JMM Journal of Menopausal Medicine
pISSN: 2288-6478, eISSN: 2288-6761
https://doi.org/10.6118/jmm.22026
J Menopausal Med 2023;29:21-28
ORIGINAL ARTICLE

Effect of Fennel-Valerian Extract on Hot Flashes and Sleep Disorders in Postmenopausal Women: A Randomized Trial

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Objectives: This study aims to evaluate the effect of a mixture of fennel and valerian extracts on hot flashes and sleep disorders of postmenopausal women in Iran. A randomized trial was conducted.

Methods: A total of 76 postmenopausal women were randomly assigned to either of the two groups: fennel-valerian extract or control. One 500 mg fennel-valerian extract capsule was given twice, daily for 8 weeks. The 500 mg oral placebo capsule (starch) was given the same way.

Results: The mean duration of hot flashes increased in both the groups over time ($P < 0.001$). The mean frequency and severity of hot flashes in the intervention group were significantly lower than in the control group, in the first and second months after intervention ($P < 0.050$). Women in the fennel-valerian extract group had a significantly lower Pittsburgh Sleep Quality Index score than the control group 2 months after intervention ($P = 0.030$).

Conclusions: This study found that fennel-valerian extract was effective for relieving sleep disorders as well as the severity and frequency of hot flashes compared with a placebo.

Key Words: Fennel, Hot flashes, Sleep disorders, Valerian

INTRODUCTION

Menopause is an important physiological phenomenon in women and it is defined as menstrual cessation for one year [1]. The gradual loss of reproductive activity and the transition to a new stage are characteristics of this period. However, many women experience many problems before and after this period [2]. Menopause may be accompanied by many symptoms including vasomotor symptoms, psychological symptoms, musculoskeletal pain, osteoporosis, sleep problems, and genitourinary symptoms [3]. Vasomotor symptoms affect 80% of menopausal women [4] and one-third of women experience sleep disorders during menopause [5]. Hormone replacement therapy, the most used and common method, increases the risk of some types of cancers, heart diseases, and embolisms. These days the use of Complementary and alternative medicine (CAM) was proposed as a way to improve menopausal symptoms and increase the sense of well-being in women. Some of the different methods used in CAM include natural products (such as nutraceuticals, functional foods, and phytopharmaceuticals), mind-body practices (hypnosis, aromatherapy, meditation), acupressure, acupuncture, homeopathy, and reflexology [6]. Among various CAM methods, the use of natural products especially herbal formulations is the most common and popular method. Statistics showed that eighty percent of postmenopausal women in the united kingdom and the united states use herbal remedies and

Received: July 20, 2022 **Revised:** January 1, 2023 **Accepted:** April 16, 2023
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60 to 70 percent of them believe in the effectiveness and safety of these remedies [7]. Previous systematic reviews revealed the effectiveness of some medicinal plants for the alleviation of menopausal signs. Soybean, vitex, flaxseed, valerian, licorice, anise, sage, black cohosh, and fennel are some of the effective plants, which contain phytoestrogens [3].

The literature survey showed many reports investigating the effects of valerian root, fennel fruit, separately, on hot flashes and sleep disorders in menopausal women. Since no study has been conducted about the effect of fennel on reducing the severity, frequency, and duration of hot flashes, and in addition, there was no study about the effect of the mixture of fennel and valerian extracts on the hot flashes and sleep disorders of postmenopausal women in Iran. Therefore, this study aimed to evaluate the effect of fennel and valerian extracts on the hot flashes and sleep disorders of postmenopausal women in the west of Iran.

Nutraceutical also known as biomedical is regarded as an alternative to pharmaceuticals. The term has a broad definition. There are different regulations for nutraceuticals in different countries. The food that has positive health effects as well as basic nutrition values, is called functional food. Phytopharmaceuticals are herbal-derived components that exert pharmacological activities. Functional foods and phytopharmaceuticals are classified as nutraceuticals [8,9].

Phytoestrogens are naturally occurring compounds that have estrogen-like activities. These nonsteroidal plant compounds increase the conversion of androstenedione to estrogen and decrease the conversion of dihydrotestosterone to testosterone in peripheral tissues, which results in the reduction of menopausal symptoms. Phytoestrogens may alleviate menopausal-related disturbances like hot flashes and sleep disorders. Phytoestrogens strength is about 1/2,000 to 1/50 steroids, and they may not accompany by hormones-related adverse effects [10]. Asian women who consume phytoestrogens of natural origin regularly, experience a low level of menopausal signs. Valerian and fennel are sources of natural phytoestrogens [3].

Valerian (*Valeriana Officinalis*) belonging to the Valerianaceae family is available in Iran. The rhizomes and roots of valerian are used in herbal products for alleviating anxiety, depressive symptoms, stress, dizziness, neural pain, neural unilateral headache, and menopausal symptoms [11]. Previous studies revealed that valerian contains phytoestrogen compounds [10]. Up to now, the valerian effects on menopausal disorders have been the subject of many clinical trials. Jenabi et al. [12] showed that valerian may be an effective pharmacological alternative for reducing the severity of hot flashes in menopausal women. Kazemian et al. [13] showed that the severity, frequency, and duration of hot flashes were significantly reduced after eight weeks of intervention by valerian. Fennel (*Foeniculum vulgare* Mill), an edible plant from the Umbelliferae family [14] is used widely for increasing breast milk, improving premenstrual symptoms, increasing libido, and improving menopausal symptoms in women [15]. Fennel fruit contains phytoestrogenic constituents such as anethole. Similar to Valerian, the fruits of fennel were the subject of the previous investigation on menopause-related problems. Golzareh et al. [16] reported that fennel as a phytoestrogen is effective in treating the physical symptoms of menopause.

MATERIALS AND METHODS

Design and participants

The study used a parallel-group (allocation ratio = 1:1) randomized controlled clinical trial performed from July 22, 2019, to October 15, 2019, among postmenopausal women in Hamadan city (west of Iran). Written informed consent was obtained from all menopausal women. The inclusion criteria were age 45–55 years, first-year after menopausal, not smoking cigarettes or consuming alcohol, not using herbal and hormonal therapies, not having physical or mental diseases, not having an individual's history of estrogen-related cancers, lack of family history of estrogen-related cancers, and not using the chemical drugs.

The subjects were informed about the research methodology and after signing the informed written consent form were considered participants. The participants using hormonal or herbal therapies, having a gynecological, endocrine, or mental disorder, uterine fibroids, experiencing drug intolerance, being allergic to valerian or fennel, having gynecological, endocrine, and mental disorders, unwilling or unable to complete the course of treatment were excluded from the study.

Participants were asked to report any side effects to the researcher, such as headache, vomiting, nausea, anorexia, and gastrointestinal problems.

Sample size

The results of a randomized controlled trial conducted

by Jenabi et al. [12] showed the mean (standard deviation) of the hot flash frequency after treatment was 3.23 (2.52) and 6.23 (4.61) in the intervention and control groups, respectively. Therefore, we reached a sample size of 38 for each group (total sample size of 76), with a two-sided type I error of 5% and 90% statistical power. Postmenopausal women with hot flashes and sleep disorders were referred to four Comprehensive Health Centers in Hamadan city for a treat. Hamadan city has 20 Comprehensive Health Centers. One Health Center was randomly selected from each of the north, south, east, and west districts using the draws; and four health centers were selected. Then, the list of the menopausal women in these centers was obtained, and women were enrolled in this study.

Of the 98 women enrolled, 22 postmenopausal women were excluded due to not meeting the inclusion criteria to participate in the study. Finally, 76 women were randomized into the fennel and valerian extract or control group (each group 38 postmenopausal women). The follow-ups were done in person.

Plant material and herbal formulation

To prepare the extracts, valerian root, and fennel fruit was prepared from the market of medicinal plants in Hamadan City. The plant samples were authenticated in the Department of Pharmacognosy, School of Pharmacy, Hamadan University of Medical Sciences (voucher numbers: *Valeriana officinalis*, 452 and *Foeniculum vulgare*, 124). The fennel fruit specimen contained 86.86% anethole in accordance with the study carried out by Yavangi et al. [17].

The extraction process was performed by macerating in alcohol for 72 hours, three times. Each time, the filtrate was separated and concentrated through rotary evaporation under reduced pressure [18]. The completely dried alcoholic extract was kept in a clean, closed container and kept in the refrigerator until use.

To investigate the formulation design and dosage, there are different reports of valerian effective doses. In case of insomnia between 400 to 900 mg of valerian is used per day [19]. In the case of fennel fruit, there are no sufficient reports to determine the appropriate dose for fennel. Different studies investigated the different doses of fennel. Shirazi et al. [20] examined 300 mg per day of fennel in sleep disorders. In the present study, Each capsule was filled with an equal amount of valerian and fennel extracts.

Data collection

Randomization and concealment

The eligible women were randomly assigned to the Fennel-Valerian extracts or control group. Randomization was performed using softwarerandomization.com.

Blinding

Drugs were concealed to menopausal women and a health staff. The statistical analyst also did not know until the data was analyzed and the labels were decoded. Therefore, the trial had a triple-blind design.

Intervention

One oral Fennel-Valerian extract 500 mg capsule was given twice per day for eight weeks. The menopausal women in the control group received the oral placebo 500 mg capsule (starch) in the same way as the oral Fennel-Valerian extracts capsule. Both the Fennel-Valerian extract and placebo drugs were packed in similar packages and given to health staff. One of the authors followed menopausal women by weekly telephone and the questionnaire during follow-up was completed by the author.

Outcome measures

The Kupperman index [21] was used for measuring the severity, duration, and frequency of hot flashes before the intervention, 4 and 8 weeks after the intervention. Reliability and validity of the Kupperman index in Iran were performed [22].

The severity of hot flashes was categorized according to the degree of the patient bother: "none" was without hot flashes, "mild": was a feeling of heat without sweating, "moderate": a feeling of heat with sweating, and "severe": feeling of heat with sweating and interfering with normal activities.

The Pittsburgh Sleep Quality Index (PSQI) was used for the quality of sleep in menopausal women. This index contains 19 self-rated questions and 5 questions. The 19 self-rated items are combined to form seven "component" scores, each of which has a range of 0–3 points. In all cases, a score of "0" shows no difficulty, while a score of "3" shows severe difficulty. The seven component scores are then added to yield one global score, with a range of 0–21 points [23]. The reliability and validity of this index in Iran were performed [24].

The Kupperman index and PSQI were filled in each visit (before the intervention, 4 and 8 weeks after intervention).

Ethical considerations

The Ethics Committee of Hamadan University of Medical Sciences confirmed the study protocol. The registry code of this study was IR.UMSHA.REC.1398.344. The research was authenticated with the Clinical Trial Registration Center IRCT20180707040370N5. Written informed consent was obtained from all menopausal women.

Data analysis

The primary outcome should be the severity, duration, and frequency of hot flashes. Qualitative data were summarized with frequency and percentage and quantitative variables with a mean ± SD. Statistical analysis was performed using the Student's *t* test for comparing continuous variables, whereas the chi-square test was used for comparing categorical variables between the intervention and control groups. Analysis of covariance (ANCOVA) and repeated measures were used to compare the changes in mean scores of PSQI, duration, frequency, and severity over three-time points. Data were analyzed using Stata Software version 14 (Stata Corp.). The significant level was considered with a *P* value less than 0.05.

Safety and compliance

Fennel and valerian were approved by Commission E. There are many formulations and products containing valerian, fennel alone, or in combination with other medicinal plants. In the present study, as in most previous studies, the duration of treatment was considered to be 8 weeks. Participants were also asked to report any side effects to the researcher.

RESULTS

Of the 76 menopausal women identified, three women in each group (Fennel-Valerian extracts and control) did not reply to the follow-up visit due to a change of residence. However, We telephoned them to send the completed questionnaire but received no response. Therefore, they were excluded from the present study, and 70 menopausal women (35 women in the Fennel-Valerian extracts group and 35 women in the control group) were included in the study (Fig. 1).

The demographic characteristics of both the intervention and control groups are shown in Table 1. Both groups were homogenous regarding age, menopause time, parity, history of abortion, education, job, and marital status ($P > 0.05$). Women in the intervention group had significantly higher body mass index (BMI) (28.02 ± 4.22 vs. 25.13 ± 4.01, $P = 0.005$), alive child number (2.57 ± 0.98 vs. 1.97 ± 0.98, $P = 0.013$), and gravity (3.14 ± 1.14 vs. 2.2 ± 1.03, $P < 0.001$).

According to Table 2 and Figure 2, we compared the primary outcome (duration, severity, and frequency of hot flashes) and the mean PSQI before the intervention, one month after the intervention, and two months after

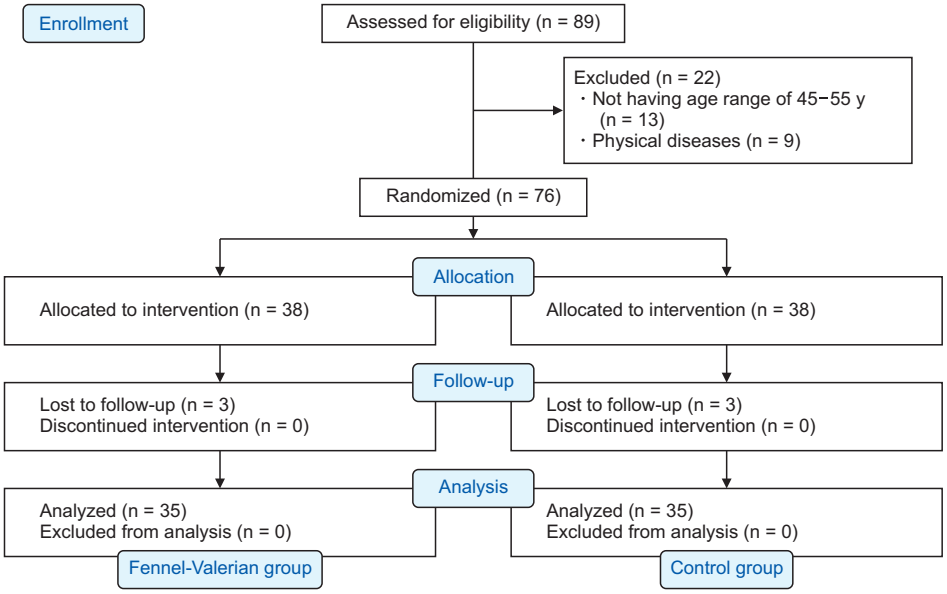

Fig. 1. Flowchart of progress through the clinical trial between Fennel-Valerian extracts group and control group.

Table 1. The demographic and characteristics of women in the two intervention and control groups

Variable		Fennel-Valerian extract (n = 35)	Placebo (n = 35)	*P* value
Continuous variables: mean ± SD				
Menopausal age (y)		51.17 ± 3.29	50.43 ± 2.65	0.312
Duration elapsed from menopause (mo)		18.03 ± 18.3	21.17 ± 22.29	0.520
BMI (kg/m^2)		28.02 ± 4.22	25.13 ± 4.01	0.005
Alive child number		2.57 ± 0.98	1.97 ± 0.98	0.013
Gravidity		3.14 ± 1.14	2.23 ± 1.03	< 0.001
Parity		2.49 ± 1.22	2.02 ± 0.89	0.081
Categorical variables: n (%)				
History of abortion	No	23 (65.71)	26 (24.29)	0.430
	Yes	12 (34.29)	9 (25.71)	
Education	Illiterate	1 (2.86)	0 (0.0)	0.051[a]
	Primary	8 (22.86)	7 (20.00)	
	Guidance	5 (14.29)	14 (40.00)	
	High school	3 (8.57)	0 (0.0)	
	Diploma	13 (37.14)	7 (20.00)	
	University	5 (14.29)	7 (20.00)	
Job	House wife	30 (85.71)	33 (94.29)	0.420[a]
	Employee	5 (14.29)	2 (5.71)	
Marital status	Married	33 (94.29)	27 (77.14)	0.070[a]
	Widow	2 (5.71)	4 (11.43)	
	Divorce	0 (0.0)	4 (11.42)	

The sum of the percentages does not equal 100% because of rounding.
BMI: body mass index.
[a]Fisher exact test.

the intervention. Women in the Fennel-Valerian extract group had a significantly lower PSQI score compared with the control group after two mounts from the beginning of the intervention ($P = 0.03$). The mean frequency of hot flashes decreased in both groups over time ($P < 0.01$). The severity of hot flashes in the intervention group was significantly lower in one month and two months after the intervention ($P < 0.05$). At baseline, no differences were observed between the two groups regarding mean PSQI, duration, severity, and frequency of hot flashes ($P > 0.05$). Results of the repeated measure analysis of variance showed that in regards to the duration of hot flash and global PSQI score significant differences were observed between time points ($P < 0.001$). but, differences observed between the treatment group were not statistically significant ($P > 0.05$). For frequency and severity of hot flashes, significant differences were observed between time points ($P < 0.001$). Additionally, significant differences were observed between groups ($P = 0.04$ for frequency and $P = 0.05$ for severity).

We adjusted the ANCOVA data analyses based on BMI (kg/m^2), live child number, and gravidity. The follow-up after the end of the intervention was conducted and none of the women reported adverse effects of the drugs. In addition, there was no difference in the effect of treatment in the two groups on the duration and severity of hot flashes on the mild, moderate, and severe scales. The side effects of the drug were not found.

DISCUSSION

Our findings showed that women in the Fennel-Valerian extract group had a significantly lower PSQI score compared with the control group after two months from the beginning of the intervention. The mean fre-

Table 2. Comparison of primary oucome (duration, severity, and frequency of hot flashes) and mean PSQI over treatment group and three-time points

Index		Before intervention	1 month after intervention	2 months after intervention	*P* value for treatment effect[a]	*P* value for time effect[a]
Duration of hot flash	Fennel-Valerian Extract	3.09 ± 1.42	3.62 ± 1.20	4.05 ± 1.06	0.380	< 0.001
	Placebo	2.95 ± 1.21	3.4 ± 1.25	3.72 ± 1.16		
	P value[b]	0.460	0.050	0.263		
Frequency of hot flash	Fennel-Valerian Extract	2.69 ± 1.33	2.06 ± 1.21	1.88 ± 1.25	0.040	< 0.001
	Placebo	3.02 ± 1.29	2.79 ± 1.11	2.51 ± 1.4		
	P value[b]	0.754	0.080	0.060		
The severity of hot flash	Fennel-Valerian Extract	2.69 ± 0.78	2.4 ± 0.83	1.99 ± 0.92	0.050	< 0.001
	Placebo	2.39 ± 1.12	2.79 ± 0.8	2.93 ± 0.73		
	P value[b]	0.520	0.002	< 0.001		
Global PSQI score	Fennel-Valerian Extract	10 ± 4.37	7.66 ± 3.54	6.37 ± 2.65	0.142	< 0.001
	Placebo	10.37 ± 4.06	9.22 ± 3.9	8.26 ± 4.28		
	P value[b]	0.477	0.098	0.030		

Values are presented as mean ± SD.
PSQI: Pittsburgh Sleep Quality Index.
[a]Repeated measure analysis of variance because the interaction of time and treatment group was not significant in any of the areas, it was excluded from the model.
[b]Analysis of covariance for comparison of scores adjusted based on body mass index (kg/m^2), alive child number, and gravidity.

quency of hot flashes decreased in both groups over time. The severity of hot flashes was decreased over the three investigated time points ($P < 0.01$). The mean of hot flash severity in the intervention group was significantly lower one month and two months after the intervention.

Jenabi et al. [12] determined the effect of oral Valerian 530 mg capsule (twice per day for two months) on hot flashes in 60 women postmenopausal. The severity of hot flashes in the Valerian group was significantly lower than in the control group at one ($P = 0.048$) and two months ($P = 0.020$) after initiation of the intervention. Compared with the control group, the mean frequency of hot flashes was significantly reduced two months after initiating the use of Valerian in comparison with the placebo ($P = 0.033$) [12]. This study is in line with our study.

Mirabi and Mojab [10] performed a similar study in 2013 in Iran, and its results also reported that Valerian reduced the frequency and severity of hot flashes one and two months after the treatment compared with the control group. However, our study didn't show a reduction in the frequency of hot flashes after the intervention compared with the control group. This issue may be due to a difference in the dose of valerian compared with previous studies.

Kazemian et al. [13] showed that the severity, frequency, and duration of hot flashes were significantly reduced after eight weeks of intervention by Valerian compared with the control group [13]. In our study, the frequency and severity of hot flashes reduced after 1 and 2 months of intervention by Fennel-Valerian extract compared with the control group. However, this association was not significant with the duration of hot flashes.

Golzareh et al. [16] showed the effect of oral Fennel capsules on menopausal symptoms in 90 postmenopausal. They used Fennel 100 mg capsule twice per day for eight weeks. The menopausal symptoms in the Fennel group were significantly lower than the control group two months after initiation of the intervention ($P < 0.001$). Therefore, they reported that Fennel is effective as a phytoestrogen in treating the physical symptoms of menopause [16]. Our study showed that Fennel-Valerian extract could reduce sleep disorders, and the frequency and severity of hot flashes two months after initiation of the intervention. Therefore, our study is in line with Golzareh's study.

Taavoni et al. [25] examined the effect of oral Valerian 530 mg capsule (twice per day for two months) on sleep disorders in 100 women postmenopausal. They reported that 40% of the women in the intervention group

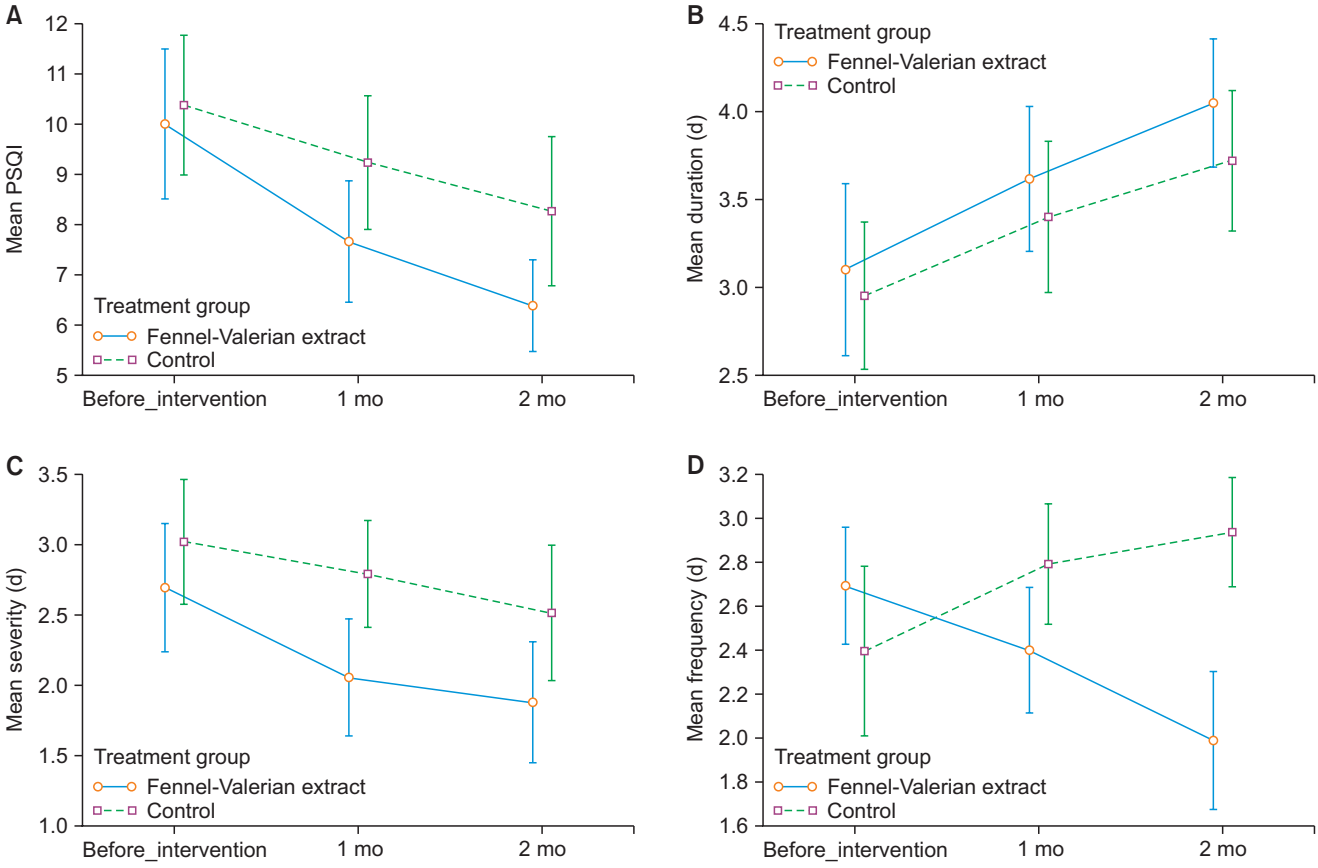

Fig. 2. Comparison of mean (A) Pittsburgh Sleep Quality Index (PSQI), (B) duration, (C) severity, and (D) frequency of hot flashes among intervention and control groups.

and 12% in the placebo group showed an improvement in the quality of sleep ($P < 0.05$) [25]. This finding is consistent with the present study.

Increasing the duration of hot flashes can be an undesirable variable for women. However, the cause may be due to the low sample size of the study. In addition, in the placebo group, there is an improvement in terms of sleep and the frequency of hot flashes.

The findings of this study showed that the Fennel-Valerian capsule is an effective drug for women with menopausal symptoms and it can be an alternative to hormone therapy. The strength of this study was the combined effect of valerian and phenol on hot flashes and sleep disorders using the randomized trial. It is suggested that this study be performed with larger sample size and in other areas.

The limitation of the study includes the lack of knowledge of participants' diets and limited study time. However, the limitation of alternative therapy is the lack of proven data about its common and rare side effects. Also, the unknown side-effects should be considered because of the paucity of data.

The results of the current study reported that the Fennel-Valerian capsule was effective for relieving sleep disorders, the severity, and frequency of hot flashes compared with the placebo. Therefore, this extract can be an alternative to hormone therapy. Health providers may consider Fennel-Valerian extract to be an effective drug for women with menopausal symptoms.

FUNDING

This work was supported by the vice-chancellor of research and technology at Hamadan University of Medical Sciences (grant number: 9806264639).

ACKNOWLEDGMENTS

The authors of the article thank the officials and staff of health centers of Hamadan University of Medical

Sciences and the participants in the study.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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