Resveratrol in Alzheimer’s disease: a review of pathophysiology and therapeutic potential

Resveratrol na doença de Alzheimer: uma revisão sobre fisiopatologia e potencial terapêutico

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ABSTRACT

Background: Alzheimer’s disease (AD) is a neurodegenerative disorder characterized by progressive and irreversible loss of cognitive function. The presence of senile plaques is one of the pathological markers of the disease and is associated with the onset of neuroinflammatory mechanisms. The exact pathophysiology of AD has not been completely understood, and there are no curative therapies yet. Resveratrol (3,5,4’-trihydroxy-trans-stilbene) is a polyphenol that is noted for its antioxidant and anti-inflammatory properties. Objective: To review the role of resveratrol in the pathophysiological aspects of AD. Methods: This study carried out a literature review using PubMed/Medline, Virtual Health Library (VHL), Web of Sciences, SCOPUS and the Cochrane Library databases. Original research articles, describing both in vitro and in vivo experiments, published between 2008 and 2018, were included. Results: We identified 667 articles, of which 619 were excluded because they were repeated or did not follow the inclusion criteria. The present study includes the remaining 48 articles. Discussion: Resveratrol demonstrates beneficial and protective effects in AD models and seems to provide a promising therapeutic alternative. Conclusion: Although resveratrol appears to mitigate some pathophysiological aspects of AD, further studies are needed to prove the safety and efficacy of this compound in humans.

Keywords: amyloid; sirtuin 1; antioxidants; polyphenols; nutraceuticals.

RESUMO

Introdução: A doença de Alzheimer (DA) é neurodegenerativa e caracterizada por perda progressiva e irreversível da função cognitiva. A presença de placas senis é um dos marcadores patológicos da doença e está associada ao aparecimento de mecanismos neuroinflamatórios. A fisiopatologia exata da DA ainda não é completamente compreendida, e ainda não existem terapias curativas. O resveratrol (3,5,4’-trihidroxi-trans-estilbeno) é um polifenol conhecido por suas propriedades antioxidantes e anti-inflamatórias. Objetivo: Revisar o papel do resveratrol nos aspectos fisiopatológicos da DA. Métodos: Este estudo realizou uma revisão narrativa da literatura a partir das bases de dados PubMed/Medline, Biblioteca Virtual em Saúde (BVS), Web of Science, SCOPUS e Cochrane Library. Foram incluídos artigos originais, realizados in vitro e in vivo, publicados entre 2008 e 2018. Resultados: Foram identificados 667 artigos, dos quais 619 foram excluídos por estarem repetidos ou não se enquadrarem nos critérios de inclusão. O presente estudo inclui os 48 artigos restantes. Discussão: O resveratrol demonstra efeitos benéficos e protetores em modelos de DA, bem como parece fornecer uma alternativa terapêutica promissora. Conclusão: Embora o resveratrol pareça atenuar alguns aspectos fisiopatológicos da DA, são necessários mais estudos para comprovar a segurança e a eficácia deste composto em seres humanos.

Palavras-chave: amiloide; sirtuina 1; antioxidantes; polifenóis; nutracêuticos.
Although there is currently no cure for AD, adopting a healthier lifestyle has been associated with a reduction of cognitive impairment and of dementia risk. Strategies include caloric restriction, physical exercise, and ingestion of antioxidant foods, which are associated with neuroprotective mechanisms.

Resveratrol (3,5,4′-trihydroxy-trans-stilbene) is a polyphenol produced by several plants, and the main food sources are grapes and red wine. This compound has gained notoriety in scientific circles, due to its biological and pharmacological properties. It seems to exert beneficial effects in vitro and in vivo, although the precise mechanisms are still poorly understood.

Turner et al. observed that resveratrol supplementation in patients with mild to moderate dementia was safe and well tolerated. Despite the fast metabolism, resveratrol and its main metabolites were identified in the plasma and cerebrospinal fluid (CSF) of the individuals, demonstrating their ability to cross the blood-brain barrier (BBB) and stabilize Aβ levels.

Given the impact of AD on the quality and life expectancy of the affected individuals and the lack of information regarding effective therapeutic alternatives, the present study aims to review the literature regarding the role of resveratrol in pathophysiological aspects of AD, especially the aggregation of Aβ peptides and consequent triggering of neuroinflammatory processes.

METHODS

A literature review of published articles was carried out between February and November of 2018 using the search terms “Alzheimer’s disease”, “resveratrol”, and “amyloid” on the PubMed/Medline, Virtual Health Library (VHL), Web of Science, SCOPUS, and Cochrane Library databases. Original experimental articles that addressed the performance of resveratrol on the pathophysiological factors of AD, especially neuroinflammation and Aβ peptide aggregation, both in vitro and in vivo, published in English, were selected. We excluded articles that were literature reviews or that did not particularly focus on the study objective.

RESULTS

We identified 667 articles, of which 619 were excluded because they did not fit the inclusion criteria. The remaining 48 articles have been included in this study. Figure 1 outlines our study selection process in a flowchart.

DISCUSSION

Alzheimer’s disease: clinical and pathophysiological aspects

The pathophysiology of AD has not been completely understood yet. However, histopathological characteristics are the focus of attention, especially the deposition of Aβ, which appears to trigger the inflammation and oxidative stress that leads to neurodegeneration. As a result, most of the AD studies in recent years have been conducted based on the amyloid cascade hypothesis, which advocates that Aβ deposition is the primary event in disease pathogenesis.

β-amyloid proteins are peptides consisting of 36 to 43 amino acids that have been derived from the sequential cleavage of the amyloid precursor protein (APP). β-secretase/BACE1 aspartic protease and γ-secretase proteolytic complex cleave APP to produce Aβ peptides. An imbalance between the production and clearance of these peptides enhances their aggregation and triggers the formation of senile plaques. However, the reason for excessive Aβ in the brain is not known.

The deposition of Aβ peptides in brain regions related to memory and learning, such as the frontal cortex and hippocampus, is considered an early event in disease progression. Even though there are several products of APP cleavage, the aggregation of peptides of 40–42 amino acids in length are important in the AD development, especially those terminated at amino acid 42 (Aβ42).

Neuroinflammation is another important characteristic feature in AD, which is manifested through the microglia proliferation and activation. Microglia are the resident macrophages of the brain and form dense clusters around β-amyloid plaques. These cells function as tracers for damage to the central nervous system and detect injuries to the cerebral parenchyma.
Upon detection of damage or immune stimulus in the brain, such as that caused by Aβ peptides, microglia are activated and produce proinflammatory mediators, for instance, tumor necrosis factor (TNF), interleukin-1β (IL-1β) and nitric oxide (NO) in response to it. The accumulation of these mediators contributes to neuronal damage and disease progression. In addition, the NF-κB transcription factor is considered the primary regulator of the inflammatory response in AD.

Free radicals also seem to play a key role in brain aging. Several studies have found an association between Aβ-promoted cytotoxicity and oxidative stress as a result from an imbalance between the production and removal of reactive oxygen species (ROS). High levels of ROS may lead to the destruction of proteins, nucleic acids and lipid peroxidation, as well as impairments in the cell membrane integrity, reduction of mitochondrial membrane potential, and an increase in plasma membrane permeability to calcium ions. This increase in reactive species, due to the reduction of antioxidant defenses, is responsible for the neurodegeneration mediated by oxidative stress.

Currently, the drugs available for treating AD are not completely effective and do not alter the disease progression. It is, therefore, critical that new therapies aimed to prevent and manage this chronic and debilitating disease be developed.

**Resveratrol**

Several foods and natural products, whose chemical components demonstrate interesting pharmacological properties, have been suggested as AD modifying agents. Polyphenols are natural compounds derived from plants, fruits and vegetables, whose biological properties have demonstrated several beneficial effects, such as antioxidant and anti-inflammatory activities.

Resveratrol is a non-flavonoid polyphenol part of the stilbene family, which can be found in grape skin and seeds, blackberries, peanuts, and vegetables. Red wine is therefore also a good source of resveratrol, to which the potential beneficial health effects of this beverage has been attributed.

The biological activity inherent to resveratrol has been discussed in literature for some time, such as its antioxidant, anti-inflammatory, anticarcinogenic and anti-aging effects in different organisms. More recently, the neuroprotective potential has also started to gain interest.

**Effects of resveratrol on Alzheimer’s disease**

**Disaggregation of Aβ-peptides**

Since β-amyloid aggregates have been strongly associated with AD pathogenesis, compounds that promote the inhibition of formation and destruction of preformed aggregates and attenuate Aβ-promoted cytotoxicity may provide an important therapeutic strategy for AD, as demonstrated by Feng et al. Although it does not prevent oligomerization of Aβ42, resveratrol seems to stabilize preformed oligomers and to attenuate oligomer toxicity. This outcome is similar to the findings of Ladiwala et al. and Rushworth et al., in which resveratrol was also able to selectively remodel Aβ oligomers to non-toxic structures.

Aromatic interactions between compounds and Aβ peptides are a determining factor in the inhibition of fibrillar formation and reduction of amyloid toxicity. As verified also by Ge et al., resveratrol was able to bind directly to the amyloid structure. Fu et al. have also noted that resveratrol binds to the N-terminus (residue 5-20) of the Aβ42 monomer and caps the height of oligomers, resulting in a reduction in toxicity. Other studies have also shown a reduction in amyloid aggregation, both at a concentration of 50 and 100 μM.

In CHO-APPswe cells, administration of resveratrol (100 μM) reduced amyloid burden, APP expression, and cleavage. Karuppounder et al. reported that 300 mg/kg/day of resveratrol supplementation also decreased the amount and amyloid burden in brain regions of mice, but this difference was not statistically significant.

Similarly, Varamini et al. found that resveratrol supplementation of 174 mg/kg/day in AβPP/PS1 mice showed no differences in amyloid burden or levels of tau phosphorylation. However, resveratrol was able to increase the levels of proteins involved in neuroprotection processes. In AD/TTR+/- mice, the same amount of resveratrol supplementation increased transthyretin levels (TTR) and stabilized TTR tetramers, which bind more strongly to Aβ peptides, preventing their aggregation.

In addition, in AβPP/PS1 mice, the supplementation of lower doses (100 ppm by weight) of resveratrol, or its synthetic analog LD55, significantly decreased the density of Aβ plaques in different brain regions, including the cortex and hippocampus. The effects of resveratrol on Aβ-peptide aggregation are summarized in Table 1.

**Neuroinflammation**

Activated microglia seem to be an important target of the neuroprotective activity of resveratrol, resulting in the reduction of pro-inflammatory factors. Regarding the findings of Solberg et al., microglial activation was physically associated with amyloid plaques. In addition, resveratrol and its analogue reduced microglia activation, both of which are inhibitors of the NF-κB pathway.

It is noteworthy that the hippocampus, which is the brain region mostly affected by neuroinflammation, presented a greater reduction in the density of activated microglia in response to the compounds. The LD55 analogue has no hydroxyl group, which is present in the resveratrol structure; therefore, it does not have antioxidant properties. However, the compound showed the same efficacy and anti-inflammatory potential of resveratrol, suggesting that the effect is independent of antioxidant function and a result of its ability to inhibit the NF-κB signaling pathway in activated microglia.
In rat astrocytes (RA) and microglia N9 cell lines, resveratrol administration also promoted anti-inflammatory effects by inhibiting NF-κB signaling and release of inflammatory cytokines at different concentrations (5, 12.5, and 25 µM in RA cell line and 10, 20, and 40 µM in N9 cell line). In this experiment, cytotoxicity was found when the concentration of resveratrol was higher than 50 µM in the RA cell line and higher than 80 µM in the N9 microglia cell line.

In another experiment, administration of resveratrol in BV-2 and RAW 264.7 cell lines and supplementation of 350 mg/kg/day in APP/PS1 mice also inhibited Aβ-mediated microglia activation and lipopolysaccharide (LPS)-stimulated activation of NF-κB, reducing the expression of its target genes, such as TNF and IL-6. In BV-2 cells activated by β-amyloid oligomers, resveratrol (1, 3, 10 or 30 µM) reduced the production of reactive species and inhibited the production of inflammatory mediators, among them NO in a dose-dependent manner. Overproduction of NO has been associated with AD, resulting in damage to DNA and the mitochondrial structure.

In HEK-AbPP cells treated with a γ-secretase inhibitor (LY450139), additional treatment with resveratrol (0.5 µM) ceased most of the neurotoxicity and pro-apoptotic effects, promoting maximum neuroprotection. The authors have also discussed the importance of associating different neuroprotective agents, such as antioxidants (resveratrol) with AD-specific drugs.

Neuroprotective effects were also observed with the injection of resveratrol in rats (100 µM/5 µL), which reduced amyloid accumulation, protected animals against neuronal death, increased antioxidant enzyme heme oxygenase-1 (HO-1) expression, and suppressed lipid peroxidation in the hippocampus. In addition, resveratrol improved spatial memory in the animals, which had been impaired by Aβ.

### Table 1. Effects of resveratrol on Aβ-peptide aggregation.

| Compound               | Sample               | Administration                                      | Results                                                                 | Reference       |
|------------------------|----------------------|-----------------------------------------------------|------------------------------------------------------------------------|-----------------|
| Resveratrol, curcumin, | Aβ42 medium          | Added in medium (2, 10 and 100 µM)                   | Resveratrol inhibited fibrillary formation and aggregation of Aβ42. It did not prevent oligomerization, but it stabilized them, and less toxic oligomers were formed. | Feng et al.26   |
| ginkgolides             |                      |                                                     |                                                                        |                 |
| Resveratrol             | Tg19959 mice         | Supplementation of 300 mg/kg/day for 45 days         | Reduced the amount and burden of amyloid plaques in the brain, but it was not statistically significant. | Karuppagounder et al.33 |
| Resveratrol             | Aβ structures samples| Added in medium (20 µM)                             | Remodeled Aβ oligomers into non-toxic oligomers and monomers.           | Ladiwala et al.27 |
| Resveratrol             | Solution of Aβ and   | Added in medium (50 µM)                             | Bound directly to the monomeric and fibrillar amyloid structure.         | Ge et al.12     |
| fibrillar Aβ             |                      |                                                     |                                                                        |                 |
| Resveratrol             | Aβ42 medium          | Added in medium (50 µM)                             | Reduced amyloid aggregation.                                            | Hung et al.30   |
| Resveratrol             | AβPP/PS1 mice        | Supplementation of 174 mg/kg/day for 16 weeks        | There was no difference in amyloid burden or tau phosphorylation levels. It increased levels of proteins involved in neuroprotective processes (GSK3 and Transfhetrin) | Varamini et al.24 |
| Resveratrol and EGC    | Aβ42 medium          | Added in medium (10:1 molar excess of resveratrol and 4:1 molar excess of EGC) | Resveratrol and EGC re-modelled fibrillar conformation of Aβ oligomers into nonfibrillar oligomers and they were no longer cytotoxic | Rushworth et al.28 |
| curcumin                |                      |                                                     |                                                                        | Fu et al.29     |
| Resveratrol and LD55    | AβPP/PS1 mice        | Supplementation of 100 ppm for 12 months             | Decreased Aβ plaque density in brain regions, such as cortex and hippocampus | Solberg et al.00 |
| Resveratrol             | Transgenic C.        | Added in medium (100 µM)                            | Resveratrol bound to the N-terminus (residue 5-20) of the Aβ42 monomer and caps the height of the oligomers, resulting in a reduction in toxicity | Regitz et al.31 |
| elegans strain CL2006,  |                      |                                                     |                                                                        |                 |
| expressing Aβ1-42       |                      |                                                     |                                                                        |                 |
| Resveratrol             | AD/TTR +/- mice      | Supplementation of 174 mg/kg/day to 5- to 8-month-old | Increased TTR levels and stabilized TTR tetramers, preventing aggregation of Aβ peptides | Santos et al.26 |
| Resveratrol             | CHO-APPswe cell      | Added in medium (100 µM)                            | Reduced amyloid burden, expression of APP and its cleavage              | Sathy et al.22   |

Aβ: β-amyloid; GSK3: glycogen synthase kinase 3; EGC: Epigallocatechin gallate; C. elegans: Caenorhabditis elegans; TTR: transthyretin; APP: amyloid precursor protein.
Resveratrol intraperitoneal injection (10, 20 and 40 mg/kg/day) in Sprague-Dawley rats also improved cognitive impairment and attenuated LPS-induced neuroinflammation in rats, by inhibiting the generation of TNF, APP cyclooxygenase (COX)-2 and NF-κB phosphorylation in the hippocampus41.

In mouse neuroblastoma (N2a) cells incubated with Aβ, pretreatment with resveratrol (5 µM) prevented the abnormal expression of peroxiredoxins and mitochondrial structural genes and preserved mitochondrial function, protecting cells against Aβ toxicity42. Also in N2a cells, resveratrol (0, 2.5, 5, 10, 25 and 50 µM) significantly reduced formaldehyde-induced cytotoxicity and cellular apoptosis, and inhibited tau protein hyperphosphorylation in a dose-dependent manner43. Similar results were found in another experiment, in which resveratrol (0, 10, 20 and 40 µM) dose-dependently increased the viability of Aβ-treated PC12 cells and stimulated HO-1 production. The cytoprotective mechanism was mediated by the PI3K/Akt/Nrf2 pathway44, which has also been found responsible for the neuroprotective effect of resveratrol, resulting in a decrease of ROS45.

Several studies have shown that the activation of AMPK (adenosine monophosphate-activated protein kinase) suppresses inflammation by inhibiting NF-κB, preventing oxidative stress. Resveratrol is a potent activator of AMPK, thereby implicating another pathway through that its neuroprotective effects may be exerted46.

An experiment in human neural stem cells (hNSCs) demonstrated that Aβ-treated cells increase the expression of TNF and IL-1β, thereby decreasing cell viability. In addition to inhibiting such deleterious effects, resveratrol (10 µM) prevented the increase of NF-κB and normalized oxidative stress. These effects were attributed to the AMPK pathway47.

The antioxidant resveratrol effects were also verified by Rege et al. in an H19-7 neuronal cell line derived from rat hippocampus. Resveratrol (10 µM) attenuated lipid peroxidation and upregulated antioxidant enzyme levels, such as catalase, superoxide dismutase (SOD), and glutathione reductase (GR). An interesting finding of this experiment was the increased levels of non-enzymatic antioxidants attributed to resveratrol, such as ascorbic acid, α-tocopherol, and glutathione48.

The same study showed that resveratrol decreased the expression of insulin-degrading enzyme (IDE). Insulin regulates neuronal function after crossing the BBB, facilitating glucose uptake by neurons. Insulin resistance, which is a characteristic of type 2 diabetes mellitus, is an important risk factor for AD49.

Another association between glucose metabolism and AD is the presence of advanced glycation end products (AGEs) from the Maillard reaction between carbohydrates and proteins. Advanced glycation end products and their receptors (RAGEs) have been identified in neurons and hippocampus and have been associated with oxidative stress-induced neurotoxicity, as demonstrated by Ko et al., in which the administration of resveratrol (10 and 20 µM) reduced ROS production in cells treated with AGEs41.

In addition, RAGEs located at the BBB are the main gateway for Aβ peptide transport to the brain. In female Wistar rats, resveratrol (20, 40 and 80 mg/kg/day for 12 weeks) protects BBB integrity by reducing RAGE expression in the hippocampus and inhibiting the expression of matrix metalloproteinase-9 (MMP-9), which is responsible for the degradation of junction proteins. It also promotes the expression of Claudine protein-5, which is related to the tight junctions that regulate BBB permeability49.

Resveratrol also attenuated the patients’ cognitive and functional decline50.

**The Sirtuin 1 (SIRT1) pathway**

One of the possible mechanisms by which resveratrol mediates neuroprotection is through the activation of the sirtuin 1 (SIRT1) pathway, which in turn inhibits the activation of the NF-κB signaling pathway. Through suppression of this pathway, SIRT1 is also able to protect neurons against Aβ toxicity51.

SIRT1 is one of a class of NAD+ dependent histone deacetylases that play an essential role in the cellular functioning regulation52. They deacetylate of substrates important in neurodegenerative diseases53. Table 2 shows the resveratrol effects on the neuroinflammation and activation of SIRT1.

Resveratrol (0, 2.5, 5, 7.5, 10 and 15 µM) protected SK-N-BE neuroblastoma cells against induced oxidative stress and increased cell viability. However, when SIRT1 was up regulated with administration of sirtinol, antioxidative activity of resveratrol was suppressed54. In PC12 cells, resveratrol (12.5, 25, 50 and 100 µM) increased cell viability, reduced apoptosis, and attenuated Aβ-induced neurotoxicity. The peptide-induced suppression of SIRT1 activity was reversed by resveratrol, indicating that the protective effects are mediated by the sirtuin pathway55.

In addition to SIRT1, sirtuin 2 (SIRT2) was also observed to participate in the regulation of neuronal survival, albeit through more diverse mechanisms. Activation of SIRT1 and inhibition of SIRT2 (through the administration of resveratrol and AGK-2, respectively) reduced the activation of RA and consequent production of proinflammatory mediators, emphasizing the role of sirtuins and their modulatory substances in strategies for AD treatment56.

**Effects on cognitive aspects**

It has been shown that SIRT1 is essential for synaptic plasticity and cognitive functioning and can modulate learning and memory by regulating cAMP response element
Table 2. Effects of resveratrol on neuroinflammation, neuroprotection, and SIRT1.

| Compound                  | Sample                          | Administration                  | Results                                                                 | Reference          |
|---------------------------|---------------------------------|---------------------------------|------------------------------------------------------------------------|--------------------|
| Resveratrol and sirtinol  | SK-N-BE neuroblastoma cells     | Added in medium (0, 2.5, 5, 7.5, 10 and 15 µM) | Protected cells from oxidative stress induced by H2O2 and 6-OHDA, increasing cell viability, Sirtinol inhibited SIRT1 | Albani et al.7     |
| Resveratrol               | Sprague-Dawley rats             | Intraperitoneal injection (10, 20 and 40 mg/kg/day) | Improved cognitive impairment and attenuated LPS-induced neuroinflammation in rats by inhibiting the generation of TNF, APP, COX-2 and NF-κB phosphorylation in the hippocampus | Gong et al.41      |
| Resveratrol               | Mouse neuroblastoma (N2a) cells | Added in medium (5 µM)          | Prevented the abnormal expression of peroxiredoxins and mitochondrial structural genes and preserved mitochondrial function, protecting cells against Aβ toxicity | Manczak et al.42   |
| Resveratrol               | Sprague-Dawley rats             | Injection of 100 µM/5 µL in the lateral ventricle for seven days | Reversed expression of iNOS, reduced amyloid accumulation, prevented neuronal death, increased HO-1 expression, suppressed lipid peroxidation in hippocampus, and improved spatial memory | Huang et al.49      |
| Resveratrol               | BV-2 microglial cells and RAW 264,7 macrophages and APP/PS1 mice | Added in medium and supplementation of 350 mg/kg/day for 15 weeks | Inhibited activation of NF-κB and its target genes (TNF and IL-6) and prevented activation of Aβ-mediated microglia | Capiralla et al.8 |
| Resveratrol               | PC12 cells                      | Added in medium (12.5, 25, 50 and 100 µM) | Increased cell viability, reduced apoptosis, attenuated Aβ-induced neurotoxicity and regenerated SIRT1 activity | Feng et al.2       |
| Resveratrol and AGK-2     | Sprague-Dawley's astrogia cell culture | Added in medium (2, 10 and 50 µM) | Resveratrol and AGK-2 reduced astrocyte activation and pro-inflammatory mediator production | Scuderi et al.9     |
| Resveratrol and LD55      | AβPP/PS1 mice                   | Supplementation of 100 ppm for 12 months | Resveratrol reduced microglia activation, mainly in the hippocampus. LD55 had the same efficacy, even without the hydroxyl group | Solberg et al.20    |
| Resveratrol               | SH-SY5Y neuroblastoma cells     | Added in medium (10 and 20 µM)  | Reduced ROS production stimulated by AGEs | Ko et al.4         |
| Trans-resveratrol         | Rat H19-7 neuronal cell line    | Added in medium (10 µM)         | Attenuated lipid peroxidation, regulated levels of antioxidant enzymes and increased non-enzymatic antioxidants levels | Rege et al.15      |
| Resveratrol               | BV-2 microglial cells           | Added in medium (1, 3, 10 or 30 µM) | Reduced ROS production and inhibited NO, TNF and IL-1β production | Yao et al.8        |
| Resveratrol               | Wistar female rats              | 20, 40 and 80 mg/kg/day for 12 weeks | Reduced expression of AGEs and MMP-9, preserving BBB integrity | Zhao et al.5       |
| Resveratrol               | HEK-AbPP cells                  | Added in medium (0.5 µM)        | Ceased most of the neurotoxicity and pro-apoptotic effects on cells treated with γ-secretase inhibitor (LY450139) | Colin et al.40     |
| Resveratrol               | Human neural stem cells (HhNSCs) | Added in medium (10 µM)         | Inhibited increase of TNF and IL-1β expression, preventing reduction on cell viability, prevented NF-κB increase, and normalized oxidative stress | Chiang et al.3     |
| Resveratrol               | Neuro-2a (N2a) cell culture     | Added in medium (0.2, 5, 10, 25 and 50 µM) | Decreased cytotoxicity and cellular apoptosis and inhibited tau hyperphosphorylation | He et al.4         |
| Resveratrol               | PC12 cell culture               | Added in medium (0, 10, 20 and 40 µM) | Increased cell viability and stimulated HO-1 production | Hui et al.3        |
| Resveratrol               | CSF samples of AD humans        | Prior treatment with an initial dose of 500 mg/day, increasing every 13 weeks until completion with 1,000 mg twice/day | Attenuated neuroinflammation, reduced proinflammatory markers and MMP-9 in the CSF, attenuated the cognitive and functional decline of individuals | Moussa et al.6     |
| Resveratrol               | Rat astrocytes (RA) and microglia N9 cell lines | Added in medium (5, 12.5, and 25 µM in RA cell line and 10, 20, and 40 µM in N9 cell line) | Inhibited the release of inflammatory cytokines by inhibiting NF-κB signaling | Haifeng et al.27   |
| Trans-resveratrol, piceatannol and trans-4-hydroxystilbene | Culture of primary neurons in the cortex of Sprague-Dawley rats | Added in medium (20 and 50 µM) | The stilbenoids inhibited Aβ-induced neurotoxicity, resulting in ROS decrease | Wen et al.17       |

Aβ: β-amyloid; H2O2: hydrogen peroxide; 6-OHDA: 6-hydroxydopamine; LPS: lipopolysaccharide; APP: amyloid precursor protein; COX-2: cyclooxygenase (COX)-2; iNOS: inducible nitric oxide synthase; HO-1: heme oxygenase-1; NF-κB: nuclear factor-κB; TNF: tumor necrosis factor; IL-6: Interleukin 6; SIRT 1: sirtuin 1; ROS: Reactive oxygen species; AGEs: advanced glycation end-products; NO: nitric oxide; IL-1β: Interleukin 1β; MMP-9: matrix metalloproteinase-9; BBB: blood–brain barrier; AD: Alzheimer’s disease; CSF: cerebrospinal fluid.
binding protein (CREB) protein expression. It is noteworthy that levels of SIRT1 and CREB protein are significantly reduced in AD brains, and this reduction is strongly associated with A\(\beta\) deposition in the cerebral cortex of these individuals. In light of this, the injection of resveratrol (0.5, 1.25, 5, 22, and 44 \(\mu\)M) in Sprague-Dawley rats prevents memory damage and A\(\beta\)-induced learning and restores SIRT1 levels and CREB phosphorylation in the hippocampus of these animals\(^{46}\). Similarly, in another experiment, CREB levels were decreased by A\(\beta\)42 peptides, and the oral administration of 20 and 40 mg/kg/day of resveratrol for three days of resveratrol reversed the condition\(^{19}\).

In an animal model of AD, 100 mg/kg supplementation of resveratrol for 10 months protected against memory impairment, improved exploratory behavior, and reduced anxiety. Resveratrol also increased AMPK levels by stimulating SIRT1 and, consequently, CREB protein. The hippocampus is one of the areas selectively affected in AD and the deterioration of hippocampal circuits contributes significantly to some effects of the disease, such as memory loss. The positive action of resveratrol on spatial learning and memory of the mice was associated with an improvement in the functioning of hippocampal circuits\(^{46}\).

Also in an animal model of AD, Porquet et al. observed that 1 g/kg/day supplementation of resveratrol increased life expectancy, reduced cognitive impairment by preserving memory, and reduced amyloid deposition in the hippocampus, and tau protein levels in the cortex and hippocampus. In addition, resveratrol activated the AMPK and SIRT1 pathways\(^{48}\). Similarly, in another study, the resveratrol injection (4 mg/kg) in mice reduced the decline of different memory types, such as working, nonspatial and locomotor functions, induced by LPS, and increased both nepriysin (NEP) and estradiol levels. In turn, estradiol also increased the NEP levels, which are responsible for decreasing A\(\beta\) deposition\(^{52}\). The effects of resveratrol on cognitive aspects are summarized in Table 3.

### Autophagic mechanisms

Among the mechanisms of neuronal protection, autophagy has been highlighted as a catabolic process related to the degradation and recycling of macromolecules and organelles\(^{10}\). There is strong evidence that, in the brain of AD patients, autophagic mechanisms are dysregulated and they participate in the intracellular degradation of A\(\beta\) in both in vitro and in vivo models\(^{46}\). Mechanisms responsible for the clearance of A\(\beta\) and tau proteins include the ubiquitin-proteasome system (UPS), the lysosomal autophagic system, and the actions of extracellular proteases\(^{18}\).

In order to determine the autophagy role in the anti-neurotoxic effect of resveratrol, PC12 cells were exposed to A\(\beta\) and induced CREB phosphorylation. It is noteworthy that levels of SIRT1 and CREB protein are significantly reduced in AD brains, and this reduction is strongly associated with A\(\beta\) deposition in the cerebral cortex of these individuals. In light of this, the injection of resveratrol (0.5, 1.25, 5, 22, and 44 \(\mu\)M) in Sprague-Dawley rats prevents memory damage and A\(\beta\)-induced learning and restores SIRT1 levels and CREB phosphorylation in the hippocampus of these animals\(^{46}\). Similarly, in another experiment, CREB levels were decreased by A\(\beta\)42 peptides, and the oral administration of 20 and 40 mg/kg/day of resveratrol for three days of resveratrol reversed the condition\(^{19}\).

### Table 3. Effects of resveratrol on cognitive aspects.

| Compound | Sample | Administration | Results | Reference |
|----------|--------|----------------|---------|-----------|
| Resveratrol | SAMR1 and SAMP8 mice | Supplementation of 1 g/kg/day for seven months | Increased life expectancy, reduced cognitive impairment, amyloid deposition in the hippocampus and tau levels in the cortex and hippocampus, activated AMPK and SIRT1 | Porquet et al.\(^{44}\) |
| Resveratrol | A\(\beta\)PP/PS1 mice | Supplementation of 16 mg/kg/day for 10 months | Prevented short-term memory loss, reduced the amount of amyloid plaques in the hippocampus and cortex, increased levels of mitochondrial complex IV | Porquet et al.\(^{51}\) |
| Resveratrol | Mice | Injection (4 mg/kg) | Reduced the decline in different memory types (working, nonspatial, and locomotor functions) induced by LPS, and increased both NEP and estradiol levels, consequently decreasing A\(\beta\) deposition | El-Sayed and Bayan\(^{18}\) |
| Resveratrol | A\(\beta\)PP/PS1 mice | Oral administration of 20 and 40 mg/kg/day for three weeks | Reduced A\(\beta\)-induced impairment on memory and learning, decreased IL-1\(\beta\), IL-6 and pro-apoptotic protein expression and reversed A\(\beta\)42-induced decrease of CREB | Wang et al.\(^{19}\) |
| Resveratrol | Sprague-Dawley rats | Injection into the hippocampus (0.5, 1.25, 5, 22, and 44 \(\mu\)M) | Prevented memory and learning impairment and restored the reduction of SIRT1 levels and CREB phosphorylation. | Wang et al.\(^{10}\) |
| Resveratrol | 3xTg-AD mice | Supplementation of 100 mg/kg/day for 10 months | Improved memory and cognition and reduced anxiety. Increased AMPK, SIRT1 and CREB phosphorylation. | Corpas et al.\(^{18}\) |

A\(\beta\): \(\beta\)-amyloid; AMPK: adenosine monophosphate-activated protein kinase; SIRT 1: sirtuin 1; IL-1\(\beta\): Interleukin 1\(\beta\); IL-6: Interleukin 6; LPS: lipopolysaccharide; NEP: nepriysin; CREB: cAMP response element binding protein.
and cell viability was reduced in a dose-dependent manner. Resveratrol (20 μM) attenuated this effect and was also responsible for regulating the expression of LC3-II and p62 proteins, which are autophagy markers. The resveratrol induced autophagic mechanism and was dependent on SIRT1.

Mitophagy is a specific autophagy form, which plays an important role in the mitochondria control. The selective removal of dysfunctional mitochondria by mitophagy is an effective way of limiting neuronal oxidative damage. In PC12 cells, resveratrol (1, 3, 10 and 30 μM) promoted mitophagy in Aβ-treated cells, in addition to reducing the oxidative state and attenuating peptide-induced apoptosis, indicating that resveratrol-induced mitophagy played a protective role against oxidative damage by removing dysfunctional mitochondria.

The mammalian rapamycin target (mTOR) is a potent inhibitor of autophagy and is negatively regulated by AMPK, which in turn controls important mechanisms for protein degradation. Vingtdeux et al. showed that the anti-amyloidogenic resveratrol mechanism involves the activation of AMPK in different cell lines and in primary mouse neurons, a process that resulted in the inhibition of mTOR, initiation of autophagy, and lysosomal clearance of Aβ.

UPS is the primary mechanism that maintains the balance between synthesis and protein degradation and is related to several neuronal functions, such as memory and plasticity. Functional changes in this system have been associated with early changes in AD. In mice, 100 mg/kg/day supplementation of resveratrol for 10 months decreased Aβ and tau levels, by reducing BACE1 enzyme and increasing nephrilysin (Aβ-degrading enzyme), in addition to normalizing ubiquitin levels.

**Metal ions and ion channels**

Another risk factor in AD onset and development in the elderly is the accumulation of metals. The metal ion homeostasis imbalance in the brain may exacerbate the oxidative properties of Aβ peptides and their toxicity through the production of ROS. Recent evidence indicates that high concentrations of metal ions such as copper, zinc and iron can bind to Aβ peptides, which promotes not only amyloid aggregation, but also accelerates ROS formation and cerebral oxidative stress.

A study conducted by Granzotto and Zatta in human neuroblastoma cells exposed to Aβ, Aβ-metal complexes, or metal ions concluded that treatment with resveratrol resulted in a neuroprotective effect, reduced the toxicity induced by Aβ-Iron and Aβ-Zinc complexes, and regulated levels of SOD antioxidant enzyme. Resveratrol concentration required to inhibit 50% (IC50) of cell viability was found to be 100 μM. A concentration of 15 μM was shown to be largely non-toxic.

It was also shown that the association of Aβ with aluminum had the most potent effect on reducing cell viability. Aluminum acts as a neurotoxin capable of enhancing neuroinflammatory processes and, as studies have demonstrated, is associated with exacerbation of oxidative stress, amyloid deposition, and plaque formation in the brain. Both Aβ peptides and aluminum are capable of potentiating the formation of ROS, leading to DNA damage.

Zaky et al. demonstrated that oral administration of 0.5 mg/kg of resveratrol in Wistar rats for one month attenuated aluminum-induced neuroinflammation, inhibiting TNF, IL-6 and iNOS release in the animals’ brains.

Ion channels have become drug targets for neurodegenerative diseases treatment and voltage-gated potassium channels (VGPC), present in the hippocampus, and play a crucial role in neuronal activity. β-amyloid peptides can cause excitotoxicity in pyramidal neurons, as demonstrated by Yin et al., in which Aβ treatment increased the excitability of these cells in the CA1 region of the rat hippocampus. Treatment with resveratrol (10 μM) attenuated this effect by recovering the activity of two important VGPCs.

**Perspectives**

The results from both in vitro and in vivo studies indicate that resveratrol is a promising and safe compound for use in the AD treatment. However, as discussed by Moussa et al., one of the major impediments to current AD therapeutic approaches is the limited evidence demonstrating significant clinical benefits. There is a lack of phase 3 clinical trials that test the clinical benefits of resveratrol in AD as a primary outcome.

Resveratrol seems to exert beneficial effects on AD due to its diverse pharmacological properties. However, applicability for disease treatment is limited by factors such as low solubility, photosensitivity, short half-life and rapid metabolism and excretion, contributing to low bioavailability.

In addition, resveratrol is poorly hydrosoluble and chemically unstable and is degraded when exposed to high temperature, pH changes, ultraviolet radiation, and some enzymes.

The BBB represents a significant obstacle to the entry of drugs into the CNS, restricting the pharmacological options for neurodegenerative diseases. However, studies show that resveratrol is able to cross the BBB as discussed by Vingtdeux et al. and Capiralla et al., in which orally administered resveratrol in rats was able to reach the brain and reduce Aβ levels and amyloid deposition in the cerebral cortex. This shows that resveratrol is not only bioavailable, but also bioactive.

The complexity of AD and lack of scientific understanding regarding the onset and progression make the search for therapeutic strategies difficult. Treatment with only either antioxidants or anti-inflammatory drugs has been shown ineffective in preventing AD. Therefore, the development of multi-target drugs is an alternative approach.

Authors of the studies reviewed herein seemingly agree that further research is needed to clarify the mechanisms by which resveratrol affects AD pathophysiology, and to demonstrate efficacy and safety in humans. Therefore, phase 3 clinical trials are required to test the clinical benefits of resveratrol. However, these studies provide an excellent foundation for future exploration.
In addition to resveratrol, other polyphenols have gained attention for playing important roles in the pathophysiological mechanisms of AD. Curcumin, isolated from the rhizome of Curcuma longa (turmeric), improved mitochondrial activity and cell viability in cells incubated with Aβ (66.3 mM final concentration)\(^6\), reduced Cavelon-1 (protein that participates in the cleavage of APP and the generation of Aβ) levels, potentially inactivating GSK-3β and inhibiting Tau hyperphosphorylation (5 μM in N2a/APP695/42 cells and 1.0 g/kg in APP/PS1 mice)\(^57\). In mice, curcumin suppressed glia activation and neuroinflammation, thereby improving induced tau/amyloid pathology and cognitive impairment (4 g/kg)\(^58\). Epigallocatechin gallate (EGCG) polyphenol found in green tea reduced in vitro amyloid accumulation and improved cognitive decline in SAMP8 mice (intragastric administration of 5 and 15 mg/kg)\(^59\), and suppressed the transcription and translation of BACE1. This attenuated Aβ formation, which reduced pro-apoptotic protein expression, NF-κB activity and inhibited oxidative stress (5–100 μM)\(^60\). EGCG also suppressed TNF, IL-6, IL-1β and iNOS expression, restored intracellular antioxidant levels, inhibited NF-κB activation and cytotoxicity (5 to 20 μM)\(^61\). Prolonged consumption of EGCG at relatively high doses (15 mg/kg) by SAMP8 mice improved animals’ memory, reduced their Aβ and BACE1 levels, prevented hyperphosphorylation of tau, and reversed the decreased synaptic protein marker\(^62\). Cocoa polyphenols have also been studied due to their possible neuroprotective effects. Cocoa extract was effective in reducing the oligomerization of Aβ and protected against Aβ-induced long-term potentiation deficit\(^63\). Cocoa polyphenols resulted in antioxidant effect and neuroprotection by brain-derived neurotrophic factor (BDNF) activation\(^64\).

The potential role of other polyphenols in the pathophysiological aspects of AD is remarkable. Chan et al., who determined the relative potencies of nine food constituents in relation to AD including curcumin and EGCG, observed resveratrol to be a weak chelating agent, with very high concentrations required for 50% metal chelation. Resveratrol was also the least antioxidant compound and 100 μM was required to inhibit 27% of the Aβ fibrillar formation\(^41\). These findings further highlight the need of studies combining polyphenols as a multi-target strategy for the prevention or treatment of AD.

**CONCLUSIONS**

Much effort has been employed in investigating the potential contribution of resveratrol to the treatment and attenuation of AD. Studies with varying scope and outcomes seemingly converge on the conclusion that this polyphenol provides a promising alternative therapeutic, capable of acting on various aspects of disease pathophysiology.

However, it is noteworthy that most of this research was conducted in cell culture or animal models, and there is a lack of human clinical studies that demonstrate the safety and efficacy of resveratrol for the treatment of AD. The exact pathophysiology of AD is poorly understood, and there are no models that accurately portray the multifactoriality of the disease; these are obstacles that present important challenges for successful outcomes of research in this area.

Although the antioxidant and anti-inflammatory function of resveratrol has been widely described in the literature, its metabolism and structural characteristics present challenges for application in therapeutic settings. The action mechanisms have not been completely understood, and the optimal dose and route of administration in AD patients are unclear. In addition, there is no consensus on the therapeutic impact of resveratrol obtained through the diet, combined with other nutrients in the food matrix, compared to its action alone, either in the form of extracts or synthetic analogues.

In view of these findings, we conclude that, although resveratrol appears to mitigate some pathophysiological aspects of AD, further studies are needed to prove the safety and efficacy of this compound in humans.

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Sousa JC et al. Resveratrol in Alzheimer's disease: a review