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REVIEW

Effects of *Melissa officinalis* (Lemon Balm) on cardio-metabolic outcomes: A systematic review and meta-analysis

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Recent evidence indicates a beneficial effect of *Melissa officinalis* (MO) intake on several chronic diseases. However, the effects of MO intake have not yet been systematically reviewed. Therefore, we conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) to evaluate the effect of MO intake and focused on several cardiometabolic outcomes. MEDLINE, Scopus, EMBASE, Web of Science and the Cochrane Central Register of Controlled Trials were searched for MO-RCTs evaluating cardiometabolic outcomes. Random-effects meta-analyses estimated the pooled standardized mean differences (SMD) between intervention and control groups. Risk of bias was assessed with the Cochrane Collaboration's tool for assessing the risk of bias in RCTs. Seven RCTs were finally deemed eligible. MO intake was associated with a reduced total cholesterol (TC) (SMD: −0.26; 95% CI: −0.52, −0.01; I^2 = 13.7%; k = 6) and a reduced systolic blood pressure (SBP) (SMD: −0.56; 95% CI: −0.85, −0.27; I^2 = 00.0%; k = 3). MO intake was not associated with statistically significant changes in triglycerides, low-density lipoprotein, diastolic blood pressure, high sensitivity c-reactive protein levels, fasting blood sugar, HbA1c, insulin or high-density lipoprotein levels. No serious adverse events were reported. The risk of bias was high in a considerable amount of studies. Our study suggests that MO is a safe supplement with beneficial effects on TC and SBP. However, the findings of our study must be seen in the light of major limitations such as a low number of included studies and a serious risk of bias. High-quality RCTs are needed for firm conclusions concerning the effects of MO on cardiometabolic outcomes.

KEYWORDS
blood pressure, cardiometabolic, cholesterol, *Melissa officinalis*

1 | INTRODUCTION

Cardiometabolic diseases such as type 2 diabetes mellitus (T2DM), arterial hypertension or coronary artery disease are common chronic diseases (Kjeldsen, Naditch-Brule, Perlini, Zidek, & Farsang, 2008; van Vliet et al., 2011). They are major contributors to morbidity and mortality worldwide. Several risk factors for the progression of cardiometabolic disorders have been identified (Guo, Moellering, & Garvey, 2014; Jafari Azad, Daneshzad, Meysamie, & Koohdani, 2020). These risk factors mainly comprise (but are not limited to) insulin resistance, increased total cholesterol (TC), triglyceride (TG) and low-density lipoprotein (LDL) cholesterol levels, decreased high-density

lipoprotein (HDL) cholesterol concentration, high blood pressure, increased inflammatory biomarkers and increased oxidative stress (Kelishadi, Gharipour, Sadri, Tavasoli, & Amani, 2008; Omidian et al., 2019).

In recent decades, medicinal plants have been getting more attention in research and in clinical practice: They usually have few side effects and are easily accessible (Dehghani et al., 2020; Michael et al., 2019). Herbal medicines are typically used as a complementary and adjunct therapy for a wide range of disorders, for example, T2DM or cardiovascular diseases (Abdollahi et al., 2019; Hashempur, Heydari, Mosavat, Heydari, & Shams, 2015; Rastogi, Pandey, & Rawat, 2016). *Melissa officinalis* (MO), also called lemon balm, is a perennial herbaceous plant in the mint family *Lamiaceae*. MO is an abundant source of active phytochemicals such as triterpenes, flavonols and phenolic acid (Shakeri, Sahebkar, & Javadi, 2016). In Asian traditional medicine, MO is used for several conditions such as rheumatoid arthritis, gastrointestinal diseases or neurological disorders (Emamghoreishi & Talebianpour, 2015; Mahboubi et al., 2016; Moradkhani et al., 2010). While there are several primary studies investigating the effect of MO in chronic cardiometabolic diseases (Asadi et al., 2019; Javid et al., 2018a; Moradkhani et al., 2010), research synthesis is lacking. No systematic review has been performed to date that summarizes the literature to provide evidence about the effect of MO on any cardiometabolic risk factors. Therefore, we conducted a systematic review and meta-analysis to evaluate the effect of MO on cardiometabolic risk factors.

2 | METHODS

2.1 | Literature search, data sources and eligibility criteria

We searched for randomized controlled trials (RCT, parallel or crossover design) investigating MO that measured cardiometabolic risk factors. The following electronic databases were searched independently by two reviewers (J.H. and M.M.): MEDLINE (1966 through November 2019); EMBASE (1974 through November 2019); Cochrane Central Register of Controlled Trials (from inception to November 2019); Scopus (from inception to November 2019); and Web of Science (from inception to November 2019). We also investigated the following electronic databases for potential ongoing trials: the National Institutes of Health Trial Register (http://www.clinicaltrials.gov/) and the ISRCTN registry (http://www.controlled-trials.com/). Reference lists of included studies as well as related systematic reviews (as identified through database searches) were also assessed for potential eligible studies. See Table S1 (Supporting Information) for detailed search strategies. Two reviewers (S.F and J.H.) separately appraised the title and abstract of every obtained record. All studies that seemed to fulfill the selection criteria as well as articles that could not be sufficiently evaluated by title and abstract alone were obtained and investigated in full text. We included randomized double blind clinical trials conducted in healthy or diseased populations (≥18 years old); only articles published in English were included. Table 1 shows the PICO framework for our meta-analysis.

TABLE 1 Description of PICO

Condition	Description
Participant	Adults
Intervention	Oral *Melissa officinalis* supplementation
Comparison	Placebo
Outcome	*TC, TG, LDL-c, HDL-c, hs-CRP, SBP, DBP, Cr, Ins, LDH, NO*
Study designs	Randomized controlled clinical trials

Abbreviations: Cr, creatinine; DBP, diastolic blood pressure; EF, ejection fraction; HDL-c, high density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; Ins, insulin; LDH, lactate dehydrogenase; LDL-c, low density lipoprotein; NO, nitric oxide; PON1, paraxonase 1; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride.

2.2 | Data extraction and quality assessment

In studies with more than two arms, only MO and placebo arms were included in the analysis. As outcomes we included several cardiometabolic risk factors: glycemic parameters (fasting blood sugar [FBS], insulin levels, Homeostasis Modell Assessment Test—Insulin Resistance [HOMA-IR], and HbA1c), serum lipids (TC, TG, LDL and HDL), and inflammatory markers (C-reactive protein [CRP] and blood pressure systolic [SBP] and diastolic [DBP]). The following information was abstracted independently by two reviewers (M.M and J.H.): the first author's name, year of publication, sample size, location, participant characteristics (mean age, sex and baseline BMI), dose of MO, form (powder, oil, extract), duration, outcomes (mean and standard deviation), and serious adverse events. As a randomized study design does not preclude the possibility of bias, a systematic risk of bias evaluation was conducted using the Cochrane risk of bias tool (Higgins & Green, 2011; Palmowski & Nielsen, 2019). Disagreements in the evaluation of data were resolved by discussion. Consensus was reached in all cases.

2.3 | Data synthesis and analysis

Meta-analysis was conducted using STATA (Version 12; STATA Corp, College Station, TX). We chose the standardized mean difference (SMD) as our effect size. Random-effects meta-analysis models (DerSimonian and Laird method) were conducted to estimate the pooled SMD across trials (DerSimonian & Laird, 1986). Standard error of mean (*SEM*) was converted to *SD* by using the following formula: $SD = SEM \times \sqrt{n}$ (n = number of participants in each group). Heterogeneity was evaluated using the *I*-squared (I^2) index. Random-effects meta-regression analyses were performed to assess the relationship between effect sizes and potential

moderator variables such as health status, duration, or dosage. We also conducted sensitivity analyses (leave-one-out approach) to evaluate the contribution of every single study to the pooled effect size.

3 | RESULTS

3.1 | Study selection

As shown in Figure 1 (PRISMA flow diagram), the electronic database searches initially retrieved 837 records. Eventually, seven RCTs (Asadi et al., 2018, 2019; Jandaghi, Noroozi, Ardalani, & Alipour, 2016; Javid et al., 2018a, 2018b; Nayebi et al., 2019; Yui et al., 2017) were deemed eligible.

3.2 | Study characteristics

Main characteristics of the included studies are presented in Table 2. The number of subjects in these studies ranged from 26 to 72. Included trials were published between 2016 and 2019 and were performed in The Iran and Japan. MO doses ranged between 1,000 and 3,000 mg/day. The duration of intervention ranged between 6 and 12 weeks. Studies enrolled participants with T2DM (Asadi et al., 2018; Nayebi et al., 2019), hyperlipidemic patients (Jandaghi

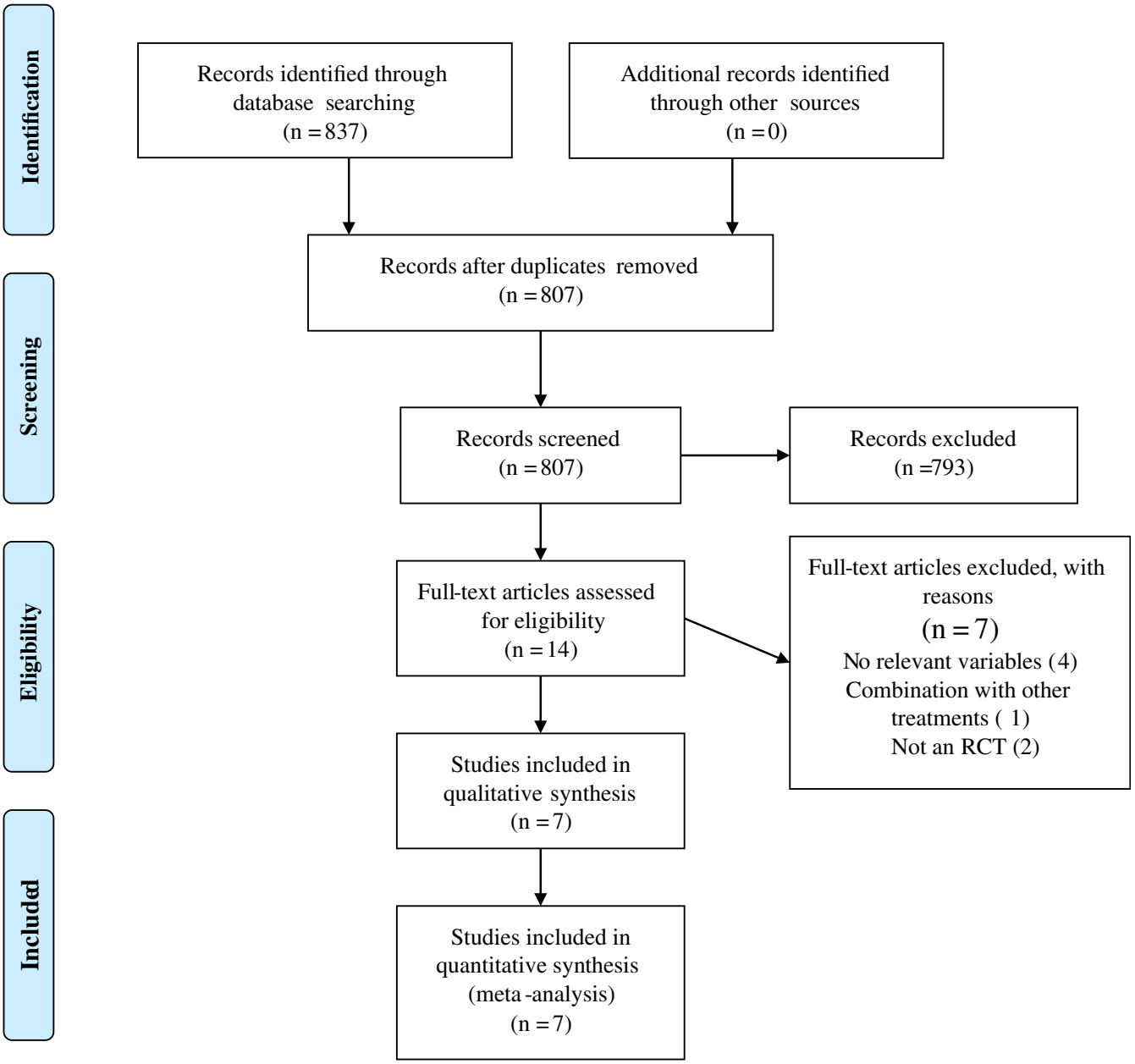

FIGURE 1 Flow diagram of the study selection [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Main characteristics of included studies

First author, year	Country	Type of study	Population	Dose of *Melissa officinalis* (mg/day)	Type of *Melissa officinalis*	Sample size		Duration (weeks)	Gender (percentage of women)	Age (mean ± *SD*)	BMI (mean ± *SD*) (kg/m^2)	Adverse events	Main results
						Intervention	Control						
Asadi et al. (2018, 2019)	Iran	Double blinded RCT-parallel	T2DM	1,400	Hydroalcoholic extract	31	31	12	45.15	MO: 53.9 ± 6.28 P: 52.77 ± 7.83	MO: 28.66 ± 4.64 P: 28.37 ± 3.71	None	↔FBS, ↓HbA1c, ↔ins, ↔HOMA-IR, ↓TG, ↑HDL, ↔TC, ↔LDL, ↓hs-CRP
Jandaghi et al. (2016)	Iran	Double blinded RCT-parallel	Hyperlipidemic patients	3,000	Capsules leaf powder	28	30	8	58.57%	MO: 46.04 ± 9.40 P: 43.37 ± 9.41	MO: 28.24 ± 3.73 P: 28.45 ± 3.99	None	↓LDL, ↔TC, ↔FBG, ↔HDL, ↔TG, ↔Cr and ↔ALT
Javid et al. (2018a)	Iran	Double blinded RCT-parallel	Chronic stable angina	3,000	Aerial parts of MO	35	38	8	50.7%	MO:58.80 ± 8.38 P: 56.53 ± 8.93	MO: 28.04 ± 3.71 P: 29.06 ± 3.74	None	↑HDL, ↓TG, ↓TC, ↓LDL, ↓MDA, ↓hs-CRP, ↑PNO1
Javid et al. (2018b)	Iran	Double blinded RCT-parallel	Chronic stable angina	3,000	Aerial parts of MO	35	38	8	50.7%	MO:58.80 ± 8.38 P: 56.53 ± 8.93	MO: 28.04 ± 3.71 P: 29.06 ± 3.74	None	↑EF,↓ LDH, ↑NO, ↓SBP, ↓DBP
Nayebi et al. (2019)	Iran	Double blinded RCT-parallel	T2DM	1,000	Aerial parts of MO	16	16	12	50%	MO: 54.9 ± 5.8 P: 53.7 ± 6.6	—	None	↔HDL, ↓TG, ↔TC, ↔LDL, ↓SBP, ↓DBP
Yui et al. (2017)	Japan	Randomized clinical trial	Healthy adults	—	Aerial parts of MO	12	14	6	50%	MO: 44.8 ± 9.6 P: 45.0 ± 7.8	—	None	↓FBS, ↓uric acid, ↔HbA1c, ↔ins, ↔HDL, ↔TG, ↔TC, ↔LDL

Abbreviations: Cr, creatinine; DBP, diastolic blood pressure; EF, ejection fraction; FBS, fasting blood sugar; HbA1c, glycated hemoglobin; HDL-c, high density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; Ins, insulin; LDH, lactate dehydrogenase; LDL-c, low density lipoprotein; MO, melissa officinalis; NO, nitric oxide; NR, not reported; P, placebo group; PON1, paraxonase 1; RCT, randomized clinical trial; SBP, systolic blood pressure; T2DM, type 2 diabetes mellitus; TC, total cholesterol; TG, triglyceride.

[a]↓ symbolizes a decrease in the intervention group, ↑ symbolizes is an increase in the intervention group, ↔ this sign indicates that there is no difference between the two groups.

et al., 2016), patients with chronic stable angina (Javid et al., 2018a) and healthy adults (Yui et al., 2017). Mean ages ranged between 43.4 and 58.8 years. All trials included patients of both genders.

3.3 | Effects of MO on the serum lipid profile

Six trials reported lipid profiles. MO treatment was associated with a statistically significant decrease in TC (SMD: −0.26; 95% CI: −0.52, −0.01; I^2 = 13.7%) (Figure 2a). Subgroup analysis indicated that the effects regarding TC were stronger in trials with a duration of ≤8 weeks (SMD: −0.35; 95% CI: −0.71, −0.00; I^2 = 29.1%) (Figure 2b) and in trials with a MO dose of ≥1,500 mg/d (SMD: −0.46; 95% CI: −0.80, −0.11; I^2 = 00.0%) (Figure 2c). There was no statistically significant effect of MO intake on TG (SMD: −0.22; 95% CI: −0.45, 0.01; I^2 = 00.0%) (Figure 2d), HDL (SMD: 0.22; 95% CI: −0.30, 0.73; I^2 = 00.0%) (Figure 2g) and LDL (SMD: −0.32; 95% CI: −0.66, 0.03; I^2 = 50.4%) (Figure 2j). Subgroup analysis suggests that the effects of MO treatment on LDL were stronger in trials including only diseased subjects (SMD: −0.42; 95% CI: −0.74, −0.09; I^2 = 39.2%) (Figure 2k). Also, MO was more effective in decreasing LDL in doses of ≥1,500 mg/d (SMD: −0.76; 95% CI: −1.12, −0.41; I^2 = 00.0%) (Figure 2m).

3.4 | Effects of MO on glycemic parameters

Figure 3 shows the effects of MO intake on glycemic parameters (four trials). We found no statistically significant effect of MO regarding FBS (SMD: −0.08; 95% CI: −0.43, 0.27; I^2 = 25.5%) (Figure 3a), HbA1c (SMD: −0.20; 95% CI: −0.72, 0.31; I^2 = 47.6%) (Figure 3b) and insulin levels (SMD: 0.00; 95% CI: −0.42, 0.42; I^2 = 00.0%) (Figure 3c).

3.5 | Effects of MO on blood pressure and inflammation

Figure 4 shows the effects of MO intake on blood pressure (three trials) and inflammatory markers (two trials). Meta-analyses indicated a statistically significant effect of MO intake on SBP (SMD: −0.56; 95% CI: −0.85, −0.27; I^2 = 00.0%) (Figure 4a) but not on DBP (SMD: −0.46; 95% CI: −0.92, 0.01; I^2 = 53.6%) (Figure 4b) or high-sensitivity CRP (SMD: -1.16; 95% CI: −2.35, 0.03; I^2 = 90.2%) (Figure 4c).

3.6 | Adverse events

No serious adverse event was reported in any trial.

3.7 | Quality appraisal and publication bias

The risk of bias evaluation is presented in Table A1. There were moderate-to-serious concerns about incomplete outcome data in most trials.

4 | DISCUSSION

Findings of this systematic review and meta-analysis of RCTs suggest a beneficial effect of MO on TC and SBP. However, cautious interpretation of our results is warranted due to a high risk of bias in most trials and great heterogeneity between them. To our knowledge, this is the first systematic review and meta-analysis of RCTs that examines the effects of MO on cardiometabolic risk factors.

We included seven RCTs with 250 adults that evaluated the impact of MO on cardiometabolic risk factors. Our analyses indicate that MO might reduce LDL in diseased patients (as opposed to healthy individuals) and at higher doses (≥1,500 mg/d); however, results of these subgroup analyses must be interpreted cautiously due to a low number of included studies. While the results were not statistically significant, further beneficial trends were observed concerning MO intake and an increase in HDL, a reduction in TG, a reduction in DBP and a reduction in high-sensitivity CRP.

MO has previously been shown the possess the potential to improve hyperlipidemia by reducing total serum lipid levels and reduce the amount of lipid peroxidation in experimental studies (Bolkent, Yanardag, Karabulut-Bulan, & Yesilyaprak, 2005). Reasons behind this positive impact on serum lipids remain unclear. MO contains flavonoids, polyphenolics and terpenoids (Carnat, Carnat, Fraisse, & Lamaison, 1998; Hohmann et al., 1999; Moradkhani et al., 2010). Major active ingredients of MO are volatile compounds (e.g., geraniol, geranial, citronellal, and neral), triterpenes (e.g., oleanolic acid and ursolic acid), and phenolics (e.g., caffeic acid derivatives, hesperidin, luteolin, and naringin) (Argyropoulos & Müller, 2014). Flavonoids and polyphenols have been shown to have a wide range of biochemical and pharmacological activities, inducing hypolipidemic, cardioprotective, and antioxidant effects. Previous research also demonstrated that MO possesses strong antioxidant activity (Chung, Cho, Bhuiyan, Kim, & Lee, 2010). Since reactive oxygen species and oxidative stress contribute to dyslipidemia and its complications (Tangvarasittichai, 2015), sufficient intake of antioxidant supplements, such as MO, may be effective to improve or prevent dyslipidemia. Moreover, it has been shown that administration of MO increases the content of antioxidant defense system parameters such as glutathione (GSH) in liver cells and in blood (Bolkent et al., 2005). Administration of MO decreased liver enzyme concentrations in serum samples with an impact comparable to that of statins (Zarei, Ashtiyani, Taheri, & Rasekh, 2014).

In recent studies, MO treatment significantly reduced plasma TG, LDL/VLDL, TC and nonesterified fatty acids (Weidner et al., 2014). Ursolic and oleanolic acids have been shown to be the responsible compounds found in MO to reduce serum TG and LDL (Somova, Nadar, Rammanan, & Shode, 2003). In another study, MO intake decreased TG levels in mice. Cellular TG and TC levels were also significantly reduced in HepG2 cells in a dose-dependent manner after treatment with MO. Hypolipidemic mechanisms may be a decreased translocation of sterol regulatory element-binding protein-1c (SREBP-1c) and its responsive genes that play roles in fatty acid synthesis through reduced P300/CBP-associated factor (PCAF) histone acetylase function, which leads to a decrease of fatty acid synthesis in the liver (Jun et al., 2012).

Our study suggests a reduction of SBP after MO intake. Possible mechanisms may be vasorelaxant endothelial effects. Experimental studies indicated that rosmarinic acid (the main component of MO) had a vasorelaxant impact by inhibition and/or modulation of angiotensin-converting enzyme (Ersoy et al., 2008). Research has shown that MO extract has an endothelium-dependent vasorelaxant impact through the NO pathway (Guginski et al., 2009). Recent investigations also indicate that MO protects the endothelium from H_2O_2 oxidative damage and reduces vasoconstriction (Safaeian, Sajjadi, Javanmard, Montazeri, & Samani, 2016).

Results of our study indicate as well that MO supplementation might reduce CRP levels. Analyses were limited by a small number of

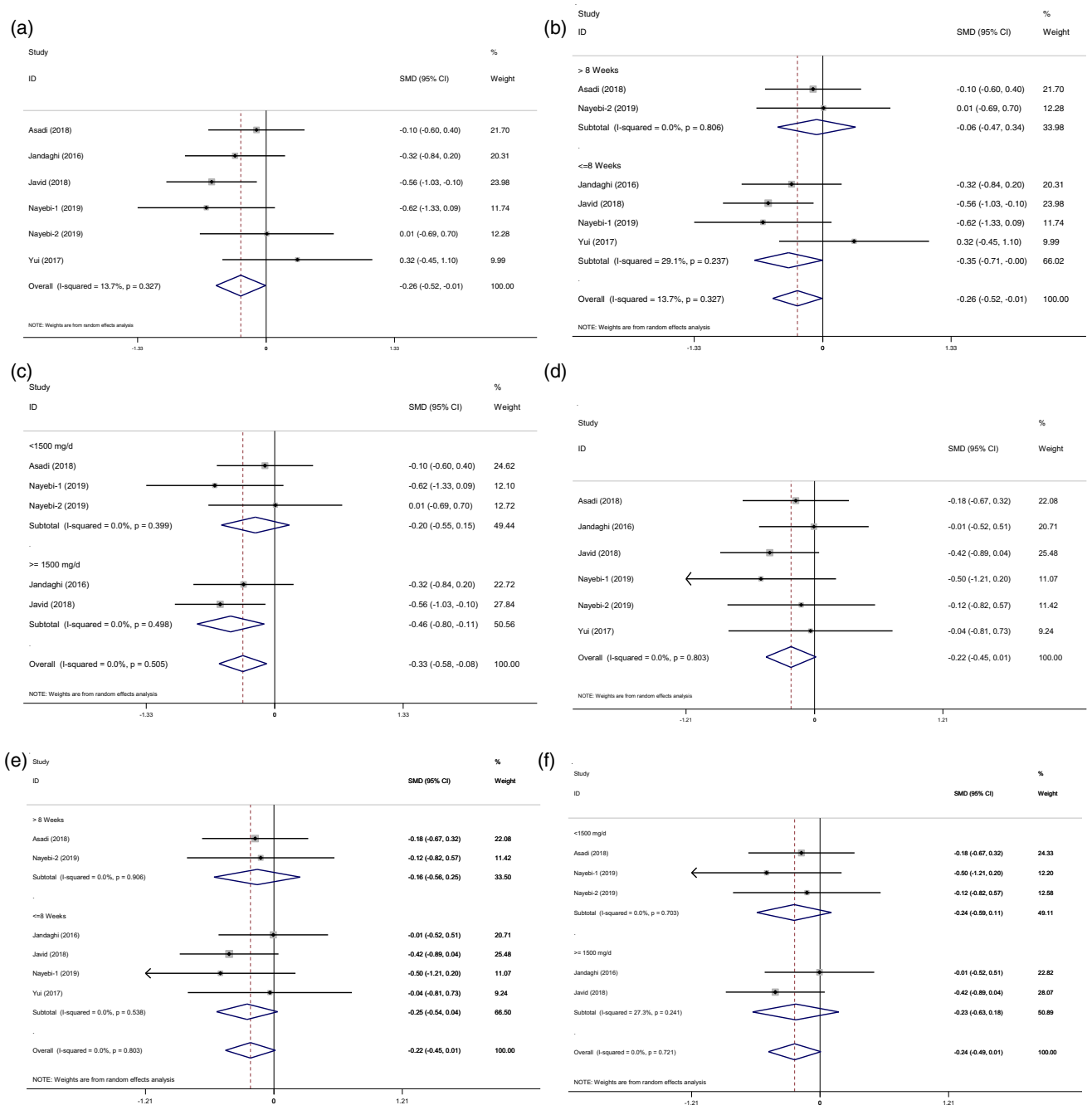

FIGURE 2 Forest plot of the effect of *Melissa officinalis* (MO) on the lipid profile. (a) Overall effect of MO on total cholesterol (TC). (b) Effect of MO on TC stratified by duration. (c) Effect of MO on TC stratified by dose. (d) Overall effect of MO on triglyceride (TG). (e) Effect of MO on TG stratified by duration. (f) Effect of MO on TG stratified by dose. (g) Overall effect of MO on high-density lipoprotein (HDL). (h) Effect of MO on HDL stratified by duration. (i) Effect of MO on HDL stratified by dose. (j) Overall effect of MO on low-density lipoprotein (LDL). (k) Effect of MO on LDL stratified by health status. (l) Effect of MO on LDL stratified by duration. (m) Effect of MO on LDL stratified by dose [Colour figure can be viewed at wileyonlinelibrary.com]

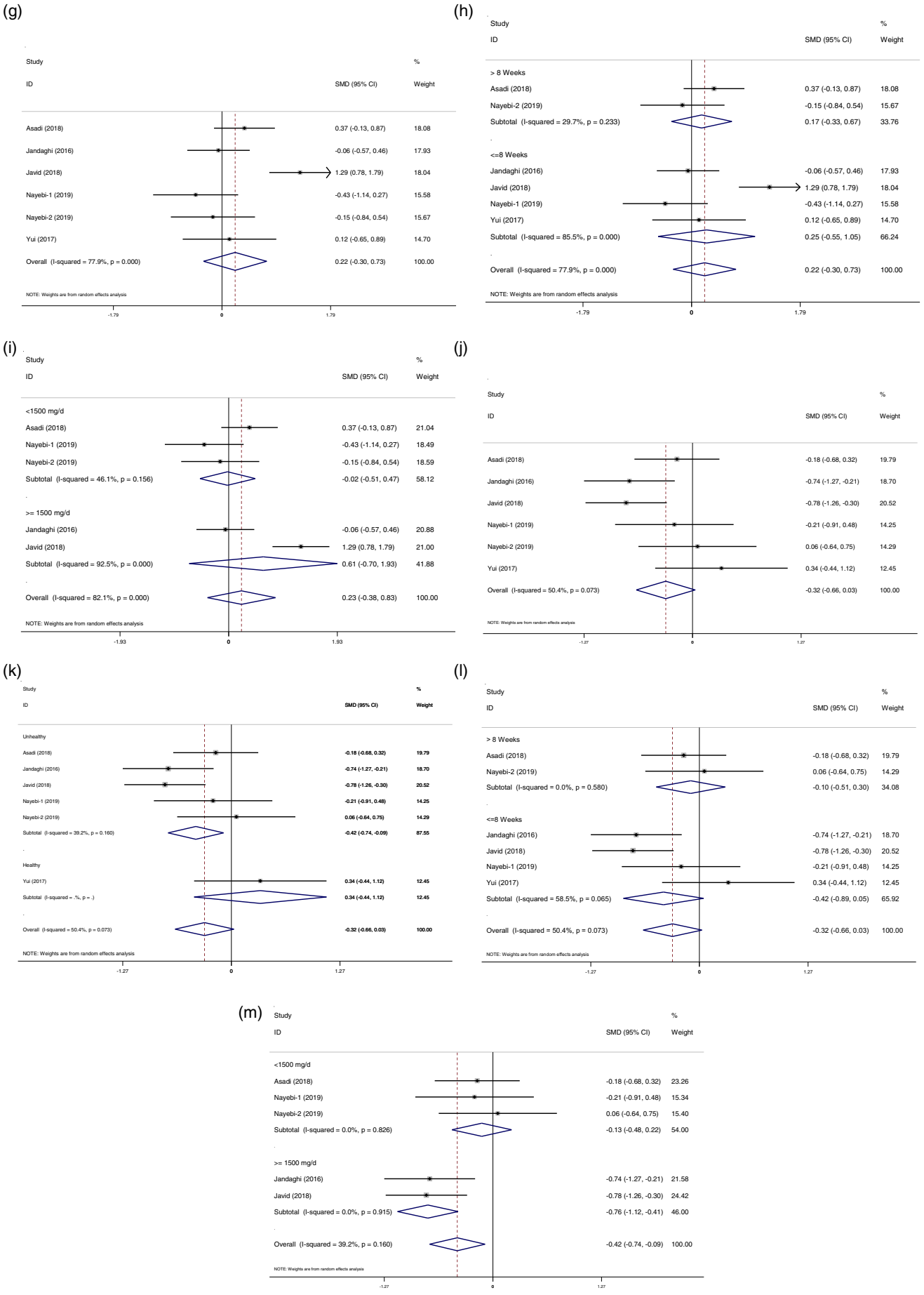

FIGURE 2 (Continued)

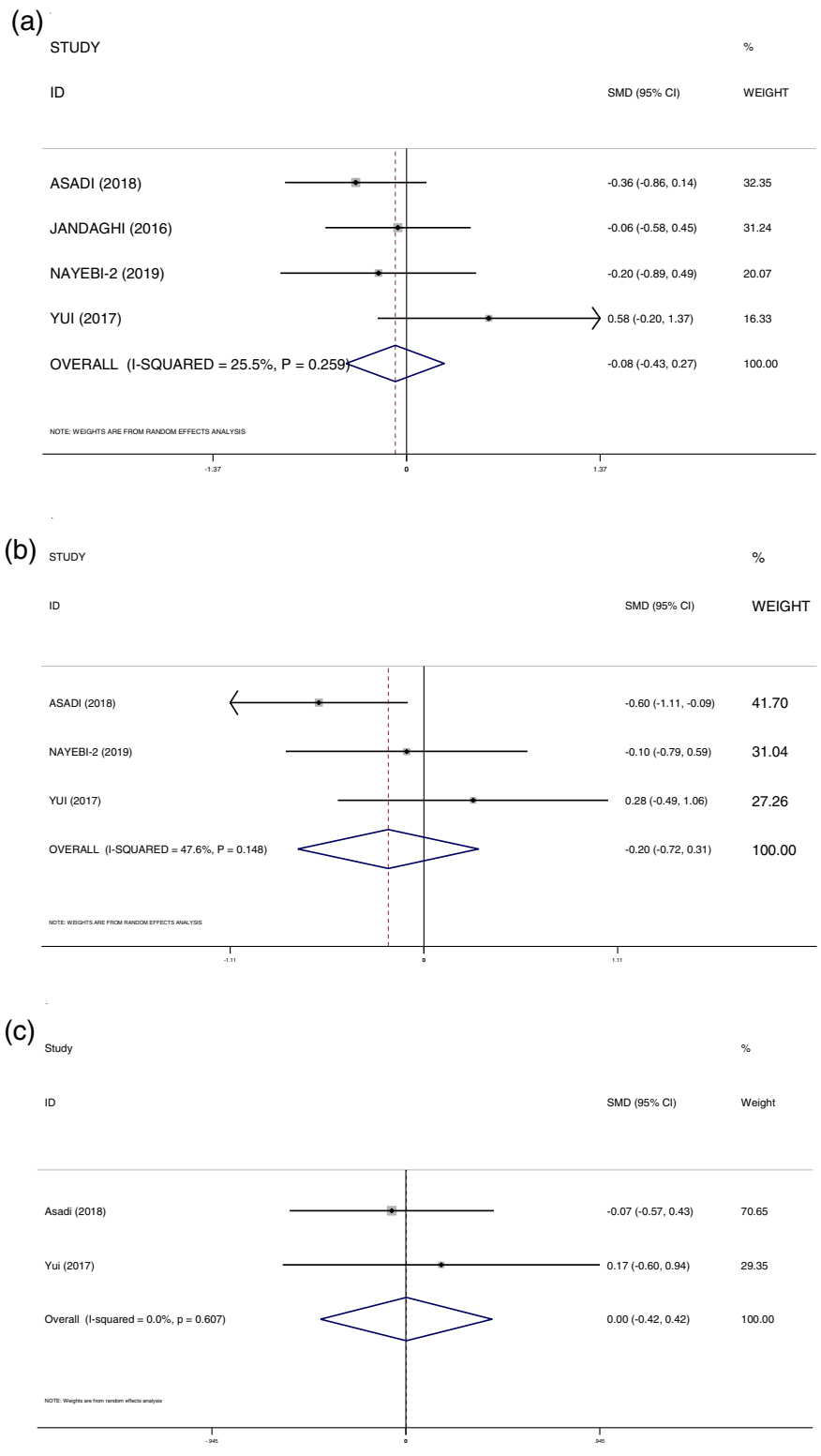

FIGURE 3 Forest plot of the effect of *Melissa officinalis* (MO) on glycemic parameters. (a) Overall effect of MO on fasting blood sugar (FBS). (b) Effect of MO on HbA1c. (c) Effect of MO on insulin [Colour figure can be viewed at wileyonlinelibrary.com]

included studies evaluating CRP. Possibly, statistical power was not sufficient to detect a statistically significant effect. Previous studies have shown that MO possesses anti-inflammatory properties (Bounihi, Hajjaj, Alnamer, Cherrah, & Zellou, 2013). Anti-inflammatory mechanisms of MO may be associated with its citral ingredients which have been shown to suppress IL-6 and TNF-α in vitro (Bounihi et al., 2013). Investigation of these inflammatory parameters in human subjects may be advisable to come to clear conclusions here.

Results of our study also indicate that MO intake exerts no significant effect on glycemic parameters such as FBS, HbA1c and insulin. While MO was found to have hypoglycemic effects in vitro, the results of experimental studies are usually obtained at high doses (Hasanein &

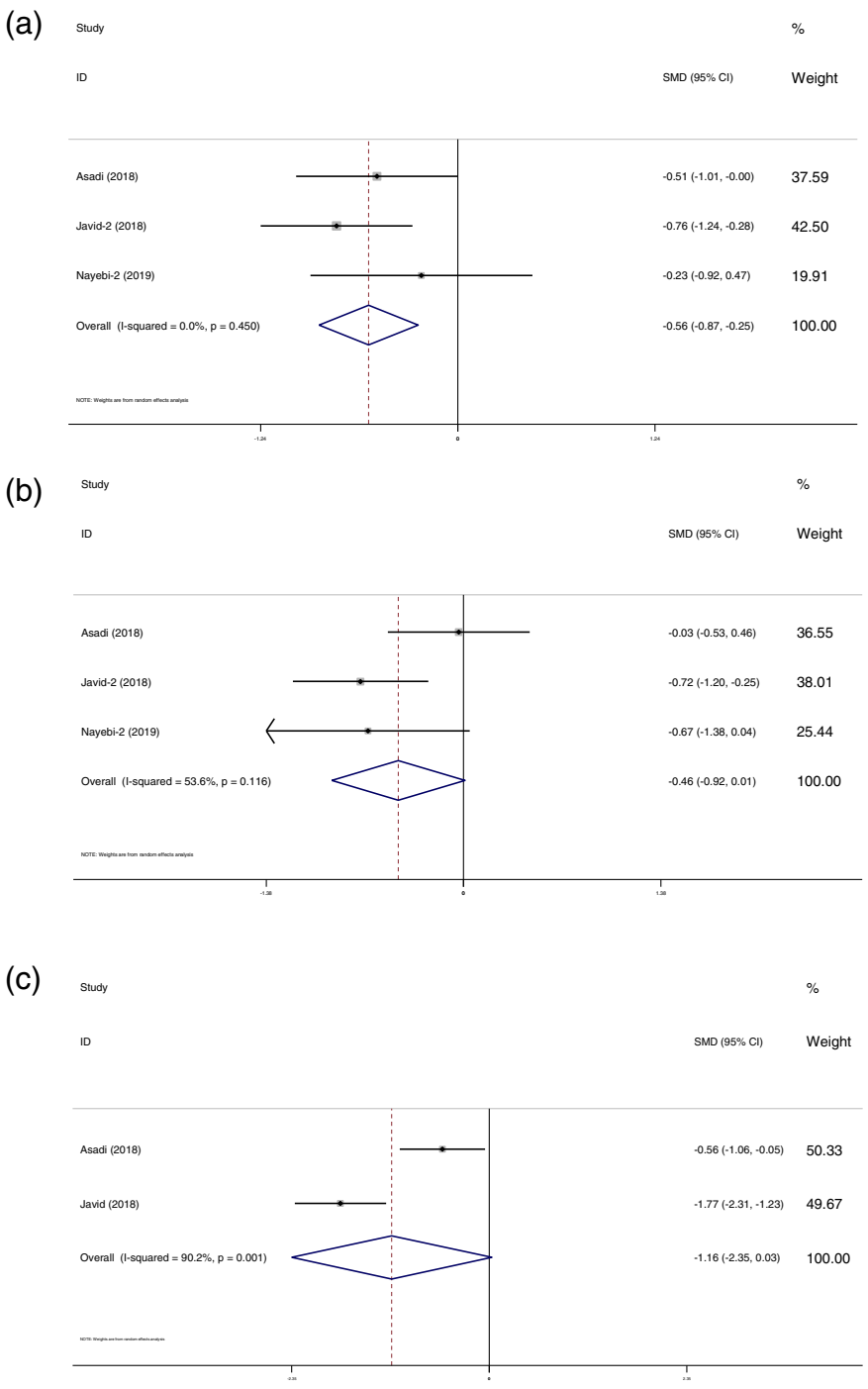

FIGURE 4 Forest plot of the effect of *Melissa officinalis* (MO) on blood pressure and inflammation parameters. (a) Overall effect of MO on systolic blood pressure. (b) Effect of MO on blood pressure diastolic DBP. (c) Effect of MO on high-sensitivity C-reactive protein [Colour figure can be viewed at wileyonlinelibrary.com]

Riahi, 2015; Weidner et al., 2014). At tolerable doses, hypoglycemic effects might not be strong enough (Nayebi et al., 2019; Yui et al., 2017).

4.1.1. | Strengths and limitations

It must be pointed out that systematic reviews and meta-analyses form the top of the clinical evidence hierarchy. The study at hand is indeed the first one about effects of MO. We searched several databases and had no limitations concerning languages. However, all included RCTs were conducted in Asia, possibly decreasing this study's generalizability. Our study had further limitations: The number of studies was small, thereby diminishing statistical power, and the risk of bias was considerable in most RCTs. Furthermore, there was a remarkable heterogeneity between the included studies. However conducting the random-effects model of analysis modulates the heterogeneity to some extent, yet the diversity in the MO intake dose, duration of studies, sample sizes and age of subjects could not be entirely covered. In addition, differences in the participants' health status might affect treatment effects. To account for this, we performed stratified sensitivity

analyses. Also, due to less rigorous regulations, manufacturers in phytotherapy are often not forced to prove efficacy, safety or the quality of a marketed product. Consequently, a lot of available herbal products might be ineffective (Williamson, Liu, & Izzo, 2019). Finally, herbal medicines may be produced and given in different ways (think of, for example, oil extract or dried powder), which might change the amount of active constituents present in the respective supplement.

5 | CONCLUSION

The results of this systematic review and meta-analysis suggest that MO intake is safe and has beneficial effects on TC and SBP. However, the majority of the trials included in our systematic review have been not conducted in line with a recent consensus document providing a perspective on best practice in pharmacological research on bioactive preparations from plants (Michael et al., 2019). Further evaluation by high-quality RCTs concerning is advisable as most included studies were small and had a considerable risk of bias.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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APPENDIX A1

TABLE A1 Risk of bias assessment

Author (year)	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Asadi et al. (2018, 2019)	?	–	–	?	+	–	–
Jandaghi et al. (2016)	–	–	–	?	?	–	–
Javid et al. (2018a)	?	–	–	?	+	–	–
Javid et al. (2018b)	?	–	–	?	+	–	–
Nayebi et al. (2019)	–	–	–	+	?	–	–
Yui et al. (2017)	–	?	–	?	–	–	–

Note: Red (+), high risk; green (–), low risk, yellow (?), unclear.