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REVIEW

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Hesperidin, a major flavonoid in orange juice, might not affect lipid profile and blood pressure: A systematic review and meta-analysis of randomized controlled clinical trials

Mohammad Mohammadi[1,2] | Nahid Ramezani-Jolfaie[1,2] | Elnaz Lorzadeh[1,2] | Yadollah Khoshbakht[1,2] | Amin Salehi-Abargouei[1,2]

[1] Nutrition and Food Security Research Center, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

[2] Department of Nutrition, School of Public Health, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

Correspondence
Amin Salehi-Abargouei, PhD in Nutritional Sciences, Department of Nutrition, School of Public Health, Sahid Sadoughi University of Medical Sciences, Yazd, Iran.
Email: abargouei@ssu.ac.ir; abargouei@gmail.com

Funding information
Nutrition and Food Security research center, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

Previous studies have led to conflicting results regarding the effect of hesperidin supplementation on cardiometabolic markers. This study aimed to evaluate the efficacy of hesperidin supplementation on lipid profile and blood pressure through a systematic review and meta-analysis of randomized controlled trials (RCTs). PubMed, Web of Science, Scopus, and Google Scholar, as well as the reference lists of the identified relevant RCTs, were searched up to May 2018. Effect sizes were pooled by using the random effects model. Ten RCTs (577 participants) were eligible to be included in the systematic review. The meta-analysis revealed that hesperidin supplementation had no effect on serum total cholesterol (weighted mean difference [WMD] = −1.04 mg/dl; 95% confidence interval [CI]: −5.65, 3.57), low-density lipoprotein cholesterol (WMD = −1.96 mg/dl; 95% CI [−7.56, 3.64]), high-density lipoprotein cholesterol (WMD = 0.16 mg/dl; 95% CI [−1.94, 2.28]), and triglyceride (WMD = 0.69 mg/dl; 95% CI [−5.91, 7.30]), with no significant between-study heterogeneity. Hesperidin supplement also had no effect on systolic (WMD = −0.85 mmHg; 95% CI [−3.07, 1.36]) and diastolic blood pressure (WMD = −0.48 mmHg; 95% CI [−2.39, 1.42]). Hesperidin supplementation might not improve lipid profile and blood pressure. Future well-designed trials are still needed to confirm these results.

KEYWORDS

blood pressure, citrus flavonoid, hesperidin, lipid profile, meta-analysis, systematic review

1 | INTRODUCTION

Clinical management of metabolic stressors such as hypertension, hyperlipidemia, and hyperglycemia results in a reduction in the health and economic burden of cardiovascular disease (CVD), worldwide (Yancy et al., 2016; Zanchetti et al., 2014). Lifestyle modification (for instance, following a healthy diet and increasing the physical activity) has been regarded as important approaches to deal with CVD risk factors (Ndanuko, Tapsell, Charlton, Neale, & Batterham, 2016; Pescatello et al., 2004).

The American college of cardiology and the American heart association recently published updated recommendations to follow a dietary pattern with high intake of vegetables, fruits, and whole grains for reducing blood pressure (Eckel et al., 2014) and also high intake of polyunsaturated fatty acids, viscous fiber, plant sterol, and soy protein for improving lipid profile (Hu, 2002). Epidemiologic studies have also suggested that foods rich in flavonoids and fibers such as fresh fruits and vegetables are associated with a reduced risk of coronary artery diseases (Chen et al., 2012; Esmaillzadeh et al., 2006; Michels et al., 2006; Rohrmann, Giovannucci, Willett, & Platz, 2007; Tsai, Leitzmann, Willett, & Giovannucci, 2006). The protective effects of polyphenol-rich foods (e.g., tea, cocoa, chocolate, fruits, and especially citrus fruit) on the intermediate risk factors for CVD have been shown by several studies (Dauchet, Amouyel, Hercberg, & Dallongeville, 2006; Hooper et al., 2008; Johnsen et al., 2003).

Citrus fruits, including clementine, lemons, grapefruit, and oranges (Gironés-Vilaplana, Moreno, & García-Viguera, 2014), are

characterized by the presence of the flavanone glycosides hesperidin and naringin as a subclass of flavonoids (Rouseff, Martin, & Youtsey, 1987). Based on the Phenol-Explorer database (Neveu et al., 2010), one glass of orange juice (150 ml) contains about 90-mg flavanone glycosides that have the highest bioavailability among the flavonoid compounds (Manach, Williamson, Morand, Scalbert, & Remesy, 2005). Approximately 90% of the flavanone glycosides found in orange juice are represented by hesperidin (3 hesperetin-7-rhamnoglucoside) that is mostly found in the solid parts and the membranes separating the pulp segments of the citrus fruits (Tomás-Barberán & Clifford, 2000).

A number of animal studies that have evaluated the cardioprotective role of hesperidin have shown its beneficial effects on CVD risk factors (Selvaraj & Pugalendi, 2010; Yamamoto, Suzuki, & Hase, 2008), whereas their findings are in contrast with some human investigations. Emerging research suggests that the consumption of orange juice or purified hesperidin might significantly cause a reduction in blood pressure and serum lipids (Haidari et al., 2015; Homayouni, Haidari, Hedayati, Zakerkish, & Ahmadi, 2018; Morand et al., 2011). On the other hand, some studies have shown that hesperidin supplementation does not significantly affect blood pressure and lipid profile (Demonty et al., 2010; Rizza et al., 2011).

The present study was designed and conducted, because no systematic review and meta-analysis has ever been conducted to study the cardioprotective effect of hesperidin as a major flavonoid found in citrus species on cardiovascular risk factors such as hypertension and dyslipidemia in humans.

2 | METHODS

The preferred reporting items for systematic reviews and meta-analyses guidelines (Knobloch, Yoon, & Vogt, 2011) were considered during implementation, analysis, and reporting of the present meta-analysis. The study protocol was registered in the prospective register of systematic reviews database (registration code: CRD42017058191; Mohammadi, Salehi-abargouei, Ramezani-Jolfaie, & Zarei, 2017).

2.1 | Search strategy

The relevant articles were identified by searching PubMed (www.pubmed.com), Scopus (http://www.scopus.com), ISI Web of Science (www.webofknowledge.com), and Google Scholar (www.scholar.google.com) up to May 2018. No restrictions were set in our literature search. Three groups of medical subject headings (MeSH) and non-MeSH keywords were selected to search the online databases, as follows; *Keywords group 1*: "hesperidin," "hesperitin," "citrus flavonoid," "orange juice"; *Keywords group 2*: "intervention," "trial," "randomized," "random," "randomly," "placebo," "assignment," "clinical trial," "RCT," "cross-over," "parallel," "blood pressure," "BP," "diastolic pressure," "systolic pressure," "pulse pressure," "hypertension," "arterial pressure," "arterial tension," "systolic blood pressure," "diastolic blood pressure," "SBP," "DBP," "MAP," "arterial blood pressure," "aortic plus pressure," "aortic pressure," "aortic tension," "systolic arterial pressure," "lipid profile," "lipoproteins," "HDL," "high density lipoproteins," "LDL," "low density lipoproteins," "TG," "triglycerides," "CH," "cholesterol." *Keywords group 3* consisted of terms that were combined by utilizing the "NOT" Boolean: "mouse," "mice," "rats," "in vitro," "pig," "rabbit," "rooster," "cell," "cow." We also searched additional studies by checking the reference lists of relevant articles.

2.2 | Study eligibility criteria

The Patient/Population, Intervention, Comparison, Outcome, Study types for this systematic review are described in Table 1. The original investigations were considered for inclusion if their design was randomized controlled trial (RCT) and were performed in human adults. To be included, the trial should have reported the effects of hesperidin on blood lipids (total cholesterol [TC], low-density lipoprotein cholesterol [LDL cholesterol], and high-density lipoprotein cholesterol [HDL] cholesterol), and triglyceride (TG), and blood pressure (systolic [SBP] and diastolic [DBP]) as primary or secondary outcomes. We excluded studies that met any of the following criteria: studies not published in English, studies with the duration of lower than 2 weeks, trials in which the difference between the intervention and the control group was other components in addition to hesperidin, studies did not report the outcomes of interest, and studies that reported duplicate data. In the case of several publications with the same data set, only the study with more complete data was selected. Two of the authors (M. M. and N. R. J.) independently screened the titles and abstracts. Any discrepancy between the authors was discussed with other authors (A. S. A. and Y. K., E. L.) until consensus was reached.

2.3 | Data extraction

The data extracting process was completed by two independent reviewers (Y. K. and M. M.). Disagreements were primarily resolved through discussion to reach a consensus and if no resolution was found, a third investigator (A. S. A.), who was responsible for verification and cross-checking the process, was contacted. We recorded the following information about each study: the last name of the first author, the year of publication, the country in which the study was implemented, the design of the study (crossover or parallel), the use of run-in or washout periods (which was mentioned only for descriptive purposes), the treatment period, the mean/range of participants' age, the number of participants who completed the follow-up period, participants' gender, the amount of hesperidin used for supplementation, the kind of diet or any other intervention carried out in the

TABLE 1 The Patient/Population, Intervention, Comparison, Outcome, Study types (PICOS) criteria

Criteria	Description
Population	Adults aged >18 years
Intervention	Hesperidin supplement, high dose of hesperidin supplementation
Comparison	Placebo capsule (cellulose, starch, and low dose of hesperidin), low dose of hesperidin supplementation
Outcome	total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglyceride, systolic blood pressure, and diastolic blood pressure
Study types	Randomized controlled clinical trials

control group, and the outcome measures. The corresponding authors of eligible studies were contacted to obtain the data that were missed from the papers.

2.4 | Risk of bias assessment

The Cochrane collaboration's risk of bias assessment tool was used to judge the risk of bias for each included study according to the following domains (Higgins & Green, 2011): 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), and selective reporting (reporting bias). Each domain was judged as "low risk of bias," "high risk of bias," or "unclear risk of bias." The overall quality of studies was eventually classified as good (low risk for more than three domains), fair (low risk for three domains), and poor (low risk for less than three domains).

We also evaluated the overall quality of the present meta-analysis using the Nutrigrade scoring system (Higgins & Green, 2011). It was done using a quality control checklist (max 10 points) which considers the following characteristics for each meta-analysis: risk of bias/study quality/study limitations (3 point), precision (1 point), heterogeneity (1 point), directness (1 point), funding bias (1 point), publication bias (1 point), and study design (2 point). This scoring system suggests four categories for the quality of meta-evidence: high (≥8 points), moderate (6–7.99 points), low (4–5.99 points), and very low (≤3.99 points).

2.5 | Statistical analysis

The main outcomes of the meta-analysis were the mean difference in change values from baseline in blood lipids (TC, LDL cholesterol, HDL cholesterol, and TG) and blood pressure between the intervention and the comparison groups. If the studies did not report the change values, the baseline and final mean values and their standard deviations (SDs) were extracted and the SD of mean changes was calculated using correlation coefficient of 0.5. We also conducted the meta-analysis by using $r = 0.2$ and $r = 0.8$ to check if the overall effects were sensitive to selected correlation coefficient.

The random effects model was incorporated to calculate the weighted mean difference (WMD) and its corresponding 95% confidence interval (CI). Statistical heterogeneity between included studies was estimated using Cochran's Q test and I^2 statistic (J. Higgins & Thompson, 2002). Substantial heterogeneity exists when I^2 exceeds 50% or p value for the Cochran's Q test was <0.05 (J. P. Higgins, Thompson, Deeks, & Altman, 2003). We also used subgroup analysis to detect probable sources of between-study heterogeneity. Meta-regressions were performed to evaluate outcomes in relation to prespecified factors such as the intervention dose and duration of hesperidin supplementation. Sensitivity analyses were performed to specify robustness of the combined effects by sequentially removing individual studies from the meta-analysis and recalculation of the effect size with the remaining trials (Egger, Davey-Smith, & Altman, 2008). To detect the potential publication bias, Egger's regression asymmetry test and Begg's adjusted rank correlation test were used; furthermore, the publication bias was checked by visual inspection of funnel plots (Egger, Smith, Schneider, & Minder, 1997). All of the analyses were performed using STATA software, version 11.2 (Stata Corp, College Station, TX). Two-tailed p values equal or less than 0.05 were considered as statistically significant.

3 | RESULTS

3.1 | Study selection

As shown in Figure 1, the online literature search identified 3,724 publications and manual searching identified one additional article, of which 1,201 were duplicates and a total of 2,524 articles remained for title and abstract screening. We included 26 articles for reading their full text after screening the titles and abstracts; of these, 16 articles were excluded for the following reasons: nine studies had interventions using other components in addition to hesperidin and the difference of interventions between the study groups was not only in hesperidin (Aptekmann & Cesar, 2010; Asgary, Keshvari, Afshani, & Amiri, 2014; Buscemi et al., 2012; Constans et al., 2015; Devaraj, Jialal, & Vega-Lopez, 2004; Goncalves et al., 2017; Linnebur, Capell, Saseen, Wolfe, & Eckel, 2007; Ribeiro, Dourado, & Cesar, 2017; Simpson, Mendis, & Macdonald, 2016); two studies were less than 2 weeks in duration (Lamport et al., 2016; Schaer et al., 2015); two articles were published in languages other than English (Hanawa et al., 2008; Tanaka et al., 2010); two studies did not report the outcomes of interest (Homayouni, Haidari, Hedayati, Zakerkish, & Ahmadi, 2017; Milenkovic, Deval, Dubray, Mazur, & Morand, 2011); and one article included a duplicate population (Miwa et al., 2005) from another included study (Miwa et al., 2004). In overall, 10 studies with a total of 577 subjects were included in the present systematic

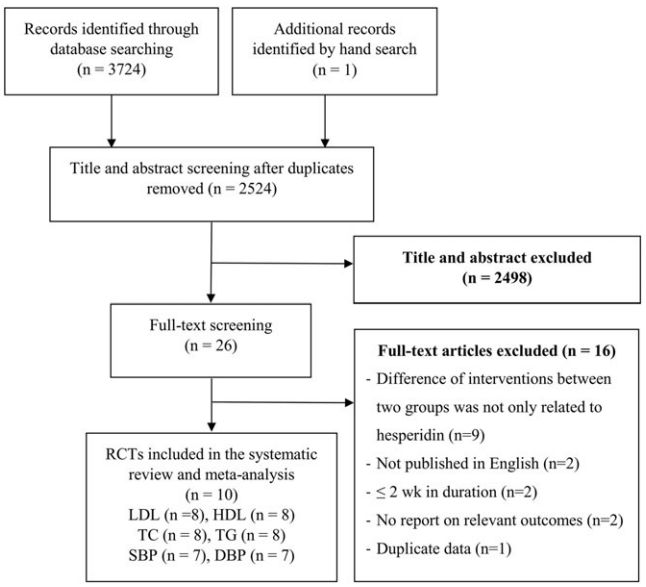

FIGURE 1 Flowchart of the study selection process. DBP: diastolic blood pressure; HDL: high-density lipoprotein; LDL: low-density lipoprotein; RCTs: randomized controlled trials; SBP: systolic blood pressure; TC: total cholesterol; TG: triglyceride

review (Demonty et al., 2010; Haidari et al., 2015; Homayouni et al., 2018; Kean et al., 2015; Miwa et al., 2004; Morand et al., 2011; Ohara, Muroyama, Yamamoto, & Murosaki, 2016; Rangel-Huerta et al., 2015; Rizza et al., 2011; Salden et al., 2016). Eight trials (including 476 participants) reported the effect of hesperidin on lipid profile and seven trials (including 392 participants) reported the effect on blood pressure.

3.2 | Characteristics of included trials

All of the included studies were RCTs published between 2004 and 2018, of which six studies had a parallel design (Demonty et al., 2010; Haidari et al., 2015; Homayouni et al., 2018; Miwa et al., 2004; Ohara et al., 2016; Salden et al., 2016), whereas the remaining studies were crossover RCTs (Kean et al., 2015; Morand et al., 2011; Rangel-Huerta et al., 2015; Rizza et al., 2011). Four studies were conducted in Asian populations (Haidari et al., 2015; Homayouni et al., 2018; Miwa et al., 2004; Ohara et al., 2016), and others were done in the European countries (Demonty et al., 2010; Kean et al., 2015; Morand et al., 2011; Rangel-Huerta et al., 2015; Rizza et al., 2011; Salden et al., 2016). The duration of the studies ranged from 3 to 12 weeks. In the majority of included studies (Demonty et al., 2010; Haidari et al., 2015; Homayouni et al., 2018; Morand et al., 2011; Ohara et al., 2016; Rizza et al., 2011; Salden et al., 2016), a range of 292–800 mg/day hesperidin was used for the intervention group and a placebo that was similar in its appearance (starch or cellulose) was provided for the control group. Two trials (Kean et al., 2015; Rangel-Huerta et al., 2015) were conducted with the use of juice containing high polyphenol concentration (549- to 582-mg hesperidin) for interventions and normal/low polyphenol concentration (64- to 237-mg hesperidin) for controls. One trial (Miwa et al., 2004) also administered high dose of hesperidin (500 mg/day) in the intervention group and low dose of hesperidin (100 mg/day) in the control group. Five studies were conducted in healthy overweight/obese individuals (Kean et al., 2015; Morand et al., 2011; Ohara et al., 2016; Rangel-Huerta et al., 2015; Salden et al., 2016), two studies were conducted in patients with diabetes (Homayouni et al., 2018) or metabolic syndrome (Rizza et al., 2011), one study in those with myocardial infarction (Haidari et al., 2015), and two studies in patients with dyslipidemia (Demonty et al., 2010; Miwa et al., 2004). The age of the participants ranged from 18 to 81 years, with an approximately equal distribution of male and female subjects. A summary of the study characteristics is provided in Table 2.

3.3 | Risk of bias assessment

Half of RCTs included in the present study were classified as good quality (Homayouni et al., 2018; Kean et al., 2015; Morand et al., 2011; Rangel-Huerta et al., 2015; Salden et al., 2016) and others were categorized as "fair" (Demonty et al., 2010; Haidari et al., 2015; Ohara et al., 2016) and "poor" (Miwa et al., 2004; Rizza et al., 2011) in their quality. All of the trials were categorized as low risk of bias for selective outcome reporting. The majority of the trials had a low risk of bias for blinding of participants and personnel. Incomplete outcome data were addressed in approximately two third of studies (Demonty et al., 2010; Homayouni et al., 2018; Kean et al., 2015; Morand et al., 2011; Ohara et al., 2016; Rangel-Huerta et al., 2015; Salden et al., 2016). In seven trials, the blinding of outcome assessment was unclear (Demonty et al., 2010; Haidari et al., 2015; Homayouni et al., 2018; Miwa et al., 2004; Ohara et al., 2016; Rangel-Huerta et al., 2015; Rizza et al., 2011). Although all of the studies were randomized, a number of them did not mention the randomization method (Demonty et al., 2010; Miwa et al., 2004; Ohara et al., 2016; Rizza et al., 2011). All but one of the included studies done by Homayouni et al. (2018) had no descriptions of allocation concealment. The details of the risk of bias assessment in individual studies are shown in Table 3 .

3.4 | Meta-analysis

3.4.1 | The effect of hesperidin on blood lipids

Meta-analysis of eight trials (Demonty et al., 2010; Haidari et al., 2015; Miwa et al., 2004; Morand et al., 2011; Ohara et al., 2016; Rangel-Huerta et al., 2015; Rizza et al., 2011; Salden et al., 2016) that reported the effect of hesperidin supplementation on blood lipids showed no significant difference in the concentrations of TC (WMD = −1.04 mg/dl, 95% CI [−5.65, 3.57], p = 0.658; Figure 2a), LDL (WMD = −1.96 mg/dl, 95% CI [−7.56, 3.64], p = 0.492; Figure 2 b), HDL (WMD = 0.16 mg/dl, 95% CI [−1.94, 2.28], p = 0.877; Figure 2c), and TG (WMD = 0.69 mg/dl, 95% CI [−5.91, 7.30], p = 0.837; Figure 2d) compared with placebo. There was no evidence of significant between-study heterogeneity (Cochran Q test, p = 0.535, I^2 = 0% for TC; Cochran Q test, p = 0.378, I^2 = 6.8% for LDL; Cochran Q test, p = 0.244, I^2 = 23.2%, for HDL; Cochran Q test, p = 0.988, I^2 = 0% for TG) in all meta-analyses. We also performed several subgroup analyses to further explore the possible different effects of hesperidin supplementation-based follow-up period (≤4/ >4 weeks), study design (parallel/crossover), type of supplement used for control group/period (cellulose or starch/low or normal hesperidin), baseline health status of the participants (healthy/cardiometabolic disorders), and study quality (good/fair/poor). However, no beneficial effect of hesperidin supplementation on blood lipids was observed in the subgroups. The pooled effects of hesperidin on blood lipids as well as subgroup analyses are summarized in Table S1.

3.4.2 | The effect of hesperidin on blood pressure

Seven studies provided data on the comparison of mean changes in SBP and DBP from baseline between the hesperidin supplementation and the control group (Haidari et al., 2015; Homayouni et al., 2018; Kean et al., 2015; Morand et al., 2011; Rangel-Huerta et al., 2015; Rizza et al., 2011; Salden et al., 2016). Two effect sizes were calculated for a study done by Kean et al. (2015), in which the results were reported for males and females, separately. With the use of random effects model, the pooled results indicated that hesperidin supplementation had no significant effect on SBP (WMD = −0.85 mmHg, 95% CI [−3.07, 1.36], p = 0.452; Figure 3a) and DBP (WMD = −0.48 mmHg, 95% CI [−2.39, 1.42], p = 0.619; Figure 3b). No considerable

TABLE 2 Characteristics of randomized clinical trials that were included in the systematic review

Study and year	Country	Number, sex (F/M)	Age (year)	RCT design	Duration (weeks)	Intervention group	Control group	Reported outcomes	Notes about participants
Homayouni et al. (2018)	Iran	60 (32F/28M)	30–65 int: 51.3 con: 54	Parallel	6	500 mg/day hesperidin	500 mg/day starch	SBP, DBP	Patients with diabetes
Salden et al. (2016)	Dutch	68 (39F/29M)	18–65 int: 54 con: 53	Parallel	6	450 mg/day hesperidin	500 mg/day cellulose	LDL, HDL TG, TC SBP, DBP	Healthy overweight individuals
Ohara et al. (2016)	Japan	29 (15F/14M)	20–65 int: 49 con: 49.4	Parallel	12	500 mg/day hesperidin	Placebo	LDL, HDL TG, TC	Healthy moderately obese individuals
Haidari et al. (2015)	Iran	75 (22F/53M)	40–65	Parallel	4	600 mg/day hesperidin	600 mg/day starch	LDL, HDL TG, TC SBP, DBP	Patients with myocardial infarction
Kean et al. (2015)	England	41 (14F/27M)	60–81	Cross-over	8	500 ml/day high flavanone orange juice hesperidin: 549 mg	500 ml/day low flavanone orange juice hesperidin: 64 mg	SBP, DBP	Healthy moderately overweight individuals
Rangel-Huerta et al. (2015)	Spain	100 F/M	18–65	Cross-over	12	500 ml/day high polyphenol juice hesperidin: 582.5 mg	500 ml/day normal polyphenol juice hesperidin: 237 mg	LDL, HDL TG, TC SBP, DBP	Healthy overweight/obese individuals
Morand et al. (2011)	France	24 (24 M)	50–65	Cross-over	4	500 ml of the control drink +292 mg hesperidin	500 ml of the control drink +292 mg starch	LDL, HDL TG, TC SBP, DBP	Healthy overweight individuals
Rizza et al. (2011)	Italy	24 (9F/15M)	21–65 int: 53 con: 50	Cross-over	3	500 mg/day hesperidin	500 mg/day cellulose	LDL, HDL TG, TC SBP, DBP	Patients with metabolic syndrome
Demonty et al. (2010)	Netherland	124 (59F/65M)	18–75 int: 61 con:60.1	Parallel	4	800 mg/day hesperidin	800 mg/day cellulose	LDL, HDL TG, TC	Moderately hypercholesterolemic subjects
Miwa et al. (2004)	Japan	32 (32 M)	27–64 int: 43.6 con: 43.8	Parallel	6	500 mg/day hesperidin	100 mg/day hesperidin	LDL, HDL TG, TC	Hyperlipidemic subjects

Note. Con: control; DBP: diastolic blood pressure; F: female; HDL: high-density lipoprotein; Int: intervention; LDL: low-density lipoprotein; M: male; RCT: randomized controlled trial; SBP: systolic blood pressure; TC: total cholesterol; TG: triglyceride.

TABLE 3 Risk of bias assessment according to the Cochrane collaboration's risk of bias assessment tool

Study and year	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Overall quality
Homayouni et al. (2018)	Low	Low	Low	Unclear	Low	Low	Good
Salden et al. (2016)	Low	Unclear	Low	Low	Low	Low	Good
Ohara et al. (2016)	Unclear	Unclear	Low	Unclear	Low	Low	Fair
Haidari et al. (2015)	Low	Unclear	Low	Unclear	Unclear	Low	Fair
Kean et al. (2015)	Low	Unclear	Low	Low	Low	Low	Good
Rangel-Huerta et al. (2015)	Low	Unclear	Low	Unclear	Low	Low	Good
Morand et al. (2011)	Low	Unclear	Low	Low	Low	Low	Good
Rizza et al. (2011)	Unclear	Unclear	Low	Unclear	Unclear	Low	Poor
Demonty et al. (2010)	Unclear	Unclear	Low	Unclear	Low	Low	Fair
Miwa et al. (2004)	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Poor

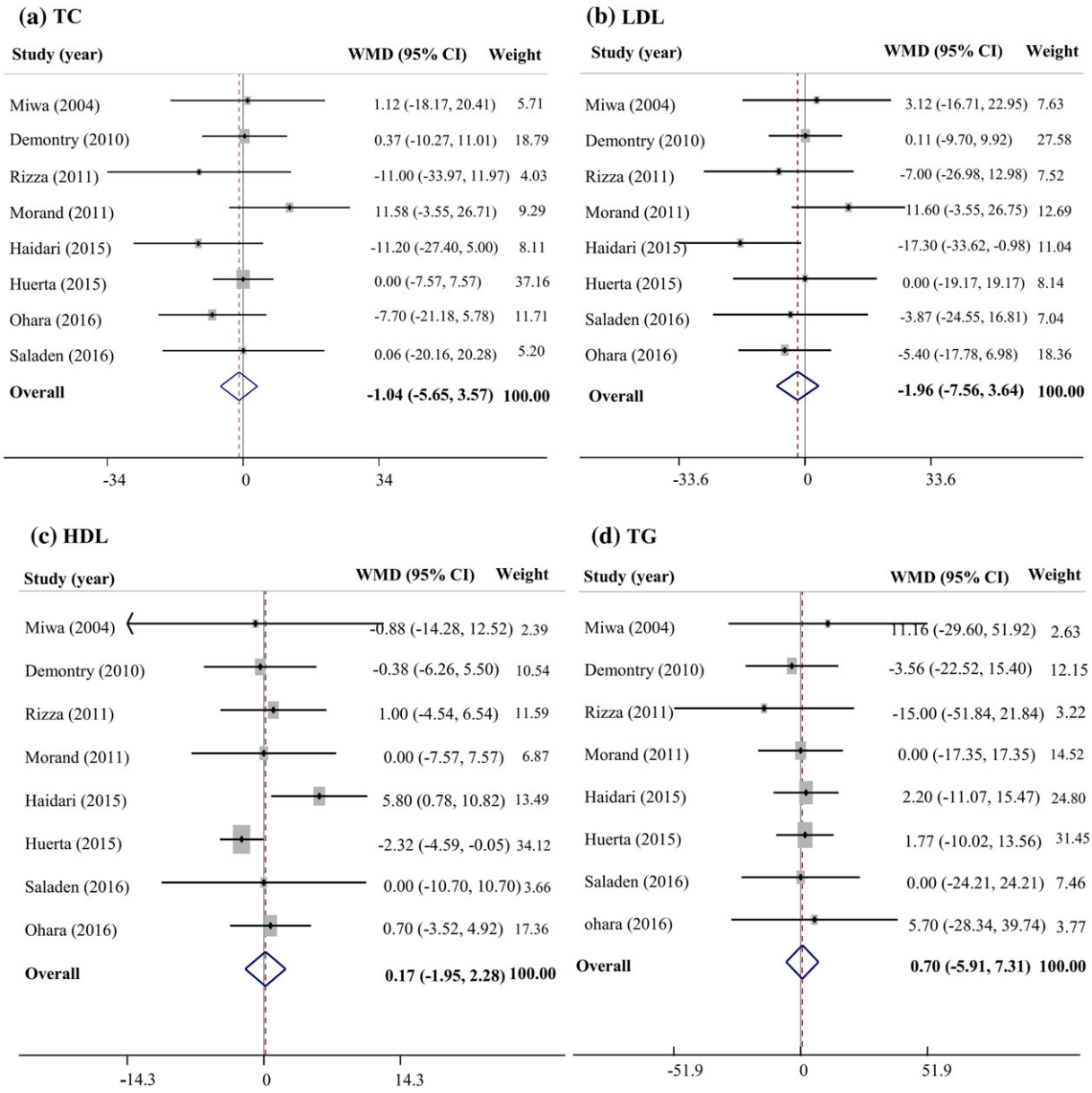

FIGURE 2 Forest plots from the meta-analysis of clinical trials investigating the effects of hesperidin supplementation on (a) total cholesterol (TC), (b) low-density lipoprotein (LDL), (c) high-density lipoprotein (HDL), and (d) triglyceride (TG). WMD: weighted mean difference [Colour figure can be viewed at wileyonlinelibrary.com]

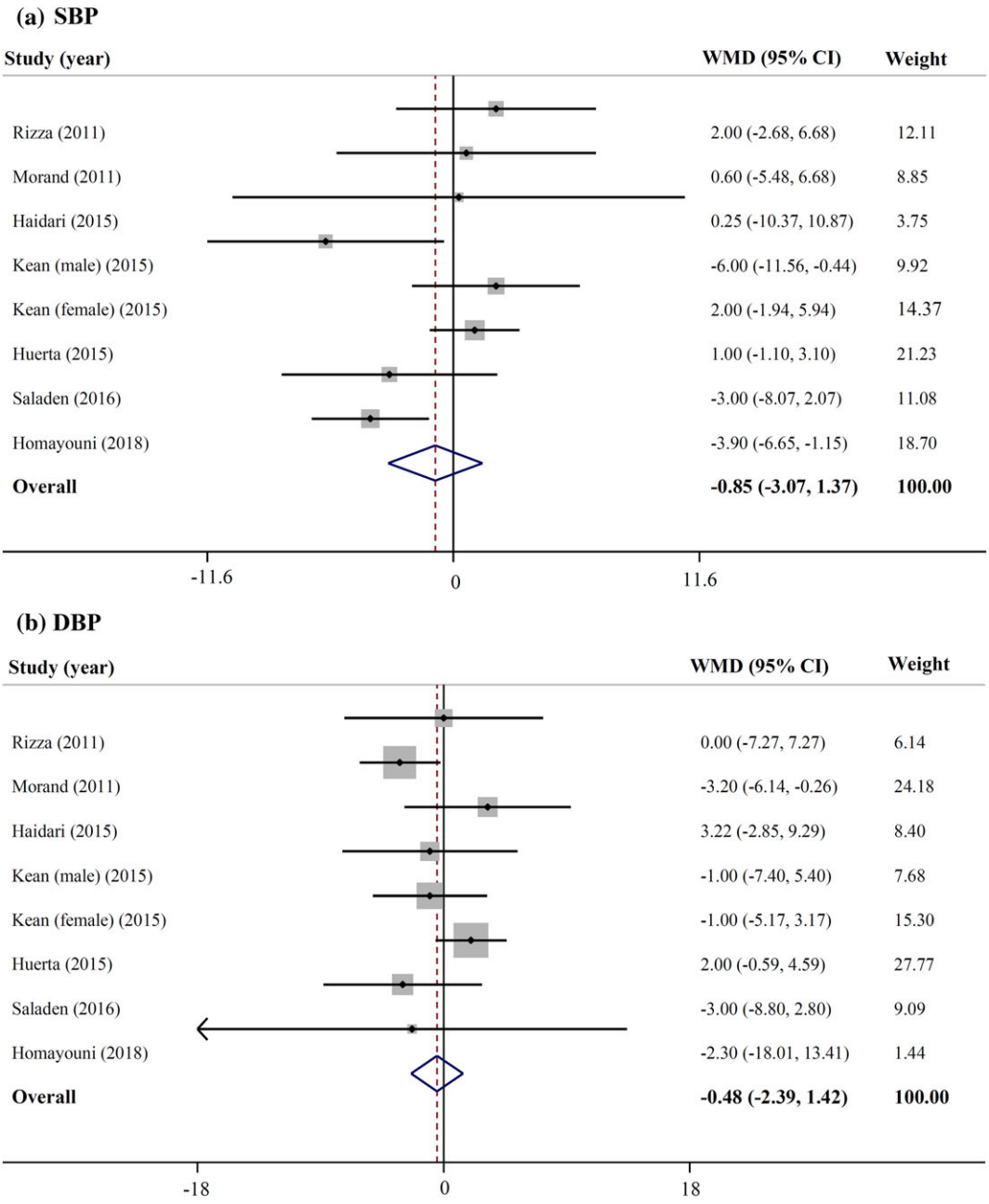

FIGURE 3 Forest plots from the meta-analysis of clinical trials investigating the effects of hesperidin supplementation on (a) systolic blood pressure and (b) diastolic blood pressure. WMD: weighted mean difference [Colour figure can be viewed at wileyonlinelibrary.com]

heterogeneity was shown in the trials for DBP (Cochran *Q* test, $p = 0.245$, $I^2 = 23.1\%$), but for SBP, there was a significant between-study heterogeneity (I^2 Cochran *Q* test, $p = 0.033$, $I^2 = 54.2\%$), which was explained by the study design. The results of subgroup analysis showed that in trials with parallel design, hesperidin supplementation significantly reduced SBP compared with control groups (WMD = −3.50 mmHg, 95% CI [−5.85, −1.14], $p = 0.004$), but there was no significant change when the analysis was done on the cross-over RCTs (WMD = 0.41 mmHg, 95% CI [−1.88, 2.72], $p = 0.722$). The I^2 values for the analyses of parallel and crossover studies were $I^2 = 0\%$ and $I^2 = 37.2\%$, respectively. Analyses of other subgroups, including study duration, type of the supplement used for the control group/period, baseline health status, and study quality, showed no significant differences between subgroups regarding both SBP and DBP. The pooled effects of hesperidin on blood pressure as well as subgroup analyses are summarized in Table S2.

3.4.3 | Publication bias and sensitivity analysis

In sensitivity analyses, the pooled effects of hesperidin supplementation on lipid profile and blood pressure did not change after dropping each trial out of the analyses, indicating robustness of the findings. The meta-analyses were also not sensitive to correlation coefficients selected to calculate the change values.

There was no evidence of publication bias for any of the meta-analyses after considering funnel plots (Figure S1) as well as Begg's and Egger's asymmetry tests: TC (Begg's test, $p = 0.266$; Egger's test, $p = 0.592$), LDL (Begg's test, $p = 0.902$; Egger's test, $p = 0.917$), HDL

(Begg's test, p = 0.386; Egger's test, p = 0.239), TG (Begg's test, p = 0.902; Egger's test, p = 0.689), SBP (Begg's test, p = 0.386; Egger's test, p = 0.741), and DBP (Begg's test, p = 0.902; Egger's test, p = 0.801).

3.4.4 | Meta-regression

Meta-regression analyses showed that the intervention duration (β = −0.158, p = 0.803 for TC; β = −0.182, p = 0.849 for LDL; β = −0.359, p = 0.164 for HDL; β = 0.273, p = 0.777 for TG; β = 0.076, p = 0.864 for SBP; and β = 0.471, p = 0.079 for DBP) and hesperidin dose (β = −0.015, p = 0.466 for TC; β = −0.015, p = 0.439 for LDL; β = 0.009, p = 0.254 for HDL; β = −0.006, p = 0.765 for TG; β = −0.01, p = 0.467 for SBP; and β = 0.008, p = 0.499 for DBP) were not significantly related to effect of hesperidin supplementation on blood lipids and blood pressure.

3.4.5 | Overall quality of meta-analyses

The overall quality of the meta-analysis that were assessed using the NutriGrade scoring system resulted in 6.2 for lipid profile, 6.3 for SBP, and 6.4 for DBP, which shows a moderate confidence for effects provided in the current analysis; which shows future well-designed clinical trials are still needed to confirm our results.

4 | DISCUSSION

To the best of our knowledge, the current systematic review and meta-analysis examined the efficacy of hesperidin supplementation on cardiometabolic risk factors including lipid profile and blood pressure, for the first time. Our meta-analysis results showed that hesperidin intake is not associated with significant changes in blood pressure and lipids. The overall effects were robust in sensitivity analyses.

Although our meta-analysis revealed that hesperidin had no effect on cardiometabolic markers, previous reviews have advocated for effective roles of hesperidin in this regard (Amiot, Riva, & Vinet, 2016; Assini, Mulvihill, & Huff, 2013; Mulvihill, Burke, & Huff, 2016; Mulvihill & Huff, 2012). A recent systematic review on the association between dietary polyphenols and metabolic syndrome suggested that hesperidin might improve the lipid metabolism (Amiot et al., 2016). Furthermore, a number of other reviews bringing together human and animal studies proposed that hesperidin might be effective in lowering blood lipids (Assini et al., 2013; Mulvihill et al., 2016; Mulvihill & Huff, 2012). However, these reviews did not use meta-analysis to assess the consistency of the results, and so their findings cannot be conclusive. Several meta-analyses investigating the effect of other flavonoids such as resveratrol, quercetin, and curcumin on cardiometabolic factors also showed that the supplementation of these compounds might not affect lipid profile (Haghighatdoost & Hariri, 2018; Sahebkar, 2014, 2017); however, a review revealed that the flavonoid quercetin significantly reduces blood pressure (Serban et al., 2016).

Given our findings, the proposed cardioprotective effects of hesperidin (Rizza et al., 2011; Salden et al., 2016) cannot be attributed to any impact of this flavonoid on lipid profile and blood pressure. On the other hand, the absence of a lipid and blood pressure-lowering effect of hesperidin cannot be associated to the doses administered to participants, because a wide range of dosages (between 292 and 800 mg/day) has been used in the included studies. Moreover, there was no significant influence of duration of hesperidin supplementation on the extent of changes in plasma lipid levels and blood pressure. The included studies in the present meta-analysis suggested that about 3–12 weeks is needed to observe, if any, a full lipid lowering effect. Indeed, a duration of 3–4 weeks is usually needed to create a new steady state that regulates the cholesterol metabolism and stabilization of plasma cholesterol values (Kris-Etherton & Dietschy, 1997; Weststrate & Meijer, 1998).

The evidence provided by animal models (mainly mice and rats) have shown that hesperidin plays cardioprotective role through multiple mechanisms. These include antilipid peroxidation and antioxidant properties (Selvaraj & Pugalendi, 2010), the inhibition of 3-hydroxy-3-methylglutaryl coenzyme A reductase (Bok et al., 1999), lowering the blood pressure (Yamamoto et al., 2008), the suppression of pancreatic lipase (Kawaguchi, Mizuno, Aida, & Uchino, 1997), antiplatelet effects (Ogoshi, Inoue, Naruse, & Takei, 2006), ameliorating endothelial dysfunction (Yamamoto, Suzuki, Jokura, Yamamoto, & Hase, 2008), improving hyperlipidemia (Liu et al., 2014), inhibition of coronary constriction (Liu et al., 2014), and attenuation of proinflammatory cytokine (Mahmoud, Ashour, Abdel-Moneim, & Ahmed, 2012); however, it should be mentioned that the lipid metabolism in rats and mice is obviously different from that in humans. Therefore, any interpretation of information from animal studies should be done with caution and verified by relevant clinical trials. In addition, the cardioprotective properties of hesperidin in animal models have been observed in the doses between 100 and 400 mg/kg (Selvaraj & Pugalendi, 2012), which is much higher than the doses used in the included clinical trials.

Several hypotheses might explain why hesperidin lacks any significant effect on serum lipid profile and blood pressure. A reason for these findings could be explained by the limited bioavailability of hesperidin, because the colon flora likely converts a large proportion of hesperidin into insoluble compounds (chalcones; Gil-Izquierdo, Gil, Ferreres, & Tomas-Barberan, 2001). For instance, one study showed that hesperidin metabolites appeared in plasma 3 hr after consuming 440 mg of hesperidin supplement and reached to the peak level after 5–7 hr of administration, which this peak can provide 1.28 mmol/L aglycone hesperetin equivalent (Manach, Morand, Gil-Izquierdo, Bouteloup-Demange, & Remesy, 2003). Therefore, it might be possible that hesperidin does not reach the sufficient concentrations that are needed for the regulation of blood pressure and lipid metabolism, in the plasma. Moreover, the homeostatic responses of the body that can partially or completely compensate the lipid-lowering effect of hesperidin might also explain not finding the effect (Demonty et al., 2010). However, the effects reported on key steps of cholesterol metabolism in animal and in vitro studies, such as decrement in the hepatic 3-hydroxy-3-methylglutaryl coenzyme A reductase and acyl CoA: cholesterol acyltransferase activities, show that the hypothesis of the presence of compensation mechanisms might not be true (Borradaile, Carroll, & Kurowska, 1999; Huong, Takahashi, & Ide, 2006; Jung, Lee, Park, Kang, & Choi, 2006; Wilcox, Borradaile, de Dreu, & Huff, 2001).

There are limitations in this meta-analysis that are in part due to inherent drawbacks of clinical trials. The included trials were heterogeneous regarding the design of the studies, included population, hesperidin dosage, number of participants, and follow-up period. We tried to check the possible effect of these differences, by conducting several subgroup analyses. Moreover, we could not perform subgroup analysis based on the subject's age, because some included studies in our meta-analysis did not reported mean age of participants. Furthermore, the studies had not evaluated the bioavailability of hesperidin, and therefore, the precise concentrations of hesperidin available in the blood after ingestion are not specified. In addition, the measurement of hesperidin and their metabolites in plasma might help in determining the compliance to the intervention protocol by the participants.

In conclusion, the results of this study suggest that hesperidin supplementation has no significant beneficial effects on blood pressure and serum concentrations of blood lipids including TC, LDL cholesterol, HDL cholesterol, and TG in adults. However, the findings should be interpreted with caution due to limited number of studies and further well-designed clinical trials, particularly in patients with dyslipidemia or hypertension, are warranted to ultimately assess the effectiveness of this flavonoid.

CONFLICTS OF INTEREST

There is no conflict of interest to report for this study.

AUTHORS' CONTRIBUTIONS

The authors' responsibilities were as follows: A. S. A., M. M., and N. R. J. developed the study concept and designed the research; M. M. and N. R. J. conducted the electronic searches and study selection; Y. K., M. M., and N. R. J. conducted data extraction and tabulated data; A S. A. and M. M. conducted the data analysis and interpretation of results; M. M., N. R. J., and E L. wrote the first draft of the manuscript; A. S. A. performed the critical review and revised the manuscript; and all authors read and approved the final version.

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ORCID

Amin Salehi-Abargouei https://orcid.org/0000-0002-7580-6717

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SUPPORTING INFORMATION

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

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