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Original article

The effects of Melissa officinalis supplementation on depression, anxiety, stress, and sleep disorder in patients with chronic stable angina☆

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SUMMARY

Background: Despite advances in the treatment of cardiovascular diseases in recent decades, patients experience high levels of depression, anxiety, stress, and insomnia. Since the calming effect of Melissa officinalis (MO) has been known, this study aimed to determine the effects of MO supplementation on depression, anxiety, stress, and sleep disturbances in patients with chronic stable angina (CSA).

Methods: In this double-blind placebo-controlled clinical trial, 80 patients with CSA were divided randomly into two groups (taking 3 g MO supplement or placebo daily for 8 weeks). The shortened 21-item version of the depression, anxiety and stress scale (DASS-21) test and Pittsburgh sleep quality index were done before and after the intervention.

Results: At the end of the study, the intervention group receiving MO capsules had a significant reduction in scores of depression, anxiety, stress, and total sleep disturbance, compared with the placebo group ($P < 0.05$).

Conclusions: The results showed that 8-week supplementation with 3 g MO can decrease depression, anxiety, stress, and sleep disorder in patients with CSA.

1. Introduction

Coronary heart disease (CHD) is a major cause of mortality caused by non-communicable diseases in the world, including Iran [1]. This disease is responsible for 3–38% annual mortality in Iran [2]. CSA is a type of myocardial ischaemia. About half of the CHD patients have symptoms of myocardial perfusion (ischaemic heart disease). Its prevalence increases with age in both sexes; it is reported in 0.1–1% of women aged 45–54 years in Europe that reaches 10–15% between the ages of 65–74 years. Also, in men aged 45–54 years, it is 2–5% that reaches 10–20% in ages 65–74 years [1].

CHD not only affects a patient's physical health, but also social relationships, lifestyle, family environment, employment and income levels [3]. The prevalence of depression is 10–60% in patients with heart failure [4], Which is two-to three-fold more than the general population [5]. Also, among cardiovascular patients, those who suffer from depression are two-to three-fold more exposed to cardiac events (both lethal and non-lethal) compared to other patients [6]. Prevalence of anxiety in patients with heart failure has been reported at 11–45% [4]. It is known that anxiety after myocardial infarction leads to negative consequences and, independent of depression, it is associated with recurrent cardiac events within six months [7]. Stress can cause cardiovascular ischaemia in patients. Finally, adverse consequences follow. So that

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it predicts mortality and re-hospitalization after one year of myocardial infarction occurrence [8].

The prevalence of sleep disorders is 31–51% in CHD patients which is higher than normal subjects [9].

Melissa officinalis (lemon balm) belongs to Lamiaceae family. According to recent studies, it improves depression [10] anxiety [11] and stress [12] in rats. In humans, it reduces anxiety [13,14], and stress [15,16] as well as sleep disorders [17,18]. Since no study has focused on the use of MO for CHD patients, this study aimed to investigate the effect of MO capsules on depression, stress, anxiety, and sleep disorders of patients with CSA.

2. Materials and methods

2.1. Plant material

The aerial parts of MO were collected in August 2016 from Botanical Garden of Tabriz University, and identified by a botanist of the Department of Botany, Tabriz University. A voucher specimen (KF1429-1) of the plant was deposited in the Herbarium Centre, Faculty of Pharmacy, Tabriz University of Medical Sciences. MO was dried in shade at room temperature for 12 days.

2.2. Participants

This randomized double-blind controlled clinical trial study involved 80 patients with CSA in 2016 (April to August 2016) conducted in Golestan Hospital, Ahwaz, Iran.

The inclusion criteria were male and female patients with CSA, 40–75 years of age, and body mass index (BMI) between 18.5 and 40. Subjects were excluded if they had history of hypertension, diabetes mellitus, arrhythmia, renal, hepatic, gastrointestinal, endocrinological or haematological disease, musculoskeletal disease or arthritis rheumatoid, depression, mental disorders, being vegan, drug abuse, smoking, alcoholism, supplement use in the last 2 months and allergic to MO.

Sample size was calculated based on type one (α) and type two errors (β) as 0.05 and 0.10 (power = 90%), respectively according to the previous study [19] considering 8.6 and 9.9 as standard deviations (SD) and 7.2 as the difference in mean or effect size (d) of serum HDL level, the main outcome. Therefore, a sample size of 35 subjects in each group was calculated. Finally regarding with some probable dropouts, 40 subjects in each group were recruited.

2.3. Intervention

Patients were randomly divided into two groups of the intervention group (n = 40), receiving 3 capsules (3 g) per day of MO, and the control group (n = 40), receiving 3 capsules (3 g) per day of placebo for 8 weeks. The capsules containing MO were prepared by an automatic filler filling with 1 g MO powder. The Placebo capsules were similarly filled with 1 g corn starch. The dose determination was based on previous studies [20].

2.4. Data collection

Body weight was measured with minimal clothing using a digital scale (Seca, Hamburg, Germany) to the nearest 0.1 kg. Height was measured to the nearest 0.1 cm using a tape measure (Seca, Hamburg, Germany). Body mass index (BMI) was calculated as weight in kg divided by height in metres squared. Waist circumference (WC) was measured using an inelastic tape measure (Seca, Germany) at the midpoint between the costal margin and the iliac crest.

Dietary record for three days (two normal days and one holiday) was completed. Then, it was analysed using Nutritionist IV software (First Databank, San Bruno, CA, USA) adjusted for Iranian foods.

Level of physical activity was assessed using the International Physical Activity Questionnaire (IPAQ), based on MET-min/week [21].

DASS-21 was used to assess depression, anxiety and stress [22]. It is a standard questionnaire with approved reliability and validity in Iran [23]. Also we examined its reliability through a pilot study on 20 patients that resulted in a Cronbach's α coefficient of 87%.

To study sleep disorders, the Pittsburgh sleep quality index was completed. It is a standard questionnaire with confirmed validity and reliability in Iran [18]. In the present study the reliability of this instrument was examined on 20 patients that resulted in a Cronbach's α coefficient of 81%.

2.5. Ethical considerations

The international instructions of the Declaration of Helsinki on research on humans were met and a completed consent was obtained from all subjects. The trial was approved by the Ethical Committee of Ahwaz Medical University of Medical Sciences and International Registry of Clinical Trials (www.irct.ir) with the code: IRCT2016052928152N1.

2.6. Statistical analysis

Normal distribution of all variables was tested by the Kolmogorov–Smirnov test. Demographic variables were analysed using a Chi-square, Mann–Whitney U test or independent sample t-test. Comparisons within groups were done by paired-sample t-test. Independent t-test was performed to detect differences between the two groups independently. Analysis of covariance (ANCOVA) was applied to identify differences between the two groups at the end of the study, adjusting for baseline value and dietary MUFA intake. $P < 0.05$ was considered statistically significant. Statistical analyses were performed using SPSS Version 20 (SPSS Inc., Chicago, Illinois, USA) (see Fig. 1) .

3. Results

A total of 73 patients completed the trial. There were no significant differences in gender, race, age, BMI, WC, marital and education status, job, economic status, disease duration, physical activity and using medications ($P > 0.05$ for all) between two groups (Table 1). No significant differences were seen in dietary intakes of total energy, carbohydrates, proteins, fat, PUFA, SFA, cholesterol, Beta-carotene, vitamins C and E except for MUFA between two groups at the end of intervention (Table 2).

Between groups analysis showed that the mean scores of depression, anxiety, and stress were significantly ($P < 0.001$) lower in the intervention group (6.46 ± 5.42, 4.85 ± 3.37, 8.91 ± 7.95 respectively) compared with the control group (6.71 ± 6.32, 5.89 ± 3.39, 9.38 ± 7.54 respectively) post intervention. For total sleep disorder score, there was significant ($P = 0.033$) decrease in the intervention group compared with control group (4.23 ± 2.78 vs. 4.24 ± 3.35) post intervention. Among seven areas of sleep disorder, the mean scores of sleep quality, sleep duration, and sleep efficiency were significantly ($P < 0.05$) lower in the intervention group (0.970 ± 0.529, 0.910 ± 0.526, 0.550 ± 0.552 respectively) compared with the control group (1.24 ± 0.629, 1.11 ± 0.737, 1.23 ± 0.43 respectively) post intervention (Table 3).

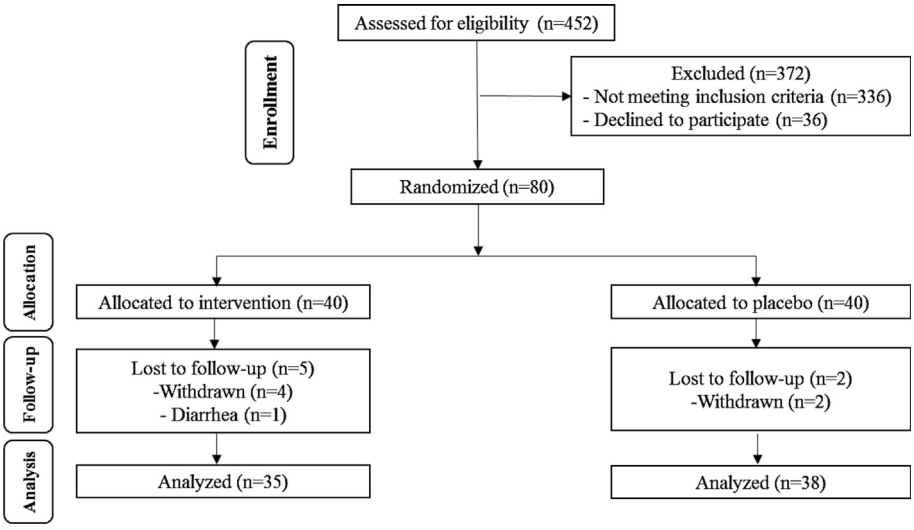

Fig. 1. Patient flow diagram.

Table 1
Demographic characteristics of the participants.

Variables		Groups		*P-value*
		Intervention (n = 35)	Placebo (n = 38)	
Sex	Male	17 (48.60)	19 (50)	0.903[b]
	Female	18 (51.40)	19 (50)	
Race	Persian	21 (60)	27 (71.1)	
	Arab	14 (40)	11 (28.9)	
Age (Year)		58.80 ± 8.38	56.53 ± 8.93	0.267[a]
BMI at study baseline (kg/m^2)		28.04 ± 3.71	29.06 ± 3.74	0.248[a]
BMI at end-of-trial (kg/m^2)		27.96 ± 3.63	29.06 ± 3.72	0.456[a]
WC (cm)		95.05 ± 11.44	100.17 ± 11.89	0.064[a]
Marital status	Singel	1 (2.9)	2 (5.3)	0.84[b]
	Married	27 (77.1)	24 (63.2)	
	Divorced	2 (5.7)	6 (15.8)	
	Widow	5 (14.3)	6 (15.8)	
Education status	Illiterate	11 (31.4)	10 (26.3)	0.63[b]
	Primary	5 (14.3)	4 (10.5)	
	Secondary	6 (17.1)	6 (15.8)	
	Diploma	6 (17.1)	4 (10.5)	
	Associate Degree	2 (5.7)	3 (7.9)	
	Bachelor	5 (14.3)	8 (21.1)	
	Highly	0 (0)	3 (7.9)	
Job	Jobless	2 (5.7)	0 (0)	0.57[b]
	Housewife	15 (42.9)	15 (39.5)	
	Worker	0 (0)	1 (2.6)	
	Employee	6 (16.1)	11 (29)	
	Free Jobs	7 (20)	6 (15.8)	
	Retired	5 (14.3)	5 (13.2)	
Economic status	Weak	9 (25.7)	9 (23.7)	0.81[b]
	Moderate	19 (54.3)	19 (50)	
	Wealthy	7 (20)	10 (26.3)	
Disease duration (Year)		4.38 ± 2.40	4.19 ± 2.50	0.751[a]
Physical activity (Met-min/week)		1578.71 ± 644.17	1739.98 ± 801.28	0.379[a]
Medication	Valsartan	0 (0–1)	0 (0–1)	0.758[c]
	Atorvastatin	0 (0–1)	0 (0–1)	0.026[c]
	ASA	1 (0–1)	1 (0–1)	0.641[c]
	Aspirin	1 (0–1)	1 (0–1)	0.745[c]
	Nitroglycin	0 (0–1)	0 (0–1)	0.462[c]

BMI: Body Mass Index. WC: Waist Circumference.
[a] *P-value* reported based on Independent Sample T test.
[b] *P-value* reported based on Chi–Square test.
[c] *P-value* reported based on Mann–Whitney U test. Quantitative data represented as Mean ± SD or median (min–max). Qualitative Data reported as frequency (Percentage).

4. Discussion

The results showed that daily consumption of 3 g of MO supplement for two months can improve depression, anxiety, stress, and sleep disorder in patients with CSA. To our best of knowledge, this is the first study to investigate the effects of MO on these parameters in CSA patients.

Other studies also found similar results, as MO reduced laboratory-induced stress [13] and improved mild-to-moderate anxiety subjects [14] in healthy subjects. In a review study, it was

Table 2
Comparison of mean and standard deviation of dietary intake in the two groups at the beginning and end of the study.

Variables		Groups				*P-value*[b]
		Intervention (n = 35)		Placebo (n = 38)		
		Mean ± SD	PC	Mean ± SD	PC	
Energy (Kcal/day)	Before	2279.81 ± 624.12	0.10	2416.24 ± 24	0.06	0.836
	After	2282.26 ± 624.82		2417.88 ± 820.84		
	P-value[a]	0.161		0.831		
Protein (g/day)	Before	103.57 ± 40.23	0.11	107.46 ± 41.67	−0.11	0.731
	After	103.67 ± 40.19		107.33 ± 41.76		
	P-value[a]	0.573		0.832		
Carbohydrates (g/day)	Before	166.55 ± 40.21	−12	140.13 ± 30.30	3.05	0.193
	After	144.89 ± 34.64		143.53 ± 29.46		
	P-value[a]	<0.001		0.135		
FAT (g/day)	Before	111.50 ± 80.09	−0.20	117.17 ± 65.18	−1.65	0.066
	After	110.82 ± 79.41		115.81 ± 65.71		
	P-value[a]	0.182		0.010		
SFA (g/day)	Before	77.78 ± 37.13	−0.31	78.92 ± 42.84	0.14	0.354
	After	77.46 ± 36.78		78.95 ± 42.46		
	P-value[a]	0.182		0.920		
MUFA (g/day)	Before	14.32 ± 5.33	2.69	15.32 ± 7.64	−3.40	0.016
	After	14.74 ± 5.71		14.81 ± 7.74		
	P-value[a]	0.163		0.038		
PUFA (g/day)	Before	19.58 ± 9.01	1.7	20.11 ± 10.97	−0.3	0.110
	After	20.27 ± 10.96		19.80 ± 10.57		
	P-value[a]	0.235		0.414		
Cholesterol (mg/day)	Before	29.74 ± 14.75	0.88	33.99 ± 22.77	1.78	0.803
	After	30.15 ± 15.39		34.51 ± 22.98		
	P-value[a]	0.325		0.080		
Beta-carotene (μg/d)	Before	255.38 ± 180.02	−0.24	250.50 ± 164.81	0.31	0.174
	After	254.98 ± 180.22		260.12 ± 164.96		
	P-value	0.188		0.345		
Vitamin E (mg/day)	Before	25.27 ± 10.51	3.81	29.72 ± 15.10	−0.008	0.424
	After	25.82 ± 10.23		29.71 ± 15.24		
	P-value[a]	0.164		0.997		
Vitamin C (mg/day)	Before	175.22 ± 82.98	0.42	171.42 ± 105.34	0.07	0.312
	After	176.16 ± 83.74		170.84 ± 104.58		
	P-value[a]	0.310		0.677		

SFAs = saturated fatty acids, PUFAs = polyunsaturated fatty acids, MUFAs = monounsaturated fatty acids, PC = percent change.
[a] P-value reported based on Paired sample *t*-test.
[b] P-value reported based on ANCOVA after baseline value adjustment.

Table 3
Comparison of mean and standard deviation of scores of depression, anxiety, stress, and sleep in the two groups at the beginning and end of the study.

Variables		Groups				*P-value*[b]	*P-value*[c]
		Intervention (n = 35)		Placebo (n = 38)			
		Mean ± SD	PC	Mean ± SD	PC		
Depression	Before	8.54 ± 7	−23.89	6.92 ± 6.36	−1.8	<0.001	<0.001
	After	6.46 ± 5.42		6.71 ± 6.32			
	P-value[a]	<0.001		0.210			
Anxiety	Before	6.38 ± 3.78	−26.68	5.83 ± 3.30	0.290	<0.001	<0.001
	After	4.85 ± 3.37		5.89 ± 3.39			
	P-value[a]	<0.001		0.744			
Stress	Before	10.42 ± 8.68	−17.74	9.25 ± 7.35	1.77	<0.001	<0.001
	After	8.91 ± 7.95		9.38 ± 7.54			
	P-value[a]	<0.001		0.765			
Total sleep	Before	6 ± 3.303	−24.31	4.55 ± 3.40	−9.27	0.016	0.033
	After	4.23 ± 2.78		4.24 ± 3.35			
	P-value[a]	0.001		0.006			
Sleep quality	Before	1.55 ± 0.617	−33.33	1.52 ± 0.509	−13.79	0.043	0.048
	After	0.970 ± 0.529		1.24 ± 0.629			
	P-value[a]	<0.001		0.030			
Sleep latency	Before	1.33 ± 0.565	−31.94	1.15 ± 0.366	−7.50	0.047	0.081
	After	0.880 ± 0.537		1.05 ± 0.394			
	P-value[a]	0.001		0.163			
Sleep duration	Before	1.50 ± 0.512	−36.36	1.26 ± 0.562	−15.78	0.022	0.031
	After	0.910 ± 0.526		1.11 ± 0.737			
	P-value[a]	<0.001		0.083			
Sleep efficiency	Before	1.36 ± 0.674	−54.54	1.23 ± 0.59	−4.16	0.001	0.001
	After	0.550 ± 0.552		1.23 ± 0.43			
	P-value[a]	0.011		0.147			

Table 3 (*continued*)

Variables		Groups				*P-value*[b]	*P-value*[c]
		Intervention (n = 35)		Placebo (n = 38)			
		Mean ± SD	PC	Mean ± SD	PC		
Sleep disturbances	Before	1.10 ± 0.301	−21.42	1.13 ± 0.344	−4.34	0.061	0.058
	After	0.860 ± 0.487		1.09 ± 0.417			
	P-value[a]	0.021		0.327			
Use of sleeping medications	Before	1.50 ± 0.570	50	1.75 ± 0.886	12.5	0.441	0.445
	After	2 ± 0.816		1.88 ± 0.835			
	P-value[a]	0.319		0.351			
Daytime dysfunction	Before	1.48 ± 0.643	−20.37	1.27 ± 0.550	−6.81	0.125	0.169
	After	1.07 ± 0.550		1.18 ± 0.588			
	P-value[a]	0.005		0.168			

PC: percent change.
[a] *P-value* reported based on Paired sample *t*-test.
[b] *P-value* reported based on ANCOVA after baseline value adjustment.
[c] *P-value* reported based on ANCOVA after baseline and MUFA PC adjustment.

reported that MO has anti-anxiety properties [24] Two other studies indicated that MO reduced stress in healthy subjects [15,16] In an animal study, MO extract prevented depression through serotonergic antidepressant activity in rats [10]. Additionally, in a study on rats, MO reduced the level of corticosterone that is the main biomarker of stress [12]. In another study, MO reduced corticosterone levels in serum and decreased GABA-T levels in the rat hippocamp [25].

The use of MO improved total sleep score in patients with CSA in the current study. MO had a positive impact on three areas of sleep disorders (sleep quality, sleep duration, and sleep efficiency). In another study, the daily intake of 500 mg dry extract of MO for a month improved total sleep score in postmenopausal women. MO also had a positive impact on five different domains of sleep disorders in that study [18]. In another study, valerin with MO improved sleep quality in healthy individuals [17].

There are three theories about the MO mechanism of action on anxiety and related neurological disorders. According to one theory, MO has serotonergic activity [10, 26]. Another theory suggests that MO decreases corticosterone level [12, 25]. On the other hand, anxiety and related neurological disorders often result from low levels of the inhibitory neurotransmitter Gama-aminobutyric acid (GABA) [27]. While $GABA_A$ receptor binding is relatively well studied in anxiolytic botanicals, one of the other mechanisms to increase GABA levels in the brain, and potentially to control anxiety, is to inhibit the enzyme GABA transaminase (GABA-T) [28]. MO is a GABA-T inhibitor [25, 29], and the major constituent for this activity is rosmarinic acid since it is present in very high quantities. Other compounds that may also play a role in the activity of MO are ursolic and oleanolic acids [29].

5. Conclusion

In the present study MO supplementation had beneficial effects on depression, anxiety, stress, and sleep disorder in patients with CSA. However, further investigations are required to confirm these results.

Conflict of interest

None declared.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.clnesp.2018.04.015.

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