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ORIGINAL ARTICLE

Cimicifuga racemosa isopropanolic extract for menopausal symptoms: an observational prospective case–control study

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ABSTRACT

Objective: We aimed to investigate the effectiveness of isopropanolic extract of Cimicifuga Racemosa (iCR) on reducing menopausal symptoms.

Materials and Methods: A single-center observational prospective case–control study was performed to assess the improvement of menopausal symptoms in menopausal women undergone iCR administration (cases) or no treatment (controls). Menopausal symptoms were assessed through a modified version of the Menopause Rating Scale questionnaire (mMRS) at T_0 (baseline), T_1 (1-month follow-up), and T_2 (3 months follow-up). Univariate comparisons between cases and controls were performed by using the unpaired T test for two-tailed P value with $\alpha = 0.05$ significance level.

Results: A total of 163 women (83 cases and 80 controls) were enrolled in the study. The difference in menopausal symptoms between cases and controls from T_0 to T_2, and from T_0 to T_1, was found significant for all analyses. In particular, the difference in all menopausal symptoms was 20.56 ± 0.90 points (95%CI: 18.77–22.33, $p < .001$) from T_0 to T_2, and 10.69 ± 0.6 (95%CI: 9.49–11.88, $p < .001$) from T_0 to T_1.

Conclusion: iCR may be effective in reducing menopausal symptoms, both after 1 month and after 3 months of treatment. The improvement was higher in vasomotor symptoms, sleep problems, and irritability.

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Introduction

Menopause is the absence of spontaneous menses for 12 months due to the loss of ovarian function [1]. Menopausal symptoms are widely different between women across the world and may be clustered in three macro-areas: vegetative, organic and metabolic [2–4]. Main symptoms include hot flushes, sweating, sexual dysfunction, bladder problems, headache, formication, paresthesia, fatigue, impaired sleep and psychological disturbances [5].

MHT (menopausal hormone therapy), with estrogens alone or estrogen–progestogen combinations, is the most effective treatment for menopausal symptoms [6–7]. However, after concerns of the Women's Health Initiative regarding the long-term use of MHT, a decreased use of MHT and simultaneously an increased use of Complementary and Alternative Medicine (CAM) therapies have been reported [8–9]. CAM was defined by the National Center for Complementary and Integrative Health as an approach to the Western conventional medicine in order to support or replace it [10]. There are several different CAM approaches for menopausal symptoms, among which dietary supplements with black cohosh holds a prominent role [11–12]. Black Cohosh is one of the common names of Cimicifuga Racemosa (binomial name *Actaea racemosa*) [13]. Many active chemical substances can be extracted from Cimicifuga Racemosa's rhizomes and roots, such as triterpene glycosides, phenolic acids and N-methylserotonin [14–16]. Cimicifuga Racemosa mechanism of action on menopausal symptoms is still unclear, but it has been proposed a selective mechanism of estrogen modulation, with also serotoninergic, anti-inflammatory and antioxidant effects [17]. However, Cimicifuga Racemosa extracts lack of significant clinical estrogen-like effects because they did not bind to estrogen receptors [18–19]. In fact, several studies showed the absence of systemic estrogenic effects on hormones secretion, breast, vagina and endometrium [19–20].

However, according to a Cochrane review on the effectiveness of black cohosh in improving menopausal symptoms [21], there is still not enough evidence to recommend its use in clinical practice [22–24]. Although further studies were performed after the Cochrane review, inconsistency between the studies' results persists due to the different extracts, plant species, doses, outcomes and study population evaluated in the studies [22–24].

This study aimed to investigate the effectiveness of isopropanolic extract of Cimicifuga Racemosa (iCR) on reducing menopausal symptoms.

Materials and methods

Study protocol

The study was designed as single-center observational prospective case–control study according to an *a priori* defined protocol. The study was reported according to the STROBE guidelines

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[25]. The improvement of menopausal symptoms was assessed in all consecutive menopausal women undergone iCR administration (cases) or no treatment (controls) admitted to the 'San Giovanni di Dio e Ruggi D'Aragona' Hospital, Department of Medicine, Surgery and Dentistry 'Scuola Medica Salernitana', University of Salerno, Italy, from September 2018 to November 2019. Controls were women meeting the selection criteria but refusing treatment with iCR.

iCR preparation administrated (Remifemin®, PharmExtracta, Piacenza, Italy) consisted of 20 mg of dry extract of root/rhizome of Cimicifuga Racemosa, which contains triterpene glycosides' exact titration (between 2-3.5%), and lacks of formononetin, an O-methylated isoflavone with phytoestrogen action. Remifemin® is a dietary supplement product included in the Italian 'Registro degli integratori del Ministero della Salute' with code 43793. iCR 20 mg tablet was administrated twice a day, 1 tablet at breakfast and 1 tablet at dinner, for 3 months.

Menopausal symptoms were prospectively assessed through the administration of a modified version of the Menopause Rating Scale questionnaire (mMRS) [26]. This modified version of the Menopause Rating Scale questionnaire came out from the integration of MRS items with 4 items (headache, formication, paresthesia, fatigue) of the Kupperman score [27] for a total of 15 items. Each item was scored from 0 to 4 points for a total of 60 points. The questionnaire was translated in Italian language, and was administrated at time 0 (T_0, first visit and enrollment of the patient in the study), at one month (T_1) and three months (T_2) follow-up visit.

The study received approval by the Institutional Review Board of the "San Giovanni di Dio e Ruggi D'Aragona" Hospital, University of Salerno, Italy (No.: 134/25.07.2018), before the beginning of the study, and the whole study was performed in accordance with the Declaration of Helsinki.

Selection criteria

Inclusion criteria were: menopausal status, age between 45 and 65 years, and nonuse of any other drug for menopausal treatment in the past six months.

Exclusion criteria were: presence of a pathologic menopausal status due to surgery or endocrine disease, MHT or any other symptomatic treatments.

Menopausal status was defined as the absence of spontaneous menses for 12 months due to the loss of ovarian function [1].

Primary and secondary outcomes

Primary outcome was the difference in all menopausal symptoms between cases and controls from T_0 to T_2. Menopausal symptoms were assessed as mean difference of total mMRS score.

Secondary outcomes were the following:

- the difference in all menopausal symptoms between cases and controls from T_0 to T_1, with menopausal symptoms assessed as mean difference of total mMRS score;
- the difference in vasomotor symptoms, heart discomfort, sleep problems, depressive mood, irritability, anxiety, physical and mental exhaustion, sexual problems, bladder problems, dryness of vagina, joint and muscular discomfort, headache, formication, paresthesia, or fatigue, between cases and controls from T_0 to T_2, and from T_0 to T_1.

Each category of symptoms was assessed as mean difference of each item of mMRS score.

Statistical analyses

Range intervals and means ± standard deviation (SD) were calculated for total mMRS score and each item at T_0, T_1 and T_2, for cases and controls.

Difference in the means ± standard deviation (SD) of total mMRS score and each item from T_0 to T_2, and from T_0 to T_1, were calculated for cases and controls. Univariate comparisons between cases and controls for the difference in menopausal symptoms between cases and controls from T_0 to T_2, and from T_0 to T_1, were performed by using the unpaired T test for two-tailed p value with $\alpha = 0.05$ significance level. Univariate comparisons in each group (i.e. cases or controls) for the difference in menopausal symptoms from T_0 to T_2, and from T_0 to T_1, were performed by using the paired T test for two-tailed p value with $\alpha = 0.05$ significance level.

Statistical analyses were performed by using Statistical Package for Social Sciences (SPSS) version 19.0 (IBM Inc., Armonk, NY, USA).

Results

Study population

A total of 163 women (83 cases and 80 controls) were included in the study. No patients were lost during follow-up. Mean age was 51,20 ± 3,63 years in cases and 54,49 ± 4,7 years in controls. Mean BMI was 25,37 ± 2,91 kg/m^2 in cases and 26,36 ± 4,39 kg/m^2 in controls.

Patients' characteristics and mean of mMRS score and each item were reported in Table 1.

Primary and secondary outcomes

The difference in menopausal symptoms between cases and controls from T_0 to T_2, and from T_0 to T_1, was found significant for all analyses.

In particular, the difference in all menopausal symptoms was 20.56 ± 0.90 points (95%CI: 18.77–22.33, $p < .001$) from T_0 to T_2, and 10.69 ± 0.6 (95%CI: 9.49–11.88, $p < .001$) from T_0 to T_1.

From T_0 to T_2, the largest differences were found in vasomotor symptoms, sleep problems, and irritability (more than 2 points).

From T_0 to T_1, the largest differences were found in vasomotor symptoms, heart discomfort, sleep problems, and irritability (more than 1 point).

In cases group, the difference in all menopausal symptoms was 17.65 ± 7.9 points (95%CI: 15.93–19.37, $p < .001$) from T_0 to T_2, and 8.64 ± 5.13 points (95%CI: 7.52–9.76, $p < .001$) from T_0 to T_1.

In controls group, the difference in all menopausal symptoms was −2.9 ± 2 points (95%CI: −.3.35, −2.45, $p < .001$) from T_0 to T_2, and −2.05 ± 1.86 points (95%CI: −2.46, −1.64, $p < .001$) from T_0 to T_1.

Mean difference of total mMRS score and each item from T_0 to T_2, and from T_0 to T_1, for cases and controls, with primary and secondary outcomes were schematically reported in Table 2.

Discussion

Main findings and interpretation

This study aimed to assess the effectiveness of iCR on reducing menopausal symptoms. We found a significant decrease in all

Table 2. Mean difference of total mMRS score and each item from T0 to T2, and from T0 to T1, for cases and controls, with primary and secondary outcomes.

	Δ T_0- T_2 (mean ± SD)		Δ T_0- T_1 (mean ± SD)		Difference between cases and controls (mean ± SE)				
ITEM	CASES	CONTROLS	CASES	CONTROLS	T_0- T_2	95%CI	*p* value	T_0- T_1	95%CI	*p* value
Total mMRS score	−17.66 ± 7.89	2.9 ± 2	−8.64 ± 5.13	2.05 ± 1.85	20.56 ± 0.90	18.77 − 22.33	<.001	10.69 ± 0.6	9.49–11.88	<.001
Vasomotor Symptoms	−2.04 ± 0.74	0.31 ± 0.52	−1.01 ± 0.65	0.16 ± 0.37	2.35 ± 0.1	2.15 − 2.55	<.001	1.17 ± 0.83	1.01–1.34	<.001
Heart Discomfort	−1.28 ± 0.98	0.06 ± 0.43	−0.67 ± 0.8	0.1 ± 0.38	1.34 ± 0.12	1.11 − 1.57	<.001	0.77 ± 0.97	0.58–0.97	<.001
Sleep Problems	−1.59 ± 0.88	0.44 ± 0.67	−0.83 ± 0.6	0.29 ± 0.58	2.03 ± 1.23	1.78 − 2.27	<.001	1.12 ± 0.09	0.94–1.3	<.001
Depressive Mood	−1.49 ± 1	0.04 ± 0.37	−0.73 ± 0.66	0.03 ± 0.32	1.53 ± 0.12	1.3 − 1.77	<.001	0.76 ± 0.08	0.6 − 0.92	<0.001
Irritability	−1.59 ± 0.86	0.41 ± 0.65	0.82 ± 0.63	0.31 ± 0.56	2 ± 0.12	1.77 − 2.24	<.001	1.13 ± 0.09	0.95–1.32	<.001
Anxiety	−1.41 ± 0.98	0.16 ± 0.6	−0.69 ± 0.64	0.02 ± 0.47	1.57 ± 0.12	1.32 − 1.82	<.001	0.74 ± 0.09	0.561–0.562	<.001
Physical and mental exhaustion	−1.23 ± 0.97	0.65 ± 0.7	−0.65 ± 0.71	0.32 ± 0.59	1.88 ± 0.13	1.62 − 2.14	<.001	0.98 ± 0.1	0.77–1.18	<.001
Sexual Problems	−1.5 ± 1.21	0.14 ± 0.38	−0.66 − 0.15	0.15 ± 0.39	1.64 ± 0.14	1.363 − 1.366	<.001	0.81 ± 0.1	0.61–1.01	<.001
Bladder Problems	−1 ± 0.96	0 ± 0.28	−0.45 ± 0.59	−0.02 ± 0.32	1 ± 0.11	0.78 − 1.21	<.001	0.42 ± 0.74	0.27–0.57	<.001
Dryness of Vagina	−1.3 ± 0.98	0.18 ± 0.50	−0.66 ± 0.69	0.19 ± 0.48	1.48 ± 0.12	1.23 − 1.72	<.001	0.85 ± 0.92	0.67–1.03	<.001
Joint – Muscular Discomfort	−1.1 ± 0.88	−0.46 ± 0.63	−0.01 ± 0.25	0.01 ± 0.19	1.08 ± 0.1	0.88 − 1.28	<.001	0.47 ± 0.7	0.33–0.61	<.001
Headache	−1.06 ± 1	0.53 ± 0.66	−0.54 ± 0.69	0.43 ± 0.59	1.58 ± 0.13	1.32 − 1.84	<.001	0.97 ± 0.1	0.77–1.16	<.001
Formication	−0.58 ± 0.71	0.04 ± 0.37	−0.25 ± 0.56	0.01 ± 0.34	0.62 ± 0.09	0.44 − 0.79	<.001	0.27 ± 0.72	0.12–0.4	<.001
Paresthesia	−0.31 ± 0.6	−0.01 ± 0.25	−0.11 ± 0.41	0.01 ± 0.3	0.3 ± 0.07	0.16 − 0.44	<.001	0.12 ± 0.06	0.01–0.23	.033
Fatigue	−0.17 ± 0.38	−0.03 ± 0.16	−0.1 ± 0.34	0.01 ± 0.19	0.14 ± 0.4	0.05 − 0.23	.002	0.11 ± 0.04	0.02–0.19	.012

mMRS: modified version of the Menopause Rating Scale questionnaire.
T_0: time 0, that is, first visit and inclusion of patient in the study.
T_1: time 1, that is, one-month follow-up visit.
T_2: time 2, that is, 3 months follow-up visit.
Δ: difference.

Table 1. Patients characteristics and mMRS score.

ITEM (mean ± SD)	Cases	Controls
Age	51,20 ± 3,63	54,49 ± 4,70
BMI	25,37 ± 2,91	26,36 ± 4,39
Total mMRS score		
T_0	26.42 ± 9.14	15.7 ± 7.86
T_1	17.78 ± 6.42	17.75 ± 7.96
T_2	8.77 ± 4.82	18.60 ± 7.8
Vasomotor Symptoms		
T_0	2,90 ± 0,84	2,18 ± 0,99
T_1	1,89 ± 0,75	2,34 ± 0,97
T_2	0,87 ± 0,66	2,49 ± 0,89
Heart Discomfort		
T_0	1,71 ± 1,13	1,30 ± 1,02
T_1	1,04 ± 0,83	1,40 ± 0,99
T_2	0,43 ± 0,55	1,36 ± 0,97
Sleep Problems		
T_0	2,31 ± 0,99	1,60 ± 1,21
T_1	1,48 ± 0,80	1,89 ± 1,10
T_2	0,72 ± 0,63	2,04 ± 1,06
Depressive Mood		
T_0	2,19 ± 1,10	1,35 ± 1,12
T_1	1,46 ± 0,77	1,37 ± 1,13
T_2	0,70 ± 0,62	1,39 ± 1,15
Irritability		
T_0	2,31 ± 1,06	1,15 ± 1,06
T_1	1,49 ± 0,86	1,46 ± 0,86
T_2	0,72 ± 0,75	1,56 ± 0,91
Anxiety		
T_0	2,05 ± 1,06	1,14 ± 1,22
T_1	1,36 ± 0,84	1,19 ± 1,14
T_2	0,64 ± 0,55	1,30 ± 1,06
Physical and mental exhaustion		
T_0	2,02 ± 1,04	1,19 ± 1,06
T_1	1,37 ± 0,76	1,51 ± 0,93
T_2	0,80 ± 0,58	1,84 ± 0,92
Sexual Problems		
T_0	2,45 ± 1,28	1,02 ± 0,98
T_1	1,78 ± 0,95	1,17 ± 0,93
T_2	0,94 ± 0,83	1,16 ± 0,91
Bladder Problems		
T_0	1,60 ± 1,18	0,49 ± 0,94
T_1	1,16 ± 0,88	0,46 ± 0,91
T_2	0,60 ± 0,76	0,49 ± 0,91
Dryness of Vagina		
T_0	2,25 ± 0,96	1,34 ± 0,87
T_1	1,59 ± 0,81	1,53 ± 0,73
T_2	0,95 ± 0,78	1,51 ± 0,73
Joint – Muscular Discomfort		
T_0	1,65 ± 0,99	0,95 ± 1,04
T_1	1,19 ± 0,82	0,96 ± 1,07
T_2	0,55 ± 0,63	0,94 ± 1,06
Headache		
T_0	1,37 ± 1,10	0,72 ± 0,91
T_1	0,83 ± 0,71	1,15 ± 0,96
T_2	0,31 ± 0,49	1,25 ± 0,94
Formication		
T_0	0,88 ± 1,01	0,70 ± 1,01
T_1	0,63 ± 0,85	0,71 ± 1,06
T_2	0,30 ± 0,62	0,74 ± 1,00
Paresthesia		
T_0	0,46 ± 0,80	0,38 ± 0,80
T_1	0,35 ± 0,69	0,39 ± 0,85
T_2	0,14 ± 0,54	0,36 ± 0,82
Fatigue		
T_0	0,25 ± 0,66	0,20 ± 0,43
T_1	0,16 ± 0,46	0,21 ± 0,47
T_2	0,08 ± 0,39	0,18 ± 0,41

mMRS: modified version of the Menopause Rating Scale questionnaire.
T_0: time 0, i.e. first visit and inclusion of the patient in the study.
T_1: time 1, i.e. 1 month follow-up visit.
T_2: time 2, i.e. 3 months follow-up visit.

menopausal symptoms compared to no treatment, both after 1 month and after 3 months of treatment. Treatment over 3 months showed an approximately 30% decrease in severity of symptoms. Such an improvement in symptoms appears clinically relevant since it regards all menopausal symptoms, which may impact women quality of life. Moreover, the improvement was higher in vasomotor symptoms, sleep problems and irritability, which are the most complained symptoms. The symptoms improvement was even more relevant since women in the control group showed a significant increase in severity of symptoms indeed.

The most important climacteric symptoms are hot flushes and night sweats [28], that we evaluated in Vasomotor Symptoms and Sleep Problems items, respectively. Usually, hot flushes are associated with intense and sudden sweating, chills and palpitations [29]. Symptoms last from few seconds up to 1 h. [30–32]. Prevalence of these symptoms varies between 24% and 93% in peri- and post-menopausal women. [33–37]. Etiology of hot flushes is not completely understood, but several authors propose that it is triggered by a changed thermoregulation set point of the hypothalamus caused by low estrogen levels during menopause [38–39] or their interaction with norepinephrine and serotonin [40]. In accordance with this hypothesis, serotonin 5-HT2A receptors in the hypothalamus showed a significant up-regulation in estrogen fall. In addition, blockage of 5-HT2A, due to use of mirtazapine (5-HT2-5HT3 receptors blocker), decreased frequency and intensity of hot flushes [41]. Hypothalamic thermoregulation is determined also by 5-HT1A, 5-HT1D and 5-HT7 receptors [42–43], and iCR extracts binds to these receptors modulating onset and severity of hot flushes [15–16]. Moreover, due to the high density of 5-HT2A receptors, estrogen fall may be linked to the onset of depressive mood in menopause [44]. In agreement, we found that vasomotor symptoms and sleep problems were the most improved symptoms after iCR treatment, showing a difference higher than two points at the questionnaire.

In our findings, another higher improvement among menopausal symptoms was about irritability. Such a change may be related to psychoactive substances within iCR preparation, such as N-methyl-serotonin and GABAergic and dopaminergic compounds [29]. None of the individual active compound in iCR seem to have better effects than other ones; rather, they appear to act synergistically to reduce climacteric complaints [19].

Given iCR safety on mammary tissue, it might be considered especially for menopausal patients with breast cancer, healthy women with increased cancer risk due to familiarity for malignances, or women who reject MHT [45].

Regarding iCR safety, in 2006, European Medicines Agency (EMA), and Committee on Herbal Medicinal Products made a statement on hepatic reactions linked to herbal medicinal products containing Cimicifugae Racemosae Rhizome. Based on this statement, iCR treatment was suspended.

In fact, there are different black cohosh extraction solvents, which affect Cimicifuga Racemosa chemical profile and biological activity, and so side effects [46]. Different extraction solvents include methanol, ethanol and isopropanol, as well as chloroform, ethyl acetate and butanol fractions of black cohosh extract [5]. Few pharmacokinetic studies of black cohosh have been published, but it was proposed that hepatic toxicity is due to electrophilic quinones that are potentially toxic to the liver, as identified in an *in vitro* model using rat liver microsomes [47]. Thus, different extraction solvents may modify the amount of electrophilic quinones and therefore the toxicity of Cimicifugae Racemosa extracts. A review by Beer *et al.* [48] analyzed different extracts, pharmaceutical quality, and indication of Cimicifuga Racemosa, pointing out that especially the isopropanolic extract (iCR) and the ethanolic extract (BNO 1055) demonstrated efficacy and a good safety profile in more than 11,000 and 500 patients, respectively [23,24,49–57].

In 2007, EMA reintroduced iCR medications with the advice to patients to stop treatment and consult their doctor if they would have developed signs and symptoms suggestive of liver injury. In 2017, EMA final assessment report, stated that the use of iCR products can be considered a safe and well tolerated treatment under the condition lined out in the European Union herbal monograph [46]. Several meta-analyses of randomized clinical trials remarked the non-evidence of hepatic adverse effects due to Cimicifuga treatment [58–60]. According to these findings, in our cohort, no women showed hepatotoxicity symptoms.

Strengths and limitations

The main strength of this study was the symptoms assessment through a modified version of the MRS [26] that included 4 items (headache, formication, paresthesia, fatigue) of the Kupperman score [27]. This questionnaire allowed to assess menopausal symptoms more comprehensively. Moreover, comparisons between cases and controls were performed for total mMRS score and each item both after 1 month and after 3 months of treatment.

On the other hand, the observational design of the study may be a limitation. In fact, a randomized placebo-controlled study would be the ideal design for the study aim (i.e. to investigate the effectiveness of iCR on reducing menopausal symptoms), especially when endpoints are subjective complaints without objective validation.

Other limitations may be the lack of a long-term symptom assessment and the inclusion of only Caucasian women with spontaneous menopause. In particular, given the symptoms difference among different ethnicities, and between spontaneous and pathological menopause [61], it would be interesting to investigate iCR effectiveness even in these groups of women.

Lastly, another limitation may be the impossibility to perform an *a priori* sample size calculation, as no prior study in the Literature assessed the difference in menopausal symptoms between cases and controls by using the mMRS score (i.e. our primary outcome). Therefore, we were unable to estimate such a difference in order to set an *a priori* sample size calculation. However, our study does not seem to be underpowered. In fact, if we adopt a non-modified version of MRS to assess the difference in menopausal symptoms between cases and controls as a surrogate of our primary outcome, we can consider some studies in the Literature. In particular, a prior study reported a decrease in MRS score by 50% in cases and by 19.6% in controls [56]. Thus, setting an α error = 0.05 and a β error= 0.20 with a study power= 0.80, we would need 74 patients (37 cases and 37 controls) to demonstrate such a difference.

Conclusion

iCR may be effective in reducing menopausal symptoms, both after 1 month and after 3 months of treatment. The improvement was higher in vasomotor symptoms, sleep problems, and irritability. In addition, iCR does not have an estrogen-like effect and it could be a safe and effective treatment for patients who are worried about the cancer risk linked to estrogen use.

Disclosure statement

The authors declare that they have no conflict of interest.

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