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Efficacy of *Melissa officinalis* L. (lemon balm) extract on glycemic control and cardiovascular risk factors in individuals with type 2 diabetes: A randomized, double-blind, clinical trial

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Melissa officinalis is a plenteous source of antioxidant flavonols and flavonoids that contain health-promoting and antidiabetic properties, so this study was undertaken to provide the first assessment of the antidiabetic properties of hydroalcoholic extract of *M. officinalis* in type 2 diabetic patients. We did a randomized, placebo-controlled trial which included 62 patients, receiving either *M. officinalis* capsules (700 mg/d; $n = 31$) or the placebo ($n = 31$) twice daily for 12 weeks. There were significant differences in serum FBS ($P = 0.007$), HbA_{1c} ($P = 0.002$), β -cell activity ($P = 0.05$), TG ($P = 0.04$), HDL-c ($P = 0.05$), hs-CRP ($P = 0.001$), and systolic blood pressure ($P = 0.04$) between the two groups at the end of the study; but total cholesterol, LDL-c, insulin, and HOMA-IR showed no significant changes between the groups. In *M. officinalis* group, there was a significant change in HDL-c ($P = 0.009$) and QUICKI ($P = 0.005$) compared with baseline values. No adverse effects were observed. It seems that *M. officinalis* is safe and effective in improvement of lipid profile, glycemic control, and reduction of inflammation.

KEYWORDS

antidiabetic, flavonoid, hypoglycemic, lemon balm, *Melissa officinalis*

1 | INTRODUCTION

Diabetes mellitus is probably the fastest growing metabolic disease of the endocrine system that about 415 million people worldwide suffer from diabetes aged 20–79 years, and this number has been estimated to be 642 million in 2040 (Ogurtsova et al., 2017). Various biochemical impairments connected with microvascular and macrovascular

complications, such as renal failure, cardiovascular disease, blindness, or liver diseases (He et al., 2011). Treatment of the hyperglycemia and reduction of inflammation to treat or control the diabetes are critically important (Lehto et al., 1997). Cardiovascular disease persists the main cause of death and inability among subjects with diabetes mellitus and management of dyslipidemia particularly lowering of LDL cholesterol concentration with blood pressure control, and

Abbreviations: AMPK/ACC, AMP-activated protein kinase/Acetyl-CoA carboxylase; ANCOVA, Analysis of covariance; DBP, diastolic blood pressure;; FBS, Fasting blood sugar; GLUT4, Glucose transporter type 4; HbA_{1c}, hemoglobin A_{1c}; HDL-C, high-density lipoprotein cholesterol; HMG-CoA, Hydroxy-3-methylglutaryl-CoA; HOMA, Homeostasis model assessment; HOMA- β , homeostasis model assessment- β cell function; hs-CRP, High-sensitivity C-reactive protein; IPAQ, International physical activity questionnaire; LDL-C, Low-density lipoprotein cholesterol; PON1, paraoxonase 1; PPAR- γ , Peroxisome proliferator-activated receptor gamma; PUFA, Polyunsaturated fatty acid; QUICKI, quantitative insulin sensitivity check index; SBP, systolic blood pressure; SREBP-1c, Sterol regulatory element-binding protein 1; TAC, Total antioxidant capacity; TC, total cholesterol; TG, triglyceride; T2DM, Type 2 diabetes mellitus.

glycemic management has resulted in substantial improvements in cardiovascular outcomes and a shift in the major causes of long-term morbidity and mortality in diabetes mellitus, which now consists of cardiovascular diseases risk (Wang, Hess, Hiatt, & Goldfine, 2016).

Most of the synthetic oral glucose-lowering drugs that used to improve glycemic control in diabetes have various side effects (Mohammed et al., 2013), and none of them have a significant effect on the reduction of hyperlipidemia in diabetic patients (Le Roith, 2001). A lot of people have used herbs to control the outcomes of diabetes (Bell, Suerken, Grzywacz, & Lang, 2006). The World Health Organization has also recommended using herbal medicines (Committee, 1980). Plants are a rich source of flavonoids and antioxidants that studies have reported their efficacy and safety in improving hyperglycemia and management of diabetes as compared with synthetic drugs (Kooti, Farokhipour, Asadzadeh, Ashtary-Larky, & Asadi-Samani, 2016).

Melissa officinalis (known as lemon balm) is a plant of the family of Lamiaceae and a rich source of flavonoids with effects of reducing fat and blood glucose (Shakeri, Sahebkar, & Javadi, 2016). Studies have shown that lemon balm contains plenty of phenolic and flavonoid compounds, including rosmarinic acid and caffeic acid (Shakeri et al., 2016), which have antioxidant, antidiabetic, and hypotensive effects (Kwon, Vatter, & Shetty, 2006). Several animal and in vitro studies have reported that *M. officinalis* have hypoglycemic, hypolipidemic effects (Chung, Cho, Bhuiyan, Kim, & Lee, 2010; Khodsooz, Moshtaghian, & Eivani, 2016; Weidner et al., 2014), anti-glycation activity (Miroliaei, Khazaei, Moshkelgosha, & Shirvani, 2011; Yui et al., 2017), and pancreatic amylase inhibitory activity (McCue & Shetty, 2004). In clinical trial studies, hypolipidemic and anti-inflammatory effects (Habib Haybar, Hosein, & Haghighizadeh, 2017; Jandaghi, Noroozi, Ardalani, & Alipour, 2016) as well as antioxidant properties (Fazli et al., 2012) of *M. officinalis* have been observed. However, there is no study that evaluated an efficacy and tolerability of *M. officinalis* L. (lemon balm) in type 2 diabetes patients; therefore, this randomized, placebo-controlled, double-blind study was conducted to determine the effects of 350-mg hydroalcoholic extract of *M. officinalis* capsules (two times per day) on glycemic control, lipid profile, paraoxonase-1 activity, hs-CRP, and total antioxidant capacity (TAC) in type 2 diabetic patients.

2 | MATERIALS AND METHODS

2.1 | Ethics approval and consent to participate

The procedures followed in this study were in accordance with the Helsinki Declaration (1989 revision). This trial and the consent form received ethical approval from the Iran University of Medical Sciences Ethics committee (IR.IUMS.REC 1395.95-04-27-9411468001; research.iums.ac.ir). This trial was registered at Iranian Registry of Clinical Trials (IRCT201701162709N41; www.irct.ir).

2.2 | Participants

The study was done on outpatients of the Iranian Diabetes Society and Endocrine Research Center, Institute of Endocrinology and

Metabolism, Iran University of Medical Sciences, Tehran, Iran, between May 2017 and November 2017. The diagnosis of diabetes will be based on medical records, using the American Diabetes Association criteria, (fasting blood sugar (FBS) ≥ 126 mg/dl or 2-hr postprandial (2HP) ≥ 200 mg/dl or HbA1c $\geq 6.5\%$; Association, 2012). Inclusion criteria were patients aged 20 to 65 years for both sexes; at least 1 year of DMT2 history; the body mass index less than 35 kg/m²; no pregnancy or lactation; triglycerides less than 400 mg/dl; HbA1c < % 8; no smoking or use of alcohol; no use of any dietary supplement for at least 3 months prior to baseline; using hypoglycemic agents but not insulin. Exclusion criteria were possessed of any codisorders including cardiovascular, liver, renal, allergic, and infectious diseases as well as thyroid disorders and glaucoma; taking nonsteroidal anti-inflammatory drugs (NSAIDS) or estrogen and progesterone; using <80% of supplements delivered to the patient. Patients using lipid-lowering and anti-hypertensive drugs were included and were asked not to change the type or the dose of all drugs and also to maintain their usual diet and physical activity level and not to alter their lifestyle during the intervention. If there was any change in type or amount of drugs, the patients were excluded from study.

2.3 | Study design

The present study was done as a 12-week randomized and double-blind clinical trial. Due to the same shape, color, weight, and size of the drug and placebo capsules and containers, the physicians, researchers, statisticians, and patients were blinded to the drug allocation. All subjects were randomly assigned to one of two treatment groups using block randomization method (block size of 4): *M. officinalis* treated group and control group. Patients in *M. officinalis* group took two capsules per day containing 350-mg hydroalcoholic extract of *M. officinalis*, and patients in placebo group received two capsules per day containing 350-mg toasted flour two times a day after lunch and dinner for the duration of the trial. The patients were followed up by telephone interviews each week, and compliance to supplements was based on the number of unused capsules at the end of every week through telephone interviews. Daily food intake was monitored by the same dietitian throughout the study, and subjects were asked to complete a 24-hr diet recall questionnaire in 3 days (two regular days and one holiday) and physical activity questionnaire (IPAQ) at the beginning, 6 and 12 weeks. Each questionnaire was completed by an educated nutritionist. The dietary intake data were analyzed by the N4 software (Nutritionist 4, First Data Bank, San Bruno, CA, USA).

Participants were wanted to prepare venous blood samples after fasting overnight for 12–14 hr on before and after 12 weeks intervention. Serum was frozen at -80°C until measurements. Blood pressure (BP) was measured after a period of rest (at least 5 min), in the sitting situation, and abstinence from coffee or use of tobacco in the past 30 min using an OMRON M6 Comfort Automatic Blood Pressure Monitor (Tokyo, Japan) by a trained research nurse at baseline and after 12 weeks of intervention. All of the anthropometric measurements (weight, height, waist circumference) were done by an expert researcher and body mass index was measured according to the following equation body mass index = weight (kg)/(m²).

2.4 | Sample size

To calculate sample size, we used the change in mean ($\mu_1 - \mu_2 = 30$) and standard deviation ($S = 38$) of TAC as the main variable obtained from a previous clinical trial (Adelifar, Motamedi, & Gholam Hossein, 2016). On the basis of a confidence interval of 95%, $\alpha = 0.05$ (type one error) and $\beta = 0.2$ (type two error) with a power of 80%, at least we needed 25 patients in each group. Anticipating 10% dropouts in each group, we considered 28 patients per group. Because the 256 patients enrolled in the study and ensuring achievement desired results for all relevant variables, we selected 70 people based on the inclusion criteria for sample size.

2.5 | Preparation of plant extract

2.5.1 | Plant collection

The *M. officinalis* aerial parts were collected from their natural habitats in Karaj province (Karaj city) and were identified and deposited in the herbarium of the Institute of Medicinal Plants with herbarium code numbers of 719.

2.5.2 | Preparation of hydroalcoholic extracts of *M. officinalis*

The plant aerial parts were washed thoroughly under running tap water and dried in shadow at room temperature. The extract preparation was performed by the Institute of Medicinal Plant Karaj Iran. Briefly, the dry plant material was powdered and immersed in hydroalcoholic (70%) solvent for 24 hr and filtered. This procedure was repeated twice more, the filtrate was mixed and concentrated to 5% ethanol by evaporator machine at 50°C, and then solvent was subjected to spray dryer to yield dry extract powder.

2.5.3 | Determination of total flavonoids and the main component

The extracts flavonoid contents were measured according to the previously developed method by Yoo et al., 2008. One milliliter of the aliquot of the appropriately diluted extract or standard solutions of Rutin in methanol (50, 100, 150, 200, and 250 mg/ml) were added to a 10-ml volumetric flask containing 4 ml of distilled water. At first, 0.3 ml of 5% (w/v) sodium nitrite was added to the flask. After 5 min, 0.3 ml of 10% (w/v) aluminum chloride ($AlCl_3$) was added, and after 6 min, 2 ml of 1 M NaOH was also added to the mixture. The procedure was followed by the addition of 3.4 ml of distilled water. The absorbance of the pink color mixture was recorded at 510 nm against prepared water blank. The flavonoids contents were expressed as mg Rutin equivalent per gram of the extract. Furthermore, rosmarinic acid was quantified in the extract by HPLC according to the techniques described previously (Liu, Wan, Zhao, & Chen, 2013). Samples were analyzed in triplicate.

2.6 | Laboratory analysis

FBS was calculated with a Cobas MIRA analyzer (Roche Diagnostic, Basel, Switzerland) by an enzymatic method (Pars Azmon Co., Tehran, Iran). Glycated hemoglobin was determined in whole blood sample by DS5 chromatography method (HbA1c Kit, Drew Scientific Limited, Villaricca, United Kingdom). Insulin levels were measured using chemiluminescence method and Abbott kit (Architect i2000SR System). Serum controls that used for measurement of FBS, HbA1C, and insulin were Randox 1530, Eurotrol, and Multi control Abbott, respectively. The sensitivity of the assays for FBS, HbA1c, and insulin were 5 mg/dl, 1% and 1 mU/L, respectively. In our study, homeostasis model assessment insulin resistance index (HOMA-IR) and beta-cell function (%) were determined using a software calculation, HOMA (HOMA calculator, version 2.2.2; Diabetes Trial Unit, University of Oxford, www.dtu.ox.ac.uk), and the quantitative insulin sensitivity check index (QUICKI) was determined using the logarithmic transformation: $1/\log \text{fasting insulin (U/ml)} + \log \text{fasting glucose (mg/dl)}$; Mozaffari-Khosravi, Hosseinzadeh-Shamsi-Anar, Salami, Hadinedoushan, & Mozayan, 2012). Triglyceride levels were determined using GOP-PAP process and a Pars Azmoon kit (Pars Azmoon Inc., Tehran, Iran). Total cholesterol was assessed using the same kit through Liasys auto analyzer device (Liasys, Roma, Italy). Biochemical analysis of HDL-C was carried out using the sedimentary method with the alike kit. Serum controls that used for measurement of TG, TC, and HDL-C were Randox 1530. The sensitivity of the assays for TG, TC, and HDL-C were 1, 3, and 2 mg/dl, respectively. LDL-C levels were estimated indirectly using Friedewald equation:

$$LDL - c = TC - (HDL - c + TG/5).$$

PON1 and TAC levels were measured by colorimetry using commercial kits (ZellBio GmbH, Germany). hs-CRP was assessed by turbidimetric method using Pars Azmoon kit (Pars Azmoon Inc., Tehran, Iran) on Hitachi 917. Serum control that used for measurement of hs-CRP was Pars Azmun TruLab hs. The sensitivity of the assays for PON1, TAC, and hs-CRP were 0.1 ng/ml, 0.1 mmol/L, and 0.1 mg/L, respectively.

2.7 | Statistical analysis

All statistical analyses were calculated by SPSS version 24 (SPSS Inc., Chicago, IL, USA). Normal distribution of data was investigated using Kolmogorov-Smirnov. Data were represented as mean $\pm$ SD or number (%). Within-group comparisons were carried out using paired samples *t* test or Wilcoxon signed-ranks test for normally and nonnormally distributed data, respectively. Between-group comparisons were produced using independent samples *t* test or Mann-Whitney U test for normally and nonnormally distributed data, respectively. Comparison of qualitative variables between the groups was conducted using Chi-square test and Fisher exact test. Univariate analysis of covariance (ANCOVA) using general linear model was used to adjust for the effect of PUFA and carbohydrate intake at baseline and middle of the study, respectively, and also baseline systolic blood pressure as potential

confounders on final results between groups. The significance level was valued at P value equal or less than 0.05.

3 | RESULTS

The formulate extract was standardized following determination of total flavonoids and rosmarinic acid as a main component. Total flavonoid contents of *M. officinalis* aerial parts extracts were found as 148.06 mg Rutin/gr of dry extract. Furthermore, the amount of rosmarinic acid in the extract capsule was 8.10 ± 0.04 mg. The values are displayed as mean $\pm$ standard deviation.

Figure 1 shows the flow of patients from enrollment to the end of the study. Of a total of 70 patients included in this study, eight subjects lost the follow-up and excluded from the study (four in HEMO group and four in placebo group) for the following reasons: unwillingness to cooperate ($n = 5$), need for insulin therapy ($n = 1$), surgery ($n = 1$), and brain ischemia ($n = 1$). Finally, 62 subjects successfully completed the follow-up, and their data were used for the statistical analysis

The patients' compliance to the treatment was in the acceptable range (over 80% compliance), and its average was about 94% in both groups.

Basic characteristics of the participants are presented in Table 1, and there were no significant differences in regard to the basic characteristics and drug use between the two groups at the baseline

(P value > 0.05 ; Table 1, Figures 2 and 3). The physical activity of participants remained stable without any significant changes during interventions (for details, see Table 2). For nutrient intake, there were significant differences in PUFA intake at baseline and carbohydrate intake at the middle (6 weeks) of study (Table 3) as well as baseline systolic blood pressure between the two groups, and these factors considered as confounder and ANCOVA adjusted for these changes. In addition, there was no significant difference within the groups except for the protein intake in the *M. officinalis* group in the middle (6 weeks) with the end (12 weeks) of the study ($P = 0.04$).

Table 4 shows mean and standard deviation of biochemical parameters and blood pressure at baseline and after the intervention. There were no statistically significant differences in all of the patients biochemical parameters and diastolic blood pressure between the two groups at the baseline (P value > 0.05). Although, the baseline values of systolic blood pressure were significantly different between the two groups ($P = 0.04$).

Significant between-group changes were sensed in FBS ($P = 0.007$), HbA1c ($P = 0.002$), HOMA- β ($P = 0.05$), TG levels ($P = 0.04$), HDL-C ($P = 0.05$), hs-CRP ($P = 0.001$), and systolic blood pressure ($P = 0.04$), but differences of the mean values in insulin, HOMA-IR, total cholesterol levels, LDL-C, and TAC were nonsignificant (Table 4). At the end of study in *M. officinalis* group, compared with placebo group, mean change of FBS (0.19 ± 18.53 versus 12.94 ± 21.44 mg/dl [$P = 0.01$], respectively), HbA1c (-0.28 ± 0.54 versus $0.10 \pm 0.81\%$ [$P = 0.006$], respectively), HDL-c (3.68 ± 7.35

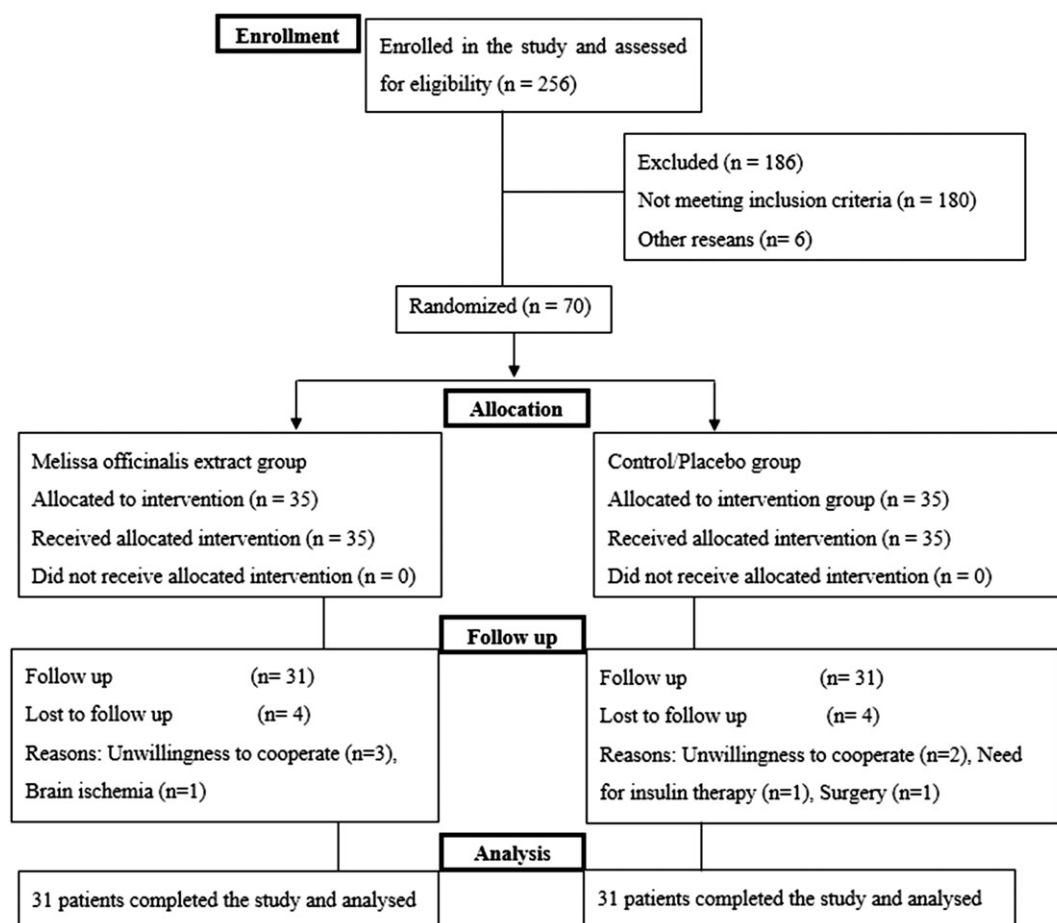


FIGURE 1 Flow of patients from enrollment to the end of the study

TABLE 1 General characteristics of T2DM patients at baseline

Variable		HEMO (n = 31)	Placebo (n = 31)	P value
Age (year)		53.90 ± 6.28	52.77 ± 7.83	0.53 [‡]
Male/female N (%)		15 (48.4)/16 (51.6)	19 (61.3)/12 (38.7)	0.30*
Height (cm)		162.67 ± 8.51	167.01 ± 9.14	0.06 [‡]
Weight (kg)		75.98 ± 13.82	79.48 ± 14.00	0.32 [‡]
BMI (kg/m ²)		28.66 ± 4.34	28.37 ± 3.71	0.55 ^{‡‡}
WC (cm)		100.38 ± 12.60	100.74 ± 9.33	0.83 [‡]
Duration of diabetes (year)		6.38 ± 3.48	6.93 ± 4.44	0.71 ^{‡‡}
Hypoglycemic agents N (%)	Metformin	7 (22.6)	7 (22.6)	1.00**
	Metformin + Glibenclamide	18 (58.1)	19 (61.3)	
	Metformin + Repaglinide	4 (12.9)	3 (9.7)	
	Metformin + Glibenclamide + Repaglinide	2 (6.5)	2 (6.5)	
Hypolipidemic agents N (%)	Atorvastatin	22 (71)	20 (64.5)	0.58*
Hypotensive agents N (%)	Losartan	12 (38.7)	14 (45.2)	0.60*

Note. Values are presented as mean ± standard deviation or n (%). HEMO: hydroalcoholic extract of *M. officinalis*; BMI: body mass index; WC: waist circumference.

*P values based on Chi-square test;

**P values based on Fisher's exact test;

[‡]P values based on independent t test;

^{‡‡}P values based on Mann-Whitney U test.

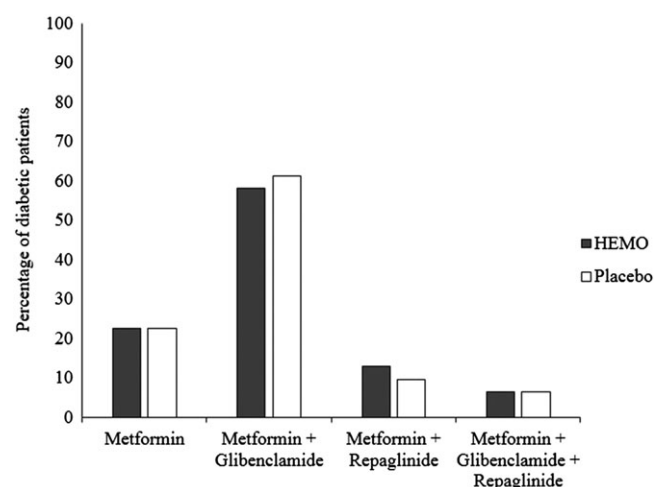


FIGURE 2 Hypoglycemic agents that have been used in HEMO and placebo groups during the study. There were no significant difference in drugs use between two groups. HEMO: hydroalcoholic extract of *M. officinalis*

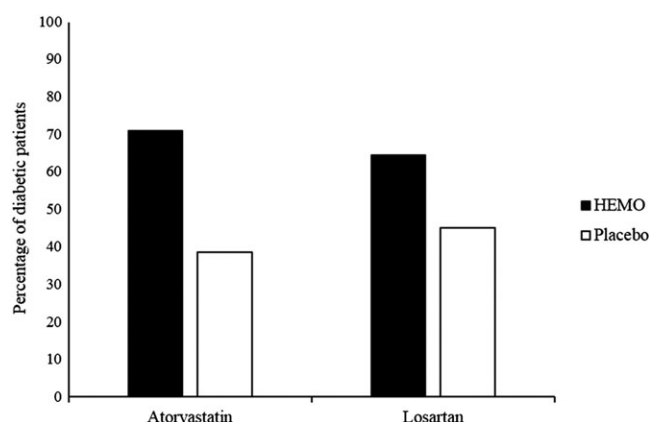


FIGURE 3 Hypolipidemic and hypotensive agents that have been used in HEMO and placebo groups during the study. There was no significant difference in drugs use between two groups. HEMO: hydroalcoholic extract of *M. officinalis*

4 | DISCUSSION

We conducted the present study as the first clinical trial to determine the clinical effect and tolerability of 700 mg/day *M. officinalis* supplementation in subjects with type 2 diabetes.

Our present data showed that *M. officinalis* supplementation causes a significant difference in fasting blood sugar level, HbA1c, and systolic blood pressure in comparison with the placebo group. Also from this study, it was found that 12 weeks of *M. officinalis* supplementation significantly decreased TG and also a significant increase in HDL-c levels and mean change of PON1 in comparison to control. We record the drug use at the beginning of study in both groups, and two points are important here. First, Table 1 shows that there was no significant difference in drug use between two groups at the beginning of study (Figures 2 and 3), and second, if the patients

versus $-0.03 \pm 6/07$ mg/dl [$P = 0.04$], respectively), hs-CRP (-0.65 ± 0.89 versus 0.44 ± 1.11 mg/L [$P = 0.002$], respectively), paraoxonase-1 (11.77 ± 36.81 versus $-4.55 \pm 39/92$ mg/dl [$P = 0.04$], respectively), and systolic blood pressure (-0.33 ± 1.35 versus 0.53 ± 1.39 mmHg [$P = 0.04$], respectively) were significantly different. Although, insulin, HOMA-IR, and pancreatic β -cell function were significantly decreased in the *M. officinalis* group as well as placebo group, decreases in the treatment group were more. Data of *M. officinalis* presented a significant increase in serum levels of HDL-c ($P = 0.009$) and QUICKI ($P = 0.005$) while showed a significant decrease in hs-CRP level ($P = 0.001$) when compared with data of this group before the intervention (Table 4).

TABLE 2 Physical activity comparison at baseline, middle, and end of study between the two groups

Variable	Baseline		Middle		End	
	HEMO	Control	HEMO	Control	HEMO	Control
Low-PA N (%)	16 (51.6)	8 (25.8)	16 (51.6)	11 (35.5)	12 (37.8)	16 (51.6)
Moderate-PA N (%)	10 (32.3)	18 (58.1)	9 (29)	16 (51.6)	13 (41.9)	11 (35.5)
High-PA N (%)	5 (16.1)	5 (16.1)	6 (19.4)	4 (12.9)	6 (19.4)	4 (12.9)
P value*	0.08		0.19		0.56	

Note. Values are presented as n (%). There were no significant differences of physical activity between the *M. officinalis* and placebo groups ($P > 0.05$). PA: physical activity; HEMO: hydroalcoholic extract of *M. officinalis*.

*Chi-square test.

TABLE 3 Energy and nutrients intake at baseline, in the middle, and at the end of the study

Nutrients	Group	Baseline mean $\pm$ SD	Middle mean $\pm$ SD	End mean $\pm$ SD	P value ^{##}		
					Baseline	Middle	End
Energy (kcal)	HEMO Control	1625.80 $\pm$ 236.35 1687.95 $\pm$ 222.60	1597.11 $\pm$ 146.70 1682.70 $\pm$ 201.29	1609.69 $\pm$ 147.49 1664.30 $\pm$ 166.47	0.11 ^{##}	0.07 [‡]	0.22 ^{##}
Protein (g)	HEMO Control	62.76 $\pm$ 10.47 63.07 $\pm$ 8.81	64.51 $\pm$ 9.91 60.41 $\pm$ 6.54	61.06 $\pm$ 8.00 61.35 $\pm$ 8.60	0.9 [‡]	0.06 [‡]	0.88 [‡]
Carbohydrate (g)	HEMO Control	226.87 $\pm$ 30.60 241.76 $\pm$ 38.80	227.59 $\pm$ 26.81 247.10 $\pm$ 43.39	230.52 $\pm$ 24.63 247.46 $\pm$ 40.18	0.09 [‡]	0.03 [‡]	0.07 [‡]
Total fat (g)	HEMO Control	49.41 $\pm$ 10.17 53.09 $\pm$ 10.92	50.09 $\pm$ 9.21 52.90 $\pm$ 9.36	51.55 $\pm$ 9.47 53.82 $\pm$ 9.08	0.17 [‡]	0.23 [‡]	0.34 [‡]
Fiber (g)	HEMO Control	15.81 $\pm$ 3.19 15.94 $\pm$ 3.14	15.95 $\pm$ 3.16 16.75 $\pm$ 3.93	15.85 $\pm$ 3.21 16.13 $\pm$ 3.38	0.87 [‡]	0.82 [‡]	0.73 [‡]
SFA (g)	HEMO Control	15.80 $\pm$ 3.66 16.00 $\pm$ 3.15	15.87 $\pm$ 3.50 16.00 $\pm$ 3.27	16.03 $\pm$ 3.37 16.05 $\pm$ 3.44	0.83 ^{##}	0.81 ^{##}	0.98 [‡]
MUFA (g)	HEMO Control	14.41 $\pm$ 3.20 15.01 $\pm$ 3.14	14.47 $\pm$ 3.00 15.08 $\pm$ 3.01	14.75 $\pm$ 3.21 15.07 $\pm$ 3.19	0.49 [‡]	0.42 [‡]	0.69 [‡]
PUFA (g)	HEMO Control	13.88 $\pm$ 3.87 15.94 $\pm$ 4.42	13.91 $\pm$ 4.20 15.58 $\pm$ 4.25	14.14 $\pm$ 14.28 15.84 $\pm$ 14.42	0.04 ^{##}	0.12 [‡]	0.13 [‡]
Cholesterol (g)	HEMO Control	172.60 $\pm$ 92.19 210.41 $\pm$ 102.7	165.89 $\pm$ 86.23 203.28 $\pm$ 93.74	163.80 $\pm$ 86.30 201.26 $\pm$ 101.98	0.10 ^{##}	0.09 ^{##}	0.13 ^{##}
Vitamin c (mg)	HEMO Control	106.21 $\pm$ 62.93 114.07 $\pm$ 46.06	112.11 $\pm$ 62.26 114.53 $\pm$ 43.03	114.94 $\pm$ 56.10 110.40 $\pm$ 44.90	0.57 [‡]	0.86 [‡]	0.90 [‡]
Vitamin E (mg)	HEMO Control	6.57 $\pm$ 3.21 7.21 $\pm$ 3.58	6.86 $\pm$ 3.13 7.11 $\pm$ 3.77	7.13 $\pm$ 3.56 7.16 $\pm$ 3.61	0.48 ^{##}	0.93 ^{##}	0.89 ^{##}
Selenium (mg)	HEMO Control	0.076 $\pm$ 0.03 0.077 $\pm$ 0.02	0.075 $\pm$ 0.03 0.074 $\pm$ 0.01	0.079 $\pm$ 0.02 0.077 $\pm$ 0.01	0.80 [‡]	0.84 [‡]	0.73 [‡]

Note. Values expressed as mean $\pm$ SD. HEMO: hydroalcoholic extract of *M. officinalis*; SFA: saturated fatty acid; MUFA: monounsaturated fatty acid; PUFA: polyunsaturated fatty acid.

^{##}P value for variable comparing between the two groups baseline, in the middle and at the end of the intervention;

[‡]Independent t test;

^{##}Mann-Whitney U test.

changed the dose or type of drug during study, they would be excluded from study. So we were sure that all of the patients which were included in study and ended the study had no change in the type and dose of drugs, we can conclude that the use of drug would not be a confounding factor for the result of study, and finally we can conclude that the significant difference of measured variables (for example, FBS, insulin resistance, and lipoproteins) between two groups were due to *M. officinalis* consumption.

Moreover, *M. officinalis* extract showed no indication of any serious side effects. Outcomes of this study revealed that use of 700 mg/day hydroalcoholic extract of *M. officinalis* in patients with

type 2 diabetes is safe and tolerable. Similarly, previous clinical trials that had evaluated the effect of leaves powder of *M. officinalis* at the dosage of 3 g/day on metabolic factors in patients with chronic disease reported no serious side effects. Although, lack of the rigorous regulations in regard to the safety of herbal supplements has raised concerns that many available herbal supplements might be ineffective, given the fact that the nutraceutical manufacturers are less enforced than in the pharmaceutical sector to prove efficacy, safety, and quality of a marketed product (Izzo, Hoon-Kim, Radhakrishnan, & Williamson, 2016; Minuz, Velo, Violi, & Ferro, 2017). However, in an animal study (Namjoo, MirVakili, & Faghani, 2013), very high doses of *M. officinalis*

TABLE 4 Comparisons of clinical and biochemical features before and after 8 weeks of intervention

Variable	HEMO (mean $\pm$ SD)		Placebo (mean $\pm$ SD)		P value ^{##}
	Before	After	Before	After	
FBS (mg/day) P value [†]	143.09 $\pm$ 37.39 0.75 [▲]	143.29 $\pm$ 33.59	138.87 $\pm$ 34.59 0.003 [▲]	151.80 $\pm$ 35.34	0.007
HbA1c (%) P value [†]	7.27 $\pm$ 0.60 0.08 [▲]	6.99 $\pm$ 0.68	7.36 $\pm$ 0.49 0.63 [▲]	7.47 $\pm$ 0.74	0.002
Insulin (mIU/ml) P value [†]	10.53 $\pm$ 3.65 0.001 [▲]	9.13 $\pm$ 3.65	10.94 $\pm$ 4.22 0.005 [▲]	9.82 $\pm$ 4.63	0.91
HOMA-IR P value [†]	1.50 $\pm$ 0.51 0.001 [▲]	1.30 $\pm$ 0.52	1.56 $\pm$ 0.62 0.01 [▲]	1.42 $\pm$ 0.67	0.21
QUICKI P value [†]	0.320 $\pm$ 0.02 0.005 [▲]	0.326 $\pm$ 0.02	0.320 $\pm$ 0.02 0.25 [▲]	0.322 $\pm$ 0.02	0.37
HOMA-b cell (%) P value [†]	55.92 $\pm$ 29.12 0.02 [▲]	47.74 $\pm$ 24.36	58.12 $\pm$ 25.52 0.001 [▲]	44.67 $\pm$ 21.27	0.05
TG (mg/day) P value [†]	135.54 $\pm$ 51.55 0.28 [▲]	122.03 $\pm$ 42.74	143.19 $\pm$ 62.19 0.63 [▲]	138.67 $\pm$ 38.52	0.04
TC (mg/day) P value [†]	142.48 $\pm$ 33.55 0.41 [▲]	145.38 $\pm$ 31.15	147.09 $\pm$ 31.85 0.10 [▲]	153.09 $\pm$ 26.97	0.61
HDL-c (mg/day) P value [†]	44.83 $\pm$ 10.87 0.009 [▲]	48.51 $\pm$ 10.55	44.64 $\pm$ 9.23 0.97 [▲]	44.61 $\pm$ 9.29	0.05
LDL-c (mg/day) P value [†]	70.53 $\pm$ 26.19 0.70 [▲]	72.46 $\pm$ 28.85	73.81 $\pm$ 28.25 0.06 [▲]	80.74 $\pm$ 25.05	0.45
PONase activity (U/ml) P value [†]	102.40 $\pm$ 72.32 0.06 [▲]	114.17 $\pm$ 54.39	118.64 $\pm$ 74.68 0.87 [▲]	114.09 $\pm$ 61.28	0.25
TAC (mM/l) P value [†]	0.499 $\pm$ 0.11 0.27 [▲]	0.523 $\pm$ 0.12	0.492 $\pm$ 0.09 0.84 [▲]	0.497 $\pm$ 0.15	0.42
hs-CRP (mg/L) P value [†]	2.15 $\pm$ 1.67 0.001 [▲]	1.50 $\pm$ 1.71	2.06 $\pm$ 1.87 0.02 [▲]	2.51 $\pm$ 2.46	0.001
SBP (mm/Hg) P value [†]	13.85 $\pm$ 2.00 0.14 [▲]	13.51 $\pm$ 1.76	12.77 $\pm$ 1.48 0.06 [▲]	13.30 $\pm$ 1.56	0.04
DBP (mm/Hg) P value [†]	8.45 $\pm$ 1.19 0.98 [▲]	8.38 $\pm$ 1.15	8.11 $\pm$ 1.17 0.90 [▲]	8.08 $\pm$ 1.17	0.95

Note. Values are presented as mean $\pm$ standard deviation. FBS: fasting blood sugar; HEMO: hydroalcoholic extract of *M. officinalis*; HbA1c: hemoglobin A1c; HDL: high-density lipoprotein; HOMA-IR: homeostasis model assessment-insulin resistance; HOMA-b cell: homeostasis model assessment-b cell function; QUICKI: quantitative insulin sensitivity check index; TG: triglyceride; TC: total cholesterol; HDL: high-density lipoprotein; LDL: low-density lipoprotein; PON1: paraoxonase-1; TAC: total antioxidant capacity; hs-CRP: high-sensitivity C-reactive protein; DBP: diastolic blood pressure; SBP: systolic blood pressure.

^{##}P value ($P < 0.05$) for variable comparing between the two groups at the end of the intervention after adjusting for basal values. Calculated by ANOVA analysis of covariance;

[†]P value for variable comparing within the two groups at the end of the intervention;

[▲]Paired samples t test;

[▲]Wilcoxon signed-ranks test.

extract (0.450 and 1.350 g/kg) showed the toxic effects on liver tissue, and further studies are needed to determine the effective dose of *M. officinalis*.

Our study shows that hydroalcoholic extract of lemon balm can suppress the increases in FBS levels. Nonsignificant changes in FBS were reported in Jandaghi (Jandaghi et al., 2016), and Yui (Yui et al., 2017) studies in subjects with borderline hyperlipidemia and healthy adults, respectively, but all of the animal studies (Chung et al., 2010; Hasanein & Riahi, 2015; Khodsooz et al., 2016; Weidner et al., 2014) showed that *M. officinalis* could decrease serum blood glucose; however, the dose of these studies was higher compared with our study. These studies indicated that the hypoglycemic effect of *M. officinalis* is due to up-regulating the synthesis of hepatic glucokinase, GLUT4, and decreasing the expression of glucose-6-phosphatase (G6Pase) as well as phosphoenolpyruvate carboxykinase (PEPCK; Chung et al., 2010). The reduction of HbA1c in our investigation may be due to

the inhibitory activity of *M. officinalis* on pancreatic alpha-amylase (McCue & Shetty, 2004) and alpha-glucosidase (Kwon et al., 2006) and reducing in postprandial blood glucose. In our research, there occurred no significant changes in the mean of insulin levels and HOMA-IR between groups at the end of the study. Yui et al. (2017) used aqueous extract of *M. officinalis* for 6 weeks in healthy adults, and there was no significant change in the mean of insulin between groups at the end of the study. One study showed that essential oil of *M. officinalis* has a significant role in increasing of serum insulin (Chung et al., 2010), but in other study, using of ethanolic extract of *M. officinalis* showed no significant change in the insulin levels (Weidner et al., 2014). *M. officinalis* treatment resulted in increased QUICKI index, but it was nonsignificant in the between groups comparison, which may be associated with its effect on increasing PPAR- γ (Chung et al., 2010). Although, we found a significant decrease in b-cell function percentage (% β) in both of groups, but

the decrease in the control group was more in comparison to the intervention group.

Our results showed that *M. officinalis* reduced TG and increased HDL-c significantly between groups at the end of the study. Habib et al. (2017) observed that using of 3 g of *M. officinalis* leaves powder per day for 8 weeks caused a significant reduction in serum TG, total cholesterol and LDL-c levels, and a significant increasing of HDL-c in 73 patients with chronic stable angina. In the study of Jandaghia et al. (2016), 3 g of *M. officinalis* leaf powder only caused a significant reduction of LDL-c in hyperlipidemic patients, and other study showed that the effect of aqueous extract of *M. officinalis* on reduction of TG and total cholesterol in occupationally exposed workers to aluminum is significant (Fazli et al., 2012). There are some controversial studies about *M. officinalis* supplementation on serum lipid profile in animals. Antihyperlipidemic effects of *M. officinalis* may be due to downregulation of HMG-CoA reductase expression and decreasing expression of SREBP-1c and its target genes involved in fatty acid synthesis such as ACC1 (Acetyl-CoA carboxylase 1), SCD1 (stearoyl CoA desaturase 1), and FAS (fatty acid synthase; Jun et al., 2012). Considering that *M. officinalis* can downregulate HMG-CoA reductase expression, non-significant changes of total cholesterol and LDL-c in our study may be due to consumption of atorvastatin medication by the majority of patients and also may be due to the low-TC observed at baseline. Studies indicated that PON1 enhances cholesterol efflux from macrophages by increasing HDL coupling interfered by ABCA1 (Yin, Liao, & Tang, 2010). Based on the results of the present study, *M. officinalis* caused a significant increase in mean change of PON1 in comparison to control. In one study in subjects with chronic stable angina (Habib Haybar et al., 2017), it was shown that *M. officinalis* supplementation could increase serum PON1 concentration.

Although an increasing trend occurred in TAC levels in the *M. officinalis* group, it was nonsignificant. Arbastan's (Arbastan et al., 2014) reports to evaluate the effect of lemon balm as an antioxidant in burning patients was in accordance with our study. Also in Adelifar et al. (2016; a before–after clinical trial without the placebo group) and Fazli et al. (2012) studies, in occupationally exposed workers to aluminum and male athletes, respectively, were inconsistent with our results. However, all of these have been used the water extract of *M. officinalis* in their studies, and it is possible that antioxidant effect of water extract of *M. officinalis* is more than other extracts of *M. officinalis* (Koksal, Bursal, Dikici, Tozoglu, & Gulcin, 2011). Significant decreasing of hs-CRP concentration in Habib et al. (2017) study was in agreement with of present results. Hence, reduction of hs-CRP perceived in diabetic patients might show that *M. officinalis* has a profitable effect against cardiovascular disease. Moreover, it has been published that *M. officinalis* is wealthy in phenolic and flavonoid compounds (Shakeri et al., 2016), and these compounds may possess anti-inflammatory activity (Tunon, Garcia-Mediavilla, Sanchez-Campos, & Gonzalez-Gallego, 2009). Antihypertension effects of *M. officinalis* perhaps due to its potential angiotensin I converting enzyme inhibitory activity (Kwon et al., 2006). Authors expected that additional investigation be conducted, considering the mechanism of *M. officinalis* outcome on blood pressure control in diabetic patients.

High percentage of the patient's compliance in consuming capsules (94%) and assessment of dietary intakes and physical activity in

the baseline, middle, and the end of the trial can be considered as the strengths of our study. Although, this study had several limitations including small sample size, using lower dosage of *M. officinalis* supplementation compared with the animal studies and not assessing the antioxidant enzyme activity such as superoxide dismutase and glutathione peroxidase.

5 | CONCLUSION

In summary, findings from this study revealed that the hydroalcoholic extract of the aerial parts of *M. officinalis* had effects to improve glyce-mic status, hyperlipidemia, and hypertension. These also reduced the inflammatory biomarker hs-CRP with a slight increase in TAC levels in type 2 diabetic patients. Further investigation with a larger sample size and longer intervention time is needed to confirm the beneficial effects of *M. officinalis* the management of diabetes complications, inflammatory parameters, antioxidant indices in type 2 diabetic patients.

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CONFLICT OF INTEREST

The authors declare that there are no conflict of interest.

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