



The efficacy of oral *Lavandula angustifolia* Mill. essential oil on menopausal symptoms, serum lipid profile, and cortisol concentration in postmenopausal women: A triple-blind, randomized, controlled trial

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ABSTRACT

Objective: To determine the effect of oral *Lavandula angustifolia* Mill. essential oil (LEO) on menopausal symptoms, serum cortisol level, and lipid profile in postmenopausal women.

Methods: This was a triple-blind parallel-armed randomized trial. Seventy-two postmenopausal women aged 50–65 years referring to healthcare centers in Tabriz, Iran with a score of 15–42 on the Green scale were included from May 10, 2022 to May 22, 2023. The participants were randomly assigned to two groups with a 1:1 ratio and using four and six blocks. One group received LEO soft gel 80 mg per day, and another group received a similar placebo for 60 days. A demographic questionnaire and a Greene menopause symptom scale were used for data collection. The lipid profile (total cholesterol, triglyceride, LDL, HDL) and the serum levels of cortisol were measured using biochemical methods. Chi-square, Fisher's exact tests, Independent samples t-test, Analysis of Covariance (ANCOVA), Repeated measure ANOVA, and Paired sample t-test were utilized for analyses. A p-value less than 0.05 was considered statistically significant.

Results: The demographic and personal characteristics of the participants were similar. After two months of intervention, all symptoms in psychological, physical, vasomotor, anxiety, depression, and sexual dysfunction domains were significantly relieved (decreased) among both groups ($p < 0.003$), except for sexual dysfunction, the reduction of which was not significant in the placebo group ($p = 0.317$). The mean (SD) total score of menopausal symptoms reduced from 27.4 (6.3) at baseline to 17.7 (4.9) at the end of the study in the LEO group ($p < 0.001$). It also decreased from 27.4 (7.1) to 17.6 (5.1) in the placebo group ($p < 0.001$). However, between-group analyses revealed that this reduction was significantly greater in the LEO group compared to the placebo group only in the sexual dysfunction (Mean (SD): 1.3 (0.6) vs. 1.0 (0.5); adjusted mean difference (95% confidence interval); $p = -0.35$ (−0.67 to −0.02); 0.039). No significant within-group changes or between-group differences were observed ($p > 0.05$) in terms of studied serum markers.

Conclusion: The oral LEO exhibited a significant enhancement in sexual dysfunction among postmenopausal women. Therefore, it can be used alongside other therapies to improve sexual dysfunction during menopause. LEO did not affect lipid profile and serum cortisol level in this study.

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1. Introduction

In recent decades, due to the increase in life expectancy in the world, about 95% of the female population enters menopause¹ and spend about a third of their life in menopause². Although menopause is a natural event,³ the transition to menopause and the associated changes are diverse.⁴ Hormonal and biochemical changes during this period lead to physiological and physical symptoms,^{5,6} which can disrupt daily activities and reduce the quality of life of this population.⁷ Hot flashes, vaginal dryness, sleep problems, and insomnia (with or without night sweats) are typical menopause symptoms. Depression, anxiety, and cognitive issues are other middle-age disorders that adversely affect women and their families.⁸ Postmenopausal women are also prone to osteoporosis and cardiovascular diseases.⁹ In addition, during this period, there is a significant decrease in sexual arousal, sexual desire, and the number of sexual activities. The prevalence of sexual dysfunction among women aged 40–80 years is reported to be 43% in the whole world.^{10,11} The management of these symptoms should include the treatment of menopausal symptoms, strategies to control psychosocial stressors, and eliminating clinical symptoms of depression and anxiety symptoms.¹²

As a woman transitions from early to late menopause, cortisol levels increase during the night.¹³ A relationship between stressors and depressive mood symptoms has been found with cortisol. High cortisol levels are linked to negative health effects, such as reduced bone density in older women and mild cognitive issues.¹⁴ Vasomotor symptoms and other disorders related to menopause can be weakened by hormone therapy, but this treatment method is associated with some side effects such as breast cancer, cardiovascular problems, and pulmonary embolism.^{15,16} Non-hormonal treatments such as phytoestrogens have been of interest to menopausal women as a safe treatment.¹⁷

Lavender (*Lavandula angustifolia* Mill.) from the Lamiaceae family is an evergreen aromatic shrub that is traditionally used as a cosmetic herb. In the traditional medicine of Europe, the West, and Asia, this plant is mainly used as an oil for inhalation or topical application for various cases.¹⁸ Due to having linalool, linalyl acetate, caryophyllene oxide, tannins, coumarin, flavonoid, and phytosterol,¹⁹ lavender has active positive effects such as relaxation,²⁰ antidepressants,²¹ and antioxidants.²² Lavender plant is used in different ways, including oral consumption and aromatherapy. Its edible forms include capsules containing dried lavender flower powder,²³ gelatin capsules containing lavender essence,^{24,25} lavender tea,²⁶ and lavender essence has been used for aromatherapy.^{27,28}

Lorazepam and gelatin capsules containing lavender essential oil (silexan) have the same effect on patients with Generalized Anxiety Disorder (GAD). Lavender capsules are more effective, have no abuse potential, and do not cause any deprivation effects. Silexan is better than benzodiazepines for relieving GAD.²⁹ In human studies, lavender has been used in the treatment of anxiety disorders and related conditions. Three clinical trials determined that the effect of Silexan once a day with a dose of 80 mg is effective in anxiety disorders as well as in restlessness and irritability.^{25,30} The positive effects of aromatherapy with a combination of basil, lavender, rosemary, and rose oil were shown to reduce headache, anxiety, and serum cortisol levels in middle-aged women.³¹ A study revealed a significant decrease in anxiety and blood cortisol levels in both lavender and control groups of open-heart surgery volunteers. The decrease was greater in the intervention group compared to the control.³²

The study on Korean menopausal women found that a combination of aromatherapy, including lavender, geranium rose, rose, and jasmine, had adverse effects on their lipid profile.³³ On the other hand, a study to determine the effect of LEO on the lipid profile in mice with induced breast cancer has shown that LEO in these mice reduced total cholesterol, triglycerides, LDL, and increased HDL.³³

Given the importance of the physical and mental health of middle-aged women and considering no study has been found on the effects

of the oral soft gel capsule form of LEO on menopausal symptoms, lipid profile, and serum cortisol level, the present study was conducted to determine the effect of oral LEO on menopausal symptoms, serum cortisol level, and lipid profile in postmenopausal women.

2. Methods and materials

2.1. Study design and setting

This study was designed as a triple-blind (people involved in selecting samples and collecting data, data analyzer, and participants) parallel armed randomized clinical trial. The target population in this study was all postmenopausal women who were referred to healthcare centers in Tabriz, Iran. This study was carried out from May 10, 2022 to May 22 2023.

2.2. Participants

2.2.1. Inclusion criteria

1) Willingness to participate in the study 2) Having enough literacy to fill out the questionnaire or the presence of a literate person in the family 3) Having normal menopause as a condition brought on by aging 4) Women whose menopause has been less than 6 years 5) Being at least 45 and at most 60 years old 6) Obtaining a minimum score of 15 and a maximum of 42 in Green's menopausal symptoms.^{34,35}

2.2.2. Exclusion criteria

1) Use of tobacco, alcoholic beverages, and herbal medicines 2) Existence of predisposing factors such as the death of first-degree relatives in the last 6 months and loss of job 3) Presence of malignant disease such as uterine cancer, breast cancer, and abnormal vaginal bleeding 4) Individuals with prior experience of using Lavender within the last three months 5) Individuals with a history of hormone therapy within the last 6 months 6) having known physical and mental diseases according to the person's statement (such as depression, uncontrolled diabetes, cardiovascular diseases, liver disease) 7) Unnatural menopause following ovarian removal, hysterectomy, chemotherapy and radiation therapy, and ovarian failure.

2.3. The sample size estimation

To determine the sample size, based on the study of Farshbaf-Khalili et al.,²³ regarding the state anxiety variable and considering $m_1 = 45.26$, $m_2 = 40.74$, $sd_1 = sd_2 = 5.72$, power 90%, $\alpha = 0.05$ and two-tailed test, the sample size was calculated 29 people for each group and based on trait anxiety variable and considering $m_1 = 43.73$, $m_2 = 39.35$, $sd_1 = sd_2 = 5.64$, power 80%, $\alpha = 0.05$ and two-tailed test, the sample size was estimated to be 30 people for each group. The sample size based on Cha et al.'s study on the effect of lavender on serum cortisol level³¹ and considering $m_1 = 35.3$, $m_2 = 47.6$, $sd_1 = 7.9$ $sd_2 = 11.1$, power 80%, $\alpha = 0.05$ and two-tailed test calculated 11 people for each group. Finally, the maximum sample size was estimated to be 36 for each group and 72 people in total according to trait anxiety data considering a 20% possible dropout in the sample.³⁶

2.4. Ethical considerations

Written informed consent was obtained from all participants after a full explanation of the objectives and method of study prior to intervention. All research stages were approved by the Research Ethics Committee of the Tabriz University of Medical Science (IR.TBZMED.REC.1400.1186). This study was registered in the Iranian Registry of Clinical Trials (IRCT), number IRCT20131009014957N13.

2.5. Enrollment, randomization, and blinding

The research environment was healthcare centers in Tabriz, Iran. By referring to the mentioned centers, the researcher first checked all postmenopausal women 50–65 in terms of inclusion and exclusion criteria. If a person had a score of 15–42 on the Greene scale and was eligible to enter the study, written informed consent was obtained. Then the social demographic questionnaire was completed. Weight was measured with minimum clothing using a Seca scale with an accuracy of 0.1 kg, and height was measured with a wall-mounted scale with an accuracy of 0.1 cm in a flat state with the back of the head, shoulders, hips, and heels touching the wall. Then, the participants were randomly assigned to two groups (receiver of soft gel lavender and placebo) with a 1:1 ratio using RAS (Random Allocation Software) and through four and six blocks. In order to conceal the allocation (Allocation Concealment), the drugs and placebo were placed in completely identical, opaque, and closed containers, which were numbered sequentially from 1 to 72 based on a randomly generated sequence by a person not involved in the study. People's medicines were placed in the same opaque and sealed packages, each of which had two identical opaque containers for the period of use for a month. The first envelope was delivered at the first visit and the second envelope was delivered one month later at the second visit after the delivery of the previously used envelope and the drug consumption checklist. Package number 1 was awarded to the first person who entered the study, package number 2 was awarded to the second person and this process continued until the end. To preserve the blinding of participants, researchers, data analyzers, and clinical trial monitors, main drugs and placebos were manufactured quite identical in appearance.

2.6. Intervention

One group as the first intervention group (36 people) received one oral Lavender soft gel 80 mg once per day for 60 days, and the second intervention group (36 people) received one oral placebo soft gel 80 mg once per day for 60 days, which was completely similar to the main drugs in terms of appearance. The Lavender and placebo soft gels were distributed by researchers according to the allocated packages. The drug/placebo intervention lasted for 2 months. The participants were instructed to take the medicine with a full glass of water and if they experienced burping, swallow the medicine with a glass of water and food. Store the medicine in a cool and dark place, away from direct sunlight, heat, and moisture. They were advised that if they were not eligible for the study during the intervention or if they encountered any side effects while notifying the researchers immediately, they should stop taking the medicine but return at the designated times to check the results of the study.

The daily drug consumption checklist was provided to the participants in order to mark the daily use of drugs at home along with the drug side effects sheet. A phone call was made by the main researcher every two weeks to ensure drug consumption. The researcher provided the participants with a phone number to call in case of side effects or any possible questions.

2.6.1. The preparation of study drugs

In this research, soft gel capsules comprising 80 mg of LEO (species: *Lavandula angustifolia* Mill. composed of Linalyl acetate 35.55%, Limonene 13.04%, Linalool 8.96%, 1,8 Cineol 37.95%, obtained through steam hydro-distillation of flowers) were produced by Barij Essence Co. (Batch no. 14012121). The quality assurance of the medication was performed by the quality assurance department of Barij Essence Company, Iran, Kashan. This product was manufactured in compliance with good manufacturing practices (NNHPR, QAI, CA) in a clean manufacturing plant without chemical pesticide activities and was released by an authorized Quality Control Unit and found to meet the specifications. The identification of the plant was confirmed using

<http://www.theplantlist.org>. The placebo, which was prepared by the same company, mimicked the soft gelatin capsules in terms of appearance (color, weight, shape) and contained inert ingredients.

2.7. Measurements

The study's primary outcomes were menopausal symptoms and serum cortisol concentration, and the secondary outcomes consisted of serum lipid profile, reported possible side effects, and satisfaction with the received intervention. Data collection was done by the questionnaire of social demographic characteristics, the Greene menopause symptom scale, a checklist of adverse events, and a checklist for measuring satisfaction with the received intervention. The social demographic questionnaire included questions related to age, length of time since menopause, age of menopause, education level, occupation, spouse's education level and occupation, number of family members, weight, height, and smoking in a person and his wife. Green's scale was invented by Professor Greene in Scotland in 1975, and its validity and reliability have been proven.³⁴ This scale independently measures psychological, physical, and vasomotor symptoms caused by menopause. This questionnaire contains 21 questions related to menopause complications, and each symptom is scored by the individual based on a Likert scale (0–3). The severity of the symptoms is scored as zero (not at all), one (mild), two (moderate), and three (severe). Questions 1 to 11 measure psychological symptoms including depression and anxiety (questions 1–6 belong to depression and 7–11 to anxiety), questions 12 to 18 measure physical menopausal symptoms, questions 19 and 20 measure vasomotor symptoms, and the question 21 measures sexual dysfunction. The overall score on this scale (0–63) is calculated by the sum of the scores of 21 questions. A score of 15 or over usually illustrates estrogen deficiency that is indicative enough to require treatment, however it is only a guide.³⁷ Greene's menopause symptoms questionnaire has been used in Iran before and its reliability has been confirmed in the study by Askari et al. In order to determine validity, content validity has been used by asking the opinion of 8 members of the academic staff of the university. The reliability and internal consistency of this instrument have been determined by test-retest and Cronbach's alpha. The correlation coefficient between the two tests $r = 0.74$ and Cronbach's alpha for the entire scale 0.87 have been obtained.³⁸ A checklist of possible side effects was designed by the research team, and the type of possible side effects and their severity were recorded by the participants in the checklist. Satisfaction with the received intervention was measured through an item that was scored from 1 to 5 based on a Likert scale. At the beginning and end of the study, an overnight fasting blood sample of at least 8–10 h was taken from the brachial vein by a nurse at 8–10 am using a 5 cc syringe and poured into a jelly test tube, then centrifuged at 3500 rpm for 10 min. The samples were immediately frozen at -70°C until measurements and all the tests were performed by one experienced laboratory expert using a specific device in the laboratory of Imam Reza educational-therapeutic hospital. The lipid profile (total cholesterol, triglyceride, LDL, HDL) was analyzed using Pars Azmoon commercial diagnostic kits; and for the serum levels of cortisol, a cortisol enzyme-linked immunosorbent assay (ELISA) kit and Stat Fax ELISA reader were used.

2.8. Statistical analysis

The results were indicated as number (percent) and mean (standard deviation). Statistical analysis was performed using SPSS PC Statistics Software, version 23.0 (SPSS Inc., Chicago, IL, USA). The Kolmogorov-Smirnov test was employed to illustrate the distribution of numerical data. Additional analyses were conducted to examine descriptive evidence such as Skewness, Kurtosis, proportionality, and reasonableness of standard deviation (in comparison to the mean). Qualitative variables were compared using Chi-square and Fisher's exact tests. For between-group comparisons of quantitative variables at baseline, an

independent samples t-test was utilized. To assess the mean of study variables after the intervention, while adjusting for the basic measurements of the variables and other potential confounders, analysis of covariance (ANCOVA) was employed for laboratory tests, and repeated measure ANOVA was employed for menopausal symptoms. A paired sample t-test was employed to compare changes in quantitative variables prior to and following the intervention within each study group. P-values less than 0.05 were deemed statistically significant. All analyses were based on intention-to-treat approach (All participants in the study, including those who stopped the assigned intervention for some reason, were invited at the end of the intervention period. Questionnaires were completed and blood samples were received).

3. Results

Seventy-two eligible postmenopausal women aged 50 to 65 (36 in each group) were included in this trial. Two women in the lavender group and three in the placebo group did not receive the assigned intervention due to unwillingness to continue the allocated intervention,

and 1 person in each group did not receive the assigned intervention due to the side effects of the intervention. Other side effects were mild and appeared only at the beginning of use and did not prevent the continuation of use. The lack of expected efficacy was reported as the main reason for unwillingness to continue the received intervention. Finally, all participants were analyzed according to an intention-to-treat approach (Fig. 1). Counting the number of soft gels not taken by women as well as the daily medication recording checklist showed that the drug **compliance** rate was 90.7% in total, which was 91.5% in the lavender group and 89.9% in the placebo group. All the quantitative variables studied in this study had a normal distribution.

3.1. Baseline characteristics

The mean (SD) age of the lavender group was 55.9 (3.9), and for the placebo group was 56.1 (5.0). The mean (SD) menopause age in the lavender and placebo groups was 50.9 (3.2) and 51.3 (3.8), respectively. In terms of educational attainment, almost all of the individuals possessed education below the level of a diploma... The mean (SD) body

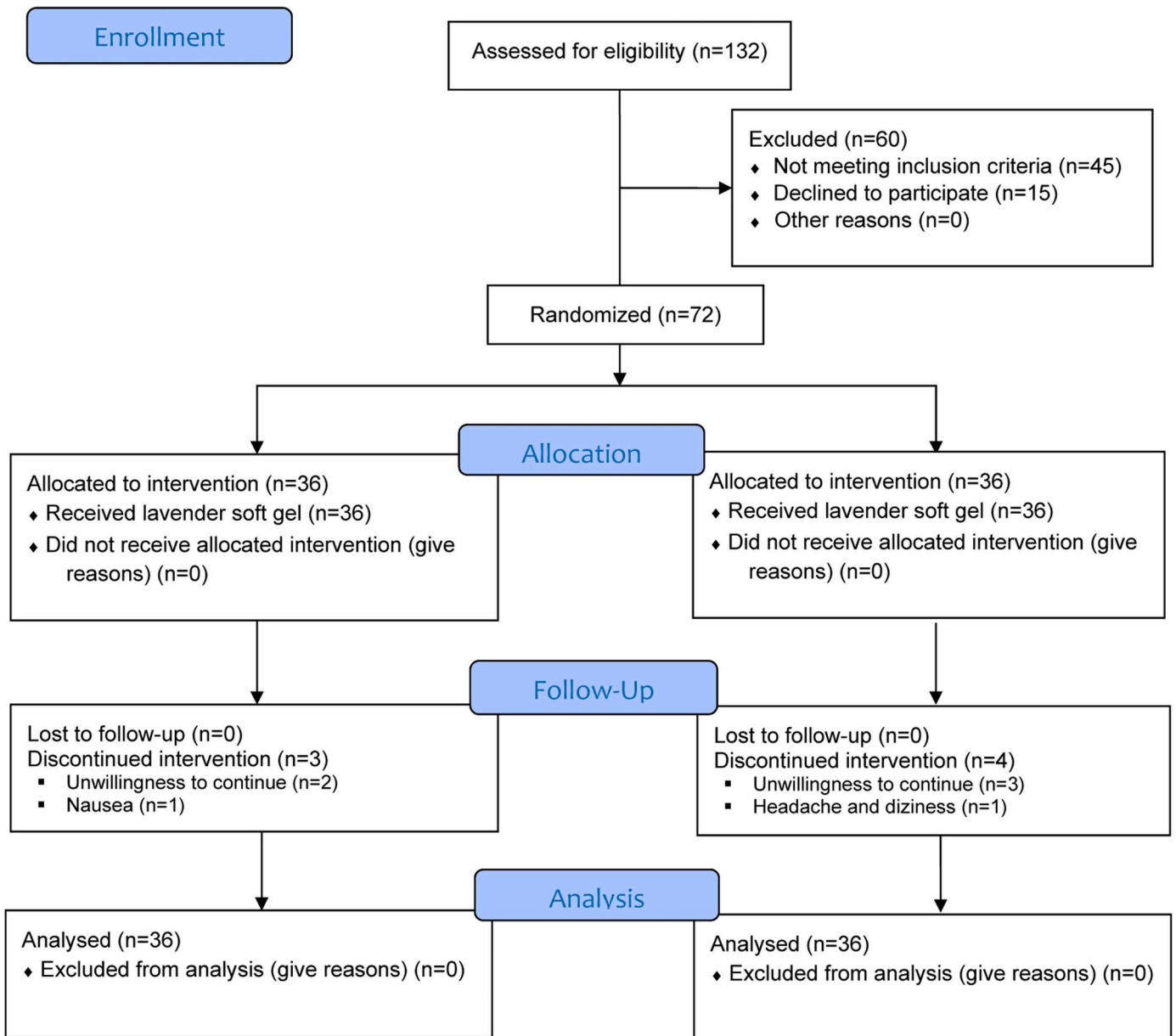


Fig. 1. The flow diagram of study.

mass index (BMI) in the lavender group (30.4 (4.6) kg/m²) and placebo (29.8 (3.8) kg/m²) was on the border between overweight and obesity. The comparison of demographic and personal characteristics of the participants between the two study groups did not indicate a statistically significant difference ($p > 0.05$) and has been shown in [Tables 1 and 2](#).

3.2. Menopausal symptoms of participants

At baseline, the total score of the menopause symptom scale (Greene Climacteric) was 27.4 (6.3), the psychological score was 12.9 (4.6), the somatic (physical) score was 7.6 (2.8), the vasomotor score was 5.3 (1.1), the anxiety score was 5.5 (2.6), depression score was 7.4 (2.9), and sexual dysfunction score was 1.5 (1.0) in the LEO group. In the placebo group, the total score of the menopause symptom scale was 27.4 (7.1), the psychological score was 13.4 (5.6); the somatic (physical) score was 7.3 (2.6); the vasomotor score was 4.8 (1.6); the anxiety score was 5.7 (2.5); the depression score was 7.7 (2.5); and sexual dysfunction score was 1.7 (1.0) ($p > 0.05$). After two months of intervention, all symptoms of various domains were significantly relieved (decreased) among both groups ($p < 0.003$), except for sexual dysfunction, the reduction of which was not significant in the placebo group ($p = 0.317$). However, between-group analyses revealed that these reductions only in the sexual dysfunction were significantly greater in the LEO compared to the placebo group (adjusted mean difference (95% confidence interval); $p: -0.35 (-0.67 \text{ to } -0.02); 0.039$). The other improvements were similar between the two groups ($p > 0.05$).

3.3. Lipid profile and cortisol serum levels

Among the LEO and placebo groups, the mean (SD) serum levels of triglyceride 176 (66) mg/dL and 171 (80) mg/dL, total cholesterol 180

Table 1
The baseline characteristics and gestational outcomes of participants in the study groups.

Variable	Lavender (n = 36) Mean (SD)	Placebo (n = 36) Mean (SD)	p-value
Age (year)	55.9 (3.9)	56.1 (5.0)	0.836*
Menopause age (year)	50.9 (3.2)	51.3 (3.8)	0.643*
Weight (kg)	76.3 (12.1)	75.1 (11.7)	0.687*
Body Mass Index (kg/m ²)	30.4 (4.6)	29.8 (3.8)	0.504*
Education			0.343**
Illiterate	22 (61.1%)	17 (47.2%)	
Under diploma	14 (38.9%)	18 (50.0%)	
Diploma & Academic degree	0 (0%)	1 (2.8%)	
Spouse Education			0.631**
Illiterate	11 (30.6%)	12 (33.3%)	
Under diploma	23 (63.8%)	20 (55.5%)	
Diploma & Academic degree	2 (5.6%)	4 (11.2%)	
Marriage			0.365 [±]
Married	31 (86.1%)	29 (80.6%)	
Single, widow, divorce	5 (13.9%)	7 (19.5%)	
BMI (kg/m ²)			0.967**
< 18.5 (underweight)	4 (11.1%)	4 (11.1%)	
18.5-24.9 (normal)	12 (33.3%)	11 (30.6%)	
25-29.9 (overweight)	20 (55.6%)	21 (58.3%)	
Delivery number	4.2 (2.0)	3.6 (1.2)	0.144 [±]
Family member			0.793 [±]
3	25 (69.4%)	27 (75.0%)	
4-6	11 (30.6%)	9 (25.0%)	
Spouse Job			0.239
Self-occupied	4 (11.1%)	10 (27.8%)	
Employee	2 (5.6%)	0	
Worker	19 (52.8%)	19 (52.8%)	
Retired	9 (25.0%)	6 (16.7%)	
Unemployed	2 (5.6%)	1 (2.8%)	
Spouse smoking	2 (5.6%)	8 (22.2%)	0.122 [±]

* Independent t-test was used to compare quantitative variables. For qualitative variables, ** Chi-square and [±] Fisher's exact test were used.

Table 2

The total score of menopause symptoms and its domains by study groups in different time points.

Variable	Lavender (n = 36) Mean (SD)	Placebo (n = 36) Mean (SD)	aMD (95% CI)	p-value	P group & time
Anxiety (0-18)					
Baseline	5.5 (2.6)	5.7 (2.5)	-	0.723 *	
After 1 month	4.1 (2.1)	4.0 (2.0)	-		
After 2 month	3.6 (1.7)	3.6 (1.7)	0.10 (-0.81 to 1.02)	0.825 [±]	0.861
p-value**	< 0.001	< 0.001			
Depression (0-15)					
Baseline	7.4 (2.9)	7.7 (3.2)	-	0.704 *	
After 1 month	5.4 (2.1)	5.5 (2.1)	-		
After 2 month	4.9 (2.3)	4.9 (2.0)	0.14 (-0.84 to 1.13)	0.766 [±]	0.958
p-value**	< 0.001	< 0.001			
Psychological scale (0-33)					
Baseline	12.9 (4.6)	13.4 (5.6)	-	0.666 *	
After 1 month	9.5 (4.2)	9.6 (3.9)	-		
After 2 month	8.5 (3.7)	8.6 (3.4)	0.25 (-1.52 to 2.02)	0.779 [±]	0.896
p-value**	< 0.001	< 0.001			
Physical scale (0-21)					
Baseline	7.6 (2.8)	7.3 (2.6)	-	0.618 *	
After 1 month	5.9 (2.2)	6.6 (1.8)	-		
After 2 month	6.0 (1.7)	5.7 (1.9)	0.03 (-0.78 to 0.84)	0.943 [±]	0.158
p-value**	0.003	0.003			
Vasomotor scale (0-6)					
Baseline	5.3 (1.1)	4.8 (1.6)	-	0.101 *	
After 1 month	2.6 (1.1)	2.6 (1.1)	-		
After 2 month	2.0 (0.7)	2.0 (0.8)	-0.19 (-0.56 to 0.17)	0.297 [±]	0.187
p-value**	< 0.001	< 0.001			
Sexual dysfunction (0-3)					
Baseline	1.5 (1.0)	1.7 (1.0)	-	0.197 *	
After 1 month	1.6 (0.7)	1.3 (0.6)	-		
After 2 month	1.3 (0.6)	1.0 (0.5)	-0.35 (-0.67 to -0.02)	0.039 [±]	0.041
p-value**	0.002	0.317			
Total score (0-63)					
Baseline	27.4 (6.3)	27.4 (7.1)	-	0.980*	
After 1 month	19.7 (6.9)	20.3 (6.4)	-		
After 2 month	17.7 (4.9)	17.6 (5.1)	0.153 (-2.18 to 2.49)	0.896 [±]	0.899
p-value**	< 0.001	< 0.001			

The higher scores indicate the higher menopause symptoms.

The bold p-values indicate the statistical significance

* Independent t-test, aMD (95% CI): adjusted Mean difference (95% confidence interval). [±] ANOVA with repeated measure adjusted for baseline values, age, menopause age, and BMI,

** Paired Samples t-test,

(38 mg/dL and 178 (44 mg/dL), LDL cholesterol 109(35) mg/dL and 108 (39) mg/dL], HDL cholesterol 36 (7) mg/dL and 38 (8) mg/dL], and cortisol 16 (4) mcg/dL and 15 (4) mcg/dL were obtained ($p > 0.05$), respectively. After two months of the intervention, no significant within-group changes or between-group differences were observed ($p > 0.05$) in terms of studied serum markers (Table 3).

3.4. The reported side effects

Six participants in each group reported side effects which consisted of headache, dizziness, nausea, numbness of extremities, and body itching (Table 4). One participant due to nausea and one because of headache and dizziness discontinued the allocated intervention at first days after initiation of the trial. In the other case, side effects were mild and did not prevent the continued consumption.

4. Discussion

This research aimed to evaluate the effect of oral LEO on menopausal symptoms, serum lipid profile, and cortisol levels in postmenopausal women. The findings showed that administration of 80 mg of lavender soft gel daily for 60 days, significantly improved sexual dysfunction compared to placebo in postmenopausal women. Despite significant improvements in the other Greene subscales (physical and psychological symptoms) in both the placebo and intervention groups, there was no significant difference between the two groups. There were no significant between-group differences in the serum lipid profile and cortisol levels following intervention. The frequency of sexual dysfunction in postmenopausal women is 4 times higher than in women of childbearing age.

Table 3
The total score of Serum Lipid Profile and Cortisol by study groups in different time points.

Variable	Lavender (n = 36) Mean (SD)	Placebo (n = 36) Mean (SD)	aMD (95% CI)	p- value [±]
Triglyceride (mg/dl)				
Baseline	176.8 (65.8)	171.0 (80.0)	-	0.816
After 2 month	159.5 (30.7)	172.0 (42.7)	11.0 (-4.5 to 26.5)	0.162
p-value*	0.703	0.659		
Total cholesterol (mg/dl)				
Baseline	180.5 (37.9)	177.9 (43.9)		0.186
After 2 month	188.5 (26.6)	176.3 (26.1)	-8.6 (-19.4 to 2.1)	0.114
p-value*	0.385	0.737		
LDL cholesterol (mg/dl)				
Baseline	109.1 (35.1)	108.2 (39.5)		0.943
After 2 month	106 (25.2)	112.3 (23.1)	-3.5 (-8.2 to 1.2)	0.241
p-value*	0.658	0.552		
HDL cholesterol (mg/dl)				
Baseline	36.0 (7.3)	38.4 (7.6)		0.349
After 2 month	37.4 (4.5)	38.8 (5.5)	0.63 (-1.5 to 2.8)	0.571
p-value*	0.870	0.622		
Cortisol (mcg/dl)				
Baseline	15.7 (4.5)	15.0 (4.5)		0.613
After 2 month	17.4 (7.2)	16.0 (4.2)	0.96 (-11.3 to 13.2)	0.876
p-value*	0.826	0.127		

The bold p-values indicate the statistical significance
* Independent t-test, aMD (95% CI): adjusted Mean difference (95% confidence interval). ± ANCOVA adjusted for baseline values, age, menopause age, and BMI, **Paired Samples t-test,

Table 4
The reported side effects following intervention by study groups.

Adverse events	Lavender (n = 36) n (%)	Placebo (n = 36) n (%)
Headache	1 (2.8%)	2 (5.6%)
dizziness	2 (5.6%)	2 (5.6%)
nausea	2 (5.6%)	1 (2.8%)
Numbness of extremities	0	1 (2.8%)
Body itching	1 (2.8%)	0

During menopause, there is a decrease in estrogen and androgen levels which can cause reduced blood flow in the vagina. This can lead to vaginal dryness, dyspareunia, and decreased mental-sexual vitality. Additionally, vulvar and vaginal atrophy negatively affect the quality of life and sexual function in postmenopausal women. Linalool and Linalyl acetate may have an impact on sexual function by stimulating the parasympathetic system. Consistent with our research, several studies also supported the effect of lavender in improving sexual dysfunction. In our previous study, conducted among 120 postmenopausal women, the intervention group inhaled 2–3 drops of an aromatic solution (of lavender, fennel, geranium, and rose) three times a day for 6 weeks. In contrast, the control group used a placebo containing propylene glycol, mimicking the method used by the intervention group. As evidenced by the findings of this investigation, a statistically substantial distinction in the overall sexual function scores was observed between the aromatherapy group and the control group. This result is consistent with the findings of the present study in spite of the variance in the difference in the route of drug administration (Lavender is most frequently suggested for oral ingestion) and the exclusive utilization of lavender. A meta-analysis was conducted to study the effects of lavender aromatherapy on menopausal women and eight studies were reviewed, involving 493 participants. The examination mainly focused on the symptoms experienced by menopausal women. The meta-analysis found that lavender alone or with other aromas can improve sexual performance.³⁹ An alternative study found that inhaling lavender for 20 min over 12 weeks increased sexual desire in menopausal individuals with hot flashes.⁴⁰

In the present study, the examination of lipid profiles (i.e., total cholesterol, triglycerides, LDL, and HDL levels) showed no significant difference between the intervention and placebo groups. Lavender's lipid-reducing effect is attributed to cineole, which inhibits the HMG-CoA enzyme.⁴¹ Perillyl alcohol in lavender also inhibits the transformation of lathesterol into cholesterol⁴². This finding aligns with a study on chickens given LEO in their drinking water. This investigation has determined that the addition of LEO did not affect cholesterol and triglyceride levels. 38 In a study by Hur et al. (2007), it was found that women experiencing menopause showed increased levels of triglycerides and decreased levels of HDL after an 8-week lavender aromatherapy treatment.³³ Furthermore, in a study conducted by Rabiei et al., the impact of lavender extract on lipids in rat serum was examined. Lavender extract reduced serum cholesterol, triglyceride, LDL, and VLDL levels in the experimental groups. At a dosage of 100 mg/kg per day, lavender extract increased serum HDL levels.⁴³ According to our obtained results, no significant difference was identified between the two groups. Literature review shows that the effect of oral or inhaled lavender on lipid profile remains unclear and more studies are needed. Since serum cortisol levels have been concurrently established as an indicator of stress hormones,^{44,45} this observation may be in accordance with our clinical findings.

Wherein, there were no significant differences between groups after intervention in anxiety, depression, psychological and physical scale, similar to serum cortisol level. However, LEO is well-known for its anxiolytic and hypnotic characteristics and has been studied extensively.⁴⁶ The influence of lavender in reducing anxiety is due to the presence of volatile linalool. Lavender's anxiolytic properties may come from its ability to block the NMDA receptor and inhibit the SERT. The

calming effects observed in animals exposed to lavender can be explained by this molecular mechanism.^{47,48} In addition, due to its estrogenic property, in addition to selectively binding to alpha and beta estrogen receptors, flavonoids also act through the GABA receptor in the brain and play a role in reducing anxiety². GABA is a neurotransmitter that has been confirmed the connection between its receptors and depression¹. On the other hand, linalool leads to sedation by acting on GABA aminobutyric acid receptors.⁴⁹ In our previous study, an study was conducted to investigate the effects of lavender and bitter orange on anxiety in postmenopausal women. This study showed a significant difference between groups in mean anxiety scores and trait anxiety scores after eight weeks of treatment. Lastly, lavender significantly reduced mean anxiety scores compared to controls.²³ The mentioned study, a triple-blind randomized controlled trial, was conducted using the lavender flower powder 500 mg to assess the effect of lavender on the level of depression in postmenopausal women. We found a positive effect and lavender significantly reduced the mean depression score compared to the control group.⁵⁰ The observed difference from our previous studies may be attributed to the difference in dosage, using whole powdered flowers, and pharmaceutical form. In a separate study, Jokar et al. conducted a clinical trial with postmenopausal women. They were given lavender essence or distilled water before bed for 4 weeks as inhalation lavender aromatherapy. Contrary to our study, mean scores for depression and anxiety were decreased in the lavender group compared to the control group.⁵¹ Observed differences from our studies may be attributed to differences in dosage and administration route. Unlike our research, which involved the oral administration of lavender, the aforementioned study examined the effects of lavender aromatherapy, indicating that the efficacy of inhalation aromatherapy may be better in alleviating symptoms of anxiety and depression. Earlier, the results of a systematic review highlighted the positive impacts of lavender aromatherapy as a complementary medicine for mild to moderate depression.⁵² Bazrafshan et al. conducted a study that revealed taking lavender tea 2 g of dried lavender leaves twice daily for two weeks could decrease anxiety and depression in postmenopausal women. Results showed a significant difference in anxiety scores before and after the intervention. Additionally, a significant difference was observed in the average depression score between the lavender-consuming group and the control group.⁵³ The variation in dosage and using dried lavender leaves may be a remarkable element in explaining the variation in the effects of lavender on alleviating depression among postmenopausal women in our research. According to prior studies, the effectiveness of silexan (LEO) in managing depression and anxiety was known to be impacted by a variety of factors, including the dosage.⁵⁴ Moreover, favorable outcomes associated with the use of inhaled LEO in alleviating anxiety among women in the postpartum period have been documented.⁵⁵ There were differences in the study population (postpartum women vs postmenopausal women in our study) and route of administration. In addition, we measured anxiety and depression scores through Greene's menopause symptoms questionnaire which is different from the instruments applied in the aforementioned studies. Hence, it is essential to determine more conclusive outcomes concerning the efficacy of lavender, especially with regards to LEO (as soft capsules) administration, in postmenopausal women, through more evaluation and extensive clinical investigations and comparing it with other preparations of Lavender.

In the present study, we discovered despite a significant difference regarding the vasomotor symptoms in the intervention group before and after the intervention there were no significant differences between the groups in terms of vasomotor symptoms. In this regard, various studies,^{40,56,57} Studies have examined the use of lavender in treating menopause symptoms, such as hot flushing, and have obtained promising results. In a parallel investigation, a double-blind crossover study was conducted to investigate the effects of inhaling lavender oil on menopausal symptoms in 100 women aged 45–55. The study revealed positive outcomes on vasomotor symptoms.⁵⁸

The major strengths of this study were the conducting of triple-blind conditions, random allocation of participants into study groups, and the fact that data collectors were uninformed of group assignments and interventions. This protocol minimizes bias. Previous research suggested lavender effects may be due to psychological conditions or placebo effect.⁵⁹ This research aimed to observe the psychological consequences of lavender and placebo on menopausal symptoms. However, the study faced limitations due to restricted pharmaceutical dosage (80 mg). Furthermore, the present study faced other limitations including the influence of undiagnosed physical or psychological disorders as well as the utilization of self-reported questionnaires. The results of this study is not generalizable to non-menopausal women and men. Therefore, it is recommended to consider the prescription of higher and safe amounts, for example, the 160 mg dosage.^{60–62} To further clarify, it would be helpful to explore the differences between the oral administration of LEO soft capsules with other pharmaceutical forms, aromatherapy, as well as comparing LEO with whole dried flowers or leaves. Due to the aromatized nature of the LEO, participants could easily identify whether they were in the active treatment or placebo group if they punctured their study capsules. Therefore, it is suggested to evaluate the success of blinding participants and evaluators in future studies.

5. Conclusion

The findings of this investigation demonstrated that the oral administration of LEO exhibited a significant enhancement in sexual dysfunction among postmenopausal women. Despite detecting substantial advancements in anxiety, depression, psychological and physical scale, and vasomotor scale in both the placebo and intervention groups, no significant differences were identified between the two groups. Thus, the utilization of oral LEO can be regarded as an efficacious therapeutic agent for improving sexuality among postmenopausal women. Moreover, lavender soft gel 80 mg/day in the current study did not affect lipid profile. Literature review indicates that the effect of oral or inhaled lavender on lipid profile remains unclear and additional investigations are required to extend a definitive conclusion.

Ethics approval

This study was approved by the regional Ethics Committee (IR.TBZMED.REC.1400.1186). The protocol of the study was recorded in the Iranian Registry of Clinical Trials (IRCT20131009014957N13). Study procedures were performed according to the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. A signed informed consent was obtained from eligible women after explaining the research objectives.

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Author statement

The work described has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki). The manuscript is in line with the Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals and aim for the inclusion of representative human populations (sex, age and ethnicity) as per those recommendations. All

participants were verbally informed about the study protocol, objectives, advantages, and disadvantages of the study, and a signed written informed consent was obtained.

CRedit authorship contribution statement

Mahnaz Shahnazi: Writing – original draft, Investigation, Data curation, Conceptualization. **Behnam Kafil:** Writing – review & editing, Validation, Formal analysis, Conceptualization. **azizeh farshbaf-khalili:** Writing – original draft, Resources, Project administration, Methodology, Formal analysis, Conceptualization. **Mina Naghdi:** Writing – review & editing, Visualization, Supervision, Data curation, Conceptualization. **Morteza Haramshahi:** Writing – review & editing, Visualization, Supervision, Data curation, Conceptualization. **Soraya Babaie:** Writing – original draft, Investigation, Data curation, Conceptualization.

Declaration of Competing Interest

There is no conflict of interest in this study.

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Authors' contributions

AFKh contributed to the conceptualization, formal analysis, methodology, project administration, resources, and manuscript writing. MN and MH contributed to the conceptualization, data interpretation, visualization, supervision, and revising of the manuscript. MSh and SB contributed to the conceptualization, data curation, investigation, and manuscript writing. BK contributed to the conceptualization, formal analysis, validation, and manuscript revision. All authors approved the final draft of the article.

Informed consent

Written informed consent was filled up by all patients who participated in the current study.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.ctim.2024.103050](https://doi.org/10.1016/j.ctim.2024.103050).

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