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Original article

The Effect of *Rheum ribes* Root (Rhubarb) on Menopausal Hot Flashes: a Randomized Double-Blind, Placebo-Controlled Trial

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Abstract

Background and objectives: Hot flashes are one of the most predominant complaints of menopause among women. The main treatment is hormone replacement therapy, which has side effects. Therefore, the use of plants with phytoestrogen has been suggested as an adjunctive treatment**.** This study aimed to estimate the efficacy of processed rhubarb (*Rheum ribes* L.) on hot flashes in postmenopausal women. **Methods:** This double-blind placebo-controlled trial was performed on postmenopausal women who were referred to public health centers at Iran University of Medical Sciences. Ninety postmenopausal women aged over 45 years with menopausal hot flashes were randomly assigned to two groups. The treatment group received 500 mg of encapsulated processed *R. ribes* twice a day for eight weeks, and the control group received placebo (starch powder) in the same manner. Data were collected using Blatt–Kupperman index at the start of the study, fourth and eighth weeks after the intervention. Descriptive and analytic statistics were used to analyze the data. **Results:** A total of 74 patients completed the study (39 participants in the intervention group and 35 in the control group). The results showed that *R. ribes* significantly decreased the mean of flashing in Blatt–Kupperman index four and eight weeks post-intervention ($p<0.001$). *Rheum ribes* showed no serious adverse effects. **Conclusion:** The findings of this study propose that treatment with *R. ribes* may be considered an adjunctive treatment for hot flashes in postmenopausal women.

Keywords: herbal medicine; hot flash; menopause; *Rheum ribes*

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Introduction

Menopause is one of the stages of life that is experienced by all women. Menopause refers to a

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period in women's life in which estrogen levels decrease in their bodies and menstruation is completely stopped due to ovarian inactivity [1]. The initiation of menopause is accompanied by hormonal changes that rationalize the symptoms (decrease in estrogen and increase in FSH (follicle-stimulating hormone) and LH (luteinizing hormone), which ultimately reduce the level of progesterone [2].

According to the World Health Organization (WHO), around 1.3 billion women will be in the postmenopausal period in 2030 [3]. Menopause is routinely initiated between the ages of 45 and 55, and about 47-80% of women experience its symptoms [4-6]. The menopausal symptoms consist of hot flashes, night sweats, redness of skin, insomnia, anxiety, depression, loss of concentration, decreased libido and skin and mucosal atrophy, which last for 5-10 years after menopause [7]. Physical, psychological, and sexual features of menopause are attributed to the decreased levels of ovarian hormones, particularly estrogen [1].

Hot flashes have been reported as the most common and challenging symptoms of menopause, which approximately 80% of women experience within three months after menopause [8]. It has been shown that hot flashes affect work, social activities, sleep, mood, attention, communication with others, sexual activities, and women's general quality of life [9]. Hot flashes are episodic flashing and sudden redness of the scalp, neck and chest, with a severe feeling of heat in the body that sometimes ends with diaphoresis, chills, palpitations, anxiety and sense of pressure in the head and chest. They typically last a few seconds to a minute and hardly up to an hour [8]. The symptoms may last for more than one year in 80% of women, more than four to five years in 50% of women, and up to 15 years in 10% of them [10].

Hormone replacement therapy is considered the main treatment for hot flashes. Though, this treatment has some side effects, including negative effects on lipids and lipase activities, an increase in risk of coronary heart diseases, breast and endometrial cancers, as well as thromboembolic and liver disorders [11]. Hormone therapy is contraindicated in women with a family history of breast cancer and fibro adenoma; consequently, alternative therapies, particularly herbal medicines, have gained huge interest in recent years [12,13].

Phytotherapy is one of the most common methods worldwide. It seems that nearly 80% of postmenopausal women use herbal medicine in some countries. More than 60% of them believe that these supplements alleviate their problems [14]. Several medicinal herbs have been studied in this area, which have phytoestrogenic properties. Phytoestrogens are estrogen-containing compounds in plants that can reduce some menopausal symptoms [15,16)]. Numerous studies have been conducted on the effects of phytoestrogens on alleviating menopausal symptoms [15-18].

Rheum ribes ("Rivand" as a Persian name), is a medicinal root that belongs to Polygonaceae family. It is distributed in Iran and several neighboring countries. This perennial plant is cultivated in some temperate countries due to its edible red stems [19].

Rheum ribes is a rich source of A, B, C, and E vitamins, and also minerals such as aluminum, calcium, iron, potassium, magnesium, sodium, phosphorus, zinc, copper, and selenium. It has chemical components, including chrysophanol, physcion, rhein, aloe-emodin, physcion-8-o-glucoside, aloe-emodin-8-O-glucoside, sennoside a, rhaponticin, and flavonoids [20,21]. This plant has antibacterial, anti-trichomonas, anticancer, anti-ulcer, hypoglycemic, hypolipidemic, reno-protective, anti-inflammatory, antioxidant, blood pressure- and weight-decreasing, and anti-Alzheimer activities. It also has protective effects on nerve, liver, kidneys, and stomach. It is used to treat anemia, anorexia, weakness, anxiety and major depressive disorder. It has also shown anti-polycystic ovarian syndrome effects [20-27].

Although there are many studies on the effects of rhubarb (as common name of *Rheum ribes*) on different diseases, there is not any study about its effects on flashing, and other parameters of menopause [28]. Due to the high prevalence of hot flashes and the importance of appropriate adjuvant therapy, and since the symptoms of hot flashes can be described from the perspective of Persian medicine (PM) under the category of liver and spleen diseases, and this plant is used to improve this category of diseases, we aimed to investigate the effects of *Rheum ribes* on hot flashes in menopausal women [29].

Materials and Methods

Ethical considerations

This clinical trial was registered at the Iranian

Registry of Clinical Trials (registration no. IRCT201815041345N1). The Research Ethics Committee of Iran University of Medical Sciences (IUMS) reviewed and approved the study protocol (registration ID: IR.IUMS.REC.1397.1286). The protocol of this study was in accordance with Helsinki declaration. All the participants were fully aware and informed about the goals and details of the study through an information sheet and written informed consent was obtained from them.

Plant material

Rheum ribes L. was purchased from an herbal drug store in Tehran in May 2019. The plant was identified and registered at the herbarium of the Faculty of Pharmacy, Shahid Beheshti University of Medical Sciences, with voucher number: SBMU_8222. For preparation of *Rheum ribes* capsules, the roots of the plant were washed and dried and placed in a mechanical grinder to prepare the powder, then capsules containing 500 mg of powdered rhubarb roots were filled for administration.

Determination of hydroxyanthracene derivatives as rhein in rhubarb extract

The hydroxyanthracene derivatives determination was performed according to the British Pharmacopoiea with methanol as blank according to the following formula [30]:

$$A \times 0.64 / M$$

Where A is the sample absorbance at 515 nm and M is the sample weight (g).

Study design

This study was a randomized, double-blind placebo-controlled trial performed in five public health centers of Iran University of Medical Sciences (IUMS) health centers, Tehran, Iran from Jun 2019 to February 2020. Eligible individuals willing to participate in the study with menopausal hot flashes were selected based on the inclusion criteria, followed by oral explanations and written consent. personal and medical information questionnaires were completed for each patient, and they were asked to complete and submit the Blatt–Kupperman index (BKI) before treatment. Following a detailed description of the research method, the individuals signed written informed consent. It was also explained that their participation was voluntary, and they could leave the research at any time of the study. The women with postmenopausal hot flashes were invited by the research team for the interview to select participants meeting the inclusion/exclusion criteria of the study.

Inclusion criteria

- Women aged 45 years and over
- Not taking hormonal medications
- No menstruation in the past 12 months
- No serious medical illness

Exclusion criteria

- Using hormonal or herbal medication to treat hot flashes
- History of allergies or skin allergies to herbal medicines or compounds
- History of bowel surgery

The subjects were divided into two random groups using the random block method (*Rheum ribes* group and control group). The women in the *Rheum ribes* group received 500 mg capsules one hour after meal twice a day, for eight weeks, and the control group received placebo (500 mg starch powder) in the same manner. The patients were evaluated in three stages, at the beginning of the study and fourth and eighth weeks after the intervention. The subjects randomly received a package containing capsules of *Rheum ribes* or placebo, which were exactly similar in physical properties. Both of the patients and researchers had no information about the contents of the treatment and were blinded to the assigned treatment groups during the study.

Outcome measurements

The main outcome was the severity of hot flashes measured with Blatt–Kupperman index). Blatt–Kupperman index is a measure of the severity of various symptoms, including hot flashes and sweat, insomnia, anger, depression, dizziness, weakness, fatigue, muscular and articular pain, headache, palpitations and numbness. The patients were asked to rate their symptoms (most commonly) based on a Likert scale from 0 to 3 (where 0 is asymptomatic, 1 is mild, 2 is moderate and 3 is severe) [31]. The Blatt–Kupperman index has been frequently used by researchers and Western-Indian women. It is also valid in Iran [10,32] and Asian populations [32].

For evaluation of flashing, the number of hot flashes in Kupperman Menopausal Index in patients were counted by a blinded researcher at the baseline, 4th and 8th weeks. The participants were evaluated by a physician at each visit to identify adverse events. Moreover, they were followed every two weeks by telephone for any side effects as well as compliance with the study.

Sample size calculation

Considering the severity of hot flashes as the main variable of the study, measurement instruments and results from previous studies, and the assumption that the drug reduced the frequency of severe symptoms by about 50%, 40 people were estimated for each group. With the addition of 10% to compensate for the sample dropout, 45 people were calculated for each group and a total of 90 people were determined.

Randomization and Blinding

Subjects were randomly divided into two groups using block randomization method. One group received *Rheum ribes* and the other received placebo. Capsules containing *Rheum ribes*, and placebo were prepared in the laboratory and set in similar boxes encoded. The person who prescribed the medications was blind to the study.

Statistical analysis

Data were analyzed with SPSS software (SPSS Inc. Version 18.0., USA). Descriptive statistics (frequency, mean, standard deviation and median) and analytical statistics (Chi-square test to compare qualitative variables, Mann-Whitney and Wilcoxon tests to compare quantitative variables) were used and the significance level (α value) was set to be 0.05. Considering the dropout of the participants in the two groups, statistical analysis was performed. Although the main variable was qualitative nature of brank, according to similar studies, the main variable was considered continuous quantitative; therefore, it was analyzed by repeated measure method [33,34].

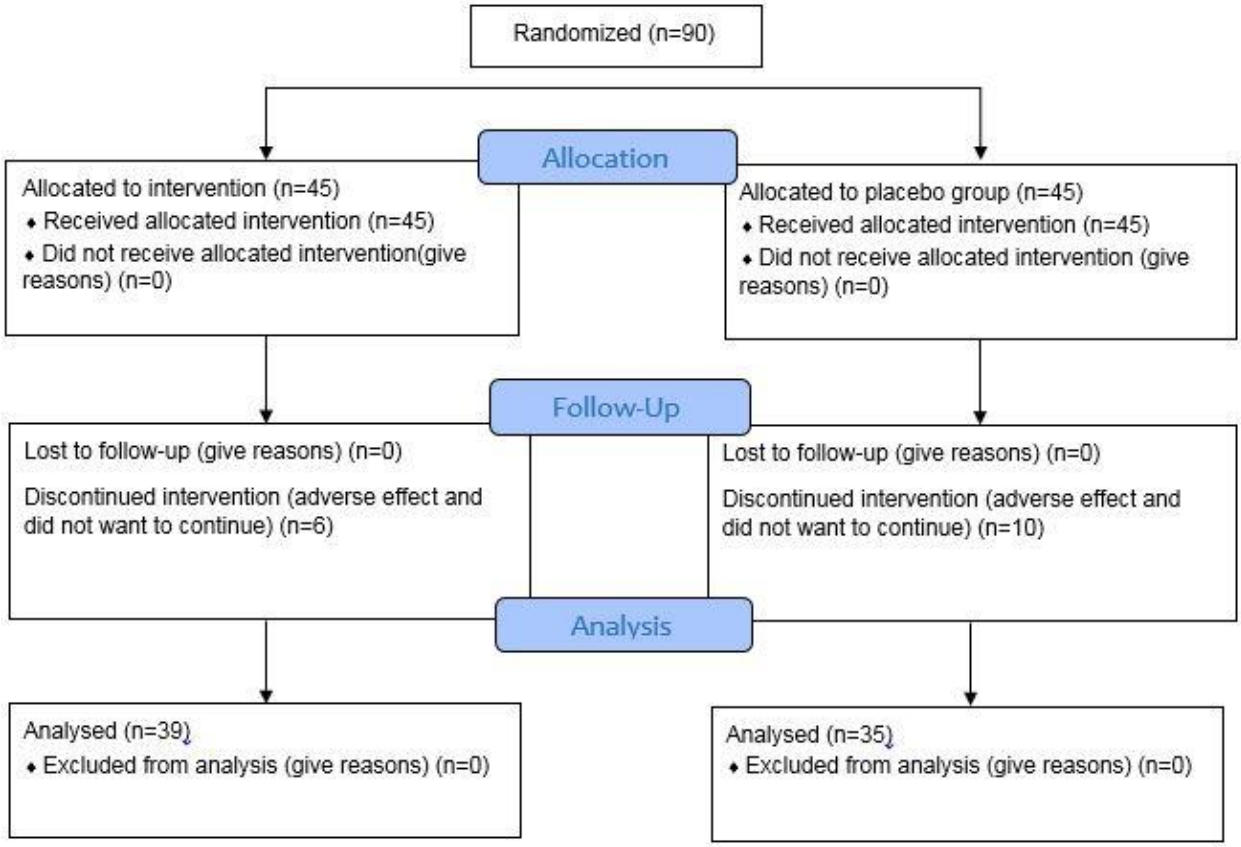

Figure 1. Consort flow diagram of *Rheum ribes* trial on hot flash

Results and Discussion

Despite the widespread use of alternative treatments, scientific evidence supporting the efficacy and safety of complementary treatments for relief of menopausal symptoms is limited. Thus, randomized controlled trials demonstrating effects of these treatments are needed.

The present randomized, placebo controlled, double blind clinical trial assessed the effectiveness and safety of the *Rheum ribes* as an herbal medicine in the alleviation of vasomotor symptoms and improvement in menopause related quality of life in menopausal women hydroxyanthracene derivatives according to rhein in rhubarb extract was calculated to be 0.302%.

Rheum ribes as a medicinal herb in the reliable and available traditional has been mentioned as laxative in Persian medicinal books and is mentioned as a treatment for hot flash like symptoms in these books. Actually, hot flash is defined under the different types of fever "Homma" in Persian traditional medicine [29].

A total of 90 postmenopausal women with hot flashes were included in the study. Finally, 74 women completed the study (39 patients in *Rheum ribes* group and 35 patients in the placebo group). During the study, 16 subjects did not complete the trial, six of which were from the *Rheum ribes* group (three people refused to cooperate, three had gastrointestinal symptoms) and ten subjects were from the control group (four people refused to cooperate, and six had gastrointestinal symptoms (Figure 1).

In the present study, we compared two groups of subjects in terms of age, marital status and educational level, number of children, body mass index, and onset age of menopause. According to independent t-test, there were no significant differences between the two groups in terms of the parameters in demographic characteristics ($p>0.05$), only the mean age at menopause in the *Rheum ribes* group was significantly higher than the placebo group ($p<0.001$) (Table 1).

Table 2 shows Blatt-Kupperman index of patients before and after 4 and 8 weeks. Although the comparison of the two groups in terms of the mean of Blatt–Kupperman index at the beginning of the study showed that the mean score of hot flashes in the *Rheum ribes* group was higher than the control group. Four and eight weeks post-intervention, the mean severity of hot flashes significantly decreased in the *Rheum ribes* group compared to the control group.

Comparison of other variables of the BKI (Blatt-Kupperman index) in the post-intervention showed a significant difference between the two groups in terms of variables of depression and dizziness (Table 3).

Today, there have been few randomized placebo controlled, double blind clinical trials on the effect of Persian herbal medicine on menopausal symptoms. Our results indicated significantly reduced symptoms on hot flashes that are the most common symptoms among menopause woman. On the other hand, *Rheum ribes* has been used in management of variable diseases in Persian traditional medicine to alleviate vasomotor symptoms in menopausal period.

According to Persian medicine, this plant has warm and dry quality. Therefore, it is a strong dissolvent "Muhallil". In chronic fever, it is useful in cooling the body by dissolving harmful substances and excreting them. It is also a laxative agent and tonic for the heart, liver, and stomach [29].

Table 1. Baseline characteristics of participants in *Rheum ribes* and control groups

Characteristics		Group		p-Value
		***Rheum ribes* group (n=39)**	**Control group (n=35)**	
Women's age (mean±SD, years)		53.38±5.92	53.09±5.52	0.824
Number of children (mean±SD)		2.92±1.34	2.83±1.17	0.095
Menopause age (mean±SD, years)		49.59±3.71	44.09±2.0	<0.001
BMI* (mean±SD, kg/m^2)		26.18±2.62	27.09±2.20	0.114
Marriage status N (%)	Single	3(7.7)	0(0.0)	0.242
	Married	36(92.3)	35(100.0)	
Education N (%)	Illiterate	3(7.7)	3(8.8)	0.450
	Primary School	10(25.6)	5(14.7)	
	High School	5(12.8)	10(29.4)	
	Diploma	13(33.3)	10(29.4)	
	Academic	8(20.5)	6(17.6)	

*BMI: body mass index

Table 2. Comparison of the hot flashes by Blatt–Kupperman index (BKI*) between *Rheum ribes* and placebo groups

Time	*Rheum ribes* group Mean ± SD	Control group Mean ± SD	p-Value of t-test	p-Value of RM**
Before drug administration	2.49±0.64	2.17±0.61	0.035	0.08
After 4 weeks	1.41±0.81	2.06±0.59	<0.001	
After 8 weeks	1.13±0.89	1.91±0.50	<0.001	

*Blatt–Kupperman index measures the severity of various symptoms such as hot flash and sweat, insomnia, anger, depression, dizziness, weakness, fatigue, muscular and articular pain, headache, palpitations, and numbness. Each symptom is scored from 0 to 3 (where 0 is asymptomatic, 1 is mild, 2 is moderate and 3 is severe) based on a Likert scale.
**Repeated-measure.

Table 3. Comparison of depression and dizziness by Blatt–Kupperman index (BKI*) between *Rheum ribes* and placebo groups

Time	*Rheum ribes* group Mean ± SD	Control group Mean ± SD	p-Value of t-test	p-Value of RM**	Total difference
Depression					
Before drug administration	0.85±0.90	1.23± 0.84	0.065	0.001	-0.624
After 4 weeks	0.54±0.82	1.20± 0.83	<0.001		
After 8 weeks	0.49± 0.75	1.31± 0.86	<0.001		
Dizziness					
Before drug administration	0.44± 0.64	0.69± 0.63	0.096	0.002	-0.424
After 4 weeks	0.23± 0.48	0.71± 0.66	<0.001		
After 8 weeks	0.21± 0.46	0.74± 0.70	<0.001		

*Blatt–Kupperman index measures the severity of various symptoms such as hot flash and sweat, insomnia, anger, depression, dizziness, weakness, fatigue, muscular and articular pain, headache, palpitations, and numbness. Each symptom is scored from 0 to 3 (where 0 is asymptomatic, 1 is mild, 2 is moderate and 3 is severe) based on a Likert scale.
**Repeated-measure.

In fact medicinal plants are considered for primary health care and as complementary therapies in various cultural traditions. However, there are challenges to their effectiveness and safety that require evidence-based studies [35].

Based on the herbal properties mentioned in Persian medicine, *Rheum ribes* may help relieve sweating and hot flashes by eliminating the waste accumulated in the body after menopause. Based on PM theory, hot flashes were explained as "Homma" (a kind of fever without an infectious source; so it is transient and intermittent; this feature needs a herb with hot temperament to treat) [29]. *Rheum ribes* belongs to Polygonaceae family. The roots of *Rheum ribes* are used to treat many disorders such as constipation, diabetes, hypertension, hypercholesterolemia, ulcers, obesity, diarrhea, and sputum. Various studies have shown the beneficial effects of *Rheum ribes* in the gastrointestinal tract [36-39]. *In vitro* studies have displayed significant cytotoxic, anticancer, antiradical and anti-inflammatory activities of *Rheum ribes* [40]. Achakzai et al.'s study demonstrated remarkable anti-inflammatory effects of this plant with minimum side effects [41].

Most clinical data support that the efficacy of estrogens prominently influence immune system and inflammatory processes. Estrogens may be implicated in a number of autoimmune diseases in postmenopausal women. In this regard, some chronic inflammatory diseases may be associated with menopause, pregnancy, and menstrual cycle. Menopausal women are more prone to robust immune responses. Deficiency of ovarian steroidal hormones aggravates the inflammatory procedure, prompting menopausal women to immune disorders [42]. In addition, various studies have shown that circulating pro-inflammatory cytokines such as IL-6 and TNF-alpha are increased in postmenopausal women [42].

In several studies, the relationship between hot flashes and inflammation has been evaluated and the results have shown that the level of circulating pro-inflammatory factors, e.g., IL-8 and macrophage inflammatory protein-1β (MIP-1β), were higher in postmenopausal women with hot flashes than postmenopausal women without hot flashes [43].

Regarding hot flashes and their effects on systemic inflammation, we suggest that *Rheum ribes* may be effective in improving hot flashes through its anti-inflammatory properties [40-44]. *Rheum ribes* is a familiar plant with potent antioxidant activity. The conformation of flavonoids (quercetin, 5-deoxy-quercetin, quercetin 3-O-rhamnoside, quercetin 3-O-galactoside and auercetin 3-O-rutinoside, and the anthraquinones, chrysophanol, physcion and

emodin) found in this plant resembles natural antioxidants [45]. Decreased estradiol levels during menopause lead to a number of uncomfortable symptoms such as vasomotor symptoms. The most distressing symptom of menopause is hot flashes [34].

Reduction of estradiol in body may raise oxidative stress because estradiol has antioxidant properties, due to its structure and its capacity to prevent oxidative stress in multiple ways, such as counteracting additional reactive oxygen species, removing free radicals, and antioxidant effects. Thus estradiol is a part of the antioxidant system that deactivates the oxidative stress in the reproductive phase [46].

During menopause, antioxidant protection is lost due to decreased estradiol production, and this is a risk factor for oxidative stress. Oxidative stress is one of the possible factors for menopausal symptoms, such as vasomotor disorders (hot flashes). Menopausal women suffer from frequent episodes of vasomotor disorders, especially hot flashes [47]. Episodes of vasomotor disorders result in oxidative stress by blocking antioxidants and their function in counteracting reactive oxygen/nitrogen species and increasing the level of oxidant species [48]. It is suggested that *Rheum ribes* can be effective in improving vasomotor symptoms, especially hot flashes, by its antioxidant properties.

During menopause, estrogen fluctuations impair the hypothalamic thermoregulatory center, eventually leading to hot flashes. Phytoestrogens can reduce hot flashes through estrogen-like hormonal activities. Also, studies have reported that some phytochemicals with estrogenic activity have beneficial effects on menopausal symptoms without side effects.

Recently, some polyphenols, especially isoflavones, have been identified as phytoestrogens due to their estrogenic activities. These compounds are used to reduce vasomotor symptoms. The effect of phytoestrogens on improving menopausal symptoms has been investigated in various studies [49]. But so far, no study has been conducted on the effect of *Rheum ribes* on improving menopausal symptoms. Only in 2010, a study was conducted in Germany on another species of the plant (*Rheum rhaponticum* L.), which revealed the effect of the extract from the roots of rhapontic rhubarb on menopausal symptoms. The results showed positive effects on the menopausal symptoms by estrogenic actions of this plant, particularly those mediated by estrogen receptor-b (ERb). These studies suggested the positive role of the anthraquinone emodin and hydroxystilbenes by estrogenic activities in the management of menopausal symptoms [50]. Moreover, another study in 2021 showed *Rheum rhaponticum* root extract improved vasomotor menopausal symptoms and estrogen-regulated targets in an ovariectomized rat model [51]. Due to the similarity of *Rheum ribes* with *Rheum rhaponticum*, both plants belong to the same family (Polygonaceae family), and the presence of emodin compounds with estrogenic properties in this plant, we suggest that this plant can be effective in improving menopausal symptoms [51-53].

Rheum ribes has antioxidant properties due to the presence of phytoestrogenic flavonoid compounds [54,55]. As mentioned, some flavonoids impact menopausal symptoms through estrogen receptors [35]. Also, the extract of different species of the Polygonaceae family have shown estrogenic and tumor necrosis factor (TNF repression) activities [56]. Therefore, it may be effective in the treatment of climacteric menopausal symptoms.

Due to the positive effects of *R. ribes* on the menopausal climacteric symptoms without noticeable side effects in this study, it can be recommended as a treatment for hot flashes. In the present study, no serious side effects were observed except for three cases with gastrointestinal disorder that was resolved with simple recommendations. There were some limitations such as available sampling, sample dropout and per protocol analysis.

Conclusion

This study suggests that treatment with *Rheum ribes* can be considered an effective complementary treatment in menopausal hot flashes.

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Author contributions

Najmeh Bagheriani was responsible for visiting and the participants. She was also involved in designing the study, and writing the manuscript. Elham Akhtari contributed to the original design of the study, supervised the project and contributed to writing the article. Mohsen Bahrami was involved in the original design of the research proposal; also, he provided valuable comments during the study. Mohammad Kamalinejad contributed to the preparation of *Rheum ribes* and placebo capsules and wrote herbal specifications. Zahra Rampisheh participated in data analysis. Maryam Kashanian participated in sampling and drafting the manuscript.

Conflict of interest

The authors declare that there is no conflict of interest. The authors alone are responsible for the accuracy and integrity of the paper content.

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Abbreviations

FSH: follicle-stimulating hormone; LH: luteinizing hormone; BKI: Blatt–Kupperman index; RM: repeated-measure; ERb: estrogen receptor-b; PM: Persian medicine