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Effects of *Melissa officinalis* L. (Lemon Balm) Extract Supplementation on Cardiovascular Risk Factors: A Pooled Analysis of Randomized Controlled Trials

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Abstract Several clinical trials have investigated the effects of Melissa officinalis (lemon balm) on cardiovascular risk factors, but have yielded conflicting results and had only modest sample sizes. The aim of this pool analysis was to summarize the evidence of the effects of Melissa officinalis supplementation on plasma lipid profiles, body weight, blood pressure and glucose levels. Original randomized controlled trials (RCTs) that assessed the clinical effects of Melissa officinalis consumption in human participants and published before June 2020 were identified by searching online databases, including PubMed, Scopus, Web of Science and Google Scholar databases. The quality of trials was assessed using the Cochrane Risk of Bias Tool. Quantitative data analysis was performed using weighed mean difference (WMD) and 95% confidence interval (CI) as summary statistics. Standard methods for assessing statistical heterogeneity and publication bias were used, respectively. Four trials with 244 participants were included in the final analysis. Pooling of results showed that Melissa officinalis significantly lowered total cholesterol (TC) (WMD, -7.55 mg/dL; 95% CI -14.99, -0.12; *P*=0.045) , low-density lipoprotein cholesterol (LDL-C) (WMD, -11.33 mg/dL; 95% CI -19.46, -3.21; *P*=0.006), glycated hemoglobin (HbA1c) (WMD, -0.35 %; 95% CI -0.64, -0.07; *P*=0.01), and Systolic blood pressure (SBP) (WMD, -0.89 mmHg; 95% CI-1.69, -0.09; *P*=0.03). The use of Melissa officinalis did not appear to significantly alter any other study endpoints. The present findings showed that supplementation with Melissa officinalis extract were associated with a significant reduction in TC, LDL-C, HbA1c, and SBP in humans.

Keywords: *blood pressure, blood glucose, CVD, lipid, melissa officinalis*

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1. Introduction

Cardiovascular disease (CVD) is the main cause of mortality throughout the world [1]. Large-scale epidemiological studies demonstrated that the potentially modifiable risk factors, including obesity, hypertension, hyperlipidemia, hyperglycemia contribute to promoting CVD pathogenesis [2,3,4]. Management of patients with CVD particularly lowering of LDL cholesterol concentration, blood pressure control, and glycemic management has resulted in substantial improvements in cardiovascular outcomes and a shift in the major causes of long term morbidity and mortality [5,6]. Currently, there is a growing interest in identifying new bioactive compounds with healthy effects on CVDs, which can then be used to develop functional foods. Findings from meta-analysis and systematic review of controlled trials have suggested that several natural products or functional foods, such as quercetin, spirulina, berries, chitosan and resveratrol may exert beneficial effects on cardiovascular risk biomarkers [7-11].

Melissa officinalis (known as lemon balm), belongs to the family of Lamiaceae, is a rich source of phytochemicals including phenolic acid, rosmarinic acid, caffeic acid, flavonol and triterpene [12]. Accumulating evidence has shown that Melissa officinalis have hypoglycemic, hypolipidemic effects, antiglycation activity, hypolipidemic, anti-inflammatory effects, and pancreatic amylase inhibitory activity [13,14]. Several well-performed clinical trials investigated the effect of Melissa officinalis on CVD risk factors have been completed [15,16,17]. However, findings from human randomized controlled trials are not consistent. To the best of our knowledge, the current scientific evidence on the effects of Melissa officinalis on CVD risk biomarkers obtained from human RCTs has not been systematically reviewed, and thus, no conclusive

remarks can be drawn. Therefore, the present systematic review aimed to investigate the overall clinical effects and safety of Melissa officinalis administration on a myriad of cardiovascular health parameters including lipid profiles, blood pressure, anthropometric parameters and glucose levels in human subjects.

2. Materials and Methods

2.1. Eligibility Criteria

To be included studies had to: 1) examine the effect of Melissa officinalis (lemon balm) with a period of ≥ 2 weeks, 2) be conducted in a human population aged ≥ 18 years, 3) data regarding at least one of the following outcome markers, including total cholesterol (TC), LDL-C, high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), fasting blood glucose (FBG), HbA1c, systolic blood pressure (SBP), diastolic blood pressure (DBP), body weight, and body mass index (BMI); 4) be a randomized placebo-controlled clinical trial or compare the supplementation arm to a control arm.

2.2. Search Strategy

This systematic review and meta-analysis was conducted followed the Cochrane Handbook for Systematic Reviews of Interventions. Results are reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [18]. The following databases were searched from their inception to 21th June 202, including PubMed, Scopus, Web of Science and Google Scholar databases. The following Medical Subject Heading (MeSH) words and their combinations were searched: “Melissa officinalis” OR “lemon balm”. References of the retrieved publications were examined to identify other potential papers for inclusion. The search was limited to human studies and randomized clinical trials (RCTs) published in English. Screening of articles involved all authors, with any disagreements discussed and resolved via consensus.

2.3. Assessment of Study Quality and Data Extraction

Risk of bias and methodological quality were assessed independently by two authors using the Cochrane Collaboration risk assessment tool [19]. Discrepancies in opinions between the 2 authors were discussed until agreement was reached. The assessment of quality characteristics used the following criteria: selective reporting, incomplete outcome data, blinding of outcome assessors, blinding of participants and study personnel, allocation concealment, randomization sequence generation, and other biases. Each of these key components of methodologic quality was assessed according to the categorizations of low, unclear, or high. The quality of studies was then determined on the basis of overall risk of bias as good, fair, or poor.

Eligible studies were reviewed and the following parameters were extracted from each study: publication year, first author’s name, location, population age and health status, number of patients allocated to each group, number of patients who completed the study, study design, intervention duration, dose of Melissa officinalis supplement, and CVD biomarkers assessed. Values of outcome variables before and after treatment in intervention and control groups were entered into statistical software and checked for accuracy. When multiple publications reported the same or a sub-sample of a participant cohort, information from the eligible studies that included the larger sample size was used. Data from the smaller study was included only if the larger study did not contain sufficient detail.

2.4. Statistical Analysis

Continuous variables were expressed as the weighted mean difference (WMD) and 95% confidence interval (CI). The I^2 statistic was used to quantify the degree of statistical heterogeneity among studies. In each analysis, heterogeneity was defined as low (I^2 < 25%), moderate (25% < I^2 < 75%), or high (I^2 > 75%) [20]. Clinical heterogeneity was accounted for by performing analyses using a random-effect model. A traditional sensitivity analyses was also completed in order to determine the impact of each study on the overall effect size by removing one study at a time and re-conducting the analyses. Potential publication bias in each analysis was assessed quantitatively using Begg’s and Egger’s tests [21,22]. Funnel plots were also used for visual assessment of publication bias. The STATA software version 12.0 (Stata Corp, USA) were used to carry out statistical analyses. Two-tailed *P* values were used with statistical significance conferred if the *P* value was less than 0.05, except where otherwise specified.

3. Results

3.1. Search Results and Trial Flow

From a total of 168 records obtained through the systematic search, 12 papers underwent full-text screening based on title and abstracts. Two eligible publications reported the same participant cohort [23,24]. Finally, a total of 4 studies with 244 participants met the inclusion criteria and were included in the current meta-analysis [15,16,17,23]. The flow diagram shows the process of literature screening, study selection, and reasons for exclusion, can be found in Figure 1.

3.2. Characteristics and Quality of Included Studies

Table 1 is a summary of study characteristics. Included studies were published from 2016 to 2019, and were conducted in Iran. There were a total of 242 subjects were randomly assigned in these trials. These trials were conducted using both sexes. The average age of participants in each trial fell between 44.70 to 57.66 years, and the mean BMI ranged from 28.34 to 28.55 kg/m^2. Melissa officinalis doses administered in the studies ranged from 350 to 3000 mg/day. The range of supplementation periods with Melissa officinalis was from

2 months up to 3 months. All trials were randomized, double - blinded, placebo - controlled trials utilizing a parallel design. Participants in these trials had hyperlipidemic, type 2 diabetic, dyslipidemic diabetic, and chronic stable angina.

A summary of the risk-of-bias systematic assessment based on different quality domains is provided in Figure 2. All of the included trials sufficiently addressed the criteria of complete outcome data, selective reporting and other biases. An adequate randomized sequence was generated in 2 trials [16,17], and the other 2 selected studies did not provide sufficient data about random sequence generation [15,23].

3.3. Effect of Melissa Officinalis Supplementation on Clinical CVD Risk Factors

Among the included studies, the net changes and corresponding 95% CI for markers of clinical outcomes for each trial are presented in Table 2. Melissa officinalis supplementation resulted in a decrease in TC (WMD, -7.55 mg/dL; 95% CI -14.99, -0.12; *P*=0.045), LDL-C (WMD, -11.33 mg/dL; 95% CI -19.46, -3.21; P=0.006), HbA1c (WMD, -0.35 %; 95% CI -0.64, -0.07; *P*=0.01), and SBP (WMD, -0.89 mmHg; 95% CI -1.69, -0.09; *P*=0.03) in comparison to the placebo group. However, there was no significant effect on HDL-C (WMD, 2.83 mg/dL; 95% CI -1.94, 7.60; *P*=0.25), TG (WMD, -11.72 mg/dL; 95% CI -28.74, 5.29; *P*=0.18), FBG (WMD, -2.29 mg/dL; 95% CI -7.97, 3.38; *P*=0.43), body weight (WMD, -1.59 kg; 95% CI -6.61, 3.43; *P*=0.54), BMI (WMD, -0.18 kg/m^2; 95% CI -1.26, 0.91; *P*=0.75), and DBP (-1.92 mmHg, 95% CI -7.80, 3.96; *P*=0.52).

3.4. Sensitivity Analysis and Publication Bias

The sensitivity analysis shown that exclusion of any single study each time did not influence the significance of our pooled effect size for either outcome. Egger's linear regression tests and Begg's rank correlation both confirmed that the current analysis was free from publication bias (for TC, *P*=1.00; for LDL-C, *P*=00.174; for HDL-C, *P*=0.497; for TG, *P*=0.34; for FBG, *P*=0.602; for HbA1c, *P*=0.317; for Body weight, *P*=0.317; for BMI, *P*= 0.602; for SBP, *P*=0.317; for DBP, *P*=0.317).

3.5. Adverse Events

Most of the studies did not mention anything about the occurrence of adverse reactions. Three studies found Melissa officinalis supplementation to be well tolerated, no serious adverse events were observed during the study. Jandaghi *et al.* reported minor adverse events such as headache and dizziness in Melissa group and one case becomes involved in Dizziness in placebo group [17].

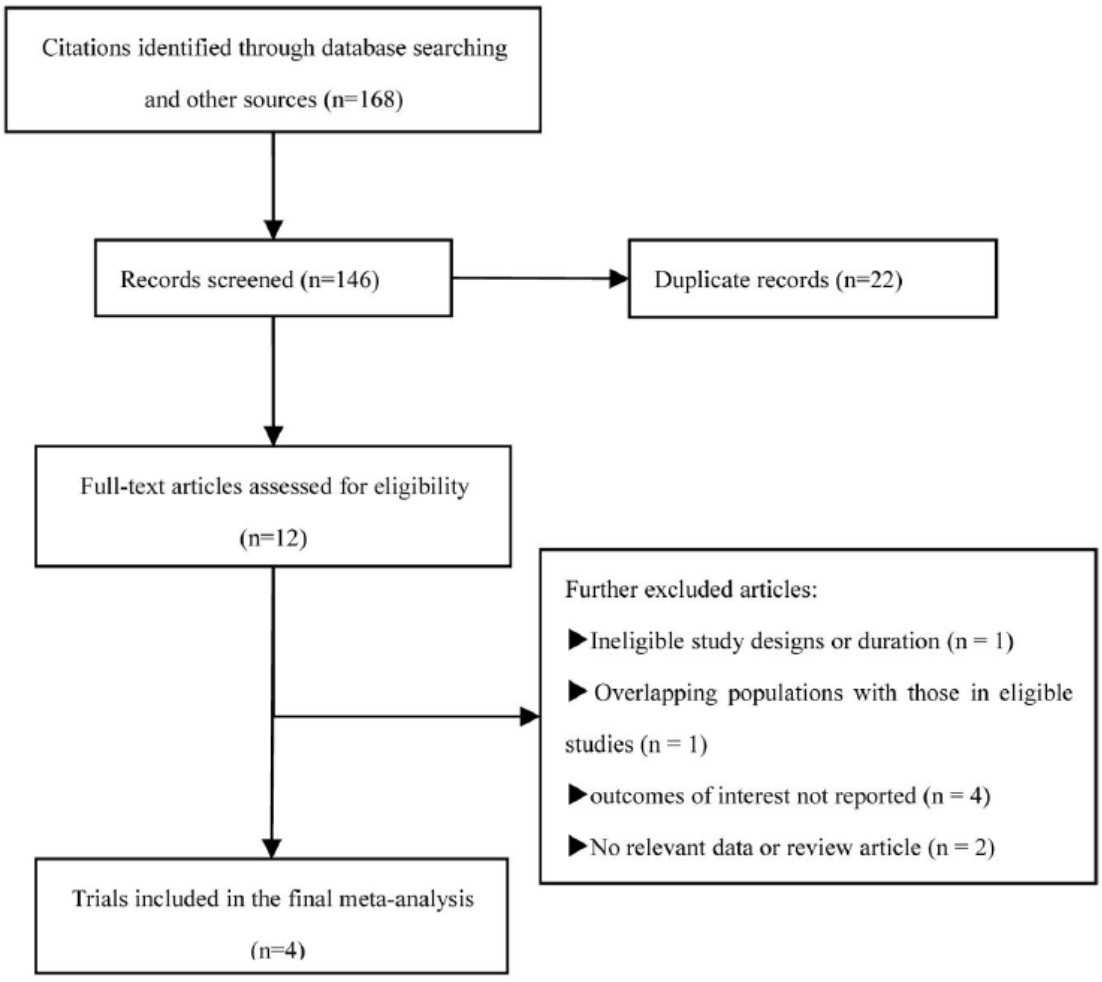

Figure 1. Flow chart of the number of studies identified and included into the meta-analysis

Table 1. Demographic characteristics of the included studies

Reference	Years	Study design	Location	Sample size	Sex (M/F)	Target Population	Mean age (year)	BMI (kg/m^2)	Intervention		Dose (mg/day)	Duration (months)	Main outcomes
									Intervention Group	Control Group			
Jandaghi et al	2016	R, DB, PC, P	Iran	58	24/34	hyperlipidemic patients	44.70	28.34	Melissa officinalis capsules	Placebo	1000	2	FBG, TC, LDL-C, HDL-C, TG
Asadi et al.	2018	R, DB, PC, P	Iran	62	34/28	type 2 diabetic patients	53.33	28.51	Melissa officinalis capsules	Placebo	700	3	FBG, HbA1c, TC, LDL-C, HDL-C, TG, SBP, DBP
Nayebi et al.	2019	R, DB, PC, P	Iran	32	16/16	dyslipidemic diabetic patients	54.30	NA	Melissa officinalis capsules	Placebo	350	2	FBG, HbA1c, TC, LDL-C, HDL-C, TG, SBP, DBP, body weight
Javid et al.	2018	R, DB, PC, P	Iran	73	36/37	patients with Chronic stable angina	57.66	28.55	Melissa officinalis capsules	Placebo	3000	2	TC, LDL-C, HDL-C, TG, BMI

C, crossover; DBP, diastolic blood pressure; DB, double-blind; FBG, fasting blood glucose; F, female; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; M, male; NA, Not applicable; PC, placebo-controlled; P, parallel; R, randomized; SBP, systolic blood pressure; TG, triglycerides; TC, total cholesterol.

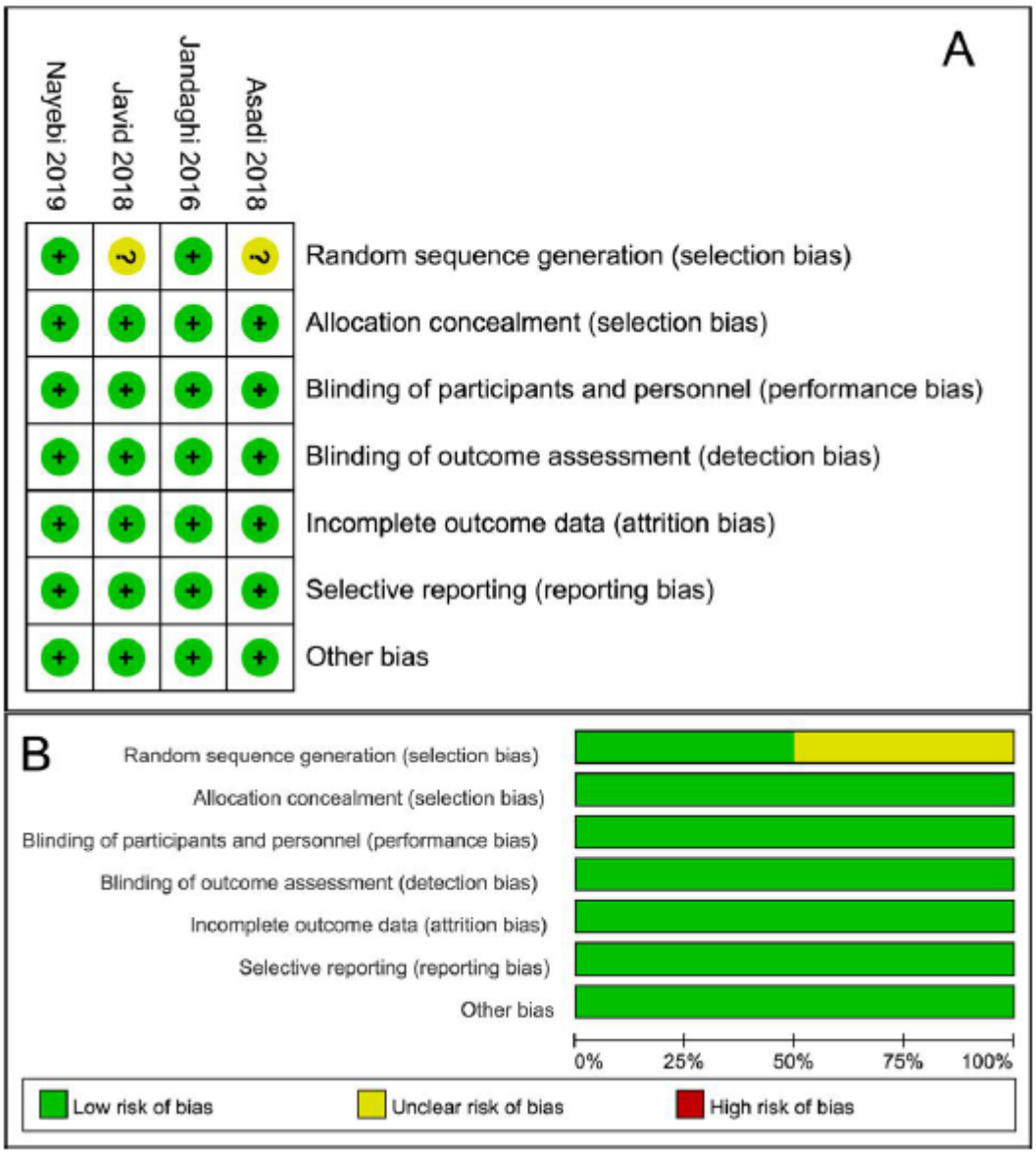

Figure 2. Results of risk of bias assessment. (A) Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies. (B) Risk of bias summary: review authors' judgments about each risk of bias item for each included study

Table 2. Meta-analysis of the effects of Melissa officinalis supplementation on CVD risk factors

Outcomes	No. of trials	No. of patients	Effect size [mean difference (95% CI)]	*P* value	I^2 (%)	*P* value of heterogeneity	Model Used
TC (mg/dL)	4	244	-7.55 (-14.99 to -0.12)	0.045*	12	0.33	F
LDL-C (mg/dL)	4	244	-11.33 (-19.46 to -3.21)	0.006*	40	0.17	R
HDL-C (mg/dL)	4	244	2.83 (-1.94 to 7.60)	0.25	78	0.003	R
TG (mg/dL)	4	244	-11.72 (-28.74 to 5.29)	0.18	0	0.54	F
FBG (mg/dL)	3	171	-2.29 (-7.97 to 3.38)	0.43	7	0.34	F
HbA1c	2	107	-0.35 (-0.64 to -0.07)	0.01*	0	0.53	F
Body weight (kg)	2	107	-1.59 (-6.61 to 3.43)	0.54	0	0.77	F
BMI (kg/m^2)	3	207	-0.18 (-1.26 to 0.91)	0.75	0	0.91	F
SBP (mmHg)	2	107	-0.89 (-1.69 to -0.09)	0.03*	0	0.60	F
DBP (mmHg)	2	107	-1.92 (-7.80 to 3.96)	0.52	56	0.13	R

FBG, Fasting blood glucose; TC, Total cholesterol; LDL-C, Low-density lipoprotein-cholesterol; HDL-C, High-density lipoprotein-cholesterol; TG, Triglycerides; BMI, Body mass index; R, Random-effects model; F, Fixed-effects model; CI, Confidence intervals.

4. Discussion

CVD events are influenced by a number of modifiable risk factors such as hypertension, dyslipidaemia and diabetes. The effects of these risk factors on the incidence of CVD rises with progressively higher levels of glucose, LDL-C, and BP. Accumulating clinical trial studies indicates that Melissa officinalis possesses protective anti-inflammatory as well as anti-oxidant effects and is able to treat metabolic syndrome. The present study aimed to determine whether Melissa officinalis supplementation have differential effects on lipid profiles, BP, anthropometric parameters and glucose levels in human subjects.

To our knowledge, this is the first meta-analysis to estimate of the relationship between Melissa officinalis consumption and changes of cardiovascular risk factors in subjects. A total of 4 trials involving 242 individuals were suitable for statistical pooling. Our analyses showed a statistically significant reduction in lowered TC, LDL-C, HbA1c, and Systolic blood pressure after Melissa officinalis consumption. However, no statistically significant effects were observed in HDL-C, TG, FBG, Body weight, BMI, and DBP with Melissa officinalis ingestion when compared with placebo. Melissa officinalis was well tolerated, and no serious adverse events were found in any of the included studies. Sensitivity analyses revealed that the pooled result was robust and possessed no significant publication bias.

The precise mechanisms responsible for the presumed lipids-lowering properties of Melissa officinalis are not fully explored. The antihyperlipidemic effects of Melissa officinalis may be due to suppression of HMGCR expression and up-regulation of LDL receptor expression [25,26]. Other mechanisms such as down-regulation of HMG-CoA reductase expression and decreasing expression of Sterol regulatory element-binding protein 1C (SREBP-1c) and its target genes involved in fatty acid synthesis such as Acetyl-CoA carboxylase 1 (ACC1), stearoyl CoA desaturase 1 (SCD1), and fatty acid synthase (FAS), may also contribute to the antihyperlipidemic effect [26]. The hypoglycemic effect of Melissa officinalis is due to up-regulating the synthesis of hepatic glucokinase, glucose transporter 4 (GLUT4), and decreasing the expression of glucose-6-phosphatase (G6Pase) as well as phosphoenolpyruvate carboxykinase (PEPCK) [25]. The reduction of HbA1c in our investigation may be due to the inhibitory activity of Melissa officinalis on pancreatic alpha-amylase and alpha-glucosidase and reducing in postprandial blood glucose [13,27].

The major strength of our meta-analysis was according to the PRISMA guidelines and applied the standardized methodology. Furthermore, all trials included in our analysis were conducted in Iran, which was highly homogeneous. Egger's linear regression tests and Begg's rank correlation both confirmed that there was no evidence of major publication bias. Most of the included studies were high-quality trials with randomization and double blinding minimizing the risks of residual confounding and bias. This made our results more reliable to some extent. However, the present study also has several limitations. Firstly, our pooled analysis is based on only 4 RCTs, and most of the included studies had relatively sample sizes in each group, which may potentially leading to overestimation of treatment effects. Secondly, due to the lack of original data of the reviewed studies, we were unable to perform the priori subgroup analysis according to the various factors. Finally, our pooled result was obtained with unadjusted estimates, preventing the exclusion of confounders acting on the relationship between Melissa officinalis and CVD risk factors (i.e. other lifestyle interventions, alcohol consumption and smoking habits).

5. Conclusion

In conclusion, this meta-analysis of available RCTs showed Melissa officinalis consumption significantly improved TC, LDL-C, HbA1c, and SBP. However, there was no significant effect of Melissa officinalis consumption on HDL-C, TG, FBG, body weight, BMI, and DBP. Melissa officinalis consumption may act as a safe complementary medicine in regulating CVD risk factors in humans. Further well-designed RCTs with longer durations of supplementation on a larger sample size with appropriate methodology are required to be conducted to incorporate the benefits of Melissa officinalis into prevention and management of CVD.

Abbreviation List

BP**,** blood pressure; CVD, Cardiovascular disease; CIs, confidence intervals; FBG, fasting blood glucose; HbA1c, glycosylated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; RCTs, randomized controlled trials; TC, total cholesterol; TG, triglycerides; WMDs, weighted mean differences.

Conflict of Interest

The authors declare no conflict of interest.

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