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Efficacy of *Cimicifuga racemosa*, *Hypericum perforatum* and *Agnus castus* in the treatment of climacteric complaints: a systematic review

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Objective: **The systematic review examines whether *Cimicifuga racemosa* (CR), *Hypericum perforatum* (HP), *Agnus castus*, vitamins and minerals, either as monotherapy or in combination, have an evidence-based impact on vasomotor, genital and psychological climacteric complaints.** ***Data sources and methods of study selection:*** **We searched in the databases EMBASE, OVID and PubMed using the keywords "vasomotor symptoms, hot flashes, vaginal atrophy, psychological problems, endometrium, sleep, concentration, cognition in combination with vitamins, multivitamins, minerals, multiminerals, black cohosh, *Cimicifuga*, *Agnus castus*, chasteberry, chaste tree, monk's pepper and menopause" for randomized controlled trials (RCT). Relevant studies were reviewed by four independent reviewers qualitatively.** ***Results:*** **Most of the studies with a comparison of CR vs. placebo do not show an evidence-based significant effect of CR on climacteric symptoms. The combination of CR and HP shows an improvement of climacteric complaints in comparison to placebo. In some RCTs, there was no significant difference between CR and hormone-replacement therapy. The combination of HP and *Agnus castus* showed no significant difference in the treatment of climacteric complaints.** ***Conclusion:*** **CR monotherapy as well as HP and *Agnus castus* showed no better effect than placebo. The combination of CR with HP demonstrated a positive effect on climacteric complaints.**

Keywords: *Agnus castus*, *Cimicifuga*, *Hypericum perforatum*, menopause

Introduction

Menopause is the time of a woman's life when reproductive capacity ceases and the production of steroid and peptide hormones falls. A variety of symptoms may occur: hot flushes, night sweats, urogenital atrophy, irregular menstruation, depression, nervous tension, palpitations, headaches, insomnia, lack of energy, and difficulty in concentrating [1].

Due to the risks that hormone-replacement therapy (HRT) bears and which have been published in the literature [2], the demand for alternative therapies to relieve climacteric complaints has increased.

Cimicifuga racemosa (CR), also called black cohosh, is a North-American plant. Among its constituents are triterpene glycosides. The effect profile of CR shows a reduction in serum luteinizing hormone production [3] and it is suggested that not-yet identified substances in the CR extract BNO 1055 bind to a yet-unknown estrogen-binding site in the endometrium [4].

Agnus castus, also called chaste tree, grows as a shrub in Mediterranean regions. The effect profile includes prolactin-suppressive and dopamine agonist activity [5]. Some ingredients of *Agnus castus* are very similar to the prolactin suppressive effect of dopamine [6].

Hypericum perforatum (HP) is native to Europe, North Africa and Western Asia, but can be found ubiquitous in the world[7]. HP has an antidepressant effect [8–10], which may be due to activation of the serotonergic, noradrenergic and dopaminergic systems [11].

Today, several products with the above-mentioned ingredients are available as monotherapy. The following products containing CR are available in Germany: Remifemin® (Schaper & Brümmer GmbH & Co. KG, Salzgitter, Germany). Cefakliman® (Cefak KG, Kempten, Germany). Klimadynon® (Bionorica, Neumarkt, Germany). Galafem® (Jenapharm, Jena, Germany). Sinei® (Steiner Arzneimittel. Steiner & Co, Berlin, Germany). Remifemin® plus (Schaper & Brümmer GmbH & Co. KG) contains a combination of CR and HP.

The aim of this systematic review is to assess the effectiveness of alternative drugs for the treatment of vasomotor, cognitive and genital climacteric complaints.

Materials and methods

Search strategy

We searched the databases Pubmed, Ovid MEDLINE (1948–2009) and EMBASE (1980–2009) systematically for randomized controlled trials (RCT) by the following keywords: vasomotor symptoms, hot flashes, vaginal atrophy, psychological problems, endometrium, sleep, concentration, cognition, in combination with vitamins, multivitamins, minerals, multiminerals, black cohosh, *Cimicifuga*, *Agnus castus*, chasteberry, chaste tree, monk's pepper and menopause. Date last searched: 14 October 2009.

Inclusion criteria

Only RCT were included in the analysis. Supplements of CR, *Agnus castus*, vitamins or minerals, subjects with vasomotor, genital and cognitive climacteric complaints, subjects with no current medication for climacteric complaints other than the study drug, drug in the control group had to be different from that in the treatment group (e.g. not dose finding studies), studies published in German and English, and only publications with ethical approval were included.

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Exclusion criteria

Studies in animal models, *in vitro* studies of mechanisms of action, biochemical studies, pharmacological studies, malignant gynaecological diseases in subjects, antidepressants as a drug in intervention/control group, isoflavones used in intervention/control group, inaccurate description of the methodology and results, and a scoring less than three on the Jadad Scale.

Selection process

After the above-described search strategy, a total of 2955 trials with potentially relevant titles were found. From the search results, the studies that met the listed criteria were selected. 2943 studies were excluded. Twelve studies were included (Figure 1).

Data extraction

All included studies were reviewed by the four independent reviewers EL, DG, KD, KJB using data-collection sheets, which included characteristics of the trial participants, type of intervention, type of outcome measures, dropouts and results. Two studies [12,13] and three studies [14–16] were evaluated together, because they are part of one publication.

Study description

The number of patients varies from 62 to 351. The total number of patients included in the studies in this analysis amounts to 1573. Eleven of the included studies have a double-blind design. One study [17] was an estrogen-controlled randomized trial without a double-blind design.

Four studies examine the effects of CR and placebo (Table I) and two studies the effect of the mixture of CR and HP in comparison to placebo (Table II). In four studies, the effect of CR and estrogens or tibolone was evaluated (Table III).

The study by Nappi et al. was excluded from the analysis due to the low quality of the publication (three points in the Jadad Scale and no description of blinding, which could cause detection and performance bias). Therapy with *Agnus castus* was only found in one RCT [18]. In this study, *Agnus castus* is administered in combination with HP (Table IV).

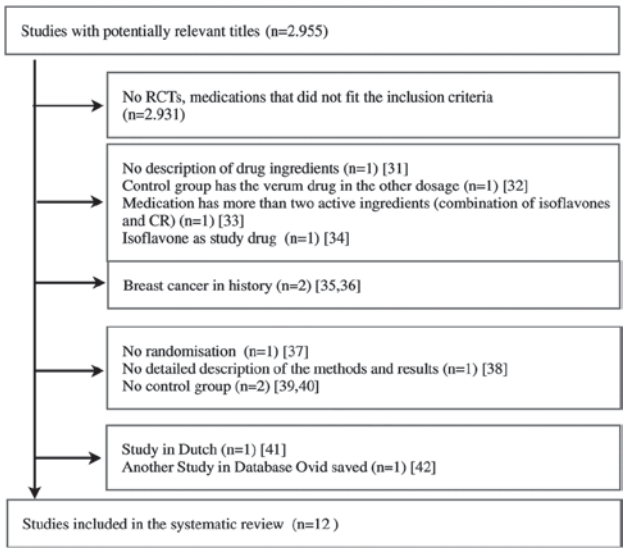

Figure 1. Overview of study selection.

The Jadad Scale [19] was used for quality assessment of the studies. The maximum score in the Jadad Scale is five. It assesses randomization, blinding and dropouts in the study. A study gets one point if randomization is mentioned, one additional point if the method is appropriate. One point must be deducted if the method of randomization is inappropriate. One point gets added if the blinding is mentioned and one additional point if blinding is appropriate. One point must be deducted if the method is inappropriate. One point is given to the study if the fate of all patients in the trial is known. None of the included studies had less than three points in Jadad Scale.

Because of missing necessary data on mean values and their standard deviations, which could also not be delivered after making personal inquiries to the study authors, the meta-analysis could not be created. Differences with $p < 0.05$ were considered to be statistically significant.

Results

CR vs. placebo

This analysis includes four studies, of which the results differ concerning the following symptoms (Table I).

Vasomotor symptoms

Three of four studies [12–16,20] showed no significant difference in the total population in the Wiklund and Vasomotor Scale [12,13], Kupperman Index and hot flashes score [20] and the Menopause Rating Scale (MRS) "hot flashes" [16]. In the study by Newton, an improvement in night sweat (after 3 months, $p = 0.030$) but no effect on other vasomotor symptoms, e.g. hot flushes, was observed. The evaluation of frequency of sweating episodes in the Wuttke et al. study showed a significant difference in the CR group, but not in the estrogen group. The studies used different scales for evaluating the symptoms, which made a quantitative comparison impossible.

Sleeping behaviour

Sleeping behaviour was only studied in Wuttke's publication. The ratio of nights with waking up early decreased significantly in the CR group (–23 % of the nights), $p < 0.05$.

Vaginal atrophy

Two studies [14–16,21] showed an improvement in vaginal atrophy in the total population. In the Osmers study [21], the MRS subscore "atrophy" was –0.053 (0.021) points ($p = 0.012$). In the study by Wuttke, a significant reduction of –0.35 points in the MRS subscore for atrophy could be observed ($p = 0.022$).

Psychological state

Two of the studies [14–16,21] showed a positive effect on the patient's psyche. The subscale "psyche" improved significantly in the Osmers study (–0.071 [0.030] points [$p = 0.019$]). In the Wuttke study, the MRS subscale "psyche" was reduced by 0.68 points, which was not significant [16]. The subscore "mental score," which, compared to "psyche," additionally includes a sexual history, was significantly reduced after 12 weeks by 0.72 points ($p < 0.05$). In the studies by Frei-Kleiner and Newton, no results on the total population were published on this issue. Because the menopausal scales for the total population in these studies have not improved significantly, it can be assumed that the psychological state of the women in these studies did not improve significantly. The overall trend shows that CR has no significant evidence-based effect on the psyche of menopausal women.

Table I. Effect of CR vs. placebo.

	Frei-Kleiner et al. [20]	Osmers et al. [21]	Newton et al. [12], Newton et al. [13]	Wuttke and Raus [15], Wuttke and Seidlova-Wuttke [16], Wuttke and Gorkow [14]
Trial medication + dosage/day	CR 6.5 mg dried rhizome extract = 29–55 mg crude drug ethanol extract	CR 5 mg isopropanolic extract = 40 mg root stock Remifemin®	CR 160 mg 2.5% triterpene glycosides 70% ethanol extract. Study medications produced according to the standards of good manufacturing practice. Black cohosh was standardised to 27-deoxyactin.	CR 40 mg = 3.32–5.72 mg native extract. Dried aqueous/ethanol extract. BNO 1055. Klimadynon®/Menofem®. Study medications produced according to the standards of good manufacturing practice.
Control group	Placebo	Placebo	Placebo	Placebo
Climacteric complaints	– KI – MRS – Hot flashes score	–MRS	– Wiklund Vasomotor Symptom Subscale score – Wiklund Menopause Symptom Subscale score – Symptom diary	MRS
Duration of medication	12 weeks	12 weeks	12 months	12 weeks
Age (mean ± SD)	52.5 ± 3.7 CR 52.2 ± 3.5 placebo	54 ± 6 CR 55 ± 6 placebo	52.0 ± 2.2 CR 52.0 ± 2.5 placebo	52.25 ± 3.19 CR 54.05 ± 4.36 placebo
Level of complaints (baseline)	19 KI points CR 18 KI points placebo	MRS 0.35 ± 0.12 CR 0.35 ± 0.12 placebo	Wiklund Menopause Symptom score 2.2 ± 1.2 CR 2.5 ± 1.2 placebo	MRS 2.73 ± 0.52 CR 3.23 ± 1.0 placebo
Number of patients CR/placebo	81/41	153/151	80/84	20/20
Result	No improvement in KI or MRS vs. placebo in the total population. In the population with KI ≥ 20 improvement in the symptoms in the CR group. Total population: hot flashes decreased by 37% in the verum group, 30% in the placebo group. KI decreased by 26% in verum, 17% in the placebo.	CR improves MRS significantly. ($p = 0.027$). The improvement is better in women in early menopause. MRS "hot flashes" decreased −0.127 (0.047), $p = 0.007$,"atrophy" decreased −0.053 (0.021), $p = 0.012$, "psyche" decreased−0.071 (0.030), $p = 0.019$	Vasomotor complaints and Wiklund Vasomotor Scale show no improvement under herbal medication vs. placebo. Vasomotor Scale: difference in mean change vs. placebo. −0.54 (−1.47–0.38), $p = 0.25$. Baseline: black cohosh approximately 6.7 symptoms/day, placebo approximately 6.1 symptoms/day.	The whole MRS: no significant improvement vs. placebo. ($p = 0.0506$). Subscore "hot flashes" and "psyche" show no significant improvement. Subscore "mental score" reduced signifcantly after 12 weeks by 0.72 ($p < 0.05$).Significant improvement in the subscore "atrophy" (−0.35 MRS points, $p = 0.022$).The ratio of nights with waking up early decreased significantly in the CR group (–23 % of the nights), $p < 0.05$.
Jadad Scale	4	5	5	4

CR, *Cimicifuga racemosa*; KI, Kupperman Index; MRS, Menopause Rating Scale; SD, standard deviation.

In summary, we could not find any evidence for the benefit of CR monotherapy in the treatment of menopausal symptoms based on the existing data. This assumption is also supported by the extensive and very high-quality study by Newton, in which an approximately four-fold–higher drug dose compared to the other studies was administered, which, nevertheless, showed no significant difference among the groups. The study by Frei-Kleiner, based on a comparable number of subjects, also did not find any significant difference for the total population.

However, a tendency observed is a minor effect of CR on vasomotor complaints but a more substantial effect on the improvement of vaginal atrophy.

CR + HP vs. placebo

Vasomotor symptoms

Two studies showed a significant improvement of vasomotor symptoms [22,23] (Table II). In the Uebelhack study, the MRS subscale "hot flashes" decreased by 53.4% in the treatment group (baseline approximately 0.58 points) and by 25.4% in the placebo group (baseline approximately 0.59 points) ($p < 0.001$). In the Chung study, after 8 weeks the scale for hot flashes decreased from an initial 7.52 ± 2.37 to 1.52 ± 1.97 in the *Cimicifuga* group and from 7.43 ± 1.71 to 3.54 ± 3.38 in the placebo group ($p = 0.021$). The baselines did not differ significantly.

Somatic complaints

The study published by Uebelhack et al. showed a significant improvement of somatic complaints. The factor "soma" in the MRS decreased by 39.5% in the treatment group and by 27.9% in the placebo group (baseline boths groups approximately 0.44 points). The *p* value was below 0.001 after the third examination. Although Chung et al. did not examine this parameter directly, there was an improvement in the Kupperman Index. After 12 weeks, the index in the active-treatment group decreased by 20.09 ± 9.75 (baseline 26.46 ± 10.64) compared to 8.24 ± 7.57 (baseline 25.38 ± 10.16) in the placebo group ($p < 0.001$).

Psychological state

On the Hamilton Scale, the Uebelhack study improved by 41.8% in the treatment group and 12.7% in the placebo group ($p = <0.001$) by intake of CR + HP. Baseline score in both groups 18.9 points. Chung et al. did not perform any specific assessment of the psychological situation.

Vaginal atrophy

Concerning vaginal atrophy after 16 weeks, Uebelhack et al. showed a significant superiority of intervention vs. placebo with $p = 0.003$ (baseline approximately 0.3 points in both groups, decrease in the treatment group of 29%). However, the authors evaluated the results to be clinically irrelevant. Chung et al. could not show a significant

Table II. Effect of a combination of CR with HP vs. placebo.

	Uebelhack et al. [22]	Chung et al. [23]
Trial medication + dosage/day	Week 1–8: double dosage of the medication in week 9–16 week 9–16:CR 3.75 mg = 22.5–41.25 mg rootstock CR (1.0 mg triterpene glycosides, calculated as 27-deoxyactein) + HP 0.25 mg total hypericine = 70 mg native extract = 245–350 mg herb 2 times/day	CR 0.0364 mL (1 mg terpene glycosides) + HP (0.25 mg hypericine) = 84 mg dried extract (methanole extract) Gynoplus®
Control group	Placebo	Placebo
Climacteric complaints assessment	-MRS -Hamilton Depression Rating Scale	-KI
Duration of medication	16 weeks	12 weeks
Age (mean ± SD)	52.4 ± 4.5 CR + HP 51.9 ± 4.0 placebo	51.02 ± 3.48 CR 50.43 ± 2.81 placebo
Level of complaints (baseline)	MRS 0.46 ± 0.13 CR + HP 0.46 ± 0.14 placebo	KI 26.46 ± 10.64 CR + HP 25.38 ± 10.16 placebo
Number of patients CR + HP/placebo	151/150	42/35
Results	Significant decrease in MRS in the verum group vs. the placebo group: "hot flashes" decreased by 53.4% in the treatment group (baseline approximately 0.58 points) and by 25.4% in the placebo group (baseline approximately 0.59 points), $p < 0.001$. "Soma" in the MRS decreased by 39.5% in the treatment group and 27.9% in placebo group, baselines both approximately 0.44, $p < 0.001$. "Atrophy" 29.0% increase in the treatment group, baseline both groups approximately 0.3 points, $p = 0.003$). Significant decrease in the Hamilton Depression Scale in the treatment group vs. placebo group (improved by 41.8% in the treatment group and 12.7% in the placebo group ($p \leq 0.001$), baseline score in both groups 18.9 points.	Decrease of KI. After 12 weeks, the index in the active-treatment group decreased by 20.09 ± 9.75 (baseline 26.46 ± 10.64) compared to 8.24 ± 7.57 (baseline 25.38 ± 10.16) in the placebo group. $p < 0.001$.Hot flashes decreased from an initially 7.52 ± 2.37 to 1.52 ± 1.97 in the *Cimicifuga* group and from 7.43 ± 1.71 to 3.54 ± 3.38 in the placebo group ($p = 0.021$). The baselines did not differ significantly. No significant improvement of vaginal atrophy.
Jadad Scale	4	3

CR, *Cimicifuga racemosa,* MRS, Menopause Rating Scale; SD, standard deviation; HP, *Hypericum perforatum.*

Table III. Effect of CR vs. estrogens/tibolone.

	Newton et al. [12], Newton et al. [13]	Wuttke and Raus [15], Wuttke and Seidlova-Wuttke [16], Wuttke and Gorkow [14]	Bai et al. [24]
Trial medication + dosage/day	CR 160 mg2.5% triterpene glycosides70% ethanol extractStudy medications produced according to the standards of good manufacturing practice. Black cohosh was standardised to 27-deoxyactin.	CR 40 mg = 3.32–5.72 mg native extractdried aqueous/ethanol extractBNO 1055Klimadynon®/ Menofem® Study medications produced according to the standards of good manufacturing practice.	CR 40 mg Drug = 5 mg ispropanolic dry extract Remifemin®
Control group	Conjugated estrogens 0.625 ± 2.5 mg medroxyprogesterone acetate	Conjugated estrogens 0.6 mg	Tibolone 2.5 mg Zi Zhu Awei®
Climacteric complaints assessment	-Wiklund Vasomotor Subscale score -Wiklund Menopause Symptom Subscale score -Symptom diary	MRS	Kupperman Menopause Index
Duration of medication	12 months	12 weeks	12 weeks
Age (mean ± SD)	CR 52.0 ± 2.2 HRT 52.3 ± 2.6	CR 52.25 ± 3.19 HRT 52.32 ± 3.03	Full analysis set CR 51.8 ± 3.7 Tibolone 51.5 ± 3.5
Level of complaints (baseline)	Wiklund Menopause Symptom score CR 2.2 ± 1.2 HRT 2.1 ± 1.0	MRS CR 2.73 ± 0.52 HRT 2.83 ± 0.51	CR and HRT Kupperman Menopause Index 24.7 ± 6.1
Number of patientsCR/HRT	80/32	20/22	122/122
Results	–	CR is equipotent to CE in alleviation of menopausal complaints.	No significant difference between CR vs. tibolone in alleviating climacteric complaints.KI declined from 24.7 ± 6.1 to 7.7 ± 5.8 after 12 weeks in the *Cimicifuga* group and to 7.5 ± 6.8 in the tiblone group (significant non-inferiority)
Jadad Scale	5	4	4

CE, Cinjugated estrogens; CR, *Cimicifuga racemosa*; MRS, Menopause Rating Scale; SD, standard deviation; HRT, hormone-replacement therapy.

Table IV. Effect of a combination of HP and *Agnus castus* vs. placebo.

Study characteristics	Van Die et al. [18]
Trial medication + dosage/day	HP 900 mg (2970 μg hypericine, 27 mg hyperforin, 54 mg flavonoidglycosides) + 1000 mg *Agnus castus*All tablets were manufactured according to the code of good manufacturing practice.The extract was obtained from the dry herb flowering top of HP (extraction ratio 6:1 g/mL) and dried *Vitex agnus castus* (extraction ratio 1:2 g/mL). The extraction solvent was 60% ethanol/water.
Control group	Placebo
Climacteric complaints assessment	Hot flashes Score, Green Climacteric Scale, Hailton Depression Inventory, Utian Quality of Life Scale
Duration of medication	16 weeks
Age (mean ± SD)	Intervention 51.9 ± 4.3Placebo 52.5 ± 3.8
Level of complaints (Baseline)	Green Climacteric Scale Intervention 21.98 ± 1.06Placebo 22.52 ± 1.06
Number of patientsCR/HRT	50/50
Results	No significant decrease in climacteric complaints in the intervention group vs. placebo group (p values > 0.05 for vasomotor symptoms, somatic complaints, sleep disorders, sexual disorders and mental disorders).
Jadad Scale	5

CR, *Cimicifuga racemosa*; SD, standard deviation; HRT, hormone-replacement therapy; HP, *Hypericum perforatum*.

difference. However, the follow-up period was only 12 weeks in the Chung study, whereas Uebelhack evaluated after 16 weeks.

A summary statement on treatment effects of the CR and HP combination vs. placebo is difficult as there are only two eligible RCTs on the subject. However, a combination of CR and HP seems to be more effective than placebo, particularly in the treatment of vasomotor complaints.

CR vs. estrogene/tibolone

Climacteric complaints

Two [14–16,24] of three studies [12–16,24] (Table III) showed no significant difference between CR and estrogens or tibolones in the treatment of climacteric complaints. However, in the study of Bai et al. the subjects received tibolone instead of estrogens. There was a significant non-inferiority in the Bai et al. study concerning hot flashes, profuse sweating, insomnia, nervousness, depressive mood, vertigo, weakness, fatigue, joint pain, headache and palpitation. The Kupperman Menopause Index decreased from 24.7 ± 6.1 to 7.7 ± 5.8 in the *Cimicifuga* group and to 7.5 ± 6.8 in the tibolone group after 12 weeks. Wuttke et al. showed a non-inferiority of CR vs. conjugated estrogens in the analysis of a total score of overall 10 MRS items [16].

This result is in contradiction with the statement from the systematic review of CR and placebo. There was a tendency towards a lack of evidence-based significant differences. The assumption that CR has the same effect with HRT implies that HRT is no more effective than placebo. However, this has been proven scientifically in several studies [25].

HP + Agnus castus vs. placebo

None of the measured end points in the study [18] (Table IV) was significant compared to placebo. These include vasomotor symptoms, somatic complaints, sleep disorders, sexual disorders and mental disorders. The corresponding p values were indicated for all the final parameters. The study has high quality and transparency.

A possible explanation for the non-significant results could be the significantly more frequent intake of isoflavones in the placebo group. This could cause a relief in climacteric complaints [26] especially concerning the vasomotor symptoms and thus cut down the treatment difference between placebo and intervention. Another explanation is that women in the treatment group consumed significantly more alcohol. This could possibly be reflected in the lack of significant differences in depression, sleep and psychological scale. A negative effect on other climacteric symptoms is also possible.

Discussion

Strength

The strength of this systematic review is the investigation of a uniform population. Patients with other diseases (e.g. breast cancer) were excluded primarily to transfer the results of this work to the total population with menopausal complaints. Studies with concurrent hormone use were not included to rule out other influential factors. Only studies of good quality were included in this review. Studies that compared CR and hormone therapy were also included, as this is the standard treatment of climacteric complaints.

Limitations

The interpretation of many studies was limited due to a lack in transparency. Surveys by the authors only rarely provided more information. Other limitations were the small number of included studies that met the criteria and different dosages of the herbal substances in the studies. Moreover, the comparison of the studies proved difficult or impossible because different scales for symptom assessment were used.

External validity

Results of this review are applicable to the general population, because subjects suffered from typical menopausal symptoms in the studies analysed. They were in menopausal/post-menopause stage and were at an appropriate age. Patients with malignancies were excluded.

Side-effects

The systematic analysis of the studies shows that the side-effects of CR, its combination with HP and a combination of *Agnus castus* and HP are comparable with placebo.

In 2006 the European Medicines Agency made public a number of case reports of liver injuries in patients using black cohosh.The Committee on Herbal Medicinal Products evaluated 50 case reports of hepatotoxicity. In four cases there was a temporal association between the start of treatment with black cohosh and the occurrence of hepatic reaction [27]. However, the publication of Teschke [28] does not support the concept of hepatotoxicity in a primarily suspected causal relationship to the use of black cohosh. Naser et al. [29] showed in the meta-analysis of RCTs also no evidence of black cohosh hepatotoxicity. Also Firenzuoli et al. [30] reported that CR should be considered safe concerning liver toxicity.

Conclusion

On the basis of all studies involved in this systematic review, we could show a significant effect of a combination of CR and HP in the treatment of climacteric complaints. More evidence-based studies are needed concerning the monotherapy with other substances.

***Declaration of Interest*:** The authors report no declarations of interest.

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