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Perspective

Wine Polyphenols and Health: Quantitative Research Literature Analysis

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Abstract: The relationship between wine polyphenols and health has been receiving growing scientific attention in the last few years. To confirm this point, the proposed paper identifies the major contributors to academic journals regarding the relationships between wine polyphenols and health. The endpoints of the proposed study are to provide a comprehensive overview and analysis of the literature regarding the relationships between wine polyphenol and health based on a bibliometric analysis. Bibliometric data were extracted from the Scopus online database using the search string TITLE-ABS-KEY (wine AND polyphenol* AND health OR ("french paradox" OR "cardiovascular disease*" OR atherosclerosis OR microbiota) and analyzed using the VOSviewer bibliometric software to generate bubble maps and to visualize the obtained results. This perspective paper analyzes: (i) the research themes addressing the relationships between wine polyphenols and health; (ii) the major contributors' origin, e.g., country and/or regions; (iii) the institutions where the research is based; (iv) the authors; and (v) the type of paper. These results represent a useful tool to identify emerging research directions, collaboration networks, and suggestions for more in-depth literature searches.

Keywords: wine; polyphenols; health; quantitative literature analysis; citation analysis; VOSviewer

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1. Introduction

It is now widely demonstrated that to modulate health status, one starting point is to take into account and properly consider both diet and lifestyle. The research for finding beneficial natural sources to promote health has focused its attention on fruits and vegetables, as their consumption has been inversely correlated with cardiovascular diseases (CHD). In the 1980s, a paradox that existed for the French population was observed, as it was shown that mortality from cardiovascular disease was very close to those found for the Chinese and Japanese populations, although the French diet was richer in saturated fats and the concentration of plasma cholesterol was much higher and not in line with the countries where the consumption of saturated fatty acids was less common [1]. To explain this so-called *French Paradox*, it has been suggested that the high consumption of red wine by the French population could likely act as a protective factor in the everyday diet [2,3]. Over time, the debate has moved on and other hypotheses have been put forward by researchers, taking into account that there are other aspects of diet and lifestyle that can be important determinants of cardiovascular health risk [4]. In this context, it was also found that fat consumption and serum cholesterol values were much lower in the French population than in countries such as the United Kingdom and United States in the years

before the 1980s. It was then hypothesized by Law and Wald [5] that within 25–35 years, there would be changes with increases in coronary heart disease caused deaths for the French population. However, although three decades have passed since the definition of the *French paradox*, the issue is still triggering interest and is the topic of wide discussion.

It is also well known that the risk of liver cirrhosis and cancer, in particular the ones affecting the upper digestive and respiratory tract, can be increased by excessive alcohol consumption, while low to moderate red wine consumption has been associated with health-promoting beneficial properties [6].

Nonetheless, is it not clear how the French are able to consume diets with a high content of saturated fats without affecting their cardiovascular health, and they also seem to have a lower risk of developing Alzheimer's disease compared to other populations that consume large amounts of fat-rich foodstuff [1].

Moreover, there is emerging evidence that there is a potential link between oral and gut microbiota alteration and some neurodegenerative disorders [7]. Diet polyphenols, and in particular those contained in wine, are among the main drivers of the composition and function of oral and gut microbiota [8–14].

As reported by Obrenovic et al. [15]: "the concept of a heart shunt within the microbiota-gut-brain axis underscores the close association between brain and heart health and the so-called *French paradox* offers clues for understanding neurodegenerative and cerebrovascular diseases".

Much research has been carried out to explain the relationship between wine consumption and health [16–18].

Snopek et al. [19] summarized the current findings about the positive influence of wine consumption on human organ function, chronic diseases, and the reduction of damage to the cardiovascular system, concluding that wine polyphenols could be effective in preventing cardiovascular diseases.

Wine, especially red wine, is a complex beverage in continuous evolution, even when it is in the bottle. It is a hydroalcoholic solution (~78% water) that includes many different chemical components, such as minerals, sugars, lipids, soluble proteins, vitamin aldehydes, esters, ketones, phenolics, and organic acids [20].

Among the many bioactive compounds contained in wine, the polyphenols represent the main class. White wines usually contain less polyphenols than red ones: total polyphenol content has been reported in amounts of about hundreds of mg GAE·L^{-1} (gallic acid equivalents·L^{-1}) in white wine, whereas in red wine the amounts are about thousands of mg GAE·L^{-1} [20,21].

Several papers [22–25] reported how the main polyphenols contained in grapes are proanthocyanidins (oligomers and polymers) and anthocyanins, with lower amounts of other phenolics. Wine polyphenols include both grape polyphenols and new phenolic products formed from them during the winemaking process. This leads to a great diversity of new polyphenols and makes wine polyphenol composition more complex.

A wide range of polyphenols are in fact present in wines, particularly in red wines; they include resveratrol, flavonols (e.g., quercetin, myricetin), phenolic acids, trihydroxystilbene, flavanols (e.g., epicatechin, catechin), procyanidins, and anthocyanins, which are responsible for the color of red wines [26]. The content and profile of polyphenols in wine is affected by grape cultivation, soil, climatic conditions, and vinification processes [27]. We can distinguish vineyard factors such as variety, climate, geographical origin, quality, and vinification factors, such as the time of grape skin contact with solid parts of the grape. Nonetheless, environmental factors like temperature, rain, sun exposure of the vines, etc., also play a role in the whole process.

Fernandes et al. [20] focused on wine flavonoids in health and disease prevention, while the sensorial properties of red wine polyphenols have been explored recently by Li et al. [28].

This proposed perspective paper gives a current overview for a better understanding of the relationship between wine polyphenols and health by analyzing research themes,

major contributors with reference to country/regions, institutions, authors, and types of papers in order to identify emerging research directions and collaboration networks and give information for more in-depth literature searches.

2. Materials and Methods

2.1. Literature Search

In November 2020, a search was conducted through the Scopus database for wine polyphenols publications. Bibliometric data were extracted from the Scopus online database (https://www.scopus.com/home.uri, accessed on 10 November 2020) using the search string: TITLE-ABS-KEY (wine AND polyphenol* AND health OR "french paradox" OR "cardiovascular disease*" OR atherosclerosis OR microbiota). The research was set up in the time range of 19902020. This search strategy identified publications that mentioned the relevant words or their derivatives in the title, abstract, or keywords. As a result, the following parameters were assessed: publication year, publication count, citation count, authorship, institution, country/region, and document type.

2.2. Data Extraction and Analysis

Bibliographic data were recorded, such as the publication year, publication count, citation count, subject area, countries/regions, institutions, authorship, and document type. The "Analyze" and "Create Citation Report" functions of the Scopus web online platform were used for the basic analyses. The "full records and cited references" were exported to VOSviewer software (version 1.6.16, www.vosviewer.com, accessed on 10 November 2020) for further bibliometric analyses and additional processing.

The VOSviewer software (v.1.6.16, 2020) analyzes the terms/words used in the titles and abstracts of publications by breaking down the paragraphs into words and phrases, linking them with the citation data of the publications, and visualizing the results in the form of a bubble map by using a term map with default settings. It has been used in different areas of study including food and in particular wine [29–32]. Default parameters were used for the analyses and visualizations; in particular, the type of analysis was based on co-occurrence, and as a unit of analysis, all keywords were considered (author and index keywords) and the counting method was full counting. Maps were created based on bibliographic data, and to create a co-authorship, keyword co-occurrence, and citation, bibliographic coupling was selected. In a term map, the size of a bubble represents how frequently a term is mentioned in the articles, i.e., the frequency of appearance of a term (multiple mentions in one article were counted once). Two bubbles are positioned more closely to each other if the terms co-appeared more often in the analyzed publications. The color of a bubble reflects the average citations per publication (CPP).

To simplify the bubble map, words/terms that appeared in at least 5 of the publications were analyzed and visualized.

As per the threshold chosen, the minimum number of occurrences of a keyword was set to 5. Of the 10,037 keywords, 1498 met the selected threshold, and 3 of them were manually excluded.

3. Results

The search returned 1497 publications covering the time period from 1990 to 2020, which were collectively cited 61,396 times, with 41.01 CPP as an average. The earliest indexed document published after 1990 was the work of Mosinger [33], describing the antioxidant properties of wine polyphenols. The authors reported how polyphenolics, but not the alcohol in beer and wine, protect serum low-density lipoprotein against atherogenic modification [33].

A total of 1495 terms were derived from the quantitative literature research on 1497 publications and they are visualized as a term map (Figure 1). The top-recurring keywords are listed in Table 1. It is interesting to observe that among the top-recurring keywords appears a compound, resveratrol, which shows that the research is mainly focused on

the biological activities of this molecule. The recent paper from Yeung et al. [34], which is a reference work for the literature quantitative research analysis approach used, provides a comprehensive literature analysis addressed on resveratrol, outlining its relevance as a highly researched commercially available dietary ingredient and food supplement. The most significant contributors came from the USA, China, Italy, South Korea, and Spain. The main part of the publications frequently investigated diseases or conditions, including Alzheimer's disease, breast cancer, obesity, atherosclerosis, and coronary heart diseases. In that paper, however, which used the same methodological approach used for this perspective, the focus was on resveratrol as one single compound among the most frequently mentioned polyphenols, and most of the publications appeared in journals specializing in biochemistry and molecular biology, pharmacology and pharmacy, food science technology, cell biology, or oncology. In the present perspective, the entire group of the polyphenolic compounds that can be identified in wine are considered the main health-capacity-possessing constituents of wine in relation to health. Among these compounds, resveratrol is more present in grape peels than in wine, and it is a component of the whole ensemble of polyphenols evaluated all together in the literature search for their effect and impact on health.

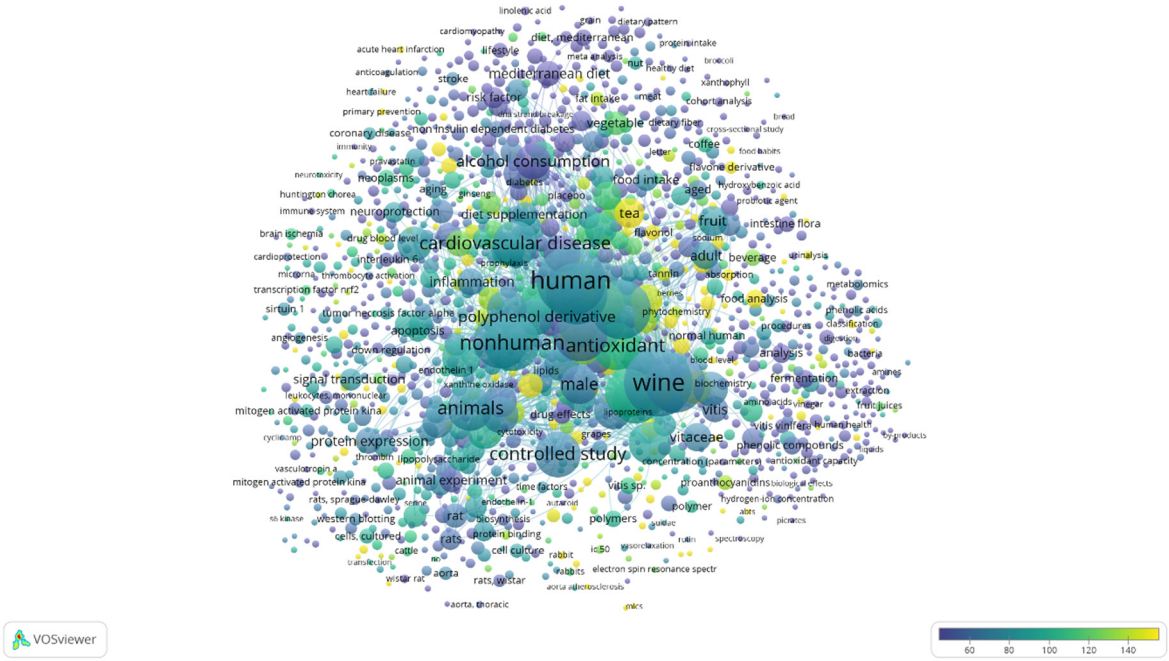

Figure 1. Term map for relationships of wine polyphenol and health research. Bubble size represents the number of publications. Bubble color represents the citations per publication (CPP). Two bubbles are closer to each other if the terms co-appeared more frequently. (Bibliometric data were extracted from the Scopus online database and elaborated by VOSviewer software).

Publications and citation trends of the relationships between wine polyphenols and health research are reported in Figure 2.

The types of documents related to the 1497 publications retrieved were distributed as reported in Figure 3. Both "Article" and "Review" account for 53.8% and 25.7%, respectively, followed by "Book chapter" (9.8%) and "Conference paper" (4.3%).

Table 1. The top-recurring terms on the relationships between wine polyphenol and health research. (Bibliometric data were extracted from the Scopus online database and elaborated by VOSviewer software).

Term	Occurrence
human/humans	1363
polyphenol/polyphenols	1108
wine	750
antioxidant/antioxidants	718
non-human	483
resveratrol	471
red wine	450
flavonoids	349
antioxidant activity	343
cardiovascular disease	330
controlled study	326
animals	322

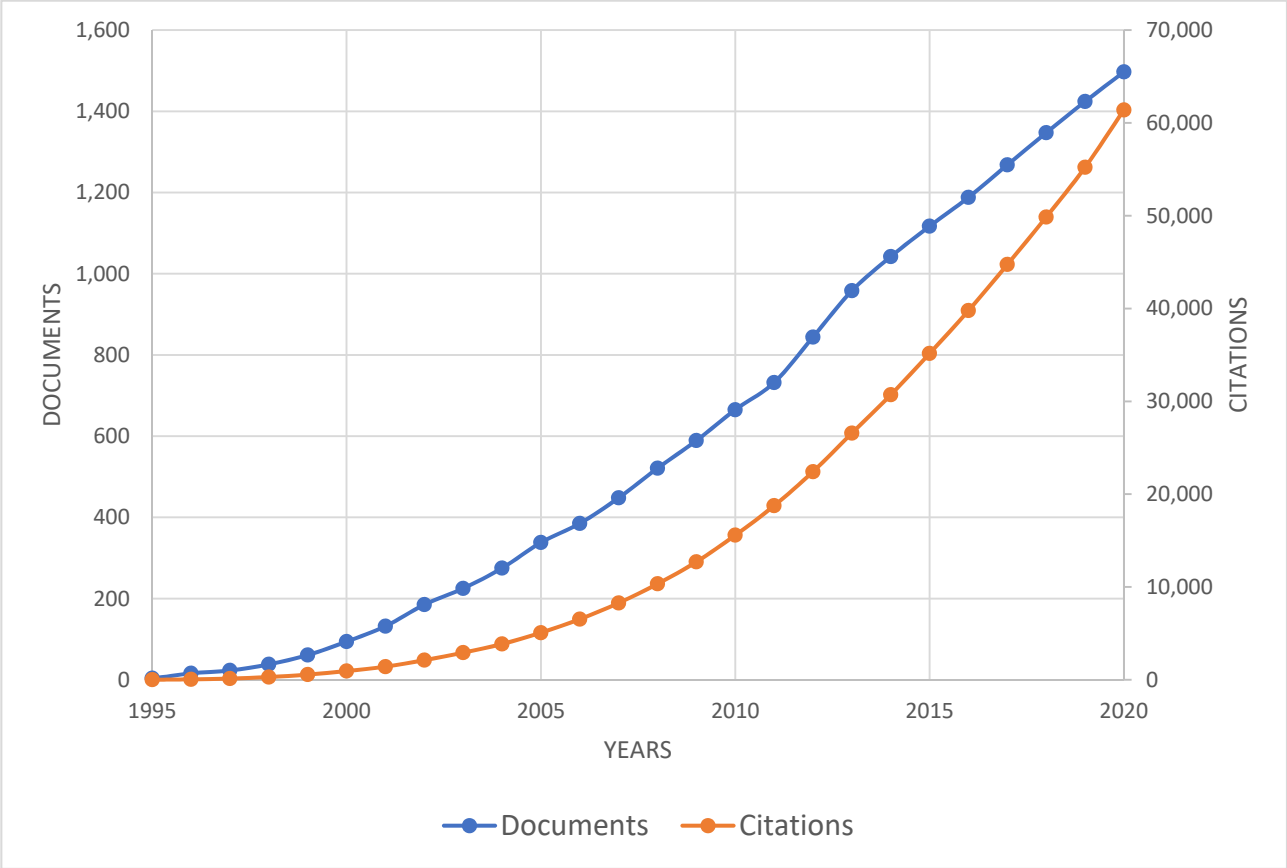

Figure 2. Publication and citation trends of the relationships between wine polyphenols and health research displayed as cumulative function. (Bibliometric data were extracted from the Scopus online database).

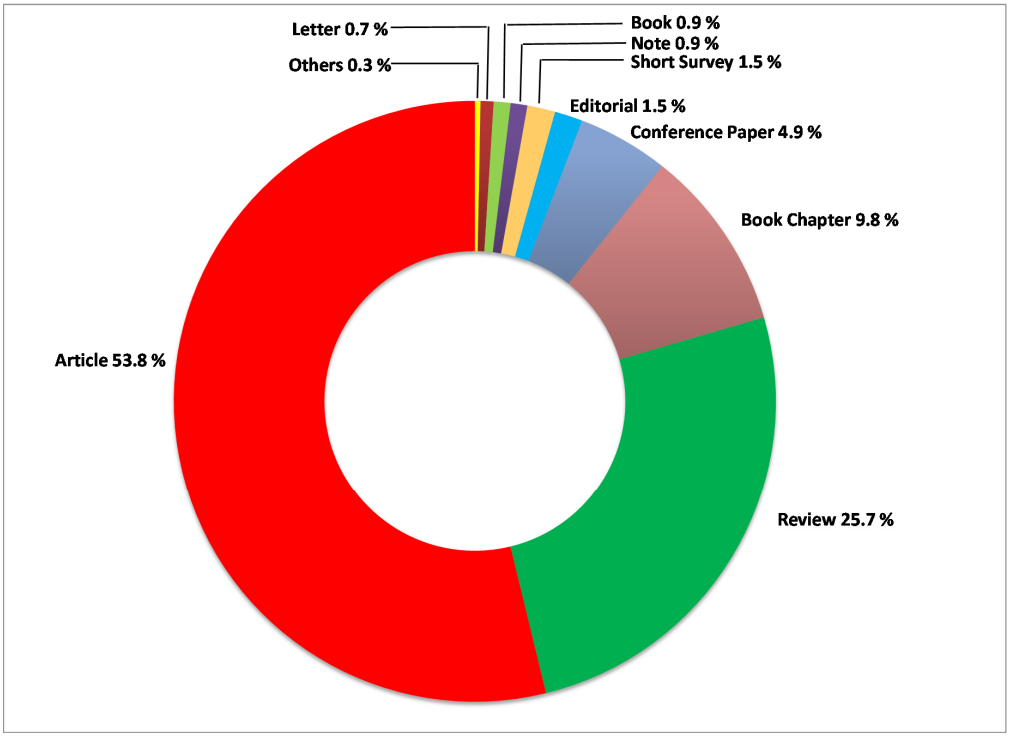

Figure 3. Distribution of documents by type. (Bibliometric data were extracted from the Scopus online database).

Figure 4 reports the most productive authors. Estruch, R. (n = 26, CPP 5.04) resulted as the most productive author. His most highly cited paper (cited 338 times) in the current dataset was a paper focused on how red wine polyphenols and ethanol can affect gut microbiota ecology and biochemical biomarkers [35]. From this in vivo study, the authors concluded that regular and moderate red wine consumption could significantly modulate the growth of select gut microbiota in humans, highlighting possible probiotic effects associated with the inclusion of red wine polyphenols in the diet [35]. In fact, this was the first in vivo study that showed that red wine polyphenols could inhibit nonbeneficial bacteria and potentiate the growth of probiotic bacteria (such as bifidobacteria), which could be implicated in the reduction of the C-reactive protein and cholesterol-promoting health benefits in the host.

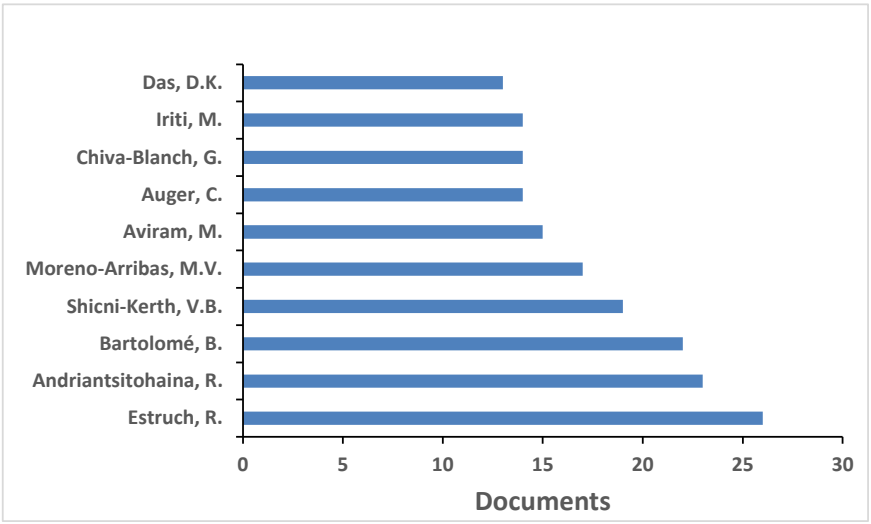

Figure 4. Most productive authors. (Bibliometric data were extracted from the Scopus online database).

The second most-cited article was a review by Arranz et al. [36] that remarked on the evidence that not only do wine polyphenols (e.g., resveratrol, anthocyanins, flavonols, and catechins) provide an abundance of health benefits, but also their metabolites could play a real role in cardiovascular and cancer protection [36].

Among the most recent works of Andriantsitohaina, R., the second most-cited author (Figure 4), some studies (reviews and clinical trials) explore the different mechanisms of the cardiovascular protective effects of polyphenols, for instance, in vascular health, stimulating the formation of vasoprotective factors (e.g., nitric oxide and endothelium-derived hyperpolarizing factor) that promote vasodilatation and prevent platelet activation [37,38]. Moreover, the author, in a further work, marked the role of wine polyphenols in improving vascular smooth muscle function, by reducing the excessive vascular oxidative stress of pathological blood vessels, probably related to changes in the expression levels of antioxidant and pro-oxidant enzymes [39].

Interestingly, the work of Bartolomè also focalizes on the interaction of wine polyphenols and gut microbiota [40]. In this review, the authors underline how the moderate consumption of red wine could modulate quantitative and qualitative changes in oral and gut microbiota by means of some polyphenols present in this beverage. The interaction of wine polyphenols (e.g., (+)-catechin and (−)-epicatechin, gallic acid) and/or their metabolites (coming from the interaction of wine polyphenols with oral and gut microbiota) leads to a modification of the gut microbiota, showing a moderately prebiotic effect and an inhibition of the pathogenic microflora [40]. For instance, Bartolomè's most-cited work investigated [41] how the gut microbiota interacts with red wine extract, leading to the formation of a wide range of phenolic microbial metabolites coming from catabolism of the main flavonoids (e.g., flavan-3-ols and anthocyanins). While the metabolites formed from anthocyanins seemed to be quickly degraded into simpler compounds, the metabolites from flavan-3-ols (such as phenyl-γ-valerolactone derivatives) were stable during absorption and could be used as a possible biomarker of red wine consumption linked to in vivo health effects. Moreover, in his recent review [42], the relationship between wine consumption, diet, and microbiome modulation in Alzheimer's disease was investigated. This study highlighted that red wine polyphenols could act in a multi-target way and that wine polyphenol could modulate the composition of gut microbiota leading to brain function and Alzheimer's disease protection with significant health consequences.

Figures 5 and 6 show the most productive institutions based on data retrieved from the Scopus database Institutional Assignment and Countries, respectively.

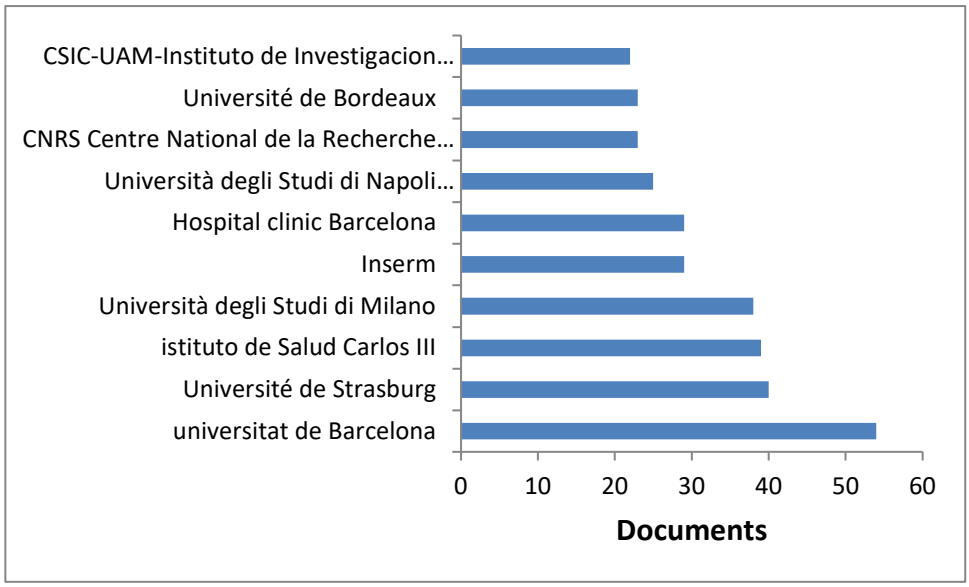

Figure 5. Most productive institutions. (Bibliometric data were extracted from the Scopus online database).

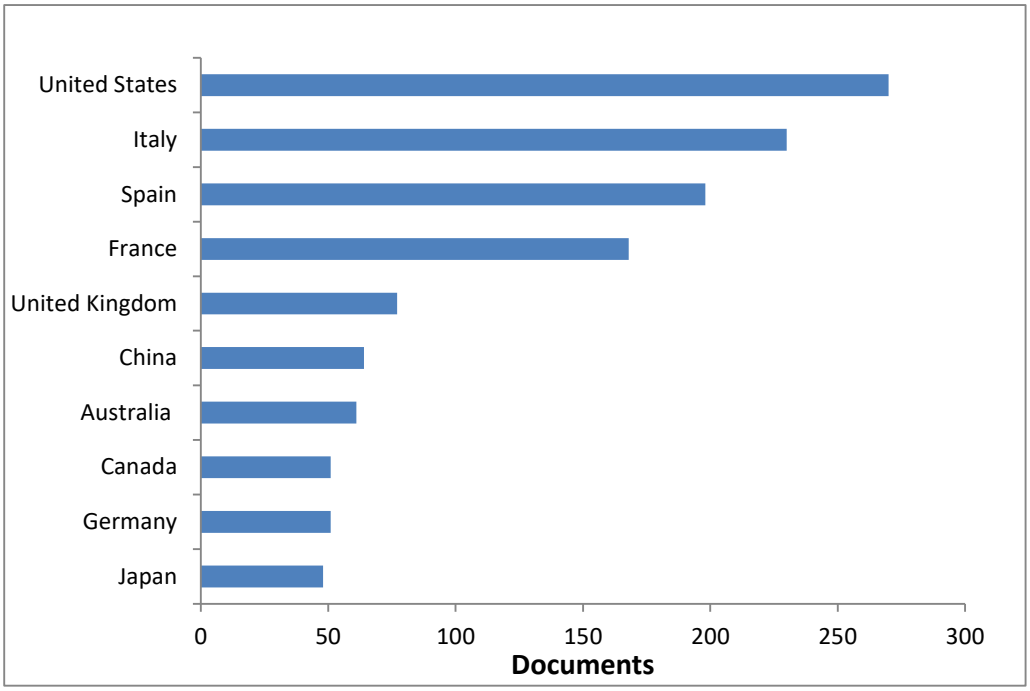

Figure 6. Most productive countries. (Bibliometric data were extracted from the Scopus online database).

The most productive institution was the Universitat de Barcelona (Figure 5). Its most highly cited paper was done by Queipo-Ortuño et al. [35] as described previously. The most recent paper published by Universitat de Barcelona was a randomized intervention trial reported by Roth et al. [43]; the authors reported how the decrease in the expression of several genes related to the appearance and progression of atherosclerosis that resulted was greater after Andalusian aged wine intake than gin intake, highlighting the potential protective role against atherosclerosis of the phenolic content of Andalusian aged wine [43]. It can be noted that Estruch was the corresponding author for the latter paper and among the co-authors for highly cited papers from the Universitat de Barcelona. All institutions reported in Figure 5 have at least 48 publications.

Among the first five most-cited from the Universitè of Strasburg, we mention the work of Diebolt et al. [44] and Oak et al. [45]. Diebolt et al. [44] showed how a short-term (seven day) oral administration of wine polyphenols decreases blood pressure in normotensive rats; the related mechanisms involve arterial vasodilatation by means of NO synthase and COX-2 protein both induced by a modest induction of gene expression within the arterial wall. The work of Oak et al. [45] is focused on the antiangiogenic properties of natural polyphenols from red wine and green tea. The authors indicated that both red wine polyphenols and green tea polyphenols have in vitro and in vivo antiangiogenic properties that inhibit the expression of two proangiogenic factors, the vascular endothelial growth factor and the Type IV collagenase (VEGF and MMP-2), by both redox-sensitive and redox-insensitive mechanisms. For the Istituto de Salud Carlo III, the most-cited paper was the work of Arranz et al. [36], as previously discussed, whereas among the five most-cited, a work on the impact of polyphenols on microbiota composition was reported and identified [46], along with other works on the protective role of wine polyphenols on cardiovascular diseases and atherosclerosis [47–49]. Etxeberria et al. [46] in their review summarized the main results from in vivo and in vitro studies by analyzing the relationship between wine polyphenol and the bacteria-growth-promoting effect of gut microbiota. Badiman et al. [47] showed that red wine consumption could prevent the acute impairment of endothelial function that occurs following cigarette smoking or the consumption of a high-fat meal. The authors also underlined that the controversial results reported in clinical trials investigating the role of antioxidants in CVD may be attributed to several factors,

and, concerning the protective effect of wine, it also appeared to be linked to ethanol per se. Chiva-Blanch et al. [48], in their randomized, controlled, clinical trial, studied the effects of red wine and dealcoholized red wine separately on the expression of adhesion molecules and inflammatory cytokines related to early stages of atherosclerosis and provided information on the separate role of ethanol and phenolic compounds of red wine. Their results suggest that both ethanol and nonalcoholic compounds, at moderate wine consumption, could contribute to the anti-inflammatory effects of red wine, modulating soluble inflammatory mediators in patients at high risk of cardiovascular disease. The same research group [48] pointed out that although heavy alcohol consumption leads to an increase in the risk of all causes of death, moderate alcohol consumption in the form of wine has cardioprotective effects demonstrated through different mechanisms.

Regarding countries/regions, the most productive was the United States (n = 270, CPP = 34.8), followed by Italy (n = 230, CPP = 23.9), Spain (n = 198, CPP = 24.0), and France (n = 168, CPP = 14.6). For the United States, the most-cited paper (881 times) was the work of Gehm et al. [50] describing the properties of resveratrol, one of the main compounds in grapes and wine (Figure 7), as a phytoestrogen, based on its structural similarity to a synthetic estrogen diethylstilbestrol. This article is of particular relevance because it extends the biological actions of resveratrol to the estrogenic ones. The study showed how resveratrol exhibits variable degrees of estrogen receptor agonism in different test systems compared to the estradiol activity. The authors also underlined that resveratrol, acting as estrogen, could produce an undesirable side effect by stimulating the growth of human breast cancer cells. This issue should be taken into account for safety reasons, especially as resveratrol is thought of as a promising pharmacological compound. Within the five most-cited papers, it is worth mentioning the work of Borra et al. [51] that illustrated the activation mechanism of sirtuin 1 (SIRT1) by resveratrol [41]: the interaction of resveratrol with SIRT1 induces a conformational change in the chemical structure of SIRT1 with the consequent activation of the enzyme. On the other hand, the most recent work in the United States was the review by Tung et al. [52] on how polyphenols bind to low-density lipoprotein at biologically relevant concentrations that are protective for heart disease. The authors found that, after a single-dose human study, the LDL lag time increased seven-fold 2 h after the consumption of red wine polyphenols (RWP), thus demonstrating RWP's ability to inhibit the oxidation of LDL. These results are relevant to heart disease, and the authors also hypothesized that the binding of polyphenols and their metabolites to LDL functions as a transport mechanism to carry these antioxidants into the cell. Interesting are also the communications of Obrenovich et al. [15] on the role of polyphenolic compounds contained in wine that could modulate health both directly and through the gut microbiota.

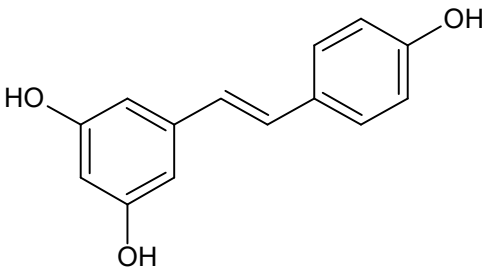

Figure 7. Chemical structure of resveratrol.

Concerning Italy, besides the most-cited paper of Del Rio et al. [53] as a reference work on dietary polyphenols in human health, reports regarding the effects of red wine and red wine (poly)phenols on BP seem in most cases not substantiated enough. The authors of this article pointed out that many of the beneficial effects related to the consumption of red wine appear in many cases to be inconsistent if poor appropriate controls have been used, as seems to happen in most of these studies. The work of Carluccio et al. [54] focusing on the antioxidant functions of polyphenols from olive oil and red wine (typical constituents

of the Mediterranean diet) suggested that at nutritionally relevant concentrations, they can transcriptionally inhibit endothelial adhesion molecule expression. The authors showed the mechanism by which several quantitatively minor components of the Mediterranean diet may directly regulate the expression on proinflammatory/proatherogenic genes preventing early atherogenesis, thus partially explaining the atheroprotection effect deriving from the adoption of the Mediterranean diet.

Concerning Spain, besides the paper of Moreno-Arribas et al. [42] previously described, another paper published in 2020 is the work of Visioli et al. [55] on the relationship between wine's phenolic compounds and health; the authors focused on the main limitation of wine (poly)phenol research (e.g., reductionist approach, search for one single mechanism of action, the fact that the biological effects of wine's phenolic compounds are minimal and very difficult to detect with current technologies, biomarkers, etc.). They concluded that, after 30 years of research, there is still a lack of solid "pharmacological" human evidence to confirm wine (poly)phenols' biological actions.

For France, the reference review with major citations is the work of Scalbert et al. [56] on the relationship among dietary polyphenols and the prevention of diseases. The authors, given the inconsistency of the experimental data regarding the correlation between dietary polyphenols (even those coming from wine), suggested the precautionary principle until the most appropriate levels of intake are determined. Until then, the authors discouraged increasing polyphenols consumption through diet and dietary supplements. After these comments, the mini review by Frèmont [57], with 1290 citations, on the biological effects of resveratrol represents a milestone on the biological activities of resveratrol that already in the 2000s were quite well identified due to the well-known structure of the molecule, which allows hypothesizing that the action mechanisms could differ somehow from that of flavonoids.

4. Conclusions

The results of this quantitative research literature analysis showed that most of the research studies' efforts in trying to establish the relationship between wine polyphenols and health status have been mainly directed, since the 1990s, towards the study of the different mechanisms of action by which wine polyphenols with biological activity (in particular but not only resveratrol) could affect the physiological state. The analysis of the publications on the relationship between wine polyphenols and health highlighted that some of the main contributors are from the USA, Italy, Spain, and France. In recent years, the focus of the research has been the study of the interaction between the phenolic compounds of wine and the human microbiota considered as an active part of the entire mechanism of action of polyphenols in wine. From this quantitative analysis, it emerges that the main diseases or health conditions studied are cardiovascular disease, Alzheimer's disease, breast cancer, atherosclerosis, the status of the intestinal microbioma, the inhibition of lipid peroxidation (LDL, membranes, etc.), the inhibition of platelet aggregation, anti-inflammatory activity, vasorelaxing activity, anticancer activity, and estrogenic activity.

The final remark of the present work could be, based on the reported data, to move the scientific debate forward to assess the limits of polyphenol research concerning wine. It seems that the research still lacks evidence to completely confirm and assess the in vivo polyphenols' biological effects of wine, widening the area of interest of explore also the possibility of their use as nutraceuticals [58]. Future research is then needed to further increase the knowledge in the area.

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