Original Article

The effects of red clover on quality of life in post-menopausal women

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Abstract

Background: Due to symptoms and its complications, menopause influences the mental, psychological and physical health, social performance and familial relationships. Because of the undesirable side effects of hormone replacement therapy, tendency and desire toward alternative treatments in relieving menopausal symptoms have increased. Among the alternative therapies are herbs and among those, herbs with phytoestrogens are more preferable. Red clover is a rich source of phytoestrogens. The present study investigated the effect of red clover on quality of life in post-menopausal women.

Materials and Methods: In a randomized, triple-blind, placebo-controlled clinical trial, 72 menopausal women who at least obtained 15 scores in Kupperman Menopausal Index, after two weeks of monitoring, were randomly allocated to receive either placebo or 45 mg of red clover isoflavones for eight weeks. Before the treatment and at the end of the study, menopause-specific quality of life questionnaire (MENQOL) was completed in the two groups.

Findings: A total of 55 women completed the study, 28 subjects in red clover and 27 in placebo group. Mean score of total quality of life ($p < 0.001$ in both groups), mean score of quality of life in vasomotor domain ($p < 0.001$ in both groups), psycho-social domain ($p < 0.001$ in red clover and $p = 0.02$ in placebo group) and physical domain ($p < 0.001$ red clover and $p = 0.01$ placebo group) significantly reduced compared to the baseline values. However, the differences between two groups were significant neither for total quality of life nor for its domains. Red clover had no side effects and all the subjects in the red clover group were satisfied with the prescribed administration

Conclusions: In the present study, the effect of red clover supplementation on menopausal women's quality of life showed no difference with the placebo. Further clinical trials are recommended.

Key words: Menopause, phytoestrogens, quality of life, red clover, symptoms.

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Introduction

The average life expectancy has increased dramatically.[1] Therefore, a woman who enters menopausal period around the age of 50 can be expected to live 30-35 years more, i.e. she will spend approximately one-third of her life after menopause.[2]

However, after menopause, production of estrogen by ovaries is greatly reduced. Therefore, symptoms and diseases caused by estrogen deficiency in this period (vasomotor symptoms, urogenital atrophy, osteoporosis, cardiovascular diseases, cancer, poor cognitive power and sexual problems) are increasingly important in women's health.[3]

Due to symptoms and complications, menopause influences mental, psychological and physical health, social performance and familial relationships. The set of these effects can be placed in a single concept as "quality of life" which is currently one of the major concerns of health professionals and experts. It is identified as an index to measure health status in a population and medical health researches.[4] In fact, quality of life is direct affected by age and intensity of menopausal symptoms.[5] Thus, proper prevention and treatment of menopausal

symptoms have a particular importance.[6]

Menopausal symptoms are conventionally treated with synthetic estrogens.[7] Women around the world have benefited from hormone therapy for alleviation of the climacteric symptoms and prevention of osteoporosis and other age-related conditions.[8] However, long-term compliance with hormone therapy is low and related to several factors including risk-benefit concerns. This regimen has been found to significantly increase the risk for cardiovascular events and breast cancer.[9] These concerns have caused a reduction in the use of hormone replacement therapy for the relief of menopausal symptoms.[10] Among the alternative treatments are herbs among which the herbs with phytoestrogens are more preferable.[7]

Phytoestrogens are weak agonists of estrogens and provide stronger estrogenic effects when the level of estrogens in the body is low. Thus, it might be reasonable to expect these substances to have greater estrogenic properties in menopausal women.[11]

Red clover, as a phytoestrogen, has been studied in other countries. It can probably have desirable effects not only on relieving the menopausal symptoms but also on cardiovascular and skeletal systems.[9] While the aerial parts of this plant are rich in isoflavones,[10] it is a cheap and easily available source for the production of isoflavone-rich food supplementations for women suffering from menopausal complications.[12]

Previous studies have reported red clover as safe and non-toxic in recommended dosages.[13] In addition, it has generally been introduced safe by the US Food and Drug Administration (FDA). Although interactions between this medication and medications containing estrogen, oral contraceptive pills (OCPs) and anticoagulants are theoretically possible due to the synergy of their effects,[14] no reports of such drug interactions are available.[13] For instance, a study investigated the effectiveness and safety of red clover isoflavone dietary supplementation on frequency of hot flashes in menopausal women. It indicated the 12-week consumption of the drug to be safe and to cause a significant reduction of the complication in the treated group.[15]

However, there are controversial results in systematic review articles from randomized clinical trials about the effect of red clover on menopause,[16-19] i.e. some studies confirmed the effectiveness of red clover on improving menopausal symptoms while others believed its effects were similar to placebo. This inconsistency in results suggests the need for further clinical trials.

Moreover, in Iran, despite wide climate diversity and wide variety of red clover,[20] no study has ever been conducted about the effect of this plant on menopause. Therefore, considering the important effects of menopausal symptoms on women's health, this randomized clinical trial investigated the effects of dietary supplementation containing red clover isoflavones on postmenopausal women's quality of life.

Materials And Methods

In a randomized, triple-blind, placebo-controlled clinical trial, data was collected in three phases including at the beginning of the study, and two and ten weeks after the study. The present study was performed in Navab Safavi Health Care Center affiliated to Isfahan University of Medical Sciences, Isfahan, Iran. Menopausal women under the coverage of this center who had the inclusion criteria entered the study. The sample size was calculated as 36 subjects considering 10% sample loss.

To select subjects, first, file numbers of women over 45 years of age were extracted from the family planning unit of the mentioned health care center. Then, the study subjects were determined using regular random sampling. After preparing a list containing the names and phone numbers of women, individuals were called, primary assessment of the inclusion criteria (menopause status and the elapsed time of menopause, diseases, drug consumption and educational level) was performed and persons who were willing to participate in the study were invited to attend the health care center. After more accurate investigation of the inclusion criteria, the subjects were referred to a physician to have their general health checked. Written informed consents were obtained from healthy subjects after providing required explanations.

Inclusion criteria:

Subjects were included if they aged over 45 years, had amenorrhea for more than 12 months and less than 5 years, had a Kupperman index score ≥ 15, were at good general health conditions (confirmed by routine health checkup), had not used medications such as hormone therapy, dietary supplementations, herbal therapy for relieving menopausal symptoms in the six month-period prior to the enrollment, were interested in participation in the study, and were able to give an informed consent (able to read and write).

Exclusion criteria:

Women were excluded if they used drugs that influenced vasomotor symptoms (including veralipride, clonidine, antidepressants, tamoxifen, raloxifen), had been under treatment with anticonvulsants, antidepressants, phenothiazines, benzodiazepines, ergot derivatives, β-blockers, central acting antihypertensive drugs, cholinesterase inhibitor or anticholinergic drugs for at least 3 months. Being a vegetarian, having hormone therapy contraindications, body mass index (BMI) > 25 kg/m^2, having any type of diseases, simultaneous participation in any other clinical trials, disorder in the metabolism or allergy to estrogen or phytoestrogens were also considered as exclusion criteria. Allergy was assessed by asking questions about the history of using OCPs and the incidence of any problems following the consumption of these pills.

In addition, occurrence of any serious events, especially those affecting quality of life and thus confounding the results, 6 months prior to the study was another exclusion criterion.

Likewise, taking drugs that might reduce absorption of isoflavones such as antibiotics (for 6 weeks), proton pump inhibitor antacids during the study, consuming less than 80% of the expected capsules during one month excluded the subjects. In case of any potential health-affecting complication during the study, the subject was referred to a physician and the treatment was conducted.

Data collection tools:

1) Menopause-specific quality of life questionnaire (MENQOL): MENQOL has been widely used in different studies and its validity and reliability have been confirmed.[6] It consists of 29 items divided into 4 domains of vasomotor (3 items), psychosocial (7 items), physical (16 items) and sexual (3 items). All items follow the same format in which the woman is asked whether she had experienced the items. If 'no', the subject would go to the next item while a 'yes' leads her to a 7-point Likert scale ranging from 0 (not at all bothered) to 6 (extremely bothered). For analysis, "no" is scored as 1, and 0 to 6 on the Likert scale are scored as 2 to 8.[21] Finally, the scores of all domains are summed up and the total score of quality of life is calculated for each subject. In this study, if the sexual domain was not answered completely (widowed women), the value was considered as the mean score obtained by the other subjects in the same group.

2) Kupperman menopausal index (KMI): KMI is widely used in Iran and its validity and reliability have been confirmed.[22] This scale was used to assess the eligibility of subjects to participate in this study. It includes eleven of the most common menopausal complications such as hot flushes, paresthesia, insomnia, nervousness, depression, vertigo, weakness, arthralgia/myalgia, headache, palpitation and formication. Each symptom is rated by a scale ranging from 0 to 3 for absent, mild, moderate, and sever complications, respectively.[5]

3) Demographic data questionnaire: The required data of the study was collected through interviews, measurements and observations.

The study medication:

Subjects were treated with capsules containing 45 mg of red clover isoflavones. The placebo pills were the same color and size as the red clover capsules but contained starch powder. All drug manufacturing processes were under the direct supervision of Department of Pharmacognosy and Isfahan Pharmaceutical Sciences Research Center, School of Pharmacy and Pharmaceutical Sciences, Isfahan University of Medical Sciences, Isfahan, Iran.

Study design:

The study protocol was approved by the Research Ethics Committee of Isfahan University of Medical Sciences. After selecting the eligible study subjects, they underwent a primary assessment of health and demographic characteristics. Height and weight were measured and BMI was calculated as weight (kg)/squared height (m^2). In this phase, the subjects were randomly allocated into two groups of receiving red clover and placebo according to the randomization process.

Randomization process:

All the studied medications were encoded by a pharmacist (36 codes related to the red clover and 36 codes for the placebo). Each code was written on a paper and placed in an envelope which was then closed. Related to each code, there was a container with the medication having the code on it. The code and the type of the medication were recorded by the pharmacist. The envelopes and containers were given to the researcher. The researcher distributed the envelopes among the subjects consecutively. Thereafter, the participants brought the envelopes on the visit at the end of the second week. The envelopes were opened and according to the code inside them, individuals received the related medication. Through this procedure, the subjects were randomly divided into two groups in a double-blind method, i.e. 36 subjects received red clover and 36 received placebo. The medication code related to each subject was recorded in a list by the researcher.

The appearance of the capsules (size and color), their containers and packing were the same. Neither the study subjects nor the researcher were aware of the content of the capsules. Only the pharmacist knew about the codes. The type of medication was revealed when the data related to the last participant was analyzed.

Intervention technique

The first two weeks of the study were the observation phase. At the end of the second week, the study subjects referred to the health care center. During their visit, MENQOL was completed by the researcher through interviewing and the total score was determined. The related medication containers were delivered to the subjects according to the codes inside the envelopes which they had been given in the first visit.

All study subjects consumed one capsule daily for eight weeks with their breakfast. Furthermore, the subjects were asked to bring the container at the final visit so that the number of the remained capsules could be counted by one of the health care center staff members who was not informed about the study process. The study subjects were explained to avoid supplements containing soy more than once a week.

During the medication intake phase, i.e. from the end of the second week to the end of the tenth week, the study subjects were phone called weekly and reminded about regular drug intake. Besides, the researcher's phone number was given to the study subjects. In the final visit at the end of the tenth week, MENQOL was recompleted by the researcher through interviewing and its score was calculated.

Statistical analysis

Considering the triple-blind design of the study, for statistical analysis, the pharmacist classified the codes into A and B in terms of the drug type (red clover or placebo). The data were entered into SPSS. Comparisons between groups were performed and data was analyzed based on groups A and B. At the end of data analysis, the codes were broken.

The confidence interval was 95% and p values < 0.05 were considered as statistically significant. Student-t and paired-t tests were used for inter-group and intra-group comparisons of quality of life scores, respectively. For determining the similarity of the two groups in terms of demographic characteristics, student-t, chi-square and Mann-Whitney tests were used. Data analysis was performed using SPSS18. Data was expressed as mean (SD).

Findings

Sampling process started at mid-November 2010 and finished at mid-April 2011. At the beginning, 72 eligible menopausal women were allocated into two groups of red clover (n = 36) and placebo (n = 36). Seventeen subjects were excluded from the study. In the red clover group 8 subjects declined to participate, 4 due to their husbands' dissatisfaction from drug consumption and attending the study, 2 due to unwillingness to continue and 2 with no special reasons. In the placebo group, on the other hand, 9 subjects were excluded, 1 due to her husband's dissatisfaction to continue the study, 2 due to lack of regular drug consumption, 1 due to going abroad and unavailability, 3 due to unwillingness to continue and 2 with no special reasons. Finally, a total of 55 women (28 in the red clover and 27 in the placebo group) completed the study and the obtained data was analyzed.

Samples characteristics

Mean age of the subjects was 52.96 (3.07) in the red clover and 53.92 (3.21) years in the placebo group. Elapsed time since menopause in the red clover and placebo groups were 2.66 (1.65) and 2.69 (1.47) years, respectively. Mean age of menopause in the red clover and placebo groups were 50.05 (1.17) and 51.38 (2.63) years, respectively. The numbers of children in the red clover and placebo groups were 1.93 (1.36) and 1.85 (1.63), respectively. BMI in the red clover and placebo groups were 21.09 (2.23) and 21.96 (1.87) kg/m2, respectively. The majority of subjects in the red clover group (89.3%) and in the placebo group (81.5%) were married. Housewives constituted 92.8% and 92.6% of the red clover placebo groups, respectively. Most of the participants in the red clover group (27 subjects; 96.4%) and the placebo group (26 subjects; 96.3%) were high school graduates or had lower education. There were no significant differences between the groups in terms of demographic characteristics.

At the end of the second week, there was no difference between the groups in mean score of total quality of life and both groups were matched ($p = 0.14$). Paired t-test showed a significant reduction in mean score of total quality of life at the end of the tenth week in both groups (red clover: $p < 0.01$ and placebo: $p < 0.01$), i.e. both the red clover and placebo had a significant effect on improving the total quality of life. However, the difference in mean scores of total quality of life was not significant between the groups ($p = 0.75$).

At the end of the second week, there was no difference between the groups in mean scores of quality of life in

vasomotor domain and the groups were matched ($p = 0.06$). However, mean scores of quality of life in vasomotor domain significantly reduced at the end of the tenth week in both groups ($p < 0.01$ for both). At the end of the study, mean scores of quality of life in this domain did not differ between the groups ($p = 0.83$), i.e. the effects of red clover and placebo on improvement of quality of life in this domain had been similar.

At the end of the second week, there was no difference in mean scores of quality of life in psychosocial domain between the groups ($p = 0.55$). At the end of the tenth week, mean scores of quality of life in both groups significantly reduced (in the red clover group: $p < 0.01$ and in the placebo group: $p = 0.02$). However, there was no significant difference in mean scores of quality of life in psychosocial domain between the groups ($p = 0.90$).

At the end of the second week, there was no difference in mean scores of quality of life in physical domain between the groups ($p = 0.32$) while at the end of the tenth week, a significant difference in mean scores of quality of life in this domain in each of the groups (red clover: $p < 0.01$ and placebo: $p = 0.01$) was observed but the two groups were not significantly different ($p = 0.10$). In other words, red clover and placebo had similar effects on improvement of physical quality of life.

At the end of the second week, the two groups had no significant difference in sexual domain ($p = 0.46$). According to paired t-test, insignificant reductions in mean scores of quality of life in sexual domain were detected in both groups at the end of the tenth week (red clover: $p = 0.12$ and placebo: $p = 0.11$). In addition, the two groups were not significantly different in sexual domain ($p = 0.12$) at the end of the tenth week, i.e. the effect of red clover had been similar to placebo in improving quality of life in sexual domain (Table 1).

Discussion

In the present study, at the end of the tenth week, women's quality of life improved in both groups. Mean score of total quality of life, obtained by adding total scores of all domains, indicates the status of quality of life related with experiences and complications of menopause and specifically reflects the aspects of these experiences which had undesirable effects on women.[21]

Abed Zadeh et al. reported menopausal women's quality of life as moderate and announced that menopause to have a negative effect on women's quality of life.[4] However, another study in Tehran indicated that most menopausal women had a proper quality of life.[23]

The difference between quality of life in the present study and other studies could be due to cultural, social and economical differences in different communities which can affect individuals' quality of life. Moreover, in our study, women were selected if they suffered from menopausal symptoms which had negative effects on their quality of life.

We found improvements in women's quality of life at the end of the 10th week in comparison with the second week. Similarly, available studies about hormonal interventions in menopause also indicated that the methods and strategies which minimize estrogens deficiency may lead to improvement in women's quality of life.[23]

Domino effect can also be considered since vasomotor symptoms can cause psychological distress and eliminating these symptoms can improve sleeping and cause more comfort among women.[24] Some prospective, cross-sectional, double-blind trials also indicated a great deal of improvements in symptoms as a result of estrogen therapy due to relief from hot flashes.[25]

It should be noted that a change in overall status of quality of life is a longitudinal process. Therefore, the duration of drug consumption in this study might not have been long enough to make significant changes in comparison with placebo. However, Geller et al. (2009) studied the subjects for 12 months and reported the difference in total scores of quality of life not to be significant between the groups.[9] Likewise, in a study by

Table 1: Scores of quality of life in the study subjects of both groups before and after the intervention

	Red clover group			placebo group		
	Baseline	At the end of the study	P*	Baseline	At the end of the study	P*
Vasomotor Domain	15.29 (3.75)	7.89 (3.32)	< 0.01	13.33 (3.83)	8.11 (4.01)	< 0.01
Psychosocial Domain	28.11 (7.32)	23.93 (7.0)	< 0.01	26.92 (7.33)	23.67 (7.73)	0.02
physical Domain	53.43 (13.19)	44.36 (12.24)	< 0.01	49.96 (12.31)	44.37 (12.55)	0.01
Sexual Domain	12.75 (4.76)	12.14 (4.85)	0.12	14.41 (6.16)	12.70 (5.89)	0.11
Total QOL	109.57 (18.48)	83.11 (18.52)	< 0.01	102.00 (19.09)	81.44 (20.03)	< 0.01

*P value for inter-group comparisons
Values are represented as mean (SD).

Lewis et al., phytoestrogens had no significant effect on quality of life among menopausal women compared to the placebo.[26]

The findings of the present study in vasomotor domain were also confirmed by Tice et al. who found significant improvements in vasomotor domain in both the red clover and placebo groups. However, there was no difference between the studied groups.[27]

One of the reasons causing the effectiveness of placebo in vasomotor domain was the role of psychological factors involved in exacerbating hot flashes. Anxiety and stress cause hot flashes through releasing small amounts of serotonin, which regulates body temperature threshold.[1] These psychological factors are sensitive to the placebo effect and respond to it.

Similar to the present study, Tice et al. reported a significant improvement in psychosocial and physical domains in all study groups after treatment for 12 weeks. However, there was no significant difference between the groups.[27] In another study by Geller et al., there was no difference between the groups in anxiety domain at the third month of treatment, but at the end of the study, the difference was significant.[9]

In the present study, at the end of the tenth week, there was no difference between the groups in sexual domain. This finding was in accordance with Tice et al. who did not observe a significant difference in sexual domain between the study groups at the end of their study. Sexual issues are an important part of health and well-being among women of all the ages. They have a complicated nature and are affected by many biological, psychological, social and cultural factors.[28] It seems that reduction in sexual activity as well as quality of life in sexual domain in menopausal women is more influenced by the individuals' culture and the behavioral pattern than by physiology or hormones status following the menopause.[25] The major effective factor on sexual relationship during menopause and post-menopause is sexual relationship pattern in reproductive years. Creating an appropriate pattern during reproductive ages would result in a continued sexual relationship in menopause and post-menopausal periods. Besides, male sexual problems caused by aging should also be considered.[29]

At the end of the present study, almost the majority of the subjects announced that they had no sexual activity during the study which could be attributable to the inefficiency of the treatment in the study groups in different studies as well as the present study.

Conclusion

Generally, the present study showed that red clover supplementation had a desirable effect on menopausal women's quality of life. However, the effects showed no difference with placebo. Therefore, further clinical trials are recommended in this regard. Moreover, red clover had no side effects and was safe and all the study subjects in the red clover group were satisfied with the prescribed medication.

Study limitations

Differences in isoflavones bioavailability in different people, due to several reasons such as the amount of estrogen receptors in different cells, gastrointestinal flora, the ratio of fat/carbohydrate diet etc. were beyond the control of the researchers and were the limitations of the present study.

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