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Effect of *Foeniculum vulgare* Mill. (fennel) on menopausal symptoms in postmenopausal women: a randomized, triple-blind, placebo-controlled trial

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Abstract

Objective: Preliminary data suggest that *Foeniculum vulgare* (fennel) can be an effective treatment for menopausal symptoms. This trial was designed to assess the efficacy of fennel in the management of menopausal symptoms in postmenopausal women.

Methods: In this triple-blind, placebo-controlled trial, 90 postmenopausal women aged 45 to 60 years in Tehran were randomly assigned to treatment (n = 45) or placebo (n = 45) groups. The participants received 8 weeks of treatment with soft capsules containing 100 mg fennel or a placebo (2 per day for each group). The participants were followed for 2 weeks postintervention to assess the continuance of the effect of intervention. The Menopause Rating Scale (MRS) questionnaire was used to assess changes in menopausal symptoms at baseline and at 4, 8, and 10 weeks after onset of intervention.

Results: The groups recorded similar mean scores on the MRS questionnaire before intervention. After intervention, the treatment group showed a significant decrease in the mean MRS score. The results of the Friedman test showed significant differences between the mean score at baseline and those at 4, 8, and 10 weeks after onset of intervention in the treatment group ($P < 0.001$), whereas there were no significant differences in the placebo group. When the fennel and the placebo groups were compared, the independent *t* test showed significant differences in mean scores between groups at 4, 8, and 10 weeks (2 weeks postintervention; $P < 0.001$).

Conclusions: Fennel is an effective and safe treatment to reduce menopausal symptoms in postmenopausal women without serious side effects. More clinical trials with larger populations are required to confirm this result.

Key Words: Fennel – *Foeniculum vulgare* – Menopause Rating Scale – Menopausal symptoms.

Menopause is the period in the life of an adult woman in which the ovaries gradually become inactive and menstruation ceases.[1] The average age of US women at menopause is 51 years[2]; however, in some countries, the age of menopause is lower. For example, the average age of menopause for Indian women is 46.2 years[3] and for Iranian women is 48.2 years.[4,5] Most women will spend more than one-third of their lives in a postmenopausal period.[2-5] The aging of the global population means that millions of women worldwide enter menopause every year. Although some women have few problems, three out of four will experience symptoms resulting from changes in estrogen and progesterone levels during this time. One in four will experience major symptoms that can affect quality of life.[6,7]

The postmenopausal symptoms can be vasomotor, urogenital, and psychological.[1,2,7] Research has shown that the most prevalent complaints reported by postmenopausal women are joint and muscular discomfort, physical and mental exhaustion, sleeping problems, hot flashes, sweating, irritability, dryness of the vagina, anxiety, and depression.[8-10] Hormone therapy (HT) with estrogen and progesterone can improve these symptoms, but can lead to serious side effects such as breast and endometrial cancer and cardiovascular disease.[2,11,12] Globally, women have turned to complementary and alternative medicine (CAM) for relief of their menopausal symptoms. The most popular CAM modality is herbal medicine (especially phytoestrogens and evening

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Author contributions: F.R. had designed and managed the study. P.G. conducted the study and wrote the paper. R.R. had a role in traditional and herbal medicine counseling, handled pharmaceutical part of project and edited the manuscript. R.B. handled pharmaceutical part of project. A.M. analyzed data.

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primrose oil).[13-15] Phytoestrogens and a phytoestrogenic diet can help prevent and treat menopausal symptoms such as skin aging, osteoporosis, cancer, cardiovascular disease, vaginal atrophy, sleep disturbances, and cognitive disorders.[16-18]

Foeniculum vulgare Mill., commonly known as fennel, is a medicinal plant from the family Umbelliferae that is used all over the world. Fennel fruit contains essential oils that are mainly composed of trans-anethole, fenchone, and estragole. The fruit also contains phenolic compounds including flavonoids (flavonoid glycoside and flavonoid aglycon), phenolic acid, hydroxycinnamic acid, coumarin, and tannin.[19] Fennel fruit has phytoestrogenic properties and has been effective for increasing breast milk,[20] improving premenstrual symptoms,[21] decreasing climacteric symptoms in men, increasing libido,[22] and improving menopausal symptoms and sexual activity in postmenopausal women.[23,24] Few clinical studies have examined the effect of fennel on menopausal symptoms. This study was designed to evaluate the effects of an herbal preparation made from fennel on the menopausal symptoms of postmenopausal women.

METHODS

Study design

This study was a randomized, triple-blind, placebo-controlled clinical trial that was approved by the Ethics Committee of Tehran University of Medical Sciences and has been registered in the Iranian Registry of Clinical Trials (code: IRCT2016050827788N1). The aim of this study was to determine the effects of fennel on menopausal symptoms in postmenopausal women.

Participants

This study follows similar previous studies on the effect of phytoestrogens on menopausal symptoms which hypothesized $P_0 = 50\%$ (ratio of severe menopausal symptoms) and projected a decrease in symptoms of 20% ($P_1 = 20\%$) after intervention. Assuming $\alpha = 0.05$ (confidence interval [CI] = 95%) and $\beta = 0.2$ (statistical power = 80%), with the use of the following theorem, a total of 40 participants was calculated for each group. To accommodate possible withdrawal of participants during the study, 45 participants were enrolled in each group.

$$n = \frac{2 \times (Z_{1-\alpha/2} + Z_{1-\beta})^2 \times pq}{(P0 - P1)^2}$$

$$= \frac{2 \times (1.96 + 0.842)^2 \times 0.35 \times 0.65}{(0.5 - 0.2)^2} = 40$$

$$\left(P = \frac{P0 + P1}{2} = 0.35 \rightarrow q = 0.65\right)$$

The participants were selected from women referred to the Farmanfarmayian Public Health Center affiliated with Tehran University of Medical Sciences in Tehran, Iran, in 2016. This center was selected because it had the highest number of postmenopausal women referred for testing of blood sugar, lipids, and blood pressure. The inclusion criteria were women aged 45 to 60 years who were married and in the first 1 to 5 years of the postmenopausal period (a woman was defined as postmenopausal beginning 1 year after her last menstrual period).[25] They had to achieve a minimum score of 9 on the Menopause Rating Scale (MRS) questionnaire (medium severity of menopausal symptoms) and also had to have a negative history of physical or psychological disease, HT, CAM for menopausal symptoms, allergies to herbal medicine, sedative or antidepressant drug use, addiction, and smoking. The participants were required to be able to read and write. Exclusion criteria were allergies to fennel/placebo during the intervention, worsening of symptoms during the intervention, poor cooperation, failure to use fennel/placebo for a total of 6 days,[26] and use of other remedies for menopausal symptoms during the study.

Randomization

After approval and registration of the proposed study plan by the Ethics Committee of Tehran University of Medical Sciences, the study sample of 90 women was selected. The randomization method was the use of random numbers as implemented on the Randomizer website (www.randomizer.org). A set of 45 random numbers between 1 and 90 was generated by the site and assigned to group A. The remaining numbers between 1 and 90 were assigned to group B. Using the numbers allocated to each group, the participants were divided into the A and B groups (each with 45 participants). This randomly generated two groups of 45 women.

Intervention

The soft fennel and placebo capsules were produced by Barij Essence Pharmaceutical Company (Iran). The essential oil was derived from fennel fruits using steam distillation, and the fennel essential oil (FEO) was formulated into soft capsules. Each 100 mg soft capsule contained 30% FEO (71-90 mg anethole) and 0.02% butylated hydroxytoluene, combined with qs to 100% wt/wt with sunflower oil. There was no difference between the fennel and placebo capsules in terms of color, odor, shape, and size, but the placebo capsules were fully filled with sunflower oil. The study was triple-blind such that the participants, investigators, and the person analyzing the data were blind. Women in the intervention group received two soft capsules containing 100 mg of fennel daily for 8 weeks, whereas those in the placebo group received two soft capsules containing 100 mg of sunflower oil daily for 8 weeks. None of the participants in either group engaged in other interventions during the study.

Outcome measures

Sociodemographic data of the women participating in the study were collected by questionnaire. The menopausal symptoms were assessed as total symptoms, somatovegetative symptoms (hot flashes, heart discomfort, sleep problems, and joint or muscular discomfort), psychological symptoms (depression, irritability, anxiety, and physical or mental exhaustion), and urogenital symptoms (sexual dysfunction,

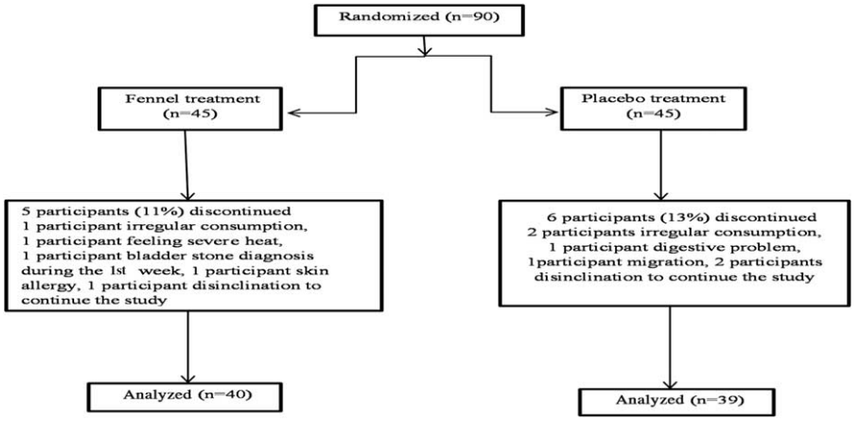

FIG. 1. Consolidated standards of reporting trials diagram reflecting flow of participants through the study.

bladder problems, and vaginal dryness) using the MRS questionnaire at baseline and at weeks 4, 8, and 10 of the study. The MRS is a standardized and formally validated scale that is used worldwide to measure the severity of 11 symptoms associated with menopause and to assess health-related quality of life of menopausal women.[27,28]

At the onset of the study and after completing the demographic and MRS questionnaires, the soft capsules for the first 4 weeks of intervention and a checklist to record daily capsule consumption were given to the participants. At the end of the first 4 weeks, a second meeting was set in which the participants handed in the first checklist, completed the second MRS questionnaire, and received the capsules and checklist for the second 4 weeks. At the end of the second phase, women participated in the third meeting, again completing the MRS questionnaire and the second checklist was handed in. At completion of 8 weeks of intervention, no further capsules or checklists were provided, but participants again completed the MRS questionnaire at 10 weeks (10 weeks after the onset of intervention).

One researcher called participants weekly to ask about capsule consumption and possible side effects. Participants were provided with the researcher's phone number should any questions or problems arise.

Statistical analysis

The data were analyzed using SPSS software (version 22). Participants who did not complete the trial were not included in the statistical analysis. The independent *t* test was used to compare the means between groups, and the Friedman test was used to compare the means of total scores before and after treatment. Demographic and clinical characteristics were analyzed using Fisher's exact test, and an α value of 0.05 was considered statistically significant.

RESULTS

In all, 40 women in the intervention and 39 women in the placebo group completed the study (Fig. 1). No serious adverse events were recorded during or after the intervention. The minor side effects were one case of allergic reaction and one case of feeling severe heat in the intervention group and one case of digestive problems in the control group. The epidemiological and clinical characteristics of age, menopausal age, number of pregnancies, number of children, body mass index (BMI), education, occupation, and economic status were similar in both groups and there were no significant differences between groups (Table 1).

In the intervention group, the mean MRS score was 20.02 ± 6.18 at baseline, which decreased to 11.20 ± 4.92 at week 4, 9.35 ± 4.54 at week 8, and 13.05 ± 4.94 at week 10. There was a significant statistical difference between the scores at baseline and weeks 4, 8, and 10 ($P < 0.001$; Table 2). In the control group, the mean MRS score was 20.37 ± 5.51 at baseline, which decreased to 19.23 ± 5.42 at week 4, 18.58 ± 6.11 at week 8, and 19.20 ± 5.97 at week 10. There were no significant differences between scores at baseline and at weeks 4, 8, and 10 ($P = 0.402$; Table 2) in the control group. When the fennel and the placebo groups were compared, there was no significant difference in mean MRS score at baseline

TABLE 1. *Demographic and clinical characteristics of menopausal women and their comparisons in two studied groups*

Group characteristic	*Foeniculum vulgare* (n = 40)	Placebo (n = 39)	*P*
Age (mean ± SD)	52.33 ± 3.12	51.91 ± 3.72	0.563
Menopausal age (mean ± SD)	49.20 ± 2.69	48.22 ± 3.22	0.122
Number of pregnancies (mean ± SD)	3.18 ± 1.41	3.11 ± 1.265	0.815
Number of children (mean ± SD)	3.07 ± 1.38	2.84 ± 1.04	0.393
BMI (mean ± SD)	28.33 ± 3.47	27.14 ± 4.87	0.073
Education status			
Primary or guidance school (%)	57.8	55.5	
High school or diploma (%)	37.8	35.6	0.797
Academic (%)	4.4	8.9	
Job status			
Homemaker (%)	97.8	95.6	1
Employed (%)	2.2	4.4	
Economic status			
Low (%)	11.1	11.1	
Middle (%)	75.6	84.5	0.376
High (%)	13.3	4.4	

BMI, body mass index; SD, standard deviation.

TABLE 2. *Comparison of total score of Menopause Rating Scale (MRS) questionnaire between the two groups in four different periods of treatment*

	Before intervention		4 weeks after intervention		8 weeks after intervention		10 weeks after intervention (2 weeks after cutting the intervention)		
Group	Mean	SD	Mean	SD	Mean	SD	Mean	SD	*P*
Foeniculum vulgare (n = 40)	20.02	6.18	11.20	4.92	9.35	4.54	13.05	4.94	<0.001
Placebo (n = 39)	20.37	5.51	19.23	5.42	18.58	6.11	19.20	5.97	0.402
P	0.77		<0.001		<0.001		<0.001		

SD, standard deviation.

between the two groups ($P > 0.05$; Table 2), but there were significant differences in the scores between groups at weeks 4, 8, and 10 ($P \leq 0.001$; Table 2), and scores in the fennel group were lower than the placebo group.

DISCUSSION

Phytoestrogens are estrogen-like chemicals in plants[1] that have been employed as a treatment for menopausal symptoms. Studies have demonstrated the estrogenic properties of fennel. It has been shown that fennel can increase the weight of the mammary glands, oviducts, cervix, and vagina in rats.[29] Human studies have shown that fennel can increase breast milk,[20] decrease hirsutism,[30] improve dysmenorea,[31] and treat amenorea[32] in women. Fennel has also been shown to improve menopausal symptoms and sexual activity in postmenopausal women.[23]

In this randomized, placebo-controlled clinical trial, the effects of fennel fruit as a medicinal herb with phytoestrogenic properties was investigated in postmenopausal women suffering from climacteric complaints. A significant improvement was observed in menopausal symptoms during the 8 weeks of intervention and 2 weeks of follow-up in fennel group. At week 10 (2 weeks postintervention), the total score had increased slightly in the fennel group, but was still markedly lower when compared with baseline.

Studies have reported that phytoestrogens can reduce the mean MRS score. The results of one 12-week study indicated that soy-derived isoflavone treatment improved general menopausal symptoms and decreased MRS scores when compared with baseline.[33] Another 12-week study that examined the effect of red clover on menopausal symptoms showed that the total MRS score decreased significantly in the intervention group.[34] Rostock et al[35] found a reduction in total MRS score after treatment with black cohosh.

An 8-week placebo-controlled study investigated the effect of fennel and St John's wort (*Hypericum perforatum*) on climacteric symptoms. Both fennel and St John's wort were found to significantly reduce menopausal symptoms when compared with placebo.[23] Another 8-week study indicated that fennel vaginal cream was effective for vaginal atrophy in postmenopausal women.[24]

The results of the present study indicate that fennel significantly reduced the total MRS score of the intervention group when compared with the placebo group, which is similar to the findings of the foregoing studies. Although many studies have confirmed the positive effects of phytoestrogens on postmenopausal symptoms,[36,37] some have shown no difference between the phytoestrogens and the placebo. One study found that pomegranate seed oil did not significantly reduce hot flashes over a 12-week observation period.[38] Amato et al[39] reported that soy isoflavone supplementation offered no benefit to quality of life in postmenopausal women. del Giorno et al[40] found that 12 months of treatment with *Trifolium pratense* had no significant effect on menopausal symptoms and sexual satisfaction. Liu et al[41] reported that whole soy and purified daidzein had no significant effect on alleviation of menopausal symptoms.

The limitations of this study were its short duration and small sample size. Studies with longer durations and larger populations are required to confirm the results of this study.

CONCLUSIONS

The results of this study show that fennel as a phytoestrogen is effective in reducing menopausal symptoms with no serious side effects. It can be considered for decreasing the menopausal symptoms in women with low estrogen levels, and those who have experienced early menopause or have had a hysterectomy or oophorectomy. Further clinical trials with a larger population and of longer duration are recommended to obtain more conclusive results.

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