iCR had significantly increased sleep efficiency ($p = 0.01$) and decreased wake after sleep onset duration ($p < 0.01$) compared to placebo. Vasomotor and physical domains of the Menopause-specific Quality of Life questionnaire also improved versus placebo[31].

The fixed combination of high-dose iCR plus low-dose St. John's wort (*Hypericum perforatum*) (iCR+HP) was significantly superior to placebo in improving MRS (−50%) and Hamilton Depression Rating Scale scores (−41.8%) ($p < 0.001$)[24].

Active-controlled RCTs
A 3-month study compared the efficacy of iCR to low-dose transdermal estradiol for climacteric symptoms[23]. Both treatments significantly reduced the number of hot flushes/day and vasomotor symptoms as well as anxiety and depression ($p < 0.001$ for all). Both treatments showed comparable efficacy without significant differences.

Chinese women with climacteric symptoms received either iCR or tibolone for 3 months in a double-blind, double-dummy trial[25]. A noticeable and clinically relevant reduction of similar size for the KMI scores was seen in both groups, significantly demonstrating non-inferiority of iCR ($p = 0.002$). Yet, due to its better tolerability, iCR was superior to tibolone in the benefit–risk ratio ($p = 0.01$).

In two further RCTs, significant KMI score reductions of perimenopausal symptoms were shown under iCR after 3 months; they were comparable to those under tibolone[52,53]. Additionally, vaginal atrophy symptoms were significantly ameliorated in both groups, without significant group differences[53].

Treatment with a standard dose (SD) or high dose (HD) of iCR for 6 months significantly decreased menopausal symptoms (KMI score reduced by 75%). The responder rate was already 70% after 3 months. These effects were maintained after 6 months[21]. For the complete study population, no differences between SD and HD could be observed. However, patients who were in the early climacteric phase benefited significantly more from HD compared to SD and also exhibited a response rate above 90% when using HD[21,54].

Women with perimenopausal depression were treated with either paroxetine or paroxetine plus iCR for 2 months[28]. The iCR group showed significantly better improvement in the Hamilton Depression Rating Scale ($p < 0.05$) and KMI ($p < 0.01$) scores compared to patients taking only paroxetine.

A 12-week iCR treatment was compared to placebo treatment in patients with postmenopausal atrophic vaginitis[27]. While atrophic vaginitis symptoms were significantly reduced in the iCR group ($p < 0.05$), there were no significant influences on vaginal pH or the maturation degree of vaginal epithelial cells.

Open, controlled studies
In a prospective, controlled observational study, 6,141 patients were treated for 6–12 months ($n = 736$) with iCR or iCR+HP according to the physicians' choices[32]. Both treatments led to significant reductions of the MRS total score and the MRS subscore 'psyche'. The iCR+HP combination was superior to the monotherapy in ameliorating psychological climacteric symptoms ($p < 0.001$).

Compared to untreated control, iCR-treated women showed significant decreases in the urinary concentration of N-telopeptides (bone resorption marker) and increases in serum alkaline phosphatase (bone formation marker) after 3 months[33].

Open, uncontrolled studies
Two studies using a 3-month iCR therapy found significant reductions in the KMI scores. The most pronounced improvements were seen for hot flushes and sweating[42,43]. Sleeping difficulties and anxiety were also greatly reduced[43]. Postmenopausal women with increased body weight taking iCR for 3 months experienced a significant increase in their quality of life (Cervantes Health-Related Quality-of-Life Scale), especially in the 'menopause/health' and 'psyche' domains[47]. Another 3-month study found that more than 70% of women using iCR had fewer hot flushes, less sweating, and fewer psychological complaints (irritability, depressive moods, and insomnia)[45]. Patients taking HD iCR for 98 days exhibited reductions in 10 typical neurovegetative climacteric symptoms. Efficacy was rated as good or very good in 80% of the cases[40]. The combination of iCR+HP ameliorated not only psychological but also neurovegetative symptoms of menopause significantly after 12 weeks of therapy. Efficacy was judged as good or very good in 81% of the cases[39].

Efficacy for iatrogenic menopausal symptoms
Placebo-controlled, double-blind RCTs
Breast cancer patients, most treated with tamoxifen, received either iCR or placebo for 2 months. While both groups had a comparable decline in the number and intensity of hot flushes, the iCR-treated women reported significantly less sweating than the placebo group ($p = 0.04$)[20].

Active-controlled RCTs
Endometriosis patients were treated with postoperative goserelin therapy, causing estrogen-deficiency symptoms[30]. Four weeks after the first goserelin injection, they received add-back therapy with tibolone or iCR for 12 weeks. Both treatments significantly reduced KMI and hot flushes/sweating scores to a comparable extent without significant group differences. The iCR group had significantly fewer adverse events and less vaginal bleeding/spotting or breast pain.

Open, controlled studies
Women with early breast cancer were treated with luteinizing hormone-releasing hormone analogue after surgery, mostly combined with endocrine therapy. They randomly received iCR or no treatment for 3 months. The iCR group had significantly lower KMI scores compared to control[50].

Patients with stage 1 endometrial cancer suffering from menopausal symptoms after surgery were treated with iCR for 24 weeks or remained untreated as control[35]. All patients were followed for 12 months. Therapy with iCR resulted in a significant decrease of the KMI score and a significant increase in bone mineral density (both $p < 0.05$).

Open, uncontrolled studies

A pilot trial in women (breast cancer, high risk, or refused hormone therapy) with significant hot flushes, partly caused by tamoxifen or raloxifene, found a reduction of hot flush frequency (−50%), severity (−22%), and sweating (−80%) after 4 weeks of iCR intake[41]. Additionally, patients reported less sleeping problems and less fatigue.

Patients after surgery for gynecological cancers (endometrial, ovarian, cervix, borderline ovarian, and breast cancers) experienced a significant reduction of KMI scores, hot flushes, sweating, and depressive moods after 3 months of treatment with iCR ($p < 0.05$)[48].

Women after breast cancer surgery suffering from tamoxifen-induced climacteric symptoms were treated with iCR for 6 months. The dosage was adapted to symptom intensity[49]. The iCR treatment led to significant reductions in the total MRS II score ($p < 0.001$). Hot flushes, sweating, sleep problems, and anxiety improved most.

Meta-analysis of the placebo-controlled RCTs

All placebo-controlled RCTs examining efficacy for neurovegetative and psychological climacteric symptoms were included in the meta-analysis[19,20,22,24,26,31]. Most of the RCTs had a low risk of bias[19,22,24]. Two RCTs raised some concerns[20,31] and one RCT was rated as high risk according to RoB 2 criteria[26] (Figure 1; extensive assessment presented in Table S2). However, the latter suffered explicitly from low-quality reporting, which may not necessarily imply an actual risk of bias. Detailed characteristics of these RCTs are presented in Table 1. Figure 2 shows a forest plot of these RCTs, revealing an overall standardized mean difference of −0.694 in favor of iCR ($p < 0.0001$). By subgroups, the standardized mean difference in favor of iCR was −0.568 for natural menopausal symptoms, −0.187 for iatrogenic symptoms, and −0.999 in favor of iCR+HP for natural climacteric symptoms.

For studies with higher iCR dosages as monotherapy or in combination with HP[19,24], the standardized mean difference in favor of iCR was −1.020 and −0.999, respectively.

Safety in general and at the liver

Treatment with iCR was generally well tolerated with few minor adverse events[19,21–23,25,30,32,33,39,41,43–45,52] or even no adverse events[27,31,35]. Compared to placebo, the frequency of adverse events under iCR or iCR+HP was not significantly different[22,24]. HD iCR demonstrated the same good tolerability as SD iCR[21]. In breast cancer patients treated with tamoxifen, typical tamoxifen-associated adverse effects occured[20,49]. Compared to tibolone, iCR treatment had significantly fewer adverse effects, especially for vaginal bleeding or spotting[25,30,52,53]. No significant influences of iCR on body weight/body mass index[22,25,35], heart rate[22], blood pressure[22,28,35], or electrocardiogram[28] were seen. Routine hematology[21,24,25,28,48], routine biochemistry[21,24,25,33,48], including kidney function tests[21,24,25,28,30,31,35,48,52,53], and urinalysis[25,28,48] remained unaffected by iCR. Regarding lipid metabolism, total cholesterol and triglycerides were not affected[23,26,30,33,35,44,48,52,53]. However, several investigators reported significant increases of high-density lipoprotein cholesterol and decreases of low-density lipoprotein cholesterol[23,26,48,52].

A meta-analysis of five double-blind RCTs including 1117 patients showed that SD or HD iCR treatment for 3–6 months did not significantly influence liver function tests and did not reveal any evidence for hepatotoxicity[18]. Ten further studies[23,26,28,30,31,35,48,52,53,55], seven of which were RCTs, including 741 patients also did not find any significant changes in liver function parameters.

Safety at estrogen-sensitive organs

Taking SD iCR for 3–6 months did not lead to significant changes in gonadotropin or estradiol levels in otherwise healthy women ($n = 481$)[21,23,26,27,31,33,40,46,52,53] or in women with estrogen-dependent diseases (breast cancer, gynecological tumors, and endometriosis) ($n = 193$)[20,30,35,48,50]. HD iCR also did not affect follicle stimulating hormone, luteinizing hormone, or estradiol[21,40]. Furthermore, prolactin, sex

RCT (Author, Year)	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall bias
Jiang, 2015	+	+	+	+	?	?
Li Yilin, 2011	?	−	−	+	?	−
Osmers, 2005	+	+	+	+	+	+
Stoll, 1987	+	+	+	+	+	+
Jacobson, 2001	?	+	+	+	?	?
Uebelhack, 2006	+	+	+	+	+	+

+ Low risk　　? Some concerns　　− High risk

Figure 1. Risk of bias assessment of the placebo-controlled randomized controlled trials (RCTs).

Table 1. Characteristics of the double-blind RCTs comparing iCR with placebo for neurovegetative and psychological menopausal symptoms, used as the basis for the meta-analysis.

First author, year of publication	Number of patients; indication; ethnicity	Daily dose; duration of application	Inclusion criteria	Exclusion criteria	Main efficacy results; standardized difference in means [95% CI]	Impact on evidence; remarks; RoB
Stoll, 1987	30 iCR, 20 placebo; ms; Caucasian	2 × 2 tab. = 8 mg extractum siccum; 3 months	46–58 years old, perimenopausal and postmenopausal patients suffering from neurovegetative, psychological, and somatic menopausal symptoms	Patients after bilateral OVX or pelvic radiation. Contraindication for HT. Other causes for symptoms than menopause. Osteoporosis. Intake of HT ≤4 weeks before study entry. Intake of antihypertensives	Significant improvement of the KMI and HAMA scores under iCR compared to placebo. Symptom intensity decreasing from moderate to mild; −1.020 [−1.586, −0.454]	⊕⊕ Well-conducted RCT; low RoB
Jacobson, 2001	42 iCR, 43 placebo; iatrogenic ms due to Tam (breast cancer); mainly Caucasian (African-American, Asian)	2 × 1 tab. ≙ 40 mg drug; 2 months	Breast cancer patients >18 years old with daily hot flushes. Completion of primary therapy including chemotherapy and radiation ≥2 months before entering study	Use of HT. Pregnancy. Major psychiatric illness. Known recurrent or metastatic breast cancer	Comparable reduction of hot flush frequency and intensity in both groups and significantly stronger reduction of sweating under iCR compared to placebo; −0.187 [−0.659, 0.285]	⊕ Study duration rather short to show efficacy; some concerns on RoB
Osmers, 2005	153 iCR, 151 placebo; ms; Caucasian	2 × 1 tab. ≙ 40 mg drug; 3 months	Postmenopausal patients ≥45 years old (≥12 months of amenorrhea or ≥6 months of amenorrhea with FSH ≥50 IU/l), Climacteric symptoms of ≥0.4 in ≥3 MRS items	BMI ≥28 kg/m². Cancer or other diseases with interference potential. Drug abuse. Participation in other trial ≤180 days before study entry. Use of HT during or ≤4 weeks before study entry. Use of non-hormonal climacteric drugs, including supplements and homeopathics. Use of anti-epileptics, psycholeptics, or psychoanaleptics, including phytotherapeutics	Significant improvement of the MRS total score vs. placebo. Strongest effect in vasomotor complaints (hot flushes, sweating, sleep disorders) and higher superiority during menopausal transition; −0.394 [−0.626, −0.162]	⊕⊕ Well-conducted RCT; low RoB
Uebelhack, 2006	151 iCR+HP 150 placebo; ms; Caucasian	Week 1–8, 2 × 2 tab. ≙ 128 mg drug; Week 9–16, 2 × 1 tab. ≙ 64 mg drug; 4 months	45–60 years old, perimenopausal and postmenopausal patients with climacteric complaints with pronounced psychological component for ≥3 months, untreated for ≥2 months. MRS of ≥0.4 in ≥3 items. HAMD scale items of ≥1 of 2 points	Use of HT, non-hormonal climacteric drugs or other treatment for climacteric symptoms ≤12 weeks before study entry. Use of synthetic or herbal anti-epileptics, psycholeptics, or psychoanaleptics ≤12 weeks before study entry. Psychological or psychiatric therapy. Bilateral OVX. Severe diseases. Abnormal TSH. Treatment with interference potential. Suicidality or attempted suicide in the past year	Significant superiority vs. placebo in the improvement of the MRS and HAMD scores; −0.999 [−1.225, −0.773]	⊕⊕ Well-conducted RCT; low RoB
Li Y, 2011	45 iCR, 32 placebo; ms; Asian	2 × 1 tab. ≙ 40 mg drug; 3 months	45–55 years old, perimenopausal patients with spontaneous menopausal status for ≥3 months with E2 ≤20 pg/ml and FSH ≥40 IU/l. KMI ≥17	History of diabetes, serious or unstable physical illness. Use of estrogen, antidepressants, or antipsychotics. Use of supplements for perimenopausal symptoms ≤3 months before study entry. Unexplained uterine bleeding, abnormal cervical smear, endometrial thickness ≥0.5 cm	Significant improvement of the KMI score and hot flushes compared to placebo; −0.792 [−1.246, −0.338]	⊕ Low quality of reporting, which may imply a high RoB
Jiang, 2015	24 iCR, 24 placebo; ms; Asian	2 × 1 tab. ≙ 40 mg drug; 6 months	45–60 years old, postmenopausal patients, STRAW +1b, +1c. BMI ≤30 kg/m². FSH ≥30 IU/l	Bilateral OVX, hysterectomy. Termination of ovarian function by chemotherapy or radiation therapy. Poorly controlled clinical diseases. Historic or present psychiatric disorders. Sleep-related respiratory or movement disorders. Use of opioids, anti-epileptics, anxiolytics, hypnotics, sedatives, antidepressants, or antihistamines ≤3 months before study entry. Use of HT or other therapy against menopausal symptoms ≤3 months before study entry. Participation in other study ≤3 months before study entry. Intake of ≥7 alcoholic drinks/week. History of drug/substance abuse	Significantly increased sleep efficiency and decreased WASO duration under iCR compared to placebo. Significantly better improvement of vasomotor and physical domains of Men-QoL by iCR; −0.836 [−1.442, −0.230]	⊕⊕ Well-conducted RCT; some concerns on RoB

BMI, body mass index; CI, confidence interval; E2, estradiol; FSH, follicle stimulating hormone; HAMA, Hamilton Rating Scale for Anxiety; HAMD, Hamilton Rating Scale for Depression; HT, hormone therapy; iCR, isopropanolic *Cimicifuga racemosa* extract; iCR+HP, fixed combination of isopropanolic *Cimicifuga racemosa* extract plus St. John's wort (*Hypericum perforatum*) extract; IU, international units; KMI, Kupperman Menopause Index; ms, menopausal symptoms; Men-QoL, Menopause-specific Quality of Life Questionnaire; MRS, Menopause Rating Scale; OVX, ovariectomy; RCT, randomized, controlled trial; RoB, risk of bias; STRAW, Stages of Reproductive Aging Workshop; Tam, tamoxifen; TSH, thyroid-stimulating hormone; WASO, wake after sleep onset; ≙: corresponding to; ⊕: exploratory evidence; ⊕⊕: confirmatory evidence.
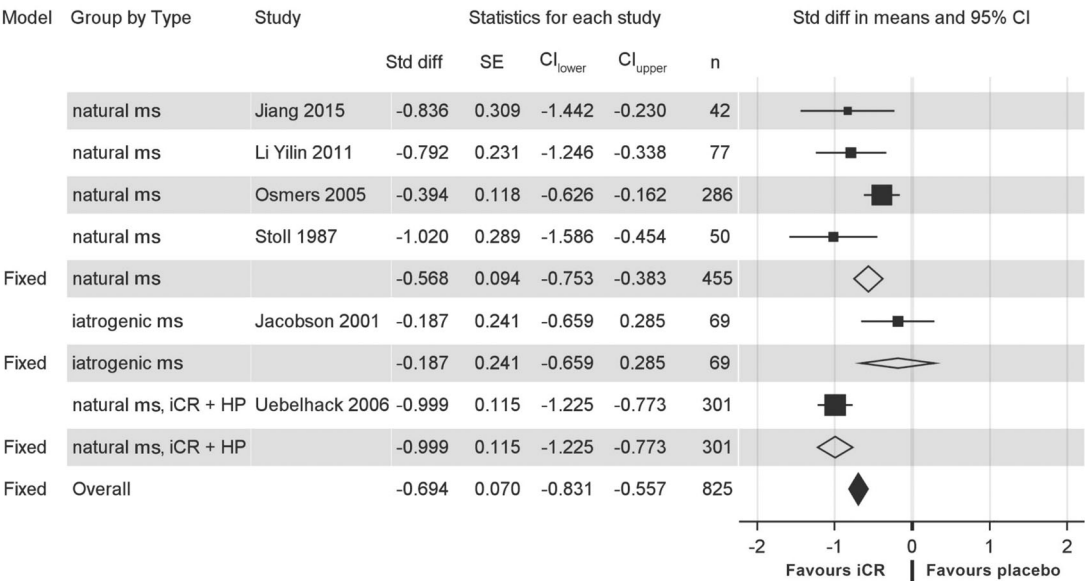
Figure 2. Forest plot of isopropanolic *Cimicifuga racemosa* extract (iCR) versus placebo in neurovegetative and psychological menopausal symptoms.
CI, confidence interval; Fixed, summary of the respective group of studies under the fixed-effect size model; HP, *Hypericum perforatum* (St. John's wort); ms, menopausal symptoms; n, number of patients; Std diff, standardized mean difference; SE, standard error of the standardized difference.

hormone binding globulin, and testosterone remained unchanged[21,23,33,40,44].

Ultrasound scans showed that endometrial thickness was not influenced by 3–6-month iCR treatment ($n = 516$)[23,25–27,31,40,44,50,52,53]. Also, in patients with uterine pathologies like endometriosis or endometrial carcinoma, pelvic ultrasound was unremarkable ($n = 86$)[30,35]. iCR therapy in goserelin-treated endometriosis patients resulted in significantly less vaginal bleeding/spotting than add-back therapy with tibolone[30]. Using iCR for 3 months led to a significant reduction of myoma volume compared to baseline (-30%) and compared to tibolone, which had no significant effects ($+4.7\%$)[29]. Patients with endometrial cancer had no increase of tumor marker CA 125 or recurrences during 6-month iCR treatment and 12-month follow-up[35]. No significant changes of vaginal cytology/maturation index or pH could be detected after 3–6-month treatment with SD or HD iCR[21,26,27,40].

Breast ultrasonography did not reveal any changes after 6-month iCR treatment in healthy women and in women after therapy for estrogen-dependent tumors ($n = 54$)[31,35]. Furthermore, no signs of increased mammographic breast density (visual assessment) or breast cell proliferation (fine-needle aspiration biopsy) were found after 6-month iCR treatment[44]. These results were confirmed by digitized assessment of the mammograms[34]. Patients with ductal carcinoma *in situ*, using iCR for 2–5 weeks pre surgery, experienced no significant changes in proliferation marker Ki67, yet a downward trend was seen[51]. Two case–control studies demonstrated that iCR use was associated with a reduced risk for breast cancer[37,38]. The larger study found that risk reduction was independent of lifestyle factors, tumor histology, and receptor status, but improved with longer treatment duration. A pharmacoepidemiological cohort study in breast cancer survivors demonstrated that women taking iCR for climacteric symptoms compared to women not using iCR had a significantly lower risk for recurrence with a 4.5-year longer recurrence-free survival on average[36].

Discussion

All studies with iCR consistently demonstrated its efficacy for natural climacteric symptoms, exhibiting significant superiority versus placebo and an efficacy comparable to low-dose transdermal estradiol or tibolone[19,21–26,28,31,32,39,40,42,43,45,47,52,53]. Yet, due to its better tolerability, iCR had a better benefit–risk profile than tibolone. These results confirm the NICE guideline meta-analyses. There, CR was significantly superior to placebo in reducing vasomotor symptom frequency, revealing a good effect size, whereas tibolone was associated with high treatment discontinuation[56]. It is noteworthy that among all non-hormonal treatments, CR exhibited the largest effect size and had the highest probability of being the best treatment[56]. However, the guideline calls for caution concerning the great variety of CR products. This makes sense because inconclusive data on CR's efficacy result from products that do not meet the strict criteria for HMPs[16,17]. With a standardized mean difference of -0.568 in favor of iCR versus placebo for natural menopausal symptoms in our meta-analysis, iCR, as an authorized HMP, offers an evidence-based, recommendable, non-hormonal treatment. The inclusion of one publication with a potential for high risk of bias[26] in our meta-analysis could be worth discussing. However, as its effect size does not deviate from the overall treatment effect, its inclusion or exclusion has no impact on the result of this meta-analysis. Most of the included studies had a low risk of bias[19,22,24].

Our meta-analysis shows higher effect sizes when higher doses of iCR (without or with HP)[19,24] were used (standard mean difference of -1.020 and -0.999, respectively), suggesting a dose-dependency. Women in their early climacteric phase may benefit from an increase from 40 mg up to

120 mg drug/day[54]. Furthermore, iCR+HP was superior to iCR in ameliorating psychological climacteric symptoms[32]. With its higher iCR dose and synergistic effects with HP, the combination offers a valuable treatment option not only in terms of its greater effect size shown in our meta-analysis but also because psychological symptoms like depressive moods often occur during perimenopause[57,58].

Efficacy data concerning iatrogenic climacteric symptoms are varied, with the findings being predominantly positive. Climacteric symptoms after endometrial cancer surgery were significantly reduced by iCR over 24 weeks compared to untreated control[35]. These positive effects are in line with results of another 24-week, hormone therapy-controlled study with iCR in hysterectomized patients[59]. For goserelin-induced symptoms in endometriosis patients, 12 weeks of iCR treatment was as effective as add-back therapy with tibolone, yet more tolerable[30]. These results were recently confirmed by a study in gonadotropin-releasing hormone analogue-treated breast cancer patients. There, iCR treatment significantly lowered KMI scores after 12 weeks compared to control[50]. In tamoxifen-treated breast cancer patients, hot flush reductions over 8 weeks under iCR were not significantly different from placebo, but the sample size was too small to prove superiority; however, iCR-treated patients still benefited from significantly less sweating[20]. This study was too short to expect significant efficacy results. The authors assumed that 'it is possible that when used for a longer period of time, black cohosh may show greater efficacy'. Excluding this study with a shorter treatment duration than the US Food and Drugs Administration and the European Medicines Agency require would have increased the homogeneity of our meta-analysis results. Significant reductions of iatrogenic hot flushes, sweating, and psychological symptoms were shown in longer open studies (12–24 weeks)[48,49]. There, tamoxifen-treated breast cancer patients were also allowed to double the standard iCR dose[49]. This could enhance treatment effects, as practical experience showed that patients with tamoxifen-induced symptoms often need higher CR doses than natural menopausal women[60]. Thus, HD iCR or iCR+HP can be used to treat climacteric symptoms induced by endocrine therapy. These patients cannot take hormones and without additional therapy may discontinue the anti-hormonal treatment due to its severe side effects[60–62].

Treatment with SD/HD iCR or iCR+HP was well tolerated with only rare minor adverse effects, no significant differences from placebo, and significantly better tolerability compared to tibolone[19,21–25,27,28,30,31,33,35,39–45,48,49,52,53]. This favorable safety profile of iCR is congruent with data analyzed for CR extracts in general[13,16,17,63]. None of the iCR studies showed liver-specific side effects. Additionally, a meta-analysis of five RCTs and 10 further studies, 1858 patients in total, showed no influence of iCR on liver function[18,23,26,28,30,31,35,48,52,53,55]. Single cases of hepatotoxicity had been reported during the use of CR products. These included FS that do not meet the strict quality criteria of HMPs and are often adulterated with different Asian *Cimicifuga* species[9]. Case report assessment with a liver-specific diagnostic algorithm did not reveal a causal relationship[64–67].

In the past it was believed that CR's efficacy may be based on estrogen-like effects due to its reputed constituent formononetin. However, this isoflavone was never detected in CR extracts used for the manufacture of iCR[68,69]. Activity on estrogen receptors was not shown for iCR[70]. Instead, binding and modulation of central nervous system key receptors for thermoregulation, mood, and sleep (e.g. serotonin, dopamine, γ-aminobutyric acid, μ-opioid) and favorable changes in brain metabolism and activity were observed[46,71–75]. These mechanisms of action explain not only the efficacy for climacteric symptoms but also the fact that iCR did not influence hormones, breast tissue density or proliferation, endometrial thickness, or vaginal cytology[20,21,23,25–27,30,31,33–35,40,44,48,50,52,53]. The amelioration of vaginal atrophy symptoms observed by some researchers can possibly be explained by anti-inflammatory and anti-oxidative effects of CR. The reduction of psychological menopausal symptoms by iCR may also play an important role in this regard, as psychological stress impairs vaginal health and sexual function. Against this background and in line with the official monographs, the benefit–risk ratio of iCR/iCR+HP is clearly positive. The resulting recommendation of iCR for patients with climacteric symptoms is fortified by results of the NICE guideline health economic model. Out of all treatments in hysterectomized women and in women with a uterus, CR had the second highest and the highest probability, respectively, of being the most cost-effective treatment[76].

Furthermore, initial data suggest additional benefits. The longer recurrence-free survival in breast cancer patients taking iCR[36] and an association of iCR therapy with a decreased risk of developing breast cancer[37,38] are substantiated by experimental data. iCR dose-dependently inhibited the proliferation of estrogen-dependent and estrogen-independent breast cancer cells due to caspase activation and induction of apoptosis; it reduced invasiveness and enhanced the effects of tamoxifen[77–81]. CR downregulated the expression of estrogen receptor-α, progesterone receptor, and BRCA1 in hormone-dependent breast cancer cells and decreased their proliferation[82]. In breast cancer animal models, application of iCR indicated a trend toward or actually led to reduced tumor growth – the latter accompanied with prolonged life span[83,84]. Combination of tamoxifen with iCR increased the incidence of tumor-free animals and reduced the individual tumor burden[85].

Further mechanisms of action of CR and its constituents may contribute to iCR's beneficial effects (not only) in breast cancer patients. Actein, a CR triterpene glycoside, had growth inhibitory effects on human breast cancer cells associated with activation of stress response pathways[86]. Actein had anti-angiogenic effects in vitro and decreased breast tumor size and metastasis in the mouse 4T1 breast tumor model[87]. Recently, actein was found to suppress human bladder cancer cell proliferation and induce autophagy and apoptosis via activation of reactive oxygen species/c-Jun N-terminal kinase and inhibition of the AKT/mammalian target

of rapamycin (mTOR) pathway. The latter is activated in breast and other cancers, leading to tumor cell growth, proliferation, metastasis, and angiogenesis, and is implicated in endocrine resistance[88–90]. Additionally, CR and some of its components activated 5′ adenosine monophosphate-activated protein kinase (AMPK) to the same extent as metformin[91]. AMPK activation and mTOR inhibition suppressed the proliferation and angiogenesis of leiomyoma cells, and mTOR inhibition decreased the tumor incidence, multiplicity, and size in the Eker rat model for myoma[92–94]. AMPK activation and mTOR inhibition may explain the observed shrinking of myoma under iCR treatment.

Clinical findings suggesting osteoprotective effects of iCR are supported by experimental data: iCR dose-dependently increased osteoprotegerin production (and thereby the osteoprotegerin–RANK ligand ratio) in human osteoblasts, which inhibits osteoclast differentiation and activity and may impede bone resorption[95,96]. The osteoblast differentiation markers osteocalcin and alkaline phosphatase activity were increased[95,96]. In the ovariectomized rat model for osteoporosis, iCR augmented bone density and quality[97], protected against bone loss, and increased trabecular bone structure and resistance[98]. 25-acetylcimigenol xylopyranoside (ACCX), a CR triterpene glycoside, inhibited osteoclastogenesis by abrogation of the nuclear factor-κB and ERK pathways induced by RANK ligand or tumor necrosis factor-α[99].

Oxidative stress and inflammatory processes play a significant role not only in menopausal vasomotor symptoms but also in the development and progression of osteoporosis, (breast) cancer, myoma, and further age-related conditions (e.g. cardiovascular disease and cognitive decline)[100–103]. As iCR exhibited anti-oxidative and mitochondria-protective effects[104] and recent evidence demonstrated strong anti-inflammatory effects for CR[105], these effects may contribute to iCR's efficacy for vasomotor symptom and to possible additional benefits for patients with breast cancer, myoma, or risk for osteoporosis. With numerous mechanisms of action that may explain such benefits, iCR offers an interesting field for future research, especially for diseases with underlying inflammatory, AMPK, or mTOR dysregulation.

Conclusion and practical consequences

In summary, the clinical data and our meta-analysis consistently demonstrate that iCR/iCR+HP is an effective and safe, evidence-based treatment option for natural neurovegetative and psychological climacteric symptoms, meeting increasing patients' demands for non-hormonal, herbal therapies. As benefits clearly outweigh risks, iCR/iCR+HP should be recommended to these women. With its good safety profile in general and at estrogen-sensitive organs, iCR can also be used in patients with hormone-dependent tumors suffering from iatrogenic menopausal symptoms. However, this should not take place in self-medication but under medical supervision. Breast-cancer patients are not appropriate candidates for non-supervised self-medication, and it seems reasonable that HD iCR or alternatively iCR+HP are more effective in patients with medication-induced symptoms. Breast cancer patients

taking iCR may possibly benefit from prolonged recurrence-free survival, which should be confirmed by further clinical trials.

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