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RESEARCH ARTICLE

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Effect of *Melissa officinalis* on systolic and diastolic blood pressures in essential hypertension: A double-blind crossover clinical trial

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For a long time, *Melissa officinalis* (*M. officinalis*) has been used to treat cardiovascular diseases. Therefore, this study aimed at evaluating the effects of *M. officinalis* on systolic and diastolic blood pressures in hypertensive patients. We conducted a double-blind, controlled, randomized crossover clinical trial on 49 patients who received either *M. officinalis* capsules (400 mg/d; $n = 23$) or the placebo ($n = 26$) three times per day for a 4-week period. After a 2-week washout period, the *M. officinalis* group received placebo and the other group received *M. officinalis* for another 4-week period. The systolic and diastolic blood pressures were measured once at baseline and then every 2 weeks for 10 weeks. The statistical analysis of the obtained data revealed that the chronology of the consumption of *M. officinalis* and placebo had no effect on the systolic and diastolic blood pressures in these two studied groups. Moreover, it was found that systolic and diastolic blood pressures significantly decreased after the consumption of *M. officinalis*, compared to placebo. Systolic and diastolic blood pressures in group A at the beginning of the study were 152.30 ± 5.312 mmHg and 95.52 ± 1.988 mmHg, respectively, and, after the first phase (drug use), reached 129.88 ± 9.009 mmHg and 80.13 ± 5.488 mmHg, respectively. Systolic and diastolic blood pressures in group B at the beginning of the study was 152.26 ± 5.640 mmHg and 94.44 ± 2.607 mmHg, respectively, and after the second phase (drug use), reached 131.77 ± 8.091 mmHg and 81.46 ± 7.426 mmHg, ($p = .005$), respectively. Also, no significant side effects were observed during the study. According to the results, *M. officinalis* can reduce systolic and diastolic blood pressures of the patients with essential hypertension.

KEYWORDS
essential hypertension, herbal medicine, lemon balm, *Melissa officinalis*, Persian medicine

1 | INTRODUCTION

Hypertension occurs when blood pressure goes above 140/90 mmHg (Bonow, Mann, Zipes, & Libby, 2015; Longo et al., 2015), which is known as a major cause of death and disability worldwide by leading to 9.4 million deaths annually (WHO, 2013). According to the statistics, more than a billion people suffer from high blood pressure worldwide and its prevalence appears to affect approximately 40% of the world population. It was shown that the prevalence of high blood pressure increases with age, so that its prevalence rate among people within the age range of 18–39 years old is 7%, whereas its prevalence rate in people aged above 59 years is 65%. In this regard (Savoia et al., 2017), the prevalence rate of high blood pressure in people aged above 18 years in Iran is estimated to

be 21.6% (22.4% in women and 20.8% in men) (Mirzaei, Moayedallaie, Jabbari, & Mohammadi, 2016).

Hypertension complications include left ventricular hypertrophy, cardiovascular diseases such as heart attack, angina, and heart failure, cerebrovascular diseases such as stroke, cerebral hemorrhage, or ischemic attack, renal vascular involvement, and peripheral vascular disease (Bonow, Mann, Zipes, & Libby, 2019). Notably, hypertension is known as the most frequent modifiable risk factor for cardiovascular disease (Fields et al., 2004). Recent studies have indicated that the complete treatment of high blood pressure reduces the mortality rate by 27%, 25%, and 35–40% in all the affected groups, cardiovascular events, and stroke, respectively (Bonow et al., 2015; Fields et al., 2004). Specifically, a 10-mmHg reduction in systolic blood pressure was followed by a 22% reduction in coronary artery disease and a 41% reduction in stroke (Fields et al., 2009).

In recent years, for the treatment of hypertension, international guidelines have been categorized in terms of the intensity of blood pressure, the presence of other cardiovascular risk factors, and organ damage (Chobanian, 2015; James et al., 2014; Wright Jr, Fine, Lackland, Ogedegbe, & Dennison Himmelfarb, 2014). Also, herbal medicines are able to lower blood pressure in most of the patients; however, the best way to lower blood pressure still is a controversial issue. Despite being aware of the complications of high blood pressure, reduction of the major risk factors, and access to antihypertensive medications, only 30% of the patients under treatments reached a blood pressure below 140.90 mmHg (Jung et al., 2013; Mazzaglia et al., 2009; Tocci et al., 2015).

Given various genetic predispositions in patients and the difference in the underlying mechanisms of hypertension, the investigation of different treatment approaches may lead to prevention and management, and even to the control of hypertension. Some changes in lifestyle such as smoking cessation, exercise, adoption of a healthy diet, and treatment of obesity can help in the prevention of or delay hypertension. The use of complementary therapies, including herbal medicines can be another option regarding the prevention and control of high blood pressure. Under laboratory conditions, it has been confirmed that some plant species such as oregano, chocolate mint, sage, and rosemary have inhibitory effects on the blood pressure control (Kwon, Varttam, & Shetty, 2006; Li et al., 2008).

Rosmarinic acid is one of the compounds of the species whose antihypertensive effects have been confirmed in many pharmacological studies (Ferreira, Celotto, Capellini, Albuque, & Nadai, 2013). Accordingly, *Melissa officinalis*, which belongs to the Lamiaceae family, is one of the plants that contain rosmarinic acid. For a long time, this plant has been used to treat various types of diseases, including cardiovascular diseases (Dastmalchi et al., 2008, 2009; Shakeri, Sahebkar, & Javadi, 2016). Moreover, the scientific evidence regarding the antioxidant, hypolipidemic, and anti-anxiety properties of *M. officinalis*, which was shown to reduce the risk of high blood pressure (Shakeri et al., 2016) indirectly, can partly explain the traditional use of this plant for the treatment of this disease. On the other hand, regarding the herbal supplements, one of the remarkable points is that the worldwide demand for the herbal supplements is growing, despite increasing criticism for the lack of clinical evidence for many products, false claims, quality concerns, and self-medication of patients with herbal supplements in serious diseases. Therefore, although there are beneficial effects of herbal supplements, it seems that their unconditional use, especially in diseases, can be dangerous (Williamson, Liu, & Izzo, 2020). Finding clinical evidence can take advantage of their beneficial effects and identify their side effects. Therefore, this study aimed at investigating the effects of *M. officinalis* extract on systolic and diastolic blood pressures in essential hypertension.

2 | MATERIALS AND METHODS

2.1 | Study design

The present randomized double-blind crossover clinical trial was performed on the patients with essential high blood pressure who were referred to the Tooba Clinic in the Mazandaran University of Medical Sciences, Sari, Mazandaran Province, Iran.

2.2 | Inclusion criteria

The inclusion criteria consisted of the age range of 30–75 years for both genders, essential hypertension (stage 1), treatment at least with one to three antihypertensive drugs in the last month, systolic blood pressure (140–159 mmHg), and diastolic blood pressure (90–99 mmHg) (mean blood pressure of three measurements from the right arm in sitting position with 5-minute intervals).

2.3 | Exclusion criteria

The exclusion criteria were blood pressure above 180.110 mmHg at the beginning or during the study, history of secondary hypertension, symptoms of damage to major organs (e.g., myocardial infarction, congestive heart failure, renal failure, or cerebrovascular accident), various types of cardiac dysrhythmias (e.g., second- and third-degree blockade), symptomatic valvular heart disease, liver dysfunction, type 1 and 2 diabetes with renal (creatinine level of >1.5 times greater than the maximum normal) and hepatic (alanine aminotransferase level >3 times greater than the normal maximal) dysfunctions, less than 100,000 platelets per microliter of blood, history of a potassium level of >5.1 or <3.5 mA/L in the first visit, history of hypothyroidism or hyperthyroidism, pregnancy and breastfeeding, taking supplements 2 to 3 months before the start of the study, and any medical or surgical procedure interfering during the study process.

2.4 | Plant material

The *M. officinalis* capsule used in this study was manufactured in the Iranian Institute of Medicinal Plants. This research obtained approval

from the Ministry of Health and Medical Education with ACT No: N.5 and IRC (Registration Code: 4380762121294705) called Melitropic capsule. Each capsule contained 400 mg of *M. officinalis* (70% hydroalcoholic extract) consisting of 8 mg of rosmarinic acid, corn starch, lactose monohydrate (milk sugar), magnesium acetate, and alpha-tocopherol. In addition, the placebo compounds included alpha-tocopherol, magnesium acetate, lactose monohydrate (milk sugar), and corn starch. The main ingredient in the placebo was cornstarch. The weight of placebo was the same as the weight of the drug capsule. All the participants were supposed to use these capsules three times per day.

2.5 | Study intervention and data collection

At first, the researchers collected the demographic and anthropometric information of the patients. Moreover, the study consisted of two phases. During the study patients continued the consumption of their previous anti hypertensive medications in terms of the treatment's protocol (one to three drugs). In the first phase of the study (4 weeks), the patients in group A received *M. officinalis* capsules, while the patients in group B received placebo capsules. All the participants received three capsules per day, one after each meal. After completing the first phase, the patients only received their antihypertensive medications during a two-week washout period. After the end of the washout period, the second phase of the study began, during which group A was given placebo, and group B was given the *M. officinalis* capsules. In the second phase of the study, the patients daily received three capsules, one after each meal as well. They also continued the consumption of their antihypertensive medications. During their visit sessions with the doctor, the number of the remaining capsules in the container was counted to see whether the patients consumed them (both of the M. *officinalis* and placebo capsules). If the patient had consumed more than 90% of the medication, the treatment was considered complete; otherwise, the patient was excluded from the study.

2.6 | Follow-up

Blood pressure of all the patients was measured once at the beginning of the study and then every 2 weeks (i.e., weeks 2, 4, 6, 8, and 10 of the study and five times in total) using a mercury sphygmomanometer (Alpk2, Japan) and Littmann stethoscope (Classic, USA). In this regard, the sphygmomanometer was calibrated once at the beginning of the study and then every 2 weeks to guarantee its accuracy. Moreover, the sphygmomanometer was calibrated using a comparative calibration method. In this method, the calibration is performed by putting the sphygmomanometer under consideration and the reference sphygmomanometer in equal conditions and comparing their outputs. The patients were visited every 2 weeks until the tenth week and five times in total. Their blood pressure was measured three times with 5-minute intervals at about 3 to 5 p.m. and their mean blood pressure was also recorded. In addition, it was measured 10 min after their arrival to the clinic in a sitting position from their naked right arm that was laid on a flat surface at heart level. The anthropometric measurements of the subjects (i.e., weight and height) were performed by an expert researcher. Moreover, the body mass index was measured in terms of the following formula: body mass index = weight (kg)/(m^2).

2.7 | Sample size

The sample size was calculated using the change in mean ($\mu 1 - \mu 2 = 11$) and *SD* ($S = 11$), as well as the minimal clinically important difference ($\Delta = 9$) from a previous clinical trial (Yang, Cheng-Chung Wei, Lee, Balance Chen, & Ueng, 2012). Notably, with a confidence interval of 95%, $\alpha = .05$ (type one error), $\beta = .2$ (type two error), and a power of 80%, we needed at least 48 patients (24 patients in each group). Since a 10% dropout was anticipated in each group, so 27 patients were finally assigned to each group. Because the 247 patients were enrolled in this study and to ensure the achievement of the desired results for all the relevant variables, eventually, we selected 54 eligible subjects for sample size.

2.8 | Randomization

At first, all patients with primary hypertension (stage 1) who were referred to Tooba Clinic in the Mazandaran University of Medical Sciences were evaluated and those who met the inclusion criteria were identified. Afterward, the study's stages, purpose, and methods were completely explained for the patients, and all of their questions were then answered. Moreover, they were assured that all of their information would be kept confidential and that they were allowed to leave the study at any time. Subsequently, written informed consent was obtained from all the eligible patients who were willing to participate in the study. Afterward, randomization was performed in random number generator software (Version 1.4). Based on the codes that they randomly received, the patients have been divided into two groups: groups A and B. The study statistician was aware of the random allocation of the patients.

2.9 | Blinding

In order to perform the study with double-blind design, the shape, color, weight, size, and the storing container of the capsules containing medicine and placebo were similar. Therefore, the researcher, cardiologist, and patients were not aware of the contents of the container that each patient received.

2.10 | Statistical analysis

The acquired data were finally analyzed using SPSS software (version 22) by descriptive statistics (mean, *SD*, frequency, and

percentage), *t*-test, and paired *t*-test. Therefore, three hypotheses were tested as follows. The first hypothesis was the period effect, and the second one was a carry-over effect. Finally, after confirming the ineffectiveness of the chronology of the treatments and the appropriateness of the washout period duration as well as the ineffectiveness of the interaction between the period and the treatment, the similarity of the effect of the treatments was tested. In this study, the period effect, carryover effect, and treatment effect were evaluated using the independent *t*-test. Furthermore, the period effect and interaction effect were evaluated by applying the independent sample *t*-test and the variable effect (i.e., blood pressure) was evaluated using the paired sample *t*-test. In this study, a $p \leq .05$ was considered statistically significant.

2.11 | Ethical considerations and consent of the participants

The study protocol was approved by the Ethics Committee in Biomedical Research of Mazandaran Medical Sciences University (IR.MAZUMS.REC.1397.156) in terms of the Helsinki Statement. Also, this study was registered in the Iranian Clinical Trials Registration Center (www.irct.ir) with the registration number IRCT20170820035796N2 (January 8, 2019). Also, the approval of the clinic participating in the study was obtained. Afterward, the procedure and purpose of the study were explained to all the patients included and their questions were answered. Moreover, all the patients were informed of the confidentiality of the data collected and signed a conscious consent form.

3 | RESULTS

3.1 | Participants

In total, 247 patients were screened and 54 eligible patients were included in the study. However, during the first week, five patients (four in group A and one in group B) were excluded from the study since they met the exclusion criteria (one patient due to increased blood pressure to 190.100, one due to surgery and hospitalization, one due to increased creatinine, and two due to personal reasons). Finally, 49 patients completed the study and their data were analyzed statistically (Figure 1).

Of 49 participants, 38 (70.38%) cases were female. The mean age of the patients was 60.18 years (within the age range of 35–73 years). There was no significant difference between the two study groups, regarding their age, gender, weight, height, BMI, level of education, marital status, and hypertensive agents N ($p < .05$). The sociodemographic/medical information of the patients is shown in Table 1.

3.2 | Outcome measurement

Based on the results of data analysis, the chronology of the treatment did not affect the outcome. The mean and *SD* of systolic blood pressure reduction in groups A and B were 13.39 ± 8.67 mmHg and 13.53 ± 11.52 mmHg, respectively ($p = .96$) (Figure 2). Moreover, the mean and *SD* of diastolic blood pressure reduction in groups A and B were 8.5 ± 13.98 mmHg and 8.84 ± 1.84 mmHg, respectively ($p = .78$) (Figure 3). In other words, the results of the independent *t*-test revealed that the chronology of the consumption of medication or placebo did not affect the outcome of the final test in both groups. Furthermore, the statistical analysis of the collected data revealed that there was no interaction between the period and treatment, which indicated the adequacy of the washout period duration and the lack of transfer of the effect of medication and placebo to the second phase of the study.

The mean and *SD* of systolic blood pressure in groups A and B were 136.56 ± 5.20 and 138.53 ± 4.46 mmHg ($p = .16$), respectively. Moreover, the mean and *SD* of diastolic blood pressure in groups A and B were 83.3 ± 97.65 mmHg and 85.88 ± 3.62 mmHg ($p = .07$), respectively. In other words, based on the results of the independent sample *t*-test, the washout period duration was sufficient and the effects of the medication and placebo were not transferred to the second phase of the study. Systolic and diastolic blood pressures were statistically analyzed at the beginning of the study and after the end of weeks 4 (end of the first phase), 6 (end of the washout period), and 10 (end of the second phase).

The mean and *SD* of systolic blood pressure in groups A and B at the beginning of the study were 152.30 ± 5.312 mmHg and 152.26 ± 5.640 mmHg, respectively. After the end of the first phase of the study (the first 4 weeks), the same values changed to 129.88 ± 9.009 mmHg and 145.31 ± 6.392 mmHg in groups A and B, respectively. These values were measured once more at the end of week 6 (after the washout phase) and were 140.43 ± 5.230 mmHg and 144.62 ± 3.930 mmHg in groups A and B, respectively. Finally, at the end of week 10 (end of the second phase of the study), these values were measured for the last time, which were 143.26 ± 2.632 mmHg and 131.77 ± 8.091 mmHg in groups A and B, respectively (Table 2).

Furthermore, at the beginning of the study, the mean and *SD* of diastolic blood pressure in groups A and B were 95.52 ± 1.988 mmHg and 94.44 ± 2.607 mmHg, respectively. After the end of the first phase of the study (the first 4 weeks), the same values changed to 80.13 ± 5.488 mmHg and 90.31 ± 5.468 mmHg in groups A and B, respectively. These values were measured again at the end of week 6 (after the washout phase) and were 83.87 ± 5.202 mmHg and 91.81 ± 3.007 mmHg in groups A and B, respectively. Eventually, at the end of week 10 (end of the second phase of the study), these values were measured for the last time, which were 88.04 ± 3.784 mmHg and 81.46 ± 7.426 mmHg in groups A and B, respectively (Table 2). The mean systolic and diastolic blood pressures were significantly reduced in both groups 4 weeks after the consumption of the medication (group A at the end of week 4 and group B at the end of week 10). The paired *t*-test showed that *M. officinalis* capsule significantly reduced systolic and diastolic blood pressures in both groups compared to placebo ($p = .005$).

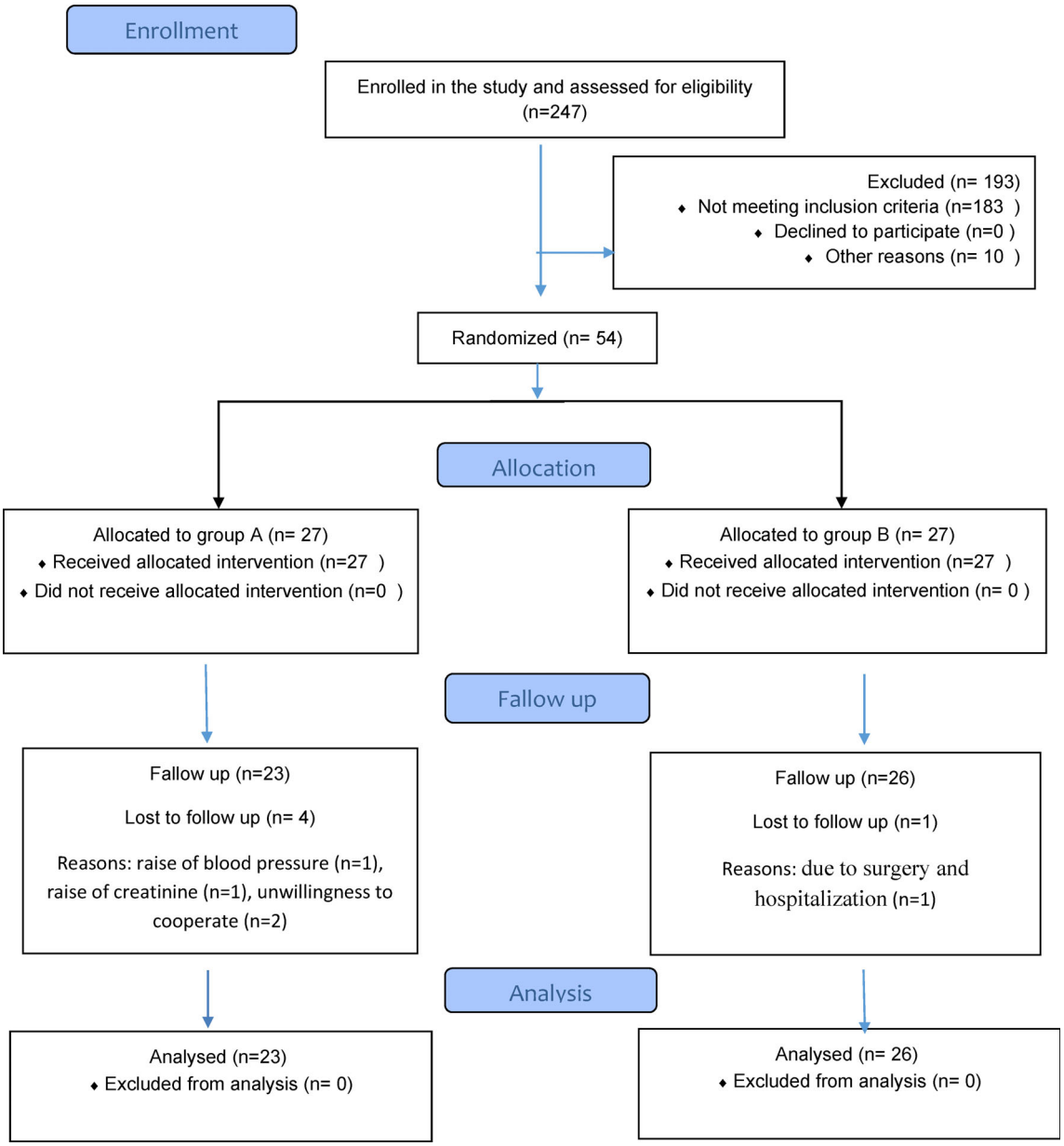

FIGURE 1 Consolidated Standards of Reporting Trials (CONSORT) flowchart

4 | DISCUSSION

Based on the review of related literature, the present study was the first double-blind crossover clinical trial that examined the effects of *M. officinalis* extract on systolic and diastolic blood pressures in patients with essential hypertension. Because disruptive factors have always been known as a major concern for researchers in interventional studies, and hypertension is affected by some factors that can interfere with the study and during the treatment process, intermittent randomized trial work has disrupted the effect of disruptive factors, which we controlled a lot. On the other hand, another advantage of this type of study is that, with a smaller number of patients and a shorter time, a suitable and comparable answer can be achieved compared to the other clinical trials in terms of confidence level and test capability. Besides, to eliminate the most important weakness of this type of study, that is, the transfer of the effect of intervention from one period to the next (carry-over effect), a suitable washing period (2 weeks) was selected. Moreover, the effects of precedence and latency of courses on treatment were evaluated and then confirmed.

The available data showed a significant effect of *M. officinalis* on systolic and diastolic blood pressures in both groups. At the beginning of the study, all the patients' antihypertensive drugs were recorded. Accordingly, the patients in both groups throughout the study used their previous antihypertensive drugs (one to three based on the protocol) and also informed the researcher if they had to change the dosage or type of medication so that they were excluded from the research. Therefore, we were assured that all the patients who entered the study and completed it, did not change their dosage or

TABLE 1 Demographic characteristics of the participants

Variables	Group A	Group B	*p* value
Age (year)	60.74 ± 10.431	59.63 ± 8.923	.67*
Weight (kg)	77.07 ± 9.907	77.89 ± 14.138	.8
Height (cm)	161.44 ± 8.050	163.22 ± 11.437	.51
BMI (kg/m^2)	29.61 ± 3.82	29.12 ± 3.73	.83
Sex			
Male	6 (22.22%)	10 (37.04%)	.23
Female	21 (77.78%)	17 (62.96%)	
Hypertensive agents *N* (%)			
Losartan	5 (18.5%)	7 (26%)	
Losartan+Amlodipine	12 (44.5%)	11 (41%)	.74
Losartan+Amilodipine+Hydrocholorothiazide	10 (37%)	9 (33%)	
Education			
Literate	13 (48.1%)	19 (70.4%)	.47
Illiterate	14 (51.9%)	8 (29.6%)	
Job status			
Employed	8 (29.6%)	15 (55.6%)	.54
Unemployed	19 (70.4%)	12 (44.4%)	
Marital status			
Married	20 (74.1%)	25 (92.6%)	.68
Single	7 (25.9%)	2 (7.4%)	

*p-value reported based on the chi-squared test.
[a]Quantitative data represented as mean (*SD*), p-value reported based on independent samples t-test, qualitative data reported as frequency (percentage).

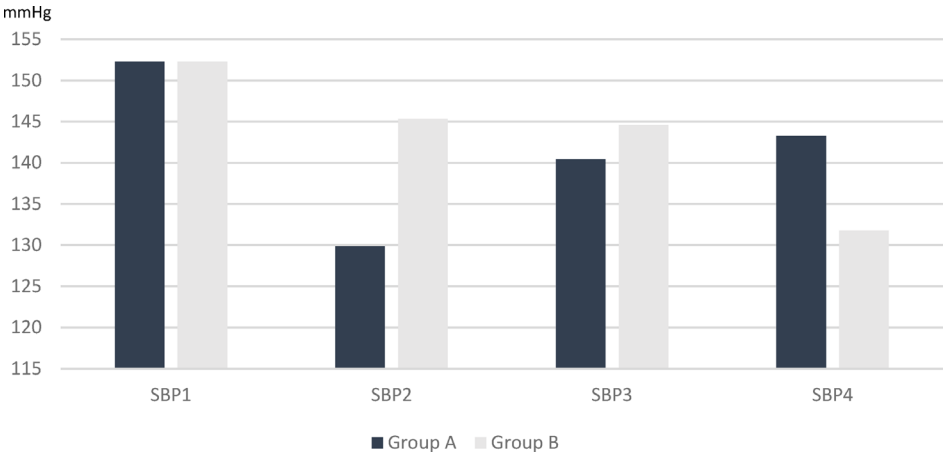

FIGURE 2 Comparison of systolic blood pressure in groups A and B at the beginning of the study (SBP1), end of week 4 (SBP2), end of week 6 (SBP3), and end of week 10 (SBP4). MmHg, The blood pressure measurement unit; SBP, Systolic blood pressure

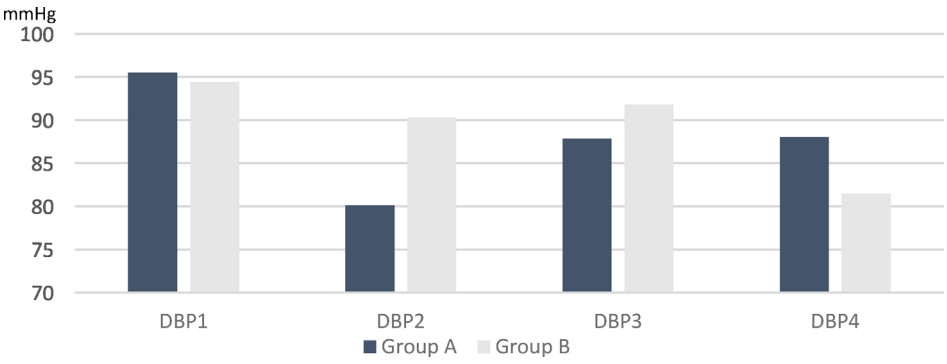

FIGURE 3 Comparison of diastolic blood pressure in groups A and B at the beginning of the study (DBP1), end of week 4 (DBP2), end of week 6 (DBP3), and end of week 10 (DBP4). DBP, Diastolic blood pressure; MmHg, The blood pressure measurement unit

TABLE 2 Point-to-point comparison of significance of difference of systolic blood pressure and diastolic blood pressure between *Melissa officinalis* and placebo during the time

		Phase 1		Phase 2		Total *p* value*
		0	4 weeks	6 weeks	10 weeks	
A-B	SBP	152.30 ± 5.312	129.88 ± 9.009	140.43 ± 5.230	143.26 ± 2.632	0. 005
	DBP	95.52 ± 1.99	80.13 ± 5.49	87.83 ± 5.20	88.04 ± 3.78	
B-A	SBP	152.26 ± 5.640	145.31 ± 6.392	144.62 ± 3.930	131.77 ± 8.091	
	DBP	94.44 ± 2.61	90.31 ± 5.47	91.81 ± 3.01	81.46 ± 7.43	

Abbreviations: A-B, *Melissa officinalis*—placebo; B-A, Placebo—*Melissa officinalis*; DBP, Diastolic blood pressure; SBP, Systolic blood pressure.
*Paired sample *t*-test.

type of antihypertensive drug. In this way, we can conclude that the consumption of antihypertensive drugs cannot act as a disruptive factor in the study. Moreover, we can finally conclude that a significant difference in systolic and diastolic blood pressures was due to the use of lemon balm.

Also, *M. officinalis* extract showed no serious side effects. The results of this study confirm that the use of 1,200 mg of 70% hydroalcoholic extract of *M. officinalis* in those patients with stage 1 primary hypertension is harmless and endurable. Likewise, previous studies have evaluated the daily effect of 700 mg of hydroalcoholic extract to be safe in patients with type 2 diabetes (Asadi et al., 2019). In another study, daily consumption of 3 g of *M. officinalis* leaf powder with no serious side effects was reported (Javid et al., 2018). In a different study, 11 healthy volunteers aged between 20 and 31 years old were evaluated for safety and tolerance to *M. officinalis* extract. Accordingly, it was shown that consuming 50 g of *M. officinalis* extract (500 mg of rosmarinic acid) was safe for humans. However, this study was performed on a small number of healthy young people (Noguchi-Shinohara et al., 2015). In addition, renal and hepatic dysfunctions may be affected by the metabolism of rosmarinic acid. Also, animal studies have examined the effect of this plant extract in different doses. Moreover, in a study on animals, high doses of lemon balm extract (0.45 and 1.350 g / kg) showed toxic effects on the liver tissue (Namjoo, MirVakili, & Faghani, 2013). Therefore, determining the effective dosage is required.

According to the results, the systolic and diastolic blood pressures in the patients with primary hypertensive (Stage 1) were still above 140.90 mmHg after the consumption of conventional pharmacological treatments. However, after the daily consumption of three capsules containing 400 mg of 70% hydroalcoholic extract of *M. officinalis* over 4 weeks (medication and placebo were given to both groups with a two-week washout period and also by considering the period effect and interaction effect), the abovementioned values significantly decreased. Furthermore, previous studies have confirmed the effects of *M. officinalis* on lowering blood sugar, blood lipids, weight, and blood pressure in certain groups. In a meta-analysis in 2020, Heshmati et al. (2020) examined the effect of *M. officinalis* on cardio-metabolic impacts. In this study, seven randomized clinical trials (RCTs) were evaluated, and the beneficial effects of *M. officinalis* on lowering triglycerides and systolic blood pressure were significantly observed. Besides, there are other beneficial trends in the role of M. *officinalis* in increasing HDL and lowering diastolic blood pressure (Heshmati et al.). Asadi et al. (2019) for the first time in their double-blind clinical trial, evaluated the effects of 700 mg of the hydroalcoholic extract of *M. officinalis* (in the form of 350 mg capsules twice a day) on blood sugar control and cardiovascular risk factors (e.g., blood pressure) in 62 patients with type 2 diabetes, compared to the placebo group in a 12-week period. At the end of week 12, fasting blood sugar, hemoglobin A1C, triglycerides (TG), and C - reactive protein (CRP), high-density lipoprotein (HDL), and systolic blood pressure of the intervention group had significant reductions, compared to the placebo group. Javid et al. (2018) in a double-blind clinical trial conducted in 2017, assessed the effects of *M. officinalis* on exercise testing, echocardiography, blood pressure, and serum biomarkers in 73 patients with chronic angina pectoralis. Each participant daily received either 3 g of *M. officinalis* or placebo capsules. Correspondingly, the results showed a higher EF, a lower serum LDH, and a higher NO level in the intervention group compared to the placebo group. Moreover, the levels of systolic and diastolic blood pressures were significantly lower in the intervention group in comparison with the placebo group (Javid et al.).

The abovementioned studies were performed on patients who did not have high blood pressure but were at the risk of high blood pressure. Therefore, their blood pressure reduced like the other risk factors. The results of the aforementioned study were in agreement with those of the present study, which confirmed the efficacy of *M. officinalis* on the reduction in blood pressure in hypertension patients.

On the other hand, our results are consistent with experimental studies conducted on animals. Ferreira et al. (2013) examined the effect of rosmarinic acid (one of the active ingredients in *M. officinalis*) on blood pressure in rats. In this regard, they tested the effect of rosmarinic acid on three doses of 25, 50, and 75 mg/kg of blood pressure in hypertensive and normotensive mice, all of which significantly reduced blood pressure in hypertensive mice. However, in mice with normal blood pressure, it had no effect. According to this study, rosmarinic acid is effective when the renin–angiotensin–aldosterone system is overactive. Ferreira et al. (2018) and Karthik, Viswanathan, and Anuradha (2011) examined the effect of rosmarinic acid on cardiac abnormalities and hypertension in fructose-fed rats. The study

duration was 60 days, and the intervention group was daily given 10 mg/kg of rosmarinic acid on the 16th day of fructose-fed rats. By the end of the 60th day, the intervention group had a significant reduction in high blood pressure, as well as an improvement in insulin sensitivity and decreased lipid levels compared to the control group (Karthik et al., 2011).

M. officinalis due to the phytochemistry is included as follows:

1. The volatile compounds that have the antibacterial and antifungal properties.
2. Triterpenes are cytotoxic, antimicrobial, antifungal, and antioxidant
3. The phenolic compounds (phenolic acids, flavonoids) are the main constituents of *M. officinalis*. Flavonoids have several biological and medicinal activities including antioxidant, antiinflammatory, antimicrobial, anticoagulant, immune-modulating, and anti-allergic activities. *M. officinalis* contains the derivatives of benzoic acid such as gallic acid and cinnamic acid. For example, caffeic acid, the antioxidant activity of *M. officinalis* extract is attributed to phenolic acid such as rosmarinic acid (Shakeri et al., 2016). Quantitative and qualitative analysis of *M. officinalis* extract showed the presence of caffeic acid, rosmarinic acid (main component), and m-coumaric (Dastmalchi et al., 2008). Flavonoids and phenolic acids have a wide range of biochemical and pharmacological activities, including hypolipidemic, cardioprotective, and antioxidant effects. In this plant, the rosmarinic acid affects blood pressure by inhibiting or modulating angiotensin-converting enzyme (Karthik et al., 2011; Verma, Jain, & Singh, 2012) or by vessels dilation which affects the endothelium (Ersoy et al., 2008; Verma et al., 2012). The mechanisms involved in arteries dilation are still unknown. However, this effect is attributed to the polyphenolic properties of rosmarinic acid, which dilates the blood vessels and lowers the blood pressure by the activation of nitric oxide pathway, endothelium-derived hyperpolarizing factor. and prostacyclin (Ersoy et al., 2008; Fernandes et al., 2005). Besides, rosmarinic acid is known as caffeic acid, which can protect the heart from high blood pressure complications with its antioxidant properties (Karthik et al., 2011). Besides, recent research shows that *M. officinalis* protects the endothelium from oxidative damage by H_2O_2, which reduces vascular contraction (Safaeian, Sajjadi, Javanmard, Montazeri, & Samani, 2016).

This study had potential limitations, such as the relatively small sample size despite the fact that it was calculated using the statistical methods. Therefore, it is recommended for future studies to include a larger sample size with a broader age range. Moreover, it is suggested to investigate the effects of this plant on the other types of blood pressure at the other stages. In addition, another limitation of the present research was its short duration, which prevented the researchers from following up on the patients for a longer period of time. On the other hand, it is also suggested for future studies to evaluate the effect of this medication in higher doses or in other forms such as an aqueous extract or dried plant. We chose a cross-sectional study to better control confounders. Besides, because the participants in this study were patients with high blood pressure who adjusted their diet and physical activity at the beginning of their visit to the cardiovascular clinic by a nutritionist, their diet and physical activity were not included in this study and this is a limitation for this study.

However, one of the strengths of this study was merely focusing on the systolic and diastolic blood pressures in the group of hypertensive subjects (stage 1), which included a wide range of hypertensive patients. Therefore, by controlling blood pressure at this stage, we can prevent its progress and, consequently, prevent its complications. On the other hand, the crossover design of this study made it possible to control the distorting factors to a large extent.

5 | CONCLUSION

Based on the results of this study, the hydroalcoholic extract of *M. officinalis* was effective in lowering systolic and diastolic blood pressures in patients with primary hypertension (stage 1). It is recommended for future studies to investigate the effect of *M. officinalis* on hypertension management at all stages (prehypertension, stages 1 and 2) on larger sample size for a longer period of time.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

AUTHOR CONTRIBUTIONS

All research was carried out by the authors. Zahra Shekarriz designed the study, drafted the initial manuscript, obtained the patient consent form, collected data, filed the patient case, and approved the final manuscript. Seyed Afshin Shorofi designed the study and revised the manuscript. Maryam Nabati confirmed the diagnosis of hypertensive patients and revised the manuscript. Bizhan Shabankhani randomized patient's analyzed data and revised the manuscript. Seyde Sedighe Yousefi supervised the various stages of the study, and revised and approved the final manuscript. All authors have confirmed the submitted manuscript and are responding to the study.

DATA AVAILABILITY STATEMENT

Data available on request from the authors.

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