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Resveratrol and neuroprotection: an insight into prospective therapeutic approaches against Alzheimer's disease from bench to bedside

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Abstract

Alzheimer's disease (AD) is the most common cause of dementia and cognitive impairment; yet, there is currently no treatment. A buildup of Aβ, tau protein phosphorylation, oxidative stress, and inflammation in AD is pathogenic. The accumulation of amyloid-beta (Aβ) peptides in these neurocognitive areas is a significant characteristic of the disease. Therefore, inhibiting Aβ peptide aggregation has been proposed as the critical therapeutic approach for AD treatment. Resveratrol has been demonstrated in multiple studies to have a neuroprotective, anti-inflammatory, and antioxidant characteristic and the ability to minimize Aβ peptides aggregation and toxicity in the hippocampus of Alzheimer's patients, stimulating neurogenesis and inhibiting hippocampal degeneration. Furthermore, resveratrol's antioxidant effect promotes neuronal development by activating the silent information regulator-1 (SIRT1), which can protect against the detrimental effects of oxidative stress. Resveratrol-induced SIRT1 activation is becoming more crucial in developing novel therapeutic options for AD and other diseases that have neurodegenerative characteristics. This review highlighted a better knowledge of resveratrol's mechanism of action and its promising therapeutic efficacy in treating AD. We also highlighted the therapeutic potential of resveratrol as an AD therapeutic agent, which is effective against neurodegenerative disorders.

Keywords Alzheimer's disease · Resveratrol · SIRT1 · Oxidative stress · Neuroinflammation · Autophagy induction

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Introduction

Alzheimer's disease (AD), classified as a neurodegenerative disease (NDD) associated with aging, affects above 40 million individuals worldwide and has grown into a prime public health concern with significant personal, societal, and economic consequences [1–4]. AD impacts the central nervous system (CNS), marked by pathological brain characteristics, involving neurofibrillary tangles, amyloid-beta (Aβ) plaques, and tau protein phosphorylation alterations [5]. The most prevalent AD signs are neurotrophin and neurotransmitter imbalance, oxidative stress (OS), decreased synaptic function, mitochondrial dysfunction, and psychiatric disorders involving memory loss and persistent intellectual disability [6–8]. Moreover, the AD physiological changes implicated may commence many years earlier significant reductions in cognitive capacity and cognition manifest. The contemporary majority opinion is that aging is considered one of the common AD risk factors pathology. Yet, the specific etiology and pathophysiology of AD are still unknown.

Moreover, there are no drugs available to slow or stop the progression of the disease [9–12]. The recent advances in pathophysiology, molecular biology, and AD diagnostics give hope for early prevention and therapeutics. Still, researchers try to understand and weaken preconceptions about the primary disease theoretical foundation [13]. Furthermore, while most therapeutic approaches focus on preventing Aβ plaque aggregation and blocking Aβ production, several scientists are working on options for tau protection from nonsteroidal anti-inflammatory medication-induced brain cell inflammation and tangle formation [14–16]. Treatments that prolong AD development for 5 years can save approximately half a million dollars per person [17]. Many studies have concentrated on the therapeutic effect of a vast range of natural products for NDDs, notably those produced from plant sources [18–21]. Natural bioactive compounds are pharmacologically desirable because of their minimal complications and multitarget mode of action, which are essential for controlling and treating multifaceted disorders that cause neurodegeneration [22, 23]. Polyphenolic substances, such as resveratrol, are among the many natural chemicals being investigated for their neuroprotective properties [24–26]. Resveratrol is a naturally occurring chemical found in plants, especially grapevines and other fruit species. It has a wide range of biological properties, namely antioxidant, anti-inflammatory, and neuroprotective properties [27, 28]. Resveratrol may provide AD neuroprotection via primarily activating silent information regulator 1 (SIRT1) expression [29]. The activation of SIRT1, which is expressed in the adult human brain, primarily in neurons, is one of the vital neuroprotective mechanisms of resveratrol. Resveratrol activates SIRT1, which inhibits Aβ-induced microglial apoptosis and improves cognitive function. Although overexpression of SIRT1 is linked to the main mechanisms of resveratrol, its subsequent neuroprotective effect is obscure [30]. SIRT1 overexpression, on the other hand, regulates reactive oxygen species (ROS), nitric oxide (NO), proinflammatory cytokine production, and Aβ expression in the brains of Alzheimer's patients and so plays a crucial role in neuronal protection [31]. Resveratrol is a polyphenol found in various plants, particularly the skin and seeds of grapes, that works as a phytoalexin against bacteria and fungi [32, 33].

Resveratrol has been shown to have a broad spectrum of biological roles in cardiovascular and cancer diseases and revenant disorders treatment, together with AD. It also has antimicrobial, phytoestrogenic, vasorelaxant, cardioprotection, and anticancer properties [34, 35]. Numerous research has been conducted to see if resveratrol has therapeutic potential for AD and other NDDs [21]. Based on existing evidence, this review highlighted exploring the prospective consequences of resveratrol usage in NDDs. Understanding the mechanisms underlying AD may aid in the development of novel therapeutic options. We also highlighted to assess if there was adequate data that resveratrol can prevent AD pathomechanisms and considerably prolong the development of the disease. In our current review, we also addressed the therapeutic benefits of resveratrol as an AD therapeutic agent which is effective against NDDs.

Methodology

This literature review searched multiple databases, namely PubMed, Scopus, and Web of Science. The keywords used were resveratrol, neurodegeneration, neuroprotection, AD, and SIRT1. English Research reports, review articles, and original research articles published from 1999 to 2022 were selected and evaluated. An algorithm exacted by the flow chart displayed in Fig. 1 (according to Page et al. recommendations [39, 40] was used), which included all of the steps/selection requirements for the necessary material in the literature.

Chemistry of Resveratrol

Resveratrol considers a member of the stilbenes family of polyphenolic chemicals, a group of secondary metabolites found in extensively spread plants. It has a double bond that can be isomerized cis or trans and two phenolic rings on either end of the double bond (Fig. 2) [41]. Trans-resveratrol is the end product of the phenylpropanoid pathway, used

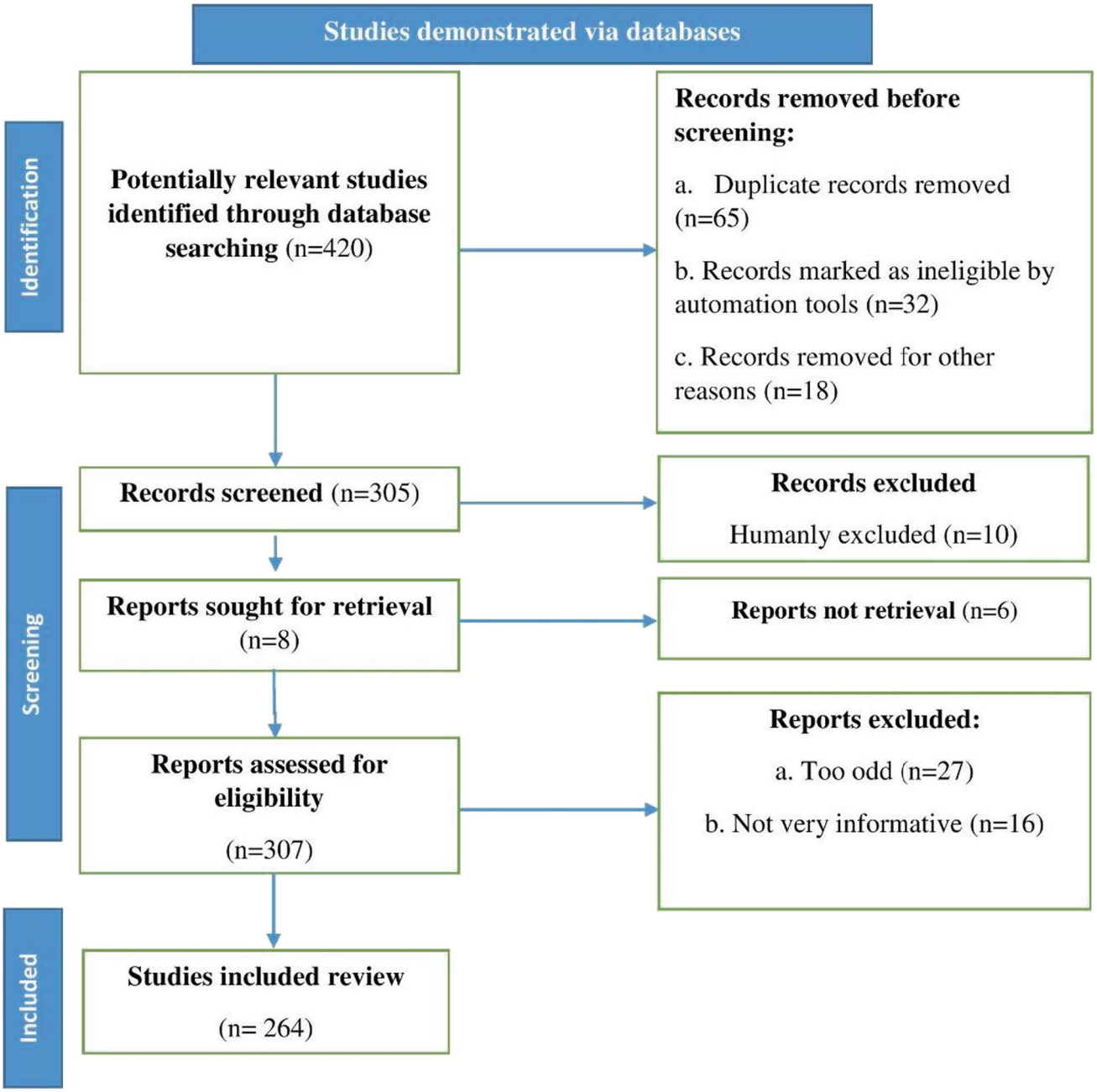

Fig. 1 Flow chart scheming the stages involved in selecting published data for inclusion in the present study; *n* = number of literature reports

to synthesize it in plants. Resveratrol can undergo multiple structural alterations after production when plants are under particular circumstances or during the postharvest period. Its trans-form can isomerize resveratrol when exposed to UV light [42]. A resveratrol aglycone can be converted to trans-picked or cis-piceid glycoside forms in resveratrol 3-O-beta-glycosyltransferases [43]. Resveratrol's stability and translocation inside the cell are influenced by the carbohydrate moiety [43, 44]. When exposing a plant to various biotic and abiotic stressors, the catalyzation of intracellular enzyme resveratrol O-methyltransferase forms the pterostilbene. A resveratrol methyl has great effectiveness and potential pharmacological properties than resveratrol [45, 46]. Isoprenylated resveratrol analogs arachidic-1 and arachidic-3 have also offered potential health benefits [47]. Plants can oligomerize resveratrol monomers to produce complex polyphenolic secondary metabolites known as "Resveratrol oligomers," involving 2–8 resveratrol units. There have been around 300 reports of resveratrol oligomers so far [48].

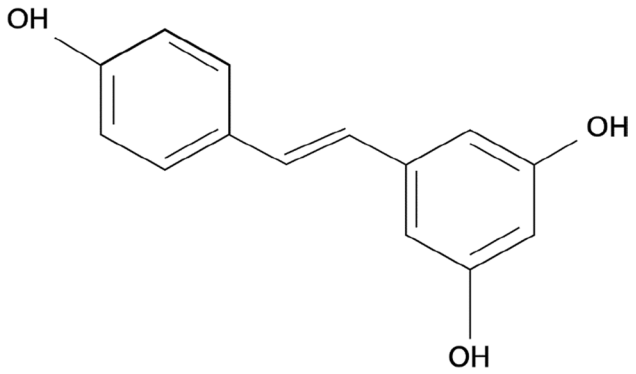

Fig. 2 Chemical structure of resveratrol

Bioavailability and Resveratrol as a Potential Therapeutic

Resveratrol is a polyphenolic phytoalexin substance present in grapes and wine. Resveratrol levels vary widely in wine, although this is greater abundance in red grapes and red wine. Animal model studies have provided information on absorption, metabolism, and subsequent bioavailability [49]. In most investigations, the oral bioavailability of resveratrol was less than 1%, explaining the inconsistencies between in vitro and in vivo studies [50, 51]. Resveratrol's low bioavailability is due to its weak water solubility, limited chemical stability, and rapid metabolism, especially when orally administered. Therefore, improving resveratrol bioavailability has been a significant problem in developing resveratrol medicines for human patients. The goal is to strengthen resveratrol's pharmacokinetics by somewhat limiting the resveratrol metabolism with the co-administration of resveratrol metabolism inhibitors because resveratrol is easily absorbed but quickly metabolized. According to the findings, glucuronidation or sulfation is used to manufacture the bulk of trans-resveratrol metabolites. Therefore, substances like piperine, an alkaloid derived from black pepper (*Piper* spp.) that inhibits glucuronidation, greatly enhanced resveratrol's in vivo bioavailability following co-administration [52–54]. In the same way, combining polyphenolic chemicals such as quercetin, genistein, curcumin, melatonin, and tea polyphenols or anticancer medications with resveratrol might enhance resveratrol in vivo activity [2, 55]. While these synergistic mechanisms of action are still unknown, more research is needed.

Resveratrol's pharmacodynamics and pharmacokinetics have been researched in several body organs. Resveratrol's therapeutic impact is primarily dosage-dependent [56]. For example, the effect on cells with Aβ 1–41 by the resveratrol effect depends on concentration and biphasic. Resveratrol defends against Aβ, which induces toxicity at lower concentrations but suppresses cellular growth regardless of amyloid plaque buildup [57]. Resveratrol can be delivered intravenously in sufficient quantities to target brain regions. Due to undesirable pharmacokinetics, dietary resveratrol has several limitations, such as relatively low stability, sensitivity to light, and the ability to be quickly metabolized earlier to enter the bloodstream [2]. Although resveratrol delivered orally increases life expectancy in transgenic mouse models, its cyclooxygenase-1 (COX-1) inhibitory effect has influenced the digestive tract [58]. A safe outcome of resveratrol and well-tolerated in humans was recently shown in phase II randomized, placebo-controlled, double-blind, multicenter investigation. The most prevalent side effects included losing weight, diarrhea, nausea, and vomiting. Resveratrol and its primary metabolites have been detected in plasma and cerebrospinal fluid (CSF), affecting the CNS by crossing the blood–brain barrier (BBB) [59].

Neuronal Protective Role of Resveratrol

Molecular Mechanism of Resveratrol-induced SIRT1

The mechanism of NDDs, including AD, is coupled to OS and the overproduction of superoxide anion, which results in neuronal membrane injury and brain damage [60]. Brain tissue is more sensitive because of its high oxygen utilization rate, limited restoration capacity, effective content of polyunsaturated fatty acid, and little antioxidant concentration [61, 62]. ROS, mainly comprised of superoxide radicals ($^{\cdot}O_2$), hydroxyl radicals ($^{\cdot}OH$), and hydrogen peroxide (H_2O_2), are essential neurotoxic mediators secreted by activated microglia. These chemicals are highly reactive, and too many of them can result in lipid peroxidation, DNA fragmentation, and oxidation of proteins, causing further cell malfunction and mortality [63]. As a result, damaged mitochondria can create ROS those damage polyunsaturated fatty acid membranes, proteins, nucleic, lipid peroxidation, deficiency of membrane reliability, and enhanced calcium (Ca^{2+}) diffusion. In vivo and in vitro, ROS promote the formation of Aβ peptides, which cause OS [64–67].

As a result, ROS vicious cycle and Aβ formation may hasten the evolution of AD [68]. ROS has been proven in vitro and in vivo to enhance Aβ production and promote OS, resulting in neuronal death and speeding up the evolution of AD [69]. AD is a disorder of the hypothalamus and the brain that might cause neurological deprivation. Simultaneously, the cause of AD is unknown; several cellular alterations have been linked to it, along with Aβ peptide synthesis and abundance, tau phosphorylation, OS, mitochondrial malfunction, synaptic impairment, and biometalsdyshomeostasis. The response of neuroinflammatory mediated by microglial stimulation and acetylcholine deficiency is thought to play an essential role in the etiology of AD [70, 71]. Aβ peptides

aggregation in the brain is a significant pathologic situation in AD [72]. Aβ is the most common component of plaques, and it is produced by the object of γ-secretase on amyloid precursor protein (APP) [73]. Aβ buildup could trigger a cascade of harmful downstream processes in Alzheimer's patients, resulting in neuronal dysfunction [74, 75]. However, OS has a role in AD production and development [76, 77]. Additionally, the buildup of reactive nitrogen species (RNS) and ROS can hasten fibrillization, boost Aβ hazard, and enhance neuronal mortality and neurodegeneration [78–81].

Reduced sirtuin balance, particularly SIRT1 expression balance, has been linked to increased Aβ formation and deposit in AD patients [82]. SIRT1 may governAβ metabolism by modulating APP processing, and SIRT1 deficiency has been linked to increased Aβ generation [43]. SIRT1 overexpression, on the other hand, reduces Aβ production [83, 84], which could be Aβ's promising treatment strategy for preventing the disease's neurodegeneration and cognitive deficits. SIRT1 is a sirtuin family member, catalyzing the deacetylation of different substrates using nicotinamide (NAD^+) as a substrate [85]. SIRT1 influences the neuron life cycle, insulin sensitivity, glucose metabolism, and mitochondrial biogenesis, essential in maintaining cellular homeostasis [86, 87]. SIRT1 has been found to require synaptic plasticity, cognitive functioning, and the modification of predictable outcomes and functions of memory in the mature brain [88, 89].

SIRT1 is involved in restoring brain systems and activity and altering synaptic plasticity and mental processes throughout normal aging [90]. The lack of SIRT1 appearance in hippocampus neurons is linked to reduced mental skills such as instant memory and spatial learning [91]. SIRT1 alleviates mitochondrial dysfunction by increasing PGC-1α activity, which inhibits Aβ synthesis and improves the dysfunction of mitochondrial [92]. Moreover, SIRT1 deacetylases various additional elements, like forehead box O (FOXO), nuclear factor kappa B (NF-κB), and p53, preventing neuronal apoptosis [20, 93–96]. As a result, pharmacological stimulation of SIRT1 could be a viable strategy for AD treatment by deposition, neurodegeneration, and avoiding Aβ [97]. As a result, reducing ROS production could be a helpful technique for preserving neuronal cells from OS and a therapeutic approach for NDDs [96, 98]. The routes via which resveratrol works on SIRT1 consider the pathophysiology of AD is summarized in Fig. 3.

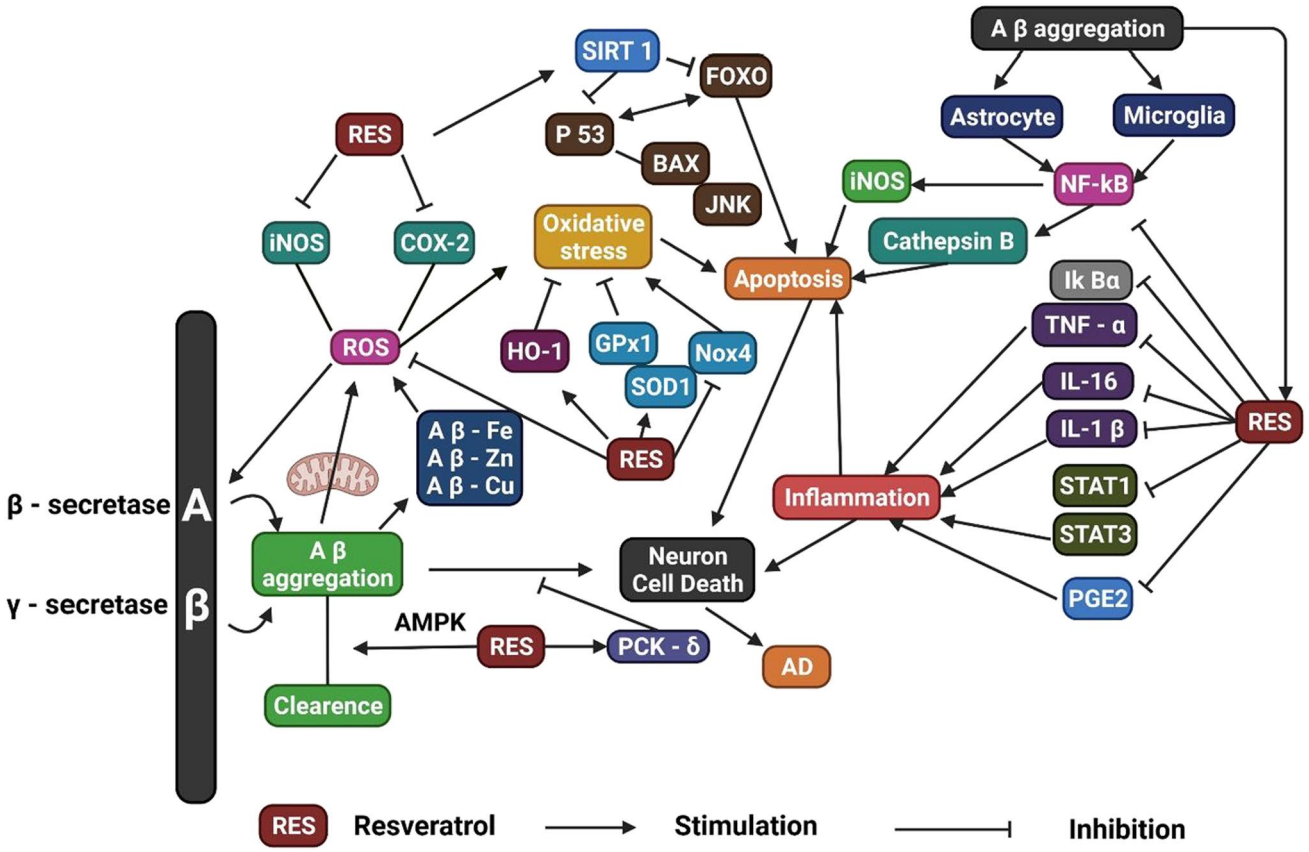

Fig. 3 The major physiological mechanisms postulated for resveratrol processes in AD [99]

Resveratrol as a Strong Antioxidant

OS causes SIRT1 neuronal damage; also, it can induce apoptosis or necrosis that leads to intracellular signaling and directs neuronal mortality. One of the most effective mechanisms of hypoxic ischemia is OS. ROS formation increases fast after hypoxia and ischemia, leading to mitochondrial dysfunction and neuronal death. Apoptosis has been connected to mitochondrial damage caused by OS. Sirtuins a family of NAD^+-dependent histone deacetylases found in all living things. SIRT1, also known as sirtuin1, is the best-researched sirtuin and has recently become a popular therapeutic target. The translated protein has a molecular weight of roughly 60kD and may deacetylate in the presence of NAD^+. SIRT1 has been shown to control diabetes-induced cardiac dysfunction and brain ischemia–reperfusion damage by avoiding mitochondrial dysfunction and reducing hepatic steatosis in previous investigations [100, 100, 101]. SIRT1 activation increases mitochondrial biogenesis and oxidative metabolic capacity via several pathways, according to many in vitro and in vivo studies [102]. SIRT1 also controls apoptosis via additional mechanisms, including the anti-inflammatory NF-κB acetylation pathway and the regulation of AMPK in autophagy [59]. Furthermore, data suggests that increasing SIRT1 activity can reduce ROS generation, neuronal and glial cell inflammation, and neuronal cell death [103].

As a result, natural and artificial antioxidant compounds (such as resveratrol) are employed to preserve neurons in NDDs, such as AD [104]. Several investigations on the antioxidant activities of resveratrol have shown decreasing the generation of malondialdehyde and nitrite by chronic resveratrol therapy besides restoring glutathione (GSH) balances [105, 106]. SIRT1 stimulation, Aβ aggregation, poisoning constriction, memory chelation, and ROS scavenging have all been characterized as additional antioxidant mechanisms of resveratrol [87, 106, 107]. These findings show that this chemical is a viable treatment option for AD. Therefore, resveratrol can affect essential glial activities such as glutamate absorption, GSH, better working salvation, reduced DNA fragmentation and apoptosis, and protection against ROS [108–110]. Red wine or resveratrol has long been known for its solid antioxidant capabilities in both in vitro and in vivo patterns of various disorders and AD. Resveratrol secures PC12 cells from A25–35, which induces toxicity, prevents the assortment of intracellular reactive oxygen intermediates, decreases variations in the mitochondrial membrane, and inhibits NF-κB stimulation. Resveratrol inhibited phosphorylation of A25–35-induced pro-apoptotic c-Jun N-terminal kinase (JNK) and lowered the production of Bax protein as a pro-apoptotic. Thus, resveratrol affects antioxidant systems and intracellular signaling pathways. AD can be treated simultaneously with the chemical resveratrol by controlling OS and decreasing inflammation in the brain [111, 112]. According to Chen et al. [113], resveratrol has been shown to benefit animal patterns of AD. The mechanism of action of resveratrol has been the subject of several ideas. The efficacy of resveratrol was investigated using rodent AD models. The findings reveal that resveratrol is an extremely powerful neuroprotective drug. It contains several clinical trials on the treatment of AD. In vivo and in vitro models have been used to evaluate the therapeutic potential of resveratrol in treating AD. However, these studies are still in their early stages, long before their therapeutic potential against AD can be appropriately established.

Further independent research, for example, has limitations in methodology, the one-sidedness of theoretical foundations, and insufficiency of study design. Through quantification of positive plaques stained by thioflavin S, Karuppagounder, S.S. [114] reported that plaque counts and plaque burden in the medial cortex and hypothalamus of resveratrol-fed mice declined significantly when compared to mice fed the control diet, and the changes can also be found in the hippocampus, which was statistically insignificant. In resveratrol-fed mice, Vingtdeux, V. [115] discovered a substantial decrease in insoluble Aβ1–40, soluble Aβ1–40, insoluble Aβ1–42, and soluble Aβ1–42 total brain homogenates as compared to control animals. Porquet, D. [116] found that resveratrol-induced SIRT1 activation reduced Aβ42 and Aβ40 accumulation in SAMP8 mice with alterations in AMPK levels or phosphorylation relative to SAMP8 control mice.

Scholars believe that tau protein abnormalities and the buildup of Aβ peptides in the brain cause AD development. Porquet, D. [116] found that resveratrol-fed mice had decreased levels of pTau in both the cortex and the hippocampus. Their findings reveal that resveratrol administration reduces CDK5 and GSK3 activity in the cortex of SAMP8 mice, both of which are essential tau kinases in AD, and that inhibiting these tau kinases inhibits tau phosphorylation in Ser396. In rats, Du, L.L. [117] found that resveratrol significantly reversed STZ-induced alterations in SIRT1 inactivation and tau hyperphosphorylation, implying that active SIRT1 inhibited tau hyperphosphorylation through lowering ERK1/2 phosphorylation.

Neuronal inflammation increases the onset and progression of various chronic NDDs, including AD. Resveratrol inhibited LPS-induced upregulation of TNF-α, COX-2, and APP mRNA and proteins, as well as phosphorylation of NF-κB in the hippocampus, according to Gong, Q.H. [118]. Zhao, H.F. [119] found that resveratrol treatment significantly reduced NF-κB p65 protein levels compared to the OVX + D-gal group. Wang, G. [120] discovered that prolonged resveratrol treatment could dramatically reduce IL-1 and IL-6 levels, confirming the effects of resveratrol in neuroinflammation. Al-Bishri, W.M. [120] indicated that

studied markers, including IL-6, CRP, TNF-α, and TGF-β, were all significantly down-modulated after resveratrol treatment, whether before or after the induction of AD.

Metal ions have also been linked to cell-to-cell communication and signaling and regulate transcription and translation via metal responsive regulators. In AD, neurodegeneration is characterized by a marked accumulation of metals, primarily Cu, Zn, Fe, and Al, in various regions of the brain [121], as well as a disruption in metal metabolism, resulting in altered metal transport and accumulation in senile plaques and other topological sites [122]. Compared to a healthy brain, significantly high amounts of Cu and Zn were observed in amyloid plaques and AD neuropil areas [123]. A gradual deposition of metals in the AD brain was also found as the disease progressed from moderate to severe AD [124]. In general, it appears that a (direct or indirect) disruption in the homeostasis of Cu, Zn, Fe, Al, calcium (Ca), and other metals is a common characteristic of several pathways underpinning neurodegeneration in AD (metal dyshomeostasis).

Nonetheless, the general metal burden in the brain is never drastically raised in AD, as it happens instead as a result of specific genetic changes in brain metal metabolism. Chelation therapy has been recommended as a treatment for lowering the abnormal buildup of essential heavy metals, including Fe, Cu, and Zn, as well as non-essential and toxic metals like lead (Pb), mercury (Hg), cadmium (Cd), and aluminum (Al) [125, 126]. Chelators bind to metal ions, increasing their excretion through urine and feces and decreasing their body concentrations gradually. Chelation therapy became a popular alternative treatment after ethylenediaminetetraacetic acid (EDTA) was found to successfully chelate and eliminate harmful metals from the blood, despite its still equivocal clinical findings [127]. Other suggestions were made after introducing EDTA into clinical practice that a treatment based on a metal chelator would benefit patients with atherosclerosis by "softening" hardened arteries by removing Ca from arterial walls [128].

Proteasome Activity of Resveratrol

Aβ toxicity in AD reduces the action of the ubiquitin–proteasome system (UPS), which is considered an essential efficient cellular protein that commands mechanisms, labeling, transporting, and finally degrading misprocessed misfolded proteins [129]. The accumulation of abnormal proteins is seen in various disorders, including AD. The proteasome activity in the AD brain declines as the number of ubiquitinated proteins and ubiquitin (UBB + 1) modified version increases. E2-25 K/Hip-2, a ubiquitin-conjugating enzyme, seems to be needed for UBB + 1-mediated neurotoxicity in AD. Approximately all APP metabolism critical components are controlled by UPS degradation: γ-secretase, presenilin-1, presenilin-2, α, APP, β-secretase, tau, and ApoE ε4 [130].

In the early year investigation of N2a cells and HEK293 shifted to APP695 of human, resveratrol (0–40 μM), without catechin or quercetin; another powerful dual antioxidant found in red wine that inhibited extracellular and intracellular released Aβ (sαβ40 and sαβ42) clearance in a dose and time-related manner. More crucially, resveratrol exhibited no effect on other metabolism components of APP that have been tested (full-length APP, sAPPa, or APP C-terminal fragments C99, C89, C83, and AICD), indicating that the resveratrol did not influence the development of α, β, or γ-releases. Additionally, resveratrol does not affect the degradation of Aβ by the important four key metalloendopeptidases-neprilysin (NEP), endothelin-converting enzyme-1, -2 (ECE-1, ECE-2), and insulin-degrading enzyme (IDE). Lactacystin, Z-GPFL-CHO, and YU101, proteasome inhibitors, effectively inhibited resveratrol-induced prohibition ofAβ action, si-RNA-mediated silence of the proteasome β5 subdivision likewise obstructed resveratrol-mediated abatement ofAβ activity [131]. Surprisingly, resveratrol was not looked through to directly boost proteasome action. Thus, resveratrol influenced proteasome-generated deterioration of Aβ by a mechanism that did not raise the whole proteasomemovement. Analogs of resveratrol, such as trans-3, 5,4trimethyloxystilbine (TMS), and trimethoxyresveratrol, were also present to reduce the entire released Aβ. Still, it was not efficient as resveratrol, implying that resveratrol governs the UPS pattern by the unidentified mechanism to regulate Aβ deterioration. Resveratrol might play a role as a significant therapeutic [3].

ResveratrolInfluence on the Arachidonic Acid Cascade from cPLA2

The cytosolic Ca^{2+-}dependent phospholipase A2 (cPLA2) controls the secretion of arachidonic acid (AA) through membranes, which serves as a precursor for the number of cellular activities. AA is identified to generate apoptosis triggered by OS and tumor necrosis factor-alpha (TNF-α) outside the CNS. Various intracellular and intercellular messengers, particularly those that transport a digressive message from postsynaptic to presynaptic nerve terminals when released substantially; however, both Aβ and nitric oxide (NO) triggered the cPLA2/AA-cascade. The limited concentrations (1 μM) of soluble αβ1–40 and αβ1–42-induced cPLA2 stimulation promoted AA-generated neuronal apoptosis in rat cortical neurons, offering that neuronal mortality in AD can also be generated through the cPLA2/AA-cascade. The cyclooxygenase-2 (COX-2) inhibitors decreased Aβ-induced cell death by 55% [132]. When produced in modest amounts, the AA and NO continuing regulated power in hippocampal neurons and played as intra- and intercellular

messengers, particularly transmitting a digressive message from postsynaptic to the presynaptic nerve ends. However, both Aβ and NO prompted the cPLA2/AA-cascade when released in substantial proportions. In synaptosomes from the rat's cortex, resveratrol treatment with (100 μM) concentrations reduced the NO-stimulated cPLA2/AA-cascade in a recent study, suggesting the newly discovered resveratrol in AD neurons as a target therapeutic [133].

Resveratrol-mediated Neuroinflammation Alter in AD

Senescent cells' proinflammatory phenotype and the upregulation of inflammatory processes as people get older have been linked to the incidence and development of aging-related disorders such as AD [134, 135]. An asymmetrical condition between pro-and anti-inflammatory cytokine levels occurs during the brain's aging process, with increased pro-inflammatory cytokines and decreasing anti-inflammatory mediators. Neuronal inflammation is related to the existence of Aβ [136–139]. Glial activation and inflammatory mediators grow significantly with age. microglia-mediated neuro-inflammation is thought to have a key role in developing and advancing's [140, 141]. The cause of increased inflammation during the process of aging is currently unknown. From the perspective of brain aging, growing data indicates that phytonutrients may have anti-inflammatory and antioxidant properties. Resveratrol has been shown to have neuroprotective properties by free radicals scavenging and inhibiting the activation of the glial [142, 143].

NF-κB signaling is a stimulator of inflammatory reactions, and various investigations have shown that it is activated during the elderly process. Resveratrol therapeutic inhibits Aβ-induced NF-κB activation in PC12 cells, implying a therapeutic role for resveratrol in modulating neuroprotection [144–146]. According to the latest research, resveratrol inhibits inflammatory cytokines such as IL-1β and TNF-α stimulated by lipopolysaccharide (LPS) or Aβ in microglia [147, 148]. Resveratrol also protects neurons from hypoxia-stimulated neurotoxicity by suppressing AP-1, phosphorylating p65NF-κB, and reducing IkappaB-alpha (IκB-α). Resveratrol can also inhibit the stimulation of c-Jun N-terminal kinase (JNK) and mitogen-activated protein kinase (MAPK) signaling cascades upstream [149]. In addition to prior research showing resveratrol's anti-inflammatory effect, it has been demonstrated that Resveratrol increases the discharge of anti-inflammatory IL-10 [150, 151]. Resveratrol could be utilized to treat AD because of its antioxidant and anti-inflammatory properties. In AD, SIRT1 activation appears to be an essential neuroprotective mechanism of resveratrol. Although the mechanisms linking resveratrol to SIRT1 overexpression and neuroprotection are unknown, its expression could be significant in neural protection against ROS, NF-κB signaling in activated microglia, Aβ toxicity prevention, and improved learning and memory [152]. By decreasing the apoptotic activities of both p53 and FOXO via SIRT1 overexpression, resveratrol can help protect neurons in AD. Although this study emphasizes the necessity of SIRT1 activation for resveratrol's neuroprotective effects, it is crucial to note that these pathways are still unknown [152].

Furthermore, resveratrol may act on the CNS by suppressing neuroinflammatory and prooxidant pathways through various routes other than SIRT-1 [153]. These mechanisms are highly complex, involving the stimulation or inhibition of multiple signaling pathways and changes in potassium channels that cause neuronal electrical activity to be inhibited. In summary, in addition to SIRT1, the primary mechanisms associated with resveratrol's neuroprotective effect include stimulation of microRNA-CREB-BDNF pathway regulation, inhibition of mTOR and AMPK-dependent signaling pathways, inhibition of enzymes (cholinesterase activity), transcription factor (NF-κB) and apoptotic pathways, and stimulation of cellular autophagy and expression of Nrf2, HO-1, and NQO1, among others [99, 154].

Effects of Resveratrol on Aβ Production

In the realm of AD, the Aβ concept that dyshomeostasis between Aβ production and clearance is an early, important molecular element in the genesis of AD has been proposed and investigated. Scientists have been looking for natural compounds or medications that can affect the dynamic equilibrium of Aβ, focusing on its synthesis and clearance [155]. Resveratrol lowers Aβ aggregation by reducing the APP's amyloidogenic cleavage, improving clearance of Aβ peptides, and decreasing APP cleavage. Resveratrol also has antioxidant capabilities, protecting neuronal function [156, 157]. Aβ-induced OS upregulates the production of a β-secretase enzyme that splits the APP to make more Aβ [155], spreading OS and exacerbating neuronal damage [158]. The activity of β-secretase is reduced by resveratrol. According to computational analysis, the prevention of OS-facilitated neuronal death and β-secretase activity by resveratrol analogs appears to link strongly [159, 160]. Resveratrol is separated into two isomers: trans-Resveratrol, which has attracted the most attention, and cis-resveratrol, which may have different biological effects [161]. Resveratrol has two aromatic rings in its structure. The transversion is more stable and effective than the cis form, which may have different biological effects. Resveratrol has a wide range of physical activities, and no significant side effects have been reported in humans or experimental animals [162–164]. In a clinical trial of oral resveratrol at a single dose of 5 g in 10 healthy volunteers, the peak level of resveratrol in plasma

was 539 ng/mL. In contrast, plasma concentrations of two resveratrol monoglucuronides and resveratrol 3-sulfate were 1285 ng/mL, 1735 ng/ml, and 4294 ng/mL, respectively [165, 166]. According to a double-blind, randomized, placebo-controlled study, resveratrol is likewise safe in healthy adults, but it creates a low plasma concentration. Resveratrol has low oral bioavailability due to its rapid metabolism and excretion [167]. Resveratrol glucuronides sulfates, and/or sulfoglucuronides are formed when it is conjugated to glucuronic acid and/or sulfate. Analogs and inhibitors of resveratrol metabolism have been developed to increase resveratrol bioavailability [155].

BACE1 Inhibition in AD

Beta-site APP cleaving enzyme 1 (BACE1), an overall reaction in brain neurons, displayed all of the well-known qualities of the β-secretase, which cleaves extracellular APP, which is critical in AD pathophysiology [168]. The activity of Aβ causes OS markers to be formed. 4-hydroxynonenal enhances BACE-1 expression in NT2 neuronal cells, encouraging elevated amyloidogenic APP processing and, as a result, increased Aβ protein accumulation [169]. As BACE is an essential target for AD treatment, scientists expect to uncover some potent chemicals or create novel medications to block BACE1 (BACE inhibitors), reducing Aβ buildup. The fluorescence resonance energy transfer (FRET) assay revealed that resveratrol and resveratrol oligomers effectively suppressed BACE activity dose-dependent [170]. Similarly, using a time-resolved fluorescence (TRF) test, researchers discovered that resveratrol and its products contained one (tert-butyl, 1-ethylpopyl) or two bulky electron-donating groups ortho to 4′-OH had different influences against BACE1, indicating that resveratrol can inhibit BACE1 function [171]. On the other hand, resveratrol inhibits Aβ production by neither affecting β- nor Aβ-secretase. Different methodologies and cells could be to blame for the contradictory results, which will require additional investigation. Some powerful BACE1 inhibitors, like E2609, AZD3293, and LY2886721, are currently undergoing clinical studies, and some side effects have been documented [172]. Detecting active ingredients including resveratrol in herbs that target β-secretase could be an approach to treating AD [173, 174]. Aβ-induced OS upregulates the production of sec β-secretase, an enzyme that cleaves the AP to produce more Aβ [175].

There are numerous obstacles to overcome in the development of potent BACE1 inhibitors. Because BACE1 is found in the brain and endosome lumens, inhibitors must first traverse the BBB) and neuronal membranes to reach the target [176]. Despite their great potency in vitro, peptidomimetic inhibitors have poor in vivo efficacy due to their inherent pharmacological features (limited brain permeability, short half-life, and low oral availability). The move from peptidomimetics to brain penetrant small molecules is, in fact, one of the fundamental difficulties in the design of present generations of inhibitors [177].

Furthermore, when developing BACE1 inhibitors, some critical structural properties of the enzyme should be considered, such as the catalytic aspartic dyad, structural flexibility, and the vast binding pocket [178]. Because of BACE1's extended catalytic pocket, inhibitors must be large enough to bind within the active site but tiny sufficient to have drug-like characteristics [179]. Furthermore, because these enzymes are closely connected, and the two catalytic aspartic acid residues are conserved across the class, it is critical to ensure that BACE1 inhibitors are selective over other aspartic proteases to avoid cross-inhibition harmful consequences [180]. Susceptibility to P-glycoprotein (P-gp) efflux and suppression of hERG (human ether-A-Go-Go ion channel) related to cardiotoxicity, as well as the inhibition of cytochrome enzymes to avoid medication interactions by BACE1 inhibitors, are all obstacles to overcome [181]. BACE1 has multiple cellular substrates in addition to APP processing, and its physiological role is necessary for normal cognitive function. Synaptic dysfunction, retinopathy, epileptic convulsions, hypomyelination, and other neural abnormalities in BACE1-null animals appear to be connected to the lack of cleavage of BACE1 substrates. Thus, BACE1 inhibitors may cause toxicity based on the mechanism [182].

Autophagy Induction

According to new findings, autophagy pathways may alter developmental and NDDs, including AD. Damaged mitochondria in neurons are also linked to the etiology of AD. In the mitochondrial membrane, the misfolded proteins are translocated and aggregated, causing oxidative phosphorylation to be disrupted and autophagy [183, 184]. As a result, synaptic plasticity, anti-inflammatory action in glial cells, oligodendrocyte formation, and the myelination process are all affected by neuronal autophagy [185–187]. Autophagy efficiency declines with age, resulting in a buildup of Aβ and cytochrome c liberation in the mitochondrial membrane, neurodegeneration, and cell death [172, 188]. Furthermore, abnormal autophagic vacuoles accumulate in the PS1/APP mouse AD model [189]. A decrease in Aβ proteolysis is caused by an inequity between autophagic flux and degradation [41]. Autophagy impairment in AD enhances PSEN1 expression, which then increases β -secretase activity, resulting in an increase in Aβ synthesis [190, 191]. PSEN1 expression was reduced by resveratrol, an autophagy inducer, indicating that Aβ production was suppressed [192]. Resveratrol can also activate the tyrosyl transfer RNA (tRNA) synthetase

(TyrRS)-auto-poly-ADP-ribosylation of poly (ADP-ribose) polymerase 1 (PARP1) SIRT1 signaling pathway in PC12 cells, causing autophagy and reducing Aβ-induced neurotoxicity [192, 193]. Resveratrol can treat AD via stimulating autophagy. Resveratrol's potential neuroprotective effect in AD has been emphasized in several reviews [194, 195]. It protects the brain through a variety of processes. The induction of proper autophagy is one crucial process. Lysosome-mediated autophagy mechanisms become abnormal in AD, which raises β-secretase activity, which boosts Aβ production. The contribution of the subdivision of general control nonderepressible 2 (GCN2) in this pathway where resveratrol seems to defend against neurotoxicity is also shown; resveratrol-mediated autophagy signals generate this protection. These signals also prevent potential mitochondrial decrease [41, 196]. AMP-activated protein kinase (AMPK), sirtuin 1 (SIRT1), and peroxisome proliferator-activated receptor coactivator-1 (PGC-1) have all been implicated in resveratrol modulating cellular activities [197, 198]. Resveratrol can boost neurogenesis by acting as a SIRT1activator, increasing the NAD^+/NADH ratio, and increasing the clearance of cellular proteins affecting the CNS disorders in an mTOR-dependent or independent manner are shown (Fig. 4) [199]. Resveratrol is also hypothesized to promote longevity in the elderly by activating AMPK, which protects mitochondrial integrity by normal cell autophagy regulation [200].

Relationship of SIRT1 with AD

SIRT1 was the first gene discovered and is the one that has been studied the most. It has been suggested that it plays a role in animal longevity and aging. It also plays a role in glucose homeostasis, lipid metabolism, energy balance, and stress, among other metabolic processes. SIRT1 indicates the cytoplasm's presence, interacting with nuclear and cytoplasmic proteins [201, 202]. Mammalian homolog SIRT1 as a nicotinamide adenine dinucleotide (NAD^+)-dependent sirtuin familydeacetylation is active in transcription factor deacetylation during inflammation and has been correlated to cellular processes [203] and may prevent apoptosis by deacetylationp53 [204]. SIRT1 affects nerve precursor cell destiny, axon extension, synaptic plasticity, dendritic branches, and endocrine function in neurons [205]. Cytoplasmic SIRT1 can enhance nerve growth factor (NGF) that induces pheochromocytoma axon growth and have a significant role in axonal differentiation and proliferation was discovered through in vitro culture experiments [206]. Even though multiple studies have shown that sirtuin activators are neuroprotective agents in brain aging, not much is known concerning SIRT1's location or activity in the aging brain [207]. According to research, aging is linked to increased SIRT1 expression but declined action [208].

SIRT1 reduction activity corresponds to the known decrease in NAD^+ levels as people age. SIRT1 activity and specific proteins overbearing may be reduced due to oxidative damage created during the aging process, causing cellular senescence [209, 210]. Sirtuinisan appealing therapeutic target and tremendous strength have gone into developing appropriate activators as tools for better understanding their

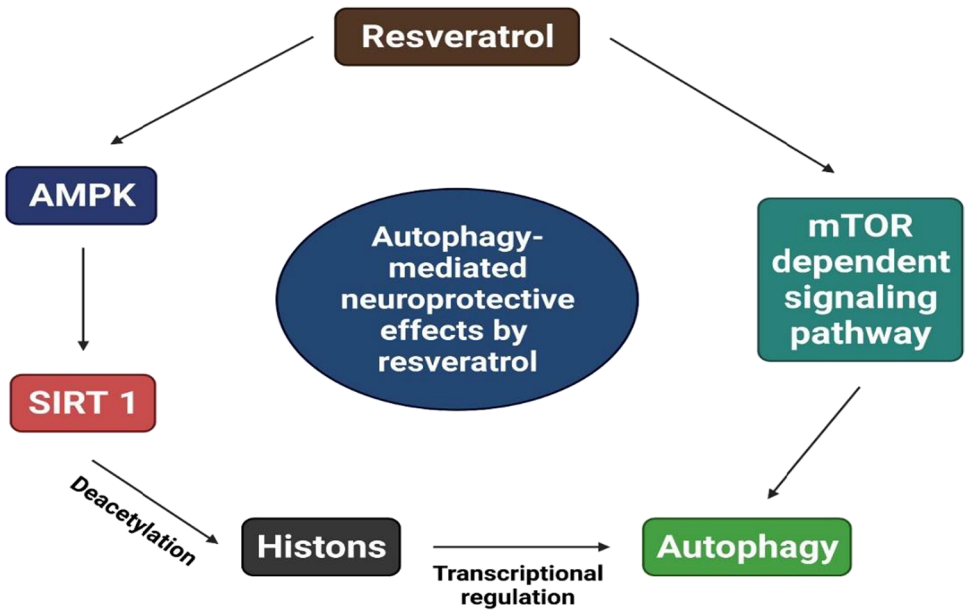

Fig. 4 Resveratrol's neuroprotective properties are regulated via autophagy. On the one hand, through the AMPK/SIRT1 signal route, SIRT1 and deacetylation histone acetylates can be activated by resveratrol. By modulating the mTOR signal pathway, resveratrol, in contrast, can directly start autophagy and exhibit neuroprotective effects. mTOR, mammalian target of rapamycin; AMPK, 5′ AMP-activated protein kinase

purpose and ability treatments for ailments such as AD [211]. Although natural and synthesized STACs have low specificity and bioavailability. Clinical studies are uncommon. A clinical trial found that resveratrol, as a STAC, can be administered safely in individuals with AD and can modify the AD biomarkers expression [212]. A study investigated the possibility of using SIRT1 as a biomarker for AD. Using surface plasmon resonance and ELISA, the researchers measured SIRT1 levels in the blood of healthy people (young and old) at the same time in patients with AD and mild cognitive impairment (MCI) [213]. They detected a significant decrease in SIRT1 serum levels in patients with MCI and AD in contrast to old and young controls. Furthermore, SIRT1 levels in healthy older individuals were significantly lower [155, 214].

The aggregation of the neurotoxic peptide Aβ in the brain is a major pathogenic event in AD [215]. The operation of two enzymes, Aβ-secretase, and β-secretase, results in the successive endoproteolysis of a longer precursor, APP. β-secretase, another enzyme, prevents Aβ synthesis by splitting APP at the Aβ sequence [216]. The β-secretase cleavage of the app has been linked to several Aβ disintegrin and metalloproteinase (ADAM) family proteases involving ADAM10. We demonstrated in 2006 that calorie restriction reduces Aβ synthesis, in part by boosting β-secretase via processes including SIRT1 activation [217, 218]. In the brain of the Tg2576 transgenic mouse model of AD, the calorie restriction increased SIRT1 expression and NAD^+ levels.

Furthermore, SIRT1 expression lowers the synthesis of Aβ from APP inAPP-transfected Chinese hamster ovary (CHO) cells and primary Tg2576 neurons via promoting β-secretase activity [219, 220]. SIRT1 expression in the brain is related to ROCK1 expression reduction and secretase activity in vivo elevation, confirming that ROCK1 is relevant in SIRT1-mediated secretase activity [221, 222]. Furthermore, investigations of the contents of cortical Aβ peptides in primates are diminished by calorie restriction in squirrel monkeys, and this decrease is contrarywise related to the concentrations of SIRT1 protein in the same brain region [223]. In vitro and in vivo, SIRT1 may deacetylate FoxO3; this deacetylation prevents inflammatory proteins are reduced by FoxO3 transcription. PGC1-1 is engaged in the biogenesis of mitochondria, and its activation can balance neuronal mitochondrial depletion, enhance synaptic protein levels, and contribute to dendritic spine development and maintenance. SIRT1 has been demonstrated to interact with peroxisome proliferator-activated receptor-gamma coactivator (PGC-1), resulting in an increase in PGC-1 activity and the encouragement of mitochondrial biogenesis [224–226]. HNF4 is an essential determining factor of the liver, and intestinal epithelial cell activity has been connected to the inflammation of the liver. Recent investigations have demonstrated that HNF4 indirectly influences the gut's flora and helps avoid the onset of inflammatory bowel illness. There has not been any research on HNF4 and neuroinflammation [227]. Because neuroinflammation of the gut-brain axis may be associated with inflammatory bowel disease, there has been an increase in related studies in recent years. Thus, considering the necessity of curing AD, research on SIRT1 has been prioritized [228].

Resveratrol Combination Therapy, Derivatives, and Analogs

A range of factors for this condition have been identified for AD, and combination medicines effectively treat such multifactorial diseases. Compared to single medication treatment, more was shown with a combination of Rresveratrol. Grape seed and concord grape juice obtain efficient memory and cognition impairment responses in AD mice models. The bioactive profile of polyphenolic metabolites in the brain is unaffected by this polyphenolic composition, and long-term potentiation deficiencies caused by Aβ plaques are improved [229–231]. By forming non-covalent interactions with Aβ, in vitro, a dimer of resveratrol-viniferinglucoside substantially lowers fibril formation and Aβ inhibition (1–40 and 1–42)-cytotoxicity-mediation [232, 233]. Many evaluations have emphasized the strategies for treating resveratrol and its analogs, which exhibit superior results than the medication itself [234].

Resveratrol-derived methoxylated compound pterostilbene, also known as 4-[(1E)-2-(3,5-dimethoxyphenyl) ethenyl] phenol or 3,5-dimethoxy-40-hydroxytoluene used as neuroprotection that alternatives two methoxy groups of the three hydroxyl groups [235–237]. This fundamental structural alteration raises lipophilicity and improves pterostilbene's dissolution rate and cell viability compared to resveratrol. Furthermore, compared to resveratrol, pterostilbene is regarded as a less favorable substrate for human Sulfotransferase, enhancing its physiological persistence and, consequently, its bioavailability [238]. Pterostilbene shields human SH-SY5Y neuroblastoma cells against OS caused by H_2O_2 via restoring cellular proliferation signaling pathways. The researchers also discovered that the estrogen receptor (ER-α) is implicated in pterostilbene's neuroprotective effects. Other researchers utilizing the identical cell line found that pterostilbene shields as opposed to OS and neuronal injury mediated by hyperglycemia via a process concerning Nrf2 signaling activation and nuclear translocation [239, 240]. Pterostilbene reduces the transcription and levels of NO and proinflammatory cytokines (IL-6, IL-1, and TNF-α) in BV-2 murine microglial cells in a model of Aβ (A1–42)-induced neuroinflammation. Pterostilbene can play a role in inflammasome NLRP3/caspase-1 (CASP1)

pathway inhibition, making it a potential therapeutic for AD [241]. Pterostilbene was proven to be more efficient than resveratrol at neuro-modulating the negative aging process and AD. SAMP8 mice, commonly utilized to research random and age-related AD compared to two glasses of wine for 8 weeks, were fed 120 mg/kg of pterostilbene and resveratrol [242, 243]. In the radial arm water maze test, pterostilbene exceeded resveratrol and increased the brain abilities of the animals. Regulating the expression of peroxisome proliferator-activated receptor (PPAR) alpha expression may be linked to activation of indicators of excitotoxicity, inflammatory responses, and AD pathophysiology, including MnSOD expression, NF-κB transcription, and JNK phosphorylation, all of which were positively impacted by pterostilbene [244]. This research also revealed large quantities of pterostilbene in brain and serum samples, whereas resveratrol was identified in low serum levels and undetected in the brain [245]. The better performance of pterostilbene can be related to its higher lipophilicity in contrast to resveratrol, which is due to the methoxy group in pterostilbene replacing the hydroxyl group in resveratrol. Pterostilbene's bioavailability may be increased due to this change, rendering its neuroprotective properties more powerful [237]. Hou et al. (2014) [246] discovered that pterostilbene has anti-inflammatory properties and enhances mental performance in mice subjected to a paradigm of neuroinflammation, a crucial constituent in the etiology of NDDs, characterized by mutualintra-hippocampal injections of lipopolysaccharide (LPS).

Prenylated resveratrol results have shown promise in developing drugs (E)-3, 5,40-trihydroxy-4-prenylstilbene showed good anti-Aβ aggregation, free radical scavenging, and modest suppression of β-secretase (BACE1), as well as additional neuroprotective and neurogenic actions. The neuroprotective impact was more significant than resveratrol and comparable to quercetin as a positive control. The compound's potential efficacy against AD is linked to substituting the – OH groups in the resveratrol structure [247]. When dopamine is recovered from the extracellular media to the cytosol, the enzyme monoamine oxidase-B (MAO-B) degrades it. MAO-B may also be linked to aberrant γ-aminobutyric acid synthesis in reactive astrocytes, making it a possible therapeutic for AD [248].

PCA is one of the most researched hydroxylated resveratrol derivatives. The impact of this chemical on D-galactose that can be aging induction in mice was studied by Zhang et al. (2018) [249]. The findings revealed that PCA treatment preserved spontaneous motor behavior, vastly improved learning and cognition in the hippocampus and cortex, and neuronal death prevention powered OS and stimulated cell proliferation. PCA, such as resveratrol, protected hippocampal neuronal cells from glutamate excitotoxicity by increasing HO-1 production through Nrf-2 activation [250]. In vitro AD experimental models were used in some investigations to assess the effects of PCA. PCA has a higher protective impact against neurotoxicity than resveratrol [251]. Patents on resveratrol derivatives applicable in neurotherapeutics areas are shown in Table 1.

Resveratrol amidation has also been an effective way to boost antioxidant and neuroprotective capability. Amide derivatives are two to three times more powerful as antioxidants than resveratrol, according to Jung et al. (2009), and can prevent LPS-induced NO production in microglial cells. Additionally, The allylamine analog trans-3,4-dihydroxy-40-(N-allylaminocarbonyl) stilbenedemonstratedhighly defensive properties against glutamate excitotoxicity in primary cortical neurons cells [252]. Li et al. (2014) developed 20 imine resveratrol derivatives as multitarget molecules for AD treatment. In neuroblastoma cells, most compounds prevented the aggregation of Aβ, functioned as metal chelators and antioxidants, and playedneuroprotectantsagainst H_2O_2. The chemical 4-((2hydroxyphenyl) imino)methyl)benzene-1,2-diol was found to be potential neuroprotection, leading to resveratrol [253].

Table 1 Patents on resveratrol derivatives applicable in neurotherapeutics areas

Patent no	Compound	Intervention	Reference
US8350093B2	The methylated curcumin-resveratrol hybrid molecule	Use in treating AD	[254]
WO2012154956	Resveratrol derivative pterostilbene	Diseases associated with an increased IL-6 serum level: depression, anxiety, migraine, chronic inflammatory disorders	[255]
WO2010004256	One or more compounds selected from a group consisting of resveratrol, tramadol, acetaminophen, xorphanol, etc	Shows anxiolytic properties	[256]
US20100310615	Composition of resveratrol, piceatannol, epsilonviniferin, pallidol, etc	Use as a neuroprotective agent	[257]
WO2011130400	4-Acetoxy-resveratrol	Anti-aging, age-related disorders	[258]
US20120165280	Stilbenoid derivatives	Enhances cognitive performances	[259]

Clinical Trial of Resveratrol in AD

In vivo and in vitro studies show that resveratrol can help with AD treatment. The evidence is overwhelming. However, there has not been comprehensive massive clinical research to date; resveratrol is quickly received, and hazard is not a significant concern. Because of its limited bioavailability, resveratrol has poor bioavailability, has limited hydrophilicity, and is chemically unstable [260]. Resveratrol was quickly metabolized in humans, with a peak occurring in 30 min and between 2 h of oral or intravenous resveratrol injection. Several in vivo studies in animals and people revealed limited intestinal absorption, making it challenging to detect unmetabolized resveratrol in the bloodstream [261]. Trans-resveratrol pharmacokinetics was found in age-independent after processing by oral of 200 mg three times per day. Despite this, trans-resveratrol plasma levels were low [262]. Although animal models have shown that resveratrol is bioavailable and active, clear findings in human trials are still forthcoming. Several experts have been trying to figure out the best ways to treat resveratrol in recent years [263]. Biologic resveratrol metabolites and analogs with similar neuroprotective effects have been discovered in several studies. Despite the enormous hurdles, several clinical trials are ongoing to investigate the effects of resveratrol on NDDs, along with AD. In the multiple cross-cheeked research of young volunteers in good health who drank 500 mg of resveratrol, total cortical hemoglobin concentrations increased considerably during task accomplishment. It did not affect cognitive performance, though 60 participants were given a fluid glucose resveratrol/maleate placebo food supplement in randomized controlled trials (RCT). The ASD-Cog readings were examined regularly for 1 year after the study [264]. The other different research trials with moderate cognitive deprivation. Resveratrol, calorie restriction, omega-three, or placebo addition assessed the ADAS-Cog rating [184] for 6 months. Analogs of resveratrol that have excellent bioavailability, effectiveness, and stability than resveratrol are being studied for their potential to treat a variety of degenerative diseases. Resveratrol derivatives have shown neuroprotective properties [2].

Conclusions and future perspectives

Because of its antioxidant behaviors and anti-inflammatory properties, resveratrol could be used to manage AD. SIRT1 activation appears to be a significant preventative strategy of resveratrol in AD. Even though the mechanisms linking resveratrol to SIRT1 overexpression and neuroprotective effects are unexplored, its development may play a pivotal part in protecting the neuronal against ROS, NF-κB signaling in activated microglia, Aβ toxicity prevention, and better cognitive performance. Resveratrol can help protect neurons in AD by suppressing the apoptotic actions of p53 via SIRT1 overexpression. Furthermore, resveratrol might influence the CNS by suppressing neuroinflammatory and oxidant pathways through various routes other than SIRT1. These procedures are highly complex, involving the activation or suppression of different signal transduction that causes neuronal electrical impulses to be suppressed. Even though resveratrol's neuroprotective prospects have been revealed in many in vitro studies, there is presently a shortage of data available from clinical studies that correspond to SIRT1 initiation and the decrease of inflammatory and oxidative status with improvements AD its progression. We underscore, nevertheless, that resveratrol is potential in terms of health enhancement, not only because of its antioxidant effects but also because of its neuroprotective and anti-inflammatory effects. Therefore, more research into different modes of administration or pharmaceutical formulations is needed to increase the targeting of tissue concentrations and enable resveratrol to exhibit its biological actions in AD.

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Declarations

Conflict of Interest The authors declare no competing interests.

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