Neuroprotective Mechanisms of Resveratrol in Alzheimer’s Disease: Role of SIRT1

Bruno Alexandre Quadros Gomes, João Paulo Bastos Silva, Camila Fernanda Rodrigues Romeiro, Sávio Monteiro dos Santos, Caroline Azulay Rodrigues, Prícula Rodrigues Gonçalves, Joni Tetsuo Sakai, Paulo Fernando Santos Mendes, Everton Luiz Pompeu Varela, and Marta Chagas Monteiro

1Neuroscience and Cell Biology Graduate Program, Institute of Biological Sciences, Federal University of Pará, Belém, Pará, Brazil
2Faculty of Pharmacy, Institute of Health Sciences, Federal University of Pará, Belém, Pará, Brazil
3Pharmaceutical Sciences Graduate Program, Institute of Health Sciences, Federal University of Pará, Belém, Pará, Brazil

Correspondence should be addressed to Marta Chagas Monteiro; martachagas2@yahoo.com.br

Received 5 March 2018; Revised 21 July 2018; Accepted 15 August 2018; Published 30 October 2018

Alzheimer’s disease (AD) is a progressive and neurodegenerative disorder of the cortex and hippocampus, which eventually leads to cognitive impairment. Although the etiology of AD remains unclear, the presence of β-amyloid (Aβ) peptides in these learning and memory regions is a hallmark of AD. Therefore, the inhibition of Aβ peptide aggregation has been considered the primary therapeutic strategy for AD treatment. Many studies have shown that resveratrol has antioxidant, anti-inflammatory, and neuroprotective properties and can decrease the toxicity and aggregation of Aβ peptides in the hippocampus of AD patients, promote neurogenesis, and prevent hippocampal damage. In addition, the antioxidant activity of resveratrol plays an important role in neuronal differentiation through the activation of silent information regulator-1 (SIRT1). SIRT1 plays a vital role in the growth and differentiation of neurons and prevents the apoptotic death of these neurons by deacetylating and repressing p53 activity; however, the exact mechanisms remain unclear. Resveratrol also has anti-inflammatory effects as it suppresses M1 microglia activation, which is involved in the initiation of neurodegeneration, and promotes Th2 responses by increasing anti-inflammatory cytokines and SIRT1 expression. This review will focus on the antioxidant and anti-inflammatory neuroprotective effects of resveratrol, specifically on its role in SIRT1 and the association with AD pathophysiology.

11. Introduction

Alzheimer’s disease (AD) is a neurodegenerative pathology that causes impaired cognitive functioning and memory [1, 2]. Despite the disease being identified over 100 years ago [3], efforts are currently being expended to discover new chemical products (i.e., natural antioxidants) that act at determined points to block the progression of the disease [4, 5]. Resveratrol has been considered as a protector compound for the treatment of neurodegenerative diseases (i.e., AD, Parkinson disease, and amyotrophic lateral sclerosis) that have high levels of oxidative damage due to its antioxidant and anti-inflammatory properties [6]. Moreover, this compound can also modulate different molecular pathways dependent on silent information regulator-1 (SIRT1) in neurodegenerative diseases [6]. However, recent reviews also report other multipathways that are involved in the neuroprotective mechanisms of resveratrol such as inhibition of...
nuclear factor-κappa B (NF-κB) expression and alteration in the signaling pathways of mitogen-activated protein kinases (P38-MAPK), extracellular signal-regulated kinase 1/2 (ERK1/2) and phosphoinositide 3-kinase (PI3K)/Akt, activation of autophagy, among others [7–10].

Interest in resveratrol has grown recently due to its beneficial effects in several neurological and autoimmune disorders [11, 12]. Resveratrol is a polyphenol that mainly occurs in grapevine species (Vitis sp.) and other fruits, and attention has been drawn to it due to its versatile biological properties, including its antioxidant, anti-inflammatory, and neuroprotective activities [13–15]. In this sense, resveratrol could indirectly activate SIRT1 expression [16] and lead to neuroprotection in AD cases [17]. SIRT1 regulates the activity of several substrates, including p53 and peroxisome proliferator-activated receptor-gamma coactivator 1α (PGC-1α) [18], which decrease the accumulation of β-amyloid (Aβ) and improve mitochondrial dysfunction [19].

Some studies have shown that resveratrol improves the impaired learning and memory in neurodegenerative disease and protects the memory decline in AD through its antioxidant activity [20]. Resveratrol is also effective at preventing blood-brain barrier (BBB) impairment and inhibiting Aβ1–42 from crossing the BBB and accumulating in the hippocampus [21, 22]. The hippocampus is a critical brain component for cognitive and memory functions, is a region that displays ongoing neurogenesis in adulthood, and is a very sensitive area in AD [23–25]. However, a significant reduction in hippocampal neurodegeneration was observed after intracerebroventricular injection of resveratrol in an animal model, which was associated with a decrease in SIRT1 acetylation [26, 27].

Karuppagounder et al. [28] showed that mice treated with resveratrol for 45 days had reduced Aβ toxicity. This suggests that the onset of neurodegeneration may be delayed by dietary chemopreventive agents (i.e., resveratrol) that protect against Aβ formation and oxidative stress [28]. Wang et al. [29] recently showed that resveratrol protected neurons against Aβ1–42-induced disruption of spatial learning, memory, and synaptic plasticity and rescued the reduction of SIRT1 expression in hippocampal rats. Thus, resveratrol is effective at reducing central nervous system (CNS) damage and decreasing the ischemia and toxicity induced by Aβ peptide, showing its potential therapeutic use in neurodegenerative diseases [30].

One of the major neuroprotective mechanisms of resveratrol is the activation of SIRT1 that is expressed in the adult mammalian brain, predominantly in neurons [31]. Activation of SIRT1 by resveratrol prevents Aβ-induced microglial death and contributes to improved cognitive function [32]. Although the major mechanisms of resveratrol are associated with the overexpression of SIRT1, its subsequent neuroprotective effect remains unknown. However, the overexpression of SIRT1 plays an important role in neuronal protection as it regulates reactive oxygen species (ROS), nitric oxide (NO), proinflammatory cytokine production, and Aβ expression in the brains of AD patients [33–36]. This review discusses the neuroprotective effects of resveratrol that are dependent on its action on SIRT1 and its implications in AD.

### 2. Resveratrol Plant Biosynthesis and Pharmacokinetics

Resveratrol (3,5,4′-trihydroxy-trans-stilbene) is a polyphenol plant secondary metabolite that has a phytoalexin role in high plant species. This metabolite is commonly found in grapevines (Vitis vinifera), grape juice, and wine [37, 38]. Others food sources, including peanuts, pomegranate, spinach, and bananas, also contain high concentrations of resveratrol [39–43]. Table 1 shows the concentration of resveratrol in some food sources.

Resveratrol is synthesized in high plant species using the phenylpropanoid pathway under biotic and abiotic stress conditions (i.e., ultraviolet (UV) light radiation and tissue disruption) and in response to fungal infections (i.e., V. vinifera leaves infected by Plasmopara viticola) [44–46]. The biosynthesis of resveratrol begins with the generation of 4-coumaroyl-CoA units in the phenylpropanoid pathway [47]. At this point, stilbene synthase (STS) and chalcone synthase (CHS) enzymes promote the chain extension of 4-coumaroyl-CoA via the addition of three malonyl-CoA molecules to generate a polyketide compound (Figure 1). Despite both enzymes using the same substrate, STS possesses substantially more amino acids than CHS (the key enzyme in flavonoid biosynthesis), which explains the difference in the end products formed [48, 49].

The polyketide peptide suffers a fold that promotes the generation of aromatic rings in a Claisen-like reaction catalyzed by STS, which produces an unstable intermediate metabolite called stilbene-2-carboxylic acid [50, 51]. The final steps involve the stepwise reactions that promote the decarboxylation, dehydration, and enolization of stilbene-2-carboxylic acid to yield the resveratrol molecule [52]. Resveratrol can undergo other biochemical reactions to produce new stilbenes, including ε-viniferin, t-piceid, t-piceatannol, and t-pterostilbene [53].

Resveratrol is well absorbed but is quickly excreted, mainly by the urinary system [54]. Calliari et al. [55] reported that the pharmacokinetics of resveratrol have been studied in several organs and that its therapeutic effect is mainly dose dependent. After oral consumption, resveratrol is primarily metabolized by phase II enzymes, especially glucuronides and sulfatases, and absorbed in the small gut, predominantly in its glucuronidated form [12, 56]. In addition to the glucuronide metabolite, sulfated products of resveratrol are also commonly found in biological samples [57]; however, only trace amounts of free resveratrol can be detected in plasma [58]. In this regard, Sergides et al. [59] demonstrated higher plasma concentrations of glucuronidated (4083.9 ± 1704.4 ng/ml) and sulfated (1516.0 ± 639.0 ng/ml) resveratrol than its unmetabolized form (71.2 ± 42.4 ng/ml) following the consumption of a single resveratrol (500 mg) tablet in healthy volunteers. Resveratrol is mainly attained by dietary intake; however, there are some concerns regarding its low concentration in food sources and its poor oral bioavailability. This has highlighted the need for strategies that allow biologically active concentrations of resveratrol to reach its target tissues, including the brain [60]. In this regard,
Oliveira et al. [12] reported that the major problem of resveratrol treatment was its low bioavailability, with some human studies reporting that even high-dose resveratrol treatment (500 mg/day) produced low plasma concentrations (10–71.2 ng/ml) of this antioxidant.

The description of resveratrol concentrations in the brain is a challenge that remains to be overcome. Frozza et al. [61] reported that intravenous administration of resveratrol reached satisfactory target brain regions, while oral resveratrol treatment was not well absorbed and resulted in reduced
stability, increased photosensitivity, and accelerated metabolism, thus making it difficult to reach the brain. Turner et al. [62] showed that resveratrol and its metabolites crossed the human BBB, and these authors detected resveratrol in both the plasma and cerebrospinal fluid, thus showing its effects on the CNS. Preclinical data suggest that the main metabolite found in the rat brain after resveratrol consumption is resveratrol-3-glucuronic acid, which is also the main metabolite found in plasma [63]. To try to overcome the low oral bioavailability, several researchers focused on the microencapsulation technique or on the creation of prodrugs that, after metabolism, will give rise to resveratrol molecules [12, 64, 65]. Studies with new conjugated particles that improve the pharmacokinetics of resveratrol in the brain are of great importance, as the biologically active concentrations observed in in vitro experiments are much higher than those achieved after oral consumption are. Frozza et al. [61, 66] demonstrated that resveratrol nanoparticles reached the brain at higher concentrations than free resveratrol, resulting in increased bioavailability and possible neuroprotective effects. Resveratrol is considered a low-toxic substance, as humans have used several resveratrol-containing foods for a long time without related toxic effects. Data also confirm the safety of resveratrol on the basis of preclinical tests and clinical trials [67, 68].

Some studies have reported that resveratrol is an activator of SIRT1 [27, 69], although further evidence shows that resveratrol is not a direct activator of SIRT1 [70], and that its role may be related to the activation of substrates of SIRT1 [71]. The overexpression of SIRT1 results in neuroprotection in AD [17]. SIRT1 inhibits NF-κB signaling by decreasing Aβ-induced toxicity in primary mouse neuronal cultures [32]. SIRT1 may be capable of determining Aβ production by modulating β-secretase 1 expression through NF-κB signaling [32].

3. Role of SIRT1 in the Pathophysiology of AD

Oxidative stress and the overproduction of ROS are associated with the pathophysiology of neurodegenerative disorders, including AD, and lead to neural membrane injury and memory impairment [72–75]. Brain tissue is more susceptible to oxidative stress due to its high oxygen consumption rate, low regenerative capability, high polyunsaturated fatty acid content, and low concentration of antioxidants [76, 77]. ROS are major neurotoxic factors released by activated microglia and include superoxide radicals (O2
\(^{-}\)), hydroxyl radicals (OH), and hydrogen peroxide (H2O2). These molecules are highly reactive, and their excessive production can induce lipid peroxidation, (deoxyribonucleic acid) DNA fragmentation, and protein oxidation and result in further cell dysfunction and cell death [78]. Therefore, mitochondria that are damaged during oxidative stress can produce ROS that damage proteins, nucleic acids, and polyunsaturated fatty acid membranes and cause lipid peroxidation, a loss of membrane integrity, and increased calcium (Ca\(^{2+}\)) permeability. ROS also increase the production of Aβ peptides, which induce oxidative stress both in vitro and in vivo [79]. Thus, a vicious cycle between ROS and Aβ accumulation may accelerate the progression of AD [80]. Studies in vitro and in vivo have shown that ROS increases Aβ production and induces oxidative stress, thus leading to neuronal apoptosis and accelerating the progression of AD [80–82].

AD is a progressive neurodegenerative disorder of the cortex and hippocampus that eventually leads to cognitive impairment. Although the etiology of AD remains unclear, multiple cellular changes have been implicated, including the production and accumulation of Aβ peptides, tau phosphorylation, oxidative stress, mitochondrial dysfunction, synaptic damage, and biometal dyshomeostasis. The neuroinflammatory response via microglial activation and acetylcholine deficits are also considered to play significant roles in the pathophysiology of AD [83, 84]. The main pathogenic event in AD is the cerebral aggregation of Aβ peptides [85]. Aβ is the major constituent of plaques and is generated from amyloid precursor protein (APP) by the action of β and γ-secretases [86]. The accumulation of Aβ could initiate a series of downstream neurotoxic events that result in neuronal dysfunction in AD patients [87, 88]. However, oxidative stress is also an important event in the pathogenesis of AD [89], as the generation and accumulation of ROS and reactive nitrogen species can accelerate fibrillization, increase the toxicity of Aβ, and promote neuronal death and neurodegeneration [90–93].

Decreased sirtuin levels, mainly SIRT1 expression levels, were recently correlated with elevated Aβ production and deposition in AD patients [94]. SIRT1 may regulate Aβ metabolism through the modulation of APP processing, and loss of SIRT1 is closely associated with exacerbated Aβ production [95]. However, SIRT1 overexpression decreases Aβ production [95, 96], which may represent an interesting therapeutic approach to block the neurodegeneration and cognitive impairments caused by the disease. SIRT1 is a member of a sirtuin family that utilizes nicotinamide (NAD\(^{+}\)) as a substrate to catalyze the deacetylation of various substrates [97]. SIRT1 plays an essential role in regulating cellular homeostasis by influencing neuron survival, insulin sensitivity, glucose metabolism, and mitochondrial biogenesis [98, 99]. In the adult brain, SIRT1 was shown to be essential for synaptic plasticity, cognitive functions [100], and the modulation of learning and memory function [101].

During normal aging, SIRT1 is responsible for the maintenance of neural systems and behavior, including the modulation of synaptic plasticity and memory processes [102]. The absence of SIRT1 expression in hippocampal neurons is correlated with impaired cognitive abilities, including immediate memory, classical conditioning, and spatial learning [100]. SIRT1 can also increase PGC-1α activity, which leads to the inhibition of Aβ production and improved mitochondrial dysfunction [19]. SIRT1 can also deacetylate a large number of other substrates, including p53, NF-κB, and Forkhead box O (FOXO), and prevent neuronal apoptosis [103, 104]. Therefore, the pharmacological activation of SIRT1 may represent a promising approach to preventing Aβ deposition and neurodegeneration in AD [105]. Thus inhibiting ROS production may be an important tool for protecting neuronal cells from oxidative damage and a therapeutic
strategy in the treatment of neurological disorders [106]. Figure 2 summarizes the pathways by which resveratrol acts on SIRT1 in the pathology of Alzheimer’s disease.

3.1. Antioxidant Mechanisms of Resveratrol in AD: Role of SIRT1. Oxidative stress induces neuronal damage, modulates intracellular signaling, and leads to neuronal death by apoptosis or necrosis. Therefore, antioxidant products (i.e., resveratrol) are used to protect against neuronal damage in neurodegenerative disorders (i.e., AD) [80]. The antioxidant properties of resveratrol were reported in several studies, which demonstrated that chronic resveratrol treatment reduced the production of malondialdehyde and nitrite and restored glutathione (GSH) levels [107, 108]. Additional antioxidant mechanisms of resveratrol were also described and include SIRT1 activation, Aβ aggregation and toxicity inhibition, metal chelation, and ROS scavenging [106, 108, 109]. These results demonstrate that this compound is an effective therapeutic strategy for AD therapy. Therefore, resveratrol not only plays a role in ROS protection but it can also modulate important glial functions, including glutamate uptake activity, GSH, improved functional recovery, and decreased DNA fragmentation and apoptosis [110–112].

3.1.1. In Vitro Studies. Resveratrol can dysregulate the metal ion balance (i.e., copper, zinc, and iron) and play a key role in neurodegeneration, which is related to cellular function changes and neuronal survival dysfunction [27]. These metal ions are able to bind Aβ and neurofibrillary tangles and promote their aggregation [106, 109], enhance the production of ROS, and contribute to AD pathogenesis. Hou et al. [113] demonstrated the interaction between resveratrol and SIRT1 using molecular dynamics simulation. The authors proposed that resveratrol was responsible for enhancing the binding affinity between SIRT1 and the substrate, thus functioning as a binding stabilizer. Nevertheless, Dasgupta and Milbrandt show that resveratrol is a potent activator of AMP-activated protein kinase (AMPK) function, and resveratrol-mediated AMPK activation was independent of SIRT1 [114]. In addition, in cell lines, resveratrol presented a decrease in the acetylation of PGC-1α, possibly due to the activation of AMPK [115]. Thus, showing a dose-dependent effect, resveratrol was able to activate AMPK independently of SIRT1 [116]. However, SIRT1 plays a key role in protecting neurons from the oxidative effects of ROS, NO, and Aβ peptides in the brains of AD subjects [117].

3.1.2. Animal Studies. One neuroprotective property attributed to resveratrol is the suppression of ROS formation through the inhibition of prooxidative genes (i.e., nicotinamide adenine dinucleotide phosphate oxidase) [118]. Huang et al. [119] showed that the neuroprotective activity of resveratrol included the suppression of inducible nitric oxide synthase (iNOS) production, which is involved in

---

**Figure 2:** Main cellular routes proposed for the mechanisms of resveratrol in Alzheimer’s disease. Modified from Ma et al. [72].
Aβ-induced lipid peroxidation and heme oxygenase-1 down-regulation, thereby protecting the rats from Aβ-induced neurotoxicity [120]. Moreover, resveratrol induced the expression of various antioxidant enzymes, such as superoxide dismutase (SOD), catalase, thioredoxin, and glutathione peroxidase (GPx) [121, 122]. However, Lee et al. [123] showed that resveratrol possesses chelator-metal ion properties to attenuate the metal imbalance and ROS production [124]. Furthermore, the oral administration of resveratrol in mice lowered the Aβ accumulation in the cortex due to the activation of AMPK signaling by enhancing cytosolic Ca2+ levels in neuronal cultures [120, 125].

Other studies also showed the neuroprotective action of resveratrol in animal models; for example, Simão et al. [126] evaluated the response to a 7-day resveratrol treatment (30 mg/kg) on postinduced ischemia in rodent models. Cerebral immunohistochemistry showed reduced activation of astrocytes and microglia in the hippocampus and suppression of the inflammatory response mediated by NF-κB, cyclooxygenase 2 (COX-2), and nitric oxide synthetase (NOS) in hippocampal cells, thus suggesting the anti-inflammatory potential of resveratrol in brain damage. Moreover, Wang et al. [127] suggested that resveratrol (200 mg/kg/day for 8 weeks) could act as an AD-adjuvant therapy after human umbilical cord stem cell transplantation. This occurred due to the increased expression of brain-derived neurotrophic factor precursor (BDNF), neuronal growth factor (NGF), and neurotrophin 3 (NT-3), which are associated with neurogenesis, survival, learning, and memory. Thus, resveratrol positively stimulated these cell-protected factors [128]. The overexpression of these neurotrophic factors is related to the ability of resveratrol to increase the activity of SIRT1 [13]. Similarly, resveratrol also induced an increase of SIRT1 in a mice model [129]. Another study also reported the preventive action of resveratrol in decrease the formation of insoluble Aβ plaques in the hippocampus of rats [21], as the etiology of the disease is associated with an imbalance in Aβ homeostasis. Resveratrol effectively reduced the cleavage activation of APP and promoted peptide clearance [10]; therefore, the authors suggested that resveratrol was efficient at reducing the formation of protein aggregates.

3.1.3. Human Studies. There are currently studies evaluating the effectiveness of resveratrol in AD; for example, a randomized double-blind placebo-controlled study evaluated the effects of resveratrol in 64 AD patients with a mild form of the disease. A resveratrol dose of 500–1000 mg was administered orally to these patients. However, the results demonstrate that resveratrol and its major metabolites able to cross the BBB and cause weight loss and reactions such as nausea and diarrhea. In addition, brain volume loss was greater in the group receiving resveratrol. Conversely, Imamura et al. [130] demonstrated the antioxidant effect of resveratrol on arterial stiffness in patients with type 2 diabetes mellitus (T2DM). In this randomized double-blind placebo-controlled clinical trial, 50 patients were selected: 25 received resveratrol (100 mg/day) and 25 received a placebo for 12 weeks. Supplementation with resveratrol improved several parameters in the T2DM patients and decreased oxidative stress, which was evaluated through metabolites of reactive oxygen. Mansur et al. [131] also conducted a study to evaluate the effects of resveratrol in humans. Slightly overweight elderly individuals were randomly divided into two groups: group one received 250 mg of resveratrol orally twice daily, while group two received a caloric restriction diet (1000 cal/day). SIRT1 concentrations were determined in both groups at the end of the 30-day treatment period. The serum concentration of SIRT1 was increased in both groups; however, this finding was not correlated with a better profile of metabolic markers for atherosclerotic processes.

3.2. SIRT1 and Anti-Inflammatory Mechanisms of Resveratrol. Neuroinflammation is an important contributor to the pathogenesis of AD [132]. Various reports show that inflammatory responses occur in the CNS, including the activation of microglia, astrocytes, lymphocytes, and macrophages that trigger numerous proinflammatory mediators and neurotransmitters [133]. However, the hallmark of brain neuroinflammation is microglia activation, which releases highly proinflammatory cytokines, ROS, and NO and leads to protein oxidation, lipid peroxidation, DNA fragmentation, neuronal inflammation, and cell death [78, 134]. Microglial cells are the resident macrophage-like population within the CNS and are a prime component of the brain immune system. In physiological conditions, microglia actively survey the microenvironment and ensure normal CNS activity by secreting neurotrophic factors (i.e., NGF). Although microglial activation plays an important role in the phagocytosis of dead cells in the CNS, overactivated microglia cause inflammatory responses that lead to neuronal and axonal degeneration and disruption of the immature BBB [135].

Inflammatory mediators such as interleukin-1β (IL-1β), interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α), and NO are produced by activated microglia and have recently been linked to the pathogenesis of neurological disorders [136]. Therefore, pharmacological interference with the over-activation of microglia may have a therapeutic benefit in the treatment of inflammation-mediated neurological disorders [137]. The activities of resveratrol against neuroinflammation appear to target activated microglia and result in the reduction of proinflammatory factors (i.e., TNF-α, IL-1β, prostaglandin E2, cyclooxygenases, and iNOS through the modulation of signal transduction pathways) [138].

Gomez et al. [139] showed that aging increased the levels of TNF-α and led to chronic neuroinflammation in the hippocampus and impaired spatial learning and memory. However, chronic administration of resveratrol reversed the cognitive deficits and inhibited the production of inflammatory cytokines. In addition, resveratrol also inhibited the activation of signal transducer and activator of transcription (STAT1 and STAT3) and prevented the proinflammatory effect of Aβ and Aβ-triggered microglial activation [140]. However, the role of resveratrol in microglia activation and the molecular mechanisms involved are not fully elucidated. The major pathway seems to involve SIRT1 activation, which promotes Th2 responses by increasing
anti-inflammatory cytokine expression and upregulating PGC-1α (Figure 3) [141, 142].

3.2.1. In Vitro Studies. Resveratrol has numerous functions in neuroinflammation, as it induces mitophagy [143, 144]. Wang et al. [80] used a differentiated lineage of cell lymphomas from rat pheochromocytoma as a cellular model of AD treated with Aβ peptide Aβ1–42 (Aβ1–42). Resveratrol decreased the mitophagy-mediated mitochondrial damage and attenuated the oxidative stress caused by Aβ1–42 [141]. Neuroinflammation may also be related to the degradation of the BBB [145]. The BBB is constituted of structural and functional elements such as brain endothelial cells [146, 147]. Thus, Annabi et al. [145] demonstrated that human brain microvascular endothelial cells treated with a carcinogen can signal through NF-κB, allowing release of inflammatory markers such as matrix metalloproteinase 9 (MMP-9) and COX-2. However, resveratrol decreased secretion of MMP-9 and expression of COX-2 [145]. It also activated the expression of SIRT1, which regulated inflammation, inhibited NF-κB signaling, and prevented Aβ-induced degeneration [148].

3.2.2. Animal Studies. Several studies suggest that pharmacological activation of SIRT1 may represent a promising approach to prevent amyloid deposition and neurodegeneration in AD [99, 149]. The relationship between SIRT1 and AD is paramount, as a study of the SIRT1 serum concentration in healthy subjects and AD patients showed a reduced serum SIRT1 concentration that correlated with the increasing age of an individual. The decline was much more pronounced in patients with AD [93].

SIRT1 also exhibited therapeutic activity in a transgenic mouse model of AD [150]. Wang et al. [127] assessed an alternative therapy for AD that used mesenchymal stem cells derived from the umbilical cord combined with resveratrol in a mouse model of AD. Resveratrol also favored the formation of neurons and regulated SIRT1 expression in the hippocampus of AD rats [127]. Resveratrol has anti-inflammatory functions and can inhibit Aβ-induced NF-κB signaling in microglia and astrocytes [151]. Another study showed that mice overexpressing SIRT1 exhibited reduced brain inflammation (due to its action in tau phosphorylation) and reduced cognitive defects that were specific to the APP transgenic mouse [149, 150].

3.2.3. Human Studies. Some neurodegenerative diseases, such as AD, are associated with oxidative stress and neuroinflammation, and proteins that are closely related to this neurological disorder (i.e., AMPK, SIRT1, and PGC-1α) can be modulated by resveratrol [152]; however, there are few clinical studies on resveratrol in AD patients. Moussa et al. [153] reported that patients treated with resveratrol (1 g/day) for 52 weeks demonstrated reduced MMP-9 levels (an inflammatory marker related to AD) compared to a placebo group. In addition, patients treated with resveratrol had less cerebrospinal fluid decline, which resulted in less Aβ accumulation in the brain. Resveratrol probably strengthened the CNS, hampered the penetration of MMP-9, and reduced the activity of this inflammatory agent [154].

The anti-inflammatory effects of resveratrol are mediated, at least in part, by suppressing the activation of NF-κB, extracellular signal-regulated kinase-1 and kinase-2, and mitogen-activated protein kinase (MAPK) signaling pathways, which are all important upstream modulators of the production of proinflammatory mediators [137]. Resveratrol-mediated overexpression of SIRT1 markedly reduced NF-κB signaling and Aβ-mediated microglial activation and had strong neuroprotective effects [68, 155]. The polymerization of Aβ peptides was markedly inhibited by resveratrol, which stimulated the proteasomal degradation of Aβ peptides [30, 75].

Studies strongly suggest that resveratrol-induced SIRT1 inhibits NF-κB signaling in microglia and astrocytes and protects AD neurons against Aβ-induced toxicity. This
NF-κB signaling controls the expression of iNOS, which mediates apoptosis and neurodegeneration [32]. Resveratrol also effectively suppresses the apoptotic activities of both p53 and FOXO via SIRT1 overexpression and confers neuronal protection in AD [152, 156].

Therefore, the potential anti-inflammatory mechanisms for resveratrol-mediated neuroprotection involve (i) reduction of proinflammatory cytokine expression, (ii) suppression of MAPK signal transduction pathways, and (iii) activation of the SIRT1 pathway, which in turn suppresses the activation of the NF-κB signaling pathway and protects neurons against microglia-dependent Aβ toxicity [134].

In this context, the neuroprotective effects of resveratrol can involve the scavenging of ROS, decreased NO levels, improved antioxidant capacity, NF-κB inhibition, inhibition of inflammatory mediators, promotion of neuronal survival via SIRT1 activation [157, 158], the prevention of DNA lesions, and the prevention of lipid peroxidation in cell membranes [85]. Animal models also indicate that resveratrol improves the spatial memory by decreasing the accumulation of Aβ peptides and lipid peroxidation in the hippocampus, thus protecting against neuronal apoptosis [159].

Therefore, it is also important to emphasize that these neuroprotective effects can also be mediated by other action mechanisms of resveratrol. Another neuroprotective mechanisms of resveratrol include the following: (i) inhibits the tauopathy by interfering with the MID1-PP2A (midline 1-pathways, promoting the activation of calcium/calmodulin-dependent protein kinase (CamKKβ)/AMPK pathway, which in turn suppresses the apoptotic activities of both p53 and FOXO via SIRT1 overexpression and confer neuronal protection in AD. Although this review focuses on the importance of SIRT1 activation for the neuroprotective role of resveratrol, it is also important to clarify that these mechanisms are still unclear and fully elucidated. In addition, resveratrol may act on CNS by inhibiting neuroinflammatory and prooxidant mechanisms by multiple action mechanisms that are independent of SIRT-1. These mechanisms are quite complex and involve stimulation or inhibition of multiple signaling pathways or alteration of potassium channels leading to inhibition of neuronal electrical activity. In summary, the major mechanisms that may be associated with the neuroprotective effect of resveratrol, in addition to SIRT1, include stimulation of regulation by microRNA-CREB-BDNF pathway, inhibition of mTOR and AMPK-dependent signaling pathways, inhibition of enzymes (cholinesterase activity), transcription factor (NF-xB) and apoptotic pathways, and stimulation of cellular autophagy and expression of Nrf2, HO-1, NQO1, among others. Therefore, we critically analyze and suggest that SIRT1 is one of the main mechanisms related to the beneficial effects of resveratrol; however, this compound can change multiple pathways simultaneously, and then, there is a need for crosstalk between signaling and regulatory functions to provide improvements in the development and progression of AD. In addition, caution is required in therapies with natural products, since intrinsic aspects of the patient, environmental factors, and characteristics of the compound studied are important for efficacy and therapeutic success.

Despite the neuroprotective potential of resveratrol demonstrated in several in vitro studies, the major limitation currently facing is the lack of information from clinical studies that correlates the SIRT1 activation and the inflammatory and oxidative status reduction associated with improvement in the development and progression
of AD. Overall, evidence from clinical trials is weak and largely inconclusive. Most human studies establish a link between consumption of foods rich in resveratrol and reducing the incidence or prevalence of AD, as well as improvement in learning, memory, visual and spatial orientation, and social behavior. However, these observed effects may be the result of complex direct and indirect interactions of the various constituents present in the diet, not only of resveratrol. In addition, other difficulties in clinical trials are the following: (i) the studies are mainly conducted with volunteers, not reflecting the target population, (ii) the participants’ age is quite broad between 18 and over 80 years of age, and (iii) sample size is rarely calculated and the slow progression of AD is not investigated because it requires longer clinical time in the trials. Another important issue is the poor bioavailability of resveratrol, which makes it difficult to link with the optimal concentrations achieved in in vitro experiments. Although preclinical studies also indicate that resveratrol is able to cross the blood-brain barrier, low concentrations of this molecule have been detected in the brain, and only higher concentrations of resveratrol and its metabolites have been found in the blood. In addition, it is emphasized that the neuroprotective effects of resveratrol are mainly short term, varying according to dose, dosage form, duration of treatment, pharmacokinetic and pharmacogenetic parameters, food and drug interactions, among others. Thus, we conclude that, to date, evidence based on clinical studies is still insufficient, contradictory, and inconclusive, so we recommend that further clinical trials be conducted to substantiate the neuroprotective effects of resveratrol and its likely mechanisms of action in the body. However, we understand that resveratrol is promising in health promotion, not only for its antioxidant activities but also for its anti-inflammatory and neuroprotective properties. Thereby, further studies assessing other routes of administration or pharmaceutical formulations (i.e., nanoencapsulation) are required to improve the tissue-targeting concentration and allow resveratrol to exert its biological activities in AD.

Conflicts of Interest
The authors declare no conflict of interests.

Authors’ Contributions
All authors participated in the design of the study and drafted the manuscript.

Acknowledgments
The authors were supported by the Brazilian agencies: Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), Fundação Amazônia Paraense de Amparo à Pesquisa (FAPESPA), and Federal University of Pará, and MCM thanks the fellowship from CNPq.

References
[1] B. J. Kelley and R. C. Petersen, “Alzheimer’s disease and mild cognitive impairment,” Neurologic Clinics, vol. 25, no. 3, pp. 577–609, 2007.
[2] H. Jahn, “Memory loss in Alzheimer’s disease,” Dialogues in Clinical Neuroscience, vol. 15, no. 4, pp. 445–454, 2013.
[3] W. Xu, C. Ferrari, and H.-X. Wang, “Epidemiology of Alzheimer’s disease,” in Understanding Alzheimer’s Disease, K. Pesek, Ed., InTech, 2013.
[4] Y. Gilgun-Sherki, E. Melamed, and D. Offen, “Antioxidant treatment in Alzheimer’s disease: current state,” Journal of Molecular Neuroscience, vol. 21, no. 1, pp. 1–12, 2003.
[5] Y. Feng and X. Wang, “Antioxidant therapies for Alzheimer’s disease,” Oxidative Medicine and Cellular Longevity, vol. 2012, Article ID 472932, 17 pages, 2012.
[6] E. Tellone, A. Galtieri, A. Russo, B. Giardina, and S. Ficarra, “Resveratrol: a focus on several neurodegenerative diseases,” Oxidative Medicine and Cellular Longevity, vol. 2015, Article ID 392169, 14 pages, 2015.
[7] R. E. González-Reyes, M. O. Nava-Mesa, K. Vargas-Sánchez, D. Ariza-Salamanca, and L. Mora-Muñoz, “Involvement of astrocytes in Alzheimer’s disease from a neuroinflammatory and oxidative stress perspective,” Frontiers in Molecular Neuroscience, vol. 10, pp. 1–20, 2017.
[8] Y. R. Li, S. Li, and C. C. Lin, “Effect of resveratrol and pterostilbene on aging and longevity,” BioFactors, vol. 44, no. 1, pp. 69–82, 2018.
[9] P. Sadhukhan, S. Saha, S. Dutta, S. Mahalanobish, and P. C. Sil, “Nutraceuticals: an emerging therapeutic approach against the pathogenesis of Alzheimer’s disease,” Pharmacological Research, vol. 129, pp. 100–114, 2018.
[10] Y. Jia, N. Wang, and X. Liu, “Resveratrol and amyloid-beta: mechanistic insights,” Nutrients, vol. 9, no. 10, pp. 1122, 2017.
[11] R. Mancuso, J. del Valle, L. Modol et al., “Resveratrol improves motoneuron function and extends survival in SOD1G93A ALS mice,” Neurotherapeutics, vol. 11, no. 2, pp. 419–432, 2014.
[12] A. L. de Brito Oliveira, V. V. S. Monteiro, K. C. Navegantes-Lima et al., “Resveratrol role in autoimmune disease—a mini-review,” Nutrients, vol. 9, no. 12, article 1306, 2017.
[13] J. Gambini, M. Inglês, G. Olaso et al., “Properties of resveratrol: in vitro and in vivo studies about metabolism, bioavailability, and biological effects in animal models and humans,” Oxidative Medicine and Cellular Longevity, vol. 2015, Article ID 837042, 13 pages, 2015.
[14] İ. Gülçin, “Antioxidant properties of resveratrol: a structure–activity insight,” Innovative Food Science & Emerging Technologies, vol. 11, no. 1, pp. 210–218, 2010.
[15] R. V. Albuquerque, N. S. Malcher, L. L. Amado et al., “In vitro protective effect and antioxidant mechanism of resveratrol induced by dapsone hydroxylamine in human cells,” PLoS One, vol. 10, no. 8, article e0134768, 2015.
[16] D. Beher, J. Wu, S. Cumine et al., “Resveratrol is not a direct activator of SIRT1 enzyme activity,” Chemical Biology & Drug Design, vol. 74, no. 6, pp. 619–624, 2009.
[17] D. Kim, M. D. Nguyen, M. M. Dobbin et al., “SIRT1 deacetylase protects against neurodegeneration in models for Alzheimer’s disease and amyotrophic lateral sclerosis,” The EMBO Journal, vol. 26, no. 13, pp. 3169–3179, 2007.
[18] K. Higashida, S. H. Kim, S. R. Jung, M. Asaka, J. O. Holloszy, and D. H. Han, "Effects of resveratrol and SIRT1 on PGC-1α activity and mitochondrial biogenesis: a reevaluation," *PLoS Biology*, vol. 11, no. 7, article e1001603, 2013.

[19] G. Sweeney and J. Song, "The association between PGC-1α and Alzheimer’s disease," *Anatomy & Cell Biology*, vol. 49, no. 1, pp. 1–6, 2016.

[20] Y. N. Zhao, W. F. Li, F. Li et al., "Resveratrol improves learning and memory in normally aged mice through microRNA-CREB pathway," *Biochemical and Biophysical Research Communications*, vol. 435, no. 4, pp. 597–602, 2013.

[21] H. F. Zhao, N. Li, Q. Wang, X. J. Cheng, X. M. Li, and T. T. Liu, "Resveratrol decreases the insoluble Aβ1–42 level in hippocampus and protects the integrity of the blood–brain barrier in AD rats," *Neuroscience*, vol. 310, pp. 641–649, 2015.

[22] S. H. Omar, "Biophenols pharmacology against the amyloidogenic activity in Alzheimer’s disease," *Biomedicine & Pharmacotherapy*, vol. 89, pp. 396–413, 2017.

[23] G. Kempermann, H. Song, and F. H. Gage, "Neurogenesis in the adult hippocampus," *Cold Spring Harbor Perspectives in Biology*, vol. 7, no. 9, pp. 220–226, 2015.

[24] B. Biscaro, O. Lindvall, G. Tesco, C. T. Ekdahl, and R. M. Nitsch, "Inhibition of microglial activation protects hippocampal neurogenesis and improves cognitive deficits in a transgenic mouse model for Alzheimer’s disease," *Neurodegenerative Diseases*, vol. 9, no. 4, pp. 187–198, 2012.

[25] J. Thomas, M. L. Garg, and D. W. Smith, "Dietary supplementation with resveratrol and/or docosahexaenoic acid alters hippocampal gene expression in adult C57Bl/6 mice," *The Journal of Nutritional Biochemistry*, vol. 24, no. 10, pp. 1735–1740, 2013.

[26] R. Lalla and G. Donmez, "The role of sirtuins in Alzheimer’s disease," *Frontiers in Aging Neuroscience*, vol. 5, p. 16, 2013.

[27] S. D. Rege, T. Geetha, G. D. Griffin, T. L. Broderick, and J. R. Babu, "Neuroprotective effects of resveratrol in Alzheimer disease pathology," *Frontiers in Aging Neuroscience*, vol. 6, pp. 1–27, 2014.

[28] S. S. Karuppagounder, J. T. Pinto, H. Xu, H.-L. Chen, M. F. Beal, and G. E. Gibson, "Dietary supplementation with resveratrol reduces plaque pathology in a transgenic model of Alzheimer’s disease," *Neurochemistry International*, vol. 54, no. 2, pp. 111–118, 2009.

[29] R. Wang, Y. Zhang, J. Li, and C. Zhang, "Resveratrol ameliorates spatial learning memory impairment induced by Aβ1–42 in rats," *Neuroscience*, vol. 344, pp. 39–47, 2017.

[30] P. Marambaud, H. Zhao, and P. Davies, "Resveratrol promotes clearance of Alzheimer’s disease amyloid-β peptides," *Journal of Biological Chemistry*, vol. 280, no. 45, pp. 37377–37382, 2005.

[31] N. Guida, G. Laudati, S. Anzilotti et al., "Resveratrol via sirtuin-1 downregulates cREI-silencing transcription factor (REST) expression preventing PCB-95-induced neuronal cell death," *Toxicology and Applied Pharmacology*, vol. 288, no. 3, pp. 387–398, 2015.

[32] J. Chen, Y. Zhou, S. Mueller-Steiner et al., "SIRT1 protects against microglia-dependent amyloid-β toxicity through inhibiting NF-κB signaling," *Journal of Biological Chemistry*, vol. 280, no. 48, pp. 40364–40374, 2005.

[33] K. C. Morris-Blanco, C. H. Cohan, J. T. Neumann, T. J. Sick, and M. A. Perez-Pinzon, "Protein kinase C epsilon regulates mitochondrial pools of Nampt and NAD following resveratrol and ischemic preconditioning in the rat cortex," *Journal of Cerebral Blood Flow & Metabolism*, vol. 34, no. 6, pp. 1024–1032, 2014.

[34] D. Li, N. Liu, L. Zhao et al., "Protective effect of resveratrol against nigrostriatal pathway injury in striatum via JNK pathway," *Brain Research*, vol. 1654, Part A, pp. 1–8, 2017.

[35] A. Salminen, K. Kaarniranta, and A. Kauppinen, "Crossstalk between oxidative stress and SIRT1: impact on the aging process," *International Journal of Molecular Sciences*, vol. 14, no. 2, pp. 3834–3859, 2013.

[36] D. Albani, L. Polito, S. Batelli et al., "The SIRT1 activator resveratrol protects SK-N-BE cells from oxidative stress and against toxicity caused by α-synuclein or amyloid-β (1–42) peptide," *Journal of Neurochemistry*, vol. 110, no. 5, pp. 1445–1456, 2009.

[37] L. F. da Silva, C. C. Guerra, D. Klein, and A. M. Bergold, "Solid cation exchange phase to remove interfering anthocyanins in the analysis of other bioactive phenols in red wine," *Food Chemistry*, vol. 227, pp. 158–165, 2017.

[38] J. Popović-Djordjević, B. Pejin, A. Dramičanin et al., "Wine chemical composition and radical scavenging activity of some Cabernet Franc clones," *Current Pharmaceutical Biotechnology*, vol. 18, no. 4, pp. 343–350, 2017.

[39] J. Gabaston, E. Cantos-Villar, B. Biais et al., "Stillbenes from *Vitis vinifera* L. waste: a sustainable tool for controlling *Plasmopara viticola*," *Journal of Agricultural and Food Chemistry*, vol. 65, no. 13, pp. 2711–2718, 2017.

[40] J. Burns, T. Yokota, H. Ashihara, M. E. J. Lean, and A. Crozier, "Plant foods and herbal sources of resveratrol," *Journal of Agricultural and Food Chemistry*, vol. 50, no. 11, pp. 3337–3340, 2002.

[41] J. P. Singh, A. Kaur, K. Shevkani, and N. Singh, "Composition, bioactive compounds and antioxidant activity of common Indian fruits and vegetables," *Journal of Food Science and Technology*, vol. 53, no. 11, pp. 4056–4066, 2016.

[42] N. Tilli, A. Feriani, E. Saadoui, N. Nasri, and A. Khalidi, "*Capparis spinosa* leaves extract: source of bioantioxidants with nephroprotective and hepatoprotective effects," *BioMedicine & Pharmacotherapy*, vol. 87, pp. 171–179, 2017.

[43] A. H. Srikanta, A. Kumar, S. V. Sukdeo, M. S. Peddha, and V. Govindaswamy, "The antioxidant effect of mulberry and jamun fruit wines by ameliorating oxidative stress in streptozotocin-induced diabetic Wistar rats," *Food & Function*, vol. 7, no. 10, pp. 4422–4431, 2016.

[44] L. Becker, S. Bellow, V. Carré et al., "Correlative analysis of fluorescent phytoalexins by mass spectrometry imaging and fluorescence microscopy in grapevine leaves," *Analytical Chemistry*, vol. 89, no. 13, pp. 7099–7106, 2017.

[45] S. Bruisson, P. Maillot, P. Schellenbaum, B. Walter, K. Gindro, and L. Deglène-Benbrahim, "Arbuscular mycorrhizal symbiosis stimulates key genes of the phenylpropanoid biosynthesis and stilbenoid production in grapevine leaves in response to downy mildew and grey mould infection," *Phytochemistry*, vol. 131, pp. 92–99, 2016.

[46] G. Chitarrini, L. Zulini, D. Masuero, and U. Vrhovsek, "Lipid, phenol and carotenoid changes in "Bianca" grapevine leaves after mechanical wounding: a case study," *Protoplasma*, vol. 254, no. 6, pp. 2095–2106, 2017.

[47] F. Sparvoli, C. Martin, A. Scienza, G. Gavazzi, and C. Tonelli, "Cloning and molecular analysis of structural
genes involved in flavonoid and stilbene biosynthesis in grape (Vitis vinifera L.),” *Plant Molecular Biology*, vol. 24, no. 5, pp. 743–755, 1994.

[48] G. Schröder, J. W. S. Brown, and J. Schröder, ”Molecular analysis of resveratrol synthase. cDNA, genomic clones and relationship with chalcone synthase,” *European Journal of Biochemistry*, vol. 172, no. 1, pp. 161–169, 1988.

[49] J. Schröder and G. Schröder, ”Stilbene and chalcone synthases: related enzymes with key functions in plant-specific pathways,” *Zeitschrift für Naturforschung C*, vol. 45, no. 1-2, pp. 1–8, 1990.

[50] P. M. Dewick, *Medicinal Natural Products*, John Wiley & Sons, Ltd, Chichester, UK, 2001.

[51] C. Rivière, A. D. Pawlus, and J.-M. Méridon, ”Natural stilbenoids: distribution in the plant kingdom and chemotaxonomic interest in Vitaceae,” *Natural Product Reports*, vol. 29, no. 11, pp. 1317–1333, 2012.

[52] N. Rupprich and H. Kindl, ”Stilbene carboxylase synthases, I enzymatic synthesis of 3,5,4-trihydroxy stilbene from p-coumaroyl coenzyme A and malonyl coenzyme A,” *Hoppe-Seyer's Zeitschrift für Physiologische Chemie*, vol. 359, no. 2, pp. 165–172, 1978.

[53] E. Hurtado-Gaitán, S. Sellés-Marchart, A. Martínez-Márquez, A. Samper-Herrero, and R. Bru-Martinez, ”A focused multiple reaction monitoring (MRM) quantitative method for bioactive grapevine stilbenes by ultra-high-performance liquid chromatography coupled to triple-quadrupole mass spectrometry (UHPLC-QqQ),” *Molecules*, vol. 22, no. 3, p. 418, 2017.

[54] Z. Qiu, J. Yu, Y. Dai et al., ”A simple LC-MS/MS method facilitated by salting-out assisted liquid-liquid extraction to simultaneously determine trans-resveratrol and its glucuronide and sulfate conjugates in rat plasma and its application to pharmacokinetic assay,” *Biomedical Chromatography*, vol. 31, no. 11, 2017.

[55] A. Calliari, N. Bobba, C. Escande, and E. N. Chini, ”Resveratrol delays Wallerian degeneration in a NAD+ and DBC1 dependent manner,” *Experimental Neurology*, vol. 251, pp. 91–100, 2014.

[56] G. Kuhnle, J. P. E. Spencer, G. Chowrimootoo et al., ”Resveratrol is absorbed in the small intestine as resveratrol glucuronide,” *Biochemical and Biophysical Research Communications*, vol. 272, no. 1, pp. 212–217, 2000.

[57] A. Courtois, M. Jourdes, A. Dupin et al., ”In vitro glucuronidation and sulfonation of e-viniferin, a resveratrol dimer, in humans and rats,” *Molecules*, vol. 22, no. 5, p. 733, 2017.

[58] T. Walle, P. Hsieh, M. DeLegge, J. E. Oatis Jr, and U. K. Walle, ”High absorption but very low bioavailability of oral resveratrol in humans,” *Drug Metabolism and Disposition*, vol. 32, no. 12, pp. 1377–1382, 2004.

[59] C. Sergides, M. Chirila, L. Silvestro, D. Pitta, and A. Pittas, ”Bioavailability and safety study of resveratrol 500 mg tablets in healthy male and female volunteers,” *Experimental and Therapeutic Medicine*, vol. 11, no. 1, pp. 164–170, 2016.

[60] C.-H. Cottart, V. Nivet-Antoine, C. Laguillier-Morizot, and J.-L. Beaudeau, ”Resveratrol bioavailability and toxicity in humans,” *Molecular Nutrition & Food Research*, vol. 54, no. 1, pp. 7–16, 2010.

[61] R. L. Frozza, A. Bernardi, K. Paese et al., ”Characterization of trans-resveratrol-loaded lipid-core nanocapsules and tissue distribution studies in rats,” *Journal of Biomedical Nanotechnology*, vol. 6, no. 6, pp. 694–703, 2010.

[62] R. S. Turner, R. G. Thomas, S. Craft et al., ”A randomized, double-blind, placebo-controlled trial of resveratrol for Alzheimer disease,” *Neurology*, vol. 85, no. 16, pp. 1383–1391, 2015.

[63] T.-Y. Chen, M. G. Ferruzzi, Q.-L. Wu et al., ”Influence of diabetes on plasma pharmacokinetics and brain bioavailability of grape polyphenols and their phase II metabolites in the Zucker diabetic fatty rat,” *Molecular Nutrition & Food Research*, vol. 61, no. 10, article 1700111, 2017.

[64] L. Biasutto, A. Mattarei, M. Azzolini et al., ”Resveratrol derivatives as a pharmacological tool,” *Annals of the New York Academy of Sciences*, vol. 1403, no. 1, pp. 27–37, 2017.

[65] G. Davidov-Pardo and D. J. McClements, ”Resveratrol encapsulation: designing delivery systems to overcome solubility, stability and bioavailability issues,” *Trends in Food Science & Technology*, vol. 38, no. 2, pp. 88–103, 2014.

[66] R. L. Frozza, A. Bernardi, J. B. Hoppe et al., ”Neuroprotective effects of resveratrol against Aβ administration in rats are improved by lipid-core nanocapsules,” *Molecular Neurobiology*, vol. 47, no. 3, pp. 1066–1080, 2013.

[67] M. Emilia Juan, M. Pilar Vinardell, and J. M. Planas, ”The daily oral administration of high doses of trans-resveratrol to rats for 28 days is not harmful,” *The Journal of Nutrition*, vol. 132, no. 2, pp. 257–260, 2002.

[68] L. Almeida, M. Vaz-da-Silva, A. Falcão et al., ”Pharmacokinetic and safety profile of trans-resveratrol in a rising multiple-dose study in healthy volunteers,” *Molecular Nutrition & Food Research*, vol. 53, Supplement 1, pp. S7–S15, 2009.

[69] K. T. Howitz, K. J. Bitterman, H. Y. Cohen et al., ”Small molecule activators of sirtuins extend Saccharomyces cerevisiae lifespan,” *Nature*, vol. 425, no. 6954, pp. 191–196, 2003.

[70] M. Pachołec, J. E. Bleasdale, B. Chrunyk et al., ”SRT 1720, SRT 2183, SRT 1460, and resveratrol are not direct activators of SIRT1,” *Journal of Biological Chemistry*, vol. 285, no. 11, pp. 8340–8351, 2010.

[71] M. Kaebelrein, T. McDonagh, B. Heitweg et al., ”Substrate-specific activation of sirtuins by resveratrol,” *Journal of Biological Chemistry*, vol. 280, no. 17, pp. 17038–17045, 2005.

[72] T. Ma, M.-S. Tan, J.-T. Yu, and L. Tan, ”Resveratrol as a therapeutic agent for Alzheimer’s disease,” *BioMed Research International*, vol. 2014, Article ID 350516, 13 pages, 2014.

[73] C. Fang, L. Gu, D. Smerin, S. Mao, and X. Xiong, ”The interrelation between reactive oxygen species and autophagy in neurological disorders,” *Oxidative Medicine and Cellular Longevity*, vol. 2017, Article ID 8495160, 16 pages, 2017.

[74] A. Y. Sun, Q. Wang, A. Simonyi, and G. Y. Sun, ”Resveratrol as a therapeutic agent for neurodegenerative diseases,” *Molecular Neurobiology*, vol. 41, no. 2-3, pp. 375–383, 2010.

[75] L. Kuršvičienė, I. Stanevičienė, A. Mongirdienė, and J. Bernatonienė, ”Multiplicity of effects and health benefits of resveratrol,” *Medicina*, vol. 52, no. 3, pp. 148–155, 2016.

[76] A. D. Romanò, G. Serviddio, A. de Matteis, F. Bellanti, and G. Vendemiale, ”Oxidative stress and aging,” *Journal of Nephrology*, vol. 23, pp. S29–S36, 2010.

[77] F. Li, Q. Gong, H. Dong, and J. Shi, ”Resveratrol, a neuroprotective supplement for Alzheimer’s disease,” *Current Pharmaceutical Design*, vol. 18, no. 1, pp. 27–33, 2012.
[78] B. Liu and J.-S. Hong, “Role of microglia in inflammation-mediated neurodegenerative diseases: mechanisms and strategies for therapeutic intervention,” *The Journal of Pharmacology and Experimental Therapeutics*, vol. 304, no. 1, pp. 1–7, 2003.

[79] J. J. Palacino, D. Sagi, M. S. Goldberg et al., “Mitochondrial dysfunction and oxidative damage in parkin-deficient mice,” *Journal of Biological Chemistry*, vol. 279, no. 18, pp. 18614–18622, 2004.

[80] H. Wang, T. Jiang, W. Li, N. Gao, and T. Zhang, “Resveratrol attenuates oxidative damage through activating mitophagy in an *in vitro* model of Alzheimer’s disease,” *Toxicology Letters*, vol. 282, pp. 100–108, 2018.

[81] B. J. Tabner, O. M. A. El-Agnaf, S. Turnbull et al., “Hydrogen peroxide is generated during the very early stages of aggregation of the amyloid peptides implicated in Alzheimer disease and familial British dementia,” *Journal of Biological Chemistry*, vol. 280, no. 43, pp. 35789–35792, 2005.

[82] C. Lu, Y. Guo, J. Li et al., “Design, synthesis, and evaluation of resveratrol derivatives as Aβ42 aggregation inhibitors, antioxidants, and neuroprotective agents,” *Bioorganic & Medicinal Chemistry Letters*, vol. 22, no. 24, pp. 7683–7687, 2012.

[83] P. H. Reddy, R. Tripathi, Q. Troung et al., “Abnormal mitochondrial dynamics and synaptic degeneration as early events in Alzheimer’s disease: implications to mitochondria-targeted antioxidant therapeutics,” *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease*, vol. 1822, no. 5, pp. 639–649, 2012.

[84] P. H. Reddy, S. Tonk, S. Kumar et al., “A critical evaluation of neuroprotective and neurodegenerative microRNAs in Alzheimer’s disease,” *Biochemical and Biophysical Research Communications*, vol. 483, no. 4, pp. 1156–1165, 2017.

[85] M. Citron, “Alzheimer’s disease: strategies for disease modification,” *Nature Reviews Drug Discovery*, vol. 9, no. 5, pp. 387–398, 2010.

[86] F. Wu, M. P. Mattson, and P. J. Yao, “Neuronal activity and the expression of clathrin assembly protein AP180,” *Biochemical and Biophysical Research Communications*, vol. 402, no. 2, pp. 297–300, 2010.

[87] M. D. Carter, G. A. Simms, and D. F. Weaver, “The development of new therapeutics for Alzheimer’s disease,” *Clinical Pharmacology & Therapeutics*, vol. 88, no. 4, pp. 475–486, 2010.

[88] J.-F. Ge, J.-P. Qiao, C.-C. Qi, C.-W. Wang, and J.-N. Zhou, “The binding of resveratrol to monomer and fibril amyloid beta,” *Neurochemistry International*, vol. 61, no. 7, pp. 1192–1201, 2012.

[89] A. Nunomura, G. Perry, G. Aliev et al., “Oxidative damage is the earliest event in Alzheimer disease,” *Journal of Neuropathology & Experimental Neurology*, vol. 60, no. 8, pp. 759–767, 2001.

[90] C. H.-L. Hung, Y.-S. Ho, and R. C.-C. Chang, “Modulation of mitochondrial calcium as a pharmacological target for Alzheimer’s disease,” *Aging Research Reviews*, vol. 9, no. 4, pp. 447–456, 2010.

[91] M. Dumont and M. F. Beal, “Neuroprotective strategies involving ROS in Alzheimer disease,” *Free Radical Biology & Medicine*, vol. 51, no. 5, pp. 1014–1026, 2011.

[92] H. F. Stanyon and J. H. Viles, “Human serum albumin can regulate amyloid-β peptide fiber growth in the brain interstitium,” *Journal of Biological Chemistry*, vol. 287, no. 33, pp. 28163–28168, 2012.

[93] R. Kumar, P. Chatterjee, P. K. Sharma et al., “Sirtuin1: a promising serum protein marker for early detection of Alzheimer’s disease,” *PLoS One*, vol. 8, no. 4, article e61560, 2013.

[94] C. Julien, C. Tremblay, V. Émond et al., “Sirtuin 1 reduction parallels the accumulation of tau in Alzheimer disease,” *Journal of Neuropathology & Experimental Neurology*, vol. 68, no. 1, pp. 48–58, 2009.

[95] J.-H. Koo, E.-B. Kang, Y.-S. Oh, D.-S. Yang, and J.-Y. Cho, “Treadmill exercise decreases amyloid-β burden possibly via activation of SIRT 1 signaling in a mouse model of Alzheimer’s disease,” *Experimental Neurology*, vol. 288, pp. 142–152, 2017.

[96] G. Marwarha, S. Raza, C. Meiers, and O. Ghribi, “Leptin attenuates BACE1 expression and amyloid-β genesis via the activation of SIRT1 signaling pathway,” *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease*, vol. 1842, no. 9, pp. 1587–1595, 2014.

[97] R. Kumar, L. Nigam, A. P. Singh, K. Singh, N. Subbarao, and S. Dey, “Design, synthesis of allosteric peptide activator for human SIRT1 and its biological evaluation in cellular model of Alzheimer’s disease,” *European Journal of Medicinal Chemistry*, vol. 127, pp. 909–916, 2017.

[98] L. Guarente, “Calorie restriction and sirtuins revisited,” *Genes & Development*, vol. 27, no. 19, pp. 2072–2085, 2013.

[99] A. Satoh and S. Imai, “Hypothalamic Sirt1 in aging,” *Aging*, vol. 6, no. 1, pp. 1–2, 2014.

[100] S. Michan, Y. Li, M. M.-H. Chou et al., “SIRT1 is essential for normal cognitive function and synaptic plasticity,” *Journal of Neuroscience*, vol. 30, no. 29, pp. 9695–9707, 2010.

[101] J. Gao, W.-Y. Wang, Y.-W. Mao et al., “A novel pathway regulates memory and plasticity via SIRT1 and mir-134,” *Nature*, vol. 466, no. 7310, pp. 1105–1109, 2010.

[102] A. Z. Herskovits and L. Guarente, “SIRT1 in neurodevelopment and brain senescence,” *Neuron*, vol. 81, no. 3, pp. 471–483, 2014.

[103] M. Bernier, R. K. Paul, A. Martin-Montalvo et al., “Negative regulation of STAT3 protein-mediated cellular respiration by SIRT1 protein,” *Journal of Biological Chemistry*, vol. 286, no. 22, pp. 19270–19279, 2011.

[104] M. R. Ramis, S. Esteban, A. Miralles, D.-X. Tan, and R. J. Reiter, “Caloric restriction, resveratrol and melatonin: role of SIRT1 and implications for aging and related-diseases,” *Mechanisms of Ageing & Development*, vol. 146–148, pp. 28–41, 2015.

[105] J. Wang, H. Fivcoat, L. Ho, Y. Pan, E. Ling, and G. M. Pasinetti, “The role of Sirt 1: at the crossroad between promotion of longevity and protection against Alzheimer’s disease neuropathology,” *Biochimica et Biophysica Acta (BBA) - Proteins and Proteomics*, vol. 1804, no. 8, pp. 1690–1694, 2010.

[106] S.-Y. Li, X.-B. Wang, and L.-Y. Kong, “Sirtuin7: a potential target for Alzheimer’s disease,” *Mechanisms of Ageing & Development*, vol. 146–148, pp. 28–41, 2015.
diseases,” *Food and Chemical Toxicology*, vol. 61, pp. 215–226, 2013.

[109] X. Yang, X. Qiang, Y. Li et al., “Pyridoxine-resveratrol hybrids Mannich base derivatives as novel dual inhibitors of AChE and MAO-B with antioxidant and metal-chelating properties for the treatment of Alzheimer’s disease,” *Bioorganic & Medicinal Chemistry*, vol. 71, pp. 305–314, 2017.

[110] S. Schweiger, F. Matthes, K. Posey et al., “Resveratrol induces dephosphorylation of tau by interfering with the MID1-PP2A complex,” *Scientific Reports*, vol. 7, no. 1, pp. 13753–13713, 2017.

[111] S. D. Rege, T. Geetha, T. L. Broderick, and J. R. Babu, “Resveratrol protects β-amyloid induced oxidative damage and memory associated proteins in H19-7 hippocampal neuronal cells,” *Current Alzheimer Research*, vol. 12, no. 2, pp. 147–156, 2015.

[112] C. Lu, Y. Guo, J. Yan et al., “Design, synthesis, and evaluation of multitarget-directed resveratrol derivatives for the treatment of Alzheimer’s disease,” *Journal of Medicinal Chemistry*, vol. 56, no. 14, pp. 5843–5859, 2013.

[113] X. Hou, D. Rooklin, H. Fang, and Y. Zhang, “Resveratrol serves as a protein-substrate interaction stabilizer in human SIRT1 activation,” *Scientific Reports*, vol. 6, no. 1, article 38186, 2016.

[114] B. Dasgupta and J. Milbrandt, “Resveratrol stimulates AMP kinase activity in neurons,” *Proceedings of the National Academy of Sciences of the United State of America*, vol. 104, no. 17, pp. 7217–7222, 2007.

[115] C. Cantó, Z. Gerhart-Hines, J. N. Feige et al., “AMPK regulates energy expenditure by modulating NAD+ metabolism and SIRT1 activity,” *Nature*, vol. 458, no. 7241, pp. 1056–1060, 2009.

[116] N. L. Price, A. P. Gomes, A. J. Y. Ling et al., “SIRT1 is required for AMPK activation and the beneficial effects of resveratrol on mitochondrial function,” *Cell Metabolism*, vol. 15, no. 5, pp. 675–690, 2012.

[117] O. B. Villalobos, Y.-J. Chen, C.-P. Chen, J.-M. Yeh, and T.-Y. Wu, “Curcuminoids and resveratrol as anti-Alzheimer agents,” *Taiwanese Journal of Obstetrics and Gynecology*, vol. 51, no. 4, pp. 515–525, 2012.

[118] A. Sahebkar, “Neuroprotective effects of resveratrol: potential mechanisms,” *Neurochemistry International*, vol. 57, no. 6, pp. 621–622, 2010.

[119] T.-C. Huang, K.-T. Lu, Y.-Y. P. Wo, Y.-J. Wu, and Y.-L. Yang, “Resveratrol protects rats from Aβ-induced neurotoxicity by the reduction of iNOS expression and lipid peroxidation,” *PLoS One*, vol. 6, no. 12, article e29102, 2011.

[120] M. Venigalla, S. Sonego, E. Gyengesi, M. J. Sharman, and G. Münch, “Novel promising therapeutics against chronic neuroinflammation and neurodegeneration in Alzheimer’s disease,” *Neurochemistry International*, vol. 95, pp. 63–74, 2016.

[121] Y. Liu, X. Chen, and J. Li, “Resveratrol protects against oxidized low-density lipoprotein-induced human umbilical vein endothelial cell apoptosis via inhibition of mitochondrial-derived oxidative stress,” *Molecular Medicine Reports*, vol. 15, no. 5, pp. 2457–2464, 2017.

[122] G. Spanier, H. Xu, N. Xia et al., “Resveratrol reduces endothelial oxidative stress by modulating the gene expression of superoxide dismutase 1 (SOD1), glutathione peroxidase 1 (GPx1) and NADPH oxidase subunit (Nox4),” *Journal of Physiology and Pharmacology*, vol. 60, Supplement 4, pp. 111–116, 2009.

[123] J.-G. Lee, J.-M. Yon, C. Lin, A. Y. Jung, K. Y. Jung, and S.-Y. Nam, “Combined treatment with capsaicin and resveratrol enhances neuroprotection against glutamate-induced toxicity in mouse cerebral cortical neurons,” *Food and Chemical Toxicology*, vol. 50, no. 11, pp. 3877–3885, 2012.

[124] A. Quincozes-Santos, L. D. Bobermin, A. C. Tramontina et al., “Oxidative stress mediated by NMDA, AMPA/KA channels in acute hippocampal slices: neuroprotective effect of resveratrol,” *Toxicology In Vitro*, vol. 28, no. 4, pp. 544–551, 2014.

[125] V. Vingtedoux, L. Giliberto, H. Zhao et al., “AMP-activated protein kinase signaling activation by resveratrol modulates amyloid-β peptide metabolism,” *Journal of Biological Chemistry*, vol. 285, no. 12, pp. 9100–9113, 2010.

[126] F. Simão, A. Matté, A. S. Pagnussat, C. A. Netto, and C. G. Salbego, “Resveratrol preconditioning modulates inflammatory response in the rat hippocampus following global cerebral ischemia,” *Neurochemistry International*, vol. 61, no. 5, pp. 659–665, 2012.

[127] X. Wang, S. Ma, B. Yang et al., “Resveratrol promotes hUC-MSCs engraftment and neural repair in a mouse model of Alzheimer’s disease,” *Behavioural Brain Research*, vol. 339, pp. 297–304, 2018.

[128] M. Tajes, J. Gutierrez-Cuesta, J. Folch et al., “Neuroprotective role of intermittent fasting in senescence-accelerated mice P8 (SAMP8),” *Experimental Gerontology*, vol. 45, no. 9, pp. 702–710, 2010.

[129] J. L. Barger, T. Kayo, J. M. Vann et al., “A low dose of dietary resveratrol partially mimics caloric restriction and retards aging parameters in mice,“ *PLoS One*, vol. 3, no. 6, article e2264, 2008.

[130] H. Imamura, T. Yamaguchi, D. Nagayama, A. Saiki, K. Shirai, and I. Tatsuano, “Resveratrol ameliorates arterial stiffness assessed by cardio-ankle vascular index in patients with type 2 diabetes mellitus,” *International Heart Journal*, vol. 58, no. 4, pp. 577–583, 2017.

[131] A. P. Mansur, A. Roggerio, M. F. S. Goes et al., “Serum concentrations and gene expression of sirtuin 1 in healthy and slightly overweight subjects after caloric restriction or resveratrol supplementation: a randomized trial,” *International Journal of Cardiology*, vol. 227, pp. 788–794, 2017.

[132] A. J. Nimmo and R. Vink, “Recent patents in CNS drug discovery: the management of inflammation in the central nervous system,” *Recent Patents on CNS Drug Discovery*, vol. 4, no. 2, pp. 86–95, 2009.

[133] A. H. Moore and M. K. O’Brien, “Neuroinflammation and anti-inflammatory therapy for Alzheimer’s disease,” *Advanced Drug Delivery Reviews*, vol. 54, no. 3, pp. 1627–1656, 2002.

[134] F. Zhang, J. Liu, and J.-S. Shi, “Resveratrol preconditioning modulates inflammation and neurodegeneration in Alzheimer’s disease,” *Neurochemistry International*, vol. 56, no. 11, pp. 585–597, 2010.

[135] C. Kaur, G. Rathnasamy, and E.-A. Ling, “Roles of activated microglia in hypoxia induced neuroinflammation in the developing brain and the retina,” *Journal of Neuroimmune Pharmacology*, vol. 8, no. 1, pp. 66–78, 2013.

[136] D. D. Lofrumento, G. Nicolardi, A. Cianciulli et al., “Neuroprotective effects of resveratrol in an MPTP mouse model..."
of Parkinson’s-like disease: possible role of SOCS-1 in reducing pro-inflammatory responses,” *Immune & Inflammation*, vol. 20, no. 3, pp. 249–260, 2014.

[137] Q. Zhang, L. Yuan, Q. Zhang et al., “Resveratrol attenuates hypoxia-induced neurotoxicity through inhibiting microglial activation,” *International Immunopharmacology*, vol. 28, no. 1, pp. 578–587, 2015.

[138] S. Bastianetto, C. Ménard, and R. Quirion, “Neuroprotective action of resveratrol,” *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease*, vol. 1852, no. 6, pp. 1195–1201, 2015.

[139] S. S. Gocmez, N. Gacar, T. Utkan, G. Gacar, P. J. Scarpace, and N. Tumer, “Protective effects of resveratrol on aging-induced cognitive impairment in rats,” *Neurobiology of Learning and Memory*, vol. 131, pp. 131–136, 2016.

[140] H. Capiralla, V. Vingtdeux, H. Zhao et al., “Resveratrol mitigates lipopolysaccharide- and Aβ-mediated microglial inflammation by inhibiting the TLR4/NF-kB/STAT signaling cascade,” *Journal of Neurochemistry*, vol. 120, no. 3, pp. 461–472, 2012.

[141] V. K. Nimmagadda, C. T. Bever, N. R. Vattikunta et al., “Overexpression of SIRT1 protein in neurons protects against experimental autoimmune encephalomyelitis through activation of multiple SIRT1 targets,” *The Journal of Immunology*, vol. 190, pp. 4595–4607, 2013.

[142] X. Yang, S. Xu, Y. Qian, and Q. Xiao, “Resveratrol regulates microglia M1/M2 polarization via PGC-1α in conditions of neuroinflammatory injury,” *Brain, Behavior, and Immunity*, vol. 64, pp. 162–172, 2017.

[143] J. Wu, X. Li, G. Zhu, Y. Zhang, M. He, and J. Zhang, "The role of resveratrol-induced mitophagy/autophagy in peritoneal mesothelial cells inflammatory injury via NLRP3 inflammasome activation triggered by mitochondrial ROS," *Experimental Cell Research*, vol. 341, no. 1, pp. 42–53, 2016.

[144] Y. Zhang, M. Chen, Y. Zhou et al., “Resveratrol improves hepatic steatosis by inducing autophagy through the cAMP signaling pathway,” *Molecular Nutrition & Food Research*, vol. 59, no. 8, pp. 1443–1457, 2015.

[145] B. Annabi, S. Lord-Dufour, A. Vézina, and R. Béliveau, “Resveratrol targeting of carcinogen-induced brain endothelial cell inflammation biomarkers MMP-9 and COX-2 is Sirt1-independent,” *Drug Target Insights*, vol. 6, article DTLS9442, 2012.

[146] S. S. Lakka, C. S. Gondi, and J. S. Rao, “Proteases and glial angiogenesis,” *Brain Pathology*, vol. 15, no. 4, pp. 327–341, 2005.

[147] A. Bonou, S. D. Mahajan, L. Ye et al., “MMP-9 gene silencing by a quantum dot–siRNA nanoparticle delivery to maintain the integrity of the blood brain barrier,” *Brain Research*, vol. 1282, pp. 142–155, 2009.

[148] L. Cao, C. Liu, F. Wang, and H. Wang, “SIRT1 negatively regulates amyloid-beta-induced inflammation via the NF-kB pathway,” *Brazilian Journal of Medical and Biological Research*, vol. 46, no. 8, pp. 659–669, 2013.

[149] G. M. Pasinetti, J. Wang, P. Marambaud et al., “Neuroprotective and metabolic effects of resveratrol: therapeutic implications for Huntington's disease and other neurodegenerative disorders,” *Experimental Neurology*, vol. 232, no. 1, pp. 1–6, 2011.

[150] G. DONmez, D. Wang, D. E. Cohen, and L. Guarante, “SIRT1 suppresses β-amyloid production by activating the α-secretase gene ADAM10,” *Cell*, vol. 142, no. 2, pp. 320–332, 2010.

[151] X. Lu, L. Ma, L. Ruan et al., “Resveratrol differentially modulates inflammatory responses of microglia and astrocytes,” *Journal of Neuroinflammation*, vol. 7, no. 1, p. 46, 2010.

[152] G. M. Pasinetti, J. Wang, L. Ho, W. Zhao, and L. Dubner, “Roles of resveratrol and other grape-derived polyphenols in Alzheimer’s disease prevention and treatment,” *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease*, vol. 1852, no. 6, pp. 1202–1208, 2015.

[153] C. Moussa, M. Hebron, X. Huang et al., “Resveratrol regulates neuro-inflammation and induces adaptive immunity in Alzheimer’s disease,” *Journal of Neuroinflammation*, vol. 14, no. 1, pp. 1–10, 2017.

[154] S. Thordardottir, A. Kinhult Ståhlbom, O. Almkvist et al., “The effects of different familial Alzheimer’s disease mutations on APP processing in vivo,” *Alzheimer’s Research & Therapy*, vol. 9, no. 1, article 9, 2017.

[155] F. Yeung, J. E. Hoberg, C. S. Ramsey et al., “Modulation of NF-kB-dependent transcription and cell survival by the SIRT1 deacetylase,” *The EMBO Journal*, vol. 23, no. 12, pp. 2369–2380, 2004.

[156] T. S. Anekonda, “Resveratrol—a boon for treating Alzheimer’s disease?,” *Brain Research Reviews*, vol. 52, no. 2, pp. 316–326, 2006.

[157] J. Moriya, R. Chen, J. Yamakawa, K. Sasaki, Y. Ishigaki, and T. Takahashi, “Resveratrol improves hippocampal atrophy in chronic fatigue mice by enhancing neurogenesis and inhibiting apoptosis of granular cells,” *Biological and Pharmaceutical Bulletin*, vol. 34, no. 3, pp. 354–359, 2011.

[158] S. T. Koz, E. O. Etem, G. Baydas et al., “Effects of resveratrol on blood homocYTEleven level, on homocystine induced oxidative stress, apoptosis and cognitive dysfunctions in rats,” *Brain Research*, vol. 1484, pp. 29–38, 2012.

[159] E.-J. Park and J. M. Pezzuto, “The pharmacology of resveratrol in animals and humans,” *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease*, vol. 1852, no. 6, pp. 1071–1113, 2015.

[160] M. C. Chiang, C. J. Nicol, and Y. C. Cheng, “Resveratrol activation of AMPK-dependent pathways is neuroprotective in human neural stem cells against amyloid-beta-induced inflammation and oxidative stress,” *Neurochemistry International*, vol. 115, pp. 1–10, 2018.

[161] M. H. Jang, X. L. Piao, J. M. Kim, S. W. Kwon, and J. H. Park, “Inhibition of cholest erase and amyloid-β aggregation by resveratrol oligomers from Vitis amurensis,” *Phytotherapy Research*, vol. 22, no. 4, pp. 544–549, 2008.

[162] H. Deng and M. t. Mi, “Resveratrol attenuates Aβ25–35 caused neurotoxicity by inducing autophagy through the TyrRS-PARP1-SIRT1 signaling pathway,” *Neurochemical Research*, vol. 41, no. 9, pp. 2367–2379, 2016.

[163] W. Hu, E. Yang, J. Ye, W. Han, and Z.-L. Du, “Resveratrol protects neuronal cells from isoflurane-induced inflammation and oxidative stress-associated death by attenuating apoptosis via Akt/p38 MAPK signaling,” *Experimental and Therapeutic Medicine*, vol. 15, pp. 1568–1573, 2018.

[164] T. Huang, D. Gao, X. Jiang, S. Hu, L. Zhang, and Z. Fei, “Resveratrol inhibits oxygen-glucose deprivation-induced MPP3 expression and cell apoptosis in primary cortical cells via the NF-κB pathway,” *Molecular Medicine Reports*, vol. 10, no. 2, pp. 1065–1071, 2014.
[165] S.-J. Park, F. Ahmad, A. Philp et al., “Resveratrol ameliorates aging-related metabolic phenotypes by inhibiting cAMP phosphodiesterases,” Cell, vol. 148, no. 3, pp. 421–433, 2012.

[166] C. Shen, W. Cheng, P. Yu et al., “Resveratrol pretreatment attenuates injury and promotes proliferation of neural stem cells following oxygen-glucose deprivation/reoxygenation by upregulating the expression of Nrf 2, HO-1 and NQO1 in vitro,” Molecular Medicine Reports, vol. 14, no. 4, pp. 3646–3654, 2016.

[167] H. Yin, H. Wang, H. Zhang, N. Gao, T. Zhang, and Z. Yang, “Resveratrol attenuates Aβ-induced early hippocampal neuron excitability impairment via recovery of function of potassium channels,” Neurotoxicity Research, vol. 32, no. 3, pp. 311–324, 2017.