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Review

Wine-Derived Phenolic Metabolites in the Digestive and Brain Function

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Received: 21 December 2018; Accepted: 4 January 2019; Published: 11 January 2019

Abstract: Wine, and specifically red wine, is a beverage with a great chemical complexity comprising a particular combination of phenolic compounds which are directly associated with its health-promoting properties. Wine polyphenols could induce changes in the composition of intestinal microbiota that would affect the production of physiologically active phenolic metabolites modifying the content and phenolic profile at the systemic level. In addition, in the human population, it seems that different "metabotypes", or patterns of metabolizing wine polyphenols, exist, which would be reflected in the different biological fluids (i.e., plasma, urine and feces) and tissues of the human body. Moreover, wine polyphenols might change the composition of oral microbiota by an antimicrobial action and/or by inhibition of the adhesion of pathogens to oral cells, thus contributing to the maintenance of oral health. In turn, polyphenols and/or its metabolites could have a direct action on brain function, by positively affecting signaling routes involved in stress-induced neuronal response, as well as by preventing neuroticism-like disorders (i.e., anxiety and depression) through anti-inflammatory and epigenetic mechanisms. All of this would condition the positive effects on health derived from moderate wine consumption. This paper reviews all these topics, which are directly related with the effects of wine polyphenols at both digestive and brain level. Further progresses expected in the coming years in these fields are also discussed.

Keywords: wine polyphenols; oral and gut microbiota; phenolic metabolites; brain function; neurodegenerative disorders

1. Introduction

The interest in the binomial "diet and health" is gaining attention as a preventive strategy, since the evidence associating specific dietary patterns with a reduced risk of chronic diseases is accumulating [1,2]. The Mediterranean diet has long been shown to be a dietary pattern for non-communicable disease prevention and as a model of healthy eating based on its relationship with keeping a good health status and quality of life [3,4]. Among other facts, the Mediterranean dietary pattern is characterized by a moderate intake of red wine during meals. Although it is undeniable that heavy or binge alcohol drinking leads to an increase in the risk of numerous causes of death and an enormous social and economic problem that must be addressed, moderate wine consumption, inside a framework of balanced life habits, has proven protective effects against certain chronic disorders [5,6]. In particular, the case of coronary diseases has been widely studied [7].

In the last decade, the focus of the scientific community on the health properties of wine has been expanded to other human organs systems and, particularly, its interaction with gut microbiota and the consequences for health has gathered their attention. Gut microbiota catabolizes dietary

polyphenols and modulates their activity, but the relationship between microbial ecology and host health continues to be a matter of investigation. Indeed, phenolic metabolic fate and mechanisms of action are more complex than previously expected. Inter-individual variations in metabolites' production might also be relevant, although there is little evidence so far.

Among the bioactive compounds present in wine, polyphenols stand out because of their relevant benefits in human health [8,9]. Polyphenols are found in the solid parts of plants and fruits, such as grape skins and seeds, forming part of the secondary metabolites produced by the plant. During the wine-making process, the phenolic compounds are extracted to the wine, constituting one of the major groups of compounds in this fermented food. According to their chemical structure, they are divided into two groups: flavonoids and non-flavonoids. Flavonoids constitute a major group of phenolic compounds which are directly associated with the organoleptic and the health-promoting properties of red wine. The flavonoid compounds are characterized by two rings of six carbons joined by a central heterocycle of 3 carbons (C6-C3-C6), differing from each other in the degree of oxidation and saturation of the central ring. Among them, flavonols (quercetin, myricetin, kaempferol, and their glycosides) and flavan-3-ols (monomers and oligomeric and polymeric proanthocyanidins) stand out. In the case of red wine, anthocyanidins are also included [9–11]. The non-flavonoid compounds are characterized by a single ring of 6 carbon (C6), and the most prominent in this group are the hydroxybenzoic (C6-C1) and hydroxycinnamic (C6-C3) acids, phenolic alcohols (C6) and stilbenes (C6-C2-C6). Phenolic acids, such as hydroxybenzoic and hydroxycinnamic acids, are of special relevance in the health field, while among stilbenes, biological properties of resveratrol have been extensively characterized [12,13].

Wine polyphenols undergo a marked metabolism during their passage through the digestive system. This metabolism starts in the oral cavity, whereas the majority of the bio-transformations take place in the gut, due to microbial enzymatic reactions [8]. Therefore, the idea that phenolic metabolites can be the real executors for the benefits implied from polyphenols intake, instead of the parent compounds, has increased the interest in the study of phenolic metabolism [14–17]. One of the essential features to understand the possible effects of metabolites derived from polyphenols, including microbial modulation, is their characterization. Additionally, it reveals useful biological pathways implicated in the health status of the organism. High inter-individual variances in gut microbiota composition/functionality determine the ability to produce a set of metabolites, and therefore, human populations could be classified according to their metabolic phenotyping characteristics into more homogeneous groups, the so-called "metabotypes" or metabolic phenotypes [18,19]. Recently, interindividual variability in the production of some phenolic metabolites originating from colonic degradation of flavan-3-ols, such as phenyl-γ-valerolactones has also been reported [20]. A metabotype would condition the benefits implied from a specific dietary or medical intervention, and therefore, there is a growing interest in improving our understanding upon distinct individual metabotypes across worldwide population, in both medical and nutritional research fields. Clustering subjects according to their metabotypes could explain the interindividual variability in the effects associated with the risk or improvement of disease on specific groups of population [21].

While the role of dietary polyphenols has been widely studied in the case of certain disorders, the protective effect of red wine and its constituents in maintenance of oral health is still in its early stages and little is known about the mechanisms of action involved [22]. While evidence demonstrated that antimicrobial activity of polyphenols against certain oral pathogens is increasing, other mechanisms of action, including anti-adherent ability, inhibition of enzymatic systems and anti-inflammatory action, need to be evaluated to consider the multiple factors involved in microbial-derived oral diseases.

Also, in the last few years, there has been a huge increase in the knowledge of the brain that enables advancement of technologies in neuroscience research. These modern network approaches have enriched our understanding of brain mapping and its function. Although the study of the neuroprotective role of polyphenols has been the area of research of numerous groups and the literature has provided great advances in understanding their impact on the brain [23], the mechanisms by which biological events lead to disease prevention are still a field with a huge research potential.

After a brief overview of the metabolism and bioavailability of wine polyphenols (Section 2), this review focuses on (i) the effects of wine polyphenols at gut level (Section 3) including their implications in oral health and their interactions with intestinal microbiota and microbial functional activity, and (ii) the role of wine and polyphenols in the brain function (Section 4) as protective agents against neurodegenerative disorders, as genetic modulators in cognitive disorders and as anti-inflammatory agents in depression and other related psychiatric diseases. Conclusions and future directions about both topics are finally summarized (Section 5).

2. Metabolism and Bioavailability of Wine Polyphenols

It is well known that the in vivo protective effects of polyphenols largely depend on their chemical structure [24], on their accessibility and extractability from food [25], on their intestinal absorption, on the final biological action in the human body, and on the potential interaction with target tissues [26].

The human body considers polyphenols to be xenobiotics, so they are widely metabolized to finally be eliminated by urine or bile [27]. The first transformation of polyphenols occurs in the oral cavity, right after ingestion, and it includes physical (chewing) and chemical (salivary and microbial enzymes) modifications. The enzymes mostly implicated are microbial β-glycosidase and esterases, which favor the release of specific aglycones [28]. However, knowledge about oral metabolism of polyphenols is still scarce, and only a limited number of studies have been focused on this topic [22,29]. Additionally, the metabolism of phenolic structures by microbial and salivary enzymes is structure-dependent [30].

Following the oral cavity, the stomach's acidic environment causes the release of high-molecular-weight phenolics from the solid food matrix, mainly in the form of monomers and dimers, making these compounds more accessible to cellular metabolism in the small intestine, where enterocytes from the intestinal brush transform a small amount of phenolics (5–10%) into phase II metabolites (mainly methylated and glucuronidated forms) [11]. The biggest subsequent conversion happens in the liver, where enteropathic transport in bile may occur, and some conjugated metabolites are recycled back to the small intestine [31]. The formation of glutathione derivatives (GSH) can occur from the conjugation reactions, which is present in significant levels in most tissues, either spontaneously or being catalyzed by phase II enzymes glutathione-S-transferases (GSTs). Despite this, the bioavailability of polyphenols is very limited. For instance, for flavan-3-ols and anthocyanins, which constitute the majority of phenolic compounds in red wine, the concentrations that could be expected to occur in plasma under a realistic dietary intake are in the nanomolar to low micromolar range [11,20].

Compounds not absorbed in the small intestine (90–95% of remaining polyphenols), reach the large intestine where they undergo extensive metabolism by action of gut microbiota, which transform them into a wide variety of low-molecular-weight compounds that could be even more bioactive than their precursors [32]. Then microbial-derived metabolites may be absorbed in the large intestine and then further metabolized in the liver by phase II enzymes into conjugated metabolites (glucuronides, methylated and sulfates), which can be distributed to the tissues through systemic circulation. Finally, conjugates are conducted to the kidneys and, after blood filtration, they are excreted in the urine (Figure 1).

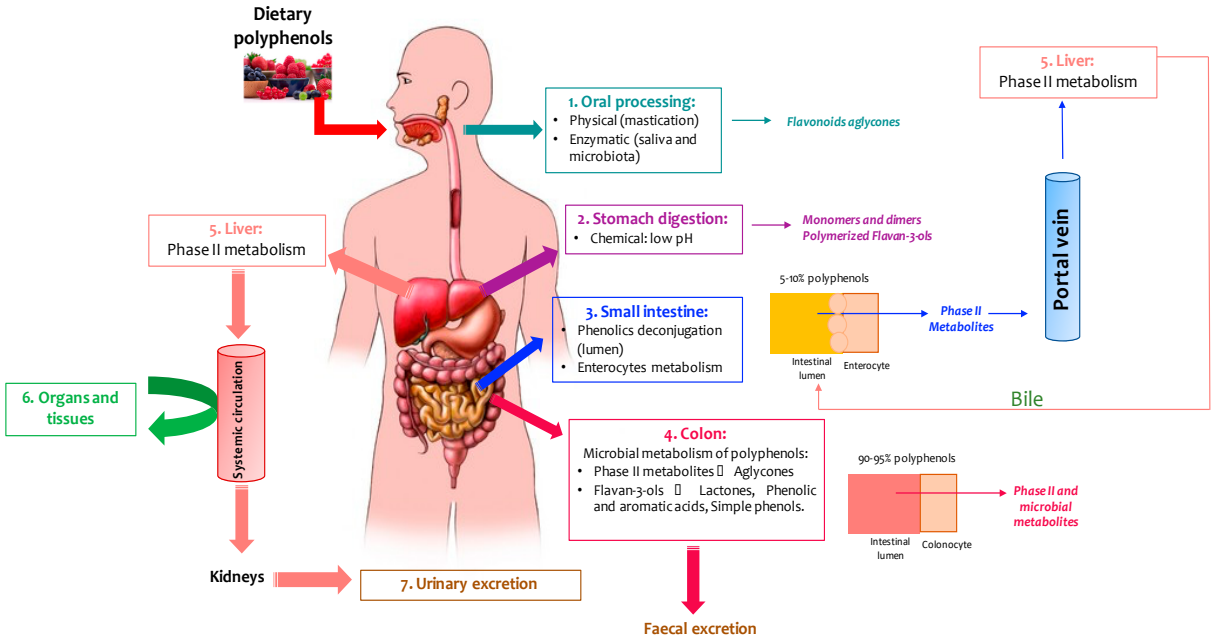

Figure 1. Schematic diagram of the steps involved in the human metabolism of polyphenols (figure adapted from others' works [8,33,34]).

Microbial catabolism pathways of the different flavonoid classes (anthocyanidins, flavonols, flavan-3-ols, etc.) are known to share similar intermediate and end-products. Recently, Cueva and co-workers reviewed the main reactions involved in the bacterial degradation of the main classes of phenolic compounds present in grapes and wine. The main phenolic compounds present in red wine (flavan-3-ols, flavonols, anthocyanins and stilbenes) share the same microbial catabolic pathways [8]. The main reactions involved are oxidations, decarboxylations, hydrolysis, demethylation, deglycosilation, ester cleavage, reductions of carbon-carbon double bonds, isomerization, ring fission and extension, and truncation of the aliphatic carbon chain, among others [33,35]. The microbial metabolism of flavan-3-ols (catechins and oligomers of proanthocyanidins) involves the opening of the C-ring and subsequent reactions of lactonization, decarboxylation, dehydroxylation and oxidation. In the case of galloyled monomeric flavan-3-ols (i.e., epicatechin-3-O-gallate), the microbial catabolism usually starts with the rapid cleavage of the gallic acid ester moiety by microbial esterases, releasing gallic acid that is further decarboxylated into pyrogallol [36]. When opened, the C-ring gives rise to 1-(3′,4′-dihydroxyphenyl)-3-(2′,4′,6′-trihydroxy)-phenyl-propan-2-ol, which is later converted into 5-(3′-4′-dihydroxyphenyl)-γ-valerolactone) in the case of (epi)catechin, or 5-(3′, 4′,5′-trihydroxyphenyl)-γ-valerolactone in the case of (epi)-gallocatechin. The valerolactone ring may later break, leading to the formation of 5-(3′,4′-dihydroxyphenyl) valeric acid and/or 4-hydroxy-5-(3′,4′-dihydroxyphenyl) valeric acid. Phenyl-γ-valerolactones and phenylvaleric acids have been described as exclusive microbial metabolites of flavan-3-ols. Subsequent biotransformations of these valeric acids may give rise to hydroxyphenylpropionic and hydroxybenzoic acids by successive loss of carbon atoms from the side chain through reactions of ß-oxidations. Furthermore, other minor catabolites, such as hippuric acid, *p*-coumaric acid, vanillic acid, homovanillic acid, homovanillyl alcohol, and 3-O-methylgallic acid have been associated with the in vivo colonic metabolism of flavan-3-ols [37].

Regarding the microbial catabolism of flavonols, this consists of the breakdown of quercetin-3-O-glucoside, which becomes transformed into dihydroquercetin. The product of this reaction will be 3-(3,4-dihydroxyphenyl) propionic acid, which will originate from protocatechuic and 2-(3,4-dihydroxyphenyl) acetic acids. In the case of anthocyanins, the molecule is cleaved into two structures, formed by A- and B-ring, respectively. The B-ring will generate different phenolic acids

(benzoic acid derivatives), whereas the A-ring will be transformed into phloroglucinol. Differentially, the catabolism of stilbenes and ellagitannins will produce different compounds than flavan-3-ols, such as dihydroresveratrol or urolithins, respectively.

The main phenolic metabolites found in urine and plasma after intake of wine polyphenols are glucuronides, sulphates and methylated derivatives of flavan-3-ols, anthocyanins and flavonols, as well as metabolites derived from their microbial catabolism, such as phenolic acids that can also be found in conjugated forms [38]. Also, some studies have reported that the phenolic profile in feces after wine consumption is mainly composed of microbial-derived phenolic acids and other related metabolites derived from the main classes of wine polyphenols [18,39].

3. Effects of Wine Polyphenols and Wine-Derived Metabolites at Oral and Intestinal Level

During red wine consumption, there is a long journey before its components can exert any health-promoting effect. As is described above, they must pass through the oral cavity and the gastrointestinal tract, undergoing the actions of microbiota and metabolic reactions, passing cellular barriers, and possibly triggering a biological action. Dietary polyphenols and/or their metabolites may generate beneficial effects at a local level, directly during their passage through the oral cavity and gastrointestinal tract, and at a systemic level, after being absorbed [8,40].

3.1. Implications in Oral Health

The oral cavity hosts the second-most complex microbial community in the human body, after the gut [9,41,42], and the establishment of the precise microbial composition is difficult. The oral cavity is an open dynamic system, furthermore, there are several niches in the mouth with selected pH, temperature or ionic conditions, which favor a high microbial diversity (i.e., tooth, tongue, cheeks, supra- and subgingival plaque). As in the colon, not only bacteria are found, but also virus, archaea, fungus and protozoa being these microorganisms organized in multi-layered structures, called biofilms, which offer them protection against adverse environmental conditions. Biofilms are formed by the sequential addition of specific bacteria: early, secondary and later colonizers. The most prevalent oral bacteria (>1%) belong to eleven genera (*Streptococcus*, *Corynebacterium*, *Neisseria*, *Haemophilus*, *Actinomyces*, *Rothia*, *Granulicatella*, *Prevotella*, *Porphyromonas*, *Capnocytophaga and Actinotignum*), although there is still an elevated number of unidentified microbial sequences, suggesting an even more complex ecology, the identification of which is not possible with current technologies [43]. The microbial composition is strongly influenced by host genetics, and it is considered relatively stable during the host lifespan; nevertheless, environmental factors such as diet, diseases or antibiotics can induce some selected changes in the microbial composition or functionality [44].

Periodontal diseases (gingivitis and periodontitis) are considered polymicrobial infections characterized by modifications in composition and volume of biofilm and an increase of Gram-(-) species whose endotoxins cause tissue damage, irritation and gum detachment [45].

Gingivitis is produced by the excessive accumulation of supragingival plaque along the gingival margins of teeth and characterized by the excessive overgrowth of Gram-(-) strains, such as *Fusobacterium nucleatum* or *Veillonella* sp. Conversely, a specific anaerobic microbiota, known as the "red complex", is directly linked to the initiation of periodontitis and includes *Porphyromonas gingivalis*, *Treponema denticola* and *Tannerella forsythia* [46]. Periodontal disease onset triggers an exacerbated inflammatory response from the host, leading to the secretion of pro-inflammatory cytokines, such as IL-1α, IL-1β, IL-6, IL-8 and TNF-α [47].

The common therapies used for the treatment of these diseases include the professional mechanical removal of the plaque, the use of mouthwashes with antimicrobial agents (i.e., chlorohexidine), and, especially, antibiotics. Although the therapy of choice for the treatment of periodontal disease depends on several factors such as the severity, evolutionary and intrinsic characteristics of the person, the removal of the subgingival plaque by scraping the area (curettage) is usually the first treatment along with antibiotic therapy to help the elimination of bacteria. However, the loss of effectiveness

of these treatments, together with the microbial acquired resistance to antibiotics have called for attention to search for alternative therapies from natural origins [48]. An improved understanding of the mechanisms behind the polyphenols' effects on mouth microbial communities could enable the development of preventative approaches and/or therapies to reverse disease-associated microbial community structures affecting their status in health, in particular when specific antimicrobial strategies (i.e., passive or active immunization) may not be effective [22]. The potential use of natural polyphenols that exhibit both anti-bacterial and anti-inflammatory properties has led to the hypothesis that wine-derived phenolic compounds could potentially be effective in the prevention and treatment of periodontal diseases. However, so far, most studies have been carried out in single-species biofilms. In this way, Muñoz-González and co-workers developed a pathogenic 5-species oral biofilm and reported the antimicrobial effect of red wine and grape seed extract against *F. nucleatum*, *Streptococcus oralis* and *Actynomyces oris* [49]. Meanwhile, Aurelie and co-workers only described a bacteriostatic effect of a grape seed extract, enriched in catechins and epicatechins, over *P. gingivalis* and *F. nucleatum* pathogens [50]. An inhibition of biofilm composed by these two anaerobes together with *S. mutans*, *S. sobrinus*, *L. rhamnosus* and *A. viscosus* was reported too [51]. Moreover, the anti-adhesive properties of wine polyphenols against periodontal and cariogenic pathogens' (*P. gingivalis*, *F. nucleatum* and *S. mutans*) adherence to human gingival fibroblasts has been evidenced, and oral, bacterial and cellular metabolism of wine polyphenols was observed [52]. This model was also implemented with the inclusion of an oral bacteria with probiotic activities (*Streptococcus dentisani* strain 7746) that showed a strong inhibitory power (>90%) of the oral probiotic against periodontal pathogens. Reciprocal benefits of these compounds together with an oral probiotic were revealed for the first time at oral level [52].

3.2. Interactions with Intestinal Microbiota and Its Functional Metabolic Activity

At least 90% of eukaryotic cells in human body correspond to human microbiota (10^{14} microbes), and therefore it supplies a combination of genes which provides us with new functionalities (the so-called microbiome). These commensal communities inhabit different niches exposed to the environment, such as the oral cavity, skin, the vaginal area, the nose, and the colon being its main locations. Currently, it is estimated that 500–1000 different microbial species inhabit the gastrointestinal tract, reaching the highest concentrations in the colon (up to 10^{12} cells per gram of feces). Only a small percentage of them are shared by most human individuals, which is called the bacterial "core" [35]. In contrast, "peripheral microbiota" refers to individual-specific metabolic activities.

The high microbial diversity characteristic of young and healthy individuals is responsible for the resilience and homeostasis of the intestinal microbiota, whereas inflammatory and metabolic disorders show changes in the composition and/or functions of the intestinal microbiota [53]. Bacteria dominate the gut microbiota, being represented principally by the phyla *Firmicutes* and *Bacteroidetes*, and by secondary phyla, such as *Actinobacteria*, *Proteobacteria*, *Synergistetes*, *Fusobacteria* and *Verrucomicrobia*. Among the main representative genera of these phyla, *Bacteroides* sp., *Faecalibacterium* sp., *Blautia* sp., *Prevotella* sp., *Clostridium* sp., *Ruminococcus* sp. and *Bifidobacterium* sp. are noteworthy due to their relatively high abundance [54], and, indeed, each one of us harbors several grams of one or more of these bacterial genera. In turn, it is assumed that several hundred species-level bacteria assemble in each individual in highly variable proportions, resulting in an individual microbial composition that remains stable over time. The temporal stability of the intestinal microbiota is probably maintained by host-encoded mechanisms in parallel with colonization resistance, and as a result, a balanced climax community would not be susceptible to new (invading) species. A new classification has been proposed, according to which all the inter-individual variability of the intestinal microbiota can be classified into three groups, the so-called "enterotypes", defined as a network of co-abundant microbial populations dominated by the prominent presence of one of these three genera: *Ruminococcus*, *Bacteroides* and *Prevotella* [55]. Some authors consider that this classification is not adequate, because they understand "enterotyping" to be too simple, since the full complexity of intestinal microbiota

cannot be reduced into three groups [56]. More than ten different bacteria phyla have been described in the gut, but the ratio *Firmicutes/Bacteroidetes* is generally used as a gastrointestinal health indicator [44]. Additionally, as described above, not only bacteria inhabit the human body; other microorganisms such as viruses ("human virome") and fungi have been described as part of the microbial ecology.

Apart from the inter-individual variation in daily intake of polyphenols, inter-individual differences in the composition of the gut microbiota may lead to differences in bioavailability and bioefficacy of polyphenols and their metabolites [57]. The scenario appears even more complex when considering the two-way relationship "polyphenols and microbiota". In fact, recent studies have suggested that both the phenolic substrates supplied to the gut bacteria through different patterns of dietary intake and the phenolic metabolites produced by these bacteria, may modulate and cause fluctuations in the colonic populations composition through prebiotic effects and antimicrobial activities against selected pathogens [18,58,59]. The formation of bioactive polyphenol-derived metabolites and the modulation of colonic microbiota may both contribute to host health benefits (Figure 2), although the mechanisms have not been delineated.

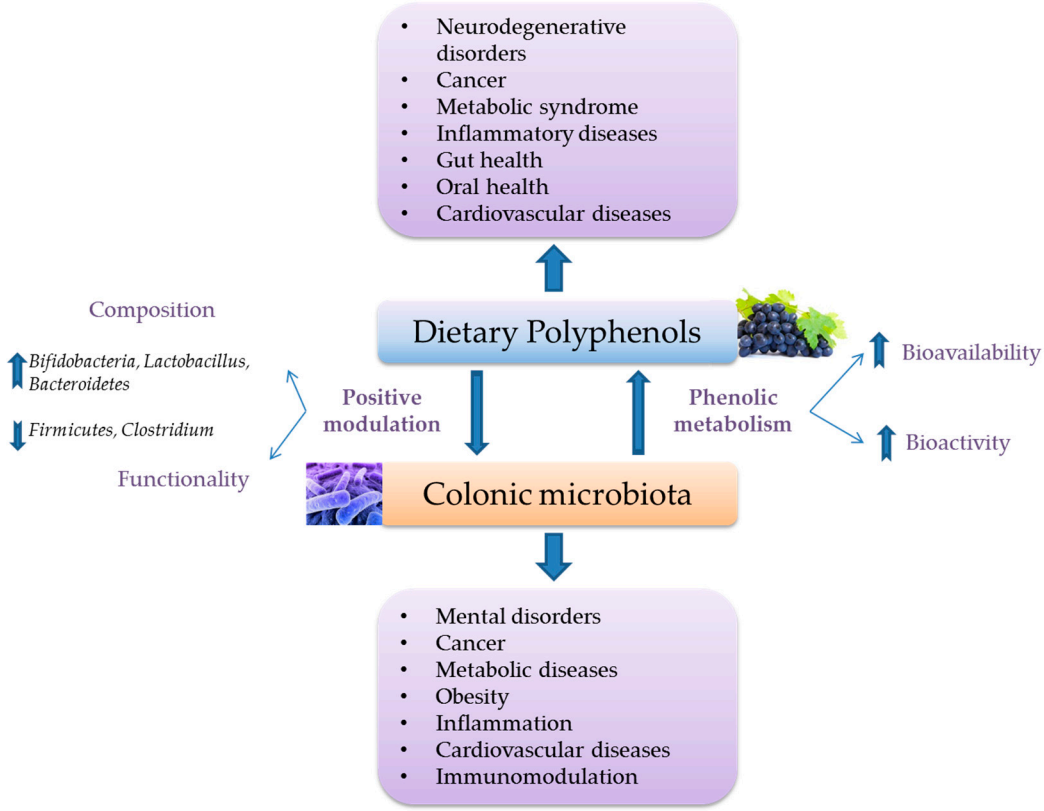

Figure 2. Scheme of the health effects implied from the two-ways interaction between polyphenols and intestinal microbiota.

Most in vitro studies indicate that wine polyphenols can affect intestinal microbiota colonization and composition; however, only a few human studies have investigated the modulating effect on intestinal microbiota derived from moderate wine consumption [8]. In a randomized, crossover and controlled trial, the effects of the intake of red wine, de-alcoholized red wine and gin were compared [59,60]. After the red wine intervention period (272 mL/day, 20 days, 8 volunteers), an increase was observed in populations of *Proteobacteria*, *Fusobacteria*, *Firmicutes* and *Bacteroidetes*, at phylum level; *Enterococcus*, *Prevotella*, *Bacteroides* and *Bifidobacterium*, at genera level; and the *Blautia coccoides-Eubacterium rectale* group and *B. uniformis* and *Eggerthella* species group. The impact of moderate regular consumption of red wine on the fecal microbial metagenomic profile of healthy

individuals has also been investigated using 16S rRNA gene sequencing [61]. An increase in microbial diversity and some differences in minority microbial groups related to phenolic metabolic phenotypes were found after wine intake, but inter-individual variability was the strongest and distinguishing feature. On the other hand, the consumption of wine, determined by a food frequency questionnaire, showed an association between high polyphenol intake and microbial abundance and/or diversity [62]. An increase in the abundance of *Faecalibacterium prausnitzii*, which has anti-inflammatory properties, was also observed by other authors [63].

Despite these studies, the latest evidence suggests that polyphenols induce changes not only at a compositional level, but also at a functional level. Due to the complexity that characterizes colonic microbiota, this idea is in accordance with the application of techniques such as proteomics, metabolomics and genomics [8]. Even being aware of the diet's impact on metabolic functions of the intestinal microbiota, it is important to note that, despite the large inter-individual variability in terms of bacterial taxonomy, the functional genetic profile expressed by the bacterial community is quite stable and similar in healthy individuals, ensuring those essential functions for the host's survival. Therefore, the microorganisms that are present in smaller quantities, but developing specific functions, could be the key to understanding the individual response to consumption of bioactive compounds (i.e., polyphenols). Furthermore, variety in the colonic metabolites and circulating forms of phase II metabolites (and therefore in the benefits implied from polyphenols consumption) depends on the ability of individual microbiota to selectively synthetize them after the intake of a specific polyphenol-rich food. Additionally, the wide inter-individual differences in the colonic microbiota composition makes it difficult to establish a general trend that has led to the definition of the so-called polyphenol metabolizing phenotypes or "metabotypes", which groups subjects with similar metabolic capacity based on the possession of a specific microbiota with similar enzymatic activities [19,64,65]. Therefore, a metabotype is characterized for both end metabolites and the microbiota population associated with their production. For instance, specific microbial communities have been linked to the production of a specific set of metabolites from isoflavones, ellagitannins, lignans and proanthocyanidins [65]. The concept of metabotyping is gaining attention, and literature reviews exhibit its potential to predict the effect of a specific dietary intervention in a more accurate way and in a personalized manner ("personalized or targeted nutrition") [66,67].

4. Role of Wine and Polyphenols in Brain Function

4.1. Neurodegenerative Disorders

Several studies have described a beneficial relationship between the intake of polyphenol-rich diets and the reduction of risk factors involved in the development of neurodegenerative disorders (i.e., dementia, Alzheimer's or Parkinson's disease), neuroticism or psychiatric diseases, such as depression or anxiety [23].

Neurodegenerative disorders are generally associated with brain aging and are characterized by an increase of overall oxidative stress, which would affect several cellular functions. Oxidative stress accumulation in the brain destructs biological components, such as lipids, proteins, nucleic acids and, ultimately, causes cellular death. Additionally, most of the neuronal disorders, which include all the diseases affecting the central and peripheral nervous system, produce a distress in cognitive function and memory. For instance, Alzheimer's disease (AD) is responsible for two out of three cases of dementia, followed by Parkinson's disease (PD) which is the second-most common neurodegenerative disorder affecting the global population [68].

Moderate wine consumption, rather than alcohol consumption per se, has been specifically associated with a lower risk of developing dementia, and specifically Alzheimer's disease. Current wine consumption of from 20 to 29 g per day was associated with a 29% decrease in the incidence of overall dementias and a 49% decrease specifically in the incidence of Alzheimer's disease [68]. These wine consumers also had better physical, as well as mental, health. The beneficial relationship between

the intake of polyphenol-rich diets and the reduction of risk factors involved in the development of neurodegenerative disorders (i.e., dementia, Alzheimer's or Parkinson's disease), neuroticism or psychiatric diseases such as depression or anxiety has also been described [23].

Several in vivo and clinical studies have observed an increase of oxidation levels in the overall redox balance of animal brains in models of neurodegeneration, and in those of patients suffering with neuronal disorders, respectively. Furthermore, this imbalance affects synaptic plasticity due to an exacerbated increase of the neurotransmitter nitric oxide (NO^-). The increase of NO^- produces nitrosative stress, which contributes to the onset of neurodegenerative diseases, such as Alzheimer's, Parkinson's and dementia [69]. This imbalance in redox homeostasis leads to neuroinflammation. The relationship between neuroinflammation and oxidative stress is bidirectional: immune inflammatory response produces reactive oxygen and nitrogen species, whereas these radicals induce the secretion of pro-inflammatory molecules, such as IL-1ß, IL-6 and TNF-α.

Despite the well-established harmful effects of heavy alcohol intake, several studies have associated a low to moderate intake of red wine with a reduction of cognitive impairment [70,71]. Furthermore, epidemiological studies have positively correlated moderate wine intake with the prevention of senile dementia and Alzheimer's disease in the elderly population [71–73] and an improvement of cognitive performance in both women and men compared to abstinent individuals [74]. These results are supported by other studies, where a monthly and weekly wine intake has been associated with a lower risk of dementia and cognitive decline [75,76]. Red wine also reduced lipid peroxidation, increased antioxidant defenses (glutathione antioxidant system) and induced antioxidant enzyme activities in rat models [77], leading to an improvement in spatial learning and memory. Reductions of β-amyloid peptide (Aβ-peptide) aggregation, a peptide related to memory deficits, was reported in a mouse model of Alzheimer's disease. However, the effectiveness seemed to be dependent on the type of wine, and thus on the phenolic composition [78,79]. For example, when 200 mg/kg/d of grape polyphenolics extract (GPE) (equivalent to a human dose of 1 g/d) were orally administered to mice models, a reduction of high-molecular-weight soluble oligomeric βamyloid-peptide in the brain was reported [80]. In a similar manner, resveratrol was also shown to reduce drug-induced neuronal death in male mice (50 or 100 mg/kg/day for 1 or 2 weeks), having an antidepressant effect on rats [23].

Different mechanisms of action for polyphenols have been described in recent years, including inhibition of Tau and β-amyloid peptides aggregation, modulation of the activation of hippocampal brain-derived neurotrophic factor (BDNF) and an increase in insulin-like growth factor-I (IGF-I), among others [80–82]. Also, inhibition of the secretion of pro-inflammatory molecules, such as TNF-α, NO, interleukins and IFN-γ has been reported [83,84].

The ability of polyphenols as scavenging radicals (i.e., anti-oxidant properties) had especially pointed them out as a potential therapy in the prevention of those previously discussed neurological disorders [85]. However, the latest evidence suggest that polyphenols are able to exert their protective effect through the interaction and modulation of genes related to stress response, neuroinflammation and cellular apoptosis [69,86,87]. Among genes modulated by polyphenols, nuclear factor erythroid 2-related factor 2 (Nrf2) [88], mediator of the adaptive response to redox stress, and nuclear factor κβ (NF-κβ) [89], which coordinates the expression and secretion of pro-inflammatory chemokines and cytokines, stand out. Nrf2 expression has been reported to be diminished in the brain of patients with neurodegenerative diseases [90], whereas the opposite is observed for NF-κβ, which is normally found to be up-regulated in patients with neurodegenerative diseases [91].

Other pathways preferentially affected by dietary polyphenols are the mitogen-activated protein kinases (MAPK), a key stone in the regulation of stress-mediated response. They are a group of serine/threonine kinases that connect extracellular and intracellular signals. Three different subfamilies are differentiated: extracellular signal regulated kinases (ERKs), the stress activated protein kinase/jun N terminal kinase (JNK), and the p38 MAPK. Meanwhile ERKs are usually associated with pro-survival routes, JNK and p38 are pro-apoptotic proteins which become activated in response to stress [92].

The phosphorylation of these proteins leads to the activation of a cascade of reactions which, as a last resort, controls the balance between cellular survival and apoptosis. Another serine/threonine protein kinase of considerable importance in neuroinflammation is the mammalian target of rapamycin (mTOR), a member of the phosphoinositide 3-kinase (PI3K) family that regulates cell growth, proliferation, metabolism, and survival in response to various environmental stimuli [93]. Polyphenols can positively modulate the activation and transcription of these genes, promoting cell resistance and survival against negative environmental stimuli [23,84,92]. However, further studies should be carried out to stablish the exact mechanisms by which wine and polyphenols may influence cognitive function and neurodegenerative diseases.

4.2. Neuroticism as Indicator of Cognitive Disorders: Polyphenols as Genetic Modulators

Mental disorders are behavioral and psychologically altered patterns that are normally associated with a present distress. Neuroticism is a personality trait which reflects the propensity to negative emotions and emotional instability, and it is used as a predictive tool for the most common mental disorders, including anxiety, depression or anhedonia [94]. Furthermore, high levels of neuroticism negatively influence the development of physical diseases, such as cardiovascular disease [95]. More than 30% of neuroticism cases are derived from altered gene expression [96], and a pleiotropic contribution of those genes to the development of neuroticism occurs. Neuroinflammation is also triggered in neuroticism-related events.

One of the diseases directly related to the neuroticism trait and neuroinflammation is depression. Major depressive disorder (MDD) is intimately associated with chronic stress and provokes a continuous activation of the sympathetic nervous, inducing the secretion of monoamines (epinephrine and norepinephrine), and subsequent decrease of acetylcholine. This imbalance increases peripheral levels of pro-inflammatory cytokines, which increases the permeability of blood brain barrier (BBB). Once in the brain, these molecules cause neurotoxic effects affecting the brain regions associated with emotions [97]. The immune system is also an essential part of this process, and in consequence, a close relationship between stress, depression and neuroinflammation has been established. However, little is known about the molecular mechanisms through which inflammation can cause depression, or if, on contrary, depression induces inflammation [98].

The consideration of polyphenols as natural anti-depressive agents, mainly due to their antioxidant and anti-inflammatory potential, are results of high novelty. Adult hippocampal neurogenesis (AHN) is negatively affected by stress, aging, anxiety and depression, and conversely is enhanced by diet modifications such as polyphenols intake from grape, blueberries and others. This is due to their antioxidant, neuroprotective and cognitive properties. Also, it has been shown that some polyphenols reduce the risk of developing age-related neurodegenerative diseases that reduce reactive oxygen species (ROS) [99]. However, other mechanisms of action have been proposed for these compounds, such as interaction with benzodiazepine receptors (i.e., GABA-A), inhibition of monoamine oxidases (MOAs), inhibition of prostaglandins, regulation of adrenocorticotrophic hormone and modulation of gene expression such as BDNF or cAMP response element binding protein (p-CREB) [99]. Anxiolytic action has been reported for chlorogenic acid [100], epigallocatechin-3-gallate [101] and blueberry anthocyanins [102], among others, whereas anti-depressant effects have been described for quercetin, kaempferol and trans-resveratrol [103,104]. These facts are in agreement with the results of Tomic and co-workers, who observed a reduction of depression and anxiety-like behaviors in rats supplemented with berry juice containing cyanidins, proanthocyanidins and chlorogenic acids [105]. Also, when Wistar rats subjected to chronic mild stress were fed with resveratrol [106], an improvement in oxidative parameters (decrease in lipid peroxidation, and activation of superoxide dismutase) was observed. Also, a restoration of the activation of Akt/mTOR route, previously reported to be diminished in the prefrontal cortex of depressed patients [107], was perceived.

4.3. Role of Inflammatory Processes in Stress-Induced Depression: Polyphenols as Preventive Agents

The main cytokine involved in depressive and anxiety disorders is IL-6 [108]. IL-6 is a small multifunctional protein, expressed by several types of cells (i.e., blood cells, endothelial cells, adipocytes, etc.). The inflammatory action of IL-6 is conducted via cellular activation of the MAPK route in astrocytes, microglia and neurons. At the same time, IL-6 gene expression is controlled by upstream genes, such as p-CREB or NF-κβ [109].

Besides signaling cascades derived from the activation of MAPK proteins, an elevated expression of IL-6 alters the ratio of T helper (Th17): T regulatory (T_{reg}) cells, favoring an inflammatory event, which in a loop, activates IL-6 expression via NF-κβ [110]. An elevated expression of peripheral IL-6 was observed in major depressive disorder (MDD) patients [111–113], as well as in those with other mental diseases such as autism [114], intellectual disability [50] and sleep alterations [15]. Altogether, these previous investigations show that this cytokine is not only an ideal predictor for mental diseases, but also a target for therapies against these disorders, to help prevent high recurrence in society.

Several studies have reported the ability of polyphenols, such as epigallocatechin gallate and quercetin [115], to reduce levels of IL-6 at the onset of neurodegenerative diseases. Also, grape phenolic extract reduced IL-6 levels in blood within a mouse model impaired with Alzheimer's disease [116], and the same effect was reported after treatment with quercetin and luteolin in an in vitro model of astrocytes stimulated by lipopolysaccharides (LPS). Additionally, this improvement was accompanied by a decrease of the expression of other pro-inflammatory cytokines (IL-1β, IL-8), as well as by activation of antioxidant mechanisms, such as superoxide dismutase enzyme [117].

The analysis of the inflammatory cytokines profile in LPS-induced raw 264.7 macrophages after the incubation with proanthocyanidins-enriched red rice extract confirmed a reduction of the expression of IL-6, as well as the modulation of genes involved in neuroinflammation, including NF-κβ and MAPK [118]. Other polyphenols, such as salicylic acid, procyanidin C1, theaflavin and apigenin, reduced IL-1β, IL-6 and TNF-α expression in different in vitro models [119–121]. These effects could be due to their chemical structure, since the treatment with curcumin and resveratrol analogues also resulted in a decrease of IL-1β, IL-6 and TNF-α [122,123].

The modulation of the secretion of cytokines is strongly influenced by epigenetic factors, understood as the environmental changes in gene expression pattern due to chemical modifications of DNA histones (methylation, acetylation, phosphorylation). In the case of pro-inflammatory cytokines IL-6, DNA methylation stands out as the most relevant epigenetic factor influencing its expression [124].

Hypo methylation of IL-6 causes an increase of this cytokine in human brain, leading to exacerbated neuroinflammation [125,126] and rising the risk in stress and depression-related disorders [127]. In agreement with this, the post-mortem analysis of Alzheimer's disease patients confirmed different methylation patterns of IL-6 genes at different stages of the disease [128]. DNA methylation/demethylation processes occurs by addition/removal of a methyl group in the C5′ position of the nucleobase cytosine in the context of CpG islands, through the action of DNA methyltransferases (DNMT) or ten-eleven translocation (Tet) demethylation enzymes, respectively. Furthermore, an aberrant expression of DNMT in the brain has been linked to cognitive and memory impairment and neurodegenerative diseases, mutations in Tet provoke depression and memory loss [129], and it has been suggested that stress can alter DNMT activity and modify the secretion of stress-related hormones and neuropeptides [127]. As anti-inflammatory agents, polyphenols are able to modulate the immune response, and recent studies suggest that at least one of their mechanisms of action would be epigenetic [130].

In parallel, transcriptomic studies of MDD subjects have identified alterations in the expression of key genes for synaptic functions [131,132]. Specifically, it has been demonstrated that subjects suffering from stress and depression present alterations in synaptic strength and connectivity in the nucleus accumbens (NAc), a subcomponent of the ventral striatum located in the basal ganglia that is important for the development of depression in response to stress [133,134].

The application of animal models to explore molecular mechanisms triggered in stress response and depressive behavior, constitutes a useful approach. The etiology of human depression shares anatomical, neuroendocrine and behavioral aspects with established animal models [99]. The Repeated Social Defeat Stress (RSDS) is a stress mouse model which mimics the symptoms of depression, anhedonia, social avoidance, anxiety and inflammatory response [135]. It is carried out over 10 consecutive days in C57BL/6 mice, which are individually exposed to a novel aggressive CD-1 mouse each day for 10 min with physical contact, followed by an overnight sensory contact with a perforated plastic partition of the cage [136].

As clinically observed, exposition to chronic stress in mice models results in anhedonia and in an increase of peripheral IL-6 levels; however, not all the assayed mice developed a psychiatric disorder. This fact is called resilience, and is based on the individual ability to adapt to stressful situations [98]. In addition, differences in IL-6 levels can be used as indicators of resilience, since IL-6 in blood levels is higher in susceptible mice, compared to in resilient mice.

5. Conclusions and Future Directions

Outstanding advances have been made over the last two decades in the knowledge of wine polyphenols bioavailability. The in vitro action of many representative polyphenols has been reported; nevertheless, their beneficial effects and their role in modulating the risk of high-prevalence diseases are difficult to demonstrate due to the wide variability of polyphenol structures and bioactive actions. In particular, the focus of the scientific community on their metabolism by the human body and interindividual variability in the polyphenol gut microbiota metabolism in each metabotype has gathered great attention. An emerging feature of the biological effects of polyphenols is related to their action on the microbial population in the healthy mouth. However, whether effects are because of specific phenolic compounds/metabolites and/or their role on the associated multiple factors involved in these alterations deserves further research.

On the other hand, the results of previously discussed investigations suggest that wine polyphenols can be considered as a potential strategy for the prevention/treatment of mental disorders, since they are able to interact at genetic and protein levels, but more studies are needed in this promising field. Connections between effects at intestinal and brain levels (the known "gut-brain axis") will be particularly investigated for polyphenols. Relevant progress should be expected in the coming years, favored by the use of the omics approaches (especially transcriptomics and metabolomics) in combination with novel computational strategies enabling the identification of potential targets of polyphenols, and thus gaining a better understanding of the therapeutic effects exerted by polyphenols, including their synergistic interactions among themselves or with other dietary bioactive components.

Author Contributions: I.Z.-P., A.E.-F., D.G.d.L., B.B., and M.V.M.-A. have contributed equally to the conceptualization, investigation, writing, review and editing of this manuscript.

Funding: Research in our lab is funded by Grants AGL2015-64522-C2-R (Spanish Ministry of Economy and Competitiveness), ALIBIRD-CM 2013 S2013/ABI-2728 and ALIBIRD-CM 2020 P2018/BAA-4343 (Comunidad de Madrid).

Conflicts of Interest: The authors declare no conflict of interest.

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