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Research Paper

Heart palpitation relief with *Melissa officinalis* leaf extract: Double blind, randomized, placebo controlled trial of efficacy and safety

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ABSTRACT

Ethnopharmacological relevance: In Traditional Iranian Medicine (TIM), *Melissa officinalis* L. is commonly regarded as an effective therapy for heart palpitations.
Objective: Heart palpitation is a common complaint that is often benign and associated with a marked distress that makes the condition difficult to treat. Herbal medicines provide an alternative to conventional drugs for treating various kinds of diseases. This study was done as a double blind randomized placebo-controlled clinical trial to evaluate the efficacy and safety of the dried extract of *M. officinalis* on adults suffering from benign palpitations.
Materials and methods: Eligible volunteers were randomly assigned as outpatients to a 14 day treatment with 500 mg twice a day of lyophilized aqueous extract of *M. officinalis* leaves (or placebo). Participants in the tests, physicians and researchers were blind to group assignments. Both primary and secondary outcomes were patient-reported. Primary outcomes were obtained from two measures: mean frequency of palpitation episodes per week, derived from patients' diaries, and mean intensity of palpitation estimated through Visual Analogue Scale (VAS) in a self-report questionnaire. Psychiatric symptoms (somatization, anxiety and insomnia, social dysfunction and severe depression) were evaluated as secondary outcomes by General Health Questionnaire-28 (GHQ-28), before and after intervention.
Results: Fifty-five volunteers out of 71 recruited study subjects completed the trial. Results showed that 14-day of treatment with lyophilized aqueous extract of *M. officinalis* leaves reduced frequency of palpitation episodes and significantly reduced the number of anxious patients in comparison to the placebo ($P=0.0001$, $P=0.004$ resp.). Also, *M. officinalis* extract showed no indication of any serious side effects.
Conclusion: Lyophilized aqueous extract of *M. officinalis* leaves may be a proper and safe herbal drug for the treatment of benign palpitations.

Abbreviations: (TIM), Traditional Iranian Medicine; (VAS), Visual Analogue Scale; (GHQ-28), *General Health Questionnaire*; (MUPS), Medically Unexplained Physical Symptom; (WMA), World Medical Association; (TUMRC), Traditional Medicine and Materia Medica Research Center; (ECG), Electrocardiography; (CBC), complete blood count; (SGOT), serum glutamic oxaloacetic transaminase; (SGPT), serum glutamic pyruvic transaminase; (BUN), blood urea nitrogen.

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1. Introduction

Palpitation is defined as an abnormal, unpleasant or heightened awareness of heartbeat (Brugada et al., 1993; Khamis and Dancy, 2009; Mayou et al., 2003; Zimetbaum and Josephson, 1998). It is the second most common reason in general practice for which patients are referred to a cardiologist (Mayou, 1998). Some palpitations may be an indication of life-threatening cardiac arrhythmias (Weber and Kapoor, 1996), but the condition is most often benign (Abbott, 2005). Benign palpitation, palpitations without any more serious underlying heart disease, remains a Medically Unexplained Physical Symptom. Although prognosis may be good in most cases, the condition causes considerable distress and disability among those affected (Price, 2008).

The high prevalence of benign palpitations, its current therapeutic methods that have side effects and are poorly officious, which induce continual recourse to healthcare facilities, calls for research to find more effective therapies.

Traditional Iranian Medicine (TIM) roots back to nearly 10,000 years ago (Rezaeizadeh et al., 2009), and it has a great potential for solving some of the present medical problems, as shown in some recent research in the field (Asghari et al., 2013; Faridi et al., 2014; Mokaberinejad et al., 2012; Mozaffarpur et al., 2012). As far as palpitation is concerned, it has been explained thoroughly in TIM and various therapies have been suggested for it (Ershadifar et al., 2014). In reviewing the literature of TIM, we found that *Melissa officinalis* is a good candidate for further research (Ghaffari et al., 2013). *M. officinalis* L. (Lamiaceae) is an aromatic herb native to southern Europe, Asia Minor and North Africa (British Herbal Pharmacopoeia, 1983). Avicenna, Razes and some other Iranian traditional physicians introduced Badranjbuyah (*M. officinalis*) as an exhilarant and a tonic for the heart, which also relieves palpitation (Aghilikhorasani, 2009; Al-Heravi, 1992; Avicenna (IbnSina), 2005; Mu'min Tonekaboni, 2007; Musavi, 2004; Razes (Razi), 2002). In addition to these reports in Traditional Iranian Medicine, *M. officinalis* (Lemon Balm) is recommended as a remedy for conditions of tension, restlessness and irritability in modern phytotherapy. Also it is considered as a safe drug, although limited research has been done on long-term effects (Brendler et al., 2005). However, to the best of our knowledge, no clinical trial has been carried out to assess the effect of *M. officinalis* L. on palpitations.

The aim of the present study was to assess the efficacy of *M. officinalis* as compared with placebo for relieving of benign palpitation in a 2-week double blind randomized trial.

2. Materials and methods

This was a 14-day, double blind, randomized, placebo controlled clinical trial. It was conducted in the outpatient clinic of the cardiology department at Shahid Mostafa Khomeni Hospital in Tehran, Iran, during November 2012 to May 2013. Research followed guidelines of the Declarations of Helsinki for humans. All participants provided written informed consent, and the protocol was approved by medical ethical committee of Shahid Beheshti University (Session no. 111, 2012-1-7(. This trial was registered in the Iranian Registry of Clinical Trials; Irct ID: IRCT2013012712303N1.

2.1. Patients

Eligible participants in this study were adult outpatients with an unpleasant sensation in the heart or awareness of heartbeat as their main complaint. Volunteers were invited through advertisement. They were initially screened by a short interview by phone, to determine palpitation characteristics and in order to take a brief record of each patient's medical history including other health problems and medications to check entry criteria for inclusion in the trial. Inclusion criteria were as follows: palpitations (abnormal awareness of heartbeat) as the main complaint, conditions experienced for at least three months; age between 18 and 60 years; and informed consent. Volunteers who met at least one exclusion criterion were not included in the trial. Exclusion criteria were as follows: mental retardation; psychosis and other serious psychiatric disorders confirmed by a psychiatrist; organic heart diseases confirmed by a cardiologist; serious chronic diseases; endocrine problems, pregnancy; lactation; consumption of beta-blockers, antidepressants, anxiolytics, hypnoinducers or sedatives 10 days before the start of the study. Drop out criteria were withdrawal of participant, or irregular use of prescribed drugs. Furthermore, patients with any clinically significant deterioration in medical condition from those of the baseline were excluded.

Eligible patients were selected then invited to the outpatient's cardiology clinic in Shahid Mostafa Khomeini Hospital. Each patient's medical history was checked by a cardiologist, and each had a physical examination and an electrocardiography test to identify those patients suffering serious problems considered under the exclusion criteria.

Panic disorder is considered in medical assessments for making a diagnosis of palpitation; accordingly, a simple screening tool was applied to identify the condition of panic disorder in patients; this was done by asking patients one single question; "Have you experienced brief periods, for seconds or minutes, of an overwhelming panic or terror that was accompanied by racing heartbeats, shortness of breath, or dizziness?" (Abbott, 2005)

2.2. Herbal drug

Melissa or Lemon Balm consist of the dried leaves of *M. officinalis* L. This is the accepted name of a species in the genus Melissa and Family Lamiaceae (www.theplantlist.org). It was obtained from the farm of Zardband Pharmaceutical Co., Gonbad, Iran. The plant was authenticated in the Herbarium of Traditional Medicine and Materia Medica Research Center (TMRC), Shahid Beheshti University of Medical Sciences, Tehran, Iran. Voucher specimens of *M. officinalis* L. (No. 3380) were deposited in the Herbarium of TMRC. Quality control tests were done according to British Pharmacopea (2009).

2.2.1. Dried extract preparation

Lyophilized aqueous extract of *M. officinalis* leaves was prepared by a modified procedure considering the methods employed in other researches (Alves et al., 2009; Koksal et al., 2011). The powdered dried leaves of *M. officinalis* (100 g) were added to boiling water (1000 ml) in a suitable beaker. The mixture was stirred, the heater turned off and the beaker was covered with a lid (aluminum foil). The mixture was allowed to steep for 15 min without additional heating (a process similar to an infusion method). Then it was filtered and 756 ml hot water extract was obtained. In the next step, the filtrate was freeze-dried in a lyophilizer at 5 mTorr pressure and −50 °C (Vir Tis benchtop SLC), to obtain 20.9 g dried herbal extract (yielding 20.9% dried extract from the original plant material).

The above mentioned procedure was done proportionally to obtain the required amount of dried extract for 28 patients (*M. officinalis* group) in the present study.

2.2.2. Capsule preparation

Dried extract of *M. officinalis* was filled in capsules as each one contained 500 mg of the dried extract. The capsules were stored in air-tight containers and kept in a refrigerator (4 °C) until time of use. The placebo was bread crumbs which was also filled in similar capsules each containing 500 mg of bread crumb.

2.3. Study design and interventions

All participants underwent a standard clinical assessment comprising medical history, physical examination and electrocardiography (ECG) examination (Abbott, 2005; Zimetbaum and Josephson, 1998). Finally, eligible participants were randomly assigned to receive a capsule of *M. officinalis* dried extract or a capsule of placebo in a 1:1 ratio using a computer generated code. An independent pharmacist was the person who set the codes on the drug or placebo packets according to the confidential list. This list consisting of the private codes was kept by him in a sealed, opaque envelope until the end of the study and until such time that they were needed for data analysis.

Herbal drug (*M. officinalis*) capsules were identical in appearance to the placebo capsules; also their packages were completely similar. They were identifiable only by a private code on the label of the container. The drug and placebo packages were mixed and placed in a single large box, which was given to the nurse. So, the nurse, who was unaware about the content of the packets, dispensed them to every patient in the order determined by the independent pharmacist.

The dispenser (nurse), cardiologist, researcher and patients were all blind to these assignments throughout the duration of the study. *M. officinalis* dried extract or placebo capsules were administered twice daily; one 500-mg capsule in the morning and the other at night. Patients were asked to fill a self-report questionnaire to record their clinical characteristics. Participants also completed a form to record side effects in order to evaluate probable adverse effects.

2.4. Outcomes

Frequency and severity of symptoms in patients with palpitations affect quality of life (Brugada et al., 1993). However, heart palpitation is a subjective complaint and there is no accurate tool available to take quantitative measurements, so changes in frequency and intensity of episodes were regarded as the primary outcomes for evaluating the condition. The frequency of palpitations per 24 h was recorded in a daily self-reported form to eliminate observer bias. Also, the average intensity of palpitations experienced recently by patients was recorded by means of Visual Analogue Scales (VAS) (Wewers and Lowe, 1990). The VAS consisted of a 10-cm line with the end points defined as “no palpitation (unpleasant sensation in heart)” to “unbearable palpitation”. Because increased attention to heartbeat may make patients sensitive and cause some degree of bias in the results, patients were asked to start recording of frequency and intensity of their palpitations, one week before the beginning of intervention and to continue throughout the duration of the study. Due to lack of validated patient-reported outcome instruments for benign heart palpitations, this innovative measure was used for evaluations of the condition.

Evaluation of psychiatric symptoms before and after intervention was done by the General Health Questionnaire-28 (GHQ-28) (Goldberg, 1989, 1972). An Iranian version of the 28-item GHQ was used. It is a brief, simple, consistent and reliable instrument and one of the most well-known questionnaires for screening psychological disorders that evaluates four symptoms, namely, somatization, anxiety and insomnia, social dysfunction and severe depression (Noorbala et al., 2004, 2011). The study used the Likert scoring method, in which the maximum score was 84. The cut-off point was considered 24 out of the total score and 6 in every subscale; so patients with equal or higher scores than the cut-off point were validated as having a psychological disorder. Accordingly, the number of the patients who had a psychological disorder was counted regarding their questionnaire scores (Table 3).

2.4.1. Safety evaluation

Patients were asked to write down any new symptom in an “adverse events form” every day throughout the duration of the study. They also could contact a responsible physician by phone in case they experienced any side effects. Also, they were contacted by a researcher every three days by phone and asked to give accurate details about consumption of drugs and whether or not they had experienced any new symptoms. In order to evaluate probable side effects of the herbal drug, checks were made for complete blood count (CBC), serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), blood urea nitrogen (BUN) and creatinine levels before and after treatment.

2.5. Statistical analysis

Data are presented as mean ± standard deviations (SD) and proportions (%). According to pilot study data and considering $\alpha = 0.05$, $\beta = 0.20$ and SD = 12 for every group and pre-estimation of difference between groups as $\Delta = 8$, the sample size calculated at least 28 in every group.

Using SPSS software (version 20), nonparametric tests were performed due to lack of normal data distribution. A Mann–Whitney *U* test was used to compare main variables between the two groups. In each group, a change of a variable from its baseline was analyzed by a Wilcoxon Signed Rank test. Differences were considered significant with $P < 0.05$. The Chi-square test was applied to compare demographic data, number of patients with scores more than the cut-off point and frequency of side effects between the protocols. The McNemar test was used to compare numbers of patients before and after the intervention.

3. Results

From the 167 volunteers experiencing palpitations as their chief complaint, 55 patients completed the trial. The flow diagram is shown in Fig. 1.

Demographic data and clinical characteristics of palpitations as well as the effective factors on palpitations are summarized in Table 1. As it is obvious, no significant differences were identified between patients in each group with regards to basic demographic data including sex and age. The results also showed that clinical characteristics were similar in both groups. The mean length of medical history was about 60 months and there was no significant difference determined between the two groups. The rate of distress from symptoms was high (85%) in both groups. Meanwhile, consumption of cigarettes and caffeine (coffee or tea) as effective factors on palpitations showed no difference between the two groups. Panic disorder had high prevalence in both groups (66.7–71.4%).

In physical examinations, there was no significant difference between groups for blood pressure readings and heart rates before and after intervention. Results of clinical laboratory tests before and after intervention were not significantly different.

3.1. Efficacy: Melissa versus placebo

3.1.1. Decrease of the frequency of palpitation episodes

After intervention, the mean frequency of palpitation episodes was 36.8% less than the baseline in *M. officinalis* extract group. This decrease was significant in comparison to the group that took the placebo ($P < 0.0001$). The intensity of palpitations sensed by participants was significantly decreased in both groups after interventions, so this decrease in *M. officinalis* group cannot be attributed to a herbal drug effect rather than a placebo effect (Table 2).

3.1.2. Decrease of the number of the anxious patients

In anxiety subscale of GHQ-28, after intervention, the number of the patients with anxiety and insomnia disorder in the herbal drug group decreased significantly ($P=0.004$), unlike that of the placebo group (Table 3).

3.2. Side effects

Nineteen complications were investigated over the trial. Difference between the effect of Melissa extract and that of the placebo in frequency of side effects was not significant, except for "increased appetite" in the group taking the herbal drug compared to the placebo group.

4. Discussion

Palpitation is a complex symptom with a multi-factorial etiology. Studies have identified several different causes that underlie the condition; cardiac 43%, psychiatric 31%, miscellaneous 10%, and unknown 16% (Weber and Kapoor, 1996).

There is little research available on benign palpitations. Routine pharmacotherapy mainly consists of mild anxiolytics; also some beta-blockers such as propranolol are used to alleviate somatic symptoms of anxiety and attenuations of tachycardia. However, in benign palpitations heart rate is often normal, so using beta-blockers has limited efficacy, with many side effects and contra-indications for some patients (suffering from asthma or diabetes).

M. officinalis is a traditional remedy proposed by TIM scholars for alleviation of palpitation and the present study was a clinical trial attempting to evaluate the efficacy and safety of its dried aqueous extract. We found that after 2 weeks, frequency of palpitation episodes and the number of the patients having anxiety decreased significantly ($P=0.0001$, $P=0.004$ respectively) in patients receiving *M. officinalis* in comparison to those that took the placebo.

Patients in drug and placebo groups had similar demographic and clinical conditions (Tables 1 and 2).The mean age of patients suffering from palpitations was 41.7 years of whom 63.7% were female. Other studies have indicated that patients with psychological disorders, who had palpitations, were most likely to be younger and female (Jonsbu et al., 2009; Lok and Lau, 1996; Weber and Kapoor, 1996). Besides, only five patients out of the

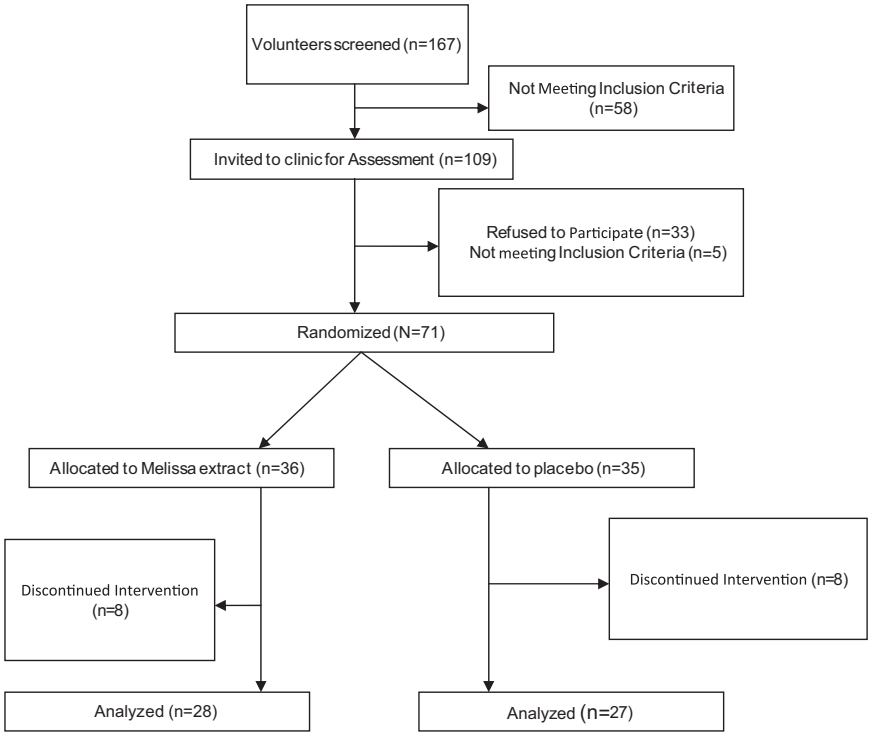

Fig. 1. Flow diagram of study participation.

Table 1
Demographic data, clinical characteristics of palpitations and the effective factors on palpitations.

	M. officinalis group ($n=28$)			Placebo group ($n=27$)			*P*-value
Demographic							
Age, years (mean, SD)	42.4(10.7)			41.1(12.3)			0.69
Female (*n*, %)	17(60.7)			18(66.7)			0.64
Palpitation							
Length of history, months (median, mean, 95%CI)	12	59.9	11.6–108.2	48	64.7	24.0–105.4	0.87
Moderate or much distress about symptom (*n*, %, 95%CI)	24	85.7	72.5–98.9	23	85.1	65.3–95.1	0.95
Consumptions (*n*, %, 95%CI)							
Cigarette	2	7.1	1.25–24.9	2	7.4	1.29–25.7	0.97
Tea/Coffee	19	67.8	47.5–83.4	21	77.7	57.2–90.6	0.64
Panic disorder[a] (*n*, %, 95%CI)	20	71.4	51.1–86.0	18	66.6	46.0–82.7	0.73

[a] A simple screening tool containing of one single question was applied to identify the condition of panic disorder in patients (Abbott, 2005).

Table 2
Scores on dependent variables at pre and post-treatment in participants treated by *M. officinalis* or placebo.

Variables	Pre-treatment	Post-treatment	*P*-value
Palpitations frequency (occurrences/168 h)	Mean(S.D.)	Mean(S.D.)	
M. officinalis group	10.6(17.7)	6.7(14.2)	**0.0001**
Placebo group	7.4(7.1)	7.09(7.2)	0.73
P-value	0.98	**0.01**	
Palpitation intensity (VAS[a] score)			
M. officinalis group	5.8(1.7)	4.4(2)	**0.002**
Placebo group	5.5(1.7)	4.6(1.6)	**0.007**
P-value	0.78	0.86	

[a] Visual Analogue Scale.

Table 3
Number of the patients with a psychological disorder[a].

Number of the patients with a psychological disorder	Before intervention *n* (%)	After intervention *n* (%)	*P*-value
Lack of good mental health (general)			
M. officinalis group ($n=28$)	20(71.4%)	16(57.1%)	0.21
Placebo group ($n=27$)	25(92.6%)	21(77.7%)	0.28
Somatization			
M. officinalis group ($n=28$)	20(71.4%)	19(67.9%)	1
Placebo group ($n=27$)	25(92.6%)	21(77.8%)	0.28
Anxiety and insomnia			
M. officinalis group ($n=28$)	21(75%)	12(42.8%)	**0.004**
Placebo group ($n=27$)	22(81.5%)	18(66.6%)	0.21
Social dysfunction			
M. officinalis group ($n=28$)	27(96.4%)	27(96.4%)	1
Placebo group ($n=27$)	26(96.3%)	27(100%)	1
Severe depression			
M. officinalis group ($n=28$)	3(10.7%)	3(10.7%)	1
Placebo group ($n=27$)	10(37%)	6(22%)	0.12

[a] According to 28-item General Health Questionnaire.

74 volunteers in the test were diagnosed with a cardiac disorder as the cause of palpitations. This finding is similar to a recent study that suggests that only 4% of evaluated patients ($n=198$) had cardiac diagnosis for chest pain and palpitations (Jonsbu et al., 2009). Considering that eligible participants in the present study were not diagnosed serious cardiac or non-cardiac diseases, it can be assumed that they were suffering from benign palpitations and as shown in related studies, we expected that psychological causes were dominant in such cases (Jonsbu et al., 2010; Mayou et al., 2003). The results indicating high incidence of panic disorder (69%) and lack of good state of mental health in 81.8% of participants (according to GHQ-28) support this diagnosis.

Overall, despite the relatively short duration of the study, a reduction of palpitation frequency by 36.8% was observed in the group taking the drug, and this is promising compared to research on other interventions such as cognitive behavioral therapy. Cognitive behavioral therapy is considered as an effective treatment for patients with benign palpitations, although tests on frequency of symptoms did not show any changes from the baseline after treatment (Jonsbu et al., 2011).

In present study, GHQ-28 results indicated a significant decrease in the number of anxious patients by 42.8% in Melissa group. So, it seems that this herbal drug can reduce anxiety. This result may be consistent with previous findings suggesting anti-anxiety or calming effect (Awad et al., 2009; Cases et al., 2011; Kennedy et al., 2004). However, some other herbal drugs are also known as promising anxiolytics but there is little conclusive evidence from clinical trials (Aparecida Gelfuso et al., 2014).

Results of these tests may also support recommendations reported in Iranian Traditional Medicine for *M. officinalis* as a restorative and tonic for the mind which improves brain function and balances the mood (Abu-Asab et al., 2013; Al-Heravi, 1992; Mu'min Tonekaboni, 2007). Avicenna who was a pioneer in cardiovascular and neurological sciences (Zargaran et al., 2012, 2013) in his book on cardiology: Kitab al-adviyat ul-Qalbiye (Book of Medication for Cardiovascular Diseases) (Faridi and Zarshenas, 2010) as well as "The Canon" states that *M. officinalis* is beneficial for heart conditions and state of mental health (Avicenna (IbnSina), 2005; Musavi, 2004) so it seems that Melissa may have a mutual effect on the heart and mind and the result of our study supports this hypothesis.

Although one study had been done on the effect of aqueous extract *of M. officinalis* on isolated hearts of rats (Gazola et al., 2004), to the best of our knowledge, no other study has been done on the effect of *M. officinalis* on the heart. This study therefore constitutes the first clinical trial to evaluate the cardiac effect of *M. officinalis*. In contrast to the above-mentioned animal study where an aqueous extract of *M. officinalis* was found to reduce heart rate without changing contractile force, we found no significant changes in human heart rate in patients treated with the plant extract. So, more specific research is recommended to be done to test the effect of *M. officinalis* on the human heart.

During this study, no clinically significant adverse reactions were observed and this is in agreement with the result of some other studies that examined the effect of *M. officinalis* extract (Akhondzadeh et al., 2003; Cases et al., 2011). The only side effect that was reported more frequently in the Melissa group as compared to the placebo group was "increased appetite". This is not a serious side effect, but may be considered to be an advantage for the application of *M. officinalis* in the management of the patients with anorexia. Besides, there are some other beneficial effects for *M. officinalis* which are explained in the literature relating to traditional medicine, such as memory enhancing, as a tonic for the heart, mind, liver and stomach; some of which have been verified in animal studies or clinical trials on humans (Akhondzadeh et al., 2003; Bolkent et al., 2005; Zarei et al., 2014; Kennedy et al., 2004; Kennedy and Scholey, 2006; Müller and Klement, 2006; Soodi et al., 2013).

Considering the side effects associated with currently available conventional drugs and low efficacy, it seems that *M. officinalis* extract is an appropriate remedy for benign palpitations and is a safe drug in current dose. The limitations of this study consist of its 14-day duration, small sample size, using only a fixed dose and lack of specific psychiatric evaluation for anxiety and depression should be considered in any further research in this area.

5. Conclusions

The results of the present innovative study provide some evidence that aqueous extract of *M. officinalis* may be a beneficial treatment for patients suffering from benign palpitations, and as a promising anxiolytic drug without any considerable side effects.

Moreover, this study demonstrates the safety of total daily dose of 1000 mg lyophilized aqueous extract of *M. officinalis* for 14 days.

Author contributions

FA was involved in all experiments. MN designed and coordinated the study. SA participated in design and coordination of the study and was the principal pharmacognosy investigator. FF was participated in design and performed the cardiological examinations. AN was the psychiatrist of the trial. SF performed statistical analysis. SS helped to draft the manuscript. All authors read and approved the submitted version of the manuscript.

Conflict of interest

None declared.

Declarations

The authors declare that this manuscript has not been submitted or published elsewhere for publication. The corresponding author declares that all the listed authors have read and approved the submitted manuscript.

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