

## Review Article

# Wine Polyphenols: Potential Agents in Neuroprotection

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There are numerous studies indicating that a moderate consumption of red wine provides certain health benefits, such as the protection against neurodegenerative diseases. This protective effect is most likely due to the presence of phenolic compounds in wine. Wine polyphenolic compounds are well known for the antioxidant properties. Oxidative stress is involved in many forms of cellular and molecular deterioration. This damage can lead to cell death and various neurodegenerative disorders, such as Parkinson's or Alzheimer's diseases. Extensive investigations have been undertaken to determine the neuroprotective effects of wine-related polyphenols. In this review we present the neuroprotective abilities of the major classes of wine-related polyphenols.

## 1. Introduction

Aging is a risk factor common to a number of neurodegenerative diseases, including Alzheimer's disease (AD) and Parkinson's disease. Moreover, associated with the population aging, the occurrence of these neurodegenerative disorders is also likely to augment [1]. In addition to the possible involvement in aging, the common characteristic of most degenerative diseases is that they result from neuronal death. Oxidative stress may play a crucial role in progressive neuronal death [2].

Free radicals are oxidative molecules that occur naturally in the environment but can also be generated *in vivo*. Reactive oxygen species (ROS) are produced by immune cells in order to sustain their antibacterial and antifungal functions [3]. When ROS are overproduced, they are taken in charge by various enzymatic pathways for inactivation (superoxide dismutase, catalase, cytochromes, etc.) [4, 5]. Although these enzymatic pathways can be overstepped, ROS accumulate and can react with the different cell molecules such as lipids, proteins, carbohydrates, and nucleic acids. These interactions with the ROS apply an oxidative stress to cells [6]. Some

tissues, particularly the brain, are highly exposed to oxidative damages because of their elevated oxygen consumption and the induced generation of large amounts of reactive oxygen species [7, 8].

Oxidative stress resulting in ROS generation and inflammation is responsible for many forms of cellular and molecular deterioration such as mitochondrial collapsing, DNA damage, and protein, carbohydrate, and lipid oxidation [9]. This damage can lead to early cell aging, cell death, and various chronic pathologies like neurodegenerative disorders, cardiovascular illnesses, cancers, or type 2 diabetes [2, 6, 10, 11]. Difficulty in treating these diseases and better understanding of their development and causes highlight the usefulness of antioxidants as prevention treatments.

A number of epidemiological studies have shown that the consumption of a diet rich in antioxidants can influence the incidence of neurodegenerative disorders [12]. Orgogozo et al. have shown a positive correlation between a moderate consumption of red wine and a decreased incidence of dementia [13, 14]. This protective effect is most likely due to the presence of phenolic compounds in wine. Wine and grape vine polyphenols are mainly flavonoids (flavanols,

flavonols, and anthocyanins) and nonflavonoids (phenolic acids, hydrolysable tannins, and stilbenes) [15]. Extensive investigations have been undertaken to determine the neuroprotective effects of wine polyphenols [16–19]. These polyphenols have displayed neuroprotective capacities in numerous *in vitro* and animal models of neurotoxicities [19]. Several neuroprotective mechanisms of action have been proposed, suggesting that polyphenols exert their activities by reducing the production and the accumulation of ROS, whose accumulation is likely to play a crucial pathological role in brain aging, reducing oxidative stress and inflammation and modulating the activity of intracellular signal transduction molecules [19–21].

In this review we investigate the neuroprotective abilities of the major classes of polyphenols in wine: flavanols, proanthocyanins, flavonols, anthocyanins, phenolic acids, tannins, and stilbenes. Each specific class of polyphenol has shown neuroprotective effects against neurodegenerative diseases. Their neuroprotective activity has been documented, and we underline the evidence suggesting that their mechanism of action involves their antioxidant activity.

## 2. Wine Polyphenols

Products such as wine extract, grape seed, and grape skin extracts are all known to contain a large variety of potent antioxidants in the form of polyphenols. Plant phenolic constituents are produced through two metabolic pathways, the main being that of shikimic acid which leads to cinnamic acids, whereas the polyacetate pathway induces the linkage of a second aromatic ring to the first pathway molecules [22–24].

Wines contain various water-soluble polyphenols including phenolic acids, stilbenes, tannins, flavanols, flavonols, and anthocyanins (see Figure 1). Wine phenolics are divided into two groups: flavonoid and nonflavonoid. The amounts of phenolic compounds in wines are highly variable due to varietal differences and process diversities. Indicative levels of phenolic components in wine are shown in Table 1 [15]. Due to wine processing, red wines contain more polyphenols than white wines. Red wine has more antioxidant capacity than white wine due to its phenolic content [25–27]. Phenolic red wines are mainly composed by flavonoids with 1450 mg/L for young wines and 1285 mg/L for aged ones. Phenolic white wines are composed principally of nonflavonoids with 164 mg/L for young wines and 245 mg/L for aged ones [15, 24].

## 3. Wine Polyphenols and Neuroprotection

### 3.1. Flavonoids and Neuroprotection

**3.1.1. Flavanols.** The flavanols, also called flavan-3-ols or catechins, are the most reduced form of flavonoids. They are present in various plants and are associated with the health benefits of green tea [28, 29]. The levels in wine depend on the different grape cultivars and are typically in the range of 20–100 mg/L. Catechin is usually the major flavanol in wine

[15, 30]. The condensations of flavanol in wine induce the formation of oligomers (proanthocyanidins and condensed tannins).

Flavanol intake has been associated with various beneficial health effects [31, 32], and flavanols are known to be brain-permeable substances [33]. Their transport is stereoselective involving one or more stereoselective entities and metabolizing with glucuronic acid, for example [34]. Numerous studies indicate that flavanols are of benefit for neuronal health. Catechin may protect against the brain injuries produced by endogenous neurotoxins involved in the onset of Parkinson's disease [35]. Catechin and epicatechin gallate have also shown an ability to suppress neuroinflammation and can attenuate and inhibit activation of microglia and/or astrocytes associated with the release of the mediators linked to the apoptotic death of neurons [36]. In addition, numerous studies indicate that catechin derivatives may delay the onset of neurodegenerative disorders such as Alzheimer's disease through a numerous different mechanisms such as iron chelators, radical scavengers, and modulators of pro-survival genes [31, 37–40].

**3.1.2. Proanthocyanidins.** Proanthocyanidins and condensed tannins are complex flavonoid polymers naturally present in cereals, legumes, and fruits [41]. They are mainly formed by the condensation of flavanol units to generate oligomers (proanthocyanidins) and polymers (condensed tannins). Their levels in wine depend on pressing techniques and grape varieties. Typically they range from 5 mg/L in white wines to 1 g/L or even higher levels in old red wines [15, 41]. They are associated with a change in wine quality such as a modification of the hue and a decrease in astringency.

Very few studies have concerned the bioavailability of proanthocyanidins. Condensed tannins should be degraded in monomeric phenols, absorbed and metabolized, as has been shown for other flavonoids [1, 2]. Numerous studies indicate that proanthocyanidins and condensed tannins might prevent both cancers and cardiovascular diseases [42, 43]. Some reports demonstrate that its biological abilities to scavenge the reactive oxygen species are associated to the degree of polyphenol oligomerization. Some of these polyphenols might have specific structures that exhibit neuroprotective effects by interacting with putative neuron-specific receptors [44]. Takahashi et al. have shown that procyanidin oligomers from grape seed exhibit higher growth-promoting activity than the monomers toward mouse hair epithelial cells *in vitro* and *in vivo*, these results indicating that the specific effect might be correlated with their structure [45]. Other research on rat brain suggests that grape seed extract enriched in proanthocyanidins might protect against pathology age-related oxidative brain damage [46].

**3.1.3. Flavonols.** Flavonols occur in a wide range of vegetables. There polyphenols are always found in glycoside forms in plants including grape berries, where they are present in the skin. Flavonol glycosides and aglycones are found in grape wine from trace amounts up to 200 mg/L in some

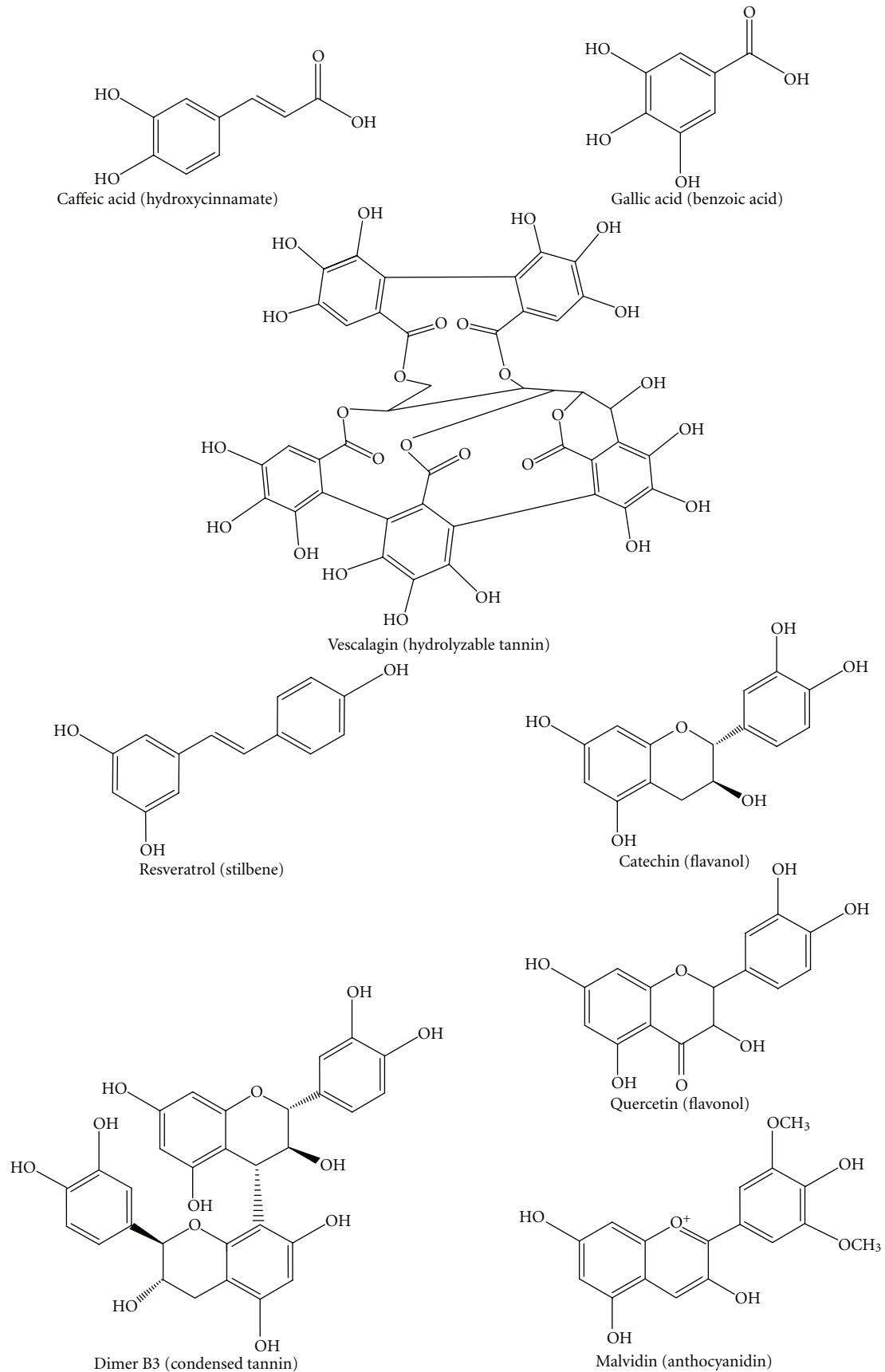


FIGURE 1: Chemical structures of some phenolic compounds from wine.

TABLE 1: The levels of principal phenolic classes (mg/L) in red and white table wine [15].

Phenol class	White wine		Red wine	
	Young	Aged	Young	Aged
nonflavonoids				
hydroxycinnamates	154	130	165	60
benzoic acids	10	15	60	60
hydrolyzable tannins	0	100	0	250
stilbenes (resveratrol)	0.5	0.5	7	7
Total mg/L	164.5	245.5	232	377
flavonoids				
flavanol monomers	25	15	200	100
Condensed tannins	20	25	750	1000
flavonols	—	—	100	100
anthocyanins	—	—	400	90
Total mg/L	45	40	1450	1285

red wines [15, 47, 48]. Myricetin, quercetin, and kaempferol conjugates are the major flavonols in wine [48, 49].

Primary results indicate that flavonols can pass the blood-brain barrier [50, 51]. Moreover, numerous studies indicated that flavonols, in addition to many other health benefits, contribute significantly to the protection of neuronal cells against oxidative-stress-induced neurotoxicity [52, 53]. In Alzheimer's disease, neuronal loss is preceded by the extracellular accumulation of amyloid- $\beta$  peptide ( $A\beta$ ). It has been shown that pretreatment of primary hippocampal cultures with quercetin significantly attenuates  $A\beta$ -induced toxicity, lipid peroxidation, protein oxidation and apoptosis [54]. A dose-response study indicated that quercetin exhibited protective capacities against  $A\beta$ -induced toxicity by modulating oxidative stress at lower doses [54]. In cerebral ischemia, calcium dysregulation is one of the main instigators of neuronal cell death and brain damage. Quercetin has been shown to exert significant protection against ischemic injury. Indeed, treatment with quercetin reduced the spectrin breakdown products caused by ischemic activation of calcium-dependent protease calpain and inhibited the acid-mediated intracellular calcium level [55].

**3.1.4. Anthocyanins.** Anthocyanins act as guard systems in plants and protect them from UV damage. They form complex molecules with other phenolic molecules and strongly contribute to the color and the aging of wine [56–58]. The aglycone ring of these flavonoids is called anthocyanidin. However, nonconjugated anthocyanidins are never found in grapes or wine, except in trace quantities. In wine there are five anthocyanidins: malvidin, cyanidin, delphinidin, peonidin, and petunidin. Malvidin is the most abundant anthocyanidin in red wines [15].

Among the wine flavonoids, anthocyanins constitute one of the higher potent antioxidants correlated to their capacity to delocalize electrons and form resonating structures [59–62]. Anthocyanins present numerous health benefits such as anticarcinogenic, anti-inflammatory, or antidiabetic effects

[61, 63–66]. Anthocyanins also possess beneficial neuroprotective abilities. Some of them have the ability to cross the blood-brain barrier and diffuse through the central nervous system [67, 68]. Anthocyanins have neuroprotective benefits in reducing age-associated oxidative stress and improving cognitive brain function [61, 69–72]. They induce significant neuroprotective effects against oxidative stress, DNA fragmentation and lipid peroxidation in mouse brain [73, 74]. Thus, it appears that the antioxidant and anti-inflammatory effects of anthocyanins contribute to its neuroprotective effect.

### 3.2. Nonflavonoids and Neuroprotection [73, 74]

**3.2.1. Phenolic Acids.** The benzoic acids are a minor component in wines. Whereas the hydroxycinnamates are the most important class of nonflavonoid phenols in grape vine and the major class of phenolics in white wine [15, 75]. The three important ones in wine are coumaric acid, caffeic acid, and ferulic acid. Amount of total hydroxycinnamates in wine are typically about 60 mg/L in reds and 130 mg/L in whites [15].

Hydroxycinnamates have an antioxidant activity by scavenging free radicals [76, 77]. Their strong antioxidant properties help to explain their beneficial role on health and in reducing disease risk. Hydroxycinnamates and other phenolic acids have received less attention. It has been shown that p-coumaric acid, hydroxycinnamates caffeic acid, and a Champagne wine extract rich in these compounds have neuroprotective effects against injury induced by 5-S-cysteinyl-dopamine *in vitro* [78]. Caffeic acid has been reported to have neuroprotective effects against  $A\beta$ -induced neurotoxicity *in vitro* and to inhibit peroxynitrite-induced neuronal injury [78–80]. Ferulic acid has been showed to protect primary neuronal cell cultures against hydroxyl- and peroxy-radical-mediated oxidative damage [81, 82].

**3.2.2. Hydrolyzable Tannins.** Tannins are water-soluble polyphenols. One of the major properties of these molecules is their capacity to precipitate proteins such as gelatin from solution [83–85]. In wine, hydrolyzable tannins arise during maturation and ageing of wines in oak barrels [86]. Castalagin and vescalagine are the main representative compounds of ellagic tannins [87]. Their levels are about 100 mg/L in aged white wines, while red wine levels are about 250 mg/L after aging in oak barrels for two or more years [15, 88]. They are mainly ellagic acid and gallic acid ester derivatives with glucose or other sugars. Due to the presence of the ester linkage, they are described as being hydrolyzable. Hydrolyzable tannins are not present in *Vitis vinifera* but are present in other fruits such as muscadine grapes and raspberries [89]. These polyphenols are excellent antioxidants and natural preservatives, also helping give the wine structure and texture. However, recent research on tannins has focused on their potential to impact positively on human health. Tannins have demonstrated a host of potent biological activities, antiperoxidation properties, inhibition of mutagenicity of carcinogens and tumor promotion, specific antitumor abilities in relation with tannin structures, antibacterial activity,

and antiviral activity [89–91]. *In vivo*, ellagitannins are mainly transformed into ellagic acid and its metabolites. In fact, they could be the agent responsible for the effects of dietary ellagitannins observed *in vivo* [92, 93].

There are few studies whose objective has been the neuroprotective activity of hydrolyzable tannins. Ellagic acid has been reported to promote the formation of  $\beta$ A fibril and significant oligomer loss, in contradiction to previous results indicating that polyphenols inhibited  $\beta$ A fibril formation [94]. Nevertheless, ellagic acid reduces significantly  $\beta$ -induced neurotoxicity in human SH-SY5Y neuroblastoma cells. These results are in agreement with the hypothesis that  $\beta$ A fibril formation may represent a protective mechanism of local  $\beta$  clearance. Thus, ellagic acid may have therapeutic value in Alzheimer's disease.

**3.2.3. Resveratrol and Other Stilbenes.** Stilbenes are secondary metabolites described as phytoalexins. Stilbenes are found in grape vine and wine [95–97]. The main characteristic of stilbenes consist of diary groups on either end of an active double bond that generates the stilbene skeleton, the so-called resveratrol. Stilbenes can also be found in oligomeric and polymeric forms in wine [98]. Resveratrol is found in wine from trace amounts up to 10 mg/L typically 0.1 mg/L in white wines and 2.0 mg/L in red wines [15, 99]. It is a substance with great potential that is being investigated intensively, and its derivatives exhibit a wide range of pharmacological and biological properties [100].

Resveratrol and its derivatives have also been reported to be active against neuron cell dysfunction and death in animal models [20, 101–104]. Resveratrol can cross the blood–brain barrier and exhibit neuroprotective properties against cerebral injury [105]. Numerous mechanisms may underline resveratrol neuroprotective effects against  $\beta$ -induced neurotoxicity [106]. Resveratrol can act by reducing the intracellular  $\beta$  level by inducing protease degradation of the peptide in Alzheimer's disease. Resveratrol and other stilbenes have been shown to inhibit  $\beta$ A fibril formation *in vitro* [107, 108]. Furthermore, resveratrol has been shown to exhibit significant free-radical scavenging abilities in numerous cellular models [109–112]. Thus, overall scientific data tend to show that among stilbenoids resveratrol has effects against brain injuries in reducing brain damage in complex manner including antioxidant properties, regulation on neurovascular system, or ability to inhibit known neuropathological processes.

## 4. Mechanisms

**4.1. Bioavailability of Wine-Related Polyphenol.** It is now well established that wine polyphenols exhibit some beneficial activities on health, particularly on neurodegenerative diseases [113]. Biological activities are often measured on cultured cells or isolated tissues using polyphenols in their form present in wine (as aglycone or their sugar derivatives). However, the question of their achievable concentration after ingestion as well as the possibility of conjugate formation has been ignored by many studies [114]. These data are though

crucial for understanding polyphenol bioactivity. Several studies indicate that the antioxidant effect *in vitro* of some polyphenols may not indicate its activity *in vivo*. Indeed, its alteration into metabolites and other derivative constituents constitute the true bioactive molecules [113, 115–118]. Polyphenols are extensively metabolized in different tissues such as colon, small intestine, and liver [119]. Polyphenols are absorbed through the gut barrier. Some of them who are not absorbed pass to the large intestine and undergo colonic biotransformation by the enzymes of the colonic microflora [118]. Polyphenols metabolized in the gastrointestinal tract undergo conjugation in the liver after absorption. Then, polyphenols are present in circulation as sulfated, glucuronidated, methylated, and as mixed forms. Moreover, a large proportion of polyphenols ingested are subjected to hydrolyses and degradation by colonic microflora to simple phenolic compounds. Wine polyphenols are grouped into two categories: flavonoids and nonflavonoids as described before. Chemical structure of polyphenol is a factor involved in the gut absorption and the metabolism. We report here data on the absorption and the metabolism of the main polyphenols found in wine.

Concerning flavonoids, flavanols were absorbed and eliminated at low micromolar amounts of their direct conjugates (methylated, sulfated, and glucuronidated derivatives) [120]. However, the degradation of flavan structure in colon leads to the formation of phenolic compounds [114, 121]. Because of their hydrosolubility and high molecular weight, proanthocyanidins are not absorbed in the gut. The large majority of proanthocyanidins cross without alteration through the small intestine after which they are transformed by the colonic microflora to produce simple phenolic acids such as phenylacetic and phenylpropionic derivatives [122]. However, Tsang et al. reported that administration of grape-seed procyanidins induce the formation of catechin glucuronide derivatives in rat plasma [123]. Flavonols are naturally occurred as glycosides. Results indicate that flavonols uptake induce a cleavage of the glycoside part in the small intestine followed by absorption and metabolism of the aglycone [124]. Aglycones are then conjugated by sulfation and glucuronidation as well as methylation of the catechol group [118]. A large number of colonic metabolites identified are simple phenolic acids [125]. Anthocyanins was absorbed and excreted at a low proportion of the intact glycosides after injection of wine extract [126, 127]. The anthocyanins degradation at the pH of the intestine in addition to the microflora activity in the colon are at least in part involved in the degradation of anthocyanins into more stable compound such as phenolic acids [113].

Concerning nonflavonoids, ellagitannins are not absorbed due to their large molecular size [128]. They are principally hydrolysed to ellagic acid under physiological conditions in small intestine [113]. Ellagic acid and ellagitannins reach the distal part of the small intestine and the colon, they are mainly transformed by gut microflora into urolithin derivatives [129]. The major stilbene compound found in wine is resveratrol; thus, bioavailability of resveratrol was investigated. Many investigations in animal models and humans have indicated that a low bioavailability of



unconjugated resveratrol. More than 70% of the resveratrol uptaked is absorbed and readily transformed to produce essentially sulphate and glucuronide derivatives [99].

The conjugation of polyphenols has been recognized for many years, most of the biological studies have only been carried with polyphenol aglycones, and very little is known about the biological properties of conjugated derivatives. Numerous studies indicate that metabolic transformations of phenolic compounds reduce their antioxidant properties leading to less active antioxidants than the original compounds [130–132]. The formation of conjugated polyphenols and degradation products such as simple phenolic compounds will modify the properties observed *in vivo* in comparison to their unconjugated forms [114]. Much research effort is still needed to evaluate the biological effects of the conjugated derivatives and microbial metabolites of wine polyphenols.

**4.2. Neurodegenerative Disorders and Oxidative Stress.** Reactive oxygen species (ROS) are generated in living organisms due to various metabolic processes [108]. The narrow definition of ROS refers to oxygen free radicals, including superoxide radical anion, hydroxyl radical, hydroperoxyl radical and nonfree radicals, which can induce the generation of free radicals through divers chemical reactions. ROS produced in the human body can cause oxidative damage. Under oxidative stress, the excessive production of ROS may directly damage proteins, lipids, carbohydrates, DNA, and even cellular molecules involved in antioxidant defense systems. The over production of free radicals is implied in the progress of numerous diseases such as cardiovascular diseases, cancer, and neurodegenerative disorders [133–137]. To control, the levels of free radicals various defense mechanisms have been promoted in living organisms such as endogenous enzymes glutathione peroxidase, catalase, or superoxide dismutase. In addition to these endogenous mechanisms, much attention has been focused on the antioxidant role of some dietary compounds like polyphenols [27, 138, 139].

**4.3. Antioxidants and Neuroprotection.** The brain is characterized by its high susceptibility to oxidative stress due to its high oxygen consumption, its high fatty acids levels, and low antioxidant enzyme levels. Numerous works in the literature indicate that wine related-phenolic compounds exhibit a positive effect on nerve cells [18, 19, 80]. The mechanism proposed as explaining the effect on wine polyphenolic compounds on health can be principally summarized as scavenging intracellular ROS and inhibition of LDL oxidation [110, 140–142]. In recent years, studies on the activity of wine polyphenols have been extended to animal models of CNS disorders and injury [18, 143]. These effects are principally associated to their strong antioxidant capacities, since they can act as free-radical scavengers and hydrogen or electron, to preventing DNA damage and lipid peroxidation [144, 145]. Antioxidant polyphenols protect cell constituents from oxidative alteration and thus limit the risk of developing degenerative disorders induced by oxidative stress, such as in ischemia, Parkinson's disease or Alzheimer's

disease. For example, an increasing number of reports has shown that acute chronic treatment of resveratrol exhibits neuroprotective effects against colchicine and nitropropionic acid [146] or motor impairment as well as hippocampal neuron loss [147, 148]. These properties are mainly associated to the antioxidant activity of resveratrol. Resveratrol decreases the oxidative damages, in reducing the levels of malondialdehyde, lipid peroxidation, xanthine oxidase, and nitric oxide, and in increasing the depleted glutathione levels and succinate dehydrogenase activity in rat brain [149, 150].

**4.4. Effect of Wine Polyphenols on Redox Imbalance.** In the living organism, free radicals are generated both enzymatically and nonenzymatically, inducing the generation of reactive oxygen species, which have a crucial role in neurodegenerative disorders. Thus, in neurodegenerative pathologies and aging, the neuronal cells of specific brain regions may be exposed to ROS attack, and apoptotic cell death occurs and progressively worsens until malfunctioning of the neural network and manifestations of neurodegenerative disorders ensue [151].

Compelling evidence supports that oxidative stress plays key role in the physiopathology of neurodegenerative disorders. ROS level augmentation induces oxidation of cellular components leading to a neurodegenerative signaling cascade, which generates cellular damages and induces cell death [152–155]. To prevent oxidative damage, mammalian cells have developed a complex antioxidant defense system converting ROS to less harmful species [156, 157]. Thus, a potential approach in the treatment of neurodegenerative disorders is the use of antioxidants. They have the capacity to scavenge ROS and to upmodulate endogenous antioxidant defenses. In brain, such compounds should have the capacity to cross the blood-brain barrier.

In cells, oxidative stress is associated to sugar, lipid, DNA, and protein damages. The imbalance between antioxidant defense mechanisms and the intracellular production of free radicals induces oxidative stress [158]. Neurons in their ability to regulate for redox imbalance have an age-related decrease, even minor cellular stresses can lead to irreversible disorders and, as such, participate to the causes of neurodegenerative pathologies [158]. The accumulation of free radicals may activate  $\beta$ -secretase, resulting in formation of  $\beta$ -amyloid, which is believed to be responsible for synaptic dysfunction and neuronal cell death in Alzheimer's disease [159, 160]. The wine polyphenols are powerful anti-oxidants that inhibit the production of free radicals [161, 162], preventing cells from free radical and cellular DNA damages [163–165]. Indeed, the overproduction of reactive nitrogen and oxygen species by phagocytes induces oxidative damage to proteins, lipoproteins, and DNA. These reactions may be harmful to cells and tissues and lead to inflammation [166, 167]. Thus, to reduce many inflammatory disorders inhibition of reactive nitrogen and oxygen species production is a popular target. Wine related polyphenols with their antioxidative capacities may have therapeutic value in the prevention of oxidative stress [168, 169]. Furthermore, results indicate

that polyphenols from wine have both the antioxidative and anti-inflammatory properties [170, 171] and that they can prevent cardiovascular diseases [172, 173]. It is also thought that polyphenols act to modulate free radical-mediated lipid peroxidation of low-density lipoproteins (LDL), which is correlated to chronic diseases such as atherosclerosis [138, 174, 175].

**4.5. Effect of Wine Polyphenols on NO Production.** In complement to the antioxidant abilities of polyphenols, they might exert protective effects by improving endothelial function as indicated by both experimental and clinical studies [176]. As known for a long time, the endothelium have a crucial function in vascular health by regulating several vasorelaxing factors such as nitric oxide (NO) and endothelium-derived hyperpolarizing factor [177–180]. Indeed, the beneficial mechanisms of red wine polyphenolic compounds mainly involve the activation of endothelial NO, release through an increase in calcium levels and activation of the phosphoinositide-3 kinase/Akt pathway in endothelial cells [178, 179, 181]. Red wine polyphenolic compounds may also regulate NO activity at the level of endothelial nitric oxide synthase (eNOS) protein expression in endothelial cells [182] and blood vessels [183]. Chronic upregulation of eNOS by red wine polyphenolic compounds might constitute a preventive approach to reduce tissue injury associated with the risk of cerebral ischemia. For example, results indicate that resveratrol protects the spinal cord from ischemia-reperfusion injury by decreasing oxidative stress and increasing NO release. Resveratrol-induced neuroprotection is thus mediated by both antioxidant- and NO-promoting properties [184]. There is substantial evidence that polyphenols in red wine can exhibit anti-inflammatory abilities. This could be due to their capacities to scavenge NO or to decrease the NO synthase activity [110, 164, 185]. Resveratrol could also inhibit the neuronal NO synthase and the inducible NO synthase isoforms [164, 186]. Therefore, resveratrol could induce the activity of vasodilator-inducing enzyme such as the endothelial isoform eNOS. This effect may be associated to the anti-inflammatory property of resveratrol [187]. Additionally, Han et al. indicated that resveratrol analogues exert neuroprotective effects by the activation of some receptor binding sites localized at the level of the cellular plasma membrane in rat brain [188]. The polyphenol binding to this specific receptor may induce nitric oxide synthase activity in the brain [189]. However, the polyphenol prolonged action could modulate the sensitivity and the tolerance of its receptor. Similarly, low and high doses of red wine polyphenolic compounds have, respectively, pro- and antiangiogenic properties on postischemic neovascularization *in vivo*. Finally, results indicate that resveratrol uptake, in association with a moderate intake of wine, induces an NO upregulation effect on human platelets [190]. In addition, wine related-polyphenols may exert other effects such as decrease LDL oxidation and increase HDL to generate [190–192]. This unique dual effect of red wine polyphenolic compounds offers important perspectives for the treatment and prevention of different diseases.

**4.6. Other Potent Effects of Wine Polyphenols.** Because oxidative and nitrosative stress have a crucial impact in the causes of neurodegenerative diseases such as Alzheimer's and Parkinson's diseases and because antioxidant activity is the most studied effect of wine polyphenols, this paper was mainly focused on oxidative damage to neuronal molecules. Nevertheless, studies have indicated that polyphenols could exert neuronal regulation at different levels such antiamyloidogenic effects, neuroprotection through modulation of neural mediators and enzymes, and interaction with signaling pathways.

Resveratrol has been identified as a potential antiaging agent and several studies have been realized on protective abilities of stilbenes (resveratrol derivatives) against aging and specific neurodegenerative disorders [19, 107, 115, 164]. The neuronal regulation of resveratrol derivatives molecules could be defined through a number of complex biological processes involving, as previously discussed upregulation of brain-redox imbalance, interactions with signaling pathways crucial in inducing neuronal function and survival, regulation on neurovascular system, and ability to inhibit known neuropathological processes. In APP695-transfected cell lines, resveratrol, could reduce the level of secreted A $\beta$  peptide without directly affecting any other components of the A $\beta$  metabolism tested [193]. The decrease of the production of A $\beta$  peptide could be related to the increase of its degradation. Also, resveratrol did not promote the A $\beta$  peptide clearance by metalloendopeptidases. The treatment of cells with proteasome inhibitors reduced the A $\beta$  decrease induced by resveratrol. Thus, resveratrol could affect the proteasome involved in the degradation of the A $\beta$  peptide. It has been shown that resveratrol could have beneficial effects on cognitive function mediated by regulation on neurovascular system. A higher microvascular density in association with the increase of cerebral blood flow might ameliorate performance by direct increase of glucose and oxygen supply in brain [194]. Furthermore, a recent study reports that resveratrol quickly enhances blood flow into the brain, followed by increased brain oxygenation which has been correlated to the increased memory capacity and improved cognition [195]. Studies revealed that resveratrol and its derivatives identified in wine such as piceid and  $\epsilon$ -viniferin glucoside inhibited *in vitro* the A $\beta$  fibrils formation [107, 108]. Examination of the inhibitory data for the stilbene monomers suggests specific structure-activity relationships [196].  $\epsilon$ -viniferin glucoside has been shown to inhibit fibrillization of A $\beta$  peptide and to protect PC12 cells against A $\beta$ -induced toxicity [197]. These results together suggest that neuroprotective action of resveratrol could protect neurons against brain injuries in reducing brain damage in complex manner. In addition to resveratrol, various polyphenols present in wine protective effects against neurodegenerative diseases by regulation at different levels [115, 198, 199].

## 5. Conclusion

Wine polyphenols appear to be potentially neuroprotective agents by their capacity to inhibit and/or modulate several

neurodegenerative processes. Their neuroprotective effects in *in vitro* and *in vivo* models of neurodegenerative disorders have been documented, and our own findings suggest that their mechanism of action involves their antioxidant activity, principally as scavenging intracellular ROS and inhibition of LDL oxidation, and also their activating effect on endothelial and inhibitory action on both neuronal and inducible nitric oxide synthase activity and subsequent NO production. On the other hand, as indicated by Singh et al., it would be unwise to extrapolate these results to human without conducting proper clinical trials in patients suffering from irreversible and extensive neuronal loss [200].

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