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Lemon balm: A promising herbal therapy for patients with borderline hyperlipidemia—A randomized double-blind placebo-controlled clinical trial

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ABSTRACT

Objective: Melissa officinalis is a perennial herb from the Lamiaceae family which has shown to have modulating effects on serum lipid profile. The aim of the current study is to explore the effects of *M. officinalis* supplementation on serum biochemical parameters of patients with borderline hyperlipidemia.
Methods: 58 hyperlipidemic patients were allocated randomly to 2 groups: first group received capsules containing 1000 mg *M. officinalis* leaf powder (MO group), and the second group received placebo capsules (P group) 3 times per day for 2 months. Fasting blood glucose (FBG), HDL, LDL, Triglyceride, Creatinine and liver function enzymes including AST and ALT were evaluated before and after study.
Results: The mean of LDL in MO group significantly decreased compared with P group after the supplementation ($P = 0.02$). Although the level of Cholesterol, FBG, HDL, Triglyceride, Creatinine and ALT did not show significant difference between two groups after 2 months ($P \geq 0.05$), the level of AST exhibited a significant difference between two groups ($P = 0.009$).
Conclusions: Our findings demonstrated that *M. officinalis* supplementation as a rich source of antioxidants and bioactive compounds can be effective in remission of LDL and AST levels in patients with borderline hyperlipidemia.

1. Introduction

Disorders of lipid metabolism, commonly known as dyslipidemias, are widespread worldwide and recognized by increased plasma levels of the various lipid and lipoprotein fractions [including total and low density lipoprotein cholesterol LDL), very low density lipoprotein cholesterol (VLDL), triglycerides, chylomicrons] and their effects on cardiovascular diseases.[1] Among the risk factors, hypercholesterolemia and the high level of LDL, play a significant role in development of cardiovascular disease (CVD). Therefore, the National Cholesterol Education Program (NCEP) Adult Treatment Panel III guidelines recommend that, the LDL should be the primary target of treatment to decrease cardiovascular events.[2,3] Despite the various lipid-lowering agents for the management of hyperlipidemia, a significant number of patients do not reach their LDL target points.[4] On the other hand, the statins are the first-line therapy for the management of high LDL level that have many adverse effects.[5] Thus, conducting studies aimed to find complementary and alternative medicines with much more efficacy and less adverse effects for normalization of lipid profile seems to be essential.

Nowadays, there is a growing interest in dietary bioactive compounds that protect humans against several diseases and/or reduce their intensity.[6–8] The *Melissa officinalis* from the Lamiaceae family is an aromatic perennial herb native to East Mediterranean region, West Asia and North Africa which is a well-known herb in treatment of many disorders like headaches, gastrointestinal diseases, neurological diseases and rheumatoid.[9,10] The fresh herb consists of phenolic compounds and essential oil. The citral and citronellal have the highest percentages among components of the essential oil in this medicinal plant.[11–14] This herb as a

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; FBG, fasting blood glucose; GCK, glucokinase; G6Pase, glucose-6-phosphatase; HMGCR, 3-hydroxy-3-methyl-glutaryl-CoA reductase; LBEO, lemon balm essential oil; PPAR, peroxisome proliferator-activated receptors; PEPCK, phosphoenolpyruvate carboxykinase; PA, physical activity; PMP, popular medical plant; SREBP, sterol regulatory element-binding proteins.

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rich source of phenolic compounds can be used for prevention and management of diseases like hyperlipidemia, type 2 diabetes and CVD.[15–17] According to the previous animal studies *M. officinaliss* essential oil and extracts could significantly increase the expression of peroxisome proliferator-activated receptors (PPARγ, PPARα, PPARs), 3-hydroxy-3-methyl-glutaryl (HMG)-CoA reductase and sterol regulatory element-binding proteins (SREBP)-1c which have important roles in regulation of the whole body glucose and lipid metabolism. The information about the efficacy of *M. officinalis* on lipid profile, glucose level and liver enzymes is not fully enough. As our best knowledge, there is only one uncontrolled clinical trial which reported that consumption of *M. officinalis* tea within a period of 4 weeks lowered plasma cholesterol and triglyceride in workers occupationally exposed to aluminum.[18] Although standards threshold of LDL and total cholesterol for prescribing hypolipidemics is based on the ATPIII guideline in Iran, aims of the present study were to evaluate the effects of *M. officinalis* leaf powder on serum glucose, lipid profile and liver enzymes in patients with borderline hyperlipidemia for the first time and to identify the chemical components of this herb by GC/MS analysis.

2. Material and methods

2.1. Study design

This is a parallel, randomized, double-blind and placebo-controlled clinical trial, with the participation of 82 patients with borderline hyperlipidemic conducted in Ansari Hospital between January and July 2014. The research was approved by Medical Ethics Commission in Qazvin University of Medical Sciences. Also the trial has been registered in the Iranian Registry of Clinical Trials at (http://www.irct.ir) with the following identification in 2014: IRCT2014042017347N1.

2.1.1. Inclusion criteria

The male and female outpatients aged 25–65; they had at least one of the following indices: serum total cholesterol ranged 200–260 mg/dl; LDL ranged 100–160 mg/dl and serum triglycerides ranged 150–300 mg/dl.

2.1.2. Exclusion criteria

The patients who used antihyperlipidemic agents, steroids; cigarette; alcohol; patients with diabetes, coronary-vascular disease; renal, hepatic, hematological, pulmonary diseases; uncontrolled hypertension; pregnant women; breast-feeding women; the patients who may suffer from undesirable complications over the study including headache, vertigo, nausea and *M. officinalis* intolerance.

2.2. Plant material

M. officinalis leaves were collected from BAGH FIRUZE medicinal plants garden in western Tehran, Iran. A voucher specimen of this plant (pmp-408) has been recorded in the Central Herbarium of the Faculty of Pharmacy, Tehran University of Medical Sciences. The leaves were separated from the stems, washed and dried at 60 °C for 24 h and stored at 5 °C and then dried leaves were processed into powder form. Finally, all capsules in the same shape, size and color were prepared by a pharmacist and packed in the same container with a code. All capsules were green color; all of them were 500 mg-capsules with the 500 mg powder of Melissa or starch. Neither capsules nor the cans consist of capsules were not recognizable as drug or placebo. Moreover all containers were labeled as A or B. Thus the kind of drugs was covered either for patient or for administrative of this double-blind study.

Table 1
Chemical compounds detected in *Melissa officinalis* by GC/MS.

No.	Compounds	%	No.	Compounds	%
1	Citronellal	13.1	20	Carvacrol	1.5
2	ß-Caryophyllene	8.7	21	1,3-octadiene	1.4
3	Citronellol	7.8	22	Alpha phellandrene	1.4
4	Linalool	6.9	23	3-methyl-2(methyl-2-2butenyl)	1.4
5	*Trans*-carveol	6.5	24	Thymol	1.4
6	Citral	5.0	25	1,3,6,-Octatriene	1.3
7	γ-3-Carene	3.1	26	Bicyclo[2.2.1] heptan-2-one	1.3
8	1,3,8,-*P*-menthatriene	2.8	27	Germacrene-D	1.3
9	Para cymene	2.1	28	Eugenol	1.3
10	Eucalyptol	2.0	29	1,Octen-3-ol	1.2
11	Isopulegol	2.0	30	Calamenene	1.2
12	Isoborneol	2.0	31	α-Muurolene	1.2
13	Carvacrol acetate	1.8	32	*Cis*-Sabinene	1.1
14	Myrcene	1.7	33	5-Hepten-1-ol	1.1
15	Limonene	1.7	34	Caryophyllen epoxide	1.1
16	β-Thujone	1.7	35	ß-bisabolene	1.1
17	Alpha-pinene	1.6	36	α-Humulene	1.0
18	3,6,-Octadienoic acid	1.6	37	ß-Cubebene	1.0
19	γ-Terpinene	1.5	38	ß-Ionone	0.9

2.3. Plant extraction and GC/MS analysis

Analysis were carried out on a Hewlett-Packard 5890 Series II included gas chromatograph interfaced to a Hewlett Packard 5989B mass spectrometer. Separations were performed on Ultra 1 (49 m _ 0.20 mm I.D., 0.11 mm, Hewlett-Packard) and DB-Wax (60 m _ 0.25 mm I.D., 0.25 mm) capillary columns. Helium was used as a carrier gas (1.0 mL/min C.F.) and the oven temperature was programmed as 65° to 230 °C with a heating rate of 2 °C/min. Injector and interface temperatures were 230 °C and 250 °C, respectively. EI mass spectra were recorded at 70 V ionization voltage over the mass range 40–400. Samples (0.5 mL of oil solutions 1:10 in hexane) were injected by split injection (1:33). Finally, 38 chemical compounds were detected in *M. officinalis* leaf (Table 1).

2.4. Interventions

The patients were divided into 2 groups randomly: *M. officinalis* group (MO group) and placebo (P group) through sortation cards, in form of randomized and blind. The MO group received *M. officinalis* capsules (500 mg—*M. officinalis* leaf powder) and P group received placebo capsules (500 mg starch powder) after taking meals (two capsules after meals, 3 times per day) for 2 months. Follow-up of the patients to control them in terms of consumption of capsules, response to the relevant questions, and prevention of sample loss and to receive capsules for the next month was performed in one's presence twice per month via monitoring the patients referring to Ansari Hospital. The participants were also advised not to change their usual diet, to avoid from self-reliant changes of their supplements doses, physical activities during the intervention and consuming other same products.

2.5. Measurements

Demographic data including age, weight, height, gender, marital status, occupation, education, medical and drug history were assessed and recorded through interview with the patients. The patients' weight with light clothing by a scale with 100 g error and height, in standing position without shoes by a height-measurer with 1 cm error were measured before and 2 months after intervention. Then, Body Mass Index (BMI) was calculated with relevant formula. To study the patients' diet in terms of daily intake of energy, carbohydrate, protein, fiber, and total fat, two 24 h-dietary-recall questionnaire was used both at the beginning and the end of the study. Iranian Food Composition Table (FCT) along with U.S.