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Review

Wine Polyphenols and Neurodegenerative Diseases: An Update on the Molecular Mechanisms Underpinning Their Protective Effects

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Abstract: Alzheimer's and Parkinson's diseases are the most common age-related and predominantly idiopathic neurodegenerative disorders of unknown pathogenesis. Although these diseases differ in their clinical and neuropathological features, they also share some common aetiologies, such as protein aggregation, mitochondrial dysfunction, oxidative stress, and neuroinflammation. Epidemiological, in vitro and in vivo evidences suggest an inverse correlation between wine consumption and the incidence of neurodegenerative disorders. Wine benefits are, in large part, attributable to the intake of specific polyphenols, which mediate cell function under both normal and pathological conditions. In this review, we aim to provide an overview of the role that wine polyphenols play in delaying neurodegenerative disorders. We discuss animal and in vitro studies in support of these actions and we consider how their biological mechanisms at the cellular level may underpin their physiological effects. Together, these data indicate that polyphenols present in wine may hold neuroprotective potential in delaying the onset of neurodegenerative disorders.

Keywords: flavonoids; ageing; brain; Alzheimer's disease; Parkinson's disease; signaling pathways

1. Introduction

Given the current ageing population demographics, the prevalence of dementia worldwide will approximately double every 20 years, increasing to 115 million by 2050 [1]. As people age, their cognitive function is threatened by the normal ageing process, as well as increasing risk for a range of neurodegenerative conditions, most notably Alzheimer's Disease (AD) and Parkinson's disease (PD) [2]. The precise cause of the neuronal degeneration underlying these disorders remains however elusive, although it is thought that several cellular and molecular events are involved in its progression, including oxidative stress increase, mitochondria function impairment, neuronal apoptosis activation, aggregated proteins deposition and excitotoxicity [2]. Existing drug treatments for neurodegenerative conditions rarely curtail the underlying disease processes, and consequently there is an urgent need to develop alternative strategies to directly prevent, slow, and even stop neurodegeneration. Lifestyle strategies, such as nutritional interventions, have potential to be a safe, cheap, and effective alternative to protect against age-related cognitive decline and neurodegeneration, resulting in significant personal and societal benefits [3].

Although the long-term high consumption of alcoholic drinks has been associated with an increased prevalence of cancer, cardiovascular diseases, cirrhosis, dementia and depression [4],

a low-moderate wine intake may reduce cognitive impairment [5–7], cardiovascular diseases [8–10] and may also decrease certain types of cancer [11,12] and/or diabetes [13,14]. In addition, data from the Personnes Agées Quid [6] study demonstrated that people drinking three to four glasses of wine per day had an 80% decreased incidence of dementia and AD three years later, compared to those who drank less or did not drink at all [7]. Wine polyphenols have been reported as potential preventive agents due to their chemical and biological properties. These compounds derive mainly from the grape seeds and skin and may be present at relatively high concentrations in wine, especially as flavonoids (flavan-3-ols, anthocyanins) and other polyphenols (resveratrol, gallic acid or cinnamates). Red wine is known to contain 10 times more phenolic compounds than white wine, most of which come from the extraction derived from the skin and seeds during the fermentation process. Wine compounds proportion, however, depends on terroir, i.e., on grape cultivar type, soil and climate features in which grapes grow, and human activity [15,16] (see Figure 1). Polyphenols have been ascribed with anti-inflammatory properties and are able to modulate signaling pathways that regulate neuronal survival [17]. As such, there is a great interest in the potential of regular and moderate wine consumption to delay the onset of neurological disorders, such as AD and PD [18].

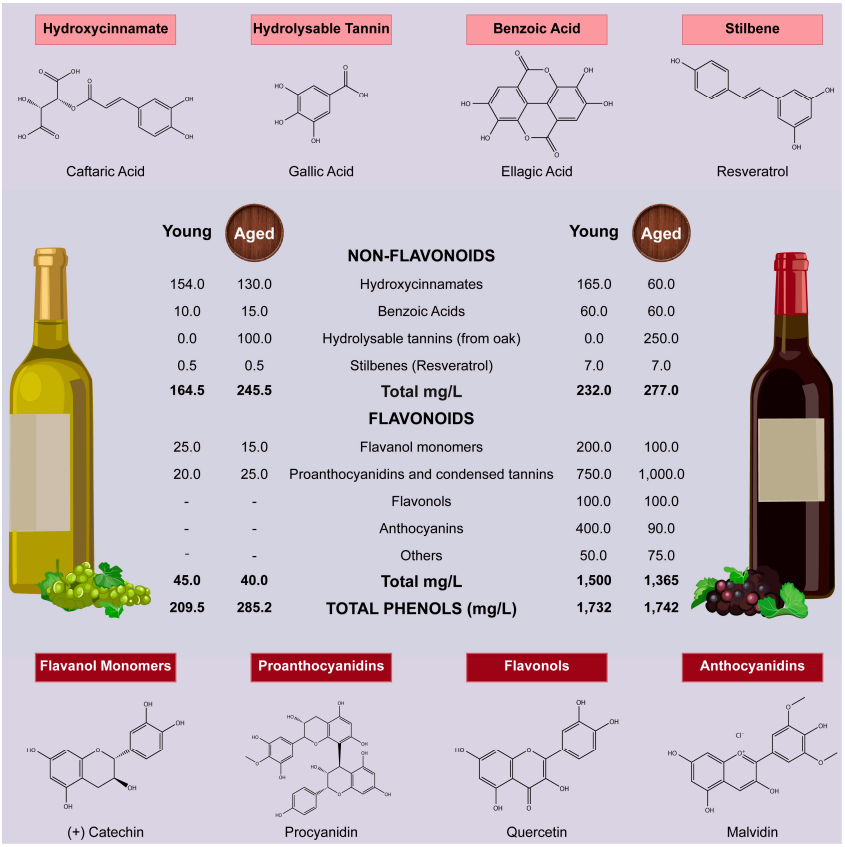

Figure 1. Red and white wine phenolic composition. Adapted from Waterhouse A.L. [16].

In this review, we summarize the most recent supporting mechanisms of AD and PD pathogenesis and progression. For both disorders, we also summarise the neuroprotective abilities of the wine compounds in correlation to the pathophysiological mechanisms involved in each neurodegenerative disease.

2. Alzheimer Disease (AD)

Alzheimer's disease is the most common cause of dementia in older adults. In this pathology the damage initially appears to take place in the hippocampus, important for memory formation. As more neurons die, additional parts of the brain, including the cerebral cortex, are affected and begin to

shrink. Such changes progressively lead to a loss of mental, behavioral and functional abilities and a decrease in the capacity of learning new things, carry out multistep tasks such as getting dressed, or cope with new situations. Age is by far the main risk factor, although genetic, environmental, and lifestyle factors may also contribute to the disease process. To date, the most prevalent hypothesis for the pathogenesis of AD is the amyloid cascade theory where, insoluble forms of amyloid-β (Aβ) plaques accumulate in extracellular spaces and in blood vessels walls. The process begins in neurons with the cleavage of the amyloid precursor protein (APP), through the activity of the β-secretase (BACE 1) and then followed by the γ-secretase. In the non-pathological pathway (non-amyloidogenic) the γ-secretase precedes by the α-secretase activity. Amyloidogenic cleavage results in production of peptides mainly of 40 and 42 amino acids, known as Aβ40 and Aβ42, respectively [19]. These peptides can be converted into diffusible and soluble oligomers (Aβo) (Figure 2). The neurotoxicity of Aβo is further exacerbated by their capacity to negatively affect long-term potentiation, therefore producing severe damages to synaptic plasticity resulting on impaired memory and learning. When Aβo are not removed by the astrocytic low-density lipoprotein receptor-related protein 1 (LRP 1), their aggregation occurs to form fibrillary structures that accumulate into Aβ plaques. The latter can be cleared from the brain through different pathways [19], including either the intervention of macrophages and microglia cells or involving astrocytes, through endoproteases such as insulin-degrading enzyme, neprilysin and matrix metalloproteinase [20].

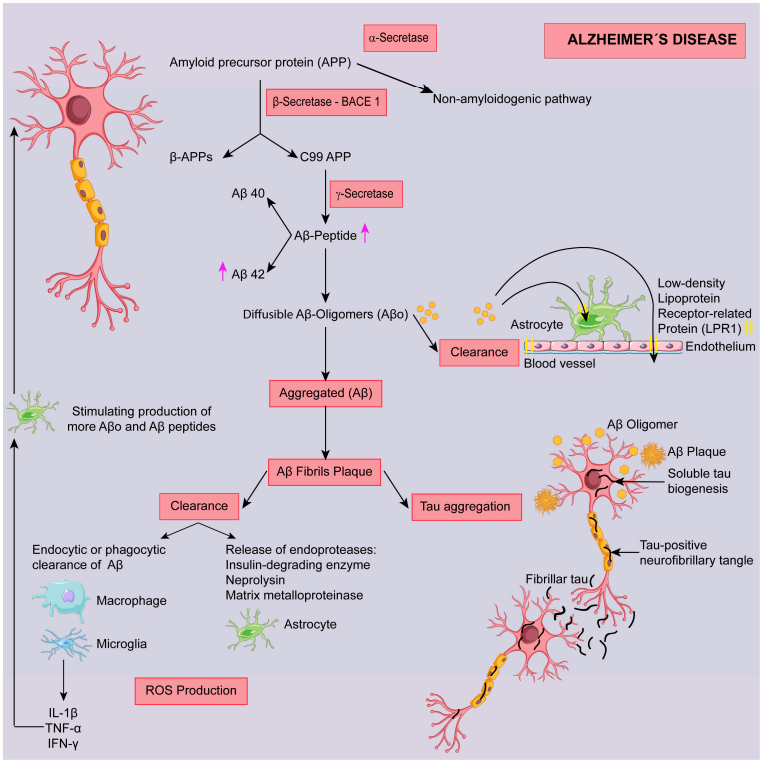

Figure 2. Diagrammatic representation of pathogenic mechanisms involved in Alzheimer's disease. Aβ, amyloid beta; Aβo, amyloid beta oligomers; APP, amyloid precursor protein; IL-1β, interleukin 1 beta; IFN-γ, interferon gamma; LPR1, low-density lipoprotein receptor-related protein 1; ROS, reactive oxygen species; TNF-α, tumor necrosis factor alpha.

Some conformational Aβo, that dissociate from both Aβ fibrils and plaques, may not be removed and are toxic to adjacent synapses and mitochondria. Furthermore, Aβo induce activation of microglia and astrocytes. With microglial activation, proinflammatory cytokines, including interleukin 1 beta (IL-1β), tumor necrosis factor alpha (TNF-α), and interferon gamma (IFN-γ) are produced. These molecules accumulate nearby astrocyte-neuron stimulating the production of more Aβo and Aβ

peptides [20]. Moreover, those Aβo induce intraneuronal accumulation of paired helical filaments hyperphosphorylated tau protein abnormalities (neurofibrillary tangles, NFTs) in the brain. The exact biochemical mechanisms of tau aggregation remain however currently unknown. Damaged neurons are the ones with Tau-positive NFTs, which extend to the dendrites, and can be released and taken up by healthy neurons, triggering tau damage in the uptaking cell (Figure 2) [21].

Brain metabolism depends exclusively on glucose utilisation and its metabolism in the mitochondria, via the Krebs cycle and the electron transport chain (ETC). It is estimated that about 2% of the O_2 used by the mitochondria is converted into superoxide radical ($O_2^{\bullet -}$), with this figure increasing in damaged or aged mitochondria [22]. Brain has also high amount of polyunsaturated fatty acids, which in the presence of redox-active metals, such as copper (Cu) and iron (Fe), are very susceptible to lipid peroxidation. When the scavenging system of the brain is not able to remove the excess of reactive oxygen species (ROS) produced then oxidative stress (OS) appears. ROS accumulate in brain tissues and cells and interact with lipids, proteins, carbohydrates and nucleic acids leading to cellular oxidative damage (Figure 3). As a result of cellular and molecular deterioration, inflammation can occur by the activation of the immune system [23]. In addition, ROS induced-defects in mitochondrial energy metabolism is linked to the disruption in calcium (Ca^{2+}) metabolism. The mitochondrial Ca^{2+} sequestering is very important to maintain neurons functionality. In neurogenerative diseases, the hyperactivation of *N*-methyl-D-aspartate-receptors (NMDA-type receptors) increases the Ca^{2+} concentration, inducing mitochondrial transition pore to open. Subsequently, pro-apoptotic proteins, such as cytochrome c and the apoptosis inducing factor (AIF), can be released to the cytoplasm therefore activating the apoptotic cascade and neuronal death. Furthermore, the decrease in nuclear factor (erythroid-derived 2)-like 2 (Nrf2) expression observed in neurodegenerative diseases, supports this theory, since Nrf2 protects neurons from the increase in intracellular Ca^{2+}, and other toxic insults such as OS and mitochondrial dysfunction. On the other hand, the NMDA-type receptors hyperactivation also results in glutamate-induced excitotoxicity that can lead to neuronal necrosis [24]. Finally, OS generated through Aβs can also activate stress kinases such as c-Jun N-terminal kinases (JNK), [25]. The high-affinity of Aβs for copper (Cu) and zinc (Zn) may also explain the formation of an oxidative microenvironment. Indeed, at low pH Cu may induce Aβ aggregation and Aβs and APPs can reduce Cu^{2+} to Cu^{+}, in a reaction that produces hydrogen peroxide (H_2O_2) [26]. Oligodendrocytes have low amount of glutathione (GSH) and high concentration of iron (Fe), therefore, they have reduced capacity to scavenge ROS, being also very susceptible to OS [27].

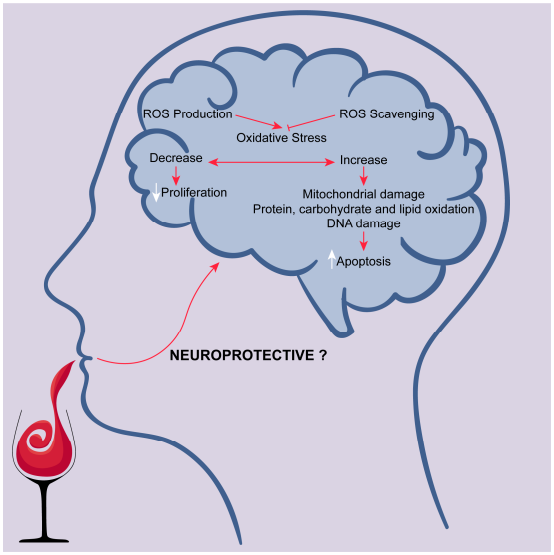

Figure 3. Oxidative stress in neurodegenerative diseases. ROS—reactive oxygen species.

2.1. Targeting Aβ Protein

2.1.1. Modulation of *Secretase Enzymes*

α-Secretase

Cleavage of APP first occurs through the activation of α-secretase or BACE 1. In the first case, it facilitates proteolysis of APP in a non-amyloidogenic pathway and prevents Aβ formation. α-Secretase activation, therefore, is a distinct and a potential therapeutic approach to decrease Aβ generation [28]. Proteases with proposed α-secretase function belong to the ADAM ("a disintegrin and metalloproteinase domain") family of proteins that include ADAM9, ADAM10 and ADAM17 [29]. All compounds considered for AD must cross the blood–brain–barrier and the plasma membrane [30]. The molecular weight of resveratrol is 228 Da, and therefore has emerged as a potential candidate since its secondary metabolites have lower molecular weight and higher lipophilicity [31]. A diet enriched with resveratrol (1g/Kg) was reported to activate α-secretase by increasing ADAM10 development expression through sirtuin 1 (SIRT1) modulation in SAMP8 mice (senescence-accelerated mice-prone) [32] and in triple transgenic AD mouse model (3xTg-AD) (Figure 4) [33]. α-Secretase activity was also elevated in the brain of mice treated with 6% Cabernet Sauvignon compared to ethanol-treated control Tg2576 mice (model AD-type Aβ neuropathology) or in primary neurons obtained from those mice (Figure 4) [34]. Similar results were also observed in SH-SY5Y cells stably overexpressing the Swedish (APPSwe) mutation when treated with 25–100 nM quercetin [35] or in primary cortical neurons treated with 1–10 μM myricetin (Figure 4) [36] In addition to flavonoids, hydroxycinnamate compounds such as caffeic acid (25 μM) and/or their derivatives (e.g., caffeic acid phenethyl ester) (30 μM) have been reported to activate α-secretase (ADAM-10) in acrolein treated mouse hippocampal HT22 cells, (Figure 4) [37]. However, 3-months treatment with ferulic acid (30 mg/kg) failed to reduce such activity in 12-month old presenilin-amyloid β-protein precursor (PSAPP) transgenic mice [38].

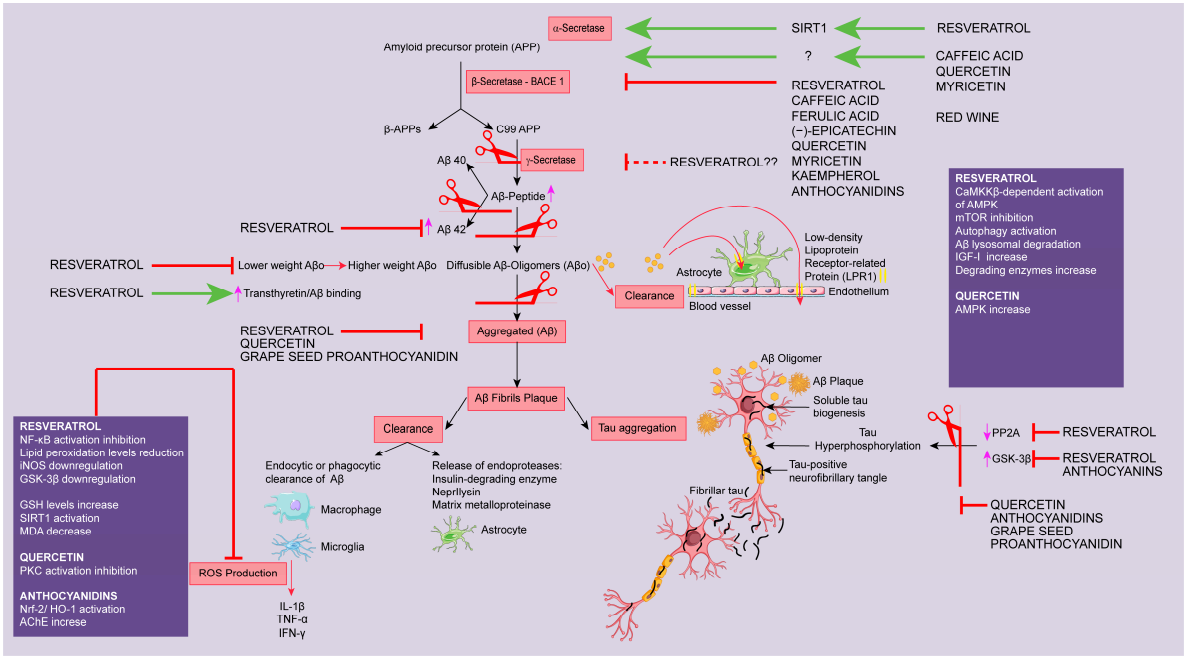

Figure 4. Effects of wine polyphenols on signaling pathways involved in Alzheimer's disease pathology.

β-Secretase

AD mechanisms analysis (Figure 2) clearly highlights the therapeutic importance of blocking BACE 1 activity to decrease Aβ accumulation. Five resveratrol oligomers isolated from the stembark extract of *Vitis vinifera* [39] along with eleven resveratrol oligomers, isolated from the seed extract of *Paeonia lactiflora* (Paeoniaceae) [40], were reported to inhibit baculovirus-expressed BACE 1 activity in a dose dependent manner. Such activity was recently confirmed in a homogeneous time-resolved fluorescence (TRF) assay [41], showing an inhibitory activity with an IC50 of 28 mM. Similarly, gnetin C, a resveratrol dimer (5–100 μM), was reported to suppress BACE 1 expression in SH-SY5Y cells, to reduce Aβ42 production and to ameliorate Aβ42-lowered cell viability [42]. Similarly, miyabenol C, a resveratrol trimer (5–20 μM), inhibited BACE1 and reduced Aβ generation in vitro (SH-SY5Y cells and mouse neuroblastoma N2a naive cells, N2aWT) [43]. In vitro studies also suggest that flavonoids may also inhibit BACE 1 activity. For example, the flavanol (−)-epicatechin (100 nM) [44], the flavanols myricetin [36,45–47], quercetin [45,48] and kaempherol (20 μM) [45], all directly inhibited BACE 1 enzymatic activity in a concentration dependent manner (Figure 4). Amin et al. [49], used SH-SY5Y cell lines treated with Aβ1–42, to estimate the biological activity and neuroprotective effect of anthocyanin loaded nanoparticles (An-NPs). The authors suggest that An-NPs are more active and potent than anthocyanin alone as it decreases the level of basic proteins associated with AD such as APP and BACE 1. The inhibitory effect on Aβ-induced activation of BACE 1 was also demonstrated for anthocyanins (malvidin and oenin; 50 μM) in an in vitro study with Neuro2a cell line (Figure 4) [50].

A reduced number of in vivo assays has been carried out with flavonoids to explore their potential as BACE 1 inhibitors. The increase of mice neuronal resistance to age related disease effect of quercetin is explained by its BACE 1 inhibitory effect, suggesting negative regulation of APP amyloidogenesis in old mouse brain (Figure 4) [51]. In a different study, however, quercetin supplementation had no effect on BACE 1 mRNA expression [52]. The experimental design of these studies was very different and may explain the different outcomes. In the former, 16-month-old male C57BL6 strain mice were fed with high-cholesterol diet supplemented with quercetin. In the latter, female C57BL6 mice were fed quercetin-enriched diets (2 mg/g diet) for 6 weeks. Age, gender and diet regimen may explain, at least partially, the differences obtained. More studies are needed to clarify whether BACE 1 can be a molecular target for quercetin (Figure 4).

In addition to flavonoids, some studies have been carried out with both stilbenes and hydroxycinnamates. For example, SAMP8 mice fed with a diet supplemented with 1 g/Kg of trans-resveratrol, from 2 until 9 months of age, showed no alterations in the pro-amyloidogenic BACE 1 enzyme quantified by Western Blot [32], although a decrease in BACE 1 protein expression was observed in the hippocampus of those mice when subjected to a combined intervention of resveratrol (0.03%) and vitamin D (500 IU) [53]. In a recent study, wild type littermates (NoTg) and AD transgenic (3xTg-AD) experimental groups were fed a diet supplemented with 100 mg/kg of trans-resveratrol from 2 months of age for 10 months. Resveratrol treatment protected against memory loss and brain pathology in 3xTg-AD mice and induced cognitive enhancement in healthy wild type mice, an observation that might be related to the modulation of BACE1 [33]. Furthermore, the hydroxycinnamic acid, caffeic acid conjugated to chito-oligosaccharides has the potential to be used as BACE 1 inhibitors to reduce the risk of AD [54]. A combination of caffeic acid/caffeic acid phenethyl ester can also restore acrolein-induced BACE 1 changes in HT22 mouse hippocampal cells [37]. However, ferulic acid (30 mg/kg) had no effect on BACE 1 activity when one-year-old mice with established β-amyloid plaques received daily doses of this non-flavonoid compound [38]. These results disagree with previous data obtained by the same research group, where the administration of the equal amount of ferulic acid inhibited amyloidogenic APP metabolism by reducing BACE 1 expression and β-secretase activity in PSAPP mice [55]. The discrepancy between results could be related with the differences in mice age and treatment duration, which were higher in the latter study.

γ-Secretase

Modulation of γ-secretase can also be a preventive/therapeutic strategy. Resveratrol (0–20 μM), oxy-resveratrol (0–80 μM), and piceatannol (0–20 μM) all decreased γ-secretase processing activity at higher doses in Neuro2a cells [56]. Resveratrol (60 μM) also inhibited γ-secretase activity in autophagy-deteriorated cells [57]. However, Marambaud et al. (2005) using HEK293 cells stably transfected with human APP695 cell line concluded that resveratrol (40 μM) does not inhibit Aβ production, partly because it has no effect on the Aβ-producing enzymes β- and γ-secretases [58].

2.1.2. Targeting Amyloid Clearance

According to the amyloid cascade hypothesis, one of the reasons for Aβo accumulation in the brain is related to the impairment of the clearance mechanisms (Figure 2). These pathways can therefore be targeted as potential preventive/treatments strategies for AD. The neuroprotective mechanism, however, remain unclear with only the activation of AMP-activated protein kinase (AMPK) signaling being proposed as one of the signaling pathways. For example, resveratrol activates AMPK by increasing cytosolic Ca^{2+} levels and by promoting $Ca^{2+/}$ Ca^{2+}-calmodulin-dependent protein kinase kinase-β (CaMKKβ) dependent phosphorylation of AMPK. Furthermore, resveratrol reduces Aβ accumulation by activating autophagy and by facilitating the lysosomal degradation of Aβ (Figure 4) [59]. Insulin-like growth factor-I (IGF-I) stimulates β-amyloid release from neurons and promotes brain amyloid clearance (Figure 4) [60]. Resveratrol (20 mg/L) increases hippocampal IGF-I production, thereby improving cognitive function in mice, probably due to an increase in amyloid clearance [61]. Resveratrol (0–20 μM) also induces autophagy in PC12 cells, a process partially mediated through the activation of the tyrosyl transferRNA (tRNA) synthetase (TyrRS)-auto-poly-ADP-ribosylation of poly (ADP-ribose) polymerase 1 (PARP1)-SIRT1 signaling pathway [62]. The flavanol quercetin (20–40 kg/kg) also increases AMPK activity in the APPswe/PS1dE9 transgenic mouse model of AD and, therefore, promotes the clearance of intracellular Aβ (Figure 4) [63].

Increasing the levels of degrading enzymes has been studied as a therapeutic possibility. Resveratrol (0–40 μM) promotes the intracellular degradation of Aβ in cell lines by a mechanism that implicates the proteasome [58]. In an in vivo AD model of *Caenorhabditis elegans* resveratrol (100 μM) increases the degradation of aged proteins by autophagosomal and proteasomal degradation [64]. Diet supplementation with resveratrol (1 g/kg) promotes an increase in neprilysin levels, one of the most important amyloid-degrading enzymes, in both 3xTg-AD and healthy wild type mice. In this study, and for the first time in vivo, it was also shown that resveratrol promotes enhancement of ubiquitin-proteasome system (UPS), which leads to a reduction of aberrant amyloid and tau proteins. Taken together these results show that resveratrol has a potential in AD prevention by increasing brain resilience against aberrant proteins (Figure 4) [33].

2.1.3. Targeting Amyloid Aggregation

AD is characterised by aggregation of Aβ monomer into multimeric aggregates (Figure 2). Resveratrol has direct effects in Aβ aggregation, both by preventing conversion of lower to higher molecular weight oligomers [65] but also by disrupting Aβ aggregates (Figure 4) [66]. Resveratrol and its glucoside are specific potent inhibitors of Aβ aggregation [67]. Resveratrol inhibits Aβ42 fibril formation in a dose-dependent way but could not prevent Aβ42 oligomerization [68]. Inhibition of Aβ42 fibril formation could be explained by ability of resveratrol to directly bind to monomer and fibril Aβ, as determined by surface plasmon resonance, thioflavin T fluorometric analysis, proton nuclear magnetic resonance, and atomic force microscopy in vitro [69]. The result is the conversion of soluble oligomers, fibrillar intermediates and amyloid fibrils to non-toxic high molecular weight conformation [70]. Moreover, resveratrol can indirectly prevent Aβ aggregation, through improvement of the binding of transthyretin to Aβ oligomers (Figure 4) [71].

In addition to resveratrol, a naturally derived grape seed polyphenolic extract (200 mg/kg/d) inhibits amyloid β-protein aggregation into high-molecular-weight oligomers in vitro. When orally administered to Tg2576 mice, this polyphenolic preparation attenuates AD-type cognitive deterioration coincidentally with reduced high-molecular-weight soluble oligomeric Aβ in the brain [72]. Furthermore, experiments carried out with quercetin (200 μM) show a potent Aβ42 anti-aggregation activity (75.4%) in combined in vitro cell-based/in silico assay approaches [73]. Such data were further confirmed where treatment with quercetin (25 mg/kg) for three months decreased β-amyloidosis in aged 3xTg-AD mice [74]. Furthermore, polyphenolic metabolites identified in the rat brain are after oral dosage of Cabernet Sauvignon red wine were tested for potential AD benefits. It was observed that quercetin-3-*O*-glucuronide (0–5 μM) reduces the generation of Aβ peptides by primary neuron cultures generated from the Tg2576 AD mouse model. Another brain-targeted metabolite, malvidin-3-*O*-glucoside (0–50 μM), has no detectable effect on Aβ generation. Quercetin-3-*O*-glucuronide also interferes with the initial protein-protein interaction of Aβ1–40 and Aβ1–42, which is necessary for the formation of neurotoxic oligomeric Aβ species (Figure 4) [75]. Finally, a preclinical study demonstrated that grape seed proanthocyanidin (GSPA), which consists of catechin, epicatechin and epicatechin gallate, can interrupt the aggregation of neurotoxic Aβ (Figure 4) [76]. Altogether these data suggest that polyphenols may have the potential to reduce protein aggregation, a phenomenon important in AD progression.

2.2. Targeting Tau Protein

Neuroprotective effects of resveratrol also result from the inhibition of tau protein hyperphosphorylation, as it was observed in N2a cells exposed to formaldehyde. Inhibition of glycogen synthase kinase (GSK-3β) and calmodulin-dependent protein kinase II (CaMKII) or the activation of protein phosphatase-2A (PP2A) by resveratrol (2.5–50 μM) protect against the hyperphosphorylation and/or mediates the dephosphorylation of tau protein, respectively (Figure 4) [77]. Resveratrol also inhibits Na_3VO_4-induced hyperphosphorylation of tau at the Ser396 (p-S396-tau) site, which is upregulated in the hippocampus of AD brains and predominantly linked to AD-associated cognitive dysfunction [78].

Recently, the inhibitory effect of quercetin on okadaic acid (OA)-induced tau protein hyperphosphorylation in HT22 cells was also explored. Western blotting results indicated that quercetin attenuates OA-induced tau protein hyperphosphorylation at the Ser396, Ser199, Thr231 and Thr205 sites. Quercetin also inhibits the activity of cyclin-dependent kinase 5 (CDK5), a key enzyme in the regulation of tau protein, and blocks the Ca^{2+}-calpain-p25-CDK5 signaling pathway. These observations indicate the ability of quercetin to decrease tau protein hyperphosphorylation and thereby to attenuate the associated neuropathology (Figure 4) [79]. Anthocyanins were reported to activate the phosphorylation of anti-phosphorylated GSK3β at Ser 9, thereby possibly preventing GSK-3β-dependent tau hyperphosphorylation at Ser 413 and 404 [80]. GSPA is also able to decrease hyperphosphorylated tau deposition in APP/PS1 male heterozygous mice (Figure 4) [76].

In addition to flavonoids, the hydroxycinnamate caffeic acid (10–20 μg/mL) was reported to protect PC12 cells against Aβ-induced toxicity by decreasing tau phosphorylation through the reduction of GSK-3β activation [81].

2.3. Targeting Oxidative Stress

Resveratrol protects the nervous tissue by reducing ROS production and by affecting several mechanistic pathways. For example, resveratrol reduces OS in the brain by preventing nuclear factor-κB (NF-κB) activation (Figure 4) [82]. AMPK is a key protein in the regulation of cell survival in response to OS insults and resveratrol is a potent AMPK-activator, as shown in Neuro2a cells and primary neuronal in vitro as well as in the brain [83]. Resveratrol also activates SIRT1 in the hippocampus [84], neuronal cells [85], rat cortical primary neurons [86] and thus reduces OS. Different results were observed by Karuppagounder et al. (2009), and they suggested that dietary

supplementation with resveratrol protects against Aβ plaque formation and OS without activation of SIRT1 [87]. Resveratrol reduces both lipid peroxidation levels and OS induced by Aβ senile plaques in hippocampal neuronal cells (Figure 4) [88]. Inducible nitric oxide synthase (iNOS) mediates the Aβ-induced lipid peroxidation and HO-1 (heme oxygenase 1) expression, and resveratrol protects adult male rats from Aβ-induced neurotoxicity through the downregulation of iNOS (Figure 4) [89]. Induction of HO-1 by resveratrol is also observed in a dose- and time-dependent manner in cultured mouse cortical neuronal cells, revealing that resveratrol provides neuroprotection from free-radical or excitotoxicity damage [90]. Resveratrol also restores intracellular antioxidant enzymes such as GSH levels in a cell culture model [91,92] or reverses Aβ-induced malondialdehyde (MDA) overproduction derived from the lipid membrane oxidation, which reflect the overall degree of free radical attack (Figure 4) [89]. Resveratrol shows antioxidant proprieties, which may contribute to ameliorate the cognitive deficits and to attenuate oxidative damage in the brain of the SAMP8 mice through scavenging free radicals and modulating activities of antioxidant enzymes (Figure 4) [93]. As aforementioned resveratrol downregulates GSK-3β, a protein that induces OS [91]. Not only resveratrol but also the flavonoids quercetin and (+)-catechin protect hippocampal cells against toxicity induced by nitric oxide (NO). Quercetin can block sodium nitroprusside-stimulated protein kinase C (PKC) activation, pointing to a possible involvement of this enzyme in the protective effects mediated by quercetin (Figure 4) [94]. Recently, effects of solid lipid nanoparticle of quercetin in pentylenetetrazole (PTZ) induced cognitive impairment of *Danio rerio* species were evaluated. The administration of quercetin nanoparticles (5 and 10 mg/kg) ameliorate the PTZ exposure induces cognitive impairment, due to its potential anti-oxidative, anti-lipid peroxidative and acetylcholinesterase (AChE) inhibitory actions [95]. Epicatechin and myricetin, could inhibit neuronal death, through antioxidative mechanisms in cultured mouse cortical neurons (Figure 4) [96]. Anthocyanins (200 mg/kg) also attenuate memory deficits, protects against oxidative damage in the brain, and restore AChE and ion pump activity in a rat experimental model of sporadic dementia of Alzheimer's (Figure 4) [97]. Finally, caffeic acid protects PC12 cells against Aβ-induced toxicity through the inhibition of OS and the inhibition of intracellular Ca^{2+} levels [81].

3. Parkinson Disease (PD)

Parkinson disease is the second most common neurodegenerative dementia and the most common neurodegenerative movement disorder. It can be inherited, but most of the cases are sporadic, still both have selective loss of dopaminergic neurons in the substantia nigra that project to the basal ganglia. It is characterized by bradykinesia, tremor, rigidity and postural instability triggered by dopamine decrease [98]. Other regions of the central and peripheral nervous system could be involved and contribute to a range of non-motor symptoms like autonomic dysfunction, depression, and cognitive deficits [99]. Most of the PD cases show Lewy pathology consisting of Lewy bodies and Lewy neurites revealed by histological techniques. α-Synuclein (α-syn) is the major component of the Lewy body (Figure 5) [100]. Natural forms of α-syn protein are the monomeric and possibly tetrameric α-syn ones, which have a physiologic function. They regulate exocytosis and promote microtubule formation through interactions with tubulin. In PD, α-syn changes from its monomer arrangement to protofibrils, fibrils and oligomers, which are involved in toxic processes, protofibril and fibril structures, being probably the most toxic ones. Their production, truncation and maintenance are fundamental to PD pathology (Figure 5). Toxic effects of α-syn include mitochondrial dysfunction, endoplasmic reticulum (ER) stress, impaired proteostasis, enhanced neuroinflammation and pathological aggregation of other proteins [101]. Protein misfolding and aggregation, mitochondrial dysfunction, cell cycle reactivation, apoptosis and excitotoxicity contribute to OS occurrence in PD (Figure 5) [102]. Another oxidative scenario arises when the dopamine is degraded to eliminate cytosolic excess of this neurotransmitter after treatment. Dopamine is easily metabolized via the monoamine oxidase (MAO) or by auto-oxidation. MAO is in outer mitochondrial membrane in neuronal and glial cells and is able of degrade dopamine, which exacerbates degeneration of dopaminergic neurons. 6-Hydroxydopamine

(6-OHDA) and H_2O_2 are products of dopamine degradation by MAO, and contribute to an increase in ROS production and OS damage [103].

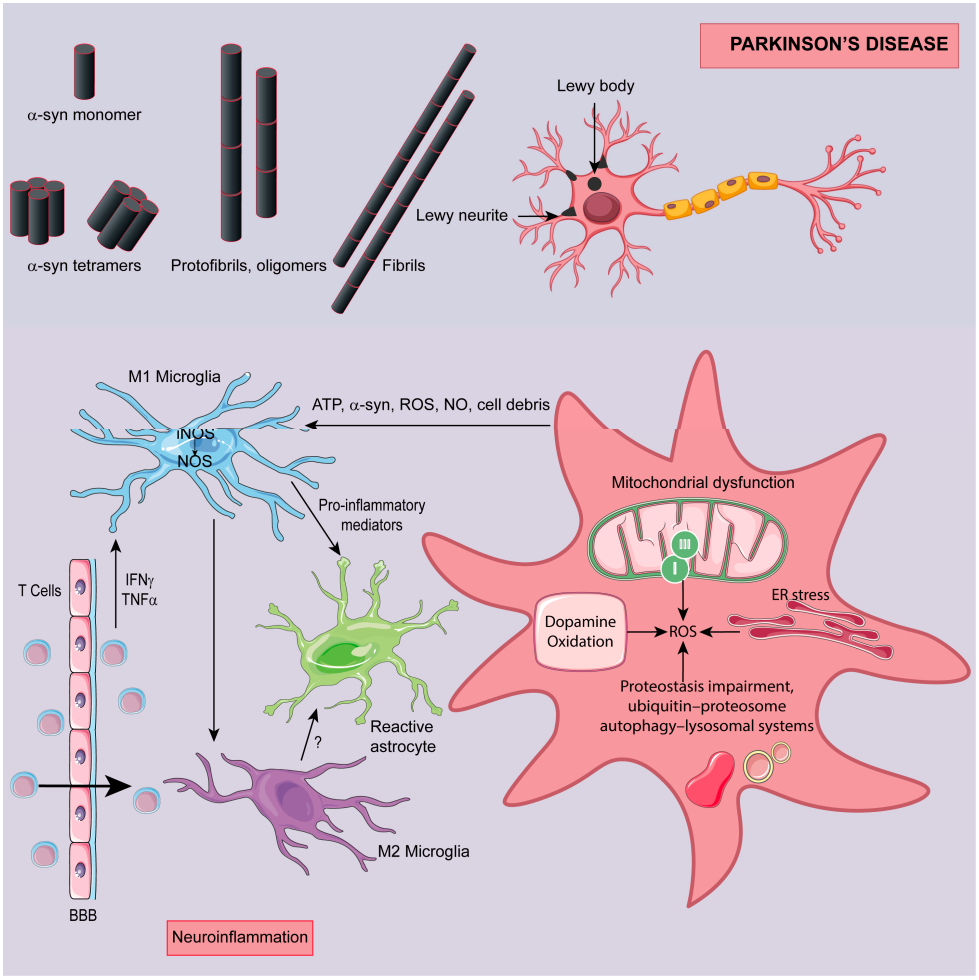

Figure 5. Diagrammatic representation of pathogenic mechanisms of Parkinson's disease. A-syn, alpha synuclein; BBB, blood brain barrier; ER stress, endoplasmic reticulum stress; iNOS, inducible nitric oxide synthetase; NO, nitric oxide; ROS, reactive oxygen species.

As in other neurodegenerative diseases, the mitochondrion plays a role in PD pathogenesis. Mitochondria are the primary source of ROS that may contribute to intracellular OS. The main sites of ROS production in mitochondria are complex I and to a smaller extent complex III in the ETC. The foremost process for ROS production in PD is complex I deficiencies, which is responsible for the majority of unfavorable neural apoptosis generation [104]. Briefly, ETC complex I deficiency, leads to ROS production, reducing levels of the GSH, which induces mitochondrial permeability by transiently opening a pore. Subsequently occurs the depolarization of the mitochondrial membrane potential (Figure 5). These events ultimately lead to neural cell death via the release of pro-apoptotic mitochondrial proteins, including cytochrome c and apoptosis-initiating factor [105].

Neuroinflammation is a characteristic of PD pathology, but it remains unknown whether neuroinflammation promotes or protects from neurodegeneration. Under pathological conditions, such as protein aggregation, gene mutations, environmental factors and cytokines released from infiltrated T cells and microglia become activated and release pro-inflammatory mediators. The latter activate astrocytes, leading to elevated production of proinflammatory factors, NO, $O_2^{\bullet -}$, contributing to degeneration of dopaminergic neurons (Figure 5). Degenerative neurons release molecules that can activate glia and increase inflammatory response. At certain stage of PD, a different microglia

subpopulation may become active releasing anti-inflammatory factors, including transforming growth factor beta (TGF-β), and exert a neuroprotective effect in PD (Figure 5) [106].

3.1. Targeting Dopaminergic Neurons Cytotoxicity

Pre-treating SH-SY5Y human neuroblastoma cells [107] and 6-OHDA rat models of PD with resveratrol (20 mg/kg) results in inhibition of dopamine cytotoxicity [108]. Resveratrol reduces intracellular OS in neurotypical SH-SY5Y, through recognized signal pathways of apoptosis. In fact, resveratrol pre-treatment led to a decrease in cleavage of PARP, an increase in the Bcl-2 protein, and activation of caspase-3 [107]. Rotenone is a popular pesticide that could produce 1-methyl-4-phenylpyridine (MPP+) and, consequently, can cause apoptosis in dopaminergic neurons [109]. Resveratrol shows concentration-dependent neuroprotective effects against sodium azide and thrombin, a mitochondrial complex IV inhibitor and a microglia-activating agent, respectively. Moreover, SIRT inhibitors such as nicotinamide and sirtinol, do not attenuate the protective effect of resveratrol against MPP^+ cytotoxicity [110]. Resveratrol also alleviates MPP^+-induce cytotoxicity and restored MPP^+-induced mitochondrial dysfunction in SN4741 cells. These results suggest that resveratrol attenuates MPP^+-induced mitochondrial dysfunction and cell apoptosis, which may be achieved through AKT/GSK-3β pathway [111].

Resveratrol (0–50 μM) also protects PC12 cells from 6-OHDA-induced OS and apoptosis via C-X-C chemokine receptor type 4 (CXCR4) signaling pathway [112]. CXCR4 is a common and highly conserved G-protein-coupled receptor (GPCR) with seven transmembrane domains and is a receptor for receptor for CXCL12 that can promote neuronal apoptosis [113]. CXCL12/CXCR4 may be involved in PD occurrence and could be a molecular target for PD [114]. Resveratrol (20 μM) protects SH-SY5Y cells against rotenone-induced neuronal apoptosis, inducing HO-1 expression and preventing dopaminergic cell death by regulating autophagic flux [115]. *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine (MNNG) is a DNA alkylating agent that causes neurotoxicity. Resveratrol (0–100 μM) suppresses MNNG-induced increase in acetylation of p53, a representative target of SIRT deacetylase activity, in midbrain slice culture [110]. Resveratrol (50 μM) inhibits 6-OHDA-induced toxicity and increased the expression of SIRT1 in PC12 cells [116]. Recently, it was observed that resveratrol (0–50 μM) reduces rotenone induced neuronal damage in PC12 cells, and it was suggested that SIRT1/Akt1 (Akt1, serine/threonine-protein kinase) signaling pathway play an essential role in this process [117]. Resveratrol (20 mg/Kg) also activates PGC-1α in dopaminergic cells via the deacetylase SIRT1, and enhanced PGC-1α gene transcription with increases in superoxide dismutase 2 (SOD2) and Trx2 in the MPTP mouse model of Parkinson's disease [118]. Ferretta et al. (2014) tested in vitro the effect of resveratrol treatment on primary fibroblast cultures from two patients with early-onset PD linked to different Park2 mutations. The authors suggested SIRT1/AMPK/PGC1-α axis as a key neuroprotective pathway [119]. On PD cellular models, resveratrol has neuroprotective effects mediated through activation of the AMPK-SIRT1-autophagy pathway [120]. As suggested by in vitro evidences, activation of SIRT1 could explain the improvement both the motor deficits and pathological changes of PD in mice. It was suggested that activation of SIRT1, led to LC3 deacetylation mediated autophagic degradation of α-syn [121]. In a different in vivo study, resveratrol improved rat's movement and spatial memory performance by rescuing the reduction of SIRT1 expression and CREB phosphorylation induced by Aβ1-42 [114]. Together, these results indicate that neuroprotective actions of resveratrol against different type of insults is related to SIRT-activating potential.

Quercetin can successfully activate PKD1, the gene that encodes the polycystin 1 protein, pro-survival signaling in dopaminergic cells. Quercetin also induces Akt and CREB phosphorylation and brain-derived neurotrophic factor BDNF expression. Therefore, PKD1/CREB/BDNF axis may at least partially mediate the neuroprotective effects of quercetin. Quercetin treatment increases mitochondrial biogenesis in dopaminergic neurons. Importantly, quercetin protects against dopaminergic neurodegeneration in the MitoPark transgenic mouse model of PD, an animal model of PD with impaired respiratory chain function in dopaminergic neurons [122]. Quercetin binds covalently with α-syn in 1

to 1 ratio. The formed quercetin-α-syn adducts attach to the α-syn oligomers or monomers, increasing the surface hydrophilicity and inhibiting the further fibrillation [123]. Also, caffeic acid proved to be an efficient inhibitor against α-syn fibrillation [124]. Gallic acid inhibits α-syn fibrillation and toxicity by stabilizing the non-toxic oligomeric structure of α-syn through oligomer binding [125].

Pure polyphenols such as gallic acid, ferulic acid, caffeic acid, coumaric acid, propyl gallate, epicatechin, epigallocatechin, and epigallocatechin gallate protect, rescue and, most importantly, restore the impaired movement activity (i.e., climbing capability) induced by paraquat in Drosophila melanogaster, a valid model of PD [126]. Interestingly, ferulic acid and exercise seem to improve the motor performance in a PD rodent model which might be due to the upregulation of Hsp70 and increasing density of dopaminergic neurons in the corpus striatum. Ferulic acid offers more protective effects than exercise and combination of both did not offer more protection than ferulic acid alone [127].

3.2. Targeting Oxidative Stress

As previously mentioned, resveratrol is a very promising antioxidant, therefore several in vitro and in vivo experiments have been carried out to evaluate its potential to ameliorate PD. In neuronal-like cells expressing mutant huntingtin from dopamine toxicity, resveratrol (100 μM) prevents the generation of ROS and restores the level of ATG4, a redox-sensitive autophagy protein that plays a pivotal role in autophagosome formation [128]. Resveratrol also prevents the decrease of dopaminergic neurons and the increase of propidium iodide uptake into midbrain slices induced by an MPP^+. In addition, resveratrol was reported to block the accumulation of ROS, the depletion of cellular GSH, and the cellular oxidative damage induced by MPP^+, suggesting the involvement of antioxidative properties in the neuroprotective action of this stilbene [110]. A botanical extract (Regrapex-R®, Interpharma Praha, a.s, Modrany, Czech Republic) prepared from whole grape (*Vitis vinifera*) and *Polygonum cuspidatum*, which contains polyphenols, including flavans, anthocyanins, emodin, and resveratrol, exhibit dose-dependent scavenging effects on ROS. Extract inhibits ROS and protein carbonyl production and protects enzyme activities of ETC (complexes I and II) and pyruvate dehydrogenase in isolated rat liver mitochondria following exposure to 2,2′-azobis (2-amidino propane) dihydrocholoride (AAPH), a potent lipid oxidant generator. The polyphenolic mixture also protects human neuroblastoma cells (SKN-MC) against AAPH induced oxidation by maintaining cell viability and inhibiting excessive ROS generation. In transgenic Drosophila expressing human α-syn, model for PD, the botanical extract improves climbing ability and extends females lifespan [129].

Resveratrol (20 mg/Kg) ameliorates 6-OHDA-induced rat brain injury [108], upregulating the antioxidant status [108], and suppressing overexpression's of cyclooxygenase-2 (COX-2), TNF-α mRNA and protein in the substantia nigra [130]. Resveratrol also mediates anti-inflammatory activities by suppressing the activity of NADPH oxidase and, further, decreasing ROS production and inhibiting the activation of mitogen activated protein kinases (MAPKs) and NF-κB cascade signaling pathways, as it was shown in lipopolysaccharide (LPS)-induced dopamine neurons [131]. Resveratrol shows potential therapeutic capacity for rotenone-induced PD in rats through inhibiting endoplasmic reticulum stress-mediated apoptosis. Resveratrol also restores redox balance as evident by suppressing xanthine oxidase activity and protein carbonyls formation; in addition to preservation of intracellular antioxidants status via activating glutathione peroxidase (GPx) and Nrf2 signaling pathway [132]. Resveratrol has neuroprotective effects, through free radical scavenging, in animals in which PD is induced with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) [133–135]. Resveratrol administration protects mice from MPTP-induced motor coordination impairment, hydroxyl radical overloading, and neuronal loss [134]. Reverses in toxic effects of MPTP were posteriorly confirmed in study with mice, intraperitoneal injected with MPTP (50 mg/kg body weight). It was observed that, resveratrol increases the levels of dopamine, its metabolites, GSH and GPx activities and reduces levels of thiobarbituric acid reactive substances (TBARS), catalase and SOD activities and enhances behavior performance [135].

Quercetin has a dual effect against the 6-OHDA-induced ROS formation in catecholaminergic SH-SY5Y neuroblastoma cells. Small concentrations of quercetin gave some protection, but at high concentrations this protective effect is reduced, or even enhanced toxicity occur [136]. The dual effect of quercetin was observed in other studies using the same [137] and a different in vitro model [138]. Quercetin protection and toxicity effects can be described in a time-based manner. At earlier exposure times, quercetin has strong protection against 6-OHDA-induced cell death in SH-SY5Y cells. In contrast, after a prolonged treatment quercetin do not protect against 6-OHDA toxicity [137]. Also, both quercetin aglycone and quercetin 3-*O*-β-d-glucuronide suppress the production of H_2O_2 by scavenging $O_2^{\bullet-}$ derived from 6-OHDA in a neuro-2a cell culture system. According with this conjugated quercetin metabolites could scavenge ROS generated from dopamine metabolism, however, their deconjugation to quercetin aglycone is essential to exert protective effects against the neuronal cell death induced by ROS. Re-conjugation is also needed to avoid the inherent cytotoxicity of quercetin aglycone [139]. Moreover, quercetin protects SH-SY5Y cells in which neurotoxicity was induced by lipopolysaccharide plus interferon-γ or interferon-γ released from activated microglia and astrocytes. Quercetin can reduce oxidative/nitrative damage to DNA as well as to the lipids, and proteins of SH-SY5Y cells. Quercetin also increases GSH concentration in SH-SY5Y cells [140]. In a study carried out by Ahn and Jeon (2015), quercetin pre-treatment increased α-syn expression in PC12 cells treated with various toxins. Knocking out α-syn, however, exerted no significant effect on cell survival. This could mean that quercetin is neuroprotective against toxic agents via affecting various mechanisms such as apoptosis, autophagy and aggresome [141].

Regarding quercetin, inconsistent results were observed in vivo, some studies suggest that quercetin has no neuroprotective effect in vivo using 6-OHDA rat models of PD [136,142], while others suggest that quercetin protects striatal dopaminergic neurons against 6-OHDA-induced OS in the rat [143]. Pre-treatment with quercetin has no effects on the number of hydroxylase (TH)-positive cells in the substantia nigra and on dopamine content in the striata [142]. Results from an in vitro and in vivo study revealed a dose-dependency of quercetin effect. Quercetin displays a clear falling of protection at higher concentrations in both viability and caspase-3 like activity in cell cultures and to some extent also in circling behavior in lesioned rats. This dose-dependency of quercetin effect occurs in a thinner range of concentrations, since cytotoxic effects of quercetin begin to take place at concentration only twofold higher than the one that provides the greatest protection [137]. In a posterior study, it was described that quercetin mitigates the loss of complex-I activity induced by rotenone in rats and enhances antioxidant enzyme activity [144]. Using the same animal model of PD, El-Horany et al. (2016) showed that quercetin attenuates rotenone-induced behavioral impairment, increases autophagy, ameliorates endoplasmic reticulum stress-induced apoptosis with attenuated OS [145]. From the current study, quercetin can act as an autophagy enhancer in PD rat model and modulates the microenvironment that leads to neuronal death. Combined strategies could be a better approach as suggested by Haleagrahara et al. (2013) after evaluating the combined treatment with quercetin and desferrioxamine on 6-OHDA-induced neurotoxicity in the striatum of rats. They observed that combined treatment has a more powerful effect in protecting the neurons and increasing the antioxidant enzymes in the striatum [146]. The combination of quercetin with other neuroprotector compounds have been suggested as a therapeutic advantage in the prevention/treatment of OS-mediated neurodegenerative conditions such as PD [147–149].

Organic and aqueous Champagne wine extracts exhibit potent neuroprotective activity against peroxynitrite-induced injury at low concentrations (0.1 μg/mL). Results suggest that neuroprotective effect against oxidative neuronal injury is in part due to the cellular actions of individual components found in the organic extracts, particularly tyrosol, caffeic acid, and gallic acid [150]. Neuroprotective effects of tyrosol, caffeic acid, gallic acid, p-coumaric acid, (+)-catechin, (−)-epicatechin and quercetin (0.1–50 μM) and organic champagne extract against CysDA-induced neuronal injury were evaluated in posterior studies, that showed that hydroxycinnamates, phenolic acids and phenolic alcohols induce neuroprotective effects, which are more powerful than that observed for flavonoids [138,151].

Gallic acid has neuroprotective activity against 6-OHDA-induced OS via enhancement of cerebral antioxidant defense, by increasing total thiol and GPx contents and decreasing MDA levels in the rat hippocampus and striatum tissues [152]. Catechin treatment restores GSH levels, and increases dopamine and 3,4-dihydroxyphenylacetic acid content, and tyrosine hydroxylase -immunoreactivity in 6-OHDA-lesioned rats [153]. Kaempferol also shows neuroprotective effects in MPTP-induced PD mice, by scavenging ROS, which results in the survival of more dopamine neurons [154].

4. Conclusions

Epidemiological studies suggest that moderate consumption of wine, an element of the Mediterranean diet, is one of the main factors behind the neuroprotective effects observed in some populations [7,155–158]. Most of the in vivo and in vitro studies evaluated wine neuroprotection indirectly by analyzing effects of the phenolic compounds of wine, mainly resveratrol. Nonetheless, much of the data obtained on their bioactivity derived from short term basis in vitro or in vivo studies where the dose used were not of nutritional relevance and unlikely achievable through moderate wine drinking. Although at the moment, the balance of evidence does suggest that polyphenol effects contribute to the benefits of a high intake of fruits and vegetables, the extent of their contribution in vivo and at physiological relevant concentrations remains uncertain. More work needs to be done to prove whether this class of compounds is most likely to result in health benefits and to determine their beneficial effects in slowly developing neurodegenerative disorders. These studies remain however fundamental to understand the effects of those compounds in the brain; to highlight that wine is a complex chemical mixture. Analysis of the literature led us to hypothesize that preventive/therapeutic efficacy of wine is more likely due to a combination of neuroprotective effects of wine phenolic compounds. Combined complementary and perhaps synergistic effects could explain the benefits of wine moderate consumption. In fact, the hypothesis that wine could be compared to combined and multi-target therapeutic strategies could explain that drinking lower doses on a "chronic" manner reduces brain damage. It is also very important to continue studying the effects of phenolic metabolites, however, a focus on gut microbiota derived phenolic acids and other metabolites should be addressed. Differences observed among populations in epidemiologic studies could be, in our opinion, attributed to differences in the gut microbiota composition since they are affected by diet. The type and quantity of metabolites produced after a meal will differ according with gut microbiota. In conclusion, wine is a complex mixture which is effective to prevent or slow age-related neurodegenerative diseases because can modulate multiple targets simultaneously involved in these diseases.

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