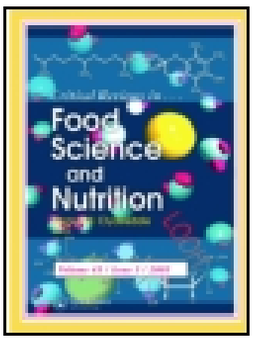

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REVIEW

Impact of hesperidin in 100% orange juice on chronic disease biomarkers: A narrative systematic review and gap analysis

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ABSTRACT

Hesperidin in orange juice may affect chronic disease biomarkers. This narrative systematic review aimed to determine appropriate recommendations toward the dose and frequency of hesperidin consumption from 100% orange juice and conduct a gap analysis. The Preferred Reporting Items for Systematic Review and Meta-analysis was conducted to identify articles through September 2020, utilizing four databases: Pub-Med Central, Agricola, Embase, and MEDLINE. Twenty articles met the inclusion criteria. Results showed that overall effect sizes from the studies were considerably weak. Although higher frequencies, doses, and concentration of hesperidin in 100% orange juice had an impact on global cognitive function, cardiac, insulin, inflammatory, antioxidant/phenolic, and oxidative stress outcomes compared to lower frequencies, doses, and concentration of hesperidin. A gap analysis demonstrated there was a variability in dose and frequency of OJ and hesperidin, diet, genetics, and evaluation measures, which made the role of hesperidin in 100% OJ on chronic diseases unclear. This review revealed a trend toward improving chronic disease biomarkers following consumption of hesperidin in 100% orange juice. Steps can be taken in future research to improve the consistency of clinical study designs, methodology and outcomes.

KEYWORDS

Adults; hesperidin; non-communicable diseases and chronic conditions; orange juice

Introduction

Globally, non-communicable diseases (NCDs) such as cardiovascular and diabetes and chronic conditions such as dementia are the leading causes of death among adults regardless of gender, race/ethnicity, or socioeconomic class (Raghupathi and Raghupathi 2018; "NCD mortality and morbidity" n.d.; WHO 2011). In the United States (US), nearly half of all adult Americans are faced with at least one NCD or chronic condition that contributes to over two-thirds of mortality and morbidity (Raghupathi and Raghupathi 2018; "The Power of Prevention. Chronic Disease … the Public Health Challenge of the 21st Century" 2009). Several contributing factors such as environment and genetics may explain the rise in these NCDs and chronic conditions, but one modifiable risk factor that contributes the most is poor diet quality (e.g., limited consumption of fruits and vegetables, and high intake of sodium, total fats and refined grains). Despite the 2015–2020 Dietary Guidelines for Americans recommendations, only 1 in 10 US adults consume the recommended amount of fruits and vegetables daily ("State Indicator Report on Fruits and Vegetables 2018). According to the 2013 report from the UN Food and Agriculture Organization (FAO), the average fruit consumption was 77.87 kg. More specifically, Africa had the lowest average consumption at 66.18 kg and North America at the highest with 107.63 kg (Ritchie and Roser 2017). Even though globally there is a low total fruit consumption, orange juice (OJ) is frequently consumed regardless of the demographic factors. In 2019, the average volume of OJ consumed was 1.1 liters per capita ("Orange Juice—Worldwide" 2020). Countries with the highest consumption were the US with an average volume of 6.5 liters per capita, Australia with an average volume of 9.5 liters per capita and the United Kingdom with an average volume of 7.2 liters per capita ("Orange Juice—United States" 2020; "Orange Juice—Australia" 2020; "Orange Juice—United Kingdom" 2020).

OJ contains antioxidants such as vitamin C to reduce various complications associated with NCDs and chronic conditions such as stroke and nerve damage ("Nutrients and Health Benefits," n.d.; Boeing et al. 2012). As similar to other citrus fruits, OJ contains two main flavonoids: hesperidin and narirutin. The chemical structure of flavonoids consists of a fifteen-carbon skeleton and a pyran ring that links two aromatic rings. Differences between the classes of flavonoids is on the level of oxidation and pyran ring

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substitutions, in which substitutions within the aromatic rings are used to identify the class compounds. Due to the chemical structure of hesperidin, it is identified as a flavanone glycoside. When ingested, hesperidin is deglycosylated by the microbiota to form its metabolite (aglycone), hesperetin, which is attached to disaccharides (glucose and rhamnose) at the seventh carbon position (Aschoff et al. 2015; Stevens et al. 2019). According to the Phenol-Explorer database, a comprehensive web-based database launched in 2009 on the content of polyphenols in foods, the amount of hesperidin in OJ varies significantly from 4-73mg/100 mL (Neveu et al. 2010). The role of hesperidin from OJ has gained attention in research, attributed to the anti-inflammatory and antioxidant properties in combination with its role in modulating key cellular enzyme function, which strongly depends on its bioavailability, structure and the food matrix (Panche, Diwan, and Chandra 2016). For example, in in-vitro and animal model studies, hesperidin has reduced inflammation, an underlying and insidious cause of many chronic maladies (Adefegha et al. 2017; Rizza et al. 2011; Benavente-García and Castillo 2008). Though in human clinical trials, positive effects of hesperidin in 100% OJ on the reduction of disease biomarkers are inconsistent. In non-diabetic volunteers, who had an increased cardiovascular risk, intake of 250 ml of red OJ daily for 1 week significantly decreased inflammatory markers (e.g., CRP, IL-6 and TNF-α), but did not alter blood glucose (Buscemi et al. 2012). In another trial, consumption of 600 ml of 100% OJ daily did not affect plasma inflammatory markers, lipid panels or blood pressure among adults who had high triglycerides and cholesterol (Foroudi et al. 2014). When comparing clinical trials, there are many reasons for discrepancies found including the dose, frequency of consumption, other food matrices consumed, demographics of participants, sample size, type of biomarkers used, and other assumptions in the methodologies. In various clinical studies, no attempts were made to control bioactive compounds from participants' diets, while in other studies, participants followed strict diets (Escudero-López et al. 2018; Erlund et al. 2001). Furthermore, studies that included participants who were at risk for NCDs or conditions varied in their diagnostic criterion (e.g., dyslipidaemia, obesity, hypertension and insulin resistance) and demographics (Grundy et al. 2005). Several systematic reviews have examined the impact juice, including OJ, and/or hesperidin has on chronic conditions. In 2018, a systematic review/meta-analysis was conducted on human randomized controlled clinical trials to assess cardio-protective effects of hesperidin in citrus species through OJ consumption and supplementation (Mohammadi et al. 2019). A total of 10 studies included in that meta-analysis demonstrated that there was no significant effect of hesperidin supplementation on total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglyceride, and systolic or diastolic blood pressure. Several subgroup analyses (e.g., study duration, baseline health, study quality and form of supplementation) were conducted to further understand possible effects of hesperidin on blood lipids and blood pressure; however, no beneficial effects were presented (Mohammadi et al. 2019). Another systematic review focused on the metabolic impact of 100% fruit juice consumption on antioxidants and lipid profiles among adults with no mention of hesperidin or OJ specification (Crowe-White et al. 2017). From the 10 studies included, results showed that consuming 100% fruit juice improved blood lipids and overall antioxidant status. Evidence-based recommendations regarding dose and frequency of juice consumption to reduce risks for chronic diseases though is limited due to poor study designs (Crowe-White et al. 2017). Even though systematic reviews have been published about the impact consumption of juice has on certain diseases, these reviews focus on one specific NCD or chronic condition and either the focus is on hesperidin amounts in supplemental form or juice, in general, amounts, rather than dose and frequency of hesperidin in 100% OJ and the subsequent impact on these diseases/conditions. Furthermore, limited reviews have explored study gaps to expound on additional human clinical research that may need to be conducted with hesperidin in 100% OJ and the effect on chronic diseases and conditions. Therefore, the purpose of this systematic review was to 1) determine appropriate recommendations toward the dose and frequency of hesperidin consumption from 100% OJ, as a mechanism to reduce and prevent complications associated with selected chronic diseases and conditions and 2) conduct a gap analysis to identify limitations in the literature and specific areas for future research.

Methods

Identification and selection of studies

This systematic review was conducted following the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) (Moher et al. 2009). The study protocol was registered in the prospective register of systematic reviews database (registration code: CRD42020162376). The PRISMA process involves four phases: identification, screening, eligibility and inclusion. Potential relevant published peer-reviewed journal articles were initially identified based on nested keyword searches. This was then followed by reviewing the title and abstracts of the articles based on determined inclusion/exclusion criteria and finally an assessment of the relevant articles that are closely associated with the original intent of the search. Eligible articles were identified in an exhaustive electronic search through July 2020, utilizing the following databases: Pub-Med Central, Agricola, Embase, and MEDLINE. One researcher (F.J.T) used the following search terms, in varying combinations, in PubMed: "orange juice [Title/Abstract]" and "hesperidin [Title/Abstract]" and "humans [Title/Abstract]" and "bone conditions or cancer or cardiovascular disease or inflammation or neurological conditions or metabolic disorders" [MeSH terms] and/or the following terms within disease conditions (Table 1). This combination of terms was carried out in the other databases using the search function for any and all terms. The researchers identified other relevant studies by

Table 1. Search terms associated with each disease condition.

Condition/disorder/disease	Search term
Bone conditions	"bone health"; "bone conditions"; "osteoporosis"; "bone biomarkers—bone turnover, bone microarchitecture";
Cancer	"cancer"; "tumor"; "metastasis"; "carcinogenesis"; "cancer biomarkers—tumor growth, tumor suppression, white blood cell";
Cardiovascular disease	"cardiovascular disease"; "hypertension/blood pressure"; "heart attack"; "stroke"; "cardiac biomarkers—cardiac troponin, creatine kinase, C-reactive protein, low density lipoprotein, lipoprotein A, serum creatinine, tumor necrosis factor α";
Inflammation	"inflammatory disease"; "arthritis"; "inflammatory bowel disease"; "celiac disease"; "hepatitis"; "inflammatory biomarkers—C-reactive protein, IFN-γR, IL-1β, IL-4, IL-10, IL-12, TNF-α";
Neurological Conditions	"neurological conditions"; "Alzheimer's disease"; "ALS"; "Cognitive Decline"; "Dementia"; "Multiple Sclerosis"; "Parkinson's"; "neurological biomarkers—C-reactive protein, IFN-γR, IL-1β, IL-4, IL-10, IL-12, TNF-α";
Metabolic Disorders	"type 2 diabetes"; "pre-diabetes"; "metabolic syndrome"; "metabolic biomarkers—hemoglobin A1C, advanced glycation end products, glycated albumin, C-reactive protein, IL-6"

searching the reference list of the retrieved studies, as well as conducted a second scan in September 2020. The search was completed for peer-reviewed articles written in English with no time restrictions to encompass the vast literature available. Literature searchers were combined into DistillerSR (Evidence Partners, Ottawa, Canada), a software to assist in screening and removing duplicate studies. Initially, 58,582 articles were identified for a total of 20 articles included in this review. Any discrepancies were discussed with the research team. See Figure 1 for a flow diagram of the article selection process.

Eligibility criteria

Studies were included if they met the following criteria: (1) published peer-reviewed articles; (2) in English; (3) study design was controlled clinical trial; (4) included participants who were human; (5) included participants over 18 years of age; (6) intervention included participants consuming OJ; (7) included measurement of hesperidin in the OJ; (8) identified the dose and/or frequency that participants consumed the OJ; and (9) outcomes included chronic disease/condition biomarkers such as CRP or insulin. Articles were excluded if the above criteria were not met. Additional, exclusion factors were non-peer reviewed articles, studies that were qualitative in design, conference abstracts, books and registered clinical trials that were unpublished.

Data extraction

All titles and abstracts were screened independently by two reviewers (F.J.T. and J.M.A), and full-text studies that were considered relevant were included for further review. Two reviewers (F.J.T and J. M. A) independently reviewed all full-text articles, and any discrepancies were resolved with consensus. These discrepancies surrounded the specific interventions, i.e., consumption of hesperidin in OJ and whether the intervention impacted the chronic disease biomarkers. Data from the studies that fulfilled the eligibility criterion were collected onto Microsoft Excel: (1) first author's last name and date of publication, (2) location and population size, (3) design and duration of the study, (4) diet, (5) intervention components, (6) amount and frequency of OJ consumption, (7) evaluation measures and (8) outcomes (Tables 2 and 3).

Quality and risk of bias assessment

Quality and risk of bias assessment of the identified randomized controlled trial (RCT) and crossover trial studies followed the Cochrane risk of bias instrument, from the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2019; Higgins, Altman, and Sterne 2017). This tool consists of 6 sources of bias: random sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, incomplete outcome data, selective outcome reporting, and other sources of bias. A series of questions were presented within each domain aimed to extract details from the studies in regard to risk of bias. Risk of bias for individual elements from the six domains were assessed as high, low, or unclear based on the answer choices 'yes,' 'no,' or 'unclear.' The last category 'unclear' indicates either lack of information or uncertainty over the potential for bias. A complete description of each criterion is found in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2019; Higgins, Altman, and Sterne 2017). Based on the handbook, if the study was judged to be at low risk across all domains, it was overall deemed 'low risk of bias.' If the study was judged to have some concerns in at least one domain, it was determined as having 'some concern.' Finally, if the study was judged to be at high risk in at least one domain or judged to have some concern in multiple domains, it was deemed overall 'high risk of bias' (Higgins et al. 2019; Higgins, Altman, and Sterne 2017) (Supplemental Table 4).

Quality and risk of bias assessment of the identified non-randomized studies (e.g., cohorts or single-study designs) followed the Newcastle-Ottawa Scale (NOS) (Wells et al. 2019). This instrument consists of three factors: (1) selection, including representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure, and demonstration that outcome of interest was not present at the start of the study; (2) comparability, based on the study design or analysis; and (3) outcome, including assessment of outcome, follow-up period and adequacy of follow-up of cohorts (Wells et al. 2019). A maximum of one star was allocated for each item within the selection and outcome domains and two stars in the comparability domain. Standard criteria for determining high quality have not been established; however, Newcastle-Ottawa scales have been converted to Agency for Health Research and Quality (AHRQ) standards (good, fair, and poor). If 3 or 4 stars

Table 2. Data extraction of studies included in narrative systematic review (n = 20).

Author (year)	Location/Population	Design/Duration	Diet	Intervention Components	Amount/Frequency	Evaluation measures
Alharbi et al. (2016)	UK Healthy Adults (n = 24)	RCT[a] (Crossover) Double-Blind 2 days/2 weeks	Low polyphenol diet; Evening at home meal prior to each test-day: low-fat standardized chicken and rice	**Intervention**: 240-ml FR[b] drink **Control**: Placebo	**Amount**: 240 ml **Frequency**: Once (5 min) **Hesperidin**: 220.5 mg/d	Cognitive Tests: Function; Subjective Mood: PANAS[c]
Buscemi et al. (2012)	Italy Non-diabetic with increased CVD risk (n = 19) Healthy, non-obese (n = 12)	RCT (crossover) Single-Blind 3 weeks	Eat the same diet 3 d preceding basal measurements and during the last 3 d of periods 1 and 2.	**Intervention**: 500 mL red OJ[d] **Control**: 500 mL placebo	**Amount**: 500 mL **Frequency**: 250 ml twice/d for 1 week **Hesperidin**: 159.5 mg/d	Inflammatory biomarkers: CRP[e], IL-6[f], TNF-α[g]; NO[h] plasma concentration; Plasma PC groups
Constans et al. (2015)	France Men with cardiovascular risk factors (n = 25)	RCT (Cross-over) 13 weeks	French National Program for Nutrition and Health (4 weeks before the study)	**Intervention**: 200 mL of blond OJ **Control**: Control beverage (mimicking OJ, including vitamin C but no phyto-micronutrients)	**Amount**: 600 mL **Frequency**: 3x daily for 4 weeks **Hesperidin**: 212 mg/d	Lipid panel: TC[i], LDL[j], HDL[k], ApoA-I[l] Antioxidant activity: ORAC[m]; FRAP[n]; CAT[o]; plasma ascorbic acid and homocysteine concentrations Endothelial function biomarkers: Plasma concentrations of sVCAM-1[p]
Pascual-Teresa et al. (2007)	Spain Healthy adults (n = 14)	Controlled study 2 weeks	Usual dietary habits and physical activity level	**Intervention 1**: Dose response test – 400 g of minimally processed oranges **Intervention 2**: Multiple-dose-response – 200 g of orange in the morning, for 2 consecutive weeks	**Amount**: Intervention 1: 400 g (200 ml) Intervention 2: 200 g (100 ml) **Frequency**: Intervention 1: Once Intervention 2: Each morning for 2 consecutive weeks **Hesperidin**: Intervention 1: 198 mg/d Intervention 2: 49 mg/d	FRAP
Dourado and Cesar (2015)	Norway Healthy Normal weight adults (n = 21) Healthy Overweight adults (n = 25)	Controlled trial 8 weeks	Usual dietary habits and physical activity level	**Intervention**: 750 mL of OJ **Control**: N/A	**Amount**: 750 ml **Frequency**: At least two intakes/d for 8 weeks **Hesperidin**: 77.5 mg/d	Lipid panel: TC, LDL, HDL, TG[q] Oxidative stress biomarker: Lipid peroxidation Plasma vitamin C and folate concentration Plasma insulin concentration Inflammatory biomarkers: CRP, cytokines (IL-4[r] and TNF-α)
Escudero-López et al. (2018)	Spain Healthy Adults Intervention	RCT 5 weeks	Limit beer or wine intake to a maximum of six servings per	**Intervention**: 500 mL- orange beverage (OB)	**Amount**: 500 mL **Frequency**: Per day for 2 weeks	Lipid Panel: TC, LDL, HDL, TG Oxidative stress

(*continued*)

Table 2. Continued.

Author (year)	Location/Population	Design/Duration	Diet	Intervention Components	Amount/Frequency	Evaluation measures
	(n = 15) Healthy Adults Control (n = 15)		week and to avoid any intake of spirits over the study period.	**Control**: Did not consume OB during a 2-week period	**Hesperidin**: 0.0025 mg/d	biomarker: TBARS[s] Plasma insulin concentration Antioxidant activity and endothelial function biomarkers: CAT; ORAC; FRAP; Plasma concentrations of sVCAM-1; Uric acid
Franke et al. (2005)	USA Healthy Adults (n = 13)	Controlled Trial 3 weeks	Usual dietary habits and physical activity level	**Intervention**: Daily 256 mg vitamin C, 229 mg hesperidin, 6 mg carotenoids, 0.16 mg folate in 236 mL of OJ **Control**: N/A	**Amount**: 236 ml **Frequency**: Daily for 3 weeks **Hesperidin**: 229 mg/d	Lipid Panel: TC, HDL, LDL, TG, HDL-LDL ratio Oxidative stress biomarker: TBARS Plasma vitamin C, folate, homocysteine and phenolic concentrations
Ghanim et al. (2007)	USA Healthy Adults (n = 32)	Controlled Trial 1 day	Usual dietary habits and physical activity level	**Intervention 1:** 300-cal drink of glucose (75 g) **Intervention 2**: 300-cal drink of fructose (75 g) **Intervention 3**: 300-cal drink of OJ **Control:** Water sweetened with saccharin	**Amount**: 300-cal (654.5 ml) **Frequency**: Single dose, within 10 min **Hesperidin**: 3.70 mg/d	Plasma insulin concentration Oxidative stress biomarker: ROS[t] generation Inflammatory biomarkers: CRP
Gonçalves et al. (2017)	Brazil Adults with chronic hepatitis C (n = 43) Intervention (n = 23) Control (n = 20)	RCT 8 weeks	Usual dietary habits and physical activity level	**Intervention**: 500 mls of OJ **Control**: No regular consumption of OJ	**Amount**: 500 ml **Frequency**: Two (250 mls) daily portions over eight consecutive weeks **Hesperidin**: 16.4 mg/d	Lipid Panels: TG, LDL, HDL, TC Oxidative stress biomarker: TBARS Plasma insulin concentration Inflammatory biomarkers: CRP
Hollands et al. (2018)	UK Men with a waist measurement >94 cm and women with >80 cm (n = 41)	RCT (crossover) 11 weeks	Excluded food sources high in total anthocyanin intake. Advised to drink the juice with a meal/food or through a straw.	**Intervention**: 500 ml blood OJ providing 50 mg anthocyanins **Control**: 500 ml blonde OJ without anthocyanins	**Amount**: 500 ml **Frequency**: Daily for 28 d **Hesperidin**: Intervention: 67 mg/d Control: 104 mg/d	Lipid Panel: TC, HDL, LDL, TG Inflammatory biomarkers: high-sensitivity CRP status; NO plasma concentration
Li et al. (2020)	UK Healthy men and premenopausal women (n = 15)	RCT (crossover) 5 weeks	Usual dietary habits and physical activity level	**Intervention:** 400 mL Blood OJ **Control:** 400 mL sugar matched control drink	**Amount:** 400 mL **Frequency:** 200 mL twice/d for 2 weeks **Hesperidin:** Intervention: 320.8 ± 10.8 mg/d Control: 25.2 ± 0.8 mg/d	Lipid Panel: TC, HDL, LDL, TG Blood Pressure: 3 consecutive measurements Inflammatory biomarkers: CRP

(*continued*)

Table 2. Continued.

Author (year)	Location/Population	Design/Duration	Diet	Intervention Components	Amount/Frequency	Evaluation measures
Kean et al. (2015)	UK Healthy Adults Intervention (n = 19) Healthy Adults control (n = 18)	RCT 20 weeks	Fast from alcohol for 48 h; Avoid polyphenol-rich foods for 24 h	**Intervention**: HF[u] drink **Control**: LF[v] drink	**Amount**: Intervention: 180 kcal/500-ml Control: 165 kcal/500-mL **Frequency**: 250 mL twice/d for 8 weeks **Hesperidin**: Intervention: 274.5 mg/d Control: 32 mg/d	Cognitive Tests: Global Cognitive Function; Subjective mood: PANAS Blood Pressure: 3 consecutive measurements
Kurowska et al. (2000)	Canada Adult Men (n = 16) and Adult Women (n = 9) with elevated plasma total and LDL-cholesterol and normal plasma TG concentrations	Crossover Trial 22 weeks	American Heart Association (AHA) Step I lipid-lowering diet; Avoid taking supplements during the study.	**Intervention**: 1, 2, or 3 cups (250 mL each) of OJ **Control**: N/A	**Amount**: 1, 2 or 3 cups (250 ml each) **Frequency**: Daily for 4 weeks **Hesperidin**: Dietary Period 1: 11.6 mg/d Dietary Period 2: 23.2 mg/d Dietary Period 3: 34.7 mg/d	Lipid panel: LDL, HDL, HDL-LDL ratio; TGs; Apo B and Apo A-1 Plasma Vitamin C, folate and homocysteine concentrations
Morand et al. (2011)	France Healthy Overweight men (n = 24)	RCT (Crossover) 18 weeks	Refrain from citrus-containing foods; Limit total intake of flavonoid rich beverages	**Intervention 1**: 500 mL OJ **Intervention 2**: 500 mL control drink plus hesperidin (CDH) **Control**: 500 mL control drink plus placebo (CDP)	**Amount**: 500 ml **Frequency**: 250 ml twice/d for 4 weeks **Hesperidin**: 292 mg/d	Lipid panel: TC, LDL, HDL, TG Blood pressure: 3 consecutive measurements Plasma ascorbic acid concentration Plasma insulin concentration Inflammatory and endothelial activation biomarkers: CRP, IL-6, sVCAM-1, NO plasma concentration; Uric acid
Perche et al. (2014)	France Healthy Adults (n = 24)	RCT (Crossover) 18 weeks	Limited consumption of polyphenol-rich drinks like coffee, tea, wine and cocoa (less than 200 mL/day).	**Intervention 1:** Orange Juice **Intervention 2:** Isocaloric control drink with 292 mg of pure hesperidin **Control:** Control drink with a placebo (292 mg starch)	**Amount:** 500 ml **Frequency:** 2 equal intakes daily **Hesperidin:** Intervention 1: 292 mg/d Intervention 2: 292 mg/d	Cytokines production (IL-4) Oxidative stress biomarker: ROS generation
Rangel-Huerta et al. (2015)	Spain Overweight/ Obese adults, 1 clinical sign of metabolic syndrome (n = 100) Intervention (n = 54) Control (n = 46)	RCT (Crossover) Double-Blind 31 weeks	Usual dietary habits Avoid heavy physical activity, alcohol use (24 h), and smoking (2 h) before visits.	**Intervention**: 1.5 g/L [OJ with a high polyphenol concentration (HPJ)] **Control**: 0.6 g/L [OJ with a normal polyphenol concentration (NPJ)]	**Amount**: 500 ml **Frequency**: 2 daily doses (250 ml/each) for 12 weeks **Hesperidin**: Intervention: 582.5 mg/d Control: 237 mg/d	Lipid metabolism: Total, HDL, LDL, TG, Apo-B, ApoA-1 Plasma insulin concentration Oxidative stress biomarker: Lipid peroxidation

(*continued*)

Table 2. Continued.

Author (year)	Location/Population	Design/Duration	Diet	Intervention Components	Amount/Frequency	Evaluation measures
						Antioxidant activity: CAT
Schar et al. (2015)	USA Healthy Adults with a 10-20% risk of CVD (n = 16)	RCT (Crossover) 1 day	Diet low in flavonoids (for 72 h); Refrain from strenuous exercise (for 48 h); Avoid alcohol, caffeine, and nitrate/ nitrite-containing foods and beverages (for 24 h).	**Intervention 1**: OJ **Intervention 2**: Hesperidin supplement **Control**: Matched for sugar and vitamin C content	**Amount**: 767 ml **Frequency**: 1 dose **Hesperidin**: 320 mg/d	Blood pressure: 3 consecutive measurements Plasma vitamin C and total plasma phenolic concentrations
Simpson, Mendis, and Macdonald (2016)	UK Healthy, overweight adults (n = 36) Intervention (n = 18) Control (n = 18)	RCT Single-Blind 12 weeks	Usual dietary habits and physical activity level	**Intervention**: 250 ml OJ/day **Control**: Energy and sugars matched orange-flavored drink	**Amount**: 250 ml **Frequency**: Once a day for 12 weeks **Hesperidin**: 135.4 mg/d	Lipid panel: TG, TC, LDL, HDL, Apo-A1, Apo-B Plasma Fasting Insulin Sensitivity Inflammatory biomarkers: CRP, TNF-α, Uric acid
Snyder et al. (2011)	USA Healthy Adults (n = 16)	RCT (Crossover) 19 weeks	Discontinue antioxidant supplements; 12-hour fast, meal: 28 g (1 cup) of Kellogg's Corn Flakes and 118 mL (1/2 cup) of 2% milk	**Intervention 1**: Fresh squeezed OJ (positive control) **Intervention 2:** Placebo plus hesperidin, luteolin, and naringenin **Intervention 3**: Placebo plus hesperidin **Control**: Placebo—ascorbic acid and sugar equivalent to OJ (negative control)	**Amount/Hesperidin**: Intervention 1: 591 mL Intervention 2: Control + 210 mg hesperidin, 22.8 mg naringenin & 3.97 luteolin Intervention 3: Control + 210 mg hesperidin Control: AA (350 mg), fructose (12.76 g), glucose (11.17 g) and sucrose (23.81 g) dissolved in 591 mL water **Frequency**: One treatment per week **Hesperidin**: 210 mg/d	Oxidative stress biomarker: Lipoprotein oxidation Antioxidant capacity: ORAC Total plasma phenolic concentrations
Valls et al. (2021)	Spain Pre- or Stage-1 hypertensive individuals (n = 159)	RCT 12 weeks	Refrain from consuming citrus-containing foods and to limit their total intake of flavonoid-rich foods	**Intervention 1:** OJ **Intervention 2:** Hesperidin-enriched OJ **Control:** Control drink	**Amount:** 500 ml **Frequency**: Once/ day for 12 weeks **Hesperidin:** Intervention 1: 345 mg/day Intervention 2: 600 mg/d	Blood pressure: 2 consecutive measurements Homocysteine concentration Inflammatory biomarkers: Uric acid

Notes. a = Randomized Control Trial; b = Flavonoid Rich; c = Positive and Negative Affect Scale; d = Orange Juice, e = C-reactive Protein, f = Interleukin 6, g = Tumor Necrosis Factor, h = Nitric oxide; i = Total Cholesterol; j = Low-density Lipoprotein; k = High-density Lipoprotein; l = Apolipoprotein A1, m = Oxygen Radical Absorbance Capacity; n = Ferric Reducing Antioxidant Power; o = catalase; p = Soluble Vascular Cell Adhesion Molecule; q = Triglyceride; r = Interleukin 4; s = Thiobarbituric Acid Reactive Substances; t = Reactive Oxygen Species; u = High-Flavanone; v = Low-Flavanone

were given in the selection domain, 1 or 2 in the comparability domain and 2 or 3 in the outcomes domain, the study was determined as 'good' quality. If 2 stars were given in the first domain, 1 or 2 in the second and 2 or 3 in the last, the quality was considered 'fair.' Finally, a 'poor' quality article was determined as having 0 or 1 star(s) in the selection domain, or 0 in comparability domain, or 0 or 1 star(s) in outcomes domain (Sharmin et al. 2017). If an article was identified as poor, it was removed from further analysis. If discrepancies existed about the quality of an article, a discussion took place until resolved (Supplemental Table 5).

Table 3. Data outcomes of studies included in narrative systematic review (n = 20).

Author (year)	Inflammation	Neurological	Cardiac	Insulin	Antioxidant/Phenolic	Oxidative Stress Biomarkers
Alharbi et al. (2016)	/	Cognitive Function Tests: No difference between control and intervention post-6 hours ($p > 0.05$) Subjective Mood: No difference between control and intervention post-6 hours ($p > 0.05$)	/	/	/	/
Buscemi et al. (2012)	CRP[a], IL-6[b], and TNF-α[c]: Between groups, significant decrease in intervention post-14 days ($p < 0.001$) NO[d]: No difference between control and intervention post-14 days ($p = 0.087$) PC[e]: No difference between control and intervention post-14 days ($p = 0.230$)	/	/	/	/	/
Constans et al. (2015)	sVCAM[f]: No difference between control and intervention post-4 weeks ($p > 0.05$)	/	HDL[g]: No difference between control and intervention post-4 weeks ($p > 0.05$) LDL[h]: No difference between control and intervention post-4 weeks ($p > 0.05$) Apo-AI[i]: Between groups, significant increase in intervention post-4 weeks ($p < 0.02$) TC[j]: No difference between control and intervention post-4 weeks ($p > 0.05$)	/	Homocysteine: No difference between control and intervention post-4 weeks ($p > 0.05$) Vitamin C: No difference between control and intervention post-4 weeks ($p > 0.05$) ORAC[k]: Between groups, significant increase in intervention post-4 weeks ($p < 0.05$) FRAP[l]: No difference between control and intervention post-4 weeks ($p > 0.05$) CAT[m]: No difference between control and intervention post-4 weeks ($p > 0.05$)	/
Pascual-Teresa et al. (2007)	/	/	/	/	FRAP: No difference within control post-6.5 hours and	/

					intervention post-14 days ($p > 0.05$)	
Dourado and Cesar (2015)	CRP: Significant decrease post-8 week intervention ($p < 0.05$) IL-4[n]: No difference post-8 week intervention ($p > 0.05$) TNF-α: No difference post-8 week intervention ($p > 0.05$)	/	TG[o]: No difference post-8 week intervention ($p > 0.05$) HDL: No difference post-8 week intervention ($p > 0.05$) LDL: Significant decrease post-8 week intervention ($p < 0.05$) TC: Significant decrease post-8 week intervention ($p < 0.05$)	No difference post-8 week intervention ($p > 0.05$)	Vitamin C: Significant increase post-8 week intervention ($p < 0.05$) Folate: Significant increase post-8 week intervention ($p < 0.05$)	Peroxidation: Significant decrease post-8 week intervention ($p < 0.05$)
Escudero-López et al. (2018)	sVCAM: No difference within control or intervention ($p > 0.05$) Uric acid: Significant decrease post-intervention and washout ($p < 0.05$; $p < 0.05$), no difference in control ($p > 0.05$)	/	TG: No difference within control or intervention post-2 weeks ($p > 0.05$) HDL: No difference within control or intervention post-2 weeks ($p > 0.05$) LDL: No difference within control or intervention post-2 weeks ($p > 0.05$) Apo-AI: No difference within control or intervention post-2 weeks ($p > 0.05$) TC: No difference within control or intervention post-2 weeks ($p > 0.05$) Apo-B[q]: No difference within control or intervention post-2 weeks ($p > 0.05$)	No difference within control or intervention post-2 weeks ($p > 0.05$)	ORAC: Significant increase post-intervention ($p < 0.01$), no difference in control ($p > 0.05$) FRAP: No difference within control or intervention post- 2 weeks ($p > 0.05$) CAT: Significant decrease post-intervention and washout ($p < 0.05$; $p < 0.001$), no difference in control ($p > 0.05$)	TBAR[p]: Significant decrease post-intervention and washout ($p < 0.05$; $p < 0.001$), and in the control group post 2-weeks ($p < 0.05$)
Franke et al. (2005)	/	/	TG: Significant increase post-3 week intervention ($p < 0.05$) HDL: No difference post-3 week intervention ($p > 0.05$) LDL: No difference post-3 week intervention ($p > 0.05$) TC: No difference post intervention ($p > 0.05$) HDL: LDL Ratio: No difference post intervention ($p > 0.05$)	/	Homocysteine: Significant increase post-3 week intervention ($p = 0.046$) Vitamin C: Significant increase post intervention at 1 and 3-weeks ($p < 0.001$) Folate: Significant increase post intervention at 1 and 3-weeks ($p = 0.018$) Phenolic: Significant increase post-3 week intervention ($p = 0.045$)	TBAR: No difference post- 3 week intervention ($p = 0.795$)
Ghanim et al. (2007)	CRP: Between OJ[r] intervention and control,	/	/	OJ intervention and glucose intervention	/	ROS[s]: No significant difference

(*continued*)

Table 3. Continued.

Author (year)	Inflammation	Neurological	Cardiac	Insulin	Antioxidant/Phenolic	Oxidative Stress Biomarkers
	significant decrease in intervention post- 1 hour ($p < 0.01$)			significantly increased compared to fructose intervention ($p < 0.05$)		between OJ intervention, fructose intervention and control post- 3 hours ($p > 0.05$)
Gonçalves et al. (2017)	CRP: Significant decrease post 8-week intervention ($p < 0.05$)	/	TG: No difference within control or intervention ($p > 0.05$) HDL: No difference within control or intervention ($p > 0.05$) LDL: Significant decrease post 8-week intervention ($p < 0.05$) TC: Significant decrease post- 8 week intervention ($p < 0.05$)	No difference within control or intervention ($p > 0.05$)	Vitamin C: Significant increase post 8-week intervention ($p < 0.05$) Folate: Significant increase post 8-week intervention ($p < 0.05$)	TBAR: Significant decrease post 8-week intervention ($p < 0.05$)
Hollands et al. (2018)	CRP: No difference between control and intervention post- 28 days ($p > 0.05$) NO: No difference between control and intervention post- 28 days ($p > 0.05$)	/	TG: No difference between control and intervention post- 28 days ($p > 0.05$) HDL: No difference between control and intervention post- 28 days ($p > 0.05$) LDL: No difference between control and intervention post- 28 days ($p > 0.05$) TC: No difference between control and intervention post- 28 days ($p > 0.05$) BP^t: No difference between control and intervention post- 28 days ($p > 0.05$)	/	/	/
Li et al. (2020)	CRP: No difference within control or intervention ($p > 0.05$)	/	TG: No difference within control or intervention ($p > 0.05$) HDL: No difference within control or intervention ($p > 0.05$) LDL: Significant decrease post 2-week intervention ($p = 0.005$) TC: No difference within control or intervention ($p > 0.05$) BP: No difference within control or intervention ($p > 0.05$)	/	/	/
Kean et al. (2015)	/	Cognitive Function: Between groups,		/	/	/

		significant increase in intervention post-8 weeks ($p < 0.05$) Subjective Mood: No difference between control and intervention post-8 weeks ($p > 0.05$)	BP: No difference between control and intervention post-8 weeks ($p > 0.05$)			
Kurowska et al. (2000)	/	/	TG: Significant increase within interventions ($p < 0.05$) HDL: Significant increase during third intervention ($p < 0.05$), unchanged in first two interventions LDL: No difference within interventions ($p > 0.05$) Apo-AI: No difference within interventions ($p > 0.05$) TC: No difference within interventions ($p > 0.05$) Apo-B^t: No difference within interventions ($p > 0.05$) HDL-LDL Ratio: Significant decrease during third intervention ($p < 0.01$), unchanged in first two interventions	/	Homocysteine: No difference within interventions ($p > 0.05$) Vitamin C: Significant increase during all interventions post- 4 weeks ($p < 0.001$) Folate: Significant increase during third intervention ($p < 0.01$), unchanged in first two interventions	/
Morand et al. (2011)	CRP: No difference between control and intervention post-4 weeks ($p = 0.209$) IL-6: No difference between control and intervention post-4 weeks ($p = 0.586$) NO: No difference between control and intervention post-4 weeks ($p = 0.080$) sVCAM: No difference between control and intervention post-4 weeks ($p = 0.089$) Uric acid: Between groups, significant decrease in intervention post-4 weeks ($p = 0.017$)	/	TG: No difference between control and intervention post-4 weeks ($p = 0.642$) HDL: No difference between control and intervention post-4 weeks ($p = 0.388$) LDL: No difference between control and intervention post-4 weeks ($p = 0.091$) TC: No difference between control and intervention post-4 weeks ($p = 0.100$) BP: Between groups, significant decrease of diastolic BP in intervention post-4 weeks ($p = 0.023$)	No difference between control and intervention post-4 weeks ($p = 0.642$)	Vitamin C: Between groups, significant increase in intervention post-4 weeks ($p = 0.0001$) FRAP: No difference between control and intervention post-4 weeks ($p = 0.905$)	/

(*continued*)

Table 3. Continued.

Author (year)	Inflammation	Neurological	Cardiac	Insulin	Antioxidant/Phenolic	Oxidative Stress Biomarkers
Perche et al. (2014)	IL-4: No difference between control and intervention post-4 weeks ($p > 0.05$)	/	/	/	/	ROS: No difference between control and intervention post-4 weeks ($p > 0.05$)
Rangel-Huerta et al. (2015)	/	/	TG: No difference between NPJ[u] and HPJ[v] groups post-2 weeks ($p > 0.05$) HDL: No difference between NPJ and HPJ groups post-12 weeks ($p > 0.05$) LDL: No difference between NPJ and HPJ groups post-12 weeks ($p > 0.05$) Apo-AI: No difference between NPJ and HPJ groups post-12 weeks ($p > 0.05$) TC: No difference between NPJ and HPJ groups post-12 weeks ($p > 0.05$) Apo-B: No difference between NPJ and HPJ groups post-12 weeks ($p > 0.05$) BP: No difference between NPJ and HPJ groups post-12 weeks ($p > 0.05$)	Between groups, significant decrease in NPJ group post-12 weeks ($p = 0.007$)	CAT: No difference between NPJ and HPJ groups post-12 weeks ($p > 0.05$)	Peroxidation: Between groups, significant decrease in NPJ group post-12 weeks ($p = 0.003$)
Schar et al. (2015)	/	/	BP: No difference between control and intervention post-5 hours ($p > 0.05$)	/	Vitamin C: No difference between control and intervention post-5 hours ($p > 0.05$) Phenolic: Between groups, significant increase in intervention post-5 hours ($p < 0.0001$)	/
Simpson, Mendis, and Macdonald (2016)	CRP: No difference between control and intervention post-12 weeks ($p = 0.118$) IL-6: No difference between control and intervention post-12 weeks ($p = 0.987$) TNF-α: No difference	/	TG: No difference between control and intervention post-12 weeks ($p > 0.05$) HDL: No difference between control and intervention post-12 weeks ($p > 0.05$) LDL: No difference between control and intervention post-	No difference between control and intervention post-12 weeks ($p > 0.05$)	/	/

	between control and intervention post-12 weeks ($p = 0.959$) Uric acid: No difference between control and intervention post-12 weeks ($p = 0.303$)		12 weeks ($p > 0.05$) TC: No difference between control and intervention post-12 weeks ($p > 0.05$) Apo-AI: No difference between control and intervention post-12 weeks ($p > 0.05$) Apo-B: No difference between control and intervention post-12 weeks ($p > 0.05$)			
Snyder et al. (2011)	/	/	/	/	ORAC: No difference between control and intervention post-3 hours ($p > 0.05$) Phenolic: No difference between control and intervention post-3 hours ($p > 0.05$)	LO[w]: No difference between control and intervention post-3 hours ($p > 0.05$)
Valls et al. (2021)	Uric acid: Between groups, significant decrease in EOJ[x] intervention post-12 weeks ($p < 0.05$)	/	BP: No difference between control and intervention on diastolic BP post- 12 weeks ($p > 0.05$). Between OJ intervention and control, systolic BP significantly decreased in intervention post-12 weeks and between EOJ intervention and control, systolic BP significantly decreased in intervention post- 2, 6, 10 and 12 weeks ($p < 0.05$)	/	Homocysteine: Between groups, significant decrease in OJ and EOJ interventions post-12 weeks ($p < 0.05$)	/

Notes. (/) No results; a = C-reactive Protein; b = Interleukin 6; c = Tumor Necrosis Factor; d = Nitric Oxide; e = Plasma Protein Carbonyl; f = Soluble Vascular Cell Adhesion Molecule; g = High-density Lipoprotein; h = Low-density Lipoprotein; i = Apolipoprotein A1; j = Total Cholesterol; k = Oxygen Radical Absorbance Capacity; l = Ferric Reducing Antioxidant Power; m = Catalase; n = Interleukin 4; o = Triglyceride; p = Thiobarbituric Acid Reactive Substances; q = Apolipoprotein B, r = Orange Juice; s = Reactive Oxygen Species; t = Blood Pressure; u = Normal-Polyphenol-Concentration Orange Juice; v = High-Polyphenol-Concentration Orange Juice; w = Lipoprotein Oxidation; x = Hesperidin-Enriched Orange Juice

Considering the heterogeneity of the outcomes of each study, changes in chronic disease/condition biomarkers between baseline and endpoint were expressed as a standardized mean difference (effect size) to compare all studies based on the same measure. The effect size of the various biomarkers were calculated using an online software tool based on the difference between the two means at the end of the intervention period, divided by the pooled estimate of the standard deviations (i.e., Cohen's *d*) (Centre for Evaluation and Monitoring 2017). Effect sizes were used to compare studies to one another, but not to categorize studies based on effect sizes (Ialongo 2016). The effect sizes can be deemed small (<0.2), medium (0.2–0.8), or large (>0.8) (Sullivan and Feinn 2012). In some cases, in which articles did not present the means, standard deviation or standard error of measurement (SEM), an attempt was made to contact corresponding authors to access this information.

Results

Study characteristics

Studies were conducted in the United States (n = 4), United Kingdom (n = 5), France (n = 3), Italy (n = 1), Spain (n = 4), Canada (n = 1), Brazil (n = 1), and Norway (n = 1). Study designs included RCT (n = 16), non-RCT (n = 3), or crossover trials (n = 1). Participants in these studies included healthy adults (n = 14), adults with cardiovascular risk factors (n = 5), or adults with chronic hepatitis C (n = 1). The total number of participants included was 751. The duration of the studies ranged from 1 day to 31 weeks, with an average duration of 10.63 weeks (Table 2).

All studies documented the frequency and amount of hesperidin in 100% OJ. OJ amounts varied from 100-767ml/day, in which studies used regular OJ (n = 14), red OJ (n = 1), blood OJ (n = 2), high flavonoid (HF) OJ (n = 2), or high polyphenol concentration (HPJ) OJ (n = 1). Hesperidin amounts provided by the OJ ranged from 0.0025-582.5 mg/day. The frequency of consuming these beverages was between once to twice daily. Beyond consuming OJ, studies had participants consume their usual diet and maintain their normal physical activity routines (n = 10), consume a low polyphenol diet (n = 8), follow the French National Program diet (n = 1), or the American Heart Association (AHA) Step I lipid lowering diet (n = 1) (Table 3).

The effect of hesperidin in OJ on neurological outcomes

Two studies that assessed participants' neurological outcomes through subjective mood tests showed no significant difference in positive and negative affect scales between groups (Kean et al. 2015; Alharbi et al. 2016). Of the two studies, one study found a significant increase in global cognitive function between control and intervention groups after an 8-week consumption of flavanone-rich 100% OJ and a diet that restricted polyphenol-rich foods for 24 hours ($p < 0.05$) (Kean et al. 2015).

The effect of hesperidin in OJ on cardiac outcomes

Fourteen studies focused on cardiac outcomes that included specific lipids and/or blood pressure, in which results varied from baseline to post-intervention (n = 6) and between groups (n = 8). Three studies reported significant increases in Apo A-1 (Constans et al. 2015), HDL (Kurowska et al. 2000) or triglyceride levels (Franke et al. 2005; Kurowska et al. 2000). Other studies reported significant decreases in total cholesterol (Dourado and Cesar 2015; Gonçalves et al. 2017), LDL (Dourado and Cesar 2015; Gonçalves et al. 2017; Li et al. 2020), and ratio of HDL to LDL (Kurowska et al. 2000), or diastolic (Morand et al. 2011) or systolic blood pressure levels (Valls et al. 2021).

The effect of hesperidin in OJ on inflammatory biomarkers

From a group analysis, results varied in demonstrating the effect the intervention had on inflammatory biomarkers from baseline to post-intervention (n = 5) and between groups (n = 8). Results showed that significant decreases were seen among IL-6 and TNF-α (Buscemi et al. 2012), CRP (Buscemi et al. 2012; Dourado and Cesar 2015; Ghanim et al. 2007; Gonçalves et al. 2017) and uric acid (Escudero-López et al. 2018; Valls et al. 2021; Morand et al. 2011).

The effect of hesperidin in OJ on insulin

In the 7 studies that analyzed the effect of hesperidin in OJ on insulin, 3 found no differences pre-/post intervention (Escudero-López et al. 2018; Dourado and Cesar 2015; Gonçalves et al. 2017), 2 found no difference between groups (Simpson, Mendis, and Macdonald 2016; Morand et al. 2011), one showed a significant increase in OJ and glucose intervention compared to fructose intervention, (Ghanim et al. 2007) and the final study showed a significant decrease in the control group compared to the intervention (Rangel-Huerta et al. 2015).

The effect of hesperidin in OJ on antioxidant/phenolic outcomes

Thirteen studies sought to evaluate the antioxidant/phenolic outcomes from OJ consumption. From the results, there was a significant decrease in catalase (Escudero-López et al. 2018) and homocysteine (Valls et al. 2021) and significant increases in folate (Franke et al. 2005; Dourado and Cesar 2015; Kurowska et al. 2000; Gonçalves et al. 2017), homocysteine (Franke et al. 2005), ORAC (Escudero-López et al. 2018; Constans et al. 2015), phenolic compounds (Franke et al. 2005; Schar et al. 2015) and vitamin C (Dourado and Cesar 2015; Kurowska et al. 2000; Morand et al. 2011; Gonçalves et al. 2017; Franke et al. 2005).

The effect of hesperidin in OJ on biomarkers of oxidative stress

Eight studies assessed the impact of hesperidin on oxidative stress biomarkers and found significant decreases among peroxidation (Dourado and Cesar 2015; Rangel-Huerta et al. 2015) and T-BARS (Escudero-López et al. 2018; Gonçalves et al. 2017) (Table 3).

Quality and risk of bias

Of the 17 RCTs and crossover trial studies, based on the Cochrane risk of bias tool, seven articles were deemed high quality, as they showed low risk of bias across all domains. Five articles were deemed to have 'some concern,' and five were considered low quality as they showed high risk of bias in one domain or some concern in multiple domains. The domains that presented unclear or high risk of bias include random sequence generation and allocation concealment. Although all of the studies were randomized, three studies did not mention the randomization method and six had insufficient information about the sequence generation. Six studies also had insufficient information of allocation concealment.

Using the Newcastle-Ottawa Scale (NOS) to assess the non-randomized studies (e.g., cohorts or single-study designs), three of the studies were determined as 'good' quality considering each met the criteria of receiving 3 or 4 stars in the selection domain, 1 or 2 in the comparability domain and 2 or 3 in the outcomes domain. The details of the risk of bias assessment in individual studies are shown in Supplemental Material Tables 1 and 2.

Data synthesis

Effect sizes were estimated for each study, separated by evaluation measures (Supplemental Material Figures 1–6). Effect sizes were considered small or negligible if the standard deviation was $\leq$ 0.2, which was observed in 14 studies. However, multiple studies used various evaluation measures and, thus, demonstrated mixed effect sizes such as ORAC with an effect size of 1.43 (Escudero-López et al. 2018). Dourado and Cesar (2015) also showed positive effect sizes with vitamin C, folate and IL-4. Two additional studies assessing vitamin C demonstrated similar effect sizes (Gonçalves et al. 2017; Kurowska et al. 2000). A positive effect size was also shown in one study assessing peroxidation through sensitive detection of malondialdehyde (0.27) (Rangel-Huerta et al. 2015).

Similarly, Escudero-Lopez et al. (2018) demonstrated positive effect sizes in multiple areas, with TG and HDL measurements (>0.2). Blood pressure was addressed in 5 studies, assessing both diastolic and systolic blood pressure. Hollands et al. (2018) demonstrated a positive effect size (0.23) when analyzing systolic blood pressure but showed a negligible effect size when looking at diastolic blood pressure. On the other hand, Morand et al. (2011) showed opposite results with diastolic blood pressure having a positive effect size (0.61) and systolic blood pressure having a negligible effect size (-1.22). Regarding the studies evaluating cognitive function through subjective mood tests (PANAS), only one of the two studies demonstrated a positive effect size (0.23) (Alharbi et al. 2016).

Discussion

This narrative systematic review examined the effect hesperidin within 100% OJ has on chronic diseases (i.e., neurological conditions, cardiovascular disease, inflammation, etc.). Overall, global cognitive function improved in 1 out of 2 studies over the intervention period. Improvements in specific evaluation measures were found in cardiac (n = 8), inflammatory (n = 7), antioxidant/phenolic (n = 9), and oxidative stress (n = 4) outcomes. For the assessment of insulin levels (n = 7), one found a significant increase following both OJ and glucose intervention compared to fructose intervention, and another found a decrease in the control versus the intervention, while the remaining studies presented a null association. Taking a closer look at effect sizes previously estimated indicates that statistically significant results were considerably weak. Thus, the first objective of this narrative systematic review aimed at determining appropriate recommendations toward the dose and frequency of hesperidin consumption from OJ, there was no clear link between amount and duration of a study. For the second objective, a gap analysis was conducted to identify limitations in the literature and specific areas for future research. Results showed that there were variabilities in diet, genetics, and evaluation measures, as well as the dose and frequency of hesperidin between studies, thus areas of considerations and future research for human clinical trials focusing on 100% hesperidin in OJ are provided.

The effect of hesperidin in OJ on chronic diseases

Based on the results, the concentration of hesperidin in 100% OJ, frequency and length of consuming OJ has an impact on chronic disease biomarkers. For TNF-α and phenolic content, a dosage of 159.5 mg/d and 229 mg/d of hesperidin had a positive effect (Schar et al. 2015; Franke et al. 2005; Buscemi et al. 2012). Whereas, TBARS was reduced with a hesperidin level of less than 16.4 mg/d (Gonçalves et al. 2017; Escudero-López et al. 2018). Although the influence hesperidin has on chronic diseases from the human clinical trials identified in this review is unclear, animal model studies; mainly mice and rats have demonstrated positive results. These studies have focused on the protective effect of hesperidin on oxidative stress and anti-inflammatory activity, indicating its therapeutic use in preventing stress induced by exercise and as a result improvement in performance (Estruel-Amades et al. 2019). Hesperidin, through a cascade of events, stimulates phosphorylation of proto-oncogene tyrosine-protein kinase (Src), protein kinase B (Akt), adenosine monophosphate-activated protein kinase (AMPK), and endothelial nitric oxide (NO) synthase, thus improving NO synthesis. This results in increased flow-mediated dilation

(Rizza et al. 2011; Martínez-Noguera et al. 2019). Furthermore, this increase in NO leads to improved endothelial function, which allows enhanced nutrient and oxygen transport to working muscles during acute and prolonged exercise.

Another study that focused on hesperidin and its role in inhibiting bone loss and decreased serum and hepatic lipids in ovariectomized mice, concluded its possible role in the prevention of lifestyle related diseases (Chiba et al. 2003). Cardio protective properties of hesperidin between 100 to 400 mg/kg have also been observed in animal models specifically in its role of anti-lipid peroxidation and antioxidant properties (Selvaraj and Pugalendi 2010). Although mice and humans are very similar biologically, these results must be interpreted with caution, and validated through human clinical trials.

Duration of consuming OJ, regardless of the amount of hesperidin, positively affected ORAC ($\geq$ 2wks), (Constans et al. 2015; Escudero-López et al. 2018) CAT ($\leq$ 2wks), (Escudero-López et al. 2018) homocysteine, ($\leq$ 3wks), (Franke et al. 2005) insulin ($\leq$ 1wk or $\geq$ 12wks), (Ghanim et al. 2007; Rangel-Huerta et al. 2015) and TC levels ($\geq$ 8 weeks, 2 doses daily) (Dourado and Cesar 2015; Gonçalves et al. 2017). Diastolic blood pressure was reduced when participants consumed OJ for 4 weeks, twice daily (Morand et al. 2011). On the other hand, systolic blood pressure was reduced with consuming OJ for 12 weeks once daily (Valls et al. 2021). Positive effect sizes (> 0.2) were demonstrated in ORAC levels and diastolic blood pressure (Escudero-López et al. 2018; Morand et al. 2011), while other statistically significant results were estimated to be weak or negligible. The variability observed among these studies may have to do with a possible therapeutic window of measurement based on the chronic disease being studied. Results from this review align with a recent meta-analysis that determined the efficacy of hesperidin supplementation on cardio metabolic risk factors. The authors' identified 10 studies, in which the OJ dose administrated to participants in all studies were too wide of a range to be solely associated with the changes observed (Mohammadi et al. 2019). The authors suggested that between $3-12$ weeks of OJ consumption is needed to observe any potential lipid lowering effects (Mohammadi et al. 2019). Variability among how these markers were collected and assessed may have contributed to the discrepancies found within the literature. Therefore, controlling the frequency and dose of hesperidin in 100% OJ with varying lengths across human clinical trials to detect the effect hesperidin in 100% OJ with chronic diseases and conditions is necessary.

Diet variation and food matrix

Diet variation was identified within the studies, in which articles did not specify any alterations to participants' dietary and physical activity levels ($n = 10$), other studies had participants adhere to low polyphenol diets ($n = 8$) or follow a specific dietary pattern such as the French national program ($n = 1$), or American Heart Association (AHA) Step I lipid lowering diet ($n = 1$). No research discussed or recorded the dietary habits of participants prior to the study, however some studies instructed participants to follow diet restrictions or specific meal patterns before the intervention began, varying from 24 hours prior (Alharbi et al. 2016; Kean et al. 2015) to 4 weeks prior (Constans et al. 2015). This is a necessary component as the relationship between macronutrients and the bioavailability of flavanones may have led to the differences observed in these studies. Mullen et al. (2008) investigated the impact consumption of 150 ml of full-fat yogurt; a natural fat/protein matrix, has on the bioavailability of hesperidin in 250 ml of OJ. Hesperidin was studied by measuring urine and plasma levels. In the first 5 hours, the quantity of hesperetin metabolites excreted was significantly reduced by the yogurt but showed little change in excretion after 24 hours. The change over time was attributed to possible prolonged transit time to reach the large intestine or the low amounts of fat in the yogurt (Mullen et al. 2008). Hesperidin has been shown to be bioavailable from OJ; however, inter-individual variation is considerable and amounts can differ when taken with meals or evaluated over time (Erlund et al. 2001). In a multiple-dose response study, plasma hesperetin levels increased from baseline to 7 days after daily ingestion of 200 g minimally processed oranges, but then remained stable from day 7 to 14, thus, indicating a saturation effect and slowing changes over time (Pascual-Teresa et al. 2007).

With the studies included in this review, no attempt was made to exclude bioactive compounds from participants' diets, increasing the variability in parameters evaluated. Of the 20 studies, only one included a description of the meal coupled with the intervention (28 g of Kellog's Corn Flakes and 118 mL 2% milk) (Snyder et al. 2011). In most cases, results were explained by possible dietary influences, such as the fructose and sucrose amounts in the OJ that most likely resulted in an increase in HDL cholesterol (Kurowska et al. 2000) or the higher carbohydrate, total sugar and energy intake of the intervention group compared to the control group (Simpson, Mendis, and Macdonald 2016). The relationship between diet and flavonoid absorption, as well as the activity, has been studied in limited amounts and has not focused on the flavonoid at hand, hesperidin. However, of the studies conducted, protein has been reported in reducing flavonoid bioavailability (Xiao et al. 2011; Smith, Halliwell, and Aruoma 1992; Arts et al. 2001). In a study on bovine milk proteins (BMP), affinity of flavonoids to milk-proteins were observed and shown to be affected by molecular properties and structure (Xiao et al. 2011). This interaction has been investigated and found to affect the bioavailability of flavonoids, as well as weaken the antioxidant capacity (Smith, Halliwell, and Aruoma 1992; Arts et al. 2001).

The binding affinity and potential (non-) covalent interactions of flavonoids with food proteins, carbohydrates, and fats are directly associated with the physicochemical properties of flavonoids ("Flavonoids" 2021). The specific binding affinity to plasma proteins which has shown to possibly lower flavonoid bioavailability is linked to structural

characteristics. Glycosylation has been shown to reduce binding affinity, therefore suggesting that aglycones (e.g., hesperetin) may be limiting the bioavailability of flavonoids (Xiao et al. 2011). A main factor for these discrepancies may be the microbiota. Following oral intake, citrus flavanones reach the distal small intestine and colon mostly intact as they are resistant to enzymatic breakdown, they then are metabolized by intestinal bacteria into their aglycones. The microbiota composition and activity are variable between individuals, which can contribute to differences in metabolites formed and potential effects (Stevens et al. 2019). Dietary intervention studies aimed at examining the effect of a flavonoids on chronic disease markers should be aware of the impact of co-administering high protein diets with flavonoids and their interaction with the gut microbiota to minimize the potential confounding variables.

Genetic variance and evaluation measures

Genetic variance is another factor that may explain the outcome differences. Studies that have evaluated inflammation markers TNF-α and IL-6 showed a significant decrease in participants who had a higher risk of cardiovascular disease (CVD) compared to participants who were considered healthy. Buscemi et al. (2012), investigated the effect of hesperidin within 100% OJ in non-diabetic participants with increased CVD risk compared to healthy, non-obese control participants. Participants consumed either 250 mls of placebo or 250 mls of red OJ with 159.5 mg of Hesperidin twice daily for 3 weeks. Results demonstrated that blood basal concentrations of CRP, IL-6, and TNF-α were significantly higher in the CVD group, and decreased after a 1-week intervention compared to the healthy control group (Buscemi et al. 2012). On the other hand studies that evaluated CAT, showed opposite results with healthy adults showing a decrease, compared to no effect on those with higher CVD risk (Constans et al. 2015). Another variation is the definition of a healthy participant, whereas some studies considered overweight or obese participants with no underlying medical conditions as healthy, (Dourado and Cesar 2015; Morand et al. 2011; Simpson, Mendis, and Macdonald 2016) others did not define the term. In Dourado and Cesar (2015) 8-week cross-over study, participants were placed into two categories, normal weight and overweight. Participants consumed 375 mls of 100% OJ with 77.5 mg/d of Hesperidin twice daily. Significant differences among triglycerides, total cholesterol, LDL levels and TNF-α were observed among the overweight compared to the healthy adults, in which overweight participants had higher levels at baseline, but improved in value, except for triglycerides post-intervention (Dourado and Cesar 2015). Hesperidin as a therapeutic agent for obesity has been studied within animal and cell models, and the mechanism in which lipid and glucose metabolism is mediated has been discussed; (Xiong et al. 2019) however, to the authors' knowledge there has not been human studies conducted on the function of flavonoids based on the body mass index (BMI) of participants. Genetic variables such as BMI, sex, age and ethnicity have been highlighted when assessing human nutrition as they contribute to inter-individual differences (Li et al. 2020; Cassidy and Minihane 2017). Understanding the metabolism and absorption of citrus flavanones has given investigators insight into possible explanations for conflicting data. Enzymes that play pivotal roles in the absorption of flavonoids have been found to vary by ethnicity. For example, lactase phlorizin hydrolase, a membrane bound β-glycosides found in the brush border of the small intestine that acts to hydrolyze polyphenol glucosides before absorption, has been shown to be present in low concentrations in European adults (5%) compared to high concentrations in African and Asian adults (90%) (Nielsen et al. 2006; Li et al. 2020). Age and sex of participants are additional differences that may contribute to heterogeneity observed. Li et al. (2020), mentions the lack of studies in the context of polyphenol interventions that discuss possible differences observed in outcomes because of sex, but goes on to identify issues associated with including premenopausal women in studies. Premenopausal women experience fluctuations in exogenous or endogenous reproductive hormones that have been seen to impact endothelial function (Li et al. 2020). The mechanisms underlying sex differences in cardiovascular risk can be understood by identifying major differences between sexes, including hormone fluctuations in women during the menstrual cycle (Williams et al. 2001). Moreover, it is necessary that studies that involve diverse populations consider these aspects when analyzing and interpreting the data to minimize any potential confounding variables that may impact the effect of hesperidin in 100% OJ on chronic diseases and conditions.

Furthermore, evaluation measures and collection times may contribute to the variation in outcomes. Blood samples taken from participants have varied in both the technique and timing within these studies. Studies specified a 12-hour overnight fasting period and standardized conditions, (Constans et al. 2015; Dourado and Cesar 2015; Gonçalves et al. 2017; Rangel-Huerta et al. 2015; Li et al. 2020) while other did not discuss methods for blood or urine collection. The time in which blood samples are taken have been shown to influence outcomes. Manach et al. (2003) sampled blood at 10 different time points over a 24-hour period to determine the nature of circulating metabolites of flavanones. Three hours after a fasting period, participants who drank OJ with hesperidin showed flavanone metabolites, reaching peak plasma concentration between 5 to 7 hours, and returning to baseline after 24 hours (Manach et al. 2003). The peak time of flavonoid concentration can also depend on manipulations made to hesperidin amounts used in studies, therefore using similar amounts would allow for better control and comparison from intervention to intervention. For blood pressure, consistency was used in regard to validated instruments; however the instruments themselves differed with the most widely used brand being OMRON (Schar et al. 2015; Kean et al. 2015; Morand et al. 2011; Valls et al. 2021; Rangel-Huerta et al. 2015), but others also using a Vicorder device (Hollands et al. 2018). Consistency was not observed with readings, as studies

either took 2 consecutive readings (Valls et al. 2021), 3 readings (Schar et al. 2015; Kean et al. 2015; Li et al. 2020; Rangel-Huerta et al. 2015; Morand et al. 2011), or did not mention this detail, as well as varied in interval times (1-5 minutes). Resting periods before readings mainly varied between 10-20 minutes; however one study measuring blood pressure completed this after a short rest period of 2-5 minutes (Valls et al. 2021). As for lipid and antioxidant measurement techniques, standardized clinical methods were used, but varied based on the diagnostic laboratory used (Labtest Diagnostica S.A., Roche Diagnostics, Instrumentation Laboratory Worldwide, Alpha Diagnostic International, Inc, BD Pharmingen, etc.). The two articles analyzing cognitive function, only used three identical tests compared to the subjective tests that matched accordingly (Alharbi et al. 2016; Kean et al. 2015). The multiple measurement techniques used are a limitation that brings forth an inability to assess outcomes. Therefore, determining valid and reliable methods to collect and assess biomarkers to ensure consistency across various human clinical trials when focusing on hesperidin in 100% OJ is necessary.

Limitations and strengths

This narrative systematic review does have its limitations. The inclusion criteria targeted a specific population of interest and certain chronic disease/condition biomarkers. The limited number of studies that did meet the criteria set also varied considerably with the methodological quality, which made comparing outcomes difficult. As previous reviews have stated, trials were also heterogeneous in regards to their study design, number of participants, evaluation measures and techniques used (Mohammadi et al. 2019). One of the strengths of this review is the gap analysis that was conducted following evaluation of the obtained evidence, which pinpoints research priority areas and specific methodologies to improve the consistency of clinical data in future research. This review is also the first to provide a thorough analysis of the literature conducted on hesperidin consumption from 100% OJ as a mechanism to reduce complications associated with various chronic diseases and conditions.

Practical implications

Future research is needed to gain a stronger understanding of the role of hesperidin in OJ on chronic diseases and conditions. Results showed positive trends in improved disease biomarkers, with the strongest association in antioxidant and phenolic biomarkers. Studies, although inconsistent, have been completed largely on cardiovascular diseases, other conditions should be investigated including cancer, irritable bowel syndrome, celiac disease, bone disease, and/or diabetes. A focus should be on those presenting with the specific NCD or chronic disease being studied and consistency in study design is crucial including setting a standard diet and using better defined measuring tools. Based on the role of hesperidin on exercise/performance and the impact diet variation and the food matrix play, it would also be of interest to study the possible role of non-pharmacological approaches that improve longevity and decrease risk of chronic age-associated diseases on increasing the effect of hesperidin.

Conclusion

In conclusion, results from this review showed that the intake of hesperidin from 100% OJ improves certain chronic disease biomarkers; however, the literature does not confidently portray this due to various confounding factors. Future research must consider the role of diet, genetics, evaluation measures and flavonoid bioavailability when making conclusions regarding flavonoid effects on chronic diseases and conditions. Higher frequencies, doses, and concentration of hesperidin in 100% orange juice had an impact on cardiac, inflammatory, antioxidant/phenolic, and oxidative stress outcomes compared to lower frequencies, doses, and concentration of hesperidin. If all factors identified from the gap analysis conducted are addressed in future research the slight effect observed from hesperidin in >500mL of OJ may become more apparent.

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Declaration of interest statement

The authors declare that they have no conflict of interest.

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