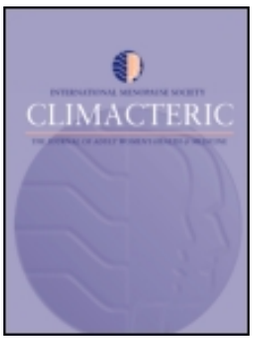

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Effectiveness of red clover in alleviating menopausal symptoms: a 12-week randomized, controlled trial

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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 changes[1]. 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 life[6]. 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 advantage[10]. 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 symptoms[17]. 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 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 colleagues[18], Heinemann and colleagues[19], and Potthof and colleagues[20] 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 2012[20]. 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).

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

Characteristics	*Intervention*	*Control*	*p 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

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 disorders[22]. These disorders may be important factors associated with diminished desire and have significant negative effects on the quality of life[23,24].

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 symptoms[27]. 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.

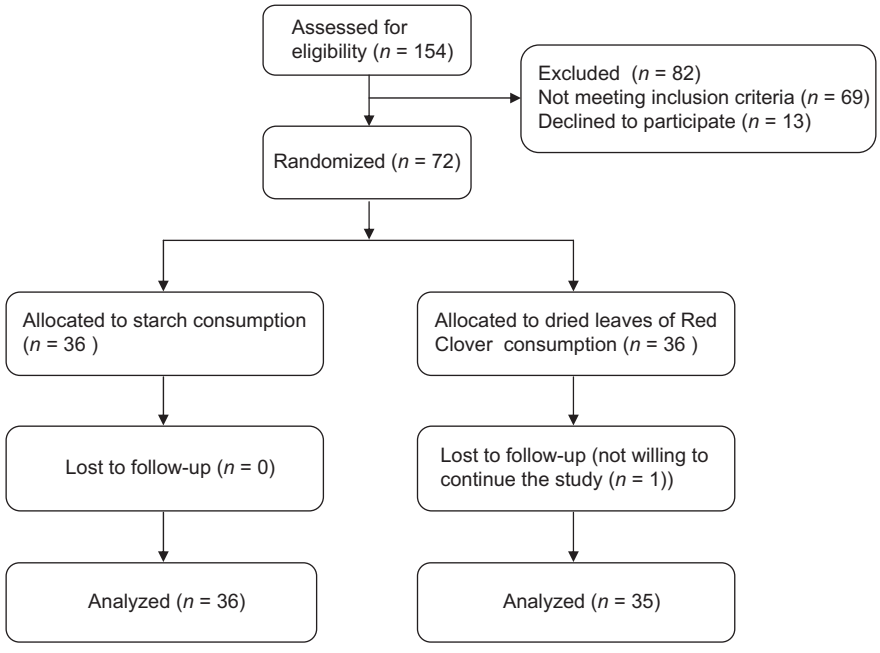

Figure 1 Recruitment flow chart. Of 154 volunteer menopausal women, 72 menopausal women entered the study and 71 of them completed the study

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)

	Before intervention		*After intervention*	
Menopausal symptoms	*Mean ± standard deviation*	*p Value*	*Mean ± standard deviation*	*p Value*
Vegetative somatic				
Intervention	7.83 ± 3.25	0.39	4.66 ± 1.41	0.002
Control	8.47 ± 3.06		6.31 ± 2.66	
Psychological				
Intervention	7.50 ± 4.24	0.29	2.69 ± 1.03	0.0001
Control	6.52 ± 3.61		6.45 ± 3.20	
Urogenital				
Intervention	5.08 ± 2.70	0.23	3.38 ± 1.82	0.25
Control	5.80 ± 2.44		4.02 ± 2.79	
Total				
Intervention	20.41 ± 6.32	0.80	10.08 ± 2.28	0.0001
Control	20.77 ± 6.15		17.25 ± 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 distress[28].

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 women[15]. Red clover also showed remarkable effects on vaginal dryness, dyspareunia, and diminished libido in a study by Hidalgo[25]. 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 Satisfaction[32], 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 17β-estradiol in Hidalgo's study[26]. It should be noted that several known factors other than hormonal changes could contribute to sexual problems[33–36].

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*	*p Value*
Sexual problems	1.00 ± 0.86	1.40 ± 1.06	0.09
Bladder problems	0.97 ± 0.77	1.37 ± 1.14	0.17
Vaginal dryness	0.78 ± 0.72	1.71 ± 1.17	0.0001

Isoflavone from red clover was not effective in relieving menopausal discomfort in some studies[32]. 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 improvement[37]. 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 symptoms[38].

Ehsanpour and colleagues conducted a study in Iran and reported that red clover supplementation did not improve the quality of life of postmenopausal women[39]. 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 bioavailabilty of isoflavones varies between individuals[40]. 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

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.

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

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References

1. Buckler H. The menopause transition: endocrine changes and clinical symptoms. *J Br Menopause Soc* 2005;11:61–5
2. Burger HG, Dudley EC, Robertson DM, Dennerstein L. Hormonal changes in the menopause transition. *Recent Prog Horm Res* 2002;57:257–75
3. Chuni N, Sreeramareddy CT. Frequency of symptoms, determinants of severe symptoms, validity of and cut-off score for Menopause Rating Scale (MRS) as a screening tool: A cross-sectional survey among midlife Nepalese women. *BMC Women's Health* 2011;11:2–9
4. Barentsen R, van de Weijer PH, Gend Sv, Foekema H. Climacteric symptoms in a representative Dutch population sample as measured with the Greene Climacteric Scale. *Maturitas* 2001;38: 123–8
5. Utian WH. Psychosocial and socioeconomic burden of vasomotor symptoms in menopause: A comprehensive review. *Health Qual Life Outcomes* 2005;3:47
6. MacLennan A, Lester S, Moore V. Oral estrogen replacement therapy versus placebo for hot flushes: a systematic review. *Climacteric* 2001;4:58–74
7. Sweetland S, Beral V, Balkwill A, *et al.* Venous thromboembolism risk in relation to use of different types of postmenopausal hormone therapy in a large prospective study. *J Thromb Haemost* 2012;10:2277–86
8. Thunell L, Milsom I, Schmidt J, Mattsson LA. Scientific evidence changes prescribing practice – a comparison of the management of the climacteric and use of hormone replacement therapy among Swedish gynaecologists in 1996 and 2003. *BJOG* 2006;113: 15–20
9. Hammar ML, van de Weijer PH, Franke HR, Pornel B, von Mauw EM, Nijland EA. Tibolone and low-dose continuous combined hormone treatment: vaginal bleeding pattern, efficacy and tolerability. *BJOG* 2007;114:1522–9
10. Dornstauder E, Jisa E, Unterrieder I, Krenn L, Kubelka W, Jungbauer A. Estrogenic activity of two standardized red clover extracts (Menoflavon®) intended for large scale use in hormone replacement therapy. *J Steroid Biochem Mol Biol* 2001;78: 67–75
11. Roudsari AH, Tahbaz F, Hossein-Nezhad A, Arjmandi B, Larijani B, Kimiagar SM. Assessment of soy phytoestrogens' effects on bone turnover indicators in menopausal women with osteopenia in Iran: a before and after clinical trial. *Nutr J* 2005;4:30
12. Booth NL, Piersen CE, Banuvar S, Geller SE, Shulman LP, Farnsworth NR. Clinical studies of red clover (Trifolium pratense) dietary supplements in menopause: a literature review. *Menopause* 2006;13:251–64
13. Messina MJ, Wood CE. Soy isoflavones, estrogen therapy, and breast cancer risk: analysis and commentary. *Nutr J* 2008;7:17
14. Ewies AA. Phytoestrogens in the management of the menopause: up-to-date. *Obstet Gynecol Surv* 2002;75:306–13
15. Imhof M, Gocan A, Reithmayr F, *et al.* Effects of a red clover extract (MF11RCE) on endometrium and sex hormones in postmenopausal women. *Maturitas* 2006;55:76–81
16. Lipovac M, Chedraui P, Gruenhut C, *et al.* The effect of red clover isoflavone supplementation over vasomotor and menopausal symptoms in postmenopausal women. *Gynecol Endocrinol* 2011;28:203–7
17. van de Weijer PH, Barentsen R. Isoflavones from red clover (Promensil) significantly reduce menopausal hot flush symptoms compared with placebo. *Maturitas* 2002;42:187–93
18. Schneider H, Heinemann L, Rosemeier HP, Potthoff P, Behre HM. The Menopause Rating Scale (MRS): reliability of scores of menopausal complaints. *Climacteric* 2000;3:59–64
19. Heinemann K, Ruebig A, Potthoff P, *et al.* The Menopause Rating Scale (MRS): a methodological review. *Health Qual Life Outcomes* 2004;2:45
20. Potthoff P, Heinemann LA, Schneider HP, Rosemeier HP, Hauser GA. The Menopause Rating Scale (MRS II): methodological standardization in the German population [in German]. *Zentralbl Gynakol* 2000;122:280–6
21. Darsareh F, Taavoni S, Joolaee S, Haghani H. Effect of aromatherapy massage on menopausal symptoms: a randomized placebo-controlled clinical trial. *Menopause* 2012;19:995–9
22. Hunter MS, Gentry-Maharaj A, Ryan A, *et al.* Prevalence, frequency and problem rating of hot flushes persist in older postmenopausal women: impact of age, body mass index, hysterectomy, hormone therapy use, lifestyle and mood in a cross-sectional cohort study of 10 418 British women aged 54–65. *BJOG* 2012;119:40–50
23. Reed SD, Newton KM, LaCroix AZ, Grothaus LC, Ehrlich K. Night sweats, sleep disturbance, and depression associated with

diminished libido in late menopausal transition and early postmenopause: Baseline data from the Herbal Alternatives for Menopause Trial (HALT). *Am J Obstet Gynecol* 2007;196:593.e1–7
24. Waidyasekera H, Wijewardena K, Lindmark G, Naessen T. Menopausal symptoms and quality of life during the menopausal transition in Sri Lankan women. *Menopause* 2009;16:164–70
25. Hidalgo LA, Chedraui PA, Morocho N, Ross S, San Miguel G. The effect of red clover isoflavones on menopausal symptoms, lipids and vaginal cytology in menopausal women: A randomized, double-blind, placebo-controlled study. *Gynecol Endocrinol* 2005;21:257–64
26. Lipovac M, Chedraui P, Gruenhutc C, Gocanc A, Stammler M, Imhof M. Improvement of postmenopausal depressive and anxiety symptoms after treatment with isoflavones derived from red clover extracts. *Maturitas* 2010;65:258–61
27. Coon JT, Pittler MH, Ernst E. Trifolium pratense isoflavones in the treatment of menopausal hot flushes: A systematic review and meta-analysis. *Phytomedicine* 2007;14:153–9
28. Burleson MH, Todd M, Trevathan WR. Daily vasomotor symptoms, sleep problems, and mood: using daily data to evaluate the domino hypothesis in middle-aged women. *Menopause* 2010;17:87–95
29. Chen MN, Lin CC, Liu C. Efficacy of phytoestrogens for menopausal symptoms: a meta-analysis and systematic review. *Climacteric* 2014 Dec 1. Epub ahead of press
30. Lethaby A, Marjoribanks J, Kronenberg F, Roberts H, Eden J, Brown J. Phytoestrogens for vasomotor menopausal symptoms. *Cochrane Database Syst Rev* 2013 Dec 10;12:CD001395
31. Geller SE, Studee L. Soy and red clover for midlife and aging. *Climacteric* 2006;9:245–63
32. del Giorno C, Fonseca AM, Bagnoli VR, Assis JS, Soares JM Jr, Baracat EC. Effects of Trifolium pratense on climacteric and sexual symptoms in postmenopausal women. *Rev Assoc Med Bras* 2010;56:558–62
33. Avis NE, Stellato R, Crawford S, Johannes C, Longcope C. Is there an association between menopause status and sexual functioning? *Menopause* 2000;7:297–309
34. Avis NE, Zhao X, Johannes CB, Ory M, Brockwell S, Greendale GA. Correlates of sexual function among multi-ethnic middle-aged women: results from the Study of Women's Health Across the Nation (SWAN). *Menopause* 2005;12:385–98
35. Dennerstein L, Dudley E, Burger H. Are changes in sexual functioning during midlife due to aging or menopause? *Fertil Steril* 2001;74:456–60
36. Gracia CR, Freeman EW, Sammel MD, Lin H, Mogul M. Hormones and sexuality during transition to menopause. *Obstet Gynecol* 2007;109:831–40
37. Auerbach L, Rakus J, Bauer C, *et al*. Pomegranate seed oil in women with menopausal symptoms: a prospective randomized, placebo-controlled, double-blinded trial. *Menopause* 2012;19:426–32
38. Rodenas S, Rodrıguez-Gil S, Merinero MC, Sanchez-Muniz FJ. Dietary exchange of an olive oil and sunflower oil blend for extra virgin olive oil decreases the estimate cardiovascular risk and LDL and apolipoprotein AII concentrations in postmenopausal women. *J Am Coll Nutr* 2005;24:361–9
39. Ehsanpour S, Salehi K, Zolfaghari B, Bakhtiari S. The effect of red clover on quality of life in post menopausal women. *Iran J Nurs Midwifery Res* 2012;17:34–40
40. Xu X, Keecha S, Harris KS, Wang HJ, Murphy PA, Hendrich S. Bioavailability of soybean isoflavones depends upon gut microflora in women. *J Nutr* 1995;125:2307–15