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To cite this article: F. Shakeri, S. Taavoni, A. Goushegir & H. Haghani (2015) Effectiveness of red clover in alleviating menopausal symptoms: a 12-week randomized, controlled trial, *Climacteric*, 18:4, 568-573, DOI: [10.3109/13697137.2014.999660](https://doi.org/10.3109/13697137.2014.999660)

To link to this article: <http://dx.doi.org/10.3109/13697137.2014.999660>



Accepted author version posted online: 12 Jan 2015.
Published online: 24 Feb 2015.



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Effectiveness of red clover in alleviating menopausal symptoms: a 12-week randomized, controlled trial

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Key words: MENOPAUSE, RED CLOVER, SYMPTOMS

ABSTRACT

Objectives Menopausal women are interested in alternative therapy to alleviate climacteric symptoms. This study aimed to investigate the effect of red clover on the severity of menopausal symptoms.

Methods This randomized, placebo-controlled, clinical trial included 72 healthy postmenopausal women, who were randomly divided into intervention and placebo groups. Women in the intervention group received two capsules containing 40 mg dried leaves of red clover daily for 12 weeks, while those in the control group received two capsules containing 40 mg starch daily for 12 weeks. Outcome measures of this study were menopausal symptoms determined using the Menopause Rating Scale (MRS) at baseline and at the end of the study. Sociodemographic data of the included women were collected using a questionnaire.

Results No significant differences were observed between the two groups with respect to the demographic characteristics and menopausal symptoms before the intervention. At the end of the study, the total score on the MRS decreased from 20.41 to 10.08 in the intervention group and from 20.77 to 17.20 in the control group. This decrease in the total score was attributed to the scores of vegetative somatic and psychological categories of menopausal symptoms. Thus, a remarkable difference was observed in the severity of the menopausal symptoms (95% confidence interval, $p = 0.0001$).

Conclusion These results indicated that, compared to placebo, dried leaves of red clover were more effective in reducing the severity of menopausal symptoms in postmenopausal women.

INTRODUCTION

Menopause refers to permanent cessation of menstruation in women and is characterized by significant hormonal changes¹. Progressive estrogenic deficiency during the menopausal transition leads to the presentation of a wide array of clinical symptoms^{2,3}. Menopausal women not only experience physical and psychosocial changes, but also complain about impairment of libido, sexual satisfaction and urinary problems^{4,5} that can negatively affect their quality of life⁶. Although hormone replacement therapy is an effective treatment for alleviating menopausal symptoms, concerns about the adverse effects of estrogen^{7,8} have led to an increased interest in alternative therapies, such as botanical and dietary supplements (phytoestrogens), for reducing the severity of menopausal

symptoms^{9,10}. Isoflavonoids are the main active substances in phytoestrogens. Compared to estrogens, isoflavones are less effective in alleviating menopausal symptoms; however, their selective binding to estrogen receptors β in the breast and endometrium is an advantage¹⁰. Therefore, isoflavones can have positive effects on various organs (such as the bone, vagina, brain and cardiovascular system), thus reducing the severity of menopausal symptoms without any effects on the uterus and breast. This property of isoflavones distinguishes them from other herbal remedies and makes them an excellent option for alternative hormone therapy^{11–13}. Isoflavones are found in high concentrations in red clover and soy bean. Red clover contains isoflavones such as genistein, daidzein, biochanin A, and formononetin, while soybean only contains two isoflavones (genistein and daidzein)¹⁴. Interest in

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isoflavones obtained from red clover extract is increasing among women and researchers because of their positive effects^{15–17}. Red clover is found in some parts of Iran and is used for preparing home-cooked meals. However, capsules containing red clover isoflavones in a standard compound are not available in Iran. Therefore, the present study aimed to investigate the effect of dried leaves of red clover on menopausal symptoms.

METHODS

Study design and participant selection

This randomized, placebo-controlled, clinical trial included postmenopausal women who visited Abuzar Clinic, a clinic for screening menopausal symptoms in Tehran, to be screened for diabetes mellitus and hypertriglyceridemia between January and September 2012. In addition, all these women experienced menopausal symptoms and were seeking treatment to alleviate these symptoms. In all, 72 postmenopausal women were included in the study by considering a power of 80%, confidence interval of 95% and type-1 error of 5%. This sample size was calculated from a previous study evaluating the efficacy of a herbal drug on menopausal symptoms¹⁷. The study protocol was approved by the Ethics Committee of the Tehran University of Medical Sciences, Tehran, Iran (reference no: 15265).

The study population consisted of 72 postmenopausal women who had naturally entered the menopausal period. The inclusion criteria of the study were age between 50 and 59 years, presence of amenorrhea for at least 12 months, and no history of chronic medical conditions. The exclusion criteria of the study were participation in another study, use of any hormonal treatment, use of medication such as antibiotics or antacids, and body mass index $> 28 \text{ kg/m}^2$. After being informed about the research method and objectives and after obtaining written consent, the women were randomly divided into two groups with 36 women in each group. For randomization, one code was allocated to each participant; each code was written on a piece of paper, enclosed in an envelope and put in a box. Next, the clinic personnel picked two envelopes from the box and the women with corresponding codes were allocated to groups A and B. Women in group A received either two capsules of the active compound (each capsule containing 40 mg dried leaves of red clover) while those in group B received two capsules of placebo (each capsule containing 40 mg starch), of equal appearance and smell, daily for 12 weeks. The capsules given to women in groups A and B were prepared from dried leaves of red clover and starch, respectively in opaque containers labelled as A or B in an Iranian pharmacy factory. Participants, investigator and statistician were blinded to the study groups until the analysis was completed. During the study, only the pharmacist knew the identity of each capsule. All the participants were followed up weekly by telephone and were requested to complete the Menopause Rating Scale (MRS) after completing the treatment.

Menopausal symptoms

Outcome measures in this study were menopausal symptoms obtained using the MRS. The MRS has been developed by Schneider and colleagues¹⁸, Heinemann and colleagues¹⁹, and Potthof and colleagues²⁰ and is used to measure the frequency and severity of aging symptoms and their impact on health-related quality of life. The symptoms assessed in the present study included hot flushes, heart discomfort, sleeping disorders, depressive mood, irritability, anxiety, physical and mental exhaustion, sexual problems, bladder problems, dryness of vagina, and joint and muscular discomfort. Three subcategories can be defined, based on 11 individual diagnostic criteria: (1) vegetative somatic problems (hot flushes, heart discomfort, sleeping disorders and joint and muscular discomfort); (2) psychological symptoms (irritability, anxiety and physical and mental exhaustion); and (3) urogenital symptoms (sexual problems, bladder problems and dryness of the vagina). Each of the 11 symptoms is scored on a scale of 0 (no complaints) to 4 (severe symptoms) depending on its severity, which was perceived by the woman. In Iran, the reliability of the translated MRS was evaluated by Darsareh and colleagues in 2012²⁰. The MRS was completed by all the participants before and at the end of the 12th week of intervention. The reliability of the MRS was calculated using Cronbach's $\alpha = 0.78$, at the end of the study.

The sociodemographic questionnaire included age, time of the last menstrual cycle, age at menarche, number of pregnancies, number of children, and body mass index.

Statistical analysis

All statistical analyses were performed using SPSS statistical software (version 14). Data are presented as mean and standard deviation. The effect of the treatment was assessed by applying a two-sided test with a significance level of 0.05. Student's *t*-test was used to compare the severity of the menopausal symptoms between the two groups after the intervention and demographic data. The MRS is a 5-point Likert scale with 11 ordinal variables. The differences between the two groups with respect to the severity of each ordinal item of urogenital menopausal symptoms after the intervention were analyzed using the Mann–Whitney *U* test.

RESULTS

The MRS was administered to 154 volunteers who visited the clinic during the study period. Overall, 123 menopausal women experienced the menopausal symptoms present in the MRS. After excluding 38 ineligible women, 85 women fulfilled the inclusion criteria and were invited to participate in the study. Of these, 72 women agreed to participate in the study and were randomized into two groups. One participant did not use the capsules in the third month of the study and was not willing to continue the study and answer the

questionnaire; therefore, she was excluded from the study. Thus, 71 participants completed the study (Figure 1).

No statistically significant differences were observed between the two groups with respect to the demographic characteristics at baseline (Table 1). Moreover, the mean menopausal score at baseline did not differ between the two groups (Table 2).

The total score of the MRS decreased from 20.41 ± 6.32 to 10.08 ± 2.28 in the intervention group and from 20.77 ± 6.15 to 17.25 ± 6.59 in the control group. The differences between the two groups were analyzed using Student's *t*-test after the intervention. A significant difference was observed between the two groups concerning the severity of the menopausal symptoms ($p = 0.0001$; Table 2). Reduction in the MRS score of menopausal symptoms can be attributed to the vegetative somatic and psychological dimensions of the menopausal symptoms. Significant improvement was observed in the severity of vaginal dryness ($p = 0.0001$); however, no remarkable decrease was observed in the severity of urogenital symptoms ($p = 0.25$; Table 3).

DISCUSSION

This randomized, triple-blind, placebo-controlled, clinical trial showed that capsules containing dried leaves of red clover substantially decreased the severity of menopausal symptoms. Vasomotor symptoms are the most prevalent and distressing symptoms experienced by menopausal women. These symptoms are usually followed by mood disorders²². These disorders may be important factors associated with diminished desire and have significant negative effects on the quality of life^{23,24}.

Table 1 Homogeneity test for demographic characteristics at baseline. Based on Student's *t*-test

Characteristics	Intervention	Control	<i>p</i> Value
Age (years)	54.92 ± 2.89	54.69 ± 2.73	0.73
Age at menarche (years)	13.81 ± 1.30	13.97 ± 1.68	0.64
Months since last menstrual period	23.42 ± 12.89	20.89 ± 8.39	0.32
Number of pregnancies	6.50 ± 2.68	5.81 ± 1.89	0.20
Number of children	5.42 ± 1.73	5.17 ± 1.74	0.54
Body mass index (kg/m ²)	20.69 ± 1.74	21.58 ± 2.16	0.059

The findings of the present study showed that treatment with dried leaves of red clover for 12 weeks improved the severity of the menopausal symptoms in postmenopausal women. This was in accordance with the result of some recent studies that used other isoflavone compounds of red clover. These studies clearly showed the superiority of red clover supplementation over placebo supplementation for treating vasomotor and menopausal symptoms^{16,25,26} and for reducing the severity of mood disorders, especially anxiety and depressive symptoms²⁷. The effectiveness of Promensil in managing hot flushes was demonstrated in a study by van De Weijer (2002)¹⁷. Although these studies showed significant improvement in the severity of mood disorders, it was unclear whether the effectiveness of red clover was directly associated with the reduction in the somatic symptoms. In our study, the most striking advantage of using red clover was observed with the reduction in the severity of psychological symptoms. It can be hypothesized that this reduction may be mediated by mechanisms other than those mediated by estrogen receptors.

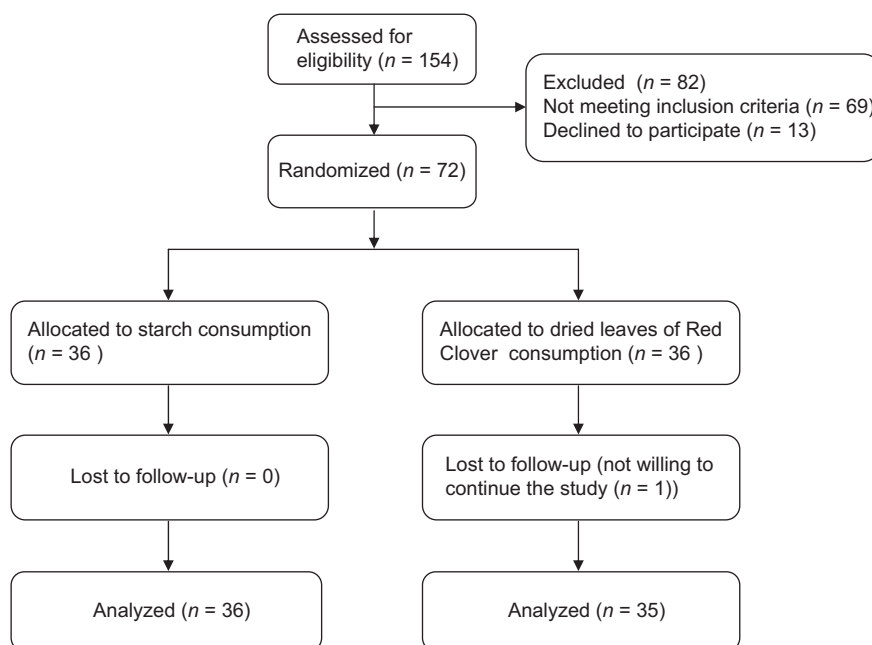


Figure 1 Recruitment flow chart. Of 154 volunteer menopausal women, 72 menopausal women entered the study and 71 of them completed the study

Table 2 Comparison of the severity of menopausal symptoms between the two groups before and after the intervention. Based on Student's *t*-test (between groups)

Menopausal symptoms	Before intervention		After intervention	
	Mean \pm standard deviation	<i>p</i> Value	Mean \pm standard deviation	<i>p</i> Value
<i>Vegetative somatic</i>				
Intervention	7.83 \pm 3.25	0.39	4.66 \pm 1.41	0.002
Control	8.47 \pm 3.06		6.31 \pm 2.66	
<i>Psychological</i>				
Intervention	7.50 \pm 4.24	0.29	2.69 \pm 1.03	0.0001
Control	6.52 \pm 3.61		6.45 \pm 3.20	
<i>Urogenital</i>				
Intervention	5.08 \pm 2.70	0.23	3.38 \pm 1.82	0.25
Control	5.80 \pm 2.44		4.02 \pm 2.79	
<i>Total</i>				
Intervention	20.41 \pm 6.32	0.80	10.08 \pm 2.28	0.0001
Control	20.77 \pm 6.15		17.25 \pm 6.59	

Sleep disturbance followed by vasomotor symptoms can negatively affect mood in menopausal women (Domino effect). Therefore, reduction in these symptoms in turn reduces the severity of mood distress²⁸.

Some studies have shown that red clover has no effect on vasomotor and psychological symptoms^{29,30}. There are differences among the results of these individual studies; moreover, systemic and meta-analyses have provided contradictory results^{12,29–32}. However, it should be noted that these studies have different designs, durations, doses, and inclusion criteria.

In a study by Imhof and colleagues, MF11RCE (a red clover extract) exerted a moderate effect on testosterone level and a positive effect on vaginal cytology in postmenopausal women¹⁵. Red clover also showed remarkable effects on vaginal dryness, dyspareunia, and diminished libido in a study by Hidalgo²⁵. In this study, no significant improvement was observed in the severity of urogenital symptoms. This was consistent with a recent Brazilian study that assessed sexual satisfaction by employing the Glombok Rust Inventory of Sexual Satisfaction³², but was in contrast to some studies that showed the effectiveness of red clover in reducing urogenital symptoms^{16,26}.

The result of our study was similar to that of Hidalgo's study with respect to vaginal dryness; however, the two studies were different considering the effect of red clover on sexual problems. It seems that severity of sexual problems

may decrease with a reduction in the severity of physical and psychological symptoms, because no significant changes were observed in levels of follicle stimulating hormone, luteinizing hormone and 17 β -estradiol in Hidalgo's study²⁶. It should be noted that several known factors other than hormonal changes could contribute to sexual problems^{33–36}.

Isoflavone from red clover was not effective in relieving menopausal discomfort in some studies³². A study by Auerbach used the MRS to evaluate the potential effect of pomegranate seed oil in reducing the severity of menopausal symptoms but did not observe any improvement³⁷. It should be noted that the present study differs from the Brazilian study in terms of scale and amount of red clover isoflavone used for treating climacteric symptoms and from Auerbach's study in terms of the type and amount of isoflavone intake. Moreover, the placebo (sun flower oil) used in this study did not have neutral effects on menopausal symptoms³⁸.

Ehsanpour and colleagues conducted a study in Iran and reported that red clover supplementation did not improve the quality of life of postmenopausal women³⁹. The difference between the two studies can be attributed to the amount of isoflavone intake, scale and cultural differences in different communities, which can affect the quality of life. Moreover, the bioavailability of isoflavones depends on colonic microflora, which metabolize isoflavones into absorbable compounds. Therefore, the bioavailability of isoflavones varies between individuals⁴⁰. Not only in these two studies but also in several other studies, the absorption level of isoflavones was not measured. Therefore, further investigation is recommended to assess the relationship between isoflavones and menopausal symptoms.

In conclusion, the present study showed that capsules containing 40 mg dried leaves of red clover reduced menopausal symptoms. In addition, these capsules did not have any negative side-effects, suggesting that the traditional herbal supplement of red clover can be a suitable alternative for treating menopausal symptoms. This study highlights the need to

Table 3 Comparison of the severity of urogenital symptoms between the two groups after the intervention. Based on the Mann–Whitney *U*-test (between groups)

Urogenital symptoms	Intervention	Control	<i>p</i> Value
Sexual problems	1.00 \pm 0.86	1.40 \pm 1.06	0.09
Bladder problems	0.97 \pm 0.77	1.37 \pm 1.14	0.17
Vaginal dryness	0.78 \pm 0.72	1.71 \pm 1.17	0.0001

conduct further studies to investigate the effects of red clover in decreasing psychological and some urogenital symptoms that are directly associated with a reduction in the somatic symptoms.

The major strength of this study was its randomized design, which has been used for investigating the efficacy of red clover in relieving climacteric symptoms. Moreover, use of the MRS, which was easily completed by women and not by their physicians, was another strength of this study.

ACKNOWLEDGEMENTS

The authors would like to thank all the women who participated in this study. This trial has been registered in the Iranian

Registry of Clinical Trials (IRCTID:IRCT201112172172N13), which is a Primary Registry in the WHO Registry Network that has been set up with the help from the Ministry of Health and Medical Education and hosted by the Tehran University of Medical Sciences.

Conflict of interest The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

Source of funding This study was a part of an MS thesis and was financially supported by the Tehran University of Medical Sciences.

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