

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'-trihidroxil-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 incluiu 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; sirtuína 1; antioxidantes; polifenóis; nutracêuticos.

The aging process physiology is associated with cognitive function loss, impacting on a decrease in abilities such as learning, memory and intellectual activity, due to the brain function degeneration¹.

Alzheimer's disease (AD) is the most common form of neurodegenerative disorder, affecting the cortex and hippocampus^{2,3}, and leads to a progressive cognitive function worsening in the individual, resulting in impairments in speech,

word and object recognition, as well as the inability to perform voluntary movements⁴. AD mainly affects the elderly and is the fifth cause of death in this population⁵.

Such disease is particularly characterized by the presence of two pathological markers: neurofibrillary tangles, resulting from hyperphosphorylation and abnormal deposition of tau protein, and presence of senile plaques, which are formed by the deposition of β -amyloid peptides ($A\beta$)⁶.

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Conflict of interest: There is no conflict of interest to declare.

Received on September 04, 2019; Received in its final form on December 24, 2019; Accepted on January 17, 2020.

Although there is currently no cure for AD⁷, 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 mechanisms¹.

Resveratrol (3,5,4'-trihydroxy-trans-stilbene) is a polyphenol produced by several plants, and the main food sources are grapes and red wine⁸. This compound has gained notoriety in scientific circles, due to its biological and pharmacological properties⁹. It seems to exert beneficial effects *in vitro* and *in vivo*, although the precise mechanisms are still poorly understood¹⁰.

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 A β levels¹¹.

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 A β 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 A β 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 A β , which appears to trigger the inflammation and oxidative stress that leads to neurodegeneration³. As a result, most of the AD studies in recent years have been conducted based on the amyloid cascade hypothesis, which advocates that A β deposition is the primary event in disease pathogenesis^{12,13,14}.

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)¹⁵. β -secretase/BACE1 aspartic protease and γ -secretase proteolytic complex cleave APP to produce A β peptides^{16,17}. An imbalance between the production and clearance of these peptides enhances their aggregation and triggers the formation of senile plaques⁶. However, the reason for excessive A β in the brain is not known¹⁸.

The deposition of A β peptides in brain regions related to memory and learning, such as the frontal cortex and hippocampus, is considered an early event in disease progression¹⁹. 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 development²⁰, especially those terminated at amino acid 42 (A β 42)¹².

Neuroinflammation is another important characteristic feature in AD, which is manifested through the microglia proliferation and activation²¹. 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 parenchyma²⁰.

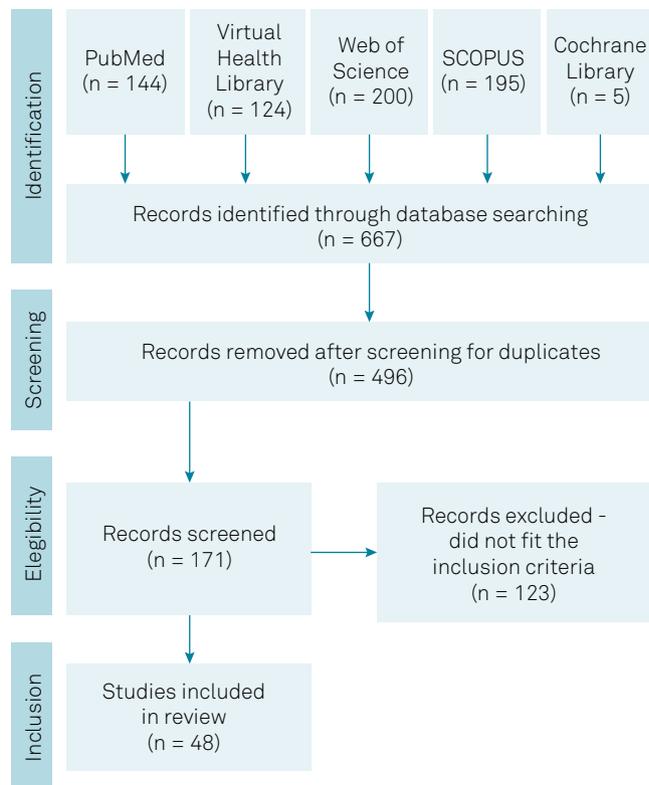


Figure 1. Flow diagram of study selection.

Upon detection of damage or immune stimulus in the brain, such as that caused by A β peptides, microglia are activated and produce proinflammatory mediators, for instance, tumor necrosis factor (TNF), interleukin-1 β (IL-1 β) and nitric oxide (NO) in response to it. The accumulation of these mediators contributes to neuronal damage and disease progression⁸. In addition, the NF- κ B transcription factor is considered the primary regulator of the inflammatory response in AD²⁰.

Free radicals also seem to play a key role in brain aging¹⁵. Several studies have found an association between A β -promoted cytotoxicity and oxidative stress as a result from an imbalance between the production and removal of reactive oxygen species (ROS)¹⁷.

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 stress¹⁵.

Currently, the drugs available for treating AD are not completely effective and do not alter the disease progression^{13,22,23}. It is, therefore, critical that new therapies aimed to prevent and manage this chronic and debilitating disease be developed²⁴.

Resveratrol

Several foods and natural products, whose chemical components demonstrate interesting pharmacological properties, have been suggested as AD modifying agents^{10,17}.

Polyphenols are natural compounds derived from plants, fruits and vegetables, whose biological properties have demonstrated several beneficial effects, such as antioxidant and anti-inflammatory activities²³.

Resveratrol is a non-flavonoid polyphenol⁸ part of the stilbene family²³, which can be found in grape skin and seeds, blackberries, peanuts, and vegetables²⁵. Red wine is therefore also a good source of resveratrol, to which the potential beneficial health effects of this beverage has been attributed²⁶.

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 interest².

Effects of resveratrol on Alzheimer's disease

Disaggregation of A β -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 A β -promoted cytotoxicity may provide an important therapeutic strategy for AD, as demonstrated by Feng et al. Although it does not prevent oligomerization of

A β 42, resveratrol seems to stabilize preformed oligomers and to attenuate oligomer toxicity²⁶. This outcome is similar to the findings of Ladiwala et al. and Rushworth et al., in which resveratrol was also able to selectively remodel A β oligomers to non-toxic structures^{27,28}.

Aromatic interactions between compounds and A β peptides are a determining factor in the inhibition of fibrillar formation and reduction of amyloid toxicity²⁶. As verified also by Ge et al., resveratrol was able to bind directly to the amyloid structure¹². Fu et al. have also noted that resveratrol binds to the N-terminus (residue 5-20) of the A β 42 monomer and caps the height of oligomers, resulting in a reduction in toxicity²⁹. Other studies have also shown a reduction in amyloid aggregation, both at a concentration of 50³⁰ and 100 μ M³¹.

In CHO-APP^{swe} cells, administration of resveratrol (100 μ M) reduced amyloid burden, APP expression, and cleavage³². Karuppagounder 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 significant³³.

Similarly, Varamini et al. found that resveratrol supplementation of 174 mg/kg/day in A β PP/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 processes³⁴. In AD/TTR+/- mice, the same amount of resveratrol supplementation increased transthyretin levels (TTR) and stabilized TTR tetramers, which bind more strongly to A β peptides, preventing their aggregation³⁵.

In addition, in A β PP/PS1 mice, the supplementation of lower doses (100 ppm by weight) of resveratrol, or its synthetic analog LD55, significantly decreased the density of A β plaques in different brain regions, including the cortex and hippocampus²⁰. The effects of resveratrol on A β -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 factors³⁶. 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- κ B pathway²⁰.

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- κ B signaling pathway in activated microglia²⁰.

In rat astrocytes (RA) and microglia N9 cell lines, resveratrol administration also promoted anti-inflammatory effects by inhibiting NF- κ B signaling and release of inflammatory cytokines at different concentrations (5, 12.5, and 25 μ M in RA cell line and 10, 20, and 40 μ M in N9 cell line). In this experiment, cytotoxicity was found when the concentration of resveratrol was higher than 50 μ M in the RA cell line and higher than 80 μ M in the N9 microglia cell line³⁷.

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 A β -mediated microglia activation and lipopolysaccharide (LPS)-stimulated activation of NF- κ B, reducing the expression of its target genes, such as TNF and IL-6³⁸. In BV-2 cells activated by β -amyloid oligomers, resveratrol (1, 3, 10 or 30 μ M) reduced the production of reactive species and inhibited the production of inflammatory mediators, among them NO in

a dose-dependent manner⁸. Overproduction of NO has been associated with AD, resulting in damage to DNA and the mitochondrial structure³⁹.

In HEK-AbPP cells treated with a γ -secretase inhibitor (LY450139), additional treatment with resveratrol (0.5 μ M) 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 drugs⁴⁰.

Neuroprotective effects were also observed with the injection of resveratrol in rats (100 μ M/5 μ L), 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 A β ³⁹.

Table 1. Effects of resveratrol on A β -peptide aggregation.

Compound	Sample	Administration	Results	Reference
Resveratrol, catechins, curcumin and ginkgolides	A β 42 medium	Added in medium (2, 10 and 100 μ M)	Resveratrol inhibited fibrillar formation and aggregation of A β 42. It did not prevent oligomerization, but it stabilized them, and less toxic oligomers were formed.	Feng et al. ²⁶
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	A β structures samples	Added in medium (20 μ M)	Remodeled A β oligomers into non-toxic oligomers and monomers.	Ladiwala et al. ²⁷
Resveratrol	Solution of A β and fibrillar A β	Added in medium (50 μ M)	Bound directly to the monomeric and fibrillar amyloid structure.	Ge et al. ¹²
Resveratrol	A β 42 medium	Added in medium (50 μ M)	Reduced amyloid aggregation.	Hung et al. ³⁰
Resveratrol	A β PP/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 Transthyretin)	Varamini et al. ³⁴
Resveratrol and EGCG	A β 42 medium	Added in medium (10:1 molar excess of resveratrol and 4:1 molar excess of EGCG)	Resveratrol and EGCG re-modelled fibrillar conformation of A β oligomers into nonfibrillar oligomers and they were no longer cytotoxic	Rushworth et al. ²⁸
Resveratrol and curcumin	A β 42 medium	Added in medium (1:1 molar ratio)	Resveratrol bound to the N-terminus (residue 5-20) of the A β 42 monomer and caps the height of the oligomers, resulting in a reduction in toxicity	Fu et al. ²⁹
Resveratrol and LD55	A β PP/PS1 mice	Supplementation of 100 ppm for 12 months	Decreased A β plaque density in brain regions, such as cortex and hippocampus	Solberg et al. ²⁰
Resveratrol	Transgenic <i>C. elegans</i> strain CL2006, expressing A β 1-42	Added in medium (100 μ M)	Reduced amyloid aggregation	Regitz et al. ³¹
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 A β peptides	Santos et al. ³⁵
Resveratrol	CHO-APPsw cell culture	Added in medium (100 μ M)	Reduced amyloid burden, expression of APP and its cleavage	Sathya et al. ³²

A β : β -amyloid; GSK3: glycogen synthase kinase 3 β ; EGCG: 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- κ B phosphorylation in the hippocampus⁴¹.

In mouse neuroblastoma (N2a) cells incubated with A β , pretreatment with resveratrol (5 μ M) prevented the abnormal expression of peroxiredoxins and mitochondrial structural genes and preserved mitochondrial function, protecting cells against A β toxicity⁴². Also in N2a cells, resveratrol (0, 2.5, 5, 10, 25 and 50 μ M) significantly reduced formaldehyde-induced cytotoxicity and cellular apoptosis, and inhibited tau protein hyperphosphorylation in a dose-dependent manner²⁴. Similar results were found in another experiment, in which resveratrol (0, 10, 20 and 40 μ M) dose-dependently increased the viability of A β -treated PC12 cells and stimulated HO-1 production. The cytoprotective mechanism was mediated by the PI3K/Akt/Nrf2 pathway⁴³, which has also been found responsible for the neuroprotective effect of resveratrol, resulting in a decrease of ROS¹⁷.

Several studies have shown that the activation of AMPK (adenosine monophosphate-activated protein kinase) suppresses inflammation by inhibiting NF- κ B, preventing oxidative stress. Resveratrol is a potent activator of AMPK, thereby implicating another pathway through that its neuroprotective effects may be exerted³.

An experiment in human neural stem cells (hNSCs) demonstrated that A β -treated cells increase the expression of TNF and IL-1 β , thereby decreasing cell viability. In addition to inhibiting such deleterious effects, resveratrol (10 μ M) prevented the increase of NF- κ B and normalized oxidative stress. These effects were attributed to the AMPK pathway³.

The antioxidant resveratrol effects were also verified by Rege et al. in an H19-7 neuronal cell line derived from rat hippocampus. Resveratrol (10 μ M) 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 glutathione¹⁵.

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 AD¹⁵.

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 μ M) reduced ROS production in cells treated with AGEs⁴⁴.

In addition, RAGEs located at the BBB are the main gateway for A β 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 permeability⁴⁵.

Plasma and CSF analyses in patients with confirmed AD showed that previous treatment with resveratrol (initial dose was 500 mg/day and was increased every 13 weeks until a final dose of 1,000 mg twice a day) attenuated neuroinflammation, reduced proinflammatory markers, and decreased MMP-9 in the CSF. Decreased levels of MMP-9 suggest that treatment with resveratrol may reduce CNS permeability and limit the infiltration of leukocytes and other inflammatory agents into the brain, thus preserving the integrity of BBB. Resveratrol also attenuated the patients' cognitive and functional decline⁴⁶.

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- κ B signaling pathway. Through suppression of this pathway, SIRT1 is also able to protect neurons against A β toxicity³⁶.

SIRT1 is one of a class of NAD⁺-dependent histone deacetylases that play an essential role in the cellular functioning regulation^{2,47}, by the deacetylation of substrates important in neurodegenerative diseases⁴⁸. Table 2 shows the resveratrol effects on the neuroinflammation and activation of SIRT1.

Resveratrol (0, 2.5, 5, 7.5, 10 and 15 μ M) protected SK-N-BE neuroblastoma cells against induced oxidative stress and increased cell viability. However, when SIRT1 was up regulated with administration of sirtinol, antioxidant activity of resveratrol was suppressed⁴⁷. In PC12 cells, resveratrol (12.5, 25, 50 and 100 μ M) increased cell viability, reduced apoptosis, and attenuated A β -induced neurotoxicity. The peptide-induced suppression of SIRT1 activity was reversed by resveratrol, indicating that the protective effects are mediated by the sirtuin pathway².

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 treatment⁴⁹.

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 H_2O_2 and 6-OHDA, increasing cell viability. Sirtinol inhibited SIRT1	Albani et al. ⁴⁷
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 $\text{A}\beta$ 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. ³⁹
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 $\text{A}\beta$ -mediated microglia	Capiralla et al. ³⁸
Resveratrol	PC12 cells	Added in medium (12.5, 25, 50 and 100 μM)	Increased cell viability, reduced apoptosis, attenuated $\text{A}\beta$ -induced neurotoxicity and regenerated SIRT1 activity	Feng et al. ²
Resveratrol and AGK-2	Sprague-Dawley's astroglia 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. ⁴⁹
Resveratrol and LD55	$\text{A}\beta\text{PP}$ /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. ⁴⁴
<i>Trans</i> -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-1 β 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. ⁴⁵
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-1 β 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, 5, 10, 25 and 50 μM)	Decreased cytotoxicity and cellular apoptosis and inhibited tau hyperphosphorylation	He et al. ²⁴
Resveratrol	PC12 cell culture	Added in medium (0, 10, 20 and 40 μM)	Increased cell viability and stimulated HO-1 production	Hui et al. ⁴³
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. ⁴⁶
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. ³⁷
<i>Trans</i> -resveratrol, piceatannol and <i>trans</i> -4-hydroxystilbene	Culture of primary neurons in the cortex of Sprague-Dawley rats	Added in medium (20 and 50 μM)	The stilbenoids inhibited $\text{A}\beta$ -induced neurotoxicity, resulting in ROS decrease	Wen et al. ¹⁷

$\text{A}\beta$: 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-1 β : Interleukin 1 β ; 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 β deposition in the cerebral cortex of these individuals. In light of this, the injection of resveratrol (0.5, 1.25, 5, 22, and 44 μ M) in Sprague-Dawley rats prevents memory damage and A β -induced learning and restores SIRT1 levels and CREB phosphorylation in the hippocampus of these animals⁵⁰. Similarly, in another experiment, CREB levels were decreased by A β 42 peptides, and the oral administration of 20 and 40 mg/kg/day of resveratrol for three days of resveratrol reversed the condition¹⁹.

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 circuits¹⁸.

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 pathways⁴⁸.

Similar results were found in another study, in which the 16 mg/kg/day supplementation of resveratrol prevented loss of short-term memory and decreased the amount and load of amyloid plaques in the hippocampus and cortex of the animals⁵¹. In addition, Wang et al. found that administration of 20 and 40 mg/kg/day of resveratrol in mice was also effective in reducing A β -induced memory and learning impairment and decreasing the expression of proinflammatory cytokines (IL-1 β and IL-6)¹⁹. Also, 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 neprilysin (NEP) and estradiol levels. In turn, estradiol also increased the NEP levels, which are responsible for decreasing A β deposition⁵². 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 organelles¹⁰. There is strong evidence that, in the brain of AD patients, autophagic mechanisms are dysregulated and they participate in the intracellular degradation of A β in both *in vitro* and *in vivo* models¹⁶. Mechanisms responsible for the clearance of A β and tau proteins include the ubiquitin-proteasome system (UPS), the lysosomal autophagic system, and the actions of extracellular proteases¹⁸.

In order to determine the autophagy role in the anti-neurotoxic effect of resveratrol, PC12 cells were exposed to A β

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. ⁴⁸
Resveratrol	A β 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 β deposition	El-Sayed and Bayan ⁵²
Resveratrol	A β PP/PS1 mice	Oral administration of 20 and 40 mg/kg/day for three weeks	Reduced A β -induced impairment on memory and learning, decreased IL-1 β , IL-6 and pro-apoptotic protein expression and reversed A β 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 μ M)	Prevented memory and learning impairment and restored the reduction of SIRT1 levels and CREB phosphorylation.	Wang et al. ⁵⁰
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	Corpas et al. ¹⁸

A β : β -amyloid; AMPK: adenosine monophosphate-activated protein kinase; SIRT 1: sirtuin 1; IL-1 β : Interleukin 1 β ; IL-6: Interleukin 6; LPS: lipopolysaccharide; NEP: neprilysin; 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 SIRT1¹⁰.

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 A β -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 mitochondria⁵³.

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 A β ¹⁶.

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 A β and tau levels, by reducing BACE1 enzyme and increasing neprilysin (A β -degrading enzyme), in addition to normalizing ubiquitin levels¹⁸.

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 A β peptides and their toxicity through the production of ROS⁶. Recent evidence indicates that high concentrations of metal ions such as copper, zinc and iron can bind to A β peptides, which promotes not only amyloid aggregation, but also accelerates ROS formation and cerebral oxidative stress⁵⁴.

A study conducted by Granzotto and Zatta in human neuroblastoma cells exposed to A β , A β -metal complexes, or metal ions concluded that treatment with resveratrol resulted in a neuroprotective effect, reduced the toxicity induced by A β -Iron and A β -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-toxic⁶.

It was also shown that the association of A β with aluminum had the most potent effect on reducing cell viability⁶. 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 A β peptides and aluminum are capable of potentiating the formation of ROS, leading to DNA damage³⁶.

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' brains³⁶.

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 A β 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 VGPCs⁵⁵.

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 treatment²⁶. However, as discussed by Moussa et al., one of the major impediments to current AD therapeutic approaches is the limited evidence demonstrating significant clinical benefits⁴⁶. 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 bioavailability²². In addition, resveratrol is poorly hydrosoluble and chemically unstable and is degraded when exposed to high temperature, pH changes, ultraviolet radiation, and some enzymes²⁵.

The BBB represents a significant obstacle to the entry of drugs into the CNS, restricting the pharmacological options for neurodegenerative diseases²². However, studies show that resveratrol is able to cross the BBB⁴⁵ 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 A β levels and amyloid deposition in the cerebral cortex. This shows that resveratrol is not only bioavailable, but also bioactive^{16,38}.

The complexity of AD and lack of scientific understanding regarding the onset and progression make the search for therapeutic strategies difficult¹³. 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 approach²³.

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 A β (66.3 mM final concentration)⁵⁶, reduced Caveolin-1 (protein that participates in the cleavage of APP and the generation of A β) levels, potentially inactivating GSK-3 β and inhibiting Tau hyperphosphorylation (5 μ M in N2a/APP695swe 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 A β formation, which reduced pro-apoptotic protein expression, NF- κ B activity and inhibited oxidative stress (5–100 μ M)⁶⁰. EGCG also suppressed TNF, IL-6, IL-1 β and iNOS expression, restored intracellular antioxidant levels, inhibited NF- κ B activation and cytotoxicity (5 to 20 μ M)⁶¹. Prolonged consumption of EGCG at relatively high doses (15 mg/kg) by SAMP8 mice improved animals' memory, reduced their A β and BACE1 levels, prevented hyperphosphorylation of tau, and reversed the decreased synaptic protein marker⁶². Cocoa polyphenols have also been studied due to their possible neuroprotective effects. Cocoa extract was effective in reducing the oligomerization of A β and protected against A β -induced long-term potentiation deficit⁶³. Cocoa polyphenols resulted in antioxidant effect and neuroprotection by brain-derived neurotrophic factor (BDNF) activation⁶⁴.

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 μ M was required to inhibit 27% of the A β fibrillar formation¹⁴. 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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