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The effectiveness of Melissa officinalis L. essential oil inhalation on anxiety and symptom burden of hemodialysis patients: a randomized trial study

Nilofar Pasyar[1], Mansoureh Aghababaei[2], Masoume Rambod[1*] and Mohammad M. Zarshenas[3,4]

Abstract

Background Hemodialysis patients suffer from physical and mental symptoms for which aromatherapy might be useful. This study aimed to determine the effectiveness of Melissa officinalis L. (Lemon Balm) essential oil inhalation on anxiety and the burden of symptoms in hemodialysis patients.

Methods This study is a randomized clinical trial with a pretest-posttest design. Sixty-eight hemodialysis patients were randomly divided into intervention (who underwent Melissa officinalis L. inhalation aromatherapy 3 times a week for one month) and control (who inhaled refined sweet almond oil) groups. The intervention in both groups was conducted during the hemodialysis session. The data were collected using the state-trait anxiety inventory and Dialysis Symptom Index. Data were analyzed through SPSS-25, using Mann-Whitney, Wilcoxon, t-tests and MANOVA.

Results Before the intervention, both groups were similar in terms of anxiety and symptoms burden ($P > 0.05$). However, after the intervention, a significant difference was found between the groups in terms of state and trait anxiety, and severity of constipation, nausea, vomit, diarrhea, swelling in legs, muscle cramps and shortness, worry, nervousness and anxiety, and trouble staying asleep. Moreover, after the intervention, a significant difference was observed between the groups regarding the prevalence of symptoms burden such as feeling anxious and having a dry mouth ($P < 0.05$).

Conclusion Melissa officinalis L. essential oil inhalation aromatherapy reduced the symptoms burden and anxiety in hemodialysis patients. Given the effectiveness of aromatherapy in hemodialysis patients, it is suggested that healthcare workers should use this complementary and integrative health to reduce the anxiety and symptoms burden in hemodialysis patients.

Trial registration RCT registry Iranian Registry of Clinical Trials (IRCT) number: IRCT20191021045178N3; Registration date 27/04/2021.

Keywords Aromatherapy, Melissa officinalis L., Anxiety, Symptom burden, Hemodialysis

*Correspondence:
Masoume Rambod
rambodma@gmail.com; rambodma@yahoo.com
[1]Community Based Psychiatric Care Research Center, School of Nursing and Midwifery, Shiraz University of Medical Sciences, Shiraz, Iran
[2]Student Research Committee of Shiraz University of Medical Sciences, Shiraz, Iran
[3]Medicinal Plants Processing Research Center, Shiraz University of Medical Sciences, Shiraz, Iran
[4]Department of Phytopharmaceuticals (Traditional Pharmacy), School of Pharmacy, Shiraz University of Medical Sciences, Shiraz, Iran

Background

Chronic kidney disease (CKD) is a fast-growing chronic disease in the world [1, 2]. The prevalence of end-stage renal disease (ESRD) has increased significantly around the world [3], including the United States [4] and Iran [5, 6]. Hemodialysis is an effective treatment for patients with ESRD and can significantly improve their quality of life and prolong their survival [7].

Hemodialysis patients experience some degree of symptom burden. Painful physical and mental symptoms are important symptoms of ESRD. They experience fatigue, itching, irritability, anxiety, nausea and vomiting, headache, hypotension, muscle cramps, fever, and chills [8]. One study reported bone and joint pain (97.4%) and irritability (94.7%) as the most common symptoms of hemodialysis patients [9]. Other symptoms, such as weakness, exhaustion, muscle cramps, anorexia, nausea, changes in sexual function, sleep problems [10], changes in body image, anxiety, discomfort, and severe worry are also due to physiological problems and complications of hemodialysis [11]. Patients also experience issues, such as family problems, feelings of guilt, and fear of death due to dependence on the dialysis machine [12]. In fact, all aspects of a health-promoting lifestyle, including health responsibility, nutrition, spiritual development, interpersonal relationships and stress management, and especially the physical activity of hemodialysis patients, are negatively affected by this disease, its treatments, and complications [13]. Owing to exposure to numerous stressful factors, some of these patients suffer from psychiatric disorders like anxiety [14].

Anxiety is a common psychological symptom in patients with ESRD undergoing hemodialysis. The results of a study indicated that approximately 38% of these patients had anxiety disorders, and this rate varied from 12 to 52% [15]. During COVID-19 pandemic, it was reported that the mental health of hemodialysis patients has been severely affected and may have increased their anxiety and depression [16]. Issues such as the patient's loneliness during hemodialysis, the alarm of the hemodialysis machine, insertion of the needle into the fistula, and central venous catheterization can cause anxiety in such patients [17].

Management of patients undergoing hemodialysis is significantly important in terms of increasing compatibility with dialysis and improving quality of life all of the time [12], especially in COVID-19 pandemic. During this period, professional healthcare workers, including nurses, who are at the forefront of the care and treatment of these patients, need to consider nursing care planning to overcome the process of COVID-19 with the least losses and reach healthy days [18], especially for hemodialysis patients. Both pharmacological and non-pharmacological methods can help manage these cases [12]. Complementary and integrative health (CIH) may be effective in managing and improving the patients' physical, psychological, and social symptoms [19–22]. The use of CIH in chronic diseases has increased all over the world during the last two decades [23]. Researchers have used different types of CIH, music therapy [24], acupuncture [25], the use of herbal medicines [26], aromatherapy [27, 28], etc.

Aromatherapy is a form of CIH. It can be used in massage, cosmetics, and olfactory issues. Olfactory aromatherapy using the essential oil aroma sends the aroma into the brain limbic system through the sense of smell. Along with other treatment methods, aromatherapy may be an effective way to manage anxiety [12]. Different essential oils, such as bergamot orange essence, lemon, lavender, and Melissa officinalis L. essential oils are used in aromatherapy [19, 21, 29, 30].

Melissa officinalis L. (Lemon balm) essential oil is an aromatic herb from the mint family (Lamiaceae) [31]. It contains volatile components such as geranial, citral, citronellal, and geraniol ones [32]. It was reported that monoterpenes of the Lamiaceae family might have peripheral and central analgesic effects [33]. Moreover, Geraniol affects cancer and inflammatory diseases [34]. Citronellal has neuro-protective effect [35]. Review studies showed Melissa officinalis L. (Lemon balm) had antioxidant properties [31], antiviral effect [36], and cardiovascular disease protection.

In in-vivo studies in animals such as mice and rats, the anti-anxiety [37] and anti-inflammatory [38, 39] effects of Melissa officinalis L. (Lemon balm) were reported. In in-vivo studies on humans, it was indicated that Melissa officinalis L. was effective in mild and moderate depression [40]. Another in-vivo study on humans such as mothers of preterm infants admitted in intensive care units showed that Melissa officinalis L. (Lemon balm) aromatherapy improved the sleep quality in these mothers [41]. In addition, Melissa officinalis L. (Lemon balm) aromatherapy reduced anxiety and improved the quality of sleep in Iranian patients undergoing coronary artery bypass surgery [42]. A systematic review and meta-analysis on 302 patients showed that Melissa officinalis L. consumption reduced triglyceride and cholesterol [43]. Another systematic review and meta-analysis indicated that Melissa officinalis L. might be effective in reducing anxiety in acute situations [44]. As mentioned, these situations and diseases are acute, and patients' anxiety and symptoms would be different from the chronic conditions. Results of a study on Iranian chronic conditions such as chronic stable angina showed using Melissa officinalis L. (Lemon balm) supplement reduced anxiety, depression, and sleep disturbance [30].

As mentioned, studies have pointed out the positive effects of Melissa officinalis L. (Lemon balm) in the

form of aromatherapy and oral consumption, etc. in in-vivo conditions. However, a few studies used this aromatherapy in chronic diseases [30]. Moreover, the effect of Melissa officinalis L. (Lemon balm) aromatherapy on chronic diseases such as ESRD patients undergoing hemodialysis and their complications is unknown. In addition, the literature review could not answer the researchers' question: Could Melissa officinalis L. (Lemon balm) essential oil aromatherapy reduce anxiety and the prevalence and severity of symptoms burden of ESRD undergoing hemodialysis? Therefore, conducting a study using Melissa officinalis L. (Lemon balm) aromatherapy on ESRD patients, as a chronic disease, would be a novel evidence-based practice. These novel findings would improve the evidence-based practice regarding the effectiveness of Melissa officinalis L. (Lemon balm) essential oil inhalation aromatherapy on anxiety and symptoms burden in hemodialysis patients. The hypotheses posed were as follows:

1) Melissa officinalis L. (Lemon balm) essential oil inhalation is effective in reducing state and trait anxiety in hemodialysis patients.

2) Melissa officinalis L. (Lemon balm) essential oil inhalation is effective in reducing the symptoms burden in hemodialysis patients.

Methods

Design

The present study is a randomized clinical trial with a pretest-posttest design and intervention and control groups. This study was registered in the Iranian Registry of Clinical Trials (IRCT) with the code number of IRCT20191021045178N3 in 27/04/2021.

Setting

The study was conducted on ESRD patients under treatment with hemodialysis in the Hemodialysis Center of Imam Reza Clinic and Nemazi Hospital affiliated with Shiraz University of Medical Sciences from July to September 2021.

Participants

The inclusion criteria for the participants were 18 years of age and older, the ability to understand and speak the Persian language, at least 6 months after the start of the current hemodialysis, and those under hemodialysis 3 times a week. Exclusion criteria included respiratory and allergic problems such as asthma, allergy to any smell, or obstruction to smell; history of allergy to plants; oral problems such as dry mouth, and parotitis; chronic mental illness; use of psychotropic medication; current or previous history of COVID-19; a known case of severe anxiety disorder based on their report; intolerance to essential oil during the intervention; any allergy to the aromatic oil used during the intervention; acute pain during the intervention; absence in more than two consecutive sessions during the intervention; and the patient's unwillingness to continue cooperation with the researcher. It is necessary to explain that we were supposed to exclude the patients who were previously, currently, or during the study infected with COVID-19, but no patient had this condition. Figure 1 shows the distribution of the hemodialysis patients during the study.

Sample size

The sample size was estimated at 27 based on the results of a similar study [12] and a comparison of two mean scores with a 5% type 1 error, and 90% power in two groups. To this end, 34 samples per group and 68 samples were considered to increase the accuracy according to a drop of 25%.

Randomization

Given the hemodialysis program for most of the patients was performed every other day, on odd and even days, we used the method of dropping a coin; even days were randomly allocated to the control group and odd days to the intervention group. This was conducted to prevent spreading the smell in the ward and its effect on the control group. The research participants were selected using the simple random sampling method. Therefore, a code was randomly assigned to each patient in the list of the patients who presented on even and odd days. Then, 68 patients (34 from even days and 34 from odd days) were randomly included in the study using a random number table.

Measurements

The patients' anxiety and symptom burden were evaluated using the Spielberger state-trait anxiety inventory (STAI) and the Dialysis Symptoms Index (DSI) before the intervention. The participants completed the demographic information forms. The researcher assistant guided the literate participants to fill out the questionnaires. The questions were read for the illiterate participants and what they said was accurately written in the questionnaires. The demographic information form included information about age, gender, education level, marital status, underlying diseases, and number of years of hemodialysis.

STAI consisted of 40 questions scored using a 4-point Likert scale. The questionnaire measured state and trait anxiety. The scores ranged from 20 to 80, and higher scores indicated greater anxiety. The internal correlation of the questionnaire ranged from 0.86 to 0.95, and the reliability coefficients of the test-retest were also reported from 0.65 to 0.75 [45]. The validity and reliability of the Persian version of the questionnaire were previously

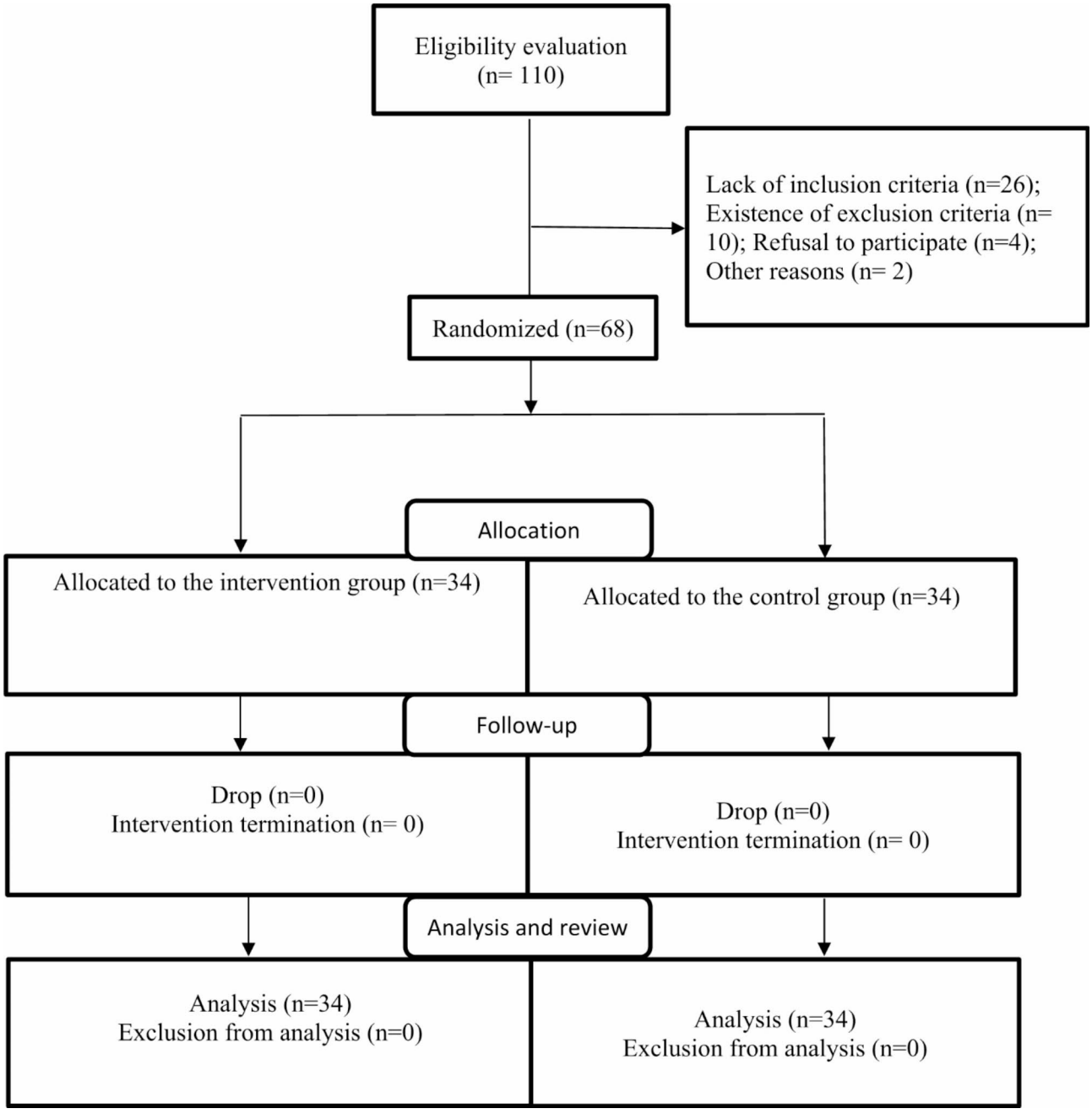

Fig. 1 Distribution of research participants

confirmed, and the Cronbach's alpha of state and trait anxiety was obtained at 0.87 and 0.90, respectively [18].

Weisbord et al. developed the Dialysis Symptom Index (DSI) in 2004. This questionnaire is used to evaluate the presence and severity of physical and mental symptoms in hemodialysis patients and includes 30 items scored based on a 5-point Likert scale. The total score of symptom severity ranges from 0 (if none of the 30 symptoms are present) to 150 (the most severe annoying state in each symptom). This questionnaire has high validity and reliability. Cronbach's α ranged from 0.82 to 0.84, and the Kappa statistics ranged from 0.06 to 0.90 for all questionnaire items [46, 47]. The validity and reliability of the Persian version of the questionnaire were confirmed with a Cronbach's alpha of 0.90 and a Kappa coefficient of 0.23 to 0.93 [48].

Intervention

The intervention group

In the intervention group, 200 µl of Melissa officinalis L. essential oil was poured on a cotton ball and attached to the patient's clothes with a pin 20 cm from the patient's

nose; then, it was inhaled by the patient for 20 min. The intervention was carried out 3 times a week during hemodialysis (first 20 min of dialysis) for one month.

The pure Melissa officinalis L. (Lemon balm) essential oil was obtained from Adonis Gol Darou Pharmaceutical Company in Tehran, Iran. In this company, Lemon balm extract is obtained from the comminuted herb of Melissa officinalis L. by extraction with particular solvents. The appearance of this essential oil is yellowish.

The composition of this essential oil was analyzed using a gas chromatography-mass spectrometry (GC/MS) device. Gas chromatography/Mass spectroscopy (GC/MS) analysis was performed via an Agilent technologies (7890 A) gas chromatograph equipped with an HP-5MS capillary column (coated with phenyl methyl siloxane, 30 m × 0.25 mm i.d.) and connected to a mass detector (Agilent technologies model 5975 C). The flow rate of the carrier gas (Helium) was adjusted as 1 ml/min with a split ratio of 1:30. The mass spectrometer was acquired in EI mode (70 eV) with a mass range of 30–600 m/z. The injector and detector temperatures were adjusted at 250 and 280 °C, respectively. The column temperature was linearly programmed from 60 to 250 °C with a rate of 5 °C/min and subsequently held at 250 °C (10 min). The data from GC/MS were used to identify the constituents of the samples. This process compared the resulting Kovats indices (KI) calculated by using a homologous series of n-alkanes C8-C22 as well as mass spectra data of the components with those mentioned in the respective literature [49].

According to the GC/MS chromatogram, 95.37 of the components, mainly monoterpenes, were identified. Both major and minor identified volatile constituents were as below: Citronellal (4.5%), Citral (37.46%), Geranial (46.16%), thymol (0.5%), Trans-Geranic acid methyl ester (0.7%), Delta-Carene (1.49%), Trans-Caryophyllene (2.14%), and Caryophyllene oxide (2.42%). Figure 2 shows the Gas chromatography/Mass spectroscopy profile for Melissa officinalis L. essential oil.

The control group

In the control group, the refined sweet almond oil prepared from Adonis Gol Darou Pharmaceutical Company in Tehran, Iran, was used as a placebo in the same method. Both control and intervention groups similarly received routine care. Owing to COVID-19 during the intervention, three-layer medical masks were used for all patients in the intervention and control groups to comply with health protocols.

Side effects and harms

Little information has been reported on the adverse effects of Melissa officinalis L. One study reported the occurrence of vomiting, dizziness, wheezing, restlessness, abdominal pain, nausea, and headache after consuming the Melissa officinalis L. extract (60 drops per day) [50]. Other reported side effects included higher appetite [51], redness, contact dermatitis, burning sensation, and skin irritation in topical use [50]. The side effects were explained to the participants, and they were asked to contact the third author in case of any complications. The trial was to be stopped in case of any side effects of aromatherapy; however, no significant side effects or complications were reported.

Outcomes

The symptom burden and anxiety questionnaires were re-completed by both groups after the intervention at the end of one month (12 hemodialysis sessions).

Blinding

One researcher, who was unaware of the classification of the groups, assisted us in performing data collection and completing the questionnaires due to the blind nature of the research. However, the differences in aromas on data collection days may lead to identification. Therefore, the only person who was effectively blinded was the statistical analyst who was unaware of the intervention and control groups.

Ethical consideration

The present study was approved by the Ethics Committee of Shiraz University of Medical Sciences (Code: IR.SUMS.REC.1400.065). The study was performed following the Declaration of Helsinki. All hemodialysis patients signed the informed consent form. The research participants were aware of the research objectives and method, confidentiality of information, side effects of the essential oil, and the right to withdraw from the study; they were assured that there would be no change in their treatment and care. Written informed consent was obtained from all participants.

Data analysis

In the present study, quantitative variables were shown with mean and standard deviation and qualitative variables with number and percentage. Independent t-tests and Mann-Whitney tests were used to measure intergroup relationships. In addition, chi-square and Fisher's exact tests were used to measure the relationship between the two qualitative variables; also, Wilcoxon and paired t-tests were employed to measure intragroup relationships. Moreover, to determine how large the effect of the intervention was on the state and trait anxiety and symptoms burden, we used Multivariate analysis of variance (MANOVA) and partial Eta Square ($\eta 2$). Based on the results, $\eta 2 = 0.01$, 0.06, and 0.14 showed a small, medium, and large effect, respectively.

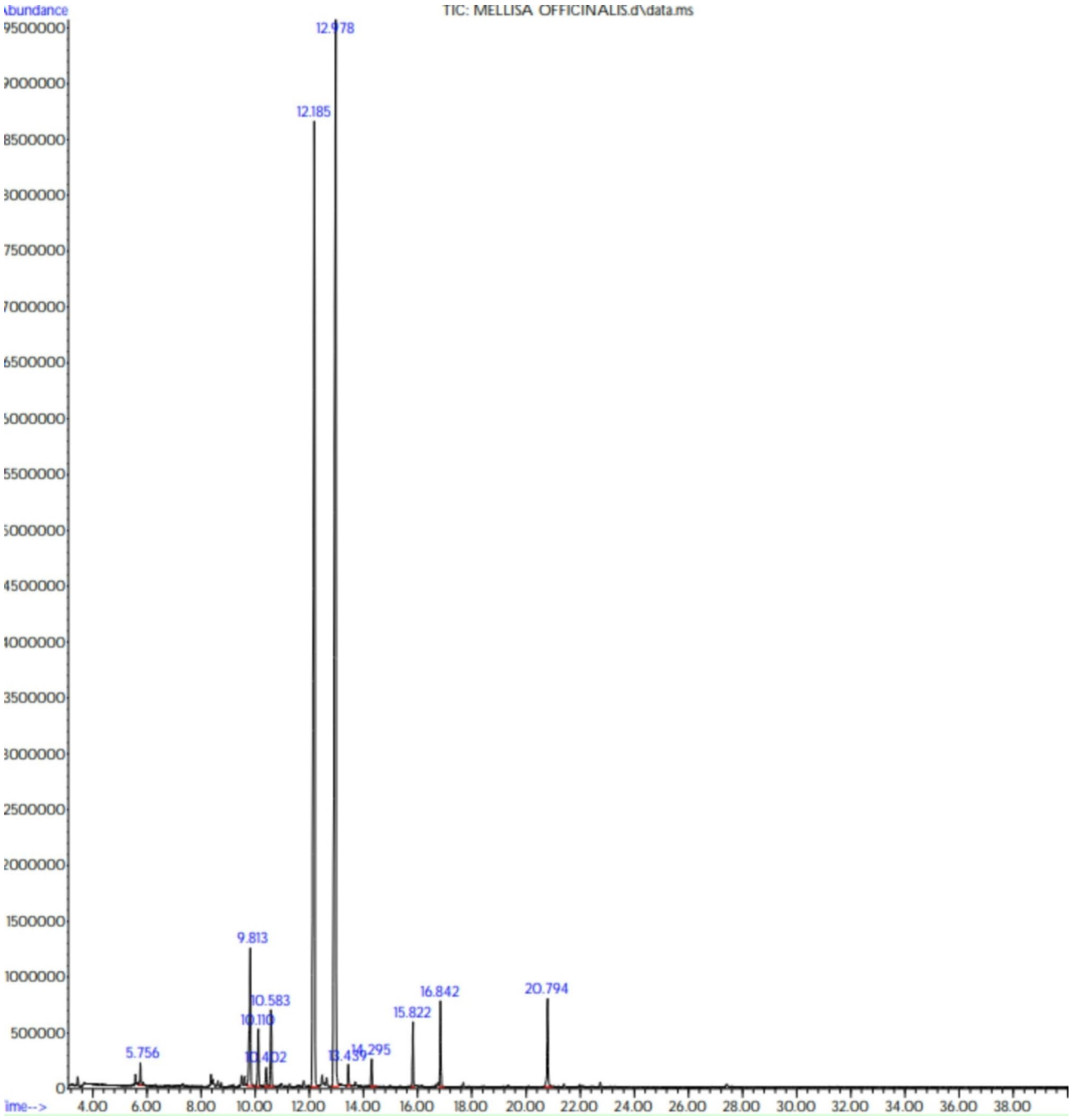

Fig. 2 Gas chromatography/Mass spectroscopy profile for Melissa officinalis L. essential oil

P values < 0.05 were considered as the significance level, and SPSS 25 was used for data analysis.

Results

In the present study, the participants' mean age was 49.79 (SD = 14.96) and 54.14 (SD = 16.07) in the intervention and control groups, respectively. Mann Whitney U test showed that both groups were similar in age (Z = 3.02, *P* = 0.41). Most of the participants were women (64.7%) in the intervention and control groups. Moreover, 70.6% of those in the intervention group and 67.6% in the control group were married. Half of the hemodialysis patients in the intervention group and 52.9% of them in the control group had primary and secondary school education. Approximately, one-third of the participants in both groups reported diabetes and coronary artery diseases. Most of the patients in the intervention group (70.6%) and control group (76.5%) had hypertension. The

Table 1 The demographic and clinical characteristics of the Hemodialysis patients in the intervention and control groups

	Intervention *n* (%)	Control *n* (%)	Test *P*-value
Gender			
Male	12 (35.3)	12 (35.3)	-
Female	22 (64.7)	22 (64.7)	$P=0.99$
Marital status			
Single	6 (17.6)	3 (8.8)	$\chi^2=3.02$
Married	24 (70.6)	23 (67.6)	$P=0.41$
Divorce	2 (5.9)	2 (5.9)	
Widow	2 (5.9)	6 (17.6)	
Educational levels			
Illiterate	4 (11.8)	5 (14.7)	$\chi^2=1.43$
Primary school	11 (32.4)	13 (38.2)	$P=0.87$
Secondary school	6 (17.6)	5 (14.7)	
High school	7 (20.6)	8 (23.5)	
Academic	6 (17.6)	3 (8.8)	
Having Diabetes			
Yes	11 (32.4)	13 (38.2)	$\chi^2=0.25$
No	23 (67.6)	21 (61.8)	$P=0.61$
Having hypertension			
Yes	24 (70.6)	26 (76.5)	$\chi^2=0.30$
No	10 (29.4)	8 (23.5)	$P=0.58$
Having coronary artery diseases			
Yes	10 (29.4)	11 (32.4)	$\chi^2=0.06$
No	24 (70.6)	23 (67.6)	$P=0.79$
Having hyperlipidemia			
Yes	8 (23.5)	14 (41.2)	$\chi^2=2.41$
No	26 (76.5)	20 (58.8)	$P=0.12$

length of time they had undergone hemodialysis was 2.97 (SD = 3.41) and 3.64 (SD = 3.26) years in the intervention and control groups, respectively. Mann Whitney U test showed that both groups were similar regarding the length of time they had undergone hemodialysis (Z = 0.14, $P=0.39$). Based on the results, the two groups were similar in terms of demographic characteristics, underlying diseases, and number of years of dialysis (P-value > 0.05) (Table 1).

State anxiety

Based on the results of the independent t-test, the mean state anxiety was not significantly different in the intervention and control groups before the intervention (P-value = 0.91). However, there was a significant difference between the intervention and control groups in terms of the mean scores of state anxiety after the intervention based on the Mann-Whitney test (P-value = 0.01). Based on the partial Eta Square (η^2) that was 0.1, a moderate effect size was estimated (Table 2).

According to the Wilcoxon test results, there was a statistically significant difference between the mean scores of state anxiety in the intervention group before and after the intervention (P-value = 0.002), revealing the effect of the intervention and reducing state anxiety. However, there was no significant difference between the mean state anxiety scores in the control group before and after the intervention (P-value = 0.15), (Table 2).

Trait anxiety

According to the results of the Mann-Whitney test, the mean trait anxiety was not significantly different between the intervention and control groups before the intervention (P-value = 0.12). Nevertheless, there was a significant difference between both groups in the mean trait anxiety scores after the intervention (P-value = 0.006). Based on the partial Eta Square (η^2) that was 0.09, a moderate effect size was estimated (Table 2).

The Wilcoxon test results showed a statistically significant difference between the trait anxiety mean scores in the intervention group before and after the intervention (P-value = 0.003), demonstrating the effect of the intervention and reduction of trait anxiety. Similarly, there was a significant difference between the mean trait anxiety scores in the control group before and after the intervention (P-value < 0.001) as the mean trait anxiety significantly decreased in the control group after the

Table 2 Determination and comparison of the mean dialysis symptom index and state and trait anxiety between and within the intervention and control groups

Variable		Group		Test, *P*-value between	Partial Eta Squared (η^2)	Interpreting η^2
		Intervention Mean (SD)	Control Mean (SD)			
Dialysis symptom index	Pre-intervention	53.08 (22.18)	49.38 (25.50)	t^a=0.63, $P=0.52$		
	Post-intervention	41.50 (21.32)	49.50 (25.06)	t^a=-1.41, $P=0.16$	0.03	Small
Test, *P*-value within		t^b =7.29, $P<0.001$	t^b =-0.14, $P=0.88$			
State anxiety	Pre-intervention	47.73 (4.53)	47.85 (4.13)	t^a =-0.11, $P=0.91$		
	Post-intervention	45.88 (3.64)	48.38 (3.63)	Z^c =-2.41,$P=0.01$	0.10	Medium effect
Test, *P*-value within		Z^d =-3.15, $P=0.002$	Z^d=-1.43, $P=0.15$			
Trait anxiety	Pre-intervention	45.44 (5.60)	46.35 (3.78)	Z^c =-1.52, 0.12		
	Post-intervention	43.41 (3.59)	45.70 (3.52)	Z^c =-0.73,$P=0.006$	0.09	Medium effect
Test, *P*-value within		Z^d=-2.97, $P=0.003$	Z^d=-3.66, $P>0.001$			

[a]: Independent t-test; [b]: Paired t-test; [c]: Mann-Whitney test, [d]: Wilcoxon test

intervention compared to that before the intervention (Table 2).

Dialysis Symptom Index (DSI)

According to the independent t-test results, as shown in Table 2, the mean dialysis symptom index was not significantly different between the intervention and control groups before the intervention (*P*-value = 0.52). There was no significant difference between the mean dialysis symptom index of the intervention and control groups after the intervention (*P*-value = 0.16). Based on the partial Eta square (η^2) which was 0.03, a small effect size was estimated.

According to the results of the paired t-test, as shown in Table 2, there was a significant difference between the mean dialysis symptom index in the intervention group before and after the intervention (*P*-value < 0.001), indicating the effect of the intervention and reduction of the dialysis symptom index. Nevertheless, the mean dialysis symptom index had no significant difference in the control group before and after the intervention according to the *P*-value = 0.88.

As Table 3 shows, no significant difference was found between the intervention and control groups in terms of the prevalence of symptoms burden before the intervention. Moreover, after it, no significant difference was observed between them in the prevalence of symptoms burden except for "feeling anxious" and "dry mouth".

As displayed in Table 4, before the intervention, there was no significant difference between the groups regarding the severity of the burden of 30 symptoms except for "difficulty concentrating" in the hemodialysis patients. On the other hand, after the intervention, a significant difference was observed between the groups in the severity of constipation, nausea, vomiting, diarrhea, muscle cramps, swelling in the legs, muscle shortness, worrying,

Table 3 Comparison of the prevalence of the symptoms burden between the intervention and control groups

	Pre-intervention					Post-intervention				
	Intervention		Control		χ^2, *P*-value	Intervention		Control		χ^2, *P*-value
	Yes n (%)	No n (%)	Yes n (%)	No n (%)		Yes n (%)	No n (%)	Yes n (%)	No n (%)	
Constipation	12 (35.3)	22 (64.7)	17 (50.0)	17 (50.0)	1.50, 0.22	14 (41.2)	20 (58.8)	15 (44.1)	19 (55.9)	0.06, 0.80
Nausea	15 (44.1)	19 (55.9)	15 (44.1)	19 (55.9)	0, > 0.99	12 (35.3)	22 (64.7)	17 (50.0)	17 (50.0)	1.50, 0.22
Vomiting	8 (23.5)	26 (76.5)	7 (20.0)	27 (79.4)	0.08, 0.77	2 (5.9)	32 (94.1)	6(17.6)	28 (82.4)	2.26, 0.13
Diarrhea	11 (32.4)	23 (67.6)	5 (14.7)	29 (85.3)	2.94, 0.08	7 (20.6)	27 (79.4)	5 (14.7)	29 (85.3)	0.40, 0.52
Decreased appetite	18 (52.9)	16 (47.1)	15 (44.1)	19 (55.9)	0.53, 0.46	19 (55.9)	15 (44.1)	16 (47.1)	18 (52.9)	0.53, 0.46
Muscle cramps	19 (55.9)	15 944.1)	16 (47.1)	18 952.9)	0.53, 0.46	19 (55.9)	15 (44.1)	14 (41.2)	20 (58.8)	1.47, 0.22
Swelling in legs	14 (41.2)	20 (58.8)	11 (32.4)	23 (67.6)	0.56, 0.45	14 (41.2)	20 (58.8)	11 (32.4)	23 (67.6)	0.56, 0.45
Shortness of breath	8 (23.5)	26 (76.5)	8 (23.5)	26 (76.5)	0, > 0.99	6 (17.6)	28 (82.4)	9 (26.5)	25 (73.5)	0.77, 0.38
Lightheadedness or dizziness	11 (32.4)	23 (67.6)	11 (32.4)	23 (67.6)	0, > 0.99	7 (20.6)	27 (79.4)	11 (32.4)	23 (67.6)	1.20, 0.27
Restless legs	12 (35.3)	22 (64.7)	12 (35.3)	22 (64.7)	0, > 0.99	10 (29.4)	24 (70.6)	11 (32.4)	23 (67.6)	0.06, 0.79
Numbness or tingling in feet	18 (52.9)	16 (47.1)	11 (32.4)	23 (67.6)	2.94, 0.08	18 (52.9)	16 (47.1)	13 (38.2)	21 (61.8)	1.48, 0.22
Feeling tired or lack of energy	31 (91.2)	3 (8.8)	27 (79.4)	7 (20.6)	1.87, 0.17	29 (85.3)	5 (14.7)	28 (82.4)	6 (17.6)	0.10, 0.74
Cough	11 (32.4)	23 (67.6)	10 (29.4)	24 (70.6)	0.06, 0.79	9 (26.5)	25 (73.5)	10 (29.4)	24 (70.6)	0.07, 0.78
Dry mouth	10 (29.4)	24 (70.6)	17 (50.0)	17 (50.0)	3.01, 0.08	9 (26.5)	25 (73.5)	17 (50.0)	17 (50.0)	3.98, 0.04*
Bone or joint pain	17 (50.0)	17 (50.0)	19 (55.9)	15 (44.1)	0.23, 0.62	16 (47.1)	18 (52.9)	19 (55.9)	15 (44.1)	0.53, 0.46
Chest pain	11 (32.4)	23 (67.6)	8 (23.5)	26 (76.5)	0.65, 0.41	8 (23.5)	26 (76.5)	9 (26.5)	25 (73.5)	0.07, 0.77
Headache	15 (44.1)	19 (55.9)	11 (32.4)	23 (67.6)	0.99, 0.31	17 (50.0)	17 (50.0)	14 (41.2)	20 (58.8)	0.53, 0.46
Muscle shortness	14 (41.2)	20 (58.8)	15 (44.1)	19 (55.9)	0.06, 0.80	10 (29.4)	24 (70.6)	17 (50.0)	17 (50.0)	3.01, 0.08
Difficulty concentrating	17 (50.0)	17 (50.0)	20 (58.8)	14 (41.2)	0.53, 0.46	15 (44.1)	19 (55.9)	8 (23.5)	26 (76.5)	3.21, 0.07
Dry skin	17 (50.0)	17 (50.0)	20 (58.8)	14 (41.2)	0.53, 0.46	16 (47.1)	18 (52.9)	18 (52.9)	16 (47.1)	0.23, 0.62
Itching	21 (61.8)	13 (38.2)	15 (44.1)	19 (55.9)	2.12, 0.14	18 (52.9)	16 (47.1)	13 (38.2)	21 (61.8)	1.48, 0.22
Worrying	32 (94.1)	2 (5.9)	32 (94.1)	2 (5.9)	0, > 0.99	26 (76.5)	8 (23.5)	30 (88.2)	4 (11.8)	1.61, 0.20
Feeling nervous	22 (64.7)	12 (35.3)	23 (67.6)	11 (32.4)	0.06, 0.79	15 (44.1)	19 (55.9)	23 (67.6)	11 (32.4)	3.81, 0.05
Trouble falling asleep	23 (67.6)	11 (32.4)	23 (67.6)	11 (32.4)	0, > 0.99	21 (61.8)	13 (38.2)	24 (70.6)	10 (29.4)	0.59, 0.44
Trouble staying asleep	22 (64.7)	12 (35.3)	25 (73.5)	9 (29.5)	0.62, 0.43	21 (61.8)	13 (38.2)	26 (76.5)	8 (23.5)	1.72, 0.18
Feeling irritable	28 (82.4)	6 (17.6)	23 (67.6)	11 (32.4)	1.96, 0.16	24 (70.6)	10 (29.4)	23 (67.6)	11 (32.4)	0.06, 0.79
Feeling sad	26 (76.5)	8 (23.5)	20 (58.8)	14 (41.2)	2.41, 0.12	22 (64.7)	12 (35.3)	21 (61.8)	13 (38.2)	0.06, 0.80
Feeling anxious	30 (88.2)	4 (11.8)	26 (76.5)	8 (23.5)	1.61, 0.20	21 (61.7)	13 (38.3)	30 (88.2)	4 (11.8)	6.35, 0.01*
Decreased interest in sex	30 (88.2)	4 (11.8)	26 (76.5)	8 (23.5)	1.61, 0.20	30 (88.2)	4 (11.8)	28 (82.4)	6 (17.6)	0.46, 0.49
Difficulty becoming sexually aroused	30 (88.2)	4 (11.8)	25 (73.5)	9 (26.5)	2.37, 0.12	30 (88.2)	4 (11.8)	28 (82.4)	6 (17.6)	0.46, 0.49

*significant

Table 4 Comparison of the severity of the symptoms burden between the intervention and control groups

	Pre-intervention			Post-intervention		
	Intervention	Control	Test [a], *P*-value	Intervention	Control	Test [a], *P*-value
	Mean (SD)	Mean (SD)		Mean (SD)	Mean (SD)	
Constipation	1.0 (1.49)	1.41 (1.57)	-1.17, 0.23	0.55 (1.0)	1.41 (1.34)	-3.38, 0.001*
Nausea	1.26 (1.54)	1.41 (1.74)	-0.26, 0.79	0.41 (1.2)	1.41 (1.30)	-3.29, 0.001*
Vomiting	0.58 (1.31)	0.52 (1.10)	-0.26, 0.79	0.11 (1.1)	0.76 (1.2)	-2.32, 0.02*
Diarrhea	0.76 (1.18)	0.44 (1.10)	-1.47, 0.13	0.14 (0.60)	0.79 (1.1)	-2.20, 0.03*
Decreased appetite	1.64 (1.80)	1.55 (1.90)	-0.31,0.75	1.35 (1.41)	1.55 (1.81)	-0.61, 0.54
Muscle cramps	1.94 (1.87)	1.61 (1.84)	-0.76, 0.44	0.84 (1.4)	1.58 (1.60)	-2.00, 0.04*
Swelling in legs	1.17 (1.67)	0.82 (1.26)	-0.80, 0.42	0.44 (1.0)	1.11 (1.50)	-2.16, 0.03*
Shortness of breath	0.55 (1.10)	0.70 (1.33)	-0.21, 0.83	0.44 (1.02)	0.76 (1.34)	-0.99, 0.31
Lightheadedness or dizziness	0.79 (1.27)	0.79 (1.20)	-0.12, 0.89	0.47 (0.96)	0.73 (1.10)	-1.07, 0.28
Restless legs	0.91 (1.33)	1.02 (1.46)	-0.28, 0.77	0.73 (1.23)	0.91 (1.37)	-0.44, 0.65
Numbness or tingling in feet	1.70 (1.80)	1.08 (1.65)	-1.42, 0.15	1.55 (1.61)	1.11 (1.53)	-1.14, 0.25
Feeling tired or lack of energy	3.52 (1.44)	2.97 (1.80)	-1.19, 0.23	2.73 (1.73)	3.05 (1.68)	-1.27, 0.20
Cough	0.70 (1.08)	0.76 (1.25)	-0.008, 0.99	0.64 (1.15)	0.79 (1.29)	-0.42, 0.66
Dry mouth	1.00 (1.66)	1.67 (1.88)	-1.64, 0.10	0.88 (1.59)	1.64 (1.75)	-1.86, 0.06
Bone or joint pain	1.55 (1.76)	2.05 (1.93)	-1.18, 0.23	1.38 (1.57)	2.05 (1.93)	-1.63, 0.10
Chest pain	0.85 (1.28)	0.61 (1.23)	-0.91, 0.35	0.55 (1.07)	0.67 (1.24)	-0.25, 0.79
Headache	1.38 (1.65)	1.05 (1.63)	-0.88, 0.37	1.32 (1.47)	1.26 (1.63)	-0.30, 0.76
Muscle shortness	1.32 (1.73)	1.35 (1.68)	-0.10, 0.91	0.79 (1.00)	1.52 (1.80)	-2.06, 0.04*
Difficulty concentrating	1.52 (1.69)	0.52 (1.02)	-2.66, 0.008*	1.26 (1.56)	0.52 (1.02)	2.27, 0.13 [b]
Dry skin	1.67 (1.90)	1.79 (1.71)	-0.35, 0.72	1.47 (1.82)	1.67 (1.73)	-0.46, 0.64
Itching	1.91 (1.69)	1.50 (1.89)	-1.06, 0.28	1.23 (1.32)	1.20 (1.71)	-0.56, 0.57
Worrying	3.47 (1.37)	3.41 (1.25)	-0.17, 0.85	2.67 (0.9)	3.14 (1.0)	-2.03, 0.04*
Feeling nervous	2.00 (1.74)	2.11 (1.63)	-0.29, 0.77	1.26 (1.54)	2.08 (1.63)	-2.10, 0.03*
Trouble falling asleep	2.47 (1.94)	2.58 (1.92)	-0.27, 0.78	1.91 (1.69)	2.64 (1.87)	-1.85, 0.06
Trouble staying asleep	2.41 (1.97)	2.79 (1.88)	-0.83, 0.40	1.26 (1.2)	2.44 (2.90)	-2.19, 0.03*
Feeling irritable	2.85 (1.61)	2.41 (1.84)	-0.79, 0.42	2.05 (1.51)	2.41 (1.86)	-1.12, 0.26
Feeling sad	2.64 (1.79)	2.05 (1.98)	-1.24, 0.21	2.02 (1.69)	2.14 (1.94)	-0.19, 0.84
Feeling anxious	3.32 (0.91)	2.97 (1.42)	-0.78, 0.43	2.05 (1.32)	2.94 (1.39)	-2.71, 0.007*
Decreased interest in sex	3.05 (1.53)	2.70 (1.80)	-0.67, 0.49	2.79 (1.37)	2.94 (1.68)	-0.80, 0.42
Difficulty becoming sexually aroused	2.80 (1.69)	1.50 (0.50)	-0.87, 0.38	2.82 (1.42)	2.94 (1.68)	-0.60, 0.54

[a] Mann-Whitney tests, [b] ANCOVA and Difficulty concentrating pre-intervention as covariate, * Significant

nervousness, anxiety, and trouble staying asleep. The burden of the other 19 symptoms was not different between the groups after the intervention.

Discussion

Based on the results of the present study, Melissa officinalis L. (Lemon Balm) essential oil inhalation aromatherapy decreased the state and trait anxiety and symptoms burden in hemodialysis patients. Moreover, using aromatherapy reduced the severity of constipation, nausea, vomiting, diarrhea, muscle cramps, swelling in legs, muscle shortness, worrying, nervousness, anxiety, and trouble staying asleep in ESRD patients undergoing hemodialysis. In addition, the prevalence of feeling anxious and dry mouth reduced after using Melissa officinalis L. (Lemon Balm) inhalation aromatherapy.

This study indicated that Melissa officinalis L. (Lemon Balm) essential oil inhalation aromatherapy reduced state anxiety, which happened in reaction to stressful situation. Moreover, Melissa officinalis L. (Lemon Balm) essential oil inhalation aromatherapy was effective in decreasing trait anxiety which is part of someone's personality or method of viewing the world. Our findings also showed that the effect of Melissa officinalis L. essential oil inhalation aromatherapy on state and trait anxiety in ESRD patients undergoing hemodialysis was at a moderate level. In a study conducted by Lotfi et al., Melissa officinalis L. inhalation aromatherapy significantly decreased anxiety in hospitalized patients with acute coronary syndrome [52]. Another study indicated that drinking Melissa officinalis L. reduced anxiety in patients undergoing coronary artery bypass surgery [42]. Veiskaramian et al. reported that Melissa officinalis L. essential oil inhalation aromatherapy could decrease stress and regulate hemodynamic changes in patients with acute coronary syndrome in emergency and acute situations [53]. Melissa officinalis L. inhalation aromatherapy reduces anxiety, regulates the cardiovascular response, and

reduces the symptoms in patients together with improvements in the balance of the autonomic nervous system in tissues, such as the heart and kidney tissues, and changes in the level of noradrenaline in the blood [53]. A review study reported that Melissa officinalis L. had a potentially wide range of effects on diseases, especially anxiety and central nervous system disorders [50].

Our findings showed that the mean trait anxiety significantly decreased in the control group (sweet al.mond oil inhalation aromatherapy) after the intervention compared to that before the intervention. In a study, it was stated that the anxiety change in the aromatherapy group with lavender (9.9), almond oil (5.3) and in the water group was 3.6 [54]. This suggests that the almond oil can reduce anxiety less than lavender but more than water. Another study indicated that foot massage using sweet al.monds decreased anxiety post-surgery [55]. It is possible that the sweet al.mond oil not only was absorbed through the skin but also entered the olfactory center through inhalation and led to the reduction of trait anxiety.

This study showed that Melissa officinalis L. inhalation aromatherapy was effective in reducing 11 symptoms burden in hemodialysis patients. Based on the literature review, no study has mentioned this finding, and it is a novel finding for hemodialysis patients. Our study indicated Melissa officinalis L. (Lemon Balm) inhalation aromatherapy reduced the prevalence of and severity of feeling anxious and severity of worrying and feeling nervous in hemodialysis patients. A review study reported that this herb was effective in mood, cognition, and memory. This study revealed that these effects were related to neurological effects such as simulation of the acetylcholine and GABAA receptors and inhibition of matrix metallo proteinase-2 [50].

Our study showed that Melissa officinalis L. (Lemon Balm) inhalation aromatherapy reduced the severity of gastrointestinal symptoms such as constipation, nausea, vomiting, and diarrhea in ESRD patients undergoing hemodialysis. A few studies reported the effect of Melissa officinalis L. inhalation on nausea, vomiting, and diarrhea [56]. It was reported that Melissa officinalis L. could be used in colic, diarrhea, and irritable bowel syndrome [56]. Based on our findings, it seems that aromatherapy with Melissa officinalis L. might have anti-inflammatory and antimicrobial effects on the gastrointestinal system. Chromatographic findings in our study showed that 46.16% of Melissa officinalis L. essential oil component was Geranial. This monoterpene has anti-inflammatory, antioxidant, and antimicrobial effects. Geranial stimulates apoptosis and cell cycle rest, regulates target molecules such as p53 and STAT3, triggers the activation of caspases, and controls inflammation [34].

This study revealed that Melissa officinalis L. (Lemon Balm) inhalation aromatherapy reduced the severity of symptoms burden such as trouble staying asleep in hemodialysis patients. Similarly, a study indicated that a combination of Melissa officinalis L. and Nepeta menthoides might improve insomnia [57]. Soltanpour et al. indicated that drinking Melissa officinalis L. improved the sleep quality in patients undergoing coronary artery bypass surgery [42]. By simulation of the acetylcholine and GABAA receptors [50], analgesic effect [33], and potentially calm and anti-spasmodic effects of Melissa officinalis L [38], it may reduce the severity of trouble staying asleep in hemodialysis patients.

This study showed Melissa officinalis L. (Lemon Balm) inhalation aromatherapy reduced the severity of muscle cramps, legs swelling, and muscle shortness in ESRD patients undergoing hemodialysis. It was shown that Melissa officinalis L. had anti-inflammatory effect [58]. Researchers indicated that oral Melissa officinalis L. supplement had anti-inflammatory effect, and C-reactive protein, as a biomarker of inflammation, was lower in chronic stable angina patients who administered this herb compared to the placebo group [58]. Studies indicated that Melissa officinalis L. relieved pain [59], led to calmness, and potentially had anti-spasmodic and anti-inflammatory effects [54]. It is an anti-spam, sedative, painkiller, and tonic inhibition herb [31]. As we reported, citronellal was one of the monoterpenes of Melissa officinalis L. Citronellal and linalool had energy affinity for "α-Synuclein, Adenosine Receptors, Monoamine Oxidase (MAO), and Dopamine D 1 receptor proteins" and reduced Parkinson disease symptoms [35]. It seems that with the mentioned effects, the severity of swelling of the leg, muscle cramps, and shortness of the muscle decreased in ESRD patients undergoing hemodialysis using Melissa officinalis L. (Lemon Balm) inhalation aromatherapy.

Despite the beneficial effects of Melissa officinalis L. (Lemon Balm) inhalation aromatherapy on various symptoms of hemodialysis patients, generalization of the results should be made with caution as there are few clinical studies on its effects on physical and mental dimensions in these patients. Determination of the exact dose and method of using the aroma is a challenge in the use of aromatherapy. Several studies have reported different amounts and methods of using the aroma; hence, more studies, particularly clinical trials with a much larger sample size, are needed to confirm the effects of Melissa officinalis L. (Lemon Balm) inhalation aromatherapy with more certainty.

This clinical trial study had some challenges including knowledge of the safety of Melissa officinalis L. essential oil, clinical protocols, selection of the product, and its administration. To tackle these challenges, an associate

professor of Traditional Pharmacy who is a member of the Medicinal Plants Processing Research Center was a member of this research team. The product was prepared by an aromatherapy specialist who was familiar with Melissa officinalis L. and the extraction method in a reliable pharmaceutical company. To ensure the product safety the research assistant was present with the patients throughout the intervention and was ready to answer their phone calls about possible side effects. Given the challenges and findings of this study, using Melissa officinalis L. (Lemon Balm) might be effective in a hemodialysis setting as an implication of this study.

The research limitations included the short duration of the study (20 min in each time), patients' visits in three separate four-hour cycles per day, fear and anxiety of the patients and the researcher about the COVID-19 pandemic, and quick and correct removal of cotton impregnated with essential oil to prevent the spread of aroma in the place after the intervention. Filling out the forms by the researcher's assistant might cause bias. Therefore, it is suggested that in another study illiterate patients should be excluded from the study to reduce the risk of researcher bias.

The results of the present study showed that sweet almond oil reduced trait anxiety. To compare its effect on trait anxiety, it is suggested that three groups of almond oil, Melissa officinalis L. (Lemon Balm), and water inhalation aromatherapy should be compared in another study to determine the effect size of each aromatherapy.

Conclusion

The present study demonstrated that Melissa officinalis L. essential oil inhalation aromatherapy decreased the symptoms burden and anxiety in hemodialysis patients. Melissa officinalis L. essential oil inhalation aromatherapy reduced the severity of constipation, nausea, vomiting, diarrhea, swelling in legs, muscle shortness, worrying, and trouble staying asleep. Moreover, this intervention reduced the prevalence of feeling anxious and dry mouth. Thus, it is suggested that healthcare workers should use this intervention. As to evidence-based practice, it is recommended that more studies should evaluate the effect of Melissa officinalis L. aromatherapy on symptoms in ESRD patients undergoing hemodialysis.

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Author contributions

MR, NP, MA and MMZ wrote the main manuscript text. The management of the data analysis was conducted by MR, NP, and MA. MMZ prepared Fig. 2. All authors reviewed and approved the manuscript.

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Data availability

The datasets of this study is available from the first author on reasonable request.

Declarations

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of Shiraz University of Medical Sciences (Code: IR.SUMS.REC.1400.065). The study was performed following the Declaration of Helsinki. All hemodialysis patients signed an informed consent form. The research participants were aware of the research objectives and method, confidentiality of information, side effects of the essential oil, and the right to withdraw from the study; they were assured that there would be no change in their treatment and care. Written and informed consent was obtained from all participants.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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References

1. Juraschek SP, Appel LJ. Chronic kidney disease: intensive blood pressure reduction lowers mortality in CKD. Nat Rev Nephrol. 2018;14(1):5.
2. Ordunez P, Nieto FJ, Martinez R, Soliz P, Giraldo GP, Mott SA, et al. Chronic kidney disease mortality trends in selected central American countries, 1997–2013: clues to an epidemic of chronic interstitial nephritis of agricultural communities. J Epidemiol Community Health. 2018;72(4):6–280.
3. Hill NR, Fatoba ST, Oke JL, Hirst JA, O'Callaghan CA, Lasserson DS, et al. Global prevalence of chronic kidney disease-a systematic review and meta-analysis. PLoS ONE. 2016;11(7):e0158765.
4. Johansen KL, Chertow GM, Foley RN, Gilbertson DT, Herzog CA, Ishani A, et al. US renal data system 2020 annual data report: epidemiology of kidney disease in the united States. Am J Kidney Dis. 2021;77(4):A7–8.
5. Sepanlou SG, Barahimi H, Najafi I, Kamangar F, Poustchi H, Shakeri R, et al. Prevalence and determinants of chronic kidney disease in the Northeast of Iran: results of the Golestan cohort study. PLoS ONE. 2017;12(5):e0176540.
6. Bouya S, Balouchi A, Rafiemanesh H, Hesaraki M. Prevalence of chronic kidney disease in Iranian general population: A Meta-Analysis and systematic review. Therapeutic Apheresis Dialysis. 2018;22(6):594–9.
7. Guan Y, He Y-x. Effect of advanced care on psychological condition in patients with chronic renal failure undergoing hemodialysis: A protocol of a systematic review. Medicine. 2019;98(10):14738.
8. Raja SM, Seyoum Y. Intradialytic complications among patients on twice-weekly maintenance Hemodialysis: an experience from a Hemodialysis center in Eritrea. BMC Nephrol. 2020;21:1–6.
9. Senanayake S, Gunawardena N, Palihawadana P, Bandara P, Haniffa R, Karunarathna R, et al. Symptom burden in chronic kidney disease; a population-based cross-sectional study. BMC Nephrol. 2017;18(1):228.
10. Rambod M, Pourali-Mohammadi N, Pasyar N, Rafii F, Sharif F. The effect of Benson's relaxation technique on the quality of sleep of Iranian Hemodialysis patients: a randomized trial. Complement Ther Med. 2013;21(6):577–84.
11. Kuo P-Y, Saran R, Argentina M, Heung M, Bragg-Gresham J, Krein S, et al. Cramping, crashing, cannulating, and clotting: a qualitative study of patients' definitions of a bad run on Hemodialysis. BMC Nephrol. 2020;21(1):1–10.

12. Sentürk A, Kartin PT. The effect of lavender oil application via inhalation pathway on Hemodialysis patients' anxiety level and sleep quality. Holist Nurs Pract. 2018;32(6):324–35.
13. Sarıaslan A, Kavurmacı M. Evaluation of healthy lifestyle behaviors and affecting factors of Hemodialysis patients. J Prev Epidemiol. 2020;5(2):e19.
14. Alfikrie F, Sari L, Akbar A. Factors associated with anxiety in patients with chronic kidney disease undergoing hemodialysis: a cross-sectional study. Int J Nurs Health Med. 2020;2(2):1–6.
15. Cohen SD, Cukor D, Kimmel PL. Anxiety in patients treated with Hemodialysis. Clin J Am Soc Nephrol. 2016;11(12):2250–5.
16. Koşunalp N, Kavurmaci M. Determination of anxiety, depression, avoidance and obsessions experienced by Hemodialysis patients during the COVID-19. Therapeutic Apheresis dialysis. 2023;27(6):1070–8.
17. Zibaei M, Nobahar M, Ghorbani R. Association of stress and anxiety with self-care in Hemodialysis patients. J Ren Injury Prev. 2020;9(2):e14–e.
18. Kavurmaci M, Demirel BC. COVID-19 and nursing Care/COVID-19 ve Hemsirelik Bakimi. J Educ Res Nurs. 2021;18(S1):14–20.
19. Pasyar N, Rambod M, Araghi F. The effect of Bergamot orange essence on anxiety, salivary cortisol, and alpha-amylase in patients prior to laparoscopic cholecystectomy: A controlled trial study. Complement Ther Clin Pract. 2020;39:101153.
20. Pasyar N, Tashnizi NB, Mansouri P, Tahmasebi S. Effect of yoga exercise on the quality of life and upper extremity volume among women with breast cancer-related lymphedema: A pilot study. Eur J Oncol Nurs. 2019;42:103–9.
21. Rambod M, Rakhshan M, Tohidinik S, Nikoo MH. The effect of lemon inhalation aromatherapy on blood pressure, electrocardiogram changes, and anxiety in acute myocardial infarction patients: A clinical, multi-centered, assessor-blinded trial design. Complement Ther Clin Pract. 2020;39:101155.
22. Kilic E, Kavurmacı M. Hemodialysis patients' knowledge of, beliefs about, and practices in using complementary and alternative medicine: an exploratory study. Altern Ther Health Med. 2022;28(6):30–4.
23. Cha JM. Complementary and alternative medicine in patients with inflammatory bowel disease: hype or evidence? Intestinal Res. 2020;18(2):141.
24. Uğraş GA, Yıldırım G, Yüksel S, Öztürkçü Y, Kuzdere M, Öztekin SD. The effect of different types of music on patients' preoperative anxiety: A randomized controlled trial. Complement Ther Clin Pract. 2018;31:158–63.
25. Wunsch JK, Klausenitz C, Janner H, Hesse T, Mustea A, Hahnenkamp K, et al. Auricular acupuncture for the treatment of preoperative anxiety in patients scheduled for ambulatory gynecological surgery: a prospective controlled investigation with a non-randomized arm. Acupunct Med. 2018;36(4):222–7.
26. Ince N, Kaya Ş, Yıldız İE, Parlak E, Bayar B. Use of complementary and alternative medicine in patients with chronic viral hepatitis in Turkey. Complement Ther Med. 2020;48:102229.
27. Li F, Jiang T, Shi T. Effect of inhalation aromatherapy on physical and psychological problems in cancer patients: systematic review and Meta-analysis. J Psychosoc Oncol. 2022;40(3):271–87.
28. Cürcani M, Tan M. The effect of aromatherapy on haemodialysis patients' pruritus. J Clin Nurs. 2014;23(23–24):3356–65.
29. Şahin S, Tokgöz B, Demir G. Effect of lavender aromatherapy on arteriovenous fistula puncture pain and the level of state and trait anxiety in Hemodialysis patients: a randomized controlled trial. Pain Manage Nurs. 2021;22(4):509–15.
30. Haybar H, Javid AZ, Haghighizadeh MH, Valizadeh E, Mohaghegh SM, Mohammadzadeh A. The effects of Melissa officinalis supplementation on depression, anxiety, stress, and sleep disorder in patients with chronic stable angina. Clin Nutr ESPEN. 2018;26:47–52.
31. Miraj S, Rafieian-Kopaei KS. Melissa officinalis L: A review study with an antioxidant prospective. J Evidence-based Complement Altern Med. 2017;22(3):385–94.
32. Petrisor G, Motelica L, Craciun LN, Oprea OC, Ficai D, Ficai A. Melissa officinalis: composition, Pharmacological effects and derived release systems—A review. Int J Mol Sci. 2022;23(7):3591.
33. Bouyahya A, Guaouguaou FE, El Omari N, El Menyiy N, Balahbib A, El-Shazly M, Bakri Y. Anti-inflammatory and analgesic properties of Moroccan medicinal plants: phytochemistry, in vitro and in vivo investigations, mechanism insights, clinical evidences and perspectives. J Pharm Anal. 2022;12(1):35–57.
34. Ben Ammar R. Potential effects of geraniol on cancer and inflammation-related diseases: A review of the recent research findings. Molecules. 2023;28(9):3669.
35. da Silva PR, de Andrade JC, de Sousa NF, Portela AC, Pires HF, Remígio MC, da Nóbrega Alves D, de Andrade HH, Dias AL, Salvadori MG, de Oliveira Golzio AM. Computational studies applied to Linalool and citronellal derivatives against Alzheimer's and Parkinson's disorders: A review with experimental approach. Curr Neuropharmacol. 2023;21(4):842.
36. Shavysi S, Mostafaloo M, Hadidi FS, Nanbakhsh S, Olangian-Tehrani S. Kheirandish11 A, Keylani12 K, Behfarnia13 P. Antiviral potential of Melissa. officinalis L.: A Literature; 2023. p. 11786388221146683.
37. Stojanović NM, Mladenović MZ, Randjelović PJ, Radulović NS. The potential of lemon balm (Melissa officinalis L.) essential oil as an anti-anxiety agent–is the citronellal the activity carrier? J Ethnopharmacol. 2023;314:116661.
38. Bounihi A, Hajjaj G, Alnamer R, Cherrah Y, Zellou A. In vivo potential anti-inflammatory activity of Melissa officinalis L. essential oil. Adv Pharmacol Pharm Sci. 2013;2013. https://doi.org/10.1155/2013/101759.
39. Draginic N, Andjic M, Jeremic J, Zivkovic V, Kocovic A, Tomovic M, Bozin B, Kladar N, Bolevich S, Jakovljevic V, Milosavljevic I. Anti-inflammatory and antioxidant effects of Melissa officinalis extracts: A comparative study. Iran J Pharm Research: IJPR. 2022;21(1):126561.
40. Araj-Khodaei M, Noorbala AA, Yarani R, Emadi F, Emaratkar E, Faghihzadeh S, Parsian Z, Alijaniha F, Kamalinejad M, Naseri M. A double-blind, randomized pilot study for comparison of Melissa officinalis L. and Lavandula angustifolia mill. With Fluoxetine for the treatment of depression. BMC Complement Med Ther. 2020;20(1):207.
41. Sinaei M, Salari R, Birjandi RM, Raesi R, Sadeghi T. The effect of inhalation aromatherapy with lemon balm (Melissa officinalis) essential oil on sleep quality in mothers of preterm infants in the neonatal intensive care unit (A randomized clinical trial Study). Open Public Health J. 2024;17(1):1–8. https://doi.org/10.2174/0118749445280519240110075936.
42. Soltanpour A, Alijaniha F, Naseri M, Kazemnejad A, Heidari MR. Effects of Melissa officinalis on anxiety and sleep quality in patients undergoing coronary artery bypass surgery: A double-blind randomized placebo controlled trial. Eur J Integr Med. 2019;28:27–32.
43. Shahsavari K, Shams Ardekani MR, Khanavi M, Jamialahmadi T, Iranshahi M, Hasanpour M. Effects of Melissa officinalis (lemon balm) consumption on serum lipid profile: a meta-analysis of randomized controlled trials. BMC Complement Med Ther. 2024;24(1):146.
44. Ghazizadeh J, Sadigh-Eteghad S, Marx W, Fakhari A, Hamedeyazdan S, Torbati M, Taheri-Tarighi S, Araj-Khodaei M, Mirghafourvand M. The effects of lemon balm (Melissa officinalis L.) on depression and anxiety in clinical trials: A systematic review and meta-analysis. Phytother Res. 2021;35(12):6690–705.
45. Spielberger CD, Gorsuch RL, Lushene R, Vagg PR, Jacobs GA. Manual for the State-Trait anxiety inventory. Palo Alto, CA, Ed. Palo Alto: Spielberger; 1983.
46. Weisbord SD, Fried LF, Arnold RM, Rotondi AJ, Fine MJ, Levenson DJ, Switzer GE. Development of a symptom assessment instrument for chronic Hemodialysis patients: the Dialysis symptom index. J Pain Symptom Manag. 2004;27(3):226–40.
47. Onsoz H, Usta Yesilbalkan O. Reliability and validity of the Turkish version of the dialysis symptom index in chronic Hemodialysis patients. Turk Neph Dial Transpl. 2013;22(1):60–7.
48. Zamanian H, Kharameh ZT. Translation and psychometric properties of the Persian version of the dialysis symptom index in Hemodialysis patients. Nephro-urology Monthly. 2015;7(1):23152.
49. Adams RP. Identification of essential oil components by gas chromatography/mass spectroscopy. Illinois, USA: Allured Publishing Corporation; 1995.
50. Shakeri A, Sahebkar A, Javadi B. Melissa officinalis L.–A review of its traditional uses, phytochemistry and Pharmacology. J Ethnopharmacol. 2016;188:204–28.
51. Alijaniha F, Naseri M, Afsharypuor S, Fallahi F, Noorbala A, Mosaddegh M, Faghihzadeh S, Sadrai S. Heart palpitation relief with Melissa officinalis leaf extract: double blind, randomized, placebo controlled trial of efficacy and safety. J Ethnopharmacol. 2015;164:378–84.
52. Lotfi A, Shiri H, Ilkhani R, Sefidkar R, Esmaeeli R. The efficacy of aromatherapy with Melissa officinalis in reducing anxiety in cardiac patients: A randomized clinical trial. Crescent J Med Biol Sci. 2019;6(3):293–9.
53. Veiskaramian A, Gholami M, Yarahmadi S, Baharvand PA, Birjandi M. Effect of aromatherapy with Melissa essential oil on stress and hemodynamic parameters in acute coronary syndrome patients: A clinical trial in the emergency department. Complement Ther Clin Pract. 2021;44:101436.
54. Grabnar M, Roach MJ, Abd-Elsayed A, Kim C. Impact of lavender on pain and anxiety levels associated with spine procedures. Ochsner J. 2021;21(4):358–63.
55. Ren N, Yang G, Ren X, Li L. Effects of foot massage on relieving pain, anxiety and improving quality of life of patients undergone a cervical spine surgery. Health Qual Life Outcomes. 2021;19:1–7.

56. Mirabi P, Alamolhoda SH, Yazdkhasti M, Mojab F. The effects of lemon balm on menstrual bleeding and the systemic manifestation of dysmenorrhea. Iran J Pharm Research: IJPR. 2018;17(2):214.
57. Ranjbar M, Firoozabadi A, Salehi A, Ghorbanifar Z, Zarshenas MM, Sadeghniiat-Haghighi K, Rezaeizadeh H. Effects of herbal combination (Melissa officinalis L. and Nepeta menthoides Boiss. & Buhse) on insomnia severity, anxiety and depression in insomniacs: randomized placebo controlled trial. Integr Med Res. 2018;7(4):328–32.
58. Abd Allah HN, Abdul-Hamid M, Mahmoud AM, Abdel-Reheim ES. Melissa officinalis L. ameliorates oxidative stress and inflammation and upregulates Nrf2/HO-1 signaling in the hippocampus of pilocarpine-induced rats. Environ Sci Pollut Res. 2022;29(2):2214–26.
59. Dastjerdi MN, Darooneh T, Nasiri M, Moatar F, Esmaeili S, Ozgoli G. Investigating the effect of Melissa officinalis on after-pains: A randomized single-blind clinical trial. J Caring Sci. 2019;8(3):129.

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