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Effects of Hesperidin Supplementation on Anthropometric Indices in Adults: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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SYSTEMATIC REVIEW and META_ANALYSIS

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ABSTRACT

Background: Although some studies have reported that flavonoids can be associated with anti-obesity effects, the putative effects of hesperidin, as a subgroup of flavonoids, on anthropometric parameters are inconclusive. Therefore, this systematic review and meta-analysis of randomized controlled trials (RCTs) was conducted to determine the effect of hesperidin supplementation on anthropometric measures in adults. **Methods:** A comprehensive literature search was performed until February 2022 in electronic databases such as PubMed, Scopus, Web of Science, and Google Scholar. The pooled results were obtained by a random-effects model. **Results:** A total of nine RCTs enrolling 493 participants were identified. Seven studies had illustrated the effect of hesperidin on weight, eight on body mass index (BMI), five on waist circumference (WC), two on waist to hip ratio (WHR), and two on hip circumference (HC). The results of the pooled analysis showed no significant changes in body weight (0.01 kg, 95% CI: -0.22, 0.24), BMI (-0.02 kg/m^2, 95% CI: -0.16, 0.13), and WC (-0.48 cm, 95% CI: -1.52, 0.55) after hesperidin supplementation compared to the control group ($P > 0.05$). Qualitative assessment of other anthropometric indices also showed no beneficial effect of hesperidin in reducing WHR and HC values; however, these findings are not conclusive because of the limited number of studies. **Conclusion:** The present study provides no evidence that hesperidin supplementation is effective in improving anthropometric measures. More high-quality RCTs especially among overweight and obese individuals are needed to strengthen the evidence.

Keywords: *Hesperidin; Body weight; Anthropometry; Systematic review; Meta-analysis*

Introduction

As a complex and chronic medical condition, obesity is a worldwide health problem (Thomas *et al.*, 2014) and it is a cluster of complications such as impaired glucose tolerance,

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dyslipidemia, hypertension, and systemic inflammation (Stoner and Cornwall, 2014). It is also a leading cause of extensive morbidity and mortality with a high economic burden in both developing and developed nations (Lehnert *et al.*, 2013, Ng *et al.*, 2014). Obesity is one of the direct sources for progression or occurrence of various diseases such as cardiovascular diseases (Mandviwala *et al.*, 2016), insulin resistance and diabetes (Genser *et al.*, 2016), non-alcoholic fatty liver disease (Li *et al.*, 2016), gallstone disease and pancreatitis (Bonfrate *et al.*, 2014), esophageal reflux (Khan *et al.*, 2016), inflammatory bowel disease (Harper and Zisman, 2016), chronic kidney disease (Briffa *et al.*, 2013), poly ovary syndrome (Orio *et al.*, 2016), neurological diseases (Martin-Jiménez *et al.*, 2017), and different types of cancer (Donohoe *et al.*, 2017). It has been reported that the prevalence of overweight and obesity has been growing from 29% to 38% in the past three decades (Ng *et al.*, 2014). Recent reports from World Health Organization in 2016 have suggested that 1.9 billion people are overweight, of whom 650 million are considered to be obese (World Health Organization, October 2017).

Different weight management strategies have been used throughout the years, including dietary regimen approaches or dietary constituents with anti-obesity potentials (Tuomilehto *et al.*, 2001). However, some of the traditional recommendations have been proved to be impractical and disappointing due to poor attendance and adherence rates (Butryn *et al.*, 2011, Huisman *et al.*, 2010, Zuckoff, 2012). Thus, novel strategies are desperately needed to be suggested as more effective ways to get rid of excessive fat (Soeliman and Azadbakht, 2014). A variety of weight loss supplements sold under the title of "slimming aids" is already available although the outcome of each remains uncertain (Derosa and Maffioli, 2012, Mousavi *et al.*, 2018, Onakpoya *et al.*, 2011). It has been demonstrated that dietary intake of a widespread group of plant polyphenols known as flavonoids can exert anti-obesity effects; however, enough evidence is not available in this regard (Bertoia *et al.*, 2016). Some trials suggest that a potential effect of polyphenols can reduce body weight by increasing energy expenditure (Barth *et al.*, 2012, Dallas *et al.*, 2014, Most *et al.*, 2014) even though other findings have shown null or contrasting results (Bell *et al.*, 2011, Janssens *et al.*, 2015).

Hesperidin is a flavonone glycoside that along with narirutin is a subgroup of flavonoids that mainly exist in the solid parts of citrus fruits and the membranes separating the pulp segments; this explains why the concentration of these flavonones is higher in whole-fruit juices (Roowi *et al.*, 2009). There is evidence on the cardio-protective effects and anti-inflammatory properties of hesperidin (Amiot *et al.*, 2016, Lorzadeh *et al.*, 2019, Mulvihill *et al.*, 2016). However, some of these results are inconsistent with recent meta-analyses suggesting hesperidin supplementation might not have any impact on lipid profile, blood pressure, and blood glucose control (Mohammadi *et al.*, 2019, Shams-Rad *et al.*, 2020). Although there is still no strong evidence on the association between flavanones and weight loss, some studies have investigated hesperidin as a supplement for obesity management and reported that it may be useful for the prevention or treatment of obesity (Ohara *et al.*, 2016). However, several other studies have not supported these claims (Demonty *et al.*, 2010, Ribeiro *et al.*, 2017, Simpson *et al.*, 2016) . Therefore, this study aims to summarize the available data of randomized controlled clinical trials (RCTs) investigating the effect of hesperidin supplementation on anthropometric parameters in adults.

Materials and Methods

The preferred reporting items of systematic reviews and meta-analysis (PRISMA) statement was followed to design perform and report this systematic review and meta-analysis (Shamseer *et al.*, 2015).

Data sources and search strategy: Medline/Pubmed, Scopus, Web of Science, and Google Scholar were systematically searched from the earliest available online indexing through February 2022. The search was limited to human

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studies, additionally, no language restriction was performed. Two investigators (Ramezani-Jolfaie N and Mohammadi M) independently assessed the relevancy of studies by their title and abstracts as well as full text if needed in the next step. Additionally, the references of selected articles were examined manually for any missing related studies. Three groups of medical subject heading terms (MeSH) and non-MeSH keywords were used in constructing the database search as follows: *group 1*: "hesperidin", "hesperitin", "citrus flavonoid", "orange juice"; *group 2*: "intervention", "trial", "randomized", "random", "randomly", "placebo", "assignment", "clinical trial", "RCT", "cross-over", "parallel", "body weight", weight, "body mass index", BMI, "waist circumference", WC, "waist-hip ratio", WHR, "hip circumference", HC, "fat free mass", FFM, "fat mass", FM, "lean body mass", LBM; *group 3*: "mouse", "mice", "rats", "in vitro", "pig", "rabbit", "rooster", "cell", "cow" that combined by utilizing the "NOT" Boolean operator.

Selection criteria: The Population, Intervention, Comparison, Outcome, and Study types (PICOS) are provided in **Table 1**. The original RCTs were considered for inclusion if they had supplemented hesperidin in human adults. Studies were excluded if they had a short duration of intervention (lower than 2 weeks), were conducted among children/adolescents below 18 years of age, and if they had no control/placebo comparison group or outcomes of interest or reported duplicate data. Studies with interventions containing the other components in addition to the hesperidin were also excluded.

Data extraction: Study details were extracted and recorded independently by two authors (Ramezani-Jolfaie N and Mohammadi M) and in case of any disagreement, a third party (Salehi-Abargouei A) was consulted to reach mutual consensus. The following information of the included RCTs was collected: study design (crossover or parallel), ethnic or country, the last name of each author, year of article publication, subject baseline characteristics (sample size, gender, age, and overall health status), intervention duration, the use of run-in or washout periods, dose of hesperidin intake (mg/day), type of intervention used in the control groups, and the number of participants who completed the follow-up period.

Risk of bias assessment: Risk of bias assessment was conducted against the following key criteria according to the recommendation of the Cochrane Collaboration (Higgins and Green, 2011): random sequence generation; allocation concealment; blinding of participants, personnel and assessors; incomplete outcome data; selective outcome reporting and other sources of bias. Determination of bias level was either low (proper methods taken to reduce bias), high (improper methods resulting in bias), or unclear (either a lack of sufficient information or uncertainty over a potential bias) risk of bias. Six domains were presented as the ('key domains') and used to decide whether each RCT was low risk (low for all key domains), high risk (high for one or more key domains), and unclear risk (unclear for at most one or more key domains). Any discrepancies were resolved by consulting with a third author if necessary (ASA).

Data analysis: The mean change values with their respective standard deviations (SDs) between baseline and end of the study in both treatment and control groups were extracted. If change values were not reported by the studies, the baseline and final mean values with their respective SDs were used to calculate the mean±SD of changes in outcomes by a correlation coefficient of 0.5. Further analyses using r = 0.1 and 0.9 were also performed to check the sensitivity of the findings to the selected correlation coefficient. The random-effects model was used to examine the weighted mean differences (WMDs) and 95% confidence intervals (CIs). To assess the between-study heterogeneity, I^2 statistics and Chi-square were incorporated which considered as significant and high by P-values < 0.05 for Chi-square and I^2 values of more than 50%, respectively. Subgroups analysis was performed according to intervention duration (<8 weeks or >=8 weeks), dosage of hesperidin (<= 500 mg/day or > 500 mg/day), and

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health status of individuals (cardio-metabolic disorders or healthy) to explore the potential sources of heterogeneity. To test the robustness of the meta-analysis results, sensitivity analysis was also conducted by removing one trial at a time and recalculating the overall effects with the remaining studies. Moreover, the visual inspection of the funnel plots represented the possibility of publication bias (Egger *et al.*, 2008). All the analyses were done by STATA software version 13.0 (StataCorp, Texas, USA) for which p-values less than 0.05 were considered statistically significant.

Results

Search results

In general, out of 6118 published articles that initially identified through systematic data search, 2180 were detected as duplicates and 3913 were excluded after title and abstract screening for not meeting the inclusion criteria. A total of 25 articles remained for full text evaluation from which 16 articles were further excluded for the following reasons: (i) did not report the outcomes of interest (n=6) (Cheraghpour *et al.*, 2019, Kean *et al.*, 2015, Martínez-Noguera *et al.*, 2020, Milenkovic *et al.*, 2011, Salden *et al.*, 2016), (ii) had interventions containing other components in addition to hesperidin (n=6) (Rangel-Huerta *et al.*, 2015, Valls *et al.*, 2021a, Valls *et al.*, 2021b, Yari *et al.*, 2021c, Yoshitomi *et al.*, 2021), (iii) had a short duration of intervention (<2 weeks, n=2) (Lamport *et al.*, 2016, Schär *et al.*, 2015), (iv) had no suitable control group (n=1) (Miwa *et al.*, 2004), (v) reported duplicate data (n=1) (Homayouni *et al.*, 2018). Nine studies were finally included in the present systematic review and meta-analysis (Demonty *et al.*, 2010, Eghtesadi *et al.*, 2016, Haidari *et al.*, 2015, Homayouni *et al.*, 2017, Ohara *et al.*, 2016, Rizza *et al.*, 2011, Yari *et al.*, 2021a, Yari *et al.*, 2021b, Yari *et al.*, 2019). Seven out of nine articles have reported data on body weight (Demonty *et al.*, 2010, Eghtesadi *et al.*, 2016, Haidari *et al.*, 2015, Homayouni *et al.*, 2017, Ohara *et al.*, 2016, Yari *et al.*, 2021b, Yari *et al.*, 2019), eight on BMI (Demonty *et al.*, 2010, Eghtesadi *et al.*, 2016, Haidari *et al.*, 2015, Homayouni *et al.*, 2017, Ohara *et al.*, 2016, Rizza *et al.*, 2011, Yari *et al.*, 2021a, Yari *et al.*, 2021b), five on waist circumference (WC) (Haidari *et al.*, 2015, Ohara *et al.*, 2016, Rizza *et al.*, 2011, Yari *et al.*, 2021a, Yari *et al.*, 2019), two on hip circumference (HC) (Haidari *et al.*, 2015, Ohara *et al.*, 2016), and two on waist to hip ratio (WHR) (Haidari *et al.*, 2015, Yari *et al.*, 2021a) **(Figure 1)**.

Study characteristics

The basic characteristics of RCTs are presented in **Table 2**. Nine randomized trials published from 2010 to 2020 were included, 8 of which had a parallel design and one was a cross-over trial (Rizza *et al.*, 2011). Nine studies included 493 participants and sample sizes ranged from 24 to 124 participants of both sexes, aged between 18 to 75 years. The treatment duration lasted for 3 to 12 weeks and the dosage of hesperidin oral administration varied from 500 mg/day to 1000 mg/day. The majority of studies have been conducted in Iran, but one was based in Netherland (Demonty *et al.*, 2010), one in Italy (Rizza *et al.*, 2011), and another one in Japan (Ohara *et al.*, 2016). The participants were either healthy with moderate obesity (Ohara *et al.*, 2016) and moderate hypercholesterolemia (Demonty *et al.*, 2010) or patients with a medical condition such as metabolic syndrome, myocardial infarction, diabetes, and non-alcoholic fatty liver diseases.

Risk of bias assessment: The risk of bias assessment of each RCT is provided in **Table 3**. Four studies out of nine used an adequate random sequence generator and had a low risk of bias for this domain (Haidari *et al.*, 2015, Homayouni *et al.*, 2017, Yari *et al.*, 2021a, Yari *et al.*, 2019), whereas the remaining five studies had an unclear risk of bias since no detailed method was suggested for randomization (Demonty *et al.*, 2010, Eghtesadi *et al.*, 2016, Ohara *et al.*, 2016, Rizza *et al.*, 2011, Yari *et al.*, 2021b). Only one study by Homayouni *et al.* (Homayouni *et al.*, 2017) applied adequate allocation concealment and other articles did not report clear data on allocation

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concealment, hence considered as unclear risk of bias. Two studies were categorized as high risk of bias for blinding of the participants and personnel (Yari *et al.*, 2021a, Yari *et al.*, 2021b); however, by providing enough information about blinding in the remaining studies, they were labeled as low risk of bias. There was no sufficient report on blinding of outcome assessment in any of the included studies. The risk of bias from incomplete outcome data was assessed as low in the majority of the articles except for two (Haidari *et al.*, 2015, Rizza *et al.*, 2011). Regarding selective outcome reporting, all the studies were judged as low risk of bias. As a result, in overall risk of bias, seven of the included studies were assessed as "unclear", since each study had an unclear risk of bias for at least one of the six domains. Two remaining trials were regarded as "high" risk of bias due to having at least one high-risk domain.

Systematic review

Effect of hesperidin supplementation on HC and WHR: Two studies (n = 104 participants) on HC (Haidari *et al.*, 2015, Ohara *et al.*, 2016) and two studies (n = 118 participants) on WHR (Haidari *et al.*, 2015, Yari *et al.*, 2021a) provided no evidence for the effectiveness of hesperidin in reducing HC and WHR values. Haidari et al. (Haidari *et al.*, 2015) reported no significant differences in HC and WHR at baseline and at the end of the study between hesperidin and placebo groups (P > 0.05). Ohara et al. (Ohara *et al.*, 2016) also showed no significant differences in reducing HC between subjects receiving placebo and those who ingested glucosyl hesperidin with or without caffeine. In a study by Yari et al. (Yari *et al.*, 2021a), hesperidin supplementation also resulted no significant changes in WHR compared to control groups.

Meta-analysis

Effect of hesperidin supplementation on body weight: As provided in **Table 4**, the pooled estimated effect size of seven studies with 426 participants (Demonty *et al.*, 2010, Eghtesadi *et al.*, 2016, Haidari *et al.*, 2015, Homayouni *et al.*, 2017, Ohara *et al.*, 2016, Yari *et al.*, 2021b, Yari *et al.*, 2019) showed no significant changes in body weight after hesperidin consumption compared to control groups (WMD=0.01 kg, 95% CI: -0.22, 0.24, *P*=0.918; **Figure 2**). There was no significant between-study heterogeneity (Q statistics=3.54, *P*=0.739, I^2=0%). We also performed some subgroup analyses to identify the possible different effects of hesperidin supplementation caused by duration and dosage of treatment and health status of the participants; however, no significant changes in weight status were observed in any of the subgroups.

Effect of hesperidin supplementation on BMI: Eight studies with 444 participants were assessed for effects of hesperidin on BMI (Demonty *et al.*, 2010, Eghtesadi *et al.*, 2016, Haidari *et al.*, 2015, Homayouni *et al.*, 2017, Ohara *et al.*, 2016, Rizza *et al.*, 2011, Yari *et al.*, 2021a, Yari *et al.*, 2021b). Hesperidin supplementation was found to have no significant effect on BMI in comparison with control groups (WMD=-0.02 kg/m^2, 95% CI: -0.16, 0.13, *P*=0.831; **Figure 3**). There was moderate between-study heterogeneity, but it was not significant (Q statistics=9.58, *P*=0.214, I^2 =26.9%). No statistical difference was observed in subgroups according to duration and dosage of treatment and health status of the participants **(Table 4)**.

Effect of hesperidin supplementation on WC: The overall effects of 5 studies including a total of 220 participants (Haidari *et al.*, 2015, Ohara *et al.*, 2016, Rizza *et al.*, 2011, Yari *et al.*, 2021a, Yari *et al.*, 2019) suggested no significant change in WC after hesperidin supplementation compared to control groups (WMD=-0.48 cm, 95% CI: -1.52, 0.55, *P*=0.362; **Figure 4**). A significant between-study heterogeneity was found (Q statistics=9.76, *P*=0.045, I^2=59%). When the subgroup analysis was performed based on duration and dosage of treatment, heterogeneity was attenuated and non-significant in their categories; however, no significant change in WC was observed in any of the subgroups **(Table 4)**.

Meta-regression

To examine the possible association of different effects of hesperidin with supplementation dose

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and study duration on body weight, the meta-regression analysis was performed, but no significant relationship was detected.

Publication bias and sensitivity analysis

The pooled effects of hesperidin intake on weight, BMI, and WC were not sensitive to any of the studies after omitting each out of analyses, suggesting the results were robust. Furthermore, correlation coefficients opted to examine the value changes in the meta-analyses revealed no indication regarding sensitivity.

No publication bias was perceived in the funnel plots and they proved to be symmetrical after considering Begg's and Egger's asymmetry tests: weight (Begg's test, P=0.133; Egger's test, P=0.027), BMI (Begg's test, P=0.266; Egger's test, P=0.062), WC (Begg's test, P=0.086; Egger's test, P=0.051).

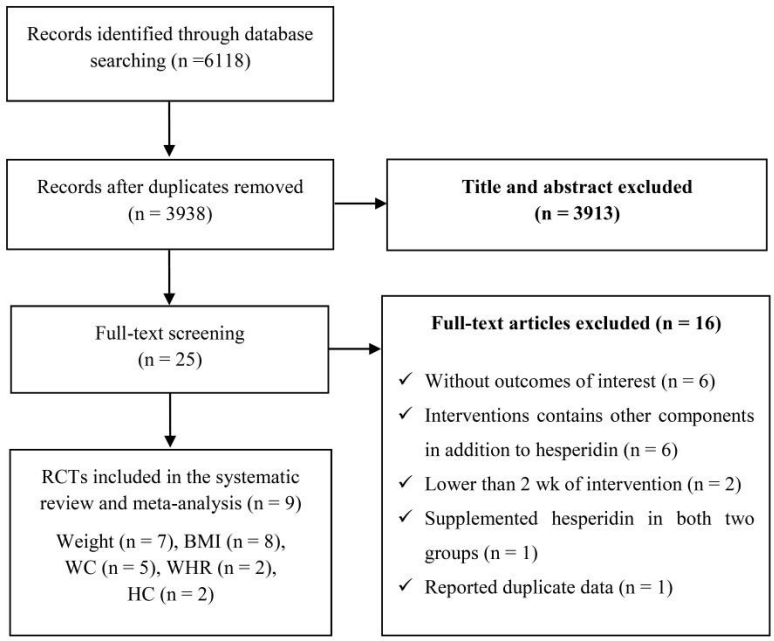

Figure 1. Flowchart of the study selection process

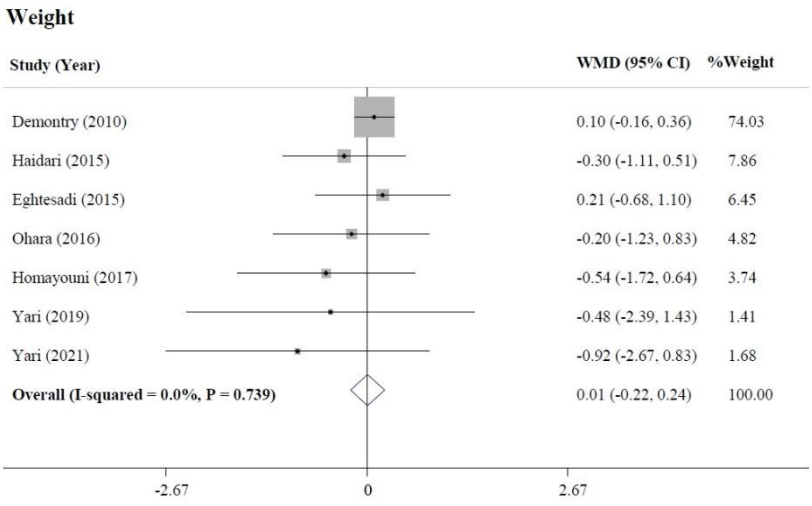

Figure 2. Forest plot from the meta-analysis of clinical trials

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investigating the effect of hesperidin supplementation on weight.

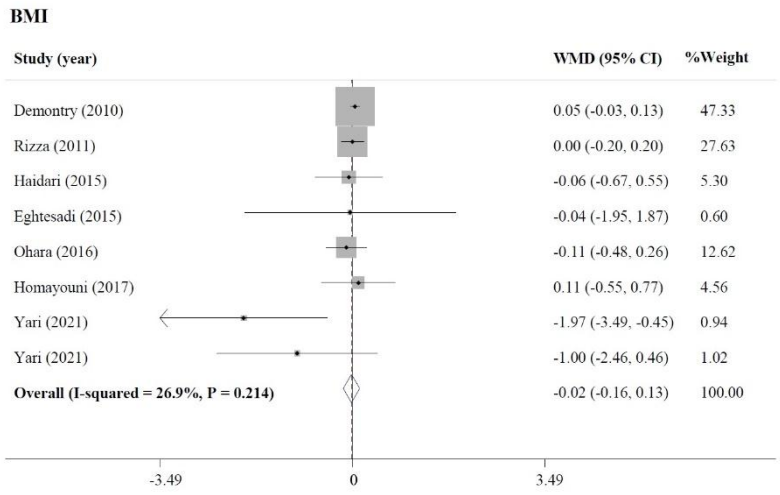

Figure 3. Forest plot from the meta-analysis of clinical trials investigating the effect of hesperidin supplementation on BMI

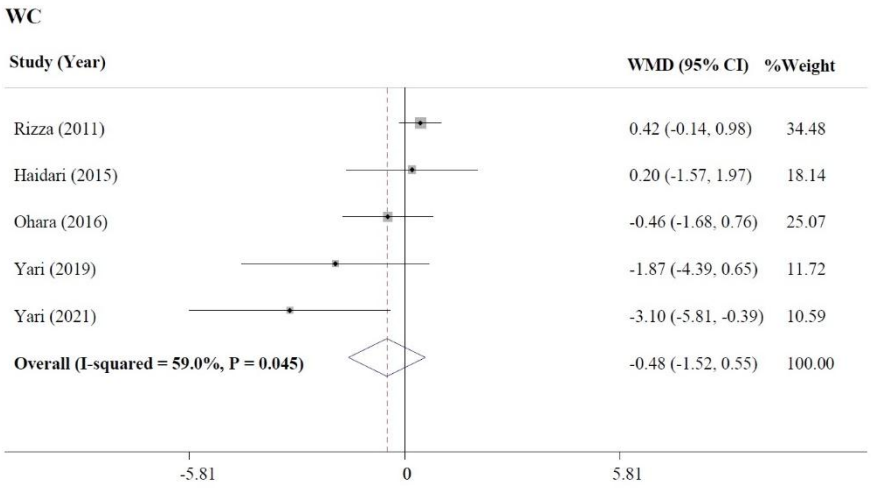

Figure 4. Forest plot from the meta-analysis of clinical trials investigating the effect of hesperidin supplementation on WC

Table 1. The Population, Intervention, Comparison, Outcome, Study types (PICOS) criteria.

Criteria	Description
Population	Adults aged >18 year
Intervention	Hesperidin supplementation
Comparison	Placebo capsule (cellulose, starch) or without treatment
Outcome	Weight, body mass index, Waist circumference, Hip circumference, and Waist to hip ratio
Study types	Randomized clinical trials

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Table 2. Characteristics of randomized clinical trials included in the systematic review

Study, Year (reference)	Country	Number, Sex (F/M)	Age (year)	RCT design	Duration (weeks)	Intervention group	Control group	Reported outcomes	Notes about participants
Demonty et al. 2010 (Demonty *et al.*, 2010)	Netherland	124 (59F/65M)	18-75 Int[1]: 61 Con[1]:60.1	Parallel	4	800 mg/day hesperidin	800 mg/day placebo (cellulose)	Weight BMI	Apparently healthy subjects with moderate hypercholesterolemia
Rizza et al. 2011 (Rizza *et al.*, 2011)	Italy	24 (9F/15M)	21-65 Int: 53 Con: 50	Cross-over	3	500 mg/day hesperidin	500 mg/day placebo (cellulose)	BMI WC	Patients with metabolic syndrome
Haidari et al. 2015 (Haidari *et al.*, 2015)	Iran	75 (22F/53M)	40-65	Parallel	4	600 mg/day hesperidin	600 mg/day placebo (starch)	Weight BMI WC, HC WHR	Patients with myocardial infarction
Ohara et al. 2016 (Ohara *et al.*, 2016)	Japan	29 (15F/14M)	20-65 Int: 49 Con: 49.4	Parallel	12	500 mg/day hesperidin	Placebo	Weight BMI WC, HC	Healthy moderately obese individuals
Eghtesadi et al. 2016 (Eghtesadi *et al.*, 2016)	Iran	45 23F/22M	Int: 53.2 Con:53.4	Parallel	8	500 mg/day hesperidin	500 mg/day placebo (cellulose)	Weight BMI	Patients with diabetes
Homayouni et al. 2017 (Homayouni *et al.*, 2017)	Iran	60 (32F/28M)	30-65 Int: 51.2 Con: 54.4	Parallel	6	500 mg/day hesperidin	500 mg/day placebo (starch)	Weight BMI	Patients with diabetes
Yari et al. 2019 (Yari *et al.*, 2019)	Iran	49 (24F/25M)	27-70 Int: 45.05 Con: 45.33	Parallel	12	1000 mg/day hesperidin	1000 mg/day placebo (starch)	Weight WC	Patients with metabolic syndrome
Yari et al. 2021 (Yari *et al.*, 2021b)	Iran	44 (21F/23M)	18-70 Int: 45.82 Con: 46.41	Parallel	12	1000 mg/day hesperidin + lifestyle modification program	lifestyle modification program	Weight BMI	Patients with metabolic syndrome
Yari et al. 2021 (Yari *et al.*, 2021a)	Iran	43 (F/21M)	18-70 Int: 45.82 Con: 46.11	Parallel	12	1000 mg/day hesperidin + lifestyle modification program	lifestyle modification program	BMI WC WHR	Patients with non-alcoholic fatty liver disease

BMI: body mass index; Con: control; F: female; M: male; HC: hip circumference; Int: intervention; RCT: randomized controlled trial; WC: waist circumference; WHR: waist to hip ratio

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

Study, year	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Overall risk of bias
Homayouni et al. 2018	Low	Low	Low	Unclear	Low	Low	Unclear
Ohara et al. 2016	Unclear	Unclear	Low	Unclear	Low	Low	Unclear
Haidari et al. 2015	Low	Unclear	Low	Unclear	Unclear	Low	Unclear
Rizza et al. 2011	Unclear	Unclear	Low	Unclear	Unclear	Low	Unclear
Demonty et al. 2010	Unclear	Unclear	Low	Unclear	Low	Low	Unclear
Eghtesadi et al. 2016	Unclear	Unclear	Low	Unclear	Low	Low	Unclear
Yari et al. 2019	Low	Unclear	Low	Unclear	Low	Low	Unclear
Yari et al. 2021	Unclear	Unclear	High	Unclear	Low	Low	High
Yari et al. 2021	Low	Unclear	High	Unclear	Low	Low	High

Table 4. Effect of hesperidin supplementation on weight and BMI based on several subgroups as well as all studies (all analyses were conducted using random effects model).

Variables	Meta-analysis			Heterogeneity		
	No. of studies	WMD (95%CI)	*P* effect	*Q* statistic	*P* within group	I^2 (%)
Weight (kg)						
Duration of intervention						
<8 weeks	3	0.04 (-0.21, 0.28)	0.778	1.81	0.405	0
>=8 weeks	4	-0.13 (-0.73, 0.47)	0.676	1.48	0.686	0
Dosage of hesperidin						
<=500 mg/d	3	-0.11 (-0.70, 0.48)	0.717	1.03	0.596	0
>500 mg/d	4	0.03 (-0.21, 0.28)	0.792	2.31	0.510	0
Baseline health status						
Cardio-metabolic disorders	5	-0.25 (-0.74, 0.25)	0.325	1.88	0.758	0
Healthy	2	0.08 (-0.17, 0.34)	0.532	0.30	0.582	0
Overall	7	0.01 (-0.22, 0.24)	0.918	3.54	0.739	0
Body mass index (kg/m^2)						
Duration of intervention						
<8 weeks	4	0.04 (-0.03, 0.12)	0.270	0.32	0.956	0
>=8 weeks	4	-0.66 (-1.55, 0.23)	0.148	6.56	0.087	54.2
Dosage of hesperidin						
<=500 mg/d	4	-0.01 (-0.18, 0.16)	0.874	0.43	0.934	0
>500 mg/d	4	-0.36 (-0.97, 0.25)	0.252	8.85	0.031	66.1
Baseline health status						
Cardio-metabolic disorders	6	-0.16 (-0.55, 0.22)	0.403	8.26	0.142	39.5
Healthy	2	0.04 (-0.04, 0.12)	0.306	0.70	0.404	0
Overall	8	-0.02 (-0.16, 0.13)	0.831	9.58	0.214	26.9
Waist circumference (cm)						
Duration of intervention						
<8 weeks	2	0.40 (-0.14, 0.94)	0.145	0.05	0.816	0
>=8 weeks	3	-1.43 (-3.00, 0.14)	0.074	3.51	0.173	43
Dosage of hesperidin						
<=500 mg/d	2	0.15 (-0.64, 0.95)	0.706	1.65	0.199	39.3
>500 mg/d	3	-1.38 (-3.38, 0.63)	0.178	4.53	0.104	55.9
Baseline health status						
Cardio-metabolic disorders	4	-0.67 (-2.15, 0.81)	0.375	8.87	0.031	66.2
Healthy	1	-0.46 (-1.68, 0.76)	0.460	0.00	-	-
Overall	5	-0.48 (-1.52, 0.55)	0.362	9.76	0.045	59

WMD: weighted wean difference

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Discussion

This meta-analysis quantifying evidence from RCTs found that intake of hesperidin had no statistically significant effects on the mean change differences in anthropometric indices compared to control groups. The results showed no different effects of hesperidin supplementation caused by the dosage and duration of treatment and the baseline health status of the participants. The findings were also robust in the sensitivity analyses.

Flavonoids are a widespread group of plant phenolic compounds which are commonly found in fruits and vegetables (Barreca *et al.*, 2021). Although there is some evidence that flavonoids can be effective in weight loss, such favorable effects of hesperidin were not observed as a group of citrus flavonoids from the flavanones subclass. A meta-analysis by Akhlaghi *et al.* assessed the effects of flavonoid subclasses including flavonols, anthocyanins, flavanones, and proanthocyanidins on obesity-related anthropometric measures and found an overall significant reducing effect of total flavonoids on BMI and WC. This review suggested that among the flavonoid subgroups, only flavanols had a significant reducing effect on these markers and there was no effect for other flavonoid subclasses. However, no significant effect of total flavonoids and their subclasses was observed on body fat percentage (Akhlaghi *et al.*, 2018).

Epidemiological evidence has also shown the role of flavonoids in weight maintenance. Three prospective cohort studies after assessing dietary intake of specific flavonoids reported that higher intake of most flavonoid subclasses was associated with less weight gain such that anthocyanins, flavonoid polymers, and flavonols had the greatest magnitude of association (Bertoia *et al.*, 2016). On the other hand, there have been several recent systematic reviews and meta-analyses of clinical trials to summarize the efficacy of some of the individual flavonoids including resveratrol, curcumin, and quercetin in weight loss. These reviews reported that resveratrol (Mousavi *et al.*, 2019) and curcumin (Akbari *et al.*, 2019) led to a significant reduction in body weight, BMI, and WC; however, quercetin supplementation was not associated with significant changes in anthropometric measures (Huang *et al.*, 2019). In the present review, hesperidin supplementation was not effective for changing anthropometric measurements. Therefore, it seems that the possible underlying mechanisms explaining the roles of several flavonoids in weight loss, such as reducing energy intake and fat absorption, increasing energy expenditure, and inhibiting adipogenesis and lipogenesis (Al Shukor *et al.*, 2016) could not be generalized to all types of flavonoids.

Although in the present study, there is no evidence associated with the anti-obesity effects of hesperidin, it should be mentioned that the majority of the studies included in this review did not report anthropometric indices as the primary outcome measures, and therefore the measurements might not be sufficiently accurate. Only one of the studies by Ohara *et al.* directly assessed the anti-obesity effects of glucosyl hesperidin, a water-soluble derivative of hesperidin, with or without caffeine in moderately obese subjects. They showed that a concomitant intake of glucosyl hesperidin and caffeine reduced body weight, BMI, and abdominal fat; however, intake of glucosyl hesperidin alone showed no significant anti-obesity effect compared to the placebo group (Ohara *et al.*, 2016). This is one of the limitations of this study and further investigations are thus required to directly assess the exact association between intake of hesperidin alone or in combination with other phytochemicals and changes in anthropometric measures as the primary outcomes. Also, the included studies have targeted a wide variety of populations including healthy adults and subjects with comorbidities such as obesity, hypercholesterolemia, metabolic syndrome, diabetes, myocardial infarction, and non-alcoholic fatty liver disease which made it difficult to determine the population that would most benefit from hesperidin. The bioavailability of hesperidin has not been also considered and evaluated in the included studies; therefore it is important to pay attention to this issue in future investigations to specify the precise concentrations of hesperidin

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available in the blood after ingestion and help to identify the ideal dosage of supplementation for maximum effectiveness. On the other hand, included RCTs were judged as being at unclear to high overall risk of bias and recruited a modest number of participants which creates the need for caution in the interpretation of results. Despite the limitations, a number of strengths can also be found in the present systematic review and meta-analysis as follows: (i) design of search strategy to find all relevant published studies that reported anthropometric indices as initial or secondary outcomes, (ii) including only RCTs to minimize the potential biases, (iii) doing subgroups analysis and meta-regression, and (iv) lack of between-study heterogeneity and sensitivity of the pooled effects suggesting the robustness of findings.

Conclusion

The results of this systematic review and meta-analysis of available literature did not provide evidence for the beneficial effect of hesperidin as a citrus flavonoid in weight management. The current evidence suggests that daily hesperidin supplementation is not recommended as a potential therapeutic strategy for weight loss. However, due to the limitations of the included studies, future studies especially on overweight and obese individuals should be conducted to further understand the anti-obesity activity of hesperidin.

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Conflict of interest

The authors declare that they have no conflict of interest.

Author's contributions

The authors' contributions were as follows: all authors contributed in conceive and design the research; Ramezani-Jolfaie N and Mohammadi M conducted systematic research and study selection; Ramezani-Jolfaie N and Mohammadi M extracted data; Mohammadi M analyzed data; Ramezani-Jolfaie N and Lorzadeh E contributed in drafting of the manuscript; and all authors read and approved the final version for submission.

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