Food Research International 149 (2021) 110655

Contents lists available at ScienceDirect

Food Research International

journal homepage: www.elsevier.com/locate/foodres

Review

Design of polyphenol-rich diets in clinical trials: A systematic review

Luis Condezo-Hoyos [a,b], Christina Gazi [a], Jara Pérez-Jiménez [a,*]

[a] Department of Metabolism and Nutrition, Institute of Food Science, Technology and Nutrition (ICTAN-CSIC), Madrid, Spain
[b] Universidad Nacional Agraria la Molina, Facultad de Industrias Alimentarias, Innovative Technology, Food and Health Research Group, La Molina, Lima, Perú

ARTICLE INFO

Keywords:
Polyphenols
Clinical trial
Systematic review
Healthy diet

ABSTRACT

Most randomized clinical trials of polyphenols focus on individual foods. Nevertheless, due to their presence in many foods and in order to reflect a real situation, clinical trials based on polyphenol-rich diets are particularly important. This systematic review explores the characteristics of the polyphenol-rich diets used in intervention studies. The bibliography search for English-language scientific papers was performed in the Elsevier Scopus Database and PUBMED in March 2020, and focused on intervention studies with whole polyphenol-rich diets, establishing several exclusion criteria. In studies fulfilling the requirements, information on the design of the polyphenol-rich diet and associated polyphenol intake was extracted and compared. A total of 5 studies were selected. Among them, substantial differences were found in the design of the polyphenol-rich diets, regarding specific instructions and concerning the foods provided. Similarly, although a median daily polyphenol intake of 2,564 mg/day (17,945 mg/week) was obtained from the studies, which corresponds to a nutritional dose, intake values varied widely both for total polyphenols (the difference between studies reached threefold), and for individual polyphenol intake (for hydroxycinnamic acids, a tenfold difference was found between percentile 25 and percentile 75 values). These differences made the comparison of results difficult and may affected the observed health effects. Thus, despite the relevance of studying polyphenol-rich diets as a whole, this systematic review found substantial differences between the studies performed, making direct comparisons difficult.

1. Introduction

Polyphenols constitute a large group of plant secondary metabolites widely distributed throughout the plant kingdom (Rodriguez-Mateos et al., 2014). They exhibit several biological activities, for instance functioning as antioxidants (Morvaridzadeh et al., 2020a) and anti-inflammatory compounds (Morvaridzadeh et al., 2020b). Cumulative scientific evidence, including the results of mechanistic experiments, assessments of metabolic fate, clinical trials and observational studies, has shown that these compounds play a promising role in the modulation of several non-communicable chronic diseases, particularly cardiometabolic diseases (Serino & Salazar, 2018; Martini et al., 2019), as well as certain kinds of cancer (Bondonno et al., 2019), neurodegenerative processes (Squillaro et al., 2018) and specific diseases such as polycystic ovarian syndrome (Heshmati et al., 2020).

However, research on polyphenols has sometimes apparently been contradictory as demonstrated, for instance, in two systematic reviews of the role of grapes (one of the fruits with the highest polyphenol content) in the regulation of metabolic syndrome (Akaberi & Hosseinzadeh, 2016; Woerdeman et al., 2017). It has been suggested that consistency in several aspects when designing and performing nutritional clinical trials would eliminate some of these discrepancies; for instance, clearly defining clinical endpoints when translating preclinical studies on polyphenols into clinical trials (Núñez-Sánchez et al., 2015). In the same way, some studies have suggested certain criteria for reporting results of inter-individual variability in the response to bioactive dietary compounds, a highly relevant aspect in the field of polyphenols (Nikolic et al., 2019), as well as for study design and analytical determinations in studies on the biological effects of bioactive compounds, including polyphenols, on gene expression (Pokimica & García-Conesa, 2018). Also, the importance of systematically measuring microbiota variations in clinical trials with polyphenols has been addressed (Marino et al., 2020). Overall, the increasing interest in recommendations on how polyphenol studies should be conducted or reported shows the relevance of study design and how it is an aspect that deserves specific attention.

Another relevant aspect is that many clinical trials with polyphenols

* Corresponding author at: Department of Metabolism and Nutrition, Institute of Food Science, Technology and Nutrition (ICTAN-CSIC), José Antonio Novais 10, 28040 Madrid, Spain.
E-mail address: jara.perez@ictan.es (J. Pérez-Jiménez).

https://doi.org/10.1016/j.foodres.2021.110655
Received 17 March 2021; Received in revised form 27 July 2021; Accepted 17 August 2021
Available online 20 August 2021

have evaluated the effect of supplementation with an individual food (Akaberi & Hosseinzadeh, 2016; Gianfredi et al., 2018; Woerdeman et al., 2017). Although such studies are absolutely needed for the identification of responses to individual foods, at the same time the effect of the whole diet may not be disregarded. Indeed, it has been pointed out that the combination of polyphenols from different foods is precisely what can give rise to biological activities (de Pascual-Teresa & Clifford, 2017). And a study (Molinar-Toribio et al., 2018) where rats consuming either a control diet of a high-fat high-sucrose diet were supplemented with grape seed extract showed that the generation of microbial-derived metabolites was decreased in the high-fat high-sucrose group, probably due to a shift in microbial communities. This might show modified biological activities of a particular polyphenol supplementation in the context of an unhealthy dietary pattern. For these reasons, some researchers have chosen to evaluate the effect of a polyphenol-rich diet (Bozzetto et al., 2015; Noad et al., 2016); they have shown beneficial effects in subjects at high cardiometabolic risk, which has increased the existing evidence on the biological relevance of polyphenols. Nevertheless, the issue of heterogeneity in the design also arises here, for example: What may be considered a polyphenol-rich diet? Which individual foods are included? In what proportions? How detailed must the instructions provided to the volunteers be? All these aspects are relevant when it comes to comparing results, as well as in order to establish public health recommendations; but to date, they have not been explored in detail.

For these reasons, we consider it is pertinent to perform a systematic review of nutritional clinical trials based on polyphenol-rich diets. The aim of this systematic review is not to address a specific clinical question, since the selected studies may have dealt with different physiological situations and focused on varied primary outcomes, but to focus on the concept of a polyphenol-rich diet itself and how it has been defined in previous studies (foods, serving sizes and associated polyphenol intake), in order to identify the main shared characteristics and divergences between them and, ultimately, to suggest criteria that will allow consistency in this kind of study. Therefore, the question we address here is: "How are polyphenol-rich diets designed in nutrition clinical trials?" We adopted an established PICOS approach, as defined below. Quantitative data on polyphenol content in the designed diets were integrated from the different studies and an overall analysis was carried out; nevertheless, since these data did not correspond to modifications in a clinical outcome, this not a *meta*-analysis.

2. Methods

This systematic review was conducted according to PRIMSA guidelines; although, as it did not deal with a specific clinical question, some aspects could not be adopted. The complete PRISMA checklist is provided as Supplementary Table 1.

2.1. Search strategy and study selection

The bibliographic databases Elsevier Scopus Database and PUBMED were systematically searched for relevant papers until March 2, 2020. No other sources were included.

The following PICOS parameters were applied: Participants, adults; Intervention, treatment with polyphenol-rich diet; Comparison, intervention treatment with low-polyphenol diet; Outcome, since the focus of the systematic review was the design of the polyphenol-rich diet, no clinical outcome was predefined; Study design, only intervention studies were selected.

The first step of the systematic search was performed with the following keyword combinations "polyphenol*" AND "diet" AND ("trial" OR "intervention") AND "human" and the papers returned were exported to Endnote software (Clarivate Analytics, PA, USA) with duplicated papers being eliminated. Once in Endnote, the titles of papers were screened for two inclusion criteria: I) trial OR intervention AND diet; and II) poly* OR flav* OR phe*. After this, the abstracts were analyzed based on the following inclusion criteria: 1) an original study; 2) conducted in humans; 3) an intervention study, including either randomized controlled trials (2 arms with and without intake of a polyphenol-rich diet) or before-and-after studies (one arm following a polyphenol-rich diet for a certain period); 4) evaluating the effect of a polyphenol-rich diet; 5) published in English; and 6) data presented in a usable format. Conversely, the following exclusion criteria for this step were defined: 1) reviews; 2) preclinical studies; 3) observational studies; 4) studies based on supplementation with a single food or additive; 5) languages other than English; 6) absence of extractable data (see below).

2.2. Quality assessment

The JADAD score evaluation system was applied for assessment of the methodological quality of the 5 clinical trials selected (Reis et al., 2019). The studies were scored according to key methodological features: randomization (R), sequence of randomization (SR), blinding (B), method of blinding (MB), withdrawals/dropout (WD), inappropriate randomization (IR) and inappropriate blinding (IB) (Bisol et al., 2020). The studies with a JADAD score $\geq$ 3 were considered to have high-quality methodology (Bisol et al., 2020).

2.3. Data collection

Data were extracted from the clinical trial studies selected with a JADAD score $\geq$ 3; although characteristics of the study design, such as randomization, would not affect the results of the present systematic review, focused on diet design, at the same time it was considered that the higher the quality of the overall study design was, the higher the probability for the existence of a detailed and justified polyphenol-rich diet was. The selected studies included: bibliographic data, study characteristics (aim, design, and location), participants (age, sex, and characteristics), and a description of the dietary intervention. Since this last aspect is the main point of interest of this systematic review, the following information was collected, when it was available: 1) specific intervention concept (polyphenol-rich diet, flavonoid-rich diet and others); 2) food groups included or excluded in the diet; 3) individual foods included or excluded in the diet; 4) instructions about number and size of servings per day or week; 5) degree of detail in the instructions (specific meals to be consumed, and general lists of recommended foods); 6) expected polyphenol intake of the subjects and degree of detail (by class or individual compounds); 7) actual polyphenol intake of the subjects and degree of detail (by class or individual compounds); 8) source of polyphenol content information (in-house data or public databases); and 9) follow-up strategy for assessing dietary adherence.

2.4. Data processing

The information provided on polyphenol intake in the selected studies was quite varied: in some cases, no information on polyphenol intake was provided (Malaveille et al., 2004), while other studies specified the value of total polyphenol intake (Della Peppa et al., 2020) or flavonoid content in the recommended foods (Chong et al., 2013). Due to this diversity, the only way to process all the studies together and obtain data on individual and total polyphenol intake, in order to address the question we have proposed for this systematic review, was to calculate the polyphenol intake for all the studies based on the information they provided on the study design. To do this, we used the validated Phenol-Explorer (Neveu et al., 2010) and USDA (Bhagwat & Haytowitz, 2007) databases, which provide composition data for thousands of individual foods from the literature, and we took into account the amount of individual foods consumed weekly. When the polyphenol content of individual foods was not available in these databases, specific research papers were used to obtain the missing information, as was the case of rocket (Santos et al., 2014), blueberry jam (Ścibisz & Mitek,

2007), cherry tomatoes (Jeż et al., 2018) and watercress (Giallourou et al., 2016).

In the case of the study by Chong et al., (Chong et al., 2013), since the subjects received an additional polyphenol dose on top of their basal intake, which was not indicated in the study, this was taken from the quintile with the lowest polyphenol intake (since these subjects were characterized by a low fruit and vegetable intake) determined in a similar cohort. Furthermore, since the subjects were instructed to consume a certain amount of fruit and vegetables distributed in several items, but without further instructions, it was assumed that all the food items were consumed in the same proportion. Finally, in that same study the weight (g) was considered equal to volume (mL) for liquid foods. Regarding the study by Malaveille et al. (2004) total and individual polyphenols were not calculated because the intake of individual foods was not provided.

The data for total and individual polyphenol intake from each study were then integrated in order to obtain p25 (percentile 25), median, p75 (percentile 75), minimum and maximum values for polyphenol intake in the studies selected. Unless expressly stated, all the results provided in the Results section below correspond to median values.

3. Results

3.1. Search and study selection

The workflow for paper selection is shown in Fig. 1A. While the initial bibliography search of the Scopus and PUBMED databases provided a total of 1,756 publications, the application of the two inclusion criteria to the titles and the exclusion of duplicated papers, resulted in the identification of 33 publications for potential inclusion. From these, reading the abstract and application of the six additional exclusion criteria explained above finally left us with just 5 nutritional intervention studies for our systematic review (Fig. 1A). The JADAD score of each of these selected publications was 3 or 4 (Fig. 1B), reflecting a high-quality methodology.

3.2. Nutritional intervention studies

Characteristics of the selected nutritional studies are summarized in Table 1. The interventions lasted from 8 to 12 weeks using mostly randomized, controlled, parallel, single-blinded designs. The studies were focused on several primary and secondary outcomes; four of the five studies selected found that the polyphenol-rich diet significantly improved the primary outcome established in each case.

Regarding subject characteristics, excepting one study (Malaveille et al., 2004) where inclusion criteria did not consider cardiovascular risk factors, ie., it was focused on male smokers of at least 15 cigarettes/day for the last 10 years, the other ones considered some aspects related to cardiovascular risk. Thus, they included both male and female subjects, aged at least 30 and with a limit between 65 and 70 years old. And, depending on the study, they should have some cardiovascular risk: hypertension; overweight/obesity alone or combined with another factor of Metabolic Syndrome; cardiovascular risk according to Framingham score

3.3. Polyphenol sources in the nutritional intervention studies

Once information on the diet in the selected studies was compiled, it was possible to establish the food groups and individual food items recommended to the volunteers in those studies. This information is shown In Fig. 2. Fruit (100%), vegetables (80%), beverages (60%) and cocoa products (60%) were the polyphenol sources in the intervention studies included. Regarding individual foods, oranges (60%), blueberries (40%), strawberries (40%) and kiwis (40%) were the most common fruit, while onion (80%), rocket (40%), spinach (40%), cabbage (40%) and tomato (40%) were selected as the richest polyphenol sources in the vegetable group. In relation to the beverage intake, decaffeinated green tea and coffee (40%) were the sources of polyphenol. Other specific food products were extra virgin olive oil (40%) and dark chocolate (60%).

3.4. Intake of total polyphenols and main polyphenol classes in the nutritional intervention studies

From the dietary recommendations given to the participants in the studies included in our review, it was possible to establish the range of total polyphenol intake as well as the intake of the different polyphenol classes for each study, as shown in Fig. 3. Total polyphenol intakes ranged from 11,394 (p25) to 27,060 (p75) mg/week, with a median value of 17,945 (Fig. 3A), which we categorized into three polyphenol groups according to the amount consumed: high, intermediate and low (Fig. 3B-D). In the high group (Fig. 3B), hydroxycinnamic acids (4,659 mg/week) were the predominant polyphenol class, followed by flavonols (4,144 mg/week), flavanols (1,593 mg/week), hydroxybenzoic acids (880.1 mg/week), anthocyanins (239 mg/week), and proanthocyanidins (>100 mg/week). In the intermediate intake category, the polyphenol classes present were flavanones (45.3 mg/week), tyrosols (35.3 mg/week) and flavones (8.7 mg/week) (Fig. 3C). Finally, the polyphenol classes with low intake were lignans (4.95 mg/week), alkylmethoxyphenols (3.78 mg/week), stilbenes (0.725 mg/week), and dihydrochalcones and isoflavones (0.0 mg/week) (Fig. 3D). It should be highlighted that most polyphenol classes showed considerable data dispersion (for instance, for hydroxycinnamic acids, p25 was 301.1 mg/week and p75 was 12,370 mg/week; and in flavonols, these values were 353.1 and 7,288 mg/week), which may lead to different physiological effects on individuals, all of whom were subjected to an overall high polyphenol intake. In contrast, in some classes such as flavanols, the values were much more tightly grouped, with a p25 value of 853.3 mg/week and a p75 value of 2,156 mg/week.

3.5. Intake of individual polyphenols in the nutritional intervention studies

We obtained the mean intakes for individual polyphenols in the different polyphenol classes in the studies included, and they are represented in Figs. 3-6. To facilitate clear data visualization, in categories where the range of intakes for the different individual compounds were very wide, they are represented as high, intermediate and low intake (for instance, for hydroxycinnamic acids) or as high and low intake (as in the case of anthocyanins).

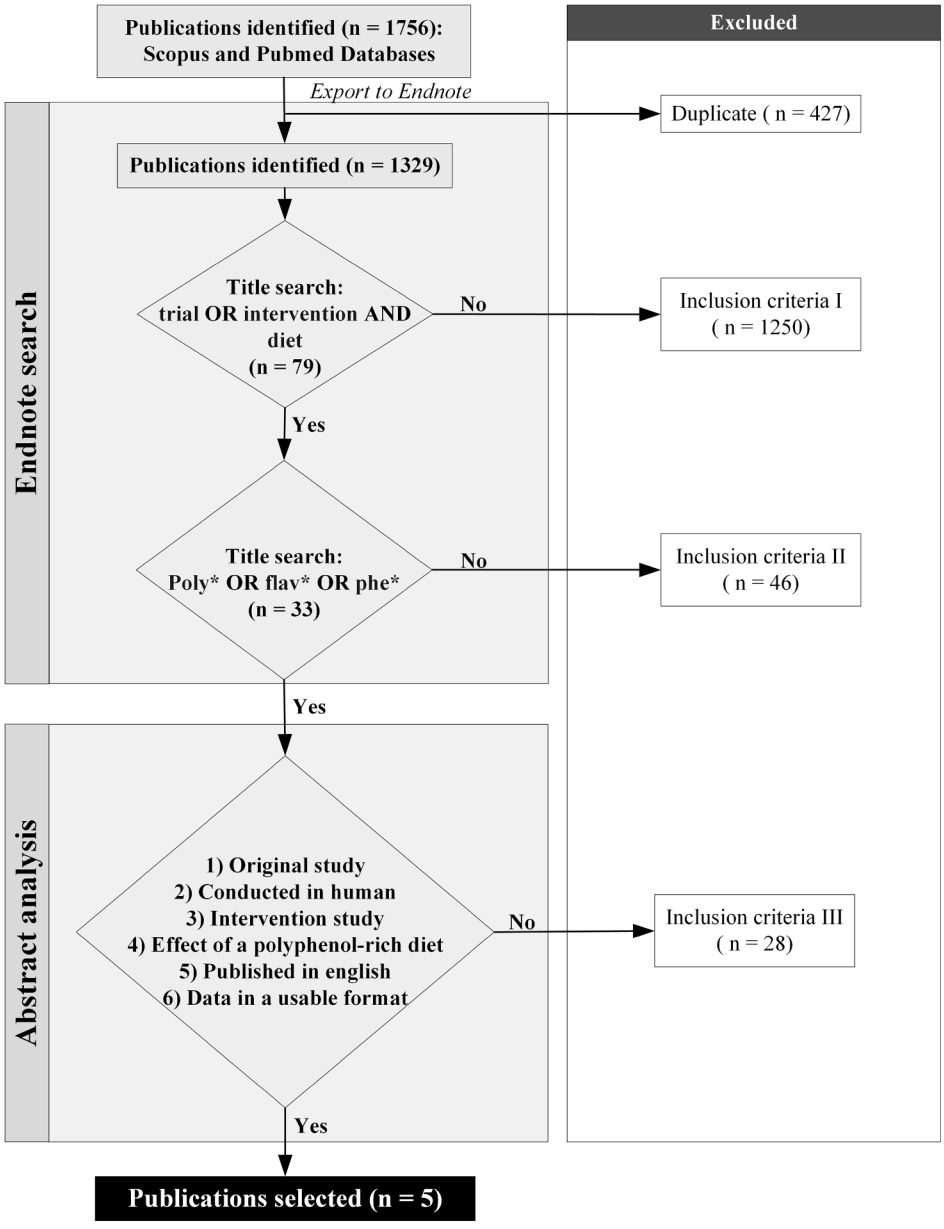
3.5.1. Hydroxycinnamic acids

5-Caffeoylquinic acid was the hydroxycinnamic acid that was most consumed in whole-diet intervention studies (1,742 mg/week), followed by 3-caffeoylquinic acid (910.8 mg/week) and 4-caffeoylquinic acid (846.2 mg/week) (Fig. 4A-1). The intermediate group of hydroxycinnamic acid intake included 4-feruloylquinic acid (133.1 mg/week), 5-feruloylquinic acid (125.8 mg/week), 4,5-dicaffeoylquinic acid (116.8 mg/week), ferulic acid (106.2 mg/week), 3,4-dicaffeoylquinic acid (105.7 mg/week) and 3,5-dicaffeoylquinic acid (88.76 mg/week) (Fig. 4A-2). Finally, three individual minor hydroxycinnamic acids were found in the intervention studies: caffeoyl glucose (0.28 mg/week), feruloyl glucose (0.28 mg/week) and cinnamic acid (0.17 mg/week) (Fig. 4A-3).

3.5.2. Flavonols

Quercetin (2,418 mg/week) was the main flavonol present in the polyphenol-rich diets in the intervention studies (Fig. 4B-1). In the intermediate consumption group, myricetin (59.4 mg/week), quercetin 3-O-rutinoside (40.9 mg/week), kaempferol (39.3 mg/week), isorhamnetin (29.1 mg/week) and quercetin 3-O-galactoside (22.2 mg/week) were found in the dietary intervention studies (Fig. 4B-2). Minor

A



B

Selected publications	Key methodological feature							JADAD score
	R	SR	B	MB	WD	IR	IB	
Della et al (2020)	+	+			+			3
Noad et al (2016)	+		+	+	+			4
Annuzzi et al (2014)	+	+			+			3
Chong et al (2013)	+		+		+			3
Malaveille (2004)	+	+	+		+			4

R: Randomization; SR: Sequence of randomization; B: Blinding; MB: Method of blinding; WD: Withdrawals/Dropouts; IR: Innappropiated randomization; IB: Innappropiated blinding

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flowchart of study inclusion (A); and JADAD scores of the selected publications according to key methodological features (B).

Table 1
General characteristics of the nutritional intervention studies included in this systematic review.

Diet design			Study design				References
Serving size	Degree of detail	Strategy for assessing dietary adherence	Study type	Subject characteristics	Primary outcome	Secondary outcomes	
NS	Meals were prepared by a qualified catering service under the supervision of the team of dietitians	Every week participants were given meals and beverages, for the whole duration of intervention, in amounts sufficient to cover overall household needs	Randomized, controlled, parallel, single-blinded	Men and women aged between 35 and 70 years with overweight or obesity (BMI 27–35), high waist circumference (above 102 cm for men or 88 cm for women), and at least one more feature of the metabolic syndrome based on the National Cholesterol Education Program/Adult Treatment Program	Postprandial lipid response*	Glucose, insulin, GLP-1, microbiota, oxidative stress	Della et al. (2020) Vetrani et al. (2020) Vetrani et al. (2018) Bozzetto et al. (2015)
Based on UK Food Standards Agency guidelines	6 daily portions of F&V including one portion of berries and 50 g of chocolate (70% cocoa) , per day.	The high-polyphenol diet had a self-selected weekly delivery of the diet, free of charge, to participants' homes from a local supermarket. Each participant was also contacted by telephone at weekly intervals	Randomized, controlled, parallel, single-blinded	Men and women aged 40–65 years, with documented grade I (140–159/90–99 mm Hg) or grade II (160–179/100–109 mm Hg) hypertension.	Forearm blood flow responses to an endothelium-dependent vasodilator*	Blood pressure, lipid profile, body mass index	Noad et al. (2016)
Green tea 400 ml, dark chocolate 25 g, blueberry jam 50 g, artichokes 300 g, onions 200 g, spinach 150 g and rocket 90 g	Meals were prepared by a qualified catering service under the supervision of the team of dietitians	To improve diet adherence, meals and beverages were provided to the participants for the whole study period in amounts sufficient to cover their household consumption	Randomized, controlled, parallel, single-blinded	Men and women aged between 35 and 70 years with overweight or obesity (BMI 27–35), high waist circumference (above 102 cm for men or 88 cm for women)	Postprandial triglycerides*	Fasting lipid profile, urinary isoprostanes	Annuzzi et al. (2014)
2 portions per day additionally every 6 weeks of the study reaching a maximum of 6 extra portions per day by week 18	Participants were encouraged to consume a variety of F&V or composite foods from the list each week and have equal proportions of F&V	Participants in the intervention groups indicated the type and number of additional portions of F&V they consumed each day on record forms. A minimum of two random structured 24 h dietary recalls	Randomized, controlled, parallel, single-blinded	Male and women aged 30–70 years. Framingham risk score system was used for recruitment based on scoring a minimum of 2 points in one or more of the following criteria: (1) total plasma cholesterol, (2) high-density lipoprotein (HDL) cholesterol, (3) blood pressure, (4) smoking status; (5) obesity/adiposity and (6) body mass index (BMI)	Vascular reactivity*	Plasma and urine vitamin C, carotenoids, flavonoids, uric acid, antioxidant capacity	Chong et al. (2013); McReady et al. (2014)
NS	The dietician developed a food-nutrient-intake matrix specifically focused on flavonoids, to quantitatively assess the intake	All participants filled in a food-frequency questionnaire (FFQ) at the beginning of the study, and then filled in a daily dietary diary during the experimental month	Randomized, controlled, parallel, single-blinded	Male smokers of at least 15 cigarettes/day for the last 10 years	Urine DNA adducts	Urine phenolic compounds	Malaveille et al. (2004)

NS, non-specified.
* Significant differences ($p > 0.05$) were observed between low- and high- polyphenol diet, showing beneficial effects of high-polyphenol diet.

flavonols included kaempferol 3-O-galactoside (11.8 mg/week), patuletin 3-O-(2''-feruloylglucosyl)(1->6)-[apiosyl(1->2)]-glucoside (7.3 mg/week), quercetin 3-O-glucuronide (4.5 mg/week) and spinacetin 3-O-glucosyl-(1->6)-glucoside (3.5 mg/week) (Fig. 4B-3).

3.5.3. Flavanols

(-)-Epigallocatechin 3-O-gallate (380.2 mg/week), (-)-epigallocatechin (275.7 mg/week), (-)-epicatechin (151.3 mg/week), (-)-epicatechin 3-O-gallate (106.6 mg/week) and cinnamtannin A2 (94.2 mg/week) were the flavanols with the highest intake in the dietary interventional studies (Fig. 4C-1). While procyanidin dimer B2 (84.9 mg/week), procyanidin trimer C1 (75.5 mg/week), (+)-catechin (55.5 mg/week), (+)-gallocatechin (31.8 mg/week), and procyanidin dimer B4 (26.9 mg/week) were identified in the intermediate intake group (Fig. 4C-2). Finally, procyanidin dimers B1 (15.7 mg/week) and B7 (13.2 mg/week) were the minor flavanols in the nutritional intervention studies (Fig. 4C-3).

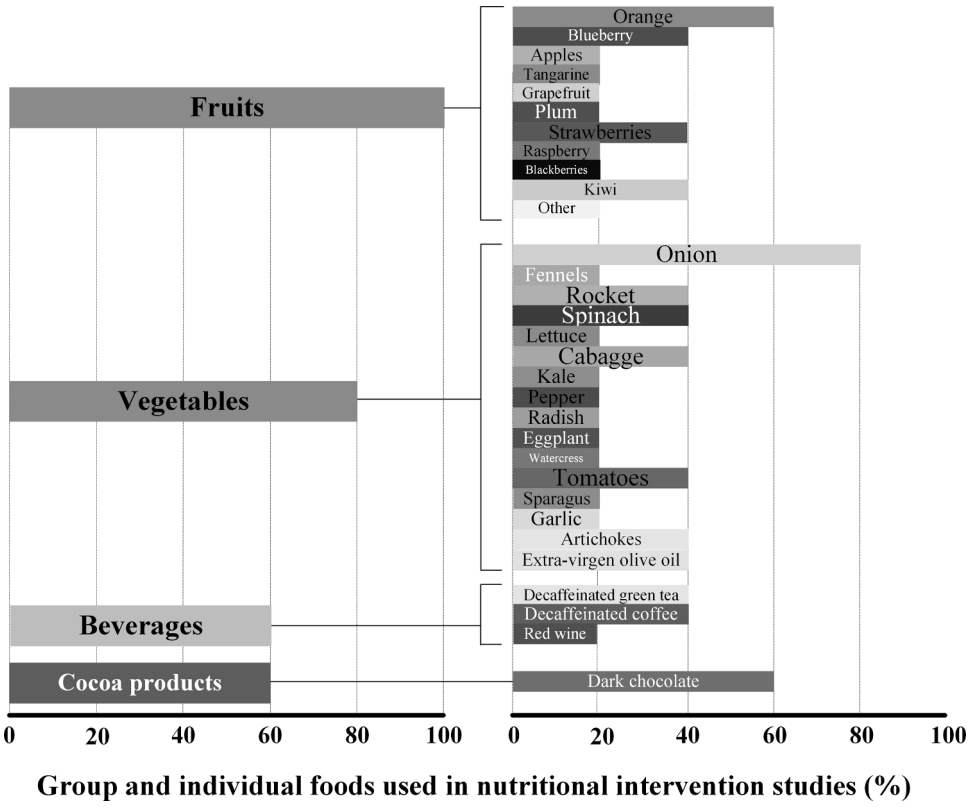


Fig. 2. Food groups and individual foods used as polyphenol sources in the nutritional intervention studies included in this systematic review.

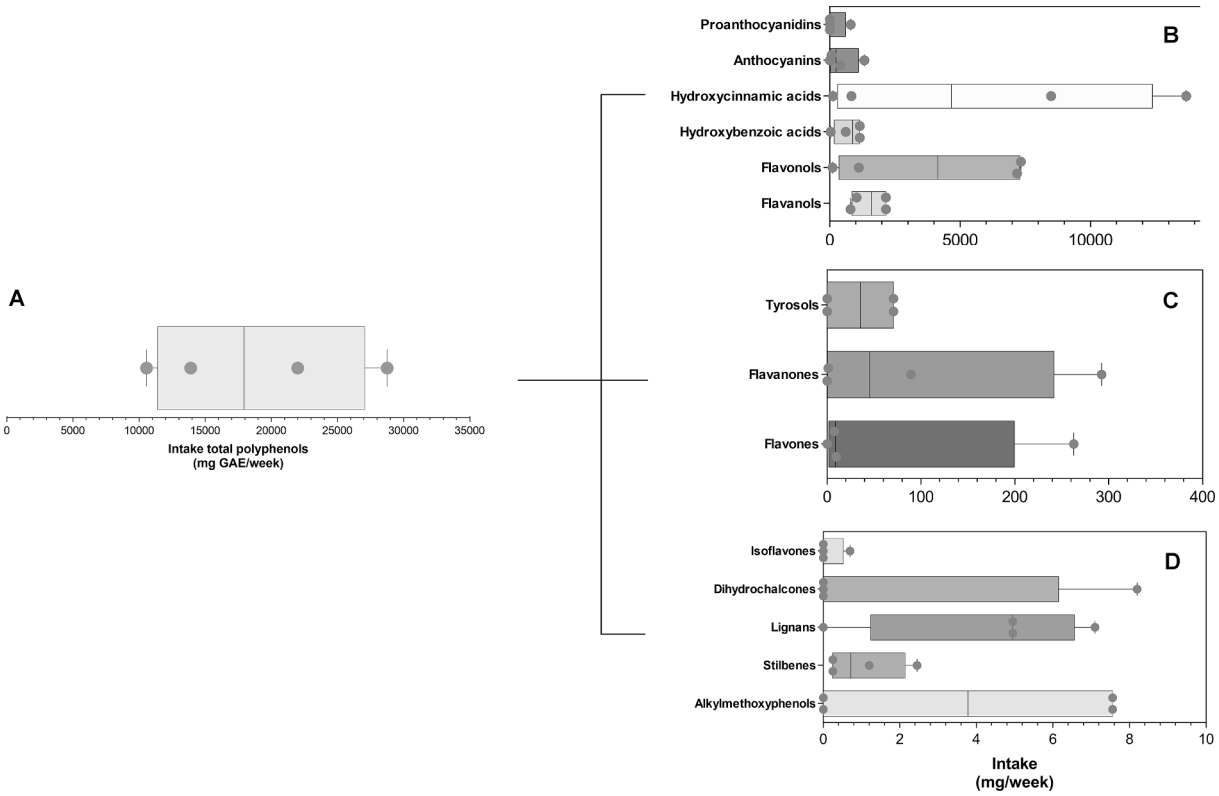


Fig. 3. Intake of total polyphenols (A), and main polyphenol classes (B-D), calculated from diets used in the nutritional intervention studies included in this systematic review. Polyphenol contents were obtained from Phenol-Explore and USDA databases, and from some specific research papers for foods missing from those databases. The values are expressed as mg/week.

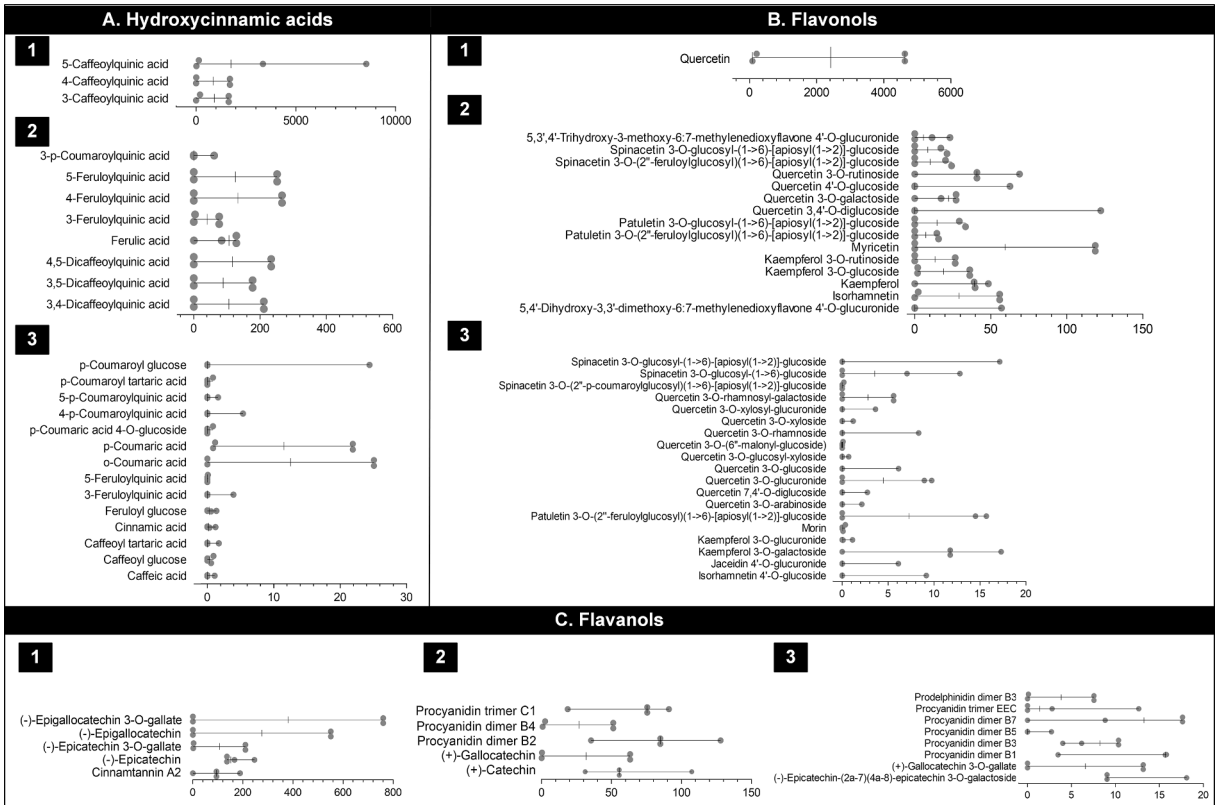


Fig. 4. Intake of individual hydroxycinnamic acids, flavonols and flavanols in the nutritional intervention studies included in this systematic review. For polyphenol class, individual compounds were grouped as high, intermediate or low intake. The values are expressed as mg of individual polyphenol/week.

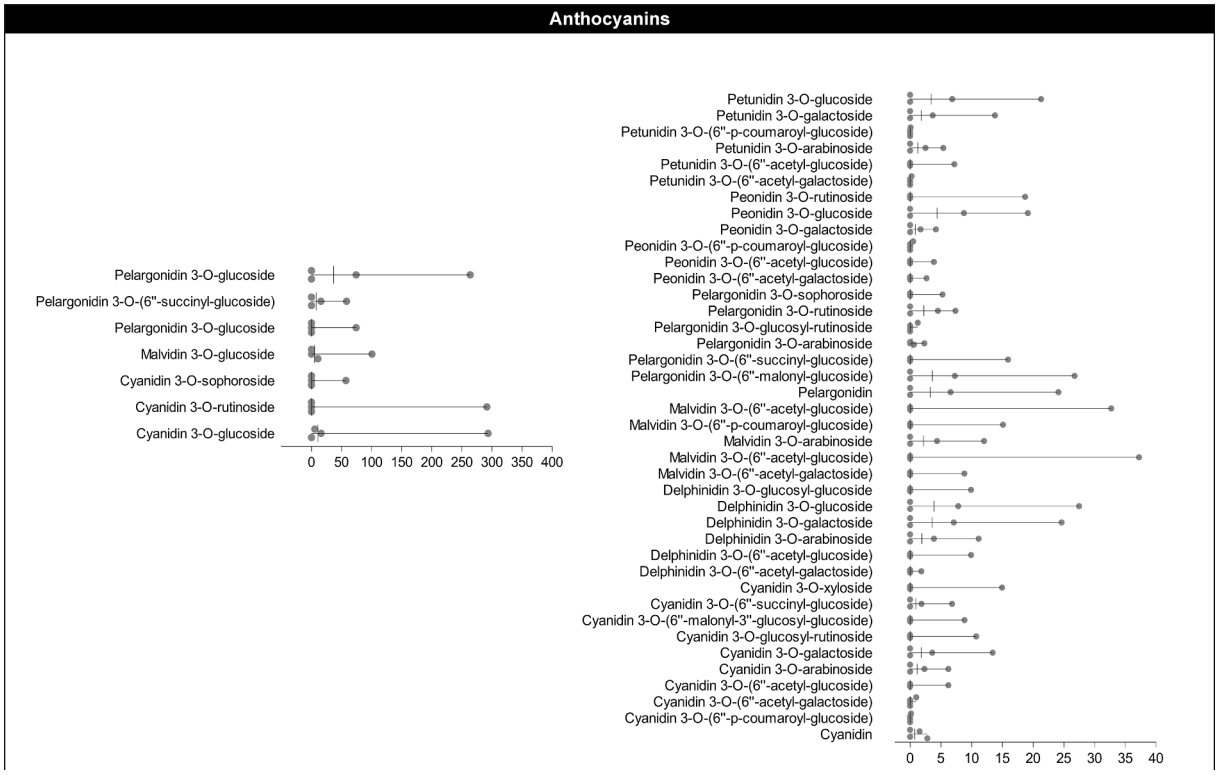


Fig. 5. Intake of individual anthocyanins in the nutritional intervention studies included in this systematic review. Individual compounds were grouped as high or low intake. The values are expressed as mg of individual anthocyanin/week.

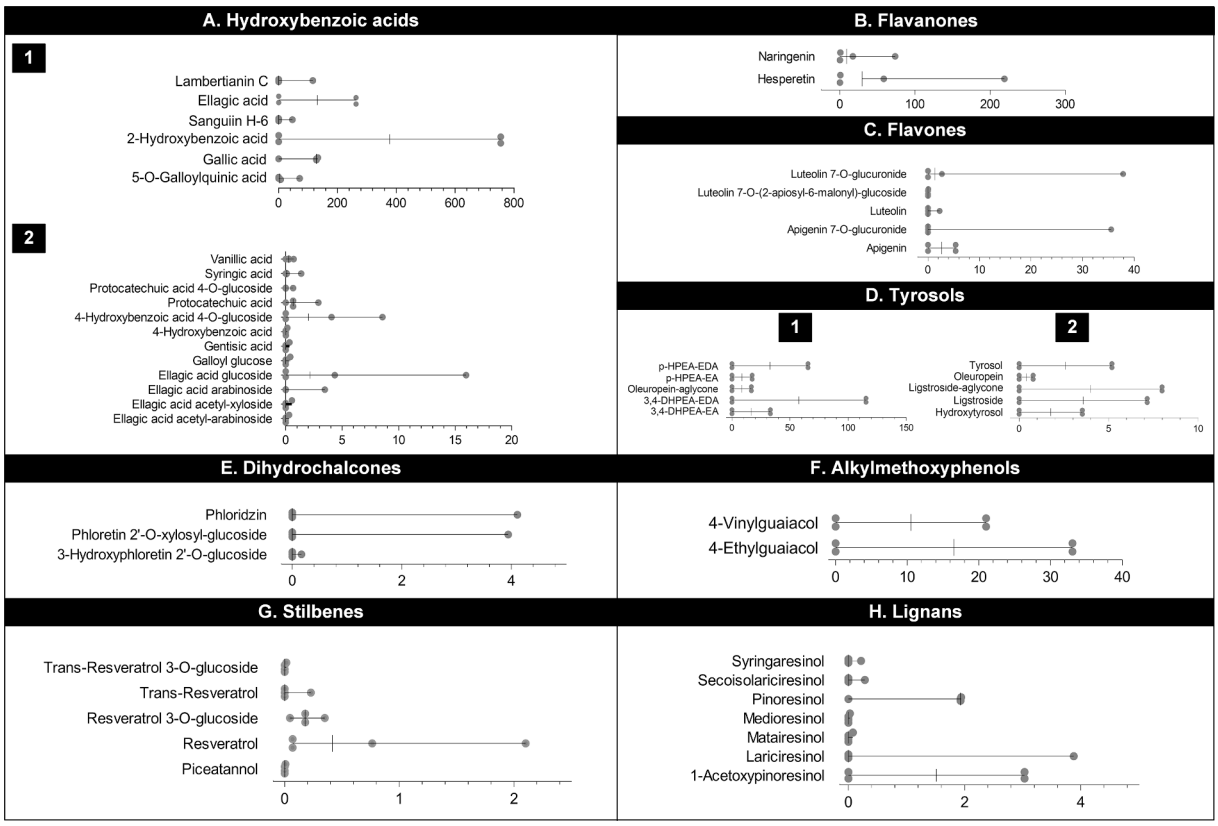


Fig. 6. Intake of individual flavanols, flavanones, flavones, tyrosols, dihydrochalcones, alkylmethoxyphenols, stilbenes and lignans in the nutritional intervention studies included in this systematic review. In each group of polyphenols, individual compounds were grouped as high, intermediate or low intake. The values are expressed as mg of individual polyphenol/week.

3.5.4. *Anthocyanins*

Forty-seven individual anthocyanins were found in the polyphenol-rich diets of the intervention studies (Fig. 5). We divided them into two categories. The first included those with a mean intake higher than 5 mg/week: pelargonidin 3-O-glucoside (37.2 mg/week), cyanidin 3-O-galactoside (11 mg/week), pelargonidin 3-O-(6′′-succinyl-glucoside) (8.0 mg/week), cyanidin-3-O-glucoside (10.8 mg/week), cyanidin 3-O-glucosyl-rutinoside (8.1 mg/week), cyanidin 3-O-(6′′-malonyl-3′′-glucosyl-glucoside) (6.6 mg/week), cyanidin 3-O-arabinoside (6.2 mg/week) and cyanidin 3-O-(6′′-acetyl-glucoside) (4.7 mg/week). The other anthocyanins had an intake of less than 5 mg/week. However, some anthocyanins in the first category, showed extremely dispersed data: for cyanidin 3-O-rutinoside and cyanidin 3-O-glucoside, intake data ranged from 0 to 300 mg/week.

3.5.5. *Hydroxybenzoic acids*

In the case of hydroxybenzoic acids, 2-hydroxybenzoic (377.6 mg/week) was the most consumed in the dietary intervention studies (Fig. 6A-1). 5-O-Galloylquinic acid (131.8 mg/week), gallic acid (97.8 mg/week), sanguiin H-6 (29.0 mg/week), ellagic acid (19.68 mg/week) and lambertianin C (11.8 mg/week) were also among the most consumed hydroxybenzoic acids (Fig. 6A-1). As minor hydroxybenzoic acids, the study diets also contained ellagic acid glucoside (2.2 mg/week) and 4-hydroxybenzoic acid 4-O-glucoside (2 mg/week) (Fig. 6A-2).

3.5.6. *Tyrosols, flavanones and alkylmethoxyphenols*

The predominant tyrosols found in the polyphenol-rich diets in the studies were 3,4-DHPEA-EDA (57.7 mg/week), p-HPEA-EDA (32.7 mg/week), 3,4-DHPEA-EA (16.6 mg/week), p-HPEA-EA (8.7 mg/week) and oleuropein-aglycone (8.4 mg/week). Minor tyrosols included ligstroside (3.6 mg/week) and ligstroside-aglycone (4.0 mg/week) (Fig. 6D). In addition, the diets provided hesperetin (29.4 mg/week) and naringenin (8.9 mg/week) as flavanones (Fig. 6B). The only alkylmethoxyphenols provided by the diets were 4-ethylguaiacol (6.5 mg/week) and 4-vinylguaiacol (10.5 mg/week) (Fig. 6F).

3.5.7. *Other minor individual polyphenols*

Flavones such as apigenin (2.7 mg/week) and luteolin 7-O-glucuronide (1.4 mg/week), the stilbenes resveratrol (0.4 mg/week) and resveratrol 3-O-glucoside (0.2 mg/week), and the lignans pinoresinol (1.9 mg/week) and 1-acetoxypinoresinol (1.5 mg/week) were all found in the diet intervention studies (Fig. 6C, 6G and 6H).

4. Discussion

The exploration of dietary patterns as a whole is increasingly promoted in the field of nutrition, and it may be applied to the topic of polyphenol research. However, the characteristics that a diet should have in order to be considered as genuinely rich in polyphenols have not been explored or discussed, despite this being a key aspect in order to be able to compare the efficiency of nutritional interventions. In the present systematic review, we aimed to explore the specific characteristics of the diets used in nutritional interventions focused on polyphenol-rich diets, in order to arrive at some general recommendations for future research. The JADAD score is considered the most valid and reliable tool to assess the methodological quality of a clinical trial, and has been applied throughout nutritional studies (Bisol et al., 2020; Neelakantan et al., 2020; Roman et al., 2018). Nonetheless, some authors have identified limitations of this system, such as not including a point for blinding during outcome assessment, only for single blinding (McCormick et al., 2013).

The first relevant observation of this study is that clinical trials assessing the effect of a polyphenol-rich diet as a whole are scarce, since most interventions involving polyphenols focus on extracts or individual foods, in order to reduce the interferences from the multiple variables present in studies on whole diets. Assessment of individual foods is clearly a necessary stage in the evaluation of the health effects of polyphenols, but it should be followed by studies of whole diets, since in a real situation these are what subjects consume. Thus, we consider efforts should be performed for increasing studies evaluating polyphenol-rich intake within a whole dietary pattern. The studies included in this systematic review evaluated several primary and secondary clinical outcomes, but we should emphasize that this systematic review focuses on the design of a polyphenol-rich diet itself. Also, there were differences among the studied subjects; although some dietary recommendations for polyphenol intake may be general for any population, in case some specific recommendation was provided due to the characteristics of the subjects (for instance, adapting isoflavone intake to menopausal situation), this should be reported.

The clinical trials included in this systematic review showed, first of all, considerable variability in terms of the instructions provided to the volunteers. They varied from studies where participants had to consume a particular food combination every day (Annuzzi et al., 2014) to others where they were instructed to consume a daily number of servings of polyphenol-rich foods which they selected themselves (Chong et al., 2013), or still others where the participants received pre-prepared meals (Della Pepa et al., 2020). Regarding the specific food classes or items recommended, although all the studied included fruit, not all recommended vegetables, cocoa products or beverages as polyphenol sources; similarly, some foods with rather characteristic polyphenol content, such as olive oil or green tea, were not included in the food selection of all the studies. This generates an initial problem when comparing the trials. At the same time, although the studies suggesting or providing volunteers with a fixed combination of foods generated a more homogenous intervention and therefore, potentially, biological responses, those where the volunteers are requested to perform their food selection are closer to a real situation, where food combinations contribute to polyphenol intake and, ultimately, to their associated health effects (de Pascual-Teresa & Clifford, 2017).

A notable aspect is that, although the clinical trials included were focused on polyphenol-rich diets, sometimes they did not include an evaluation of the polyphenol intake of the subjects (either total or by individual compounds), which we therefore calculated specifically for this study using existing databases. Thus, one recommendation would be that, in such studies as these, an initial estimation of the polyphenol intake of the volunteers should be made, in order to know exactly how far or close to usual polyphenol intake the diet provided will be in that population or in similar ones. Overall, the median polyphenol intake of the volunteers in the clinical trials was about 2 g/day, which corresponds to a high polyphenol intake, compared to those reported in several populations (Nascimento-Souza et al., 2018; Pérez-Jiménez et al., 2011; Tresserra-Rimbau et al., 2013), but within the range that may be achieved by a standard diet, without supplementation. Despite this general characteristic of a high polyphenol intake, which is in agreement with the purposes of the studies included, considerable variation in polyphenol intake was observed between the studies, with a more than two-fold difference between p25 and p75 values. This affected most polyphenol classes, (for instance, in hydroxycinnamic acids, weekly intake p75 values were up to ten-fold higher than p25 values) and also individual polyphenols, although in some classes (e.g., flavanols) the intake range was very similar between the studies. In general, these substantial differences in the polyphenol intake of the volunteers make it rather difficult to compare them between the clinical trials, and this may contribute to explaining some of the discrepancies observed in the results. Nevertheless, most of the studies evaluating biochemical outcomes found beneficial effects derived from a polyphenol-rich diet, independently on whether they were in the low (Noad et al., 2016) or the high (Annuzzi et al., 2014; Della Pepa et al., 2020) polyphenol intake range. (Although one of the studies did not find any effect on the formation of urinary DNA adducts (Malaveille et al., 2014) but, as stated below, the information provided did not allow us to calculate individual polyphenol intake in this case.) This was due to the fact that, despite the differences in polyphenol intake between the specific studies, they all corresponded to a high polyphenol intake, so this is in agreement with the reported biological effects associated with this condition. To be more precise, the studies with the lowest weekly polyphenol intake (10 g/week) provided a polyphenol dose which was clearly higher than that observed for the quartile with the lowest polyphenol intake in a Brazilian population, which was about 4 g/week (Nascimento-Souza et al., 2018).

At the same time, we cannot ignore that the estimation of polyphenol intake from databases is subject to all the well-known drawbacks that those databases still possess, due to analytical limitations such as the problem for properly estimating proanthocyanidin content (Pérez-Jiménez et al., 2010) or the lack of inclusion of non-extractable polyphenols, despite their contribution to total polyphenol intake (Pérez-Jiménez & Saura-Calixto, 2015). This is combined with the potential lack of or partial compliance on the part of participants, which means that determination of polyphenol metabolites in biological fluids is highly recommended in this kind of study, as they can be used as biomarkers of intake according to robust procedures (Dragsted et al., 2018), and to establish associations between circulating doses and associated health outcomes, especially as the metabolic fate of polyphenols is highly affected by inter-individual variability (Morand & Tomás-Barberán, 2019).

A general reflection arises from this systematic review. Currently, there is a tendency to study dietary patterns as a whole. This includes, for instance, the widely studied Mediterranean diet, but also dietary patterns focused on both health and sustainability (Willett et al., 2019). In this context, some intervention studies have explored the role of polyphenol-rich diets as a whole; especially because, as recently reviewed, there is evidence of an association between polyphenol-rich dietary patterns assessed in observational studies and different health outcomes (Del Bo' et al., 2019). However, the present systematic review shows that the amounts of polyphenols provided in these clinical trials may differ widely. This situation is similar to other aspects of polyphenol research, where differences in study design (Núñez-Sánchez et al., 2015; Mariano et al., 2020), analytical determinations (Pokimica & García-Coonesa, 2018), data reporting (Nikolic et al., 2019) or nomenclature (Kay et al., 2020) have been observed by researchers and have led to joint recommendations for homogenization. Similarly, a joined effort by polyphenol researchers community could be made to establish certain parameters for a polyphenol-rich diet. This does not mean a single, universal model (clearly, it makes no sense to recommend daily consumption of tropical fruit in northern countries, for example). However, in the same way that different indexes have been established for the Mediterranean dietary pattern which does not mean that the diet is the same in Italy and Turkey, some general concepts about a polyphenol-rich dietary pattern could be established. These could include ranges for total polyphenol intake, polyphenol classes and certain individual polyphenols (based on current knowledge, from both observational and intervention studies), which could then be adapted to local food consumption patterns. Indeed, it has been observed that some current dietary guidelines already promote polyphenol-rich dietary patterns (Castro-Acosta et al., 2019) so they would not require substantial modifications. And epidemiological studies have shown that it is possible to reach a similar polyphenol intake based on different characteristic local products, such as black beans in Brazil (Nascimento –Souza et al., 2018) or olives and olive oil in Spain (Tresserra-Rimbau et al., 2013). Of course, at the same time, studies focused on individual compounds or foods are clearly needed in order to advance our knowledge of the health effects of polyphenols, for which information is still limited in many aspects.

This systematic review is the first simultaneous comparison of intervention studies based on the concept of a polyphenol-rich diet, and it raises some aspects not previously observed, such as the differences in intake, in particular for some polyphenol classes. This study also has some limitations though, such as the small number of trials identified that fulfil our inclusion and exclusion criteria; the differences in the populations studied; the different approaches for estimating polyphenol intake in the studies; and the different biases that affect all intervention studies, particularly nutritional ones. At the same time, it obtained some useful take-away findings: more intervention studies should explore the effects of polyphenol-rich diet; such studies should provide information as detailed as possible on the dietary recommendations provided to the subjects (products, amount, cooking conditions, food origin, etc.); information on expected individual polyphenol intake by study subjects and how it was determined should also be provided; in case specific polyphenol intake recommendations were done due to the characteristics of the population, this should be stated.

5. Conclusions

The number of clinical trials that assess the effect of polyphenol-rich diets on health biomarkers is still limited. Moreover, such studies show important differences in terms of the details provided to the volunteers or the foods included, and therefore the total and individual polyphenol intake. This may affect the results observed and make the comparison of different nutritional interventions difficult. Due to the evidence on the health-related properties of polyphenols and the need to develop holistic approaches to dietary patterns, some general characteristics of a polyphenol-rich diet may deserve further exploration.

CRediT author contribution statement

J. Pérez-Jiménez conceived the study and supervised all the tasks; C. Gazi and L. Condezo-Hoyos performed the bibliography search; L.C.-H. carried out data curation and visualization; J.P.-J. and L.C.-H. interpreted the results and wrote the first draft of the manuscript. This final version of the manuscript has been reviewed and approved by all the authors.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

Miss Christina Gazi was the recipient of an Erasmus+grant, a programme from the European Union Language revision by Christopher Evans is acknowledged.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.foodres.2021.110655.

References

Akaberi, M., & Hosseinzadeh, H. (2016). Grapes (Vitis vinifera) as a Potential Candidate for the Therapy of the Metabolic Syndrome. *Phytotherapy Research : PTR, 30*. https://doi.org/10.1002/ptr.5570.

Annuzzi, G., Bozzetto, L., Costabile, G., Giacco, R., Mangione, A., Anniballi, G., Vitale, M., Vetrani, C., Cipriano, P., Della Corte, G., Pasanisi, F., Riccardi, G., & Rivellese, A. A. (2014). Diets naturally rich in polyphenols improve fasting and postprandial dyslipidemia and reduce oxidative stress: A randomized controlled trial. *American Journal of Clinical Nutrition*. https://doi.org/10.3945/ajcn.113.073445.

Bhagwat, S., & Haytowitz, D. B. (2007). USDA Database for the Flavonoid Contents of Selected Foods. *Release, 08*.

Bisol, Â., de Campos, P. S., & Lamers, M. L. (2020). Flavonoids as anticancer therapies: A systematic review of clinical trials. *Phytotherapy Research*. https://doi.org/10.1002/ptr.6551.

Bondonno, N. P., Dalgaard, F., Kyrø, C., Murray, K., Bondonno, C. P., Lewis, J. R., Croft, K. D., Gislason, G., Scalbert, A., Cassidy, A., Tjønneland, A., Overvad, K., & Hodgson, J. M. (2019). Flavonoid intake is associated with lower mortality in the Danish Diet Cancer and Health Cohort. *Nature Communications*. https://doi.org/10.1038/s41467-019-11622-x.

Bozzetto, L., Annuzzi, G., Pacini, G., Costabile, G., Vetrani, C., Vitale, M., Griffo, E., Giacco, A., De Natale, C., Cocozza, S., Della Pepa, G., Tura, A., Riccardi, G., & Rivellese, A. A. (2015). Polyphenol-rich diets improve glucose metabolism in people at high cardiometabolic risk: A controlled randomised intervention trial. *Diabetologia, 58*(7), 1551–1560. https://doi.org/10.1007/s00125-015-3592-x.

Castro-Acosta, M. L., Sanders, T. A. B., Reidlinger, D. P., Darzi, J., & Hall, W. L. (2019). Adherence to UK dietary guidelines is associated with higher dietary intake of total and specific polyphenols compared with a traditional UK diet: Further analysis of data from the Cardiovascular risk REduction Study: Supported by an Integrated Dietary Approach (CRESSIDA) randomised controlled trial. *The British Journal of Nutrition, 121*(4), 402–415. https://doi.org/10.1017/S0007114518003409.

Chong, M. F., George, T. W., Alimbetov, D., Jin, Y., Weech, M., MacReady, A. L., Spencer, J. P. E., Kennedy, O. B., Minihane, A. M., Gordon, M. H., & Lovegrove, J. A. (2013). Impact of the quantity and flavonoid content of fruits and vegetables on markers of intake in adults with an increased risk of cardiovascular disease: The FLAVURS trial. *European Journal of Nutrition, 52*(1), 361–378. https://doi.org/10.1007/s00394-012-0343-3.

de Pascual-Teresa, S., & Clifford, M. N. (2017). Advances in Polyphenol Research: A Journal of Agricultural and Food Chemistry Virtual Issue. *Journal of Agricultural and Food Chemistry, 65*(37), 8093–8095. https://doi.org/10.1021/acs.jafc.7b04055.

Del Bo', C., Bernardi, S., Marino, M., Porrini, M., Tucci, M., Guglielmetti, S., Cherubini, A., Carrieri, B., Kirkup, B., Kroon, P., Zamora-Ros, R., Liberona, N. H., Andres-Lacueva, C., & Riso, P. (2019). Systematic Review on Polyphenol Intake and Health Outcomes: Is there Sufficient Evidence to Define a Health-Promoting Polyphenol-Rich Dietary Pattern? Nutrients, 11(6). https://doi.org/10.3390/nu11061355.

Della Pepa, G., Vetrani, C., Vitale, M., Bozzetto, L., Costabile, G., Cipriano, P., Mangione, A., Patti, L., Riccardi, G., Rivellese, A. A., & Annuzzi, G. (2020). Effects of a diet naturally rich in polyphenols on lipid composition of postprandial lipoproteins in high cardiometabolic risk individuals: An ancillary analysis of a randomized controlled trial. *European Journal of Clinical Nutrition*. https://doi.org/10.1038/s41430-019-0459-0.

Dragsted, L. O., Gao, Q., Scalbert, A., Vergères, G., Kolehmainen, M., Manach, C., Brennan, L., Afman, L. A., Wishart, D. S., Andres Lacueva, C., Garcia-Aloy, M., Verhagen, H., Feskens, E. J. M., & Praticò, G. (2018). Validation of biomarkers of food intake-Critical assessment of candidate biomarkers. *Genes and Nutrition, 13*(1), 1–14. https://doi.org/10.1186/s12263-018-0603-9.

Giallourou, N., Oruna-Concha, M. J., & Harbourne, N. (2016). Effects of domestic processing methods on the phytochemical content of watercress (Nasturtium officinale). *Food Chemistry, 212*, 411–419. https://doi.org/10.1016/j.foodchem.2016.05.190.

Gianfredi, V., Salvatori, T., Nucci, D., Villarini, M., & Moretti, M. (2018). Can chocolate consumption reduce cardio-cerebrovascular risk? A systematic review and meta-analysis. *Nutrition (Burbank, Los Angeles County, Calif.), 46*, 103–114. https://doi.org/10.1016/j.nut.2017.09.006.

Heshmati, J., Golab, F., Morvaridzadeh, M., Potter, E., Akbari-Fakhrabadi, M., Farsi, F., Tanbakooei, S., & Shidfar, F. (2020). The effects of curcumin supplementation on oxidative stress, Sirtuin-1 and peroxisome proliferator activated receptor γ coactivator 1α gene expression in polycystic ovarian syndrome (PCOS) patients: A randomized placebo-controlled clinical trial. *Diabetes & Metabolic Syndrome: Clinical Research and Reviews, 14*, 77–82. https://doi.org/10.1016/j.dsx.2020.01.002.

Jeż, M., Wiczkowski, W., Zielińska, D., Białobrzewski, I., & Błaszczak, W. (2018). The impact of high pressure processing on the phenolic profile, hydrophilic antioxidant and reducing capacity of purée obtained from commercial tomato varieties. *Food Chemistry, 261*, 201–209. https://doi.org/10.1016/j.foodchem.2018.04.060.

Kay, C. D., Clifford, M. N., Mena, P., McDougall, G. J., Andrés-Lacueva, C., Cassidy, A., Del Rio, D., Kuhnert, N., Manach, C., Pereira-Caro, G., Rodríguez-Mateos, A., Scalbert, A., Tomás-Barberán, F. A., Williamson, G., Wishart, D. S., & Crozier, A. (2020). Recommendations for standardizing nomenclature for dietary (poly)phenol catabolites. *American Journal of Clinical Nutrition, 112*, 1051–1068. https://doi.org/10.1093/ajcn/nqaa204.

Malaveille, C., Fiorini, L., Bianchini, M., Davico, L., Bertinetti, S., Allegro, G., Hautefeuille, A., Sacerdote, C., & Vineis, P. (2004). Randomized controlled trial of dietary intervention: Association between level of urinary phenolics and anti-mutagenicity. *Mutation Research - Genetic Toxicology and Environmental Mutagenesis*. https://doi.org/10.1016/j.mrgentox.2004.03.007.

Marino, M., Del Bo, C., Martini, D., Porrini, M., & Riso, P. (2020). A review of registered clinical trials on dietary (poly)phenols: Past efforts and possible future directions. *Foods, 9*, 1606–1621. https://doi.org/10.3390/foods9111606.

Martini, D., Chaiavaroli, L., González-Sarrías, A., Bresciani, L., Palma-Durán, S., Dall'Asta, M., Deligiannidou, G. E., Massaro, M., Scoditti, E., Combet, E., Maskimova, V., Urpi-Sarda, M., Kontogiorgis, C. A., Andrés-Lacueva, C., Gibney, E. R., Del Rio, D., Morand, C., García-Aloy, M., Rodríguez-Mateos, A., & Mena, P. (2019). Impact of foods and dietary supplements containing hydroxycinnamic acids on cardiometabolic biomarkers: A systematic review to explore inter-individual variability. *Nutrients, 5–34*. https://doi.org/10.3390/nu11081805.

McCormick, F., Cvetanovich, G. L., Kim, J. M., Harris, J. D., Gupta, A. K., Abrams, G. D., Romeo, A. A., & Provencher, M. T. (2013). An assessment of the quality of rotator

cuff randomized controlled trials: Utilizing the Jadad score and CONSORT criteria. *Journal of Shoulder and Elbow Surgery, 22*(9), 1180–1185. https://doi.org/10.1016/j.jse.2013.01.017.

McReady, George, T.W., Chong, M.F., Alimbetov, D.S., Jin, Y., Vidal, A., Spencer, J.P.E., Kennedy, O.B., Tuohy, K.M., Minihane, A.M., Gordon, M.H., Lovegrove, J. A. (2014) Flavonoid-rich fruit and vegetables improve microvascular reactivity and inflammatory status in men at risk of cardiovascular disease-FLAVURS: A randomized controlled trial. American Journal of Clinical Nutrition, 99, 479-89. https://doi.org/ 10.3945/ajcn.113.074237.

Molinar-Toribio, E., Fuguet, E., Ramos-Romero, S., Taltavull, N., Méndez, L., Nogués, M. R., Medina, I., Torres, J. L., & Pérez-Jiménez, J. (2018). A high-fat high-sucrose diet affects the long-term metabolic fate of grape proanthocyanidins in rats. *European Journal of Nutrition*. https://doi.org/10.1007/s00394-016-1323-9.

Morand, C., & Tomás-Barberán, F. A. (2019). Interindividual Variability in Absorption, Distribution, Metabolism, and Excretion of Food Phytochemicals Should Be Reported. *Journal of Agricultural and Food Chemistry, 67*(14), 3843–3844. https://doi.org/10.1021/acs.jafc.9b01175.

Morvaridzadeh, M., Sepidarkish, M., Daneshzad, E., Akbari, A., Mobini, G.R., Heshmati, J. (2020A) The effect of pomegranate on oxidative stress parameters: A systematic review and meta-analysis. Complementary Therapies in Medicine, 48, Article ID 102252, https://doi.org/10.1016/j.ctim.2019.102252.

Morvaridzadeh, M., Fazelian, S., Agah, S., Khazdouz, M., Rahimlou, M., Agh, F., Potter, E., Heshmati, S. & Heshmati, J. (2020) Effect of ginger (Zingiber officinale) on inflammatory markers: A systematic review and meta-analysis of randomized controlled trials. Cytokine, 135, Article ID 155224, https://doi.org/10.1016/j.cyto.2020.155224.

Nascimento-Souza, M. A., de Paiva, P. G., Pérez-Jiménez, J., do Carmo Castro Franceschini, S., & Ribeiro, A. Q. (2018). Estimated dietary intake and major food sources of polyphenols in elderly of Viçosa, Brazil: A population-based study. European Journal of Nutrition, 57(2), 617–627. https://doi.org/10.1007/s00394-016-1348-0.

Neelakantan, N., Seah, J. Y. H., & van Dam, R. M. (2020). The Effect of Coconut Oil Consumption on Cardiovascular Risk Factors: A Systematic Review and Meta-Analysis of Clinical Trials. *Circulation, 141*(10), 803–814. https://doi.org/10.1161/CIRCULATIONAHA.119.043052.

Neveu, V., Perez-Jiménez, J., Vos, F., Crespy, V., du Chaffaut, L., Mennen, L., Knox, C., Eisner, R., Cruz, J., Wishart, D., & Scalbert, A. (2010). Phenol-Explorer: An online comprehensive database on polyphenol contents in foods. Database: The Journal of Biological Databases and Curation, 2010. https://doi.org/10.1093/database/bap024.

Nikolic, M., Konic Ristic, A., González-Sarrías, A., Istas, G., Urpi-Sarda, M., Dall'Asta, M., Monfoulet, L.-E., Cloetens, L., Bayram, B., Tumolo, M. R., Chervenkov, M., Scoditti, E., Massaro, M., Tejera, N., Abadjieva, D., Chambers, K., Krga, I., Tomás-Barberán, F. A., Morand, C., … Mena, P. (2019). Improving the reporting quality of intervention trials addressing the inter-individual variability in response to the consumption of plant bioactives: Quality index and recommendations. European Journal of Nutrition, 58(Suppl 2), 49–64. https://doi.org/10.1007/s00394-019-02069-3.

Noad, R. L., Rooney, C., McCall, D., Young, I. S., McCance, D., McKinley, M. C., Woodside, J. V., & McKeown, P. P. (2016). Beneficial effect of a polyphenol-rich diet on cardiovascular risk: A randomised control trial. *Heart*. https://doi.org/10.1136/heartjnl-2015-309218.

Núñez-Sánchez, M. A., González-Sarrías, A., Romo-Vaquero, M., García-Villalba, R., Selma, M. V., Tomás-Barberán, F. A., García-Conesa, M.-T., & Espín, J. C. (2015). Dietary phenolics against colorectal cancer–From promising preclinical results to poor translation into clinical trials: Pitfalls and future needs. *Molecular Nutrition & Food Research, 59*(7), 1274–1291. https://doi.org/10.1002/mnfr.201400866.

Pérez-Jiménez, J., Fezeu, L., Touvier, M., Arnault, N., Manach, C., Hercberg, S., Galan, P., & Scalbert, A. (2011). Dietary intake of 337 polyphenols in French adults. *The American Journal of Clinical Nutrition, 93*(6), 1220–1228. https://doi.org/10.3945/ajcn.110.007096.

Pérez-Jiménez, J., Neveu, V., Vos, F., & Scalbert, A. (2010). Systematic analysis of the content of 502 polyphenols in 452 foods and beverages: An application of the phenol-explorer database. *Journal of Agricultural and Food Chemistry, 58*(8), 4959–4969. https://doi.org/10.1021/jf100128b.

Pérez-Jiménez, J., & Saura-Calixto, F. (2015). Macromolecular antioxidants or non-extractable polyphenols in fruit and vegetables: Intake in four European countries. *Food Research International, 74*, 315–323. https://doi.org/10.1016/j.foodres.2015.05.007.

Pokimica, B., & García-Conesa, M. T. (2018). Critical evaluation of gene expression changes in human tissues in response to supplementation with dietary bioactive compounds: Moving towards better-quality studies. *Nutrients, 10*, 807–844. https://doi.org/10.3390/nu10070807.

Reis, C. E. G., Dórea, J. G., & da Costa, T. H. M. (2019). Effects of coffee consumption on glucose metabolism: A systematic review of clinical trials. *Journal of Traditional and Complementary Medicine, 9*(3), 184–191. https://doi.org/10.1016/j.jtcme.2018.01.001.

Rodriguez-Mateos, A., Vauzour, D., Krueger, C. G., Shanmuganayagam, D., Reed, J., Calani, L., Mena, P., Del Rio, D., & Crozier, A. (2014). Bioavailability, bioactivity and impact on health of dietary flavonoids and related compounds: An update. *Archives of Toxicology, 88*(10), 1803–1853. https://doi.org/10.1007/s00204-014-1330-7.

Roman, P., Carrillo-Trabalón, F., Sánchez-Labraca, N., Cañadas, F., Estévez, A. F., & Cardona, D. (2018). Are probiotic treatments useful on fibromyalgia syndrome or chronic fatigue syndrome patients? *A systematic review. Beneficial Microbes, 9*(4), 603–611. https://doi.org/10.3920/BM2017.0125.

Santos, J., Oliveira, M. B. P. P., Ibáñez, E., & Herrero, M. (2014). Phenolic profile evolution of different ready-to-eat baby-leaf vegetables during storage. *Journal of Chromatography. A, 1327*, 118–131. https://doi.org/10.1016/j.chroma.2013.12.085.

Ścibisz, I., & Mitek, M. (2007). The changes of antioxidant properties in highbush blueberries (Vaccinium corymbosum L.) during freezing and long-term frozen storage. *Acta Scientiarum Polonorum Technologia. Alimentaria, 6*(4). https://www.food.actapol.net/volume6/issue4/abstract-7.html.

Serino, A., & Salazar, G. (2018). Protective Role of Polyphenols against Vascular Inflammation, Aging and Cardiovascular Disease. *Nutrients, 11*(1). https://doi.org/10.3390/nu11010053.

Squillaro, T., Schettino, C., Sampaolo, S., Galderisi, U., Di Iorio, G., Giordano, A., & Melone, M. A. B. (2018). Adult-onset brain tumors and neurodegeneration: Are polyphenols protective? *Journal of Cellular Physiology, 233*(5), 3955–3967. https://doi.org/10.1002/jcp.26170.

Tresserra-Rimbau, A., Medina-Remón, A., Pérez-Jiménez, J., Martínez-González, M. A., Covas, M. I., Corella, D., Salas-Salvadó, J., Gómez-Gracia, E., Lapetra, J., Arós, F., Fiol, M., Ros, E., Serra-Majem, L., Pintó, X., Muñoz, M. A., Saez, G. T., Ruiz-Gutiérrez, V., Warnberg, J., Estruch, R., & Lamuela-Raventós, R. M. (2013). Dietary intake and major food sources of polyphenols in a Spanish population at high cardiovascular risk: The PREDIMED study. *Nutrition, Metabolism and Cardiovascular Diseases, 23*(10), 953–959. https://doi.org/10.1016/j.numecd.2012.10.008.

Vetrani, C., Vitale, M., Bozzetto, L., Della Pepa, G., Cocozza, S., Costabile, G., Mangione, A., Cipriano, P., Annuzzi, G., & Rivellese, A. A. (2018). Association between different dietary polyphenol subclasses and the improvement in cardiometabolic risk factors: Evidence from a randomized controlled clinical trial. *Acta Diabetologica*. https://doi.org/10.1007/s00592-017-1075-x.

Vetrani, C., Maukonen, J., Bozzetto, L., Della Pepa, G., Vitale, M., Costabile, G., Riccardi, G., Rivellese, A. A., Saarela, M., & Annuzzi, G. (2020). Diets naturally rich in polyphenols and/or long-chain n-3 polyunsaturated fatty acids differently affect microbiota composition in high-cardiometabolic-risk individuals. *Acta Diabetologica, 57*(7), 853–860. https://doi.org/10.1007/s00592-020-01494-9.

Willett, W., Rockström, J., Loken, B., Springmann, M., Lang, T., Vermeulen, S., Garnett, T., Tilman, D., DeClerck, F., Wood, A., Jonell, M., Clark, M., Gordon, L. J., Fanzo, J., Hawkes, C., Zurayk, R., Rivera, J. A., De Vries, W., Sibanda, L. M., Afshin, A., Chaudhary, A., Herrero, M., Agustina, R., Branca, F., Lartey, A., Fan, S., Crona, B., Fox, E., Bignet, V., Troell, M., Lindahl, T., Singh, S., Cornell, S. E., Reddy, K. S., Narain, S., Nishtar, S., & Murray, C. J. L. (2019). Food in the Anthropocene: The EAT–Lancet Commission on healthy diets from sustainable food systems. *The Lancet, 393*, 447–492. https://doi.org/10.1016/S0140-6736(18)31788-4.

Woerdeman, J., van Poelgeest, E., Ket, J. C. F., Eringa, E. C., Serné, E. H., & Smulders, Y. M. (2017). Do grape polyphenols improve metabolic syndrome components? A systematic review. *European Journal of Clinical Nutrition, 71*(12), 1381–1392. https://doi.org/10.1038/ejcn.2016.227.