*horticulturae*

MDPI

*Systematic Review*

# Grape and Grape-Based Product Polyphenols: A Systematic Review of Health Properties, Bioavailability, and Gut Microbiota Interactions

**Paloma Rodriguez-Lopez [1], Ascensión Rueda-Robles [1], Isabel Borrás-Linares [2,*], Rosa María Quirantes-Piné [3], Tatiana Emanuelli [4], Antonio Segura-Carretero [2,†] and Jesús Lozano-Sánchez [1,†]**

1 Department of Food Science and Nutrition, Faculty of Pharmacy, University of Granada, Campus Universitario s/n, 18071 Granada, Spain; palomarlopez@ugr.es (P.R.-L.); ruedarobles@ugr.es (A.R.-R.); jesusls@ugr.es (J.L.-S.)
2 Department of Analytical Chemistry, Faculty of Sciences, University of Granada, 18071 Granada, Spain; ansegura@ugr.es
3 Research and Development Functional Food Centre (CIDAF), Health Science Technological Park, Avenida del Conocimiento 37, EdificioBioRegión, 18016 Granada, Spain; rquitantes@cidaf.es
4 Department of Food Technology and Science, Center of Rural Sciences, Federal University of Santa Maria, Camobi, Santa Maria 97105-900, RS, Brazil; tatiana.emanuelli@ufsm.br
* Correspondence: iborras@ugr.es; Tel.: +34-958637083
† These authors are joint senior authors on this work.

**Abstract:** Grapevine-derived products have been widely studied for their reported benefits, especially those related to the prevention of cardiovascular diseases. However, in recent years, the interest in the study of grapes and their non-fermented derivatives (grape juices) has gained prominence over the well-known interest in red wine, since grapes and grape juices seem to be widely related to the beneficial effects associated with the Mediterranean diet, and consequently to the presence of phenolic compounds. The focus of this systematic review was the phenolic profiles of grape, juice, and wine, as well as the possible beneficial effects of their consumption on the human microbiota through a systematic literature review. PubMed and Scopus were accessed during April 2021 and the PRISMA methodological protocol was followed. To the best of our knowledge, this is the first time that the PRISMA methodology has been applied to this systematic knowledge. This methodology allowed for a scientific description of: (a) the comparison between grapes and their derived products as source of phenolic compounds, (b) great possibilities for working on a new line of investigation based on the synergy between polyphenol consumption and microbiota, and (c) the urgent need for strategies to improve the bioavailability of these compounds.

**Keywords:** grapes; phenolic compounds; bioaccessibility; bioavailability; gut microbiota

check for updates

**Citation:** Rodriguez-Lopez, P.; Rueda-Robles, A.; Borrás-Linares, I.; Quirantes-Piné, R.M.; Emanuelli, T.; Segura-Carretero, A.; Lozano-Sánchez, J. Grape and Grape-Based Product Polyphenols: A Systematic Review of Health Properties, Bioavailability, and Gut Microbiota Interactions. *Horticulturae* **2022**, *8*, 583. https://doi.org/10.3390/horticulturae8070583

Academic Editor: Rosario Paolo Mauro

Received: 6 June 2022
Accepted: 25 June 2022
Published: 28 June 2022



## 1. Introduction

The beneficial effects of the Mediterranean diet are widely known and for decades have been traditionally attributed to the consumption of at least two of the elements of the Mediterranean triad: olive oil and the vine. One of the best-known products derived from grapes is red wine, which has shown an inverse association between wine consumption and mortality in epidemiological studies. These beneficial effects can be attributed to the presence of bioactive compounds, concretely phenolic compounds.

Polyphenols are chemical substances that have at least one aromatic ring with a hydroxyl group in their structure including functional derivatives (esters, methyl esters, glycosides, etc.). They are synthesised via the shikimic acid and phenylpropanoid pathways, and they are considered to be one of the main secondary metabolites of plants. They can be classified according to different criteria based on to their structural diversity, with two main groups being differentiated: flavonoids and non-flavonoids [1].

In recent decades, a large number of studies have shown the presence of phenolic compounds in grapes, wine, and grape by-products. These phenolic compounds have beneficial properties for the body, especially related to the antioxidant activity of phenolic compounds and the widely known promotion of cardiovascular health. In grapes, the phenolic compounds found primarily include anthocyanins, flavanols, flavonols, stilbenes (including resveratrol, although other stilbene compounds have also been identified, such as picetannol [2]), and phenolic acids. Polyphenols are mainly found in the solid parts of the grape cluster (skins, seeds, and stems). Only proanthocyanidins (condensed tannins) occur as oligomers and polymers, while other classes of polyphenols in grapes are present in monomeric or low molecular weight forms. The seeds contain the highest proportion of total proanthocyanidins in the entire grape bunch, followed by the stem and the skin, while the pulp is free or lacks these compounds. Anthocyanins are mainly found in the grape skin and provide pigmentation. Flavonoids are found in grapes, especially in the seeds and stems, and contain mainly catechins, epicatechins, and procyanidin polymers. Anthocyanins are the main polyphenols in red grapes, while flavanols are more characteristic of white grapes [3].

In reference to the different parts of the grape, the seeds contain phenolic acids, flavonols, proanthocyanidins, and stilbenes; in the pomace, there are phenolic acids, flavanols, flavonols, anthocyanins, stilbenes, and proanthocyanidins; in the skin, there are phenolic acids, flavonols, flavanols, anthocyanins, and stilbenes; and in the stem, there are phenolic acids, flavanols, flavonols, anthocyanins, and stilbenes [2].

In relation to their absorption, it is believed that phenolic compounds are absorbed via passive diffusion or by carriers within the intestine, such as P-glycoprotein and co-transporters for the sodium-glucose cotransporter 1 (SGLT1) [4]. After that, they can be hydrolysed by intestinal enzymes or by the colonic microflora. Moreover, polymeric or glycosylated phenolic compounds must undergo transformation in the small or large intestine for flavonoids to be absorbed [5]. On the contrary, food phenolic acids are absorbed partially in the small intestine and further modified and absorbed in the colon [6]. In regards to alcoholic beverages rich in polyphenols, such as wine, some authors have declared that the presence of ethanol does not affect the absorption of polyphenols. In this sense, studies have shown that catechin is absorbed in the same extension from de-alcoholised red wine and from alcoholic red wine [7–9]. In contrast, other authors suggest that red wine is a poor source of bioavailable polyphenols [10], so further studies are needed on this aspect.

One of the main derivatives of the grape, wine, has a much more complex composition of polyphenols than that of the grape since it includes both polyphenols from the grape due to the extraction itself and new phenolic products formed from the process of winemaking and storage. Proanthocyanidins (or condensed tannins) are responsible for the characteristic astringency of wine, defined as "the complex of sensations due to the shrinking, stretching or wrinkling of the epithelium as a result of exposure to substances such as tannins". This process is due to the formation of complexes of tannins with salivary proteins. Astringency is an essential characteristic of red wine [3].

For decades, the biological effects and antioxidant properties of grape and wine polyphenols have been studied. These include procyanidin dimers and trimers, catechin, epicatechin, resveratrol and its derivatives, flavonols, flavones, phenolic acids, and anthocyanins. Along with tannins, the main beneficial effects for red wine have been attributed to the presence of resveratrol. Nonetheless, these effects could be related to the presence of other phytochemicals, such as simple forms of phenolic compounds, e.g., tyrosol (Tyr) and hydroxytyrosol (OH-Tyr), which possess antioxidant and anti-inflammatory properties and are also characteristic of white wine and extra virgin olive oil [11].

In the last decades, the moderate consumption of wine has steadily gained popularity due to the high level of phenolic compounds present in its matrix and the publicity of their beneficial impact on health. However, in recent years, the interest in the study of grapes and their non-fermented derivatives (grape juice) has gained prominence over the study of wine since the content of alcohol in wine has proven to have adverse effects on

health. In this sense, the non-alcoholic grape products possess the phytochemicals present in wine and consequently the beneficial effects associated with the wine present in the Mediterranean diet [12,13].

Grapevine products have been widely studied for their reported benefits, especially related to the prevention of cardiovascular diseases. This fact was supported in the low incidence of these pathologies in countries with a high consumption of grapes and/or grape derivatives. These beneficial effects could be associated with grape polyphenols and their antioxidant capacity [13]. Indeed, the relationship between the consumption of grape polyphenols and derivatives (including wine) and modulating effects of important physiological parameters have been studied. It should be mentioned that they have a role in insulin sensitivity [12], chronic metabolic diseases [12], chronic inflammation [11], decreased lipid peroxidation [13,14], lowering blood pressure [15], improvement in health-related quality of life [16], and even improvement of cognitive function [17].

Some of the most characteristic phenolic compounds present in wine are phenolic acids, which in turn can be differentiated according to the number of carbons into hydroxybenzoic acids and hydroxycinnamic acids. They are present in their free and conjugated or esterified forms in wine. Hydroxycinnamic acids can act as oxidation substrates and as precursor compounds for the browning of white wines. Moreover, flavonoids are present in the most common forms of anthocyanins, flavanols, and flavan-3-ols in their free or conjugated form. Anthocyanins are characterized as one of the quality indices to value wine, since each grape variety presents a different pattern of anthocyanins. As for tannins, they can be divided according to whether they are hydrolysable or condensed (also known as proanthocyanidins). They have a great influence on the organoleptic properties of wine such as bitterness, astringency, and colour stabilization. Finally, there are stilbenes, whose main protagonists are resveratrol and its derivatives (i.e., piceid or resveratrol glycoside). These phenolic compounds differ depending on grape variety an are useful for discriminating different varieties [11–13].

The establishment of new research on other non-fermented vine products, also rich in polyphenols, which provide similar amounts of these compounds with bioactive characteristics without the intake of alcohol deserves further attention. It is important to highlight that the promotion of food or derivatives based on bioactive compounds including alcohol in their composition does not have positive effects on the population.

In addition to the aforementioned effects, the consumption of phenolic compounds seems to have a close relationship with the gut microbiota's health status, experiencing synergistic effects between the consumption of polyphenols and intestinal health [18–20]. Once the beneficial effects associated with the consumption of these compounds are known, it is important to identify the quality of the different sources responsible for the bioactive properties of grapevine derivatives, as well as their possible interactions with the microbiota and the bioavailability of phenolic compounds in the human body.

In this context, the aim of this systematic review was to determine the phenolic profiles of grape, juice, and wine and to assess the impact of the consumption of these compounds on the gut microbiota. We also aim to study the advances made to date in terms of the bioavailability of these compounds.

## 2. Materials and Methods

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [21,22].

### *2.1. PICO Format on the Research Question*

The first eligibility criteria listed in Table 1 was based on the PICO strategy—population (P), intervention (I), comparison (C), and outcome (O)—because it has shown a greater number of hits in the search [23,24]. However, a second, modified version of PICO was also used, with the addition of the qualitative search term "study design" (S) (PICOS), limiting

the number of irrelevant articles (Table 2). This PICOS search strategy showed a lower sensitivity and a higher specificity compared to the first one.

**Table 1.** PICO format on the research question of grape and grape by-products polyphenols.

| **What Are the Health and Microbiota Effects of Grapes and Grape Derivatives Polyphenols, and How Could Their Bioavailability Be Improved?** | |
|---|---|
| Population | Healthy subjects |
| Intervention | Research for the developped strategies to improve the bioavailability of grape and derived products polyphenols, associated healthy properties and interaction with the intestinal microbiota |
| Comparison | Fermented grape derivatives (wine) |

**Table 2.** DeCS and MeSH descriptors according to PICO format on grape, grape by-products polyphenols, gut microbiota and health.

| **Sentence** | **Natural Word** | **DeCS/MeSH** |
|---|---|---|
| **Population** | **Healthy Subjects** | |
| Intervention | Grape<br>Grape by–products<br>Polyphenols source<br>Healthy properties<br>Bioavailability/bioaccesibility<br>Gut microbiota | *Vitis*/Grapes/*Vitis vinifera*<br>Grape by–products<br>Polyphenols/phenolic compounds/source<br>Healthy properties<br>Bioavailability<br>Gut microbiota/gastrointestinal microbioma/gut microflora |
| Comparison | Wine | Wine |
| Study type | Randomized controlled trial<br>Meta-analysis<br>Systematic review<br>Clinical trial | |
| Limits | Articles published in the last 10 years<br>Humans<br>Healthy subjects<br>Terms in Title/Abstract/Keywords<br>No language restriction | |

DeCS and MeSH descriptors were according to PICO format. The descriptors used to obtain the search equations of the present systematic review were DeCS, MeSH and free terms using the boolean operators "AND" and "OR". "*Vitis*", "grape-by-products", "polyphenols", "gut microbiota", and "health" were the terms used in the search. The results are developed in the following table (Table 2). Moreover, Table 3 shows the number of results obtained following the "PICO" methodology and after the separator bar "/", the articles obtained after filtering by randomized controlled trial, meta-analysis, systematic review, and clinical trial [23]. According to the extracted terms related to grape studies and grape by-product polyphenols were combined in the following strategy (Table 4).

Regarding the need to seek strategies to improve the bioavailability of these compounds, after conducting the systematic search, only one article was found. This publication was not eligible to be included in the present systematic review, as although it studied the bioavailability of polyphenols in healthy subjects, the matrix was not the grape or grape-derived products but instead apple juice.

**Table 3.** Database searching (April 2021) format on grape, grape by-products polyphenols, gut microbiota, and health.

| Databases | PubMed | Scopus | TOTAL | TOTAL after Removing Duplicate Items |
|---|---|---|---|---|
| *Vitis*/grapes/*Vitis vinifera*/wine/grape by–products AND polyphenols/phenolic compounds AND healthy subjects | 25/12 | 65/23 | 35 * | 34 |
| PubMed | (((*Vitis*[Title/Abstract] OR grapes[Title/Abstract] OR *Vitis vinifera*[Title/Abstract] OR wine[Title/Abstract] OR (grape[Title/Abstract] AND (by–products)))[Title/Abstract]) AND (AND (polyphenols[Title/Abstract] OR phenolic compounds)[Title/Abstract])) AND ((healthy[Title/Abstract] AND subjects)[Title/Abstract]) | | | |
| Scopus | (TITLE-ABS-KEY (*vitis*) OR (grapes) OR (*vitis* AND *vinifera*) OR (wine) OR (grape AND by AND products) AND TITLE-ABS-KEY (polyphenols) OR (phenolic AND compounds) AND TITLE-ABS-KEY (healthy AND subjects)) AND TITLE (metaanalysis OR (clinical AND trial) OR (systematic AND review) OR (randomized AND controlled AND trial)) AND (LIMIT-TO (PUBYEAR, 2021) OR LIMIT-TO (PUBYEAR, 2019) OR LIMIT-TO (PUBYEAR, 2017) OR LIMIT-TO (PUBYEAR, 2016) OR LIMIT-TO (PUBYEAR, 2015) OR LIMIT-TO (PUBYEAR, 2014) OR LIMIT-TO (PUBYEAR, 2013) OR LIMIT-TO (PUBYEAR, 2012) OR LIMIT-TO (PUBYEAR, 2011)) | | | |
| *Vitis*/grapes/*Vitis vinifera*/wine/grape by—products AND polyphenols/phenolic compounds AND Gut microbiota/gastrointestinal microbiome/gut microflora AND healthy subjects | 4/2 | 6/3 | 5 * | 5 |
| PubMed | (((*Vitis*[Title/Abstract] OR grapes[Title/Abstract] OR (grape[Title/Abstract] AND (by–products) OR wine [Title/Abstract]) OR [Title/Abstract]) AND (polyphenols[Title/Abstract] OR phenolic compounds[Title/Abstract])) AND ((Gut[Title/Abstract] AND microbiota)[Title/Abstract] OR (gastrointestinal[Title/Abstract] AND microbiome)[Title/Abstract] OR (gut[Title/Abstract] AND microflora)[Title/Abstract])) AND ((healthy[Title/Abstract] AND subjects)[Title/Abstract]) | | | |
| Scopus | (TITLE-ABS-KEY (*vitis*) OR (grapes) OR (*vitis* AND *vinifera*) OR (wine) OR (grape AND by AND products) AND TITLE-ABS-KEY (polyphenols) OR (phenolic AND compounds) AND TITLE-ABS-KEY (healthy AND subjects)) AND TITLE-ABS-KEY ((gut AND microbiota) OR (gastrointestinal AND microbiome) OR (gut AND microflora)) AND TITLE (metaanalysis OR (clinical AND trial) OR (systematic AND review) OR (randomized AND controlled AND trial)) AND (LIMIT-TO (PUBYEAR, 2021) OR LIMIT-TO (PUBYEAR, 2019) OR LIMIT-TO (PUBYEAR, 2017) OR LIMIT-TO (PUBYEAR, 2016) OR LIMIT-TO (PUBYEAR, 2015) OR LIMIT-TO (PUBYEAR, 2014) OR LIMIT-TO (PUBYEAR, 2013) OR LIMIT-TO (PUBYEAR, 2012) OR LIMIT-TO (PUBYEAR, 2011)) | | | |
| *Vitis*/grapes/*Vitis vinifera*/wine/grape by—products AND polyphenols/phenolic compounds AND Bioavailability/Bioaccessibility NOT healthy subjects | 101/4 | 362/0 | * 4 | 4 |
| PubMed | (((*Vitis*[Title/Abstract] OR grapes[Title/Abstract] OR *Vitis vinifera*[Title/Abstract] OR wine[Title/Abstract] OR (grape[Title/Abstract] AND by–products)[Title/Abstract]) AND (polyphenols[Title/Abstract] OR phenolic compounds[Title/Abstract])) AND (Bioavailability[Title/Abstract] OR Bioaccessibility[Title/Abstract])) | | | |

**Table 3.** *Cont.*

| Databases | PubMed | Scopus | TOTAL | TOTAL after Removing Duplicate Items |
|---|---|---|---|---|
| Scopus | (TITLE-ABS-KEY (*vitis* OR grapes OR (*vitis* AND *vinifera)* OR wine OR (grape AND by AND products)) AND TITLE-ABS-KEY (polyphenols OR (phenolic AND compounds)) AND TITLE-ABS-KEY (bioavailability OR inaccessibility) AND TITLE (metanalysis) AND TITLE (clinical AND trial) AND TITLE (systematic AND review) AND TITLE (randomized AND controlled AND trial)) AND PUBYEAR > 2010 | | | |

* Total qualitatively screened articles, using the "PICOS" methodology.

For this reason, a new search equation was developed, which included those articles not carried out in healthy population, eliminating the term "healthy subjects" from the equation. The purpose of this new search was to find new trials in which the phenolic compounds of grapes and their derivatives were characterized, as well as in vitro and in vivo (animals and humans) experimental tests were carried out, both acute and long-term. Additionally, the term "Bioaccessibility" was added to expand the obtained results including this important factor of health effects of polyphenols. Thus, 463 articles were obtained, and after applying the quality filtering (randomized controlled trial, meta-analysis, systematic review, and clinical trial), this number was reduced to four publications. This marked decrease in results may be explained by the fact that screening by "clinical trial" reduce the results since this type of bioavailability study is very limited compared to the studies carried out in vitro.

**Table 4.** Search strategy and equations on grape, grape by-products polyphenols, gut microbiota, and health.

| **Comparison between Grape and Its By-Products as Source of Phenolic Compounds** |
|---|
| *Vitis*/grapes/*Vitis vinifera* AND polyphenols/phenolic compounds AND wine/grape by–products |
| **Great Possibilities for Working on a New Research Line Focus on the Synergy between Polyphenol Consumption and Microbiota Health Status** |
| *Vitis*/grapes/*Vitis vinifera* AND polyphenols/phenolic compounds AND Gut microbiota/gastrointestinal microbiome/gut microflora |
| **The Urgent Need for Novel Strategies to Improve the Bioavailability of These Bioactive Compounds** |
| *Vitis*/grapes/*Vitis vinifera* AND polyphenols/phenolic compounds AND Bioavailability |

### *2.2. Search Strategy and Equations*

Literature search was conducted on two electronic databases (PubMed and Scopus). All studies found through the search strategy were exported into Mendeley reference manager.

### *2.3. Inclusion and Exclusion Criteria*

To avoid selection bias, inclusion and exclusion criteria were defined before the literature search. In this sense, randomised controlled trial, meta-analysis, systematic review, and clinical/experimental in vitro/in vivo trials carried out in animals and humans were included. There was no language restriction in the selection of the literature and duplicate studies were excluded.

### *2.4. Quality Assessment and Risk of Bias*

The included studies were submitted to a quality assessment by Cochrane guidelines. In Cochrane's risk of bias tool for randomized trials (RoB2), the risk of bias can be assessed on five levels: risk of bias arising from randomization process, risk of bias due to deviations

from intended interventions, bias due to missing outcome data, bias in the measurement of the outcome, and bias in selection of the reported result.

## 3. Results

### *3.1. Study Selection*

The study selection process is shown in Figure 1. Based on the search strategy, 563 articles were found after applying the PICO methodology, and 44 publications once the PICOS quality filter was applied (after filtering by randomized controlled trial, meta-analysis, systematic review, and clinical trial). From these results, one was a duplicated paper and it was properly excluded, resulting in a total of 43 studies to be studied and evaluated according to the eligibility criteria.

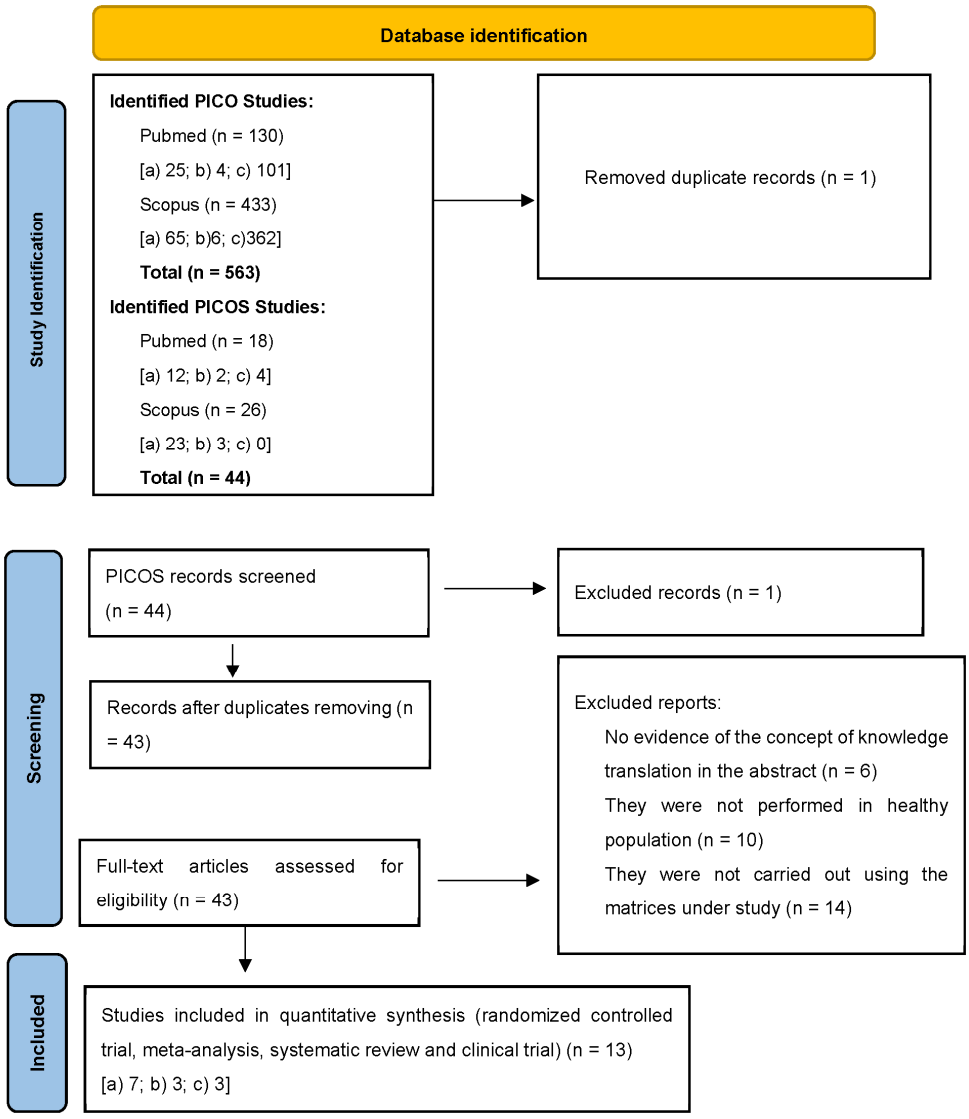


**Figure 1.** PRISMA 2020 flowchart of the search strategy on grape, grape by-products polyphenols, gut microbiota, and health [22].

During the review of these publications, most of them were excluded because they did not meet the eligibility criteria. The main reasons for these exclusions were as follows: the studies were not performed on healthy subjects (except overweight and obese patients and subjects with an ileostomy), the authors did not study any of the matrices of interest or used them in a very low proportion with respect to other ingredients, or the results

and discussion sections varied greatly with respect to the information that appeared in the abstract. Consequently, a total of 13 studies were selected for data extraction and conclusion. It should be mentioned that, despite healthy subjects being a filtering criterion, overweight and/or obese subjects were collected since although they have a predisposition to suffer from metabolic diseases, at the time of the study they were considered to be healthy subjects. Nonetheless, regarding the bioavailability studies, only the research conducted in healthy subjects was chosen, except for patients with a performed ileostomy (without a functional colon).

### *3.2. Comparison between Grapes and Its By-Products as Source of Phenolic Compounds*

The application of the PRISMA methodology provided a careful selection of articles on grapes and grape by-products' phenolic compounds concerning their health effects after their consumption (chronically in most studies) (Table 5). It is worth noting that the descriptions of the studied matrices are in separated sections: (a) grapes, (b) grape juices, (c) non-alcoholic fermented grape juices, and (d) red wine.

**Table 5.** Selected studies for the comparison between grapes and their by-products as a source of phenolic compounds.

| Study Type | Matrix | Population | Dose | Duration | Nutritional Design | Results and Conclusions | Reference |
|---|---|---|---|---|---|---|---|
| **Randomized in a double-blind controlled trial** | Grapes | 38 healthy volunteers with high metabolic risk (healthy overweight/obese first-degree relatives of type 2 diabetic patients) | 2 g/day grape polyphenols | 9 weeks | Avoid foods rich in polyphenols and dietary control. Balanced and isocaloric diet | All effects induced by the consumption of fructose (3 g/kg fat-free mass/day of fructose) (decreased hepatic insulin sensitivity index, decreased glucose infusion rate, increased systemic oxidative stress, decreased mitochondrial genes and decreased mitochondrial respiration) were completely eliminated in the group that also supplemented with grape polyphenols. | [12] |
| **Prospective, single blind, randomized, cross-over trial** | Wine | 10 healthy volunteers and 10 patients with CKD (chronic kidney disease) K-DOQI stage III-IV | White wine (4 mL/kg body weight, 0.48 g/kg of alcohol 12%, corresponding to 2–3 glasses/daily) | 2 weeks | Two-week washout from alcoholic beverages | Reduction in plasma markers of chronic inflammation associated with the combined consumption of white wine and olive oilh in patients with chronic kidney disease (CKD). | [11] |

**Table 5.** *Cont.*

| Study Type | Matrix | Population | Dose | Duration | Nutritional Design | Results and Conclusions | Reference |
|---|---|---|---|---|---|---|---|
| **Randomized, controlled, crossover study with three intervention periods** | Grape juice (*V. lambrusca* L.) | 30 healthy volunteers | 400 mL of conventional red grape juice (Bordo/Isabel) and 400 mL of organic red grape juice (Bordo) | Acute intervention (3 interventions) | Avoid foods rich in polyphenols and dietary control | Reduction of lipid peroxides in the blood of healthy individuals after ingestion of organic and conventional red grape juices rich in polyphenols. | [13] |
| **Randomized controlled clinical trial** | Hardaliye drink | 89 healthy adults | 500 mL and 250 mL of hardaliye per day | 40 days | Dietary control | Reduction of lipid oxidation markers and plasma homocysteine levels associated with the consumption of a non-alcoholic fermented drink rich in polyphenols. | [14] |
| **Randomized, crossover, double-blind, sex-stratified, placebo-controlled clinical control trial** | Preparation based on micronized fruit and vegetables including grapes | 92 healthy adults | Product with 119 polyphenolic compounds | 2 periods of 16 weeks each | Dietary control | Improvement of executive functions such as working memory (planning capacity, alternation and fluidity of the motor response), and short-term memory associated with the chronic consumption of a polyphenolic extract of fruits and vegetables for 4 months | [17] |

**Table 5.** *Cont.*

| Study Type | Matrix | Population | Dose | Duration | Nutritional Design | Results and Conclusions | Reference |
|---|---|---|---|---|---|---|---|
| **Randomised, double-blinded, placebo-controlled trial** | Polyphenol-rich juice made from red grapes, cherries, chokeberries, and blueberries + similar juice enriched with polyphenol-rich extracts from blackcurrant press residues | 134 healthy individuals, aged 50–70 years, with high-normal range blood pressure (BP). Concretely, 72 subjects with BP 130/85–139/89 mmHg and 62 people on stage 1–2 hypertension with BP 140/90–179/109 mmHg). | 500 mL (2 juices rich in polyphenols of different fruits including 67.7% of *Vitis vinifera* grapes in the composition of one of the juices). | 12 weeks | Dietary control | Significant reduction in BP and BP variability in subjects who consumed the polyphenol-rich berry juice, being more pronounced in hypertensive subjects. | [15] |
| **Randomized, double-blinded, placebo-controlled clinical trial.** | Fiit-ns® Ingredient rich in extracted polyphenols inspired by the Mediterranean diet. | 92 healthy overweight and obese subjects | 450 mg capsules | 16 weeks | Dietary control. Balanced and isocaloric diet | The supplemented individuals experienced a significant improvement in HRQL (Health-Related Quality of Life) that encompasses a perceived physical and mental improvement, with factors such as body pain, vitality, and general health. | [16] |

### *3.3. Grapes and Derivatives Phenolic Composition*

(a) The composition of the grape involves a multitude of phenolic compounds, such as anthocyanins, flavanols, flavonols, stilbenes (such as resveratrol and piceid), and phenolic acids. The greatest presence of polyphenols is in the solid parts of the grape cluster (holes, seeds, and scratches). Anthocyanins are polyphenols more representative of red grapes, while flavanols are more characteristic of white grapes. [12].

(b) Grape juices, either alone or combined with other polyphenol-rich foods [15–17], are derived from unfermented grapes. Their composition of phenolic compounds is highly variable, since it depends on the variety of grape from which they are made. Other factors such as the state of maturity of the grape, the harvesting period, and climatic factors influence the composition of grape derivatives. In addition, the production processes themselves can affect its content due to possible degradations or losses. In general terms, higher sugar contents are found in grape juices made from white grapes than red grape juices. On the contrary, a greater quantity of polyphenols is found in red grape juices, the most predominant in the market. This includes flavonols (kaempferol, quercetin, and myricetin), flavanols (catechin, epicatechin, epigallocatechin, and epicatechin gallate), individual anthocyanins, condensed tannins, trans-resveratrol, and phenolic acids (vanillic, protocatechuic, caffeic, transcaphtharic and ferulic acids) [13].

(c) Non-alcoholic fermented grape juices, which seem to be a promising alternative to wine due to the negative effects of alcohol consumption while maintaining the high levels of phenolic compounds present in wine associated with the enzymatic reactions that occur in the winemaking processes. It has been reported that the total phenolic content of non-alcoholic fermented grape juice (2128 $\pm$ 188.09 mg gallic acid equivalent (GAE)/L) [14], is higher than that of conventional juices, but slightly lower than the concentration of organic red juice, total polyphenol content (TPC) of 3378.33 $\pm$ 50.08 mg GAE/L [13]. However, there is a large increase in some phenolic acids and flavonols, such as quercetin, in fermented juice without alcohol [13,14]. An important aspect to take into consideration, not shown in the chemical characterization of these studies, is the sugar content. Theoretically, it should be much lower in non-alcoholic fermented juice compared to non-fermented juices, which in many cases reduces their nutritional quality due to the large contribution of simple sugars.

(d) Red wine is an essential component of the Mediterranean triad whose consumption has been moderately recommended for several decades. It is a highly complex matrix composed of macromolecules and polysaccharides. The interactions of these compounds affect its organoleptic properties, such as the properly known astringency of red wine associated with the presence of tannins. Regarding the content of phenolic compounds, there is a great variety between the different types of wines, from their raw materials to the vinification techniques. However, some of the organoleptic properties established in viticultural practices as quality indices are parallelly related to certain phenolic profiles. Thus, the grape phenolic compounds can be transformed during the winemaking process in secondary metabolites. In this regard, wine phenolic compounds can be classified into phenolic acids, flavonoids, tannins, and stilbenes [11].

### *3.4. Effects Attributed to the Consumption of Grapes and Derivatives*

Considering grape consumption, a study performed in 2013 by Hokayem et al. [12] evaluated the impact of grape polyphenol consumption in healthy but metabolically predisposed subjects (healthy overweight/obese first-degree relatives of type 2 diabetic patients). The dietary pattern under study was a high-fructose diet which could be induced to develop insulin resistance. The results showed that all the deleterious effects of fructose (decreased insulin sensitivity, increased muscle and systemic oxidative stress, down-regulation of mitochondrial genes, and decreased mitochondrial respiration) were completely mitigated by grape polyphenol supplementation [12].

Regarding the phenolic compounds present in the must, Toaldo et al. [13] in 2015, analysed the composition of phenolic compounds in juices obtained from two red grape

varieties (organic and conventional). For the elaboration of the organic must, the cultivars of *V. labrusca L.* were "Bordo", "Isabel" and "Niagara Branca", and they were processed following the standards for the "ecological" determination. Conventional wines were made with "Isabel" and "Bordo" cultivars following conventional technological processes. These authors performed an acute intervention in thirty healthy subjects with control group (water), washout periods between interventions and a low consumption of foods rich in phenolic compounds. The results show a decrease in lipid peroxides after the consumption of both varieties of red grape juices, both organic and conventional [13].

Another way of study in relation to the consumption of grape phenolic compounds is the possible improvement of age-related cognitive decline, including an improvement of cognitive functions (immediate and working memory, and sustained/selective attention). A recently published study, carried out by Carrillo et al. [17], studied the sustained consumption of a mixture of fruits and vegetables, including grapes, for four months in healthy subjects, with a total of 119 phenolic compounds. The results, despite the fact that a general consumption of phenolic compounds from various plant foods was determined, showed positive results for the processes involved in executive functions such as working memory and short-term memory [17].

Moreover, a study carried out in healthy and hypertensive subjects reported the impact on the consumption of two drinks formulated with red fruits (red grapes, cherries, chokeberries, and blueberries) as source of phenolic compounds. In addition, one of two formulations, was also enriched with polyphenol-rich extracts from blackcurrant press residues. The results showed that polyphenol-rich berry juice may contribute to a blood pressure-lowering effect. These results indicated out positive effects on reducing blood pressure (BP), showing a more pronounced impact in hypertensive subjects [15].

Continuing the line of food mixtures rich in phenolic compounds, Romain et al. [16] published a study of an enriched polyphenolic ingredient obtained through the hydro-alcoholic extraction of grapefruit, grape (*Vitis vinífera* L.) and guarana seed in 2021. The trial was carried out in healthy subjects, all of them overweight or obesity, excluding those with metabolic syndrome (MS). The individuals presented a significant improvement in health-related quality of life (HRQL), including aspects regarding physical and mental perception, and an improvement in other health parameters, such as body pain, vitality, and general health [16].

Despite the fact that both grape and grape juices are rich in phenolic compounds, fermentation processes seem to increase the presence of phenolic compounds due to the transfer of polyphenols from grape seeds, skins, and stems to the juice. A study carried out by Amoutzopoulos et al. [14] in 2013 analysed a drink from Turkish origin called hardaliye. This beverage is based on red grapes, sour cherry leaves, and mustard seeds, which are fermented by lactic acid bacteria. The final product does not include alcohol in its composition thanks to the presence of allyl isothiocyanate (AITC) from mustard seeds, which inhibits the presence of yeast and the alcoholic content as a result. The consumption of this drink rich in polyphenols (total phenolic content: 2128 $\pm$ 188.09 mg GAE/L reduces biomarkers of lipid oxidation (dien conjugate (DC) and malondialdehyde (MDA) derivatives), although the effects on antioxidant capacity were not clear in the study [14].

Regarding the consumption of wine combined with another food rich in phenolic compounds, such as extra virgin olive oil (EVOO), a study carried out by Migliori et al. [11] in 2015 compared the effects of the combined consumption of EVOO together with white wine (4 mL/kg body weight), with the isolated consumption of EVOO for two weeks in healthy participants and in patients with chronic kidney disease (CKD). The results show a reduction in chronic inflammation markers in CKD patients during the combined consumption of white wine and EVOO. Additionally, a significant increase in Tyr and OH-Tyr in urine was observed, both with recognized health effects. This conclusion suggests an anti-inflammatory effect associated with the combined consumption of two essential elements of the Mediterranean diet: wine and olive oil [11].

### *3.5. Great Possibilities for Working on a New Research Line Focus on the Synergy between Polyphenol Consumption and Microbiota Health Status*

Table 6 summarises the results for the literature search of studies regarding the effects of grape phenolics consumption on the microbiota.

A study carried out by Queipo-Ortuño et al. [18] compares the effect on the microbiota of healthy subjects of wine, non-alcoholic wine, and gin during four intervention periods of 20 days each (one corresponding to a washout). For each of the wines, the doses were 272 mL/d and the gin dose was 100 mL/d. Changes in the faecal microbiota were analysed by total faecal DNA, in addition to measuring other biochemical markers in blood and urine. Dealcoholized red wine possessed the same composition and phenolic content as normal red wine, except for ethanol, which contained only 0.42%. As expected, the gin drink did not contain phenolic compounds. The alcohol content was 30 g per 100 mL in red wine and gin. The results showed relevant differences in the microbiota after the different intervention periods, establishing a clear relationship between red wine consumption and its possible probiotic effect, as well as acting as an inhibitor of some of the non-beneficial bacteria. The main differences between the consumption of alcoholic and dealcoholized red wines lied in the diversity of the modifications of the different bacterial strains, depending on the dietary intervention. Both types of wines seemed to show a probiotic effect. Regarding other biochemical changes, a reduction in BP and lipid markers (such as total cholesterol and triglycerides) was observed after ingestion of both wines, suggesting that bacterial groups could also be involved in these aspects. An example of this is the growth of bifidobacterias involved in lowering cholesterol. However, no conclusive conclusions were drawn about the possible effects of ethanol on the microbiota [18].

Furthermore, another study carried out by Barroso et al. [19] published in 2016 studies the phylogenetic profile of the intestinal microbiota in 20 healthy adults after moderate intake of red wine during one month and after a washout period (diet low in polyphenols and no alcohol consumption). The faecal samples collected before the intervention showed a diversity in the metabolic capacity of their intestinal microbiota regarding wine polyphenols, which divided the group into three populations (high, moderate, and low metabolizers). The findings showed that after moderate consumption of red wine for a month, the differences in the microbial composition between the different groups disappeared, increasing the diversity of microbial groups in all individuals [19].

On the other hand, Muñoz-González et al. [20] published a study in 2013 on the effect of the microbiota on polyphenols from wine (once again supporting the idea of the synergy between microbiota and phenolic compounds). After moderate wine consumption, the results show an increase in 10 of the 33 analysed metabolites, showing a large variability between subjects. Those individuals could be divided into three groups based on the metabolising capacity of their microbiota. These findings are relevant in the study of polyphenols and their intestinal effect, promoting the metabolic proliferation of polyphenols and suggesting a close relationship between the possible positive effects that these metabolites exert in the body [20].

It should be noted that no intervention studies have been found that relate the consumption of grapes and other grape derivatives (except wine) with microbiota, according to the established search criteria. This fact suggests the need to focus on this line of study to obtain more conclusive results.

**Table 6.** Selected studies on the study of grape phenolic compounds' health effects in gut microbiota.

| Study Type | Matrix | Population | Dose | Duration | Gut Microbiota Interactions | Nutritional Design | Results and Conclusions | Reference |
|---|---|---|---|---|---|---|---|---|
| **Randomized, crossover, controlled intervention study** | Red wine and ethanol | 10 healthy adult mens aged 48 ± 2 years | De-alcoholized red wine (272 mL/d), red wine (272 mL/d) and gin (100 mL/d). | 4 periods of 20 days each | After the red wine period, the bacterial concentrations of *Proteobacteria*, *Fusobacteria*, *Firmicutes*, and *Bacteroidetes* were significantly increased. For dealcoholized wine, the *Fusobacteria* population increased whereas *Bacteroidetes* and *Firmicutes* decreased as compared to regular red wine | No changes in the dietary pattern or lifestyle habits was found. Subjects avoided other alcoholic beverages during the study. | The resveratrol content in urine increased 24 h after the intake of the red wines (alcohol-free and with alcohol) but did not increase with the intake of gin. Dihydroresveratrol, produced by the gut microbiota, also increased. Changes in the microbiota occurred associating the consumption of wine with a possible probiotic effect. | [18] |
| **Randomized and controlled study** | Red wine | 20 healthy volunteers with no recent history of gastrointestinal disease and not receiving antibiotics for at least 6 months before | 250 mL of red wine per day | 1 month of wine consumption after a two-week washout period | Volunteers were classified into three metabolic types regarding the metabolic capacity of their gut microbiota (low, moderate, and high wine polyphenol metabolizers). The consumption of red wine seems to increase the microbial diversity, suppressing the differences in the microbial metabolization of each one of the study groups. | Diet low in polyphenols during the two weeks of washing and without alcohol consumption. | Despite these differences between individuals, the consumption of red wine was associated with an increase in the diversity of microbial groups. | [19] |
| **Controlled and randomized trial study** | Red wine | 41 healthy volunteers (33 intervention and 8 control subjects) | 250 mL of red wine per day (equivalent to a dose of 450 mg of total polyphenols/day) | 1 month of wine consumption after a two-week washout period | Synergistic interactions between microbiota and polyphenols, increasing the proliferation of polyphenol metabolites, produced by the microbiota | Diet low in polyphenols during the two weeks of washing and without alcohol consumption. | Increase in 10 of 33 metabolites studied, with differences between subjects. | [20] |

### *3.6. The Urgent Need for Novel Strategies to Improve the Bioavailability of These Bioactive Compounds*

In recent decades, the bioactive compounds present in many foods have become a topic of growing interest, especially phenolic compounds coming from the plant kingdom and present in many fruits and vegetables with many attributable bioactive properties. They have been shown to act as preventive agents of various chronic pathologies, especially related to its great antioxidant potential. In this context, the consumer demand for new foods rich in these types of compounds is increasing exponentially. However, the potential benefit associated with the consumption of these compounds is related to fact that these compounds or their metabolites should be bioavailable in order to exert their effect at the site of action. There are many strategies under investigation to improve their bioavailability, which is scarce in most cases, such as nanoencapsulation techniques. Nevertheless, in terms of improving the bioavailability of polyphenols, the role of the microbiota in conjunction with the above-mentioned factor, once again highlights the close synergistic relationship between health, microbiota, and phenolic compounds.

In this regard, a study was conducted in healthy volunteers that led to two publications [25,26], one with ileostomy subjects (healthy, but without a functional colon) and another in healthy individuals with a functional colon. The ileostomy allows for the recovery of the ileal eluent after ingestion. The subjects consumed 350 mL of grape juice from the "Concord" variety, with a total of 528 μmol of polyphenolic compounds. After ingestion, 40% of the intact compounds were recovered of the compounds in the ileal effluent. This indicates that these components pass to the large intestine, where they would be subjected to the action of the microbiota. For the study of these undigested compounds upon reaching the colon, an in vitro model of colonic fermentation was used. This fermentation led to the identification of 16 phenolic acids derived from colonic metabolism, of which 13 urinary phenolic acids and aromatic compounds were excreted in significantly higher amounts after juice ingestion by healthy volunteers, while only two of these compounds were excreted in elevated amounts by ileostomists. This fact suggests that the colonic microbiota have an impact on the bioavailability and metabolism of phenolic compounds derived from (poly)phenolic compounds.

Furthermore, twenty-four urine samples were also collected before and after the consumption of grape juice (in this case in healthy subjects and in healthy ileostomised individuals). In the urine collected from healthy subjects after the juice intake, 21 phenolic acids and aromatic compounds were identified, whereas 15 of them was detected in the urine of ileostomised subjects. However, compared to baseline urine samples, only 13 metabolites were excreted in significantly higher amounts after juice intake, while ileostomists only excreted two of these compounds in significant amounts. This fact is of great importance and suggests that most of the metabolization of phenolic compounds occurs after their degradation by the colonic microbiota. Tthe only compound excreted at a similar amount in the urine of both groups was tartaric acid (resulting from the hydrolysis of transcaphtharic, transcutaneous, and transfertaric acids), suggesting that the in vivo metabolism of this compound occurs in the proximal gastrointestinal tract rather than in the distal gastrointestinal tract [25,26].

As seen in the present review, symbiotic mechanisms between polyphenols and the gut microbiota seem to be feasible. The phenolic compounds that reach the colon exert a positive action on the microbiota, which degrades them to a series of simpler phenolic acids before being absorbed through the portal vein [18–20]. Catabolic processes carried out by colon bacteria include hydrolysis, hydroxylation, hydrogenation, decarboxylation, and dehydroxylation. The metabolites resulting from the effect of the microbiota exert, in turn, positive effects on the organism, which deserve a detailed investigation. The fermentation that occurs in the colon results in a greater bioavailability of ingested phenolic compounds and results in a wide variety of compounds with beneficial properties. This fact highlights, once again, the role of the microbiota, this time within the framework of improving the bioavailability of ingested phenolic compounds [25,26].

The results are similar to those of another study carried out with the same characteristics, with the exception of the polyphenolic matrix, which in this case came from green tea, apples, grapes, grape pomace, and citrus fruits (total polyphenols: 718.4 µmol in 350 mL). The phenolic fraction was composed of flavan-3-ols, procyanidins, dihydrochalcones, 5-*O*-caffeoylquinic acid, flavanones, anthocyanins, and gallic acid. It was found that 40% of the ingested phenolic compounds passed into the colon to be degraded by the intestinal microbiota, exerting a synergistic action [27].

## 4. Discussion

In relation to the results obtained, it should be taken into account that a strict and careful process of searching the scientific literature has been followed, especially through filtering by type of study. For this reason, the resulting findings on the positive effects of the consumption of phenolic compounds from grapes and products derived from the vine are surely much less than the real benefits associated with their consumption.

According to the search carried out, the results of the evaluated studies have pointed out the positive results on the regulation of insulin sensitivity, as well as on the reduction of damage caused by oxidative stress associated with the consumption of phenolic compounds present in grapes. Consumption of grape polyphenols is associated with a reduction in negative effects related to fructose consumption, such as decreased hepatic insulin sensitivity index, decreased glucose infusion rate, increased systemic oxidative stress, decreased mitochondrial genes, and decreased mitochondrial respiration [12]. These antidiabetic effects related to the consumption of polyphenols could be explained by the inhibition of the kir6.2 channel, encoded by the KCNJ11 gene, whose mutation is widely related to the presence of type I diabetes. Pterostilbene, as an active component of *V. vinifera*, has strong inhibitory effects in kir6.2 models [2]. Another possible explanation for the antidiabetic effects is found at the intestinal level: in vitro assays showed that grape polyphenols seem to inhibit the enzymes α-amylase and α-glucosidase, both key enzymes in the digestion of carbohydrates. In addition, they appear to increase insulin-mediated tissue glucose uptake by activating adenosine monophosphate 5′-activated protein kinase (AMPK) in the skeletal muscle and liver [28].

On the other hand, the phenolic composition of grapes is a collection of polyphenols including anthocyanins and flavanols such as quercetin. Several studies have shown that monomeric flavonoids and flavan-3-ols can improve glucose transport and reduce hyperglycaemic effects [29,30] Interestingly, despite the fact that participants in this study [12] consumed high doses of fructose, all of the detrimental effects were mitigated, suggesting a preventive nature character associated with the consumption of grapes. These effects have been previously observed in other trials. In the study conducted by Mohammad et al. [31] in adolescents with metabolic syndrome, consumption of a grape seed extract rich in phenolic compounds was also able to improve insulin concentration and insulin resistance. Consumption of "Concor" grape juice (*Vitis lambrusca*) composed of a unique combination of polyphenolic compounds was also associated with lower glycaemic responses in adults with excess body weight when consumed outside of meals [32]. This fact supports the idea of the importance of including grape polyphenols in the diet, combined with an adequate intake of fruits and vegetables, which are also rich in phenolic compounds, in the context of a varied, balanced, and healthy diet.

Regarding the consumption of wine, despite the high number of studies which have been published in recent years, specific exclusion criteria have been applied in this review. These criteria have been approached with the aim of clarifying the compiled information as well as the applicability to the literature scientific in healthy subjects. As a result, one article has been obtained [11], which studied the consumption of wine in combination with EVOO. These two elements, typical of the Mediterranean diet, are extraordinarily rich in phenolic compounds. In this case, the study was carried out with white wine; however, it is well known that red wine contains the greatest bioactive properties. The ingestion of white wine in combination with EVOO showed a reduction in chronic inflammation

markers. However, it should be noted that the effects were more noticeable in subjects with chronic kidney disease (CKD). In this context, the study compared the effects in CKD patients, as well as healthy subjects, which is why it was selected in the present systematic review. It is of interest to highlight that most of the human studies on wine consumption are conducted on diseased subjects, studying the improvement or regulation of illnesses such as cardiovascular disease. This may be due to publication bias, i.e., there are greater effects in diseased subjects than in healthy individuals, and consequently there is a gap in the literature. However, although not as remarkable, the preventive effect in healthy subjects associated with the consumption of phenolic compounds, as well as a healthy diet rich in fruits and vegetables, should be further studied.

On the other hand, as a result of the long contact time with grape skins and seeds during wine production, red wines tend to be higher in polyphenol content than white wines, generally around six times higher. It was discovered that the phenolic compound content in red wines varies from 1800 to 3000 mg/L [33] Furthermore, it is important to highlight the importance of making an adequate selection of grape variety as well as winemaking processes used for polyphenol enrichment, since the quality of the phenolic compounds may be highly variable. In this regard, it has been shown that the use of ultrasound and horizontal rotary stainless steel wine fermenters during vinification can increase the polyphenol content, varying according to the type of cultivar [34].

Another product derived from the vine, grape juice, is an unfermented derivative of grapes, rich in phenolic compounds such as anthocyanins, flavan-3-ols, flavanols, phenolic acids, and resveratrol. It showed positive results in reducing lipid oxidation in healthy individuals. These results are already well known with reference to the consumption of foods rich in polyphenols [13]. This activity is associated with its modulating role in antioxidant mechanisms and its effects against peroxidation and the elimination of free radicals [35–37] The consumption of must shows positive effects on the inhibition of lipid peroxidation. However, it should be taken into account that the composition varies greatly depending on the grape variety and type of grape cultivation, as well as the industrial processes to which the product is subjected. Despite being a developing field of research, hardly any studies were found that were conducted in healthy humans that evaluate this bioactivity associated with grape juice consumption. These well-known bioactive properties open an interesting field in the food industry for the application of strategies that add value to previously commercialized products. For example, with grape juice, possible strategies include highlighting healthful properties, such as its preventive nature against oxidation [34].

As it is commonly known, grapes are not the only source of phenolic compounds, so fruit juices with bioactive properties promise to provide a high antioxidant capacity. In clinical studies, these juices have shown to induce a reduction in lipid oxidation markers [14], a reduction in BP [15], an improvement in cognitive functions [17], and an improvement in quality of life indices [16]. These bioactive properties are associated with reduced damage caused by oxidative stress and the strong ability of phenolic compounds to reduce markers of inflammation and oxidation.

It should be noted that, as mentioned before, wine seems to contain a higher amount of phenolic compounds than grapes or grape juice due to the production process itself, which brings the mixture of precursors and enzymes that give rise to fermentation in contact with higher amount of phenolic compounds. However, although wine is part of the triad of the Mediterranean diet and its moderate consumption has been traditionally recommended [38], there is also evidence that alcohol consumption has harmful effects on health [39]. Thus, the consumption of alcoholic beverages such as wine could be replaced by other phenolic-enriched drinks which possess only the beneficial health effects. Therefore, the results suggest that the consumption of non-alcoholic fermented vine-derived products could be the best source of phenolic compounds with greater health benefits and without associated damage. In addition, the fermentation process itself should theoretically reduce the sugar level, which will eliminate another risk factor. Another example of a beneficial

drink is the hardaliye drink [14] from Turkey, a non-alcoholic fermented drink produced from a mixture of fruits and vegetables with a TPC of 2128 ± 188.09 mg GAE/L. The doses supplied in the study were 250 and 500 mL, providing 533 and 1066 mg GAE polyphenols per day, respectively (assessed with ORAC). These results provide greater amounts of polyphenols than grape juice itself or isolated orange or pomegranate juices or even some table wines.

In addition to the already known positive effects associated with the consumption of polyphenols from vine derived products, in recent years, the intestinal microbiota is an emerging concept in terms of health. There appears to be some synergistic effects between the consumption of polyphenols and the health of the microbiota [40].

Currently, human intervention studies in this area are limited, although they are of great interest as they study the impact of grapes on disease biomarkers and their relationship with the microbiota. One of the aspects to consider in favour of this type of intervention is the great interindividual variability that exists in the human microbiome. Although not specifically addressed in this review, there are other lines of research in this field that contemplate other study models such as animal models and studies carried out with dynamic gastrointestinal simulators. These dynamic studies have expressly contributed to the identification of metabolites derived from phenolic compounds of grapes/wine, with the action of the microbiota, as well as the microbial communities susceptible to being modified by the action of polyphenols. Animal models help to relate the activity of phenolic compounds at the systemic level and relate it to changes in the composition and functionality of the microbiota [41].

On the one hand, the microbiota metabolizes polyphenols, helping to extract and absorb metabolites with bioactive effects for the health of the host. On the other hand, the presence of polyphenols seems to stimulate the proliferation of the healthy microbiota strains and helps to eliminate the microbiota associated with pathogenicity. The findings obtained in the present review [18–20] help to understand this synergy. All the found studies were carried out with red wine and in healthy subjects, studying the effects of its consumption on the microbiota. It is important to bear in mind that red wine, in addition to phenolic compounds, also has alcohol in its composition.

The study carried out by Queipo-Ortuño [18] examined the effect of regular red wine, dealcoholized red wine, and gin. All of the interventions showed changes in the microbiota; however, an increase in the proliferation of beneficial microbiota was only found after the consumption of the two red wines, which suggests a probiotic effect of red wine polyphenols. The results showed that although the non-dominant bacterial population was maintained, there were increases after consumption for 4 weeks in *Enterococcus*, *Prevotella, Bacteroides*, *Bifidobacterium*, *Bacteroides uniformis*, *Eggerthella tarda* and *Blautia coccoides-Eubacterium rectale* for the groups that drank red wine and not for the group that drank gin. Despite the detected differences in the proliferation of certain bacterial strains associated with the consumption of regular and dealcoholized red wines, no conclusions could be drawn about the effect of ethanol in wine. It should be noted that positive effects were also observed in the lipid profile of the participants who consumed red wine (both types). In comparison to the initial values, a reduction was observed in the concentrations of triglycerides, total cholesterol, and HDL cholesterol. In addition, a significant univariate correlation has been found between changes in the number of specific bacteria and the lipid profile. These changes in the bacterial population caused by polyphenols in wine clearly showed that both alcoholic and dealcoholized red wine significantly decreases lipid markers except cholesterol. The authors determined that this effect may be due to the increase induced by polyphenols of *Bacterioides* genera, while the decrease in cholesterol concentration observed could be related to the significant increase in *Bifidobacterium*.

In reference to the effects at the cardiovascular level, a close relationship was found between the consumption of both types of wine in the reduction of systolic blood pressure (SBP). In addition, a reduction in C-reactive protein (CRP) was found after treatment with alcoholic and dealcoholized red wine. CRP is a blood marker of inflammation and an

increase in its concentration is associated with a high risk of cardiovascular events in healthy subjects. The decrease in SAP (systolic arterial pressure) is related to an increase in the genus Bacterioides, while the decrease in CRP could be related to an increase in Bifidobacterium. These changes in the microbiota are associated with the aforementioned symbiotic relationship between wine polyphenols and gut microbiota [18]. These results agree with the well-known cardioprotective effects associated with the consumption of grapes and their derivatives [12–15].

The consumption of red wine has been associated with cardiovascular protection for decades. An example of this claim is the "French paradox", which relates a low prevalence of heart disease associated with wine consumption. However, in recent years debate continues on the effect of alcohol, especially on the consequences of promoting the consumption of an alcoholic beverage, when it is possible to obtain similar benefits from other compounds derived from the same raw material, the grape [42]. One of the most studied phenolic compounds in wine in relation to cardioprotective effects is resveratrol. It is known for its anti-inflammatory and antioxidant properties, among which are the reduction of free radicals, limiting peroxidation processes or reduction of oxidative stress induced by glucose, and especially for its ability to upregulate endothelial NO synthase (eNOS) [42]. However, it is not only resveratrol has cardiovascular protective effects. Many other phenolic compounds from grapes are associated with improved vascular health, reducing the risk of hypertension and cardiovascular disease [43–46].

In the same line of thought, a subsequent study found that the chronic consumption of red wine was able to increase the amounts of *Bifidobacterium* and *Prevotella*, leading to possible beneficial effects as a consequence of a lower concentration of lipopolysaccharide [47]. In the same way, Barroso et al. [19] demonstrated in 2016 that after consuming red wine for a month, an increase in microbial proliferation was observed in terms of increased diversity. These effects were shown to the same extent among all the groups, despite the fact that the individuals under study presented differences in the ability to metabolize polyphenols by the microbiota. These results suggest that the consumption of red wine has positive effects on the microbiota and reduces the differences in microbial metabolism capacity [19,48].

In addition to the probiotic effect associated with the consumption of red wine, the microbiota also presents synergistic effects with polyphenols, increasing the profile of phenolic metabolites. In this regard, after wine ingestion a total of 33 metabolites were identified, of which 10 (mainly benzoic and 4-hydroxyvaleric acids) showed significant increases after the intake. In addition, three different groups could be established based on the metabolization of wine polyphenols taking into account their phenolic content in faeces (500, 500–1000 and >1000 μg/g). This variability between individuals suggests that there is a different microbial capacity in terms of metabolizing phenolic compounds in the human population [20]. In this context, it can be concluded that although no studies have been found with other vine-derived polyphenolic matrices, positive results have been found in the synergy of the consumption of polyphenols from red wine with the microbiota. In conclusion, polyphenols in the colon increase the diversity of the microbiota and the microbiota increase the presence of polyphenolic metabolites with possible beneficial effects for the body. Human studies linking polyphenol intake and beneficial changes in the microbiota are still limited. Although a symbiotic relationship appears to exist, resulting in the formation of beneficial metabolites and changes in the capacity and functionality of the microbiota, it remains to be determined whether these changes in the microbiota are due to the metabolites or the parent compound. However, this field has a promising future [42,49].

Once the positive effects of polyphenol consumption are known, it is important to study novel strategies for improving their bioavailability, which is considered the major bottleneck for phenolic bioactivity. Interestingly, the results of the literature survey for in vivo studies on bioavailability of polyphenols once again leads to the microbiota. Several studies exist [25–27] that compare the metabolization of polyphenols both in grape juice and juice from various ingredients, including grapes, in healthy subjects with and without a functional colon (ileostomists). The result of this research showed very significant differ-

ences in the excretions of metabolites in urine between the participants. Thus, a large part of the ingested phenolic compounds passed intact to the colon, where they were fermented by the microbiota. Furthermore, once the grape juice was consumed, the intestinal content was analysed after digestion (up to the ileum area), resulting in 40% of the original phenolic compounds found intact in the intestinal fluid. Thus, the microbiota acts as an agent responsible for increasing the bioavailability of a large number of metabolites, especially those derivatives from phenolic acids with a multitude of beneficial properties.

In addition, other types of strategies should be assessed, such as compound encapsulation techniques to promote actions at specific sites and influence the promotion of dietary intervention strategies that positively modulate the microbiota, thus generating more bioavailable phenolic metabolites and benefit from its beneficial effects at the systemic level [50].

The results showed a clear positive effect associated with the consumption of phenolic compounds from various foods, such as grapes, wine or grape juice. These positive effects are clearly associated with the well-known antioxidant and anti-inflammatory properties of grape phenolic compounds. These substances could exert a preventive effect associated with the age-related deterioration or sedentary lifestyle and the onset of damage associated with oxidative stress [51–53]. Therefore, future research should not only focus on improving underlying pathologies with antioxidant therapy, but also on prevention, through chronic supplementation with a polyphenol-rich ingredient. In addition, the consumption of a varied diet rich in fruits and vegetables, as well as EVOO, should be promoted, and substances that generate oxidative stress, such as the alcohol in the wines themselves, should be avoided. For this reason, it is proposed to continue the research on the formulation of plant-based foods (typical of the Mediterranean diet) with high antioxidant capacity, subjected to a process of preparation and fermentation that increases their content of phenolic compounds, but eliminating the alcohol content.

It should be noted that the present systematic review has the following limitations: (a) Although all the selected studies have characterized their sources of phenolic compounds, the specific doses in each of the interventions have not been taken into account because they have not been characterized with the same analytical methodology, which could alter the composition results. (b) No specific phenolic compound has been studied, but rather the antioxidant capacity of each of the matrices under study, so it would be necessary to inquire about which phenolic compounds present in the different matrices have greater bioactive properties and better bioavailability. Taking these data into account, it could be further refined in the third point of this review, improving the efficacy of possible ways or strategies to improve the bioavailability of compounds with greater properties. (c) Not entirely a limitation, this review has focused its search on healthy subjects, opening a line of research more focused on prevention than on the improvement of pathologies. For this reason, in some cases the selected studies were conducted in healthy subjects but with the potential for developing some disease, such as metabolic syndrome in healthy but obese or overweight subjects [16] and in subjects who are direct relatives of people with some metabolic syndrome disease [12], as well as studies that have compared the effect of the supplement between healthy subjects and patients with any disease [11,15]. (d) Furthermore, there are great differences in the nutritional design of the intervention across studies. In some cases, the diet is modified, the content of polyphenols through the diet is decreased, or no dietary modification was made at all. This fact is important since nutritional intervention itself may act as a bias in the intervention. (e) Regarding the studies carried out on the microbiota, the main limitation found in this systematic review was the lack of information available in the literature regarding the effect of polyphenols on the microbiota derived from foods other than red wine [18–20]. More research is also needed on the possible effect of ethanol on the synergy between red wine polyphenols and microbiota. (f) Finally, concerning bioavailability studies, several limitations have been found regarding the search for studies carried out in humans, due to the fact that these trials are very invasive. Fortunately, thanks to the collaboration of ileostomy subjects [25–27],

relevant conclusions could be drawn. Currently, the research lines are focused on the study of the in vitro bioavailability of polyphenols with gastrointestinal simulators, which simulate physiological conditions with great accuracy and convenient sampling.

## 5. Conclusions

This review supports the role of grape polyphenols and grape-based products on gut microbiota, health, and their bioavailability following the PRISMA methodology. With the established search criteria, it was not possible to include a large number of studies in the results of the systematic search. However, it must be taken into account that the quality of the selection provides great reliability of the presented results.

Polyphenols present in both grapes and grape juices have been shown to exert beneficial effects on lipid peroxidation, oxidative stress, insulin resistance, improvement of cognitive functions, and reduction of blood pressure. As a general rule, the composition of phenolic compounds is higher in wines or fermented products than in juices. This is due to the enzymatic processes that they undergo during processing. It has also been found that there are a multitude of factors, such as ecological processing, that could increase the quantity of phenolic compounds. However, in order to not promote the consumption of alcoholic beverages, further research is proposed on non-alcoholic fermented beverages based on polyphenol-rich foods with less sugar content due to fermentation. These products could be of great interest to the food industry as a springboard for preventive nutrition in healthy subjects or special groups, such as athletes.

Regarding the effects of the consumption of grape polyphenols on the microbiota, studies using red wine indicate that its consumption alters both the quantity and quality of gut bacteria in a beneficial way for the host, even showing a possible probiotic effect; however, it is necessary to clarify this. Research shows a synergistic effect between polyphenols and microbiota. After the consumption of compounds rich in polyphenols such as grapes, a greater proliferation of beneficial bacteria is observed, and on the contrary, the microbiota seems to exert a positive effect in the presence of new metabolites of polyphenols (simple phenols and other metabolites), increasing its diversity and beneficial effects. In addition, this new microbiota seems to have effects on certain physiological markers, such as those related to cardiovascular health. It is necessary to study whether these effects are due to the polyphenol metabolites produced by the microbiota, to the consumption of polyphenols themselves, or to the effect on the strains of the microbiota due to the presence of polyphenols.

In terms of bioavailability, the found in vivo studies shed light on the importance of one of the factors in increasing phenolic bioavailability. The microbiota appears to act as a powerful factor to increase the bioavailability of phenolic compounds. It is estimated that 40% of phenolic compounds reach the microbiota intact, where they are metabolized. The resulting simple phenols, in turn, provide bioactive properties. The current line of research on improving availability seeks strategies such as encapsulation of phenolic compounds. However, it would also be interesting to focus research on the great benefits of this tandem between phenolic compounds and the microbiota.

**Author Contributions:** Conceptualization, P.R.-L., A.R.-R., J.L.-S.; methodology, P.R.-L. and A.R.-R.; validation, I.B.-L., A.S.-C. and J.L.-S.; investigation, P.R.-L., A.R.-R., I.B.-L., J.L.-S.; data curation, P.R.-L., A.R.-R., R.M.Q.-P., T.E.; writing—original draft preparation, P.R.-L.; writing—review and editing, A.R.-R., J.L.-S., I.B.-L., R.M.Q.-P., T.E., A.S.-C.; supervision, J.L.-S.; funding acquisition, A.S.-C., J.L.-S. All authors have read and agreed to the published version of the manuscript.

**Funding:** The authors reported no funding received for this study. This research received no external funding.

**Institutional Review Board Statement:** Not applicable.

**Data Availability Statement:** All the data generated by this research have been included in the article. It is possible to contact the corresponding author for any request of information.

**Conflicts of Interest:** Author disclosures: P.R.-L., A.R.-R., I.B.-L., RMQP, T.E., A.S.-C. and J.L.-S., no conflicts of interest.

## References


1. Giampieri, F.; Eseberri, I.; Trepiana, J.; Léniz, A.; Gómez-García, I.; Carr-Ugarte, H.; González, M.; Portillo, M.P. Variability in the Beneficial Effects of Phenolic Compounds: A Review. *Nutrients* **2022**, *14*, 1925. [CrossRef]
2. Nassiri-Asl, M.; Hosseinzadeh, H. Review of the Pharmacological Effects of Vitis vinifera (Grape) and its Bioactive Constituents: An Update. *Phyther. Res.* **2016**, *30*, 1392–1403. [CrossRef] [PubMed]
3. Li, L.; Sun, B. Grape and wine polymeric polyphenols: Their importance in enology. *Crit. Rev. Food Sci. Nutr.* **2019**, *59*, 563–579. [CrossRef] [PubMed]
4. Castello, F.; Costabile, G.; Bresciani, L.; Tassotti, M.; Naviglio, D.; Luongo, D.; Ciciola, P.; Vitale, M.; Vetrani, C.; Galaverna, G.; et al. Bioavailability and pharmacokinetic profile of grape pomace phenolic compounds in humans. *Arch. Biochem. Biophys.* **2018**, *646*, 1–9. [CrossRef]
5. Ribas-Agustí, A.; Martín-Belloso, O.; Soliva-Fortuny, R.; Elez-Martínez, P. Food processing strategies to enhance phenolic compounds bioaccessibility and bioavailability in plant-based foods. *Crit. Rev. Food Sci. Nutr.* **2017**, *58*, 2531–2548. [CrossRef]
6. Crozier, A.; Del Rio, D.; Clifford, M.N. Bioavailability of dietary flavonoids and phenolic compounds. *Mol. Aspects Med.* **2010**, *31*, 446–467. [CrossRef]
7. Goldberg, D.M.; Yan, J.; Soleas, G.J. Absorption of three wine-related polyphenols in three different matrices by healthy subjects. *Clin. Biochem.* **2003**, *36*, 79–87. [CrossRef]
8. Bell, J.R.; Donovan, J.L.; Wong, R.; Waterhouse, A.L.; German, J.B.; Walzem, R.L.; Kasim-Karakas, S.E. (+)-Catechin in human plasma after ingestion of a single serving of reconstituted red wine. *Am. J. Clin. Nutr.* **2000**, *71*, 103–108. [CrossRef]
9. Donovan, J.L.; Bell, J.R.; Kasim-Karakas, S.; German, J.B.; Walzern, R.L.; Hansen, R.J.; Waterhouse, A.L. Catechin Is Present as Metabolites in Human Plasma after Consumption of Red Wine. *J. Nutr.* **1999**, *129*, 1662–1668. [CrossRef]
10. De Vries, J.H.M.; Hollman, P.C.H.; Van Amersfoort, I.; Olthof, M.R.; Katan, M.B. Red Wine Is a Poor Source of Bioavailable Flavonols in Men. *J. Nutr.* **2001**, *131*, 745–748. [CrossRef]
11. Migliori, M.; Panichi, V.; De La Torre, R.; Fitó, M.; Covas, M.; Bertelli, A.; Muñoz-Aguayo, D.; Scatena, A.; Paoletti, S.; Ronco, C. Anti-Inflammatory Effect of White Wine in CKD Patients and Healthy Volunteers. *Blood Purif.* **2015**, *39*, 218–223. [CrossRef] [PubMed]
12. Hokayem, M.; Blond, E.; Vidal, H.; Lambert, K.; Meugnier, E.; Feillet-Coudray, C.; Coudray, C.; Pesenti, S.; Luyton, C.; Lambert-Porcheron, S.; et al. Grape polyphenols prevent fructose-induced oxidative stress and insulin resistance in first-degree relatives of type 2 diabetic patients. *Diabetes Care* **2013**, *36*, 1454–1461. [CrossRef] [PubMed]
13. Toaldo, I.M.; Cruz, F.A.; Alves, T.D.L.; De Gois, J.S.; Borges, D.L.G.; Cunha, H.P.; Da Silva, E.L.; Bordignon-Luiz, M.T. Bioactive potential of Vitis labrusca L. grape juices from the Southern Region of Brazil: Phenolic and elemental composition and effect on lipid peroxidation in healthy subjects. *Food Chem.* **2015**, *173*, 527–535. [CrossRef] [PubMed]
14. Amoutzopoulos, B.; Löker, G.B.; Samur, G.; Çevikkalp, S.A.; Yaman, M.; Köse, T.; Pelvan, E. Effects of a traditional fermented grape-based drink "hardaliye" on antioxidant status of healthy adults: A randomized controlled clinical trial. *J. Sci. Food Agric.* **2013**, *93*, 3604–3610. [CrossRef] [PubMed]
15. Tjelle, T.E.; Holtung, L.; Bohn, S.K.; Aaby, K.; Thoresen, M.; Wiik, S.Å.; Paur, I.; Karlsen, A.S.; Retterstol, K.; Iversen, P.O.; et al. Polyphenol-rich juices reduce blood pressure measures in a randomised controlled trial in high normal and hypertensive volunteers. *Br. J. Nutr.* **2015**, *114*, 1054–1063. [CrossRef]
16. Romain, C.; Chung, L.H.; Marín-Cascales, E.; Rubio-Arias, J.A.; Gaillet, S.; Laurent, C.; Morillas-Ruiz, J.M.; Martínez-Rodriguez, A.; Alcaraz, P.E.; Cases, J. Sixteen weeks of supplementation with a nutritional quantity of a diversity of polyphenols from foodstuff extracts improves the health-related quality of life of overweight and obese volunteers: A randomized, double-blind, parallel clinical trial. *Nutrients* **2021**, *13*, 492. [CrossRef]
17. Carrillo, J.Á.; Arcusa, R.; Zafrilla, M.P.; Marhuenda, J. Effects of fruit and vegetable-based nutraceutical on cognitive function in a healthy population: Placebo-controlled, double-blind, and randomized clinical trial. *Antioxidants* **2021**, *10*, 116. [CrossRef]
18. Queipo-Ortuño, M.I.; Boto-Ordóñez, M.; Murri, M.; Gomez-Zumaquero, J.M.; Clemente-Postigo, M.; Estruch, R.; Cardona Diaz, F.; Andrés-Lacueva, C.; Tinahones, F.J. Influence of red wine polyphenols and ethanol on the gut microbiota ecology and biochemical biomarkers. *Am. J. Clin. Nutr.* **2012**, *95*, 1323–1334. [CrossRef]
19. Barroso, E.; Muñoz-González, I.; Jiménez, E.; Bartolomé, B.; Moreno-Arribas, M.V.; Peláez, C.; del Carmen Martínez-Cuesta, M.; Requena, T. Phylogenetic profile of gut microbiota in healthy adults after moderate intake of red wine. *Mol. Nutr. Food Res.* **2017**, *61*, 1600620. [CrossRef]
20. Muñoz-González, I.; Jiménez-Girón, A.; Martín-Álvarez, P.J.; Bartolomé, B.; Moreno-Arribas, M.V. Profiling of microbial-derived phenolic metabolites in human feces after moderate red wine intake. *J. Agric. Food Chem.* **2013**, *61*, 9470–9479. [CrossRef]
21. Moher, D.; Liberati, A.; Tetzlaff, J.; Altman, D.G. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Med.* **2009**, *6*, e1000097. [CrossRef] [PubMed]
22. Page, M.J.; McKenzie, J.E.; Bossuyt, P.; Boutron, I.; Hoffmann, T.C.; Mulrow, C.D.; Shamseer, L.; Tetzlaff, J.M.; Akl, E.; Brennan, S.E.; et al. The prisma 2020 statement: An updated guideline for reporting systematic reviews. *Med. Flum.* **2021**, *57*, 444–465. [CrossRef]

23. Methley, A.M.; Campbell, S.; Chew-Graham, C.; McNally, R.; Cheraghi-Sohi, S. PICO, PICOS and SPIDER: A comparison study of specificity and sensitivity in three search tools for qualitative systematic reviews. *BMC Health Serv. Res.* **2014**, *14*, 579. [CrossRef] [PubMed]
24. Mamédio, C.; Roberto, M.; Nobre, C. The Pico Strategy for the Research Question. *Rev. Latino-am Enferm.* **2007**, *15*, 508–511.
25. Stalmach, A.; Edwards, C.A.; Wightman, J.D.; Crozier, A. Colonic catabolism of dietary phenolic and polyphenolic compounds from Concord grape juice. *Food Funct.* **2013**, *4*, 52–62. [CrossRef]
26. Stalmach, A.; Edwards, C.A.; Wightman, J.D.; Crozier, A. Gastrointestinal stability and bioavailability of (poly)phenolic compounds following ingestion of Concord grape juice by humans. *Mol. Nutr. Food Res.* **2012**, *56*, 497–509. [CrossRef]
27. Borges, G.; Lean, M.E.J.; Roberts, S.A.; Crozier, A. Bioavailability of dietary (poly)phenols: A study with ileostomists to discriminate between absorption in small and large intestine. *Food Funct.* **2013**, *4*, 754–762. [CrossRef]
28. Kim, Y.A.; Keogh, J.B.; Clifton, P.M. Polyphenols and Glycemic Control. *Nutrients* **2016**, *8*, 17. [CrossRef]
29. Schewe, T.; Steffen, Y.; Sies, H. How do dietary flavanols improve vascular function? A position paper. *Arch. Biochem. Biophys.* **2008**, *476*, 102–106. [CrossRef]
30. Rivera, L.; Morón, R.; Sánchez, M.; Zarzuelo, A.; Galisteo, M. Quercetin ameliorates metabolic syndrome and improves the inflammatory status in obese Zucker rats. *Obesity* **2008**, *16*, 2081–2087. [CrossRef]
31. Mohammad, A.; Shahnaz, T.; Sorayya, K. Effect of 8 weeks' supplementation grape seed extract on insulin resistance in iranian adolescents with metabolic syndrome: A randomized controlled trial. *Diabetes Metab. Syndr. Clin. Res. Rev.* **2021**, *15*, 197–203. [CrossRef] [PubMed]
32. Coelho, O.G.L.; Alfenas, R.D.C.G.; Debelo, H.; Wightman, J.D.; Ferruzzi, M.G.; Mattes, R.D. Effects of Concord grape juice flavor intensity and phenolic compound content on glycemia, appetite and cognitive function in adults with excess body weight: A randomized double-blind crossover trial. *Food Funct.* **2021**, *12*, 11469–11481. [CrossRef] [PubMed]
33. Minzer, S.; Estruch, R.; Casas, R. Wine Intake in the Framework of a Mediterranean Diet and Chronic Non-Communicable Diseases: A Short Literature Review of the Last 5 Years. *Molecules* **2020**, *25*, 5045. [CrossRef]
34. Gambacorta, G.; Trani, A.; Punzi, R.; Fasciano, C.; Leo, R.; Fracchiolla, G.; Faccia, M. Impact of ultrasounds on the extraction of polyphenols during winemaking of red grapes cultivars from southern Italy. *Innov. Food Sci. Emerg. Technol.* **2017**, *43*, 54–59. [CrossRef]
35. Yassa, N.; Razavi Beni, H.; Hadjiakhoondi, A. Free radical scavenging and lipid peroxidation activity of the Shahani black grape. *Pakistan J. Biol. Sci.* **2008**, *11*, 2513–2516. [CrossRef]
36. Sánchez-Moreno, C.; Larrauri, J.A.; Saura-Calixto, F. Free radical scavenging capacity and inhibition of lipid oxidation of wines, grape juices and related polyphenolic constituents. *Food Res. Int.* **1999**, *32*, 407–412. [CrossRef]
37. Park, Y.K.; Park, E.; Kim, J.S.; Kang, M.H. Daily grape juice consumption reduces oxidative DNA damage and plasma free radical levels in healthy Koreans. *Mutat. Res. Mol. Mech. Mutagen.* **2003**, *529*, 77–86. [CrossRef]
38. Golan, R.; Gepner, Y.; Shai, I. Wine and Health–New Evidence. *Eur. J. Clin. Nutr.* **2018**, *72*, 55–59. [CrossRef]
39. Bagnardi, V.; Rota, M.; Botteri, E.; Tramacere, I.; Islami, F.; Fedirko, V.; Scotti, L.; Jenab, M.; Turati, F.; Pasquali, E.; et al. Alcohol consumption and site-specific cancer risk: A comprehensive dose–response meta-analysis. *Br. J. Cancer* **2014**, *112*, 580–593. [CrossRef]
40. Mithul Aravind, S.; Wichienchot, S.; Tsao, R.; Ramakrishnan, S.; Chakkaravarthi, S. Role of dietary polyphenols on gut microbiota, their metabolites and health benefits. *Food Res. Int.* **2021**, *142*. [CrossRef]
41. Zorraquín, I.; Sánchez-Hernández, E.; Ayuda-Durán, B.; Silva, M.; González-Paramás, A.M.; Santos-Buelga, C.; Moreno-Arribas, M.V.; Bartolomé, B. Current and future experimental approaches in the study of grape and wine polyphenols interacting gut microbiota. *J. Sci. Food Agric.* **2020**, *100*, 3789–3802. [CrossRef] [PubMed]
42. Chimento, A.; De Amicis, F.; Sirianni, R.; Sinicropi, M.S.; Puoci, F.; Casaburi, I.; Saturnino, C.; Pezzi, V. Progress to Improve Oral Bioavailability and Beneficial Effects of Resveratrol. *Int. J. Mol. Sci.* **2019**, *20*, 1381. [CrossRef] [PubMed]
43. Gross, M. Grape Polyphenols in the Prevention of Cardiovascular Disease. In *Grapes and Health*; Springer: Berlin/Heidelberg, Germany, 2016; pp. 27–52. [CrossRef]
44. Rasines-Perea, Z.; Teissedre, P.L. Grape Polyphenols' Effects in Human Cardiovascular Diseases and Diabetes. *Mol. A J. Synth. Chem. Nat. Prod. Chem.* **2017**, *22*, 68. [CrossRef] [PubMed]
45. Breuss, J.M.; Atanasov, A.G.; Uhrin, P. Resveratrol and Its Effects on the Vascular System. *Int. J. Mol. Sci.* **2019**, *20*, 1523. [CrossRef]
46. Zhao, C.N.; Meng, X.; Li, Y.; Li, S.; Liu, Q.; Tang, G.Y.; Li, H. Bin Fruits for Prevention and Treatment of Cardiovascular Diseases. *Nutrients* **2017**, *9*, 598. [CrossRef]
47. Wilkinson, S.B.; Tarnopolsky, M.A.; MacDonald, M.J.; MacDonald, J.R.; Armstrong, D.; Phillips, S.M. Erratum. *Am. J. Clin. Nutr.* **2013**, *98*, 512. [CrossRef]
48. Shah, M.A.; Bosco, S.J.D.; Mir, S.A. Plant extracts as natural antioxidants in meat and meat products. *Meat Sci.* **2014**, *98*, 21–33. [CrossRef]
49. Nash, V.; Ranadheera, C.S.; Georgousopoulou, E.N.; Mellor, D.D.; Panagiotakos, D.B.; McKune, A.J.; Kellett, J.; Naumovski, N. The effects of grape and red wine polyphenols on gut microbiota—A systematic review. *Food Res. Int.* **2018**, *113*, 277–287. [CrossRef]
50. Zhao, D.; Simon, J.E.; Wu, Q. A critical review on grape polyphenols for neuroprotection: Strategies to enhance bioefficacy. *Crit. Rev. Food Sci. Nutr.* **2020**, *60*, 597–625. [CrossRef]

51. Elejalde, E.; Villarán, M.C.; Alonso, R.M. Grape polyphenols supplementation for exercise-induced oxidative stress. *J. Int. Soc. Sports Nutr.* **2022**, *18*, 3. [CrossRef]
52. Domínguez-Perles, R.; Baenas, N.; García-Viguera, C. New Insights in (Poly)phenolic Compounds: From Dietary Sources to Health Evidence. *Foods* **2020**, *9*, 543. [CrossRef] [PubMed]
53. Arif, M.U.; Khan, M.K.I.; Riaz, S.; Nazir, A.; Maan, A.A.; Amin, U.; Saeed, F.; Afzaal, M. Role of fruits in aging and age-related disorders. *Exp. Gerontol.* **2022**, *162*, 111763. [CrossRef] [PubMed]