

The impact of aromatherapy with Citrus bergamia-Lavandula angustifolia essential oil and/or mindfulness-behavioral therapy on menopausal health: A factorial randomized controlled trial

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Abstract

Psychological support is essential for women after menopause as a period with a high prevalence of mental health problems. It was observed a gap in the literature on the impact of bergamot and lavender aromatherapy and/or consultation with the mindfulness-behavioral therapy (MBT) approach on postmenopausal health. This study aimed to determine the effect of combined aromatherapy with lavender (*Lavandula angustifolia* Mill.) essential oil (LEO) and Bergamot (Citrus×bergamia (Risso) Risso & Poit) essential oil (BEO) and/or MBT on menopausal symptoms, sleep quality, and serum cortisol. This factorial randomized controlled trial was done on 132 postmenopausal women aged 50–60 years who had mild to moderate anxiety. The recruited women were divided into four groups receiving: 1) Usual care-placebo (Placebo), 2) MBT-placebo (Therapy), 3) LEO-BEO Aromatherapy-usual care (Aromatherapy), and 4) MBT- LEO-BEO aromatherapy (Therapy & Aromatherapy). They received daily aroma for eight weeks. The weekly MBT sessions were held for two months. The study outcomes were evaluated at baseline, after the intervention, and after an eight-week follow-up. The study groups were similar regarding baseline characteristics. After a two-month intervention, the total score of menopausal symptoms [aMD (95% CI): -5.7 (-9.5 to -1.8)] and anxiety [aMD (95% CI): -1.9 (-3.4 to -0.4)] significantly decreased in the Aromatherapy compared to Placebo. The total score of sleep quality (PSQI) in each of the Therapy [aMD (95% CI): -2.6 (-4.2 to -1.0)] and Aromatherapy [aMD (95% CI): -1.7 (-3.3 to -0.1)] groups significantly decreased compared to Placebo. The combination of Aromatherapy - Therapy had no significant effect compared to Placebo ($p > 0.05$). The serum cortisol level decreased in all four groups; however, the reductions were not statistically significant in the Aromatherapy and/or Therapy groups compared to the Placebo group ($p > 0.05$). Each method of intervention separately was accompanied by a favorable response in the management of menopausal symptoms. Furthermore, this study had a new approach toward combination therapy with aroma (LEO-BEO) and MBT.

1. Introduction

Poor sleep quality vasomotor symptoms ¹, depression ^{2,3}, loss of interest in enjoyable activities, appetite changes, tiredness, low energy, feeling of sadness, and even suicidal thoughts ⁴ are among the common complaints during the menopause transition period ⁵. Anxiety is the other common problem in menopause because of impaired self-confidence, disability of usual activities, impaired relationship with friends and relatives, physical and financial dependence, and chronic diseases ⁶. Anxiety independently associated with severe symptoms of menopause and severe impairment of life quality ⁷. As a woman is transferred from the early the late transition stage of menopause, overnight cortisol levels decrease ⁸. A direct relationship has been established between stressors and depressed mood symptoms with cortisol ⁹.

Hormone replacement therapy has been the preferred treatment for relieving menopausal symptoms. However, many women cannot receive hormone therapy because of the associated health risks.

Accordingly, complementary and alternative medicines are commonly preferred to improve menopausal symptoms ¹⁰.

Aromatherapy is an alternative and complementary intervention that applies essential oils to amend psychological, mental, and emotional states and different disorders through massage, inhalation, and therapeutic baths. Many benefits of aromatherapy have been indicated in declining anxiety, stress, pain, and relaxation through the stimulation of endorphin production ^{11,12}. Although serum cortisol increases in stressful conditions, a meta-analysis did not show a significant impact of aromatherapy with some plants on serum cortisol levels ¹³.

Citrus×bergamia (Risso) Risso & Poit. [a synonym of *Citrus limon* (L.) Osbeck] (The World Flora Online), commonly known as Bergamot, is a member of the Rutaceae family ^{14 15}The bergamot fruit's essential oils, which are obtained by rasping and cold pressing the fruit peel, are its primary use ¹⁵. Bergamot essential oil (BEO) causes anti-anxiety behaviors and decreases the activity of the HPA axis by decreasing the response of corticosterone to stress ¹⁶. BEO has sedating properties and would be beneficial for menopausal symptoms including depression, anxiety, and insomnia ¹⁷. Its traditional use dates back to various ancient civilizations such as Egypt, China, and India for a minimum of 6,000 years ¹⁸. The utilization of BEO, as antimicrobial agents for the topical management of infections, is widely recognized in popular tradition ¹⁹. This therapeutic approach represents a natural way of restoring an individual's mental, physical, and spiritual well-being ¹⁸. Recent investigations have disclosed that, despite the centuries-long purported effective use of BEO as traditional medicine, there exists a dearth of substantiated scientific proof to substantiate this application specifically, the pharmacology of essential oil and/or their individual chemical constituents remains largely unexplored ¹⁸.

Aromatherapy using lavender (*Lavandula angustifolia* Mill.) essential oil (LEO), belonging to the Lamiaceae family, has shown improving effects on the quality of sleep in depressed participants ²⁰. Lavender oil as a floral aroma is traditionally used for its anxiolytic features ²¹. The utilization of lavender among ordinary individuals for the purpose of manipulating psychological states, such as calming, relaxation, and facilitating sleep, has a longstanding presence in traditional customs and practices ²². Due to the calming and sedative effect of bergamot and lavender, their inhalation blend has been proposed to be used at night for night sweats and insomnia ¹⁷. The value of scientific investigation lies in its ability to explore and establish the authenticity of these potentialities ²³. Aroma components possess therapeutic efficacy, as they exert direct influence on cortical areas and can penetrate the blood-brain barrier ²².

Mindfulness-behavioral therapy (MBT) is another complementary and alternative medicine intervention that uses a variety of exercises to improve awareness, attention, focus on the present moment, and acceptance. Mindfulness may affect cortisol levels, but findings are inconclusive ²⁴. A meta-analysis illustrated that MBT significantly improved the total score of life quality, vasomotor, and physical domains in comparison with control groups in menopausal women. It indicated no efficacy on

psychological and sexual subscales. The authors concluded that further research is required to verify these effects²⁵. MBT seems to be a helpful treatment for adults who encounter chronic insomnia²⁶. However, the effectiveness of web-based MBT through videoconferencing during the COVID-19 pandemic showed that this approach might not help improve sleep quality²⁷. Some studies indicated that MBT alongside massage-aromatherapy improved depression, quality of life, perceived stress, and sleep quality of elderly women who had chronic pain²⁸.

Psychological support is essential during menopause as a life course accompanied by a high occurrence of problems in mental health. Based on the observed gap in the literature on the impact of bergamot and lavender aromatherapy and/or consultation with the MBT approach in postmenopausal women and the recommendation of a systematic review to examine the effect of MBT on cortisol²⁴, this study aimed to determine the impact of aromatherapy with LEO-BEO and/or MBT on menopausal symptoms, sleep quality, and serum cortisol in postmenopausal women with a positive screening of anxiety.

2. Materials and Methods

2.1. Type of study and participants

One hundred and thirty menopausal women were examined in this factorial randomized clinical trial. This is part of a larger research that was approved by the Regional Ethics Committee of Tabriz University of Medical Sciences (ID: IR.TBZMED.REC.1398.775). The protocol of the study was recorded in the Iranian Registry of Clinical Trials (IRCT20131009014957N8) on 04/12/2019. Study procedures were performed according to the Helsinki Declaration and Tokyo for humans, and informed consent was obtained. Six healthcare centers with different socio-economic conditions were selected among 87 healthcare centers in Tabriz-Iran. The number of 22 women aged 50–60 covered by each of the six healthcare centers was selected by convenience sampling. A signed informed consent was obtained from eligible women after explaining the research objectives.

Inclusion criteria were married postmenopausal women, willing to participate, aged between 50–60 years, with mild or moderate anxiety according to the anxiety scale Beck, obtaining a score of 15–42 on the Greene scale, and a score of five or higher in The Pittsburgh Sleep Quality Index (PSQI). Exclusion criteria were self-reported uncontrolled mental and physical disorders (depression, mental disability, cardiovascular disease, diabetes), regular use of drugs that affect sleep quality, history of allergy to herbs, olfactory disorders, loss of one of the close relatives at the last 3 months, and using hormone therapy during the past six months.

2.2. Sample size

The sample size was estimated using G*Power 1.3 considering the effect of Lavender and Bergamot on cortisol levels [mean1 = 10.6, mean2 = 14.4, sd1 = 2.5, sd2 = 4.4, α = 0.05, β = 0.2, two-tailed test]^{12,16}, state anxiety [mean1 = 45.26, mean2 = 40.74, sd1 = sd2 = 5.72, α = 0.05, β = 0.2, two-tailed test], and trait

–anxiety [mean1 = 43.73, mean2 = 39.35, sd1 = sd2 = 5.64, $\alpha = 0.05$, $\beta = 0.2$, two-tailed test]⁶]. According to the difference between the two independent means, the sample size was calculated 27. Considering a 20% loss to follow-up, the final sample size was computed to equal 33 women in each group.

2.3. Randomization and intervention

Random Allocation Software (version 1.0.0) was used to generate allocation sequence by the random blocks sized 4 and 8 and an allocation ratio 1: 1: 1: 1. Study participants were divided into four groups receiving 1) Placebo: Usual care & Placebo, 2) Therapy: Mindfulness behavioral therapy & Placebo, 3) Aromatherapy: LEO-BEO Aromatherapy & Usual care, and 4) Therapy & Aromatherapy: Mindfulness-behavioral therapy & LEO-BEO aromatherapy. In order to allocate concealment, a non-researcher clinician provided intervention packs according to the generated sequence and numbered them from 1 to 132. The packs from the first to the last were given based on the order of entry into the study.

Primary outcomes were the score of menopausal symptoms, sleep quality, and the mean concentration of serum cortisol, and secondary outcomes were possible adverse events among study groups. In groups without MBT, which should be consumed aroma or placebo, we did telephone calls with the participants weekly to remind the consumption of the delivered intervention.

2.4. Mindfulness- behavioral therapy (MBT)

MBT is a new technique in behavioral therapy including observation, feeling, awareness, and love structures, which focuses on the present facilitating concentration, and attaining awareness²⁹. In the present study, MBT was performed weekly in the teaching room of health care centers with the presence of eight women. MBT counseling was conducted by a co-author who was an expert in counseling under the supervision of an expert psychologist. Only the statistical analyzer and outcome assessor were bind to MBT or usual care. The content of the intervention has been shown in Supplementary Table 1.

2.5. Aroma and placebo preparation

All methods for aroma and placebo preparation were carried out in accordance with institutional, national, and international guidelines and legislation. For this purpose, the essential oil of *Lavandula angustifolia* was obtained through hydro-distillation using a Clevenger apparatus. About 100 g of dried plants (flowers) were used and distillation was conducted for 4 h. The samples were stored in the dark and less than 4° C. The essential oil of *Citrus bergamia* was prepared by rasping and cold pressing the fruit peel. The preparation of these aromas was ordered to **Gol Daru** Pharmaceutical Company, Isfahan, Iran. Bergamot and Lavender essential oils were analyzed using a Quadrupole mass spectrometry chromatography apparatus (Supplementary Tables 2 and 3). A combined aroma of bergamot essential oil (BEO) 0.04% and lavender essential oil (LEO) 5% was prepared in 60% ethanol solution under the supervision of a pharmacognosist in the Biotechnology Research Center. The plant name has been checked with <http://www.worldfloraonline.org> on 13 June 2023. The placebo (composed of propylene glycol) was prepared in a 30-ml dark and sealed bottle similar to the main aroma in appearance. One LB aroma or an identical placebo bottle was delivered to every participant according to the random

allocation sequence. The participants were instructed to rub 2–3 drops on the skin of the forearm and inhale three times/day for eight weeks. The participants, the researcher, and the statistical analyzer were blind to aroma or placebo.

2.6. Data collection tools

A demographic questionnaire consisted of questions regarding age, postmenopausal years, weight, education, occupation, history of hormone therapy, the consumption of Soy, vitamin D3 supplementation, the Greene Climacteric Scale, the Pittsburgh Sleep Quality Index (PSQI), a checklist for recording daily use of aroma, and a checklist for reporting the possible side effects were used for collecting data.

2.6.1. Greene Climacteric Scale

The Greene Climacteric Scale was developed by Professor. Greene in Scotland in 1975³⁰. This scale comprises 21 questions. For scoring, the observed symptom is scored one, two, or three for low, medium, and high intensity, respectively. 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 19–20 measure vasomotor symptoms, and question 21 represents sexual dysfunction. The Greene Climacteric Scale has been previously applied in Iran and Askari et al. approved its reliability³¹.

2.6.2. The Pittsburgh Sleep Quality Index (PSQI)

PSQI 'invented by Buysse et al. in 1989' is a questionnaire for measuring sleep quality in the past month. It comprises of a total of nine major questions, wherein questions 1–4 are open-ended, brief, and necessitate a singular choice response. Conversely, questions 5–9 are presented in a multiple-choice format. Moreover, the maximum achievable score is subject to variation, ranging from 0 to 21. The higher the score, the poorer the quality of sleep. A score higher than 5 indicates poor sleep quality. In the study conducted by Malekzadegan and colleagues in Iran, the validity and reliability of this questionnaire were confirmed³².

In this study, all participants completed the Greene Climacteric Scale and PSQI at baseline, end of the eight-week intervention, and follow-up (eight weeks after intervention). They recorded the daily use of medicines and adverse events in a checklist during the study.

2.6.3. Measurement of biochemical assessment

We took 5 ml of blood sample at 8 am, poured it into gel tubes without anticoagulant and centrifuged at room temperature at 3000 rpm for 10 minutes, and kept the isolated sera at – 70° C until the analysis. The serum cortisol was measured through the enzyme-linked immunosorbent assay (ELISA) method using MonoKit licensed by Monobind Inc. made by USA (Cat No: 3625-300A) according to the manufacturer's instructions and reagents and materials inside the pack in the required conditions and temperatures at baseline and after eight week-intervention.

2.7. Data analysis

SPSS software version 21 was applied for data analyses. Data normality was assessed using Kolmogorov-Smirnov. The vasomotor and sexual sub-domains of the Greene had non-normal distributions. Number and percent y, mean (standard deviation: SD), and median (inter-quartile range: IQR) were used for describing variables. Chi-square, Fisher's exact test, one-way ANOVA with Tukey's post hoc, ANCOVA adjusted for baseline values, repeated ANOVA, and Mann-Whitney U were used for analyzing variables. A p-value < 0.05 was considered statistically significant. All data were analyzed based on the intention-to-treat approach.

3. Results

This research began on December 4, 2019, and follow-ups were accomplished on November 21, 2020. In this RCT, 132 women were randomly allocated into four 32-individual groups. A total of 18 women in different groups dropped out of the study. Other participants were followed up and completed this RCT (Fig. 1).

3.1. Baseline characteristics

Nearly half of the participants belonged to each 50–55 and 56–60 year groups. The mean (SD) postmenopausal years and weight were 5.3 (3.9) and 75.5 (11.8) kg, respectively. The majority of the studied women (84.1%) were housekeepers and more than half of them (58.3%) consumed vitamin D3 supplements. There were no significant differences between the study groups in the basic characteristics of the participants ($P > 0.05$). (Table 1)

Table 1
Baseline characteristics of the postmenopausal women who participated in the study

Variable	Placebo (n = 33)	Therapy (n = 33)	Aromatherapy (n = 33)	Therapy + Aromatherapy (n = 33)	P- value
Age (year)/ n (%)					
50–55	15 (45.5)	15 (45.5)	18 (54.5)	19 (57.6)	0.437
56–60	18 (54.5)	18 (54.5)	15 (45.5)	14 (42.4)	
Postmenopausal years/ mean (SD)	5.8 (3.7)	5.6 (4.1)	4.5 (3.3)	5.3 (3.8)	0.554
Weight (kg)/ mean (SD)	75.3 (9.7)	73.6 (9.7)	75.5 (12.7)	77.4 (14.9)	0.684
Education/ n (%)					0.223
Less than diploma	25 (75.8)	26 (78.8)	22 (6.5)	22 (6.5)	
Diploma or collegiate	8 (24.2)	7 (21.2)	11 (34.5)	11 (34.5)	
Occupation/ n (%)					0.420
Housewife	27(81.8)	28(84.8)	26(78.8)	30(90.9)	
Occupied or retired	6(18.2)	5(15.2)	7(21.2)	3(9.1)	
History of hormone therapy (yes)/ n (%)	0 (0.0)	1 (3.0)	2 (6.1)	0 (0.0)	0.789
Consumption of Soy (yes)/ n (%)	0 (0.0)	0 (0.0)	2 (6.1)	2 (6.1)	0.068
Vitamin D3 supplementation (yes)/ n (%)	19 (57.5)	22(66.7)	18 (54.5)	18 (54.5)	0.711
1) Placebo: Usual care + Placebo, 2) Therapy: Mindfulness behavioral therapy + Placebo, 3) Aromatherapy: LEO-BEO Aromatherapy + Usual care, and 4) Therapy + Aromatherapy: LEO-BEO aromatherapy + Mindfulness-behavioral therapy					
Quantitative variables were analyzed using one-way ANOVA and qualitative valuables were analyzed using Chi-square or Fisher exact test.					

Primary outcomes

The total score of Greene and its psychological, physical, vasomotor, and sexual sub-domains were similar in the study groups at baseline. After the eight-week intervention, the total score of Greene [aMD (95%CI); p-value: -5.7 (-9.5 to -1.8); 0.004] and anxiety [aMD (95%CI); p-value: -1.9 (-3.4 to -0.4); 0.013] significantly decreased in the Aromatherapy compared to Placebo. In the follow-up stage, only the score of vasomotor significantly reduced in the Aromatherapy compared to the Placebo group (p = 0.036).

Repeated Measure ANCOVA using Greenhouse-Geisser showed a significant difference ($p = 0.002$) in total menopausal score between study groups during the intervention (Table 2).

Table 2

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

Variable	Placebo (n = 29) Mean (SD)	Therapy (n = 28) Mean (SD)	Aromatherapy (n = 29) Mean (SD)	Therapy + Aromatherapy (n = 29) Mean (SD)	aMD (95% CI) p- value*	aMD (95% CI) p- value [±]	aMD (95% CI) p- value [†]
Anxiety (0–18)							
Baseline	6.8 (3.3)	5.8 (2.6)	7.7 (3.7)	7.4 (3.2)	0.679	0.705	0.890
After 8 weeks	5.2 (2.5)	5.1 (2.4)	3.6 (1.6)	6.1 (3.0)	0.3 (-1.8 to 1.2)	-1.9 (-3.4 to -0.4)	0.7 (-0.7 to 2.2)
					0.680	0.013	0.333
Follow-up	6.1 (2.5)	5.6 (2.1)	5.8 (2.4)	6.4 (3.1)	-1.4 (-1.8 to 1.5)	-0.8 (-2.4 to 0.9)	0.01 (-1.6 to 1.6)
					0.865	0.364	0.989
Depression (0–15)							
Baseline	6.3 (3.0)	4.8 (2.2)	6.1 (2.7)	5.5 (2.6)	0.382	0.996	0.819
After 8 weeks	3.8 (1.7)	4.5 (2.2)	2.5 (1.2)	4.7 (2.3)	1.3 (-0.0 to 2.6)	-1.2 (-2.5 to 0.1)	1.2 (-0.1 to 2.5)
					0.051	0.060	0.065
Follow-up	4.5 (2.1)	4.5 (2.1)	4.1 (2.0)	4.8 (2.2)	0.5 (-0.9 to 2.1)	-0.3 (-1.8 to 1.2)	0.6 (-0.9 to 2.2)
					0.477	0.704	0.397
Repeated Measure ANOVA using Greenhouse-Geisser showed a significant difference for time & group effect (p = 0.002) in total menopausal score between study groups during the intervention							
1) Placebo: Usual care + Placebo, 2) Therapy: Mindfulness behavioral therapy + Placebo, 3) Aromatherapy: LEO-BEO Aromatherapy + Usual care, and 4) Therapy + Aromatherapy: Mindfulness behavioral therapy + LEO-BEO aromatherapy							
2) aMD: Adjusted Mean Difference for baseline values, p-values at baseline were computed by independent t-test. All between-group p-values after intervention were reported by ANCOVA adjusted for baseline. Vasomotor and sexual domains had not normal distribution which was described with Median (Interquartile) and analyzed using Mann-Whitney U test. p-value*: Therapy compared to Placebo; p-value [±] : Aromatherapy compared to Placebo; p-value [†] : Therapy + Aromatherapy compared to placebo							

Variable	Placebo (n = 29) Mean (SD)	Therapy (n = 28) Mean (SD)	Aromatherapy (n = 29) Mean (SD)	Therapy + Aromatherapy (n = 29) Mean (SD)	aMD (95% CI) p- value*	aMD (95% CI) p- value [±]	aMD (95% CI) p- value [†]
Psycho (0–33)							
Baseline	13.1 (6.0)	10.7 (4.7)	13.8 (6.5)	12.9 (6.1)	0.442	0.970	1.0
After 8 weeks	9.0 (4.4)	9.7 (4.2)	7.8 (3.5)	10.8 (4.3)	1.7 (-0.8 to 4.2)	-1.5 (-3.9 to 1.0)	1.9 (-0.5 to 4.3)
					0.179	0.238	0.126
Follow-up	10.7 (5.1)	10.1 (4.4)	9.9 (4.2)	11.2 (5.2)	0.5 (-2.3 to 3.4)	-1.1 (-3.9 to 1.6)	0.6 (-2.1 to 3.4)
					0.711	0.425	0.653
Physical (0–21)							
Baseline	6.8 (2.9)	5.6 (2.2)	6.9 (3.2)	7.6 (3.3)	0.632	0.992	0.850
After 8 weeks	5.6 (2.3)	5.0 (2.4)	4.3 (2.1)	7.0 (3.2)	-0.0 (-1.5 to 1.4)	-1.4 (-2.9 to -0.0)	0.8 (-0.6 to 2.3)
					0.952	0.050	0.257
Follow-up	6.8 (3.1)	5.5 (2.3)	5.7 (2.3)	6.2 (2.9)	-0.7 (-2.4 to 0.8)	-1.2 (-2.8 to 0.4)	-1.1 (-2.6 to 0.5)
					0.343	0.130	0.189
Repeated Measure ANOVA using Greenhouse-Geisser showed a significant difference for time & group effect (p = 0.002) in total menopausal score between study groups during the intervention							
1) Placebo: Usual care + Placebo, 2) Therapy: Mindfulness behavioral therapy + Placebo, 3) Aromatherapy: LEO-BEO Aromatherapy + Usual care, and 4) Therapy + Aromatherapy: Mindfulness behavioral therapy + LEO-BEO aromatherapy							
2) aMD: Adjusted Mean Difference for baseline values, p-values at baseline were computed by independent t-test. All between-group p-values after intervention were reported by ANCOVA adjusted for baseline. Vasomotor and sexual domains had not normal distribution which was described with Median (Interquartile) and analyzed using Mann-Whitney U test. p-value*: Therapy compared to Placebo; p-value [±] : Aromatherapy compared to Placebo; p-value [†] : Therapy + Aromatherapy compared to placebo							

Variable	Placebo (n = 29) Mean (SD)	Therapy (n = 28) Mean (SD)	Aromatherapy (n = 29) Mean (SD)	Therapy + Aromatherapy (n = 29) Mean (SD)	aMD (95% CI) p-value*	aMD (95% CI) p-value [±]	aMD (95% CI) p-value [†]
Vasomotor (0–6)	Median (IQ)	Median (IQ)	Median (IQ)	Median (IQ)	p-value*	p-value [±]	p-value [†]
Baseline	3.0 (2.0)	3.0 (3.5)	3.0 (2.0)	3.0 (2.0)	0.926	0.812	0.751
After 8 weeks	2.0 (3.0)	2.0 (3.5)	2.0 (2.0)	1.0 (4.0)	0.437	0.088	0.230
Follow-up	3.0 (2.5)	2.0 (2.75)	2.0 (2.0)	2.0 (4.0)	0.088	0.036	0.089
Sexual (0– 3)	Median (IQ)	Median (IQ)	Median (IQ)	Median (IQ)	p-value*	p-value [±]	p-value [†]
Baseline	1.0 (1.5)	1.0 (2.0)	2.0 (1.5)	1.0 (2.0)	0.656	0.581	0.863
After 8 weeks	1.0 (1.5)	1.0 (2.0)	1.0 (0.5)	1.0 (2.0)	0.840	0.973	0.980
Follow-up	1.0 (2.0)	1.0 (1.75)	1.0 (1.0)	1.0 (1.0)	0.138	0.792	0.863
Total score (0–63)							
Baseline	24.3 (8.8)	21.0 (7.2)	25.2 (10.9)	24.7 (10.6)	0.539	0.980	0.998
After 8 weeks	18.3 (8.4)	18.0 (8.7)	13.2 (6.4)	20.9 (9.3)	1.6 (-2.3 to 5.5) 0.415	-5.7 (-9.5 to -1.8) 0.004	2.4 (-1.4 to 6.2) 0.213
Repeated Measure ANOVA using Greenhouse-Geisser showed a significant difference for time & group effect (p = 0.002) in total menopausal score between study groups during the intervention							
1) Placebo: Usual care + Placebo, 2) Therapy: Mindfulness behavioral therapy + Placebo, 3) Aromatherapy: LEO-BEO Aromatherapy + Usual care, and 4) Therapy + Aromatherapy: Mindfulness behavioral therapy + LEO-BEO aromatherapy							
2) aMD: Adjusted Mean Difference for baseline values, p-values at baseline were computed by independent t-test. All between-group p-values after intervention were reported by ANCOVA adjusted for baseline. Vasomotor and sexual domains had not normal distribution which was described with Median (Interquartile) and analyzed using Mann-Whitney U test. p-value*: Therapy compared to Placebo; p-value [±] : Aromatherapy compared to Placebo; p-value [†] : Therapy + Aromatherapy compared to placebo							

Variable	Placebo (n = 29) Mean (SD)	Therapy (n = 28) Mean (SD)	Aromatherapy (n = 29) Mean (SD)	Therapy + Aromatherapy (n = 29) Mean (SD)	aMD (95% CI) p- value*	aMD (95% CI) p- value [±]	aMD (95% CI) p- value [†]
Follow-up	21.8 (9.3)	18.7 (8.9)	19.0 (8.6)	20.9 (9.1)	-1.2 (-5.6 to 3.2) 0.593	-3.4 (-7.8 to 0.9) 0.119	-1.2 (-5.6 to 3.1) 0.573
Repeated Measure ANOVA using Greenhouse-Geisser showed a significant difference for time & group effect (p = 0.002) in total menopausal score between study groups during the intervention							
1) Placebo: Usual care + Placebo, 2) Therapy: Mindfulness behavioral therapy + Placebo, 3) Aromatherapy: LEO-BEO Aromatherapy + Usual care, and 4) Therapy + Aromatherapy: Mindfulness behavioral therapy + LEO-BEO aromatherapy							
2) aMD: Adjusted Mean Difference for baseline values, p-values at baseline were computed by independent t-test. All between-group p-values after intervention were reported by ANCOVA adjusted for baseline. Vasomotor and sexual domains had not normal distribution which was described with Median (Interquartile) and analyzed using Mann-Whitney U test. p-value*: Therapy compared to Placebo; p-value [±] : Aromatherapy compared to Placebo; p-value [†] : Therapy + Aromatherapy compared to placebo							

The total score of PSQI was similar in the study groups at baseline. After the intervention, the total score of PSQI in the Therapy [aMD (95%CI); p-value: -2.6 (-4.2 to -1.0); 0.002] and Aromatherapy [aMD (95%CI); p-value: -1.7 (-3.3 to -0.1); 0.036] groups significantly decreased compared to Placebo. Repeated-measure test using Sphericity Assumed showed a significant difference (p = 0.043) in total PSQI score between study groups during the intervention (Table 3).

Table 3

The total score of the Pittsburgh Sleep Quality Index (PSQI) by study groups at different time points

Total PSQI	Placebo (n = 29) Median (IQ)	Therapy (n = 28) Median (IQ)	Aromatherapy (n = 29) Median (IQ)	Therapy + Aromatherapy (n = 29) Median (IQ)	p- value*	p- value [±]	p- value [†]
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	aMD (95% CI)	aMD (95% CI)	aMD (95% CI)
					p- value*	p- value [±]	p- value [†]
Baseline	7.9 (1.9)	7.4 (2.1)	7.5 (2.5)	7.5 (2.8)	0.539	0.980	0.998
After 8 weeks	7.4 (2.7)	4.5 (1.6)	5.4 (2.2)	6.5 (2.5)	-2.6 (-4.2 to -1.0) 0.002	-1.7 (-3.3 to -0.1) 0.036	-1.2 (-2.8 to 0.5) 0.159
Follow- up	7.6 (3.1)	6.6 (2.2)	7.9 (2.7)	6.7 (2.5)	-0.7 (-2.5 to 1.0) 0.398	-0.3 (-2.0 to 1.5) 0.767	-0.7 (-2.4 to 1.0) 0.407
Repeated Measure test using Sphericity Assumed showed a significant difference (p = 0.043) in total PSQI score between study groups during intervention (time & group)							
1) Placebo: Usual care + Placebo, 2) Therapy: Mindfulness behavioral therapy + Placebo, 3) Aromatherapy: LEO-BEO Aromatherapy + Usual care, and 4) Therapy + Aromatherapy: Mindfulness behavioral therapy + LEO-BEO aromatherapy. All components had no normal distribution which was analyzed using the Mann-Whitney U test.							
p-value*: Therapy compared to Placebo; p-value [±] : Aromatherapy compared to Placebo; p-value [†] : Therapy + Aromatherapy compared to placebo. aMD: Adjusted Mean Difference for baseline values, p-values at baseline for total PSQI were computed by independent t-test. All between-group p-values after intervention were reported by ANCOVA adjusted for baseline.							

The mean (SD) serum cortisol was 16.6 (7.6), 18.3 (7.7), 16.8 (7.8), and 16.9 (6.4) µg/dL among the Placebo, Therapy, Aromatherapy, and Therapy + Aromatherapy groups at baseline, respectively. No significant differences were indicated between Placebo with the other study groups after intervention ($p < 0.05$). A significant increase in pulse rate was illustrated in the Aromatherapy compared to the Placebo group [adjusted mean difference (aMD) 95%CI; p-value: 3.4 (0.2 to 6.7); 0.038] (shown in Table 4).

Table 4

The concentration of serum cortisol and pulse rate by study groups at different time points

Variable	Placebo (n = 29) Mean (SD)	Therapy (n = 28) Mean (SD)	Aromatherapy (n = 29) Mean (SD)	Therapy+ Aromatherapy (n = 29) Mean (SD)	aMD (95% CI) p- value*	aMD (95% CI) p- value [±]	aMD (95% CI) p- value [†]
Serum cortisol (µg/dL)							
Baseline	16.6 (7.6)	18.3 (7.7)	16.8 (7.8)	16.9 (6.4)	0.957	0.653	0.710
After 8 weeks	15.2 (6.2)	16.0 (6.2)	15.9 (5.6)	15.7 (4.9)	0.8 (-2.9 to 4.6) 0.647	0.7 (-2.9 to 4.4) 0.704	0.5 (-3.2 to 4.3) 0.769
Pulse rate (beat)							
Baseline	78.6 (5.9)	77.1 (5.4)	78.1 (8.1)	79.1 (7.0)	0.812	0.988	0.992
15 min after the first usage	78.2 (6.2)	78.4 (5.3)	81.4 (7.5)	81.3 (6.9)	0.7 (-2.5 to 4.0) 0.664	3.4 (0.2 to 6.7) 0.038	2.9 (-0.4 to 6.2) 0.083
1) Placebo: Usual care + Placebo, 2) Therapy: Mindfulness behavioral therapy + Placebo, 3) Aromatherapy: LEO-BEO Aromatherapy + Usual care, and 4) Therapy + Aromatherapy: Mindfulness-behavioral therapy + LEO-BEO aromatherapy.							
p-value*: Therapy compared to Placebo; p-value [±] : Aromatherapy compared to Placebo; p-value [†] : Therapy + Aromatherapy compared to placebo. aMD: Adjusted Mean Difference, p-values at baseline were computed by independent t-test. All between-group p-values after intervention were reported by ANCOVA adjusted for baseline.							

3.2. Side effects

Vomiting (by one woman in the Therapy and two women in each Aromatherapy and Therapy + Aromatherapy groups), tachycardia (by three ones in the Therapy, five in Placebo, two in Therapy + Aromatherapy, and four in Aromatherapy groups), headache (by one in the Therapy, five in each Placebo, Therapy + Aromatherapy, and ten in Aromatherapy groups), nasal congestion (one in the LB Aromatherapy group), and cough (two in the Therapy, and one in each Placebo and Therapy + Aromatherapy groups) were reported. These problems reported in early intervention did not stop the study.

4. Discussion

To the best of our knowledge, this was the first study that investigated the efficacy of aromatherapy with the combination of BEO and LEO and/or MBI on menopausal symptoms. Our results showed that the total score of menopausal symptoms and subscale of anxiety improved in the Aromatherapy group. The total score of PSQI improved in each of the separate groups of Aromatherapy and Therapy compared to the Placebo group following the intervention. The score of vasomotor symptoms was alleviated in the follow-up period in the group receiving aromatherapy compared to the control group. In addition, the results showed that the serum cortisol reductions were not statistically significant in the Aromatherapy and/or Therapy groups compared to the Placebo group. In recent years, mindfulness has become a popular approach besides herbal medicine in many psychosomatic disorders ^{33,34}.

4.1. Effect of aromatherapy on physical and psychological symptoms

For centuries, EOs as a fragrance with the ability to heal the body, mind, and soul have found a special place in society ¹¹. Many projects have been performed to discover their nature and role in disorders ³⁵. The impact of lavender in reducing stress or sleep disturbances in the menopausal period was documented in previous studies. Similar to most volatile oils, bergamot has specific neuropharmacological effects. Antidepressants, calming, relaxing, and sedatives are some of these effects ³⁶. A systematic review reported the effective role of aroma inhalation in improving sleep problems and other psychophysical symptoms such as anxiety, depression, and vasomotor symptoms in menopause ³⁷.

In line with our study, Cho et al. evaluated the effect of aromatherapy with EOs of lavender, roman, chamomile, and neroli, on 46 patients who underwent percutaneous coronary intervention (PCI) and indicated that aromatherapy reduced anxiety and improved sleep quality in comparison with conventional nursing intervention ³⁸. Kamalifard et al. (2018) indicated that bitter orange and lavender aromatherapy were efficient in reducing depression ³⁹ or sleep quality in menopausal women.

Cha et al. (2010) conducted a study on the beneficial effects of aromatherapy using a blend of basil, lavender, rosemary and rose oils in middle-aged women. The study aimed to reduce headache, anxiety, and serum cortisol levels. In a previous study, Hosseini et al. (2016) investigated the effects of lavender essence on anxiety levels and blood cortisol in individuals undergoing open-heart surgery. Both the study and control groups showed a significant decrease in anxiety levels, with a greater reduction in the intervention group. This finding was consistent with another study on surgical patients conducted by Babashahi et al. (2010). Watanabe et al. (2015) also reported low salivary cortisol levels in the group treated with BEO aromatherapy. These studies suggest that aromatherapy can have a therapeutic effect on stress-related factors, particularly cortisol levels. Although our study demonstrated a decrease in

serum cortisol levels, it was not significant. The possible cause of this difference can be attributed to the herbal compounds, their prescription route, and their concentration.

4.2. Effect of MBT on physical and psychological symptoms

The exact psychotherapeutic effect of mindfulness meditation in the reduction of some disorders is not well recognized. However, neuroimaging studies including EEG ³⁸, and functional MRI ⁴⁰, showed that different gray matter morphometry is exhibited in cases who underwent meditations in comparison with non-meditating individuals. In addition, activation of the hippocampus and the right anterior insula in meditation has been revealed ⁴¹.

In alternative medicine, mindfulness improves some psychological symptoms including anxiety, depression as well and health-related quality of life ⁴². Two systematic reviews were published on the effect of psychosocial interventions for menopause. The frequency and severity of vasomotor symptoms (especially in the presence of insomnia, fatigue, anxiety, or depression) were reduced in cases who underwent Cognitive Behavioral Therapy (CBT) ^{43,44}.

Cho, et al., in a review article, concluded that mind and body practices such as biofeedback, mindfulness-based stress reduction, and relaxation techniques reduced stress and improved quality of life ¹⁰. Another study reported the psychological, physical, and quality of life outcomes following MBSR in nursing home residents in Germany or a significant improvement in vitality and role limitations due to physical health problems ⁴⁵.

In our study, MBT led to significant improvement in sleep quality at the end of the eight-week intervention, and despite the return of these symptoms eight weeks after cessations, it didn't reach the baseline and shows the durability of its effect. The probable inconsistencies with previous studies regarding no efficacy of MBT on menopausal symptoms could be related to the used tools, or the population being studied, as well as the coincidence of the study with the COVID-19 epidemic, which may have affected the correct performance of MBT exercises at home.

4.3. Effect of combination therapy with aroma and MBT on physical and psychological symptoms

In recent years, combined method interventions including aromatherapy and MBT have been noticed in the management of menopause symptoms.

McBee reported the outcomes of her mixed method of mindfulness meditation with aromatherapy study on both residents of a nursing home and caregivers ⁴⁶. Their intervention reduced agitation and behavioral problems among nursing home residents ⁴⁷. Finally, they reported that an adapted 8-week Mindfulness-Based Stress Reduction (MBSR) program reduced psychological distress symptoms and improved health-related quality of life when compared to the control group. Some studies demonstrated the improved role of mindfulness besides aromatherapy massages with lavender on quality of life,

quality of sleep, and reducing chronic pain in elderly women ²⁸, or with EO of *S. brevicalyx* and *S. boliviana* in reducing anxiety in participants between 25 and 45 years old ⁴⁸. In the present study, aromatherapy with the combination of lavender and bergamot was accompanied by favorable outcomes in the reduction of vasomotor symptoms and improvement of sleep quality compared to routine care-placebo. However, it should be considered that the mentioned effects were not significant and we did not observe the superior effect of mixed intervention compared to the MBI or aromatherapy alone but it seems that the durability of combination therapy at 8 weeks follow up after ending interventions was high.

4.4. Limitations

It was not possible to completely equalize the smell of the aroma in the main and placebo groups. However, the appearance of the sealed dark glasses was the same and the researcher was unaware of their contents. This study was conducted on postmenopausal women with positive anxiety screening, so the findings are not generalizable to all postmenopausal women. In addition, LEO-BEO aromatherapy can be used in different concentrations. Moreover, due to the many intervention groups in this study, we could not consider pure aromatherapy interventions using any of the aromas to compare the effects with the combined aromatherapy used in this study, so future studies in this regard are suggested.

Conclusion

Our results showed that each method of intervention separately was accompanied by a favorable response in the management of menopausal symptoms including total menopausal symptoms, anxiety, sleep quality in the eight-week intervention, or vasomotor symptoms in the follow-up period in the group receiving aromatherapy. In addition, the serum cortisol level decreased in all four groups, however, it was not statistically significant. The combination of LB aromatherapy and MBT had no significant effect compared to placebo ($p > 0.05$).

Abbreviations

BEO
Bergamot essential oil
LEO
Lavender essential oil
MBT
Mindfulness-behavioral therapy
Placebo
Usual care + Placebo
Therapy
Mindfulness behavioral therapy + Placebo
Aromatherapy
LEO-BEO Aromatherapy + Usual care

Therapy & Aromatherapy
LB aromatherapy + Mindfulness-behavioral therapy
LEO-BEO Aromatherapy
L-B aroma
aMD
adjusted mean difference
CI
Confidence Interval
PSQI
Pittsburgh Sleep Quality Index
RCT
Randomized controlled trial
ELISA
Enzyme-linked immunosorbent assay
ANCOVA
Analysis of covariance
SPSS
Statistical Package for the Social Sciences
SD
Standard deviation
IQR
Inter-quartile range

Declarations

Acknowledgment

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Competing Interest

The authors declare no conflict of interest

Authors' contributions

AFKh contributed to the conceptualization, formal analysis, methodology, project administration, resources, and manuscript writing. AO and HSP contributed to the conceptualization, data interpretation, visualization, supervision, and revising of the manuscript. MM contributed to the conceptualization, data curation, investigation, and manuscript writing. SA contributed to the conceptualization, formal analysis, validation, and manuscript revision. All authors approved the final draft of the article.

Ethics approval

This study was approved by the regional Ethics Committee (ID IR.TBZMED.REC.1398.775). The protocol of the study was recorded in the Iranian Registry of Clinical Trials (IRCT20131009014957N8). 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.

Informed consent

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

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Data availability

The data from this study are available from the corresponding author upon reasonable request.

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Figures

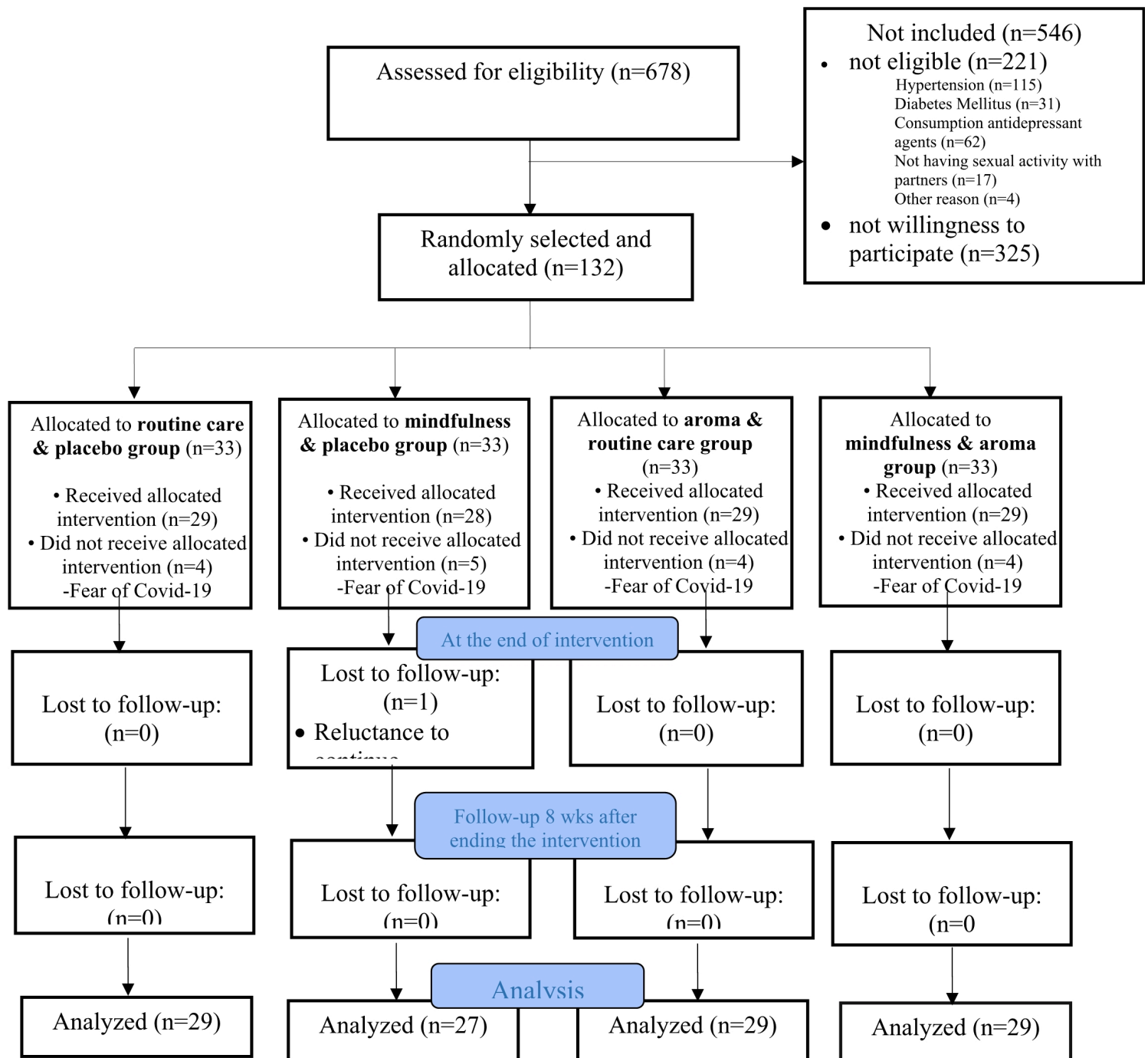


Figure 1

The Flowchart of study process

Supplementary Files

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