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REVIEW

Interaction between resveratrol and SIRT1: role in neurodegenerative diseases

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Abstract

Neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, and Huntington's disease, pose significant health challenges and economic burdens worldwide. Recent studies have emphasized the potential therapeutic value of activating silent information regulator-1 (SIRT1) in treating these conditions. Resveratrol, a compound known for its ability to potently activate SIRT1, has demonstrated promising neuroprotective effects by targeting the underlying mechanisms of neurodegeneration. In this review, we delve into the crucial role of resveratrol-mediated SIRT1 upregulation in improving neurodegenerative diseases. The role of the activation of SIRT1 by resveratrol was reviewed. Moreover, network pharmacology was used to elucidate the possible mechanisms of resveratrol in these diseases. Activation of SIRT1 by resveratrol had positive effects on neuronal function and survival and alleviated the hallmark features of these diseases, such as protein aggregation, oxidative stress, neuroinflammation, and mitochondrial dysfunction. In terms of network pharmacology, the signaling pathways by which resveratrol protects against different neurodegenerative diseases were slightly different. Although the precise mechanisms underlying the neuroprotective effects of resveratrol and SIRT1 activation remain under investigation, these findings offer valuable insights into potential therapeutic strategies for neurodegenerative diseases.

Keywords Resveratrol · SIRT1 · Alzheimer's disease · Parkinson's disease · Huntington's disease

Introduction

Neurodegenerative diseases, such as Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD), are characterized by abnormal protein aggregation, leading to neuronal damage. Without effective treatment, the number of affected individuals with these diseases is projected to double every 20 years (Komorowska et al. 2020). Given the complexity of diseases, the quest for effective treatments remains challenging. However, there is promising evidence that plant-derived polyphenolic compounds, such as resveratrol, could serve as potential neuroprotective agents. Resveratrol, a polyphenolic compound abundant in various plants, has been extensively studied and documented for its antiaging, anti-inflammatory, and antibacterial properties (Bartra et al. 2024; Hosoda et al. 2023; Vestergaard and Ingmer 2019). This compound is a potent activator of silent information regulator-1 (SIRT1) and has the ability to cross the blood–brain barrier, offering neuroprotection within the central nervous system (dos Santos et al. 2022; Surya et al. 2023). In this report, we reviewed recent studies that have shed light on the role of SIRT1 in neurodegenerative

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diseases. The aim of this study was to provide a reference for the development of resveratrol as a novel therapeutic agent for treating these conditions. By understanding the involvement of SIRT1 in neurodegenerative diseases and exploring the therapeutic potential of resveratrol, researchers have attempted to pave the way for the development of innovative strategies that can effectively manage and treat these debilitating conditions.

Sources, isomers, and bioavailability of resveratrol

Resveratrol, also called 3,5,4′-trihydroxystilbene in chemistry, was first identified from the roots of white hellebore in 1939 (Pezzuto 2019). Resveratrol is classified as a phytoalexin that is secreted by at least 100 different plants as a defense mechanism in response to multiple environmental stresses, including pathogen infection, mechanical injury, UV irradiation, and immense heat. The content of resveratrol in plants is limited and is abundant mainly in the edible portions. The health benefits of resveratrol have been highlighted since the French paradox in 1992. The results of the French paradox study indicated that moderate red wine consumption reduced the incidence of ischemic heart disease because of the abundance of resveratrol in red wine, despite the consumption of a diet rich in saturated fatty acids in French people (Buja 2022). Owing to the various beneficial health effects of resveratrol, people are passionate about drinking red wine to ingest resveratrol. To date, resveratrol has been detected in many common human diets at varying concentrations, including fruits, nuts, fruit juices, and cocoa, and some of them have a higher content of resveratrol than that in red wine (Table 1).

Resveratrol has two isomers in nature, cis-resveratrol and trans-resveratrol (Fig. 1). The basic structure of resveratrol consists of two phenolic rings bonded with a double styrene bond. This double bond is responsible for the conversion of the isometric cis- and trans-forms of resveratrol (Gambini et al. 2015). The stability of the cis form is low, and it is stable only at a neutral pH and in the absence of light. The trans isomer is stable at an acidic pH and various temperatures, but is unstable at an alkaline pH, under light, and at increased temperatures (> 100 °C) (Bancuta et al. 2018; Zupančič et al. 2015). However, the trans isomer of resveratrol can convert to the cis isomer after exposure to high temperatures, an alkaline pH, or ultraviolet irradiation (Zupančič et al. 2015). Initially, the trans isomer was thought to be the main bioactive form of resveratrol, which has higher bioactivity than the cis isomer (Tomić et al. 2023). Current studies have indicated that both cis-resveratrol and trans-resveratrol have bioactivity, and the isomers sometimes have opposite effects

Table 1 The diet sources of resveratrol

Diet sources	Concentration of resveratrol	Ref
Red wine	0.11–3.19 mg/100 ml	(Lamikanra et al. 1996)
Mulberry	5.061 mg/100 g dry weight	(Shrikanta et al. 2013)
Jamun pulp	1.37 mg/100 g dry weight	(Shrikanta et al. 2013)
Strawberry	0.35 mg/100 g fresh weight	(Ehala et al. 2005)
Cowberry	3 mg/100 g fresh weight	(Ehala et al. 2005)
Red currant	1.57 mg/100 g fresh weight	(Ehala et al. 2005)
Cranberry	1.92 mg/100 g fresh weight	(Ehala et al. 2005)
Peanuts	1.12 mg/100 g fresh weight	(Chukwumah et al. 2006)
Dark chocolate	0.04 mg/100 g fresh weight	(Counet et al. 2006)
Blueberry	0.383 mg/100 g fresh weight	(Carey et al. 2013)
Pistachio	0.11 mg/100 g fresh weight	(Tokuşoğlu et al. 2005)

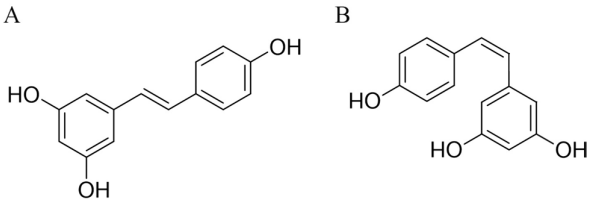

Fig. 1 The trans- (**A**) and cis- (**B**) isomer of resveratrol

(Jeon et al. 2023; Jhanji et al. 2020). Recently, they were found to have opposite effects on neuronal survival under stress conditions by regulating tyrosine tyrosyl-tRNA synthetase levels in rat cortical neurons. Cis-resveratrol has a protective effect against oxidative DNA damage in neurons (Jhanji et al. 2022).

The water solubility of resveratrol is low, only approximately 0.02–0.03 mg/mL (Chung et al. 2020). Although 75% of resveratrol can be absorbed in the intestine by passive diffusion or membrane transporters after oral administration, the bioavailability of resveratrol is still very low and is less than 1% due to its rapid metabolism (Walle 2011). Moreover, repeated administration or increased dosage administration cannot increase the bioavailability of resveratrol when orally administered (Almeida et al. 2009; Brown et al. 2010). Absorbed resveratrol is rapidly and extensively converted by glucuronic acid conjugation and sulfation in the intestine and liver (Wenzel and Somoza 2005). Although free resveratrol can be detected in the bloodstream, glucuronide and sulfate

metabolites constitute the majority of metabolites produced after its administration (Gambini et al. 2015).

Biological activity and effect mechanism of resveratrol

Resveratrol, which is reported to influence various cellular signaling pathways, has diverse pharmacological effects, including anticancer, antioxidant, anti-inflammatory, and antimicrobial effects. As reported, it modulates many microRNAs involved in the initiation and progression of cancer and inflammatory disorders (Amiri et al. 2020; Ungurianu et al. 2023). Additionally, it induces tumor cell apoptosis, thereby exerting anticancer effects (Brockmueller et al. 2023). Resveratrol suppresses neuroinflammation by partially inhibiting the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) signaling pathway to alleviate mechanical allodynia in a rat model of spinal cord injury (Han et al. 2023). Resveratrol has been shown to reduce the inflammatory response and oxidative stress and to improve poststroke cognitive disorders by regulating the JAK/extracellular signal-regulated kinase (ERK)/STAT signaling pathway (Chang et al. 2018).

Interaction of SIRT1 and resveratrol

Mammalian sirtuins comprise seven homologs (SIRT1–SIRT7), unique histone deacetylases, and accomplish nicotinamide adenine dinucleotide (NAD)-dependent deacetylation, which has received considerable interest as a potential mediator of lifespan extension in model animals (Chojdak-Łukasiewicz et al. 2022; Jęśko et al. 2016). SIRT1, an NAD-dependent histone deacetylase, modulates the expression of genes via histone deacetylation. SIRT1 is expressed in most body parts, including the brain, heart, kidney, liver, pancreas, spleen, skeletal muscle, endothelial tissue, and white adipose tissue (Elibol and Kilic 2018). SIRT1 plays an important role in many physiological and pathological processes, and finding small molecule activators that regulate SIRT1 activity is an effective strategy for treating related diseases.

Resveratrol, a small molecule activator of SIRT1, has been shown to stimulate the activity of native SIRT1 in vivo. Twenty years ago, researchers discovered that resveratrol can reduce the Michaelis constant of the acetylated substrate NAD-SIRT1 and extend the lifespan of *Saccharomyces cerevisiae* by activating SIRT1-dependent deacetylation of p53 (Howitz et al. 2003). Although the question of whether resveratrol can directly activate SIRT1 is controversial, allosteric mechanism studies have shown that resveratrol can strengthen the "loose-binding" of SIRT1 and substrates containing bulky hydrophobic groups. Resveratrol can not only improve the binding of SIRT1 to its substrates but also significantly increase the expression of SIRT1. To investigate the conditions underlying the activation of SIRT1 by resveratrol, three different synthesized p53 acetyl peptide substrates were used for testing. Researchers have reported that in the presence of resveratrol, substrates containing fluorescent groups bind more tightly to SIRT1. By constructing a model of SIRT1 binding to the 7-amino-4-methylcoumarin (AMC)-containing peptide of p53, they reported that the binding of resveratrol to SIRT1 promotes conformational changes, leading to better adaptation of the connected coumarin groups (Borra et al. 2005). With further progress, researchers have crystallized SIRT1 with resveratrol and the p53-AMC peptide to construct a complex structure (Cao et al. 2015). Three resveratrol molecules were found in this structure, two of which are involved in mediating the interaction of the AMC peptide and the N-terminal domain of SIRT1 and are crucial for resveratrol-dependent stimulation of p53-AMC, both of which are located in the N-terminal domain (Fig. 2). The third one is located next to the catalytic domain of SIRT1, situated on the opposite side of the coumarin ring. These findings provide clear evidence for the direct binding and activation of SIRT1 by resveratrol.

SIRT1 in neurodegenerative diseases

Currently, the fundamental pathogenic mechanism of neurodegenerative diseases such as AD, PD, and HD involves mainly misfolded proteins. The aggregation of misfolded proteins, including amyloid beta (Aβ), tau, and alpha-synuclein (α-syn), in the central nervous system, is apparent in different neurodegenerative diseases (Ma et al. 2020; Zhang

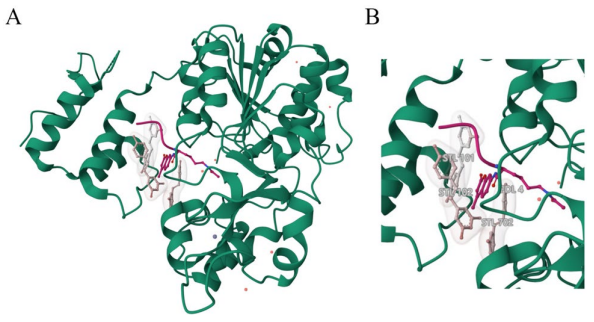

Fig. 2 Interaction between SIRT1 and resveratrol. **A** The overall structure of the interaction between SIRT1 and resveratrol. The SIRT1 protein in the image is green, which possesses a binding region containing three resveratrol molecules (carbon-colored white) and the p53-AMC peptide (carbon-colored red) (PDB ID 5BTR). (B) B is a locally enlarged image of A. The molecules of resveratrol are labeled as STL101, STL102, and STL702, respectively

et al. 2020). The formation of senile plaques and neurofibrillary tangles in specific brain areas causes synaptic dysfunction and neuronal loss in AD. The aggregation of α-syn leads to dopaminergic neuronal death in PD (Bourdenx et al. 2020; Uddin et al. 2020). In addition, mitochondrial dysfunction, correlated with the onset of neurodegenerative diseases, can attenuate glucose and oxygen metabolism in the brain and can impair respiratory chain function. The amyloid pathology and accumulation of α-syn might be bidirectionally related to mitochondrial dysfunction (Monzio Compagnoni et al. 2020). Recent studies have shown that SIRT1 is ubiquitously present in AD pathology-associated brain regions, such as the hippocampus and the prefrontal cortex (Wong and Tang 2016). Reactive oxygen species and the inflammatory response are increased, whereas the SIRT1 level is decreased in the brains of patients with neurodegenerative diseases (Singh and Ubaid 2020). In addition, SIRT1 has neuroprotective effects on synaptic plasticity and cognitive performance. The overexpression of SIRT1 can protect against amyloid/tau pathologies and α-syn degradation, whereas an abnormal reduction in SIRT1 might cause cognitive dysfunction in neurodegenerative diseases (Kreiner et al. 2019; Lim et al. 2018; Tang et al. 2020). As mentioned above, SIRT1 plays crucial roles in neuroprotection, anti-inflammatory activities, and the inhibition of p53 activity. Thus, it has received considerable attention as an epigenetic regulator of the etiological mechanism of neurodegenerative diseases.

SIRT1 in AD

AD is a chronic progressive neurodegenerative disease with clinical characteristics such as dementia, memory impairment, and mental stress. AD is a common disease of dementia. The population of people with AD and related dementias increased to 51.62 million in 2019 and will reach 152.8 million by 2050, which has gained global attention (Mobaderi et al. 2024). Until now, the U.S. Food and Drug Administration has only certified six drugs for the treatment of AD; however, most drugs can only relieve symptoms without slowing the progression of the disease (Tagliapietra 2022). Therefore, cognitive impairment and dementia have become severe socioeconomic burdens.

Resveratrol-dependent SIRT1 activation has protective effects through antioxidant, anti-inflammatory, and neuroprotective functions. SIRT1 is expressed in the hippocampus and prefrontal cortex and is expressed mainly in neurons, astroglia, and oligodendroglia and is correlated with learning memory. In the central nervous system of aged neurons, the expression of SIRT1 decreases. Studies have shown that oxidative stress can contribute to a decrease in SIRT1 activity, particularly in aging animals (Elibol and Kilic 2018). Research has shown that SIRT1 knockout mice have a reduction in dendritic branching and density and a defect in long-term potentiation of the hippocampal Schaffer collateral pathway (Wong and Tang 2016). Zhou et al. established a rat model of cognitive impairment by subjecting the animals to long-term anesthesia with sevoflurane (Zhou et al. 2021). When resveratrol was administered, cognitive function improved in the rat model, along with an increase in SIRT1 expression and a reduction in neuronal apoptosis.

Aβ, the main component of senile plaques in the brain, damages the structure and function of synapses and can ultimately cause AD. Aβ is produced by cleavage of the sequences of amyloid precursor protein (APP). It has been shown that α-secretase cleavage of APP obstructs subsequent amyloidogenic processing of APP and directly affects the formation of Aβ plaques, a neuropathological hallmark of AD (Wongchitrat et al. 2018). A disintegrin and metalloproteinase 10 (ADAM10), an antiamyloidogenic α-secretase, has been found to be a direct competitor for APP at the cell surface (Scharfenberg et al. 2019). SIRT1 attenuates the toxicity and aggregation of Aβ peptides in the hippocampus of AD patients to prevent hippocampal damage (Gomes et al. 2018). Researchers have discovered that SIRT1 enhances ADAM10 expression to increase the level of α-APPs and decrease the β-secretase β-site APP-cleaving enzyme 1 (BACE1) level, ultimately leading to a reduction in the level of Aβ, possibly through the mitogen-activated protein kinase (MAPK)/ERK signaling pathway (Shah et al. 2020; Thonda et al. 2021). A previous study demonstrated that a reduction in the level of Aβ via SIRT1 regulation of BACE1 transcription is associated with attenuating the activation and transcriptional activity of nuclear factor-kappa B (NF-κB) by reducing the acetylation of the P65 subunit (Marwarha et al. 2014). However, the deficiency of α-APPs has not been confirmed to be directly correlated with the onset of AD. Therefore, understanding the relationship between secretase and SIRT1 is highly important for the use of SIRT1 as a therapeutic target for the development of new drugs for AD. In addition, SIRT1 activation directly reduces Aβ peptide and APP-CTFβ levels via autophagy in neurons (Ginsberg et al. 2015). Recent studies have shown that activation of the SIRT1-forkhead box O (FOXO) axis decreases the accumulation of Aβ plaques and reverses mitochondrial dysfunction through PTEN-induced kinase 1 (PINK1)/Parkin-mediated mitophagy in the hippocampus of APP/PS1 mice (Fig. 3) (Zhao et al. 2021, 2022). Lin et al. conducted an experiment on the neuronal damage caused by chronic lead exposure in mice and reported that resveratrol administration significantly reduced Aβ levels (Bai et al. 2021). The experimental results further revealed that the antiamyloid effect of resveratrol was achieved by inhibiting the activity of BACE1. In addition, resveratrol administration significantly reduced the LC3-II/LC3-I ratio and p62, indicating that resveratrol can

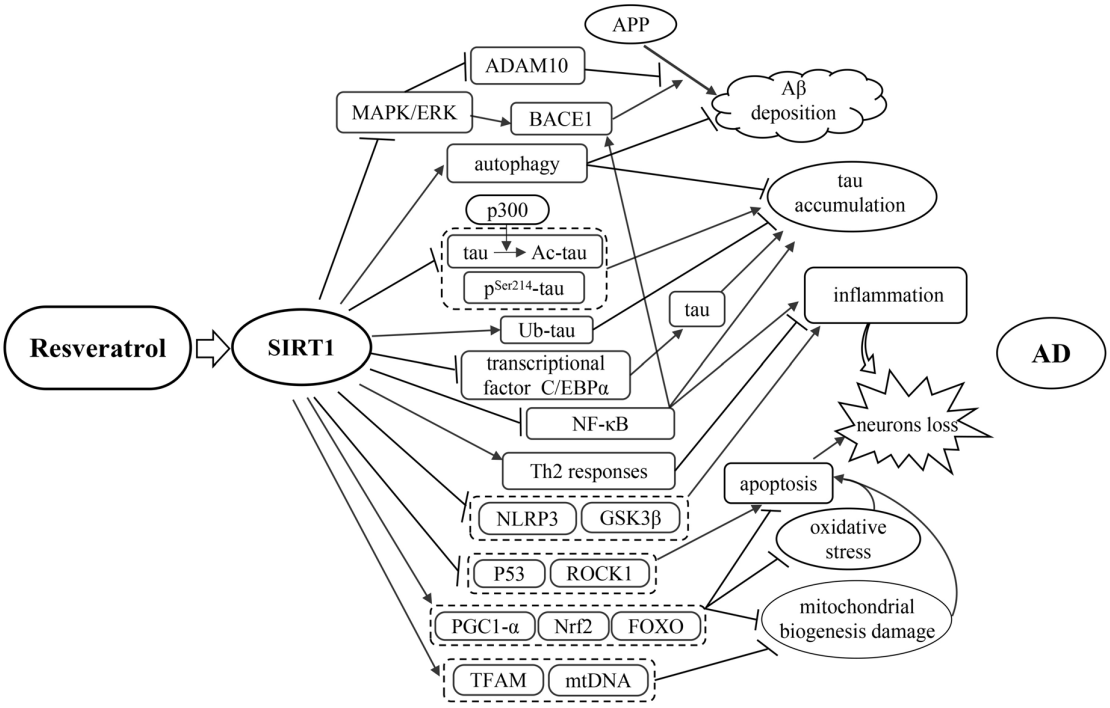

Fig. 3 The role of resveratrol and SIRT1 in AD. (→ indicates promotion; ⊣ indicates inhibition)

regulate the autophagy process by activating SIRT1, thereby promoting the clearance of Aβ.

Abnormally hyperphosphorylated tau is the major protein involved in neurofibrillary tangles in AD, and the suppression of tau phosphorylation or its levels might ameliorate AD (Jiang et al. 2020). Research has shown that tau is acetylated by the histone acetyltransferase p300 and is deacetylated by SIRT1 (Alquezar et al. 2021; Shin et al. 2021). The inhibition of SIRT1 can aggravate tau accumulation through increasing acetylation, decreasing the ubiquitination of tau in primary neurons and transgenic HEK293T cells (Zhang et al. 2020), and through increasing the level of p^{Ser214}-tau in the hippocampus of ovariectomized/d-galactose AD model rats (Ibrahim et al. 2022). A recent study revealed that SIRT1 inhibits the expression of tau at the transcriptional level through the transcriptional factor C/EBP (Yin et al. 2021). Moreover, SIRT1 plays a role in the clearance of phosphorylated tau by activating the mammalian target of rapamycin (mTOR)-dependent autophagy (Fig. 3) (Li et al. 2021).

Some studies have indicated that the activation of SIRT1 decreases the accumulation of Aβ and tau pathology through the NF-κB signaling pathway (Elibol and Kilic 2018). NF-κB is also an essential element in regulating inflammation to protect neurons in the nervous system. It can modulate many chemokines, cytokines, enzymes, and other molecules in the process of inflammation. The overexpression of SIRT1 can suppress the NF-κB signaling pathway induced by $Aβ_{1-42}$ in cultured microglial BV2 cells and attenuate Aβ toxicity in primary cortical cultures (Chen et al. 2005). Moreover, the activation of SIRT1 may promote Th2 responses and inhibit the NOD-, LRR-, and pyrin domain-containing protein 3 (NLRP3) signaling pathways to produce anti-inflammatory effects (Feng and Zhang 2019). A recent study revealed that SIRT1 may attenuate astrocytic inflammation by modulating the glycogen synthase kinase 3 beta (GSK3β) signaling pathway in a rat model of AD (Fig. 3) (Abozaid et al. 2022). Wei et al. (2023) created animal models of anxiety and depression through maternal separation experiments. Researchers have shown that resveratrol can inhibit the NF-κB signaling pathway by activating Sirt1, reducing the levels of NF-κB p65 and acetylated NF-κB p65, and thus improving the inflammation, anxiety, and depression-like behaviors caused by maternal separation. As indicated above, the molecular mechanisms involving SIRT1 and neuroinflammation in AD are complicated.

SIRT1 is also present in mitochondria and is reported to modulate mitochondrial biogenesis. One study revealed that the inhibition of SIRT1 can obstruct the increase in mitochondrial transcription factor A (TFAM) and mitochondrial DNA copy number to damage memory (Ansari Dezfouli et al. 2019). The activation of SIRT1 inhibits apoptosis through negatively regulating Rho-associated kinase 1 (ROCK1) and p53 signaling pathway (Pant et al.

2013). Reports have indicated that peroxisome proliferator-activated receptor-gamma coactivator 1 alpha (PGC-1α), FOXO, and nuclear factor erythroid 2-related factor 2 (Nrf2) play essential roles in mitochondrial biogenesis, the oxidative response and apoptosis, which are associated with the expression of SIRT1 (Fig. 3) (Dong et al. 2020; Pratiwi et al. 2021; Yin et al. 2022; Zhu et al. 2021, 2022). Herein, we used network pharmacology to elucidate the potential mechanisms of resveratrol in AD. Drug targets of resveratrol were searched and collected from the SwissTargetPrediction, SEA, and PharmMapper databases. Disease targets of AD were searched and collected from the GeneCards and OMIM databases. After the key genes were screened, gene ontology (GO) functional enrichment and Kyoto Encyclopedia of Genes Genomes (KEGG) pathway analyses were performed via the DAVID database. For the enriched KEGG pathways, the top 20 items with p values ≤ 0.01 were screened to draw bubble maps (Fig. 4). Current studies have investigated the role of resveratrol in improving AD through its main pathological features. According to the network pharmacology results, lipid and atherosclerosis, endocrine resistance and chemical carcinogenesis-receptor activation may play a role in the improvement of AD by resveratrol, which provides a basis for follow-up research.

SIRT1 in PD

PD is an epidemic in the elderly population and affects approximately 1–2% of people over the age of 65 (Morales et al. 2021). It damages the motor system, mental system, and nervous system. Numerous deaths of dopaminergic neurons (DNs) and glial dysfunction in the substantia nigra pars compacta are observed in PD (Bloem et al. 2021; Tamtaji et al. 2020). The main neuropathological hallmarks of PD are the aggregation of α-syn to form insoluble fibrils of Lewy bodies and the loss of DNs (Lang et al. 2022). Moreover, the oxidative stress and activated microglia that promote inflammatory processes are the major harms to DNs in PD (Guzman-Martinez et al. 2019). The pathogenesis of PD has not been clarified clearly until now. Genetics, environment, and age may be the inducing factors (Batiha et al. 2022). With increasing age, the level of dopamine in the body decreases gradually until the content of striatal dopamine decreases to 80%, and people exhibit Parkinson's disease clinical symptoms.

A previous study revealed that α-synuclein regulates pathological events that cascade the response in PD (Zoey et al. 2021). Preventing or reducing the production and promoting the elimination of α-synuclein, which can delay disease progression, is a promising therapeutic strategy for PD. SIRT1, which is downregulated in PD, plays a neuroprotective role in experimental PD models. SIRT1 inhibits the formation of α-syn aggregates upon oxidative stress, which is regulated by reducing the expression of NF-κB and cleaved poly (ADP-ribose) polymerase 1 (cPARP-1) (Singh et al. 2017). Moreover, SIRT1 inhibits α-synuclein aggregation by deacetylating proteins such as heat shock protein (HSP), FOXO, and PGC-1α (Chen et al. 2018; Elibol and Kilic 2018). Autophagy is correlated with the deterioration of impaired organelles such as mitochondria, the endoplasmic

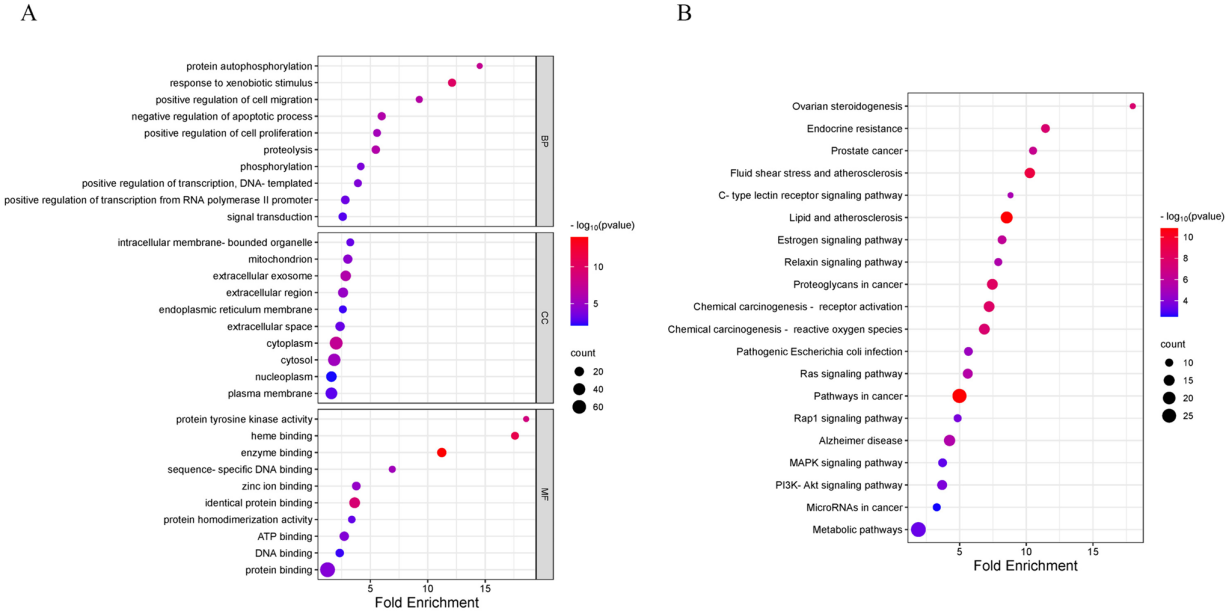

Fig. 4 GO (**A**) and KEGG (**B**) analyses of gene-encoding proteins targeted by resveratrol in AD

reticulum, and peroxisomes, and this process could enhance the clearance of damaged materials (Zhang et al. 2020). The activation of SIRT1 induces a decrease in acetylated LC3 levels to increase the level of LC3-II, which eliminates the accumulation of α-synuclein in DNs (Guo et al. 2016). The inhibition of SIRT1 affects the AMP-activated protein kinase (AMPK)/mTOR pathway to inhibit autophagy (Chen et al. 2022). Moreover, SIRT1-mediated regulation of FOXO is associated with increased autophagy, which may improve PD-like symptoms (Chen et al. 2018). Wu et al. reported that in PC12 cells, resveratrol can promote the autophagic degradation of α-synuclein and increase the level of LC3 II (Wu et al. 2011). Further studies revealed that resveratrol can activate SIRT1, leading to LC3 deacetylation and the autophagic degradation of α-synuclein, which can improve motor deficits and pathological changes in PD model mice (Fig. 5) (Guo et al. 2016).

Apoptosis is considered an important cause of DN loss in the pathogenesis of PD (Al-kuraishy et al. 2022). SIRT1 may play a role in the induction of DN apoptosis through regulating the p53 signaling pathway (Salimian et al. 2018). In SH-SY5Y cells, SIRT1 directly deacetylates the H3K9 residue of the p53 promoter and resists apoptosis to attenuate dopaminergic neurodegeneration (Xu et al. 2018). Moreover, SIRT1 provides protection against 1-methyl-4-phenylpyridinium (MPP+)-induced apoptosis and oxidative stress by suppressing the MAPK signaling pathway (Wang et al. 2017). In PC12 cells, the SIRT1/PGC-1α signaling pathway also provides protection against oxidative stress induced by MPP+ as well as N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine in PD model mice (Mudò et al. 2011; Ye et al. 2012). Ferroptosis is a new type of regulated cell death, and its inhibition can alleviate motor behavior and neuronal loss in the PD (Mahoney-Sánchez et al. 2021). It has been reported that the SIRT1/Nrf2 signaling pathway regulates iron metabolism and mitigates ferroptosis in PD models (Zheng et al. 2023). Neuroinflammation is considered to play an important role in the development of PD. The NLRP3 inflammasome is involved in the pathogenesis of PD and induces the release of proinflammatory cytokines. In the rat brain, activation of the NLRP3 inflammasome induced by subarachnoid hemorrhage is inhibited by SIRT1 (Fig. 5) (Zhang et al. 2021). Through network pharmacology, the top 20 items were screened via KEGG analysis with p values ≤ 0.01, which included mainly lipid and atherosclerosis, pathways related to cancer and chemical carcinogenesis-receptor activation, etc. (Fig. 6). The results of the KEGG analysis revealed that the enrichment pathways of resveratrol were similar to those of AD and PD, but the significance of enrichment differed. Considering the role of SIRT1 in PD, more studies are needed to explore this topic.

SIRT1 in HD

HD is a hereditary autosomal-dominant neurodegenerative disease caused by a mutation of a protein called huntingtin (HTT), which contains a sequence with expanded CAG repeats. It is considered that 40 or more CAG repeats in HTT alleles increase the tendency of the mutant HTT (mHTT) protein to accumulate as toxic aggregates in the brain (Chang et al. 2021). The symptoms of HD in humans with involuntary movement spirit and progressive dementia

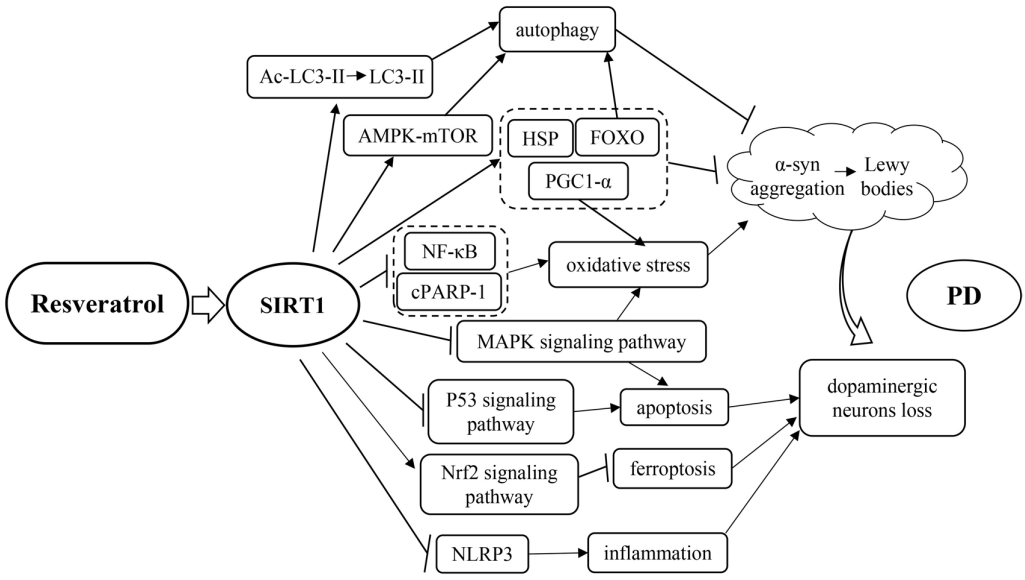

Fig. 5 The role of resveratrol and SIRT1 in PD. (→ indicates promotion; ⊣ indicates inhibition)

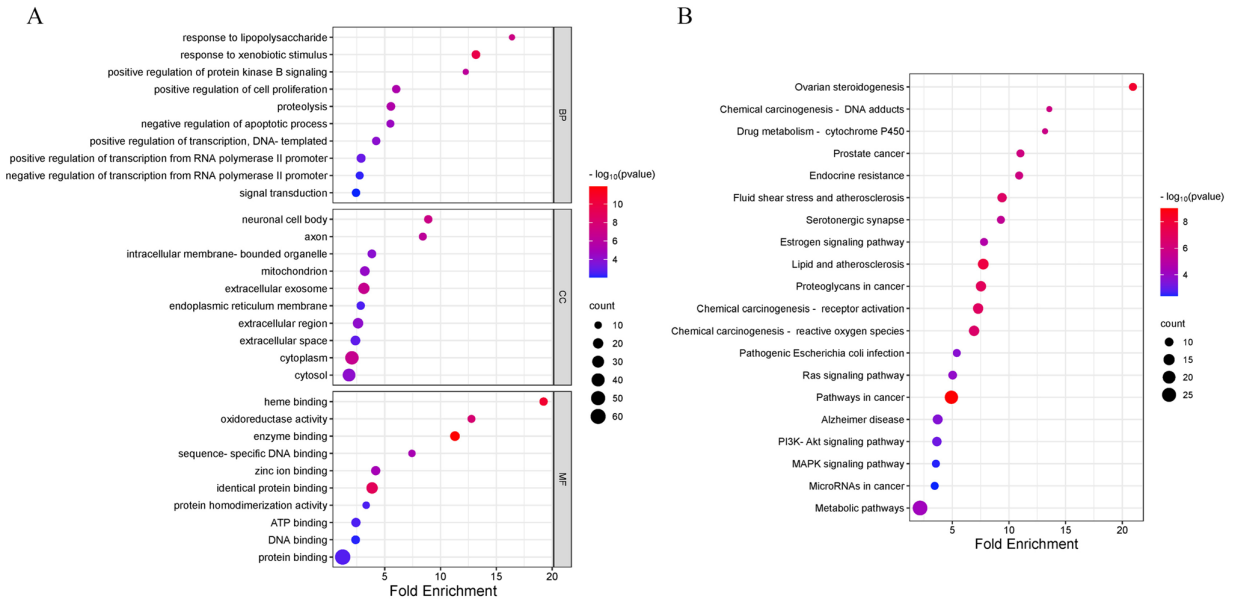

Fig. 6 GO (**A**) and KEGG (**B**) analyses of gene-encoding proteins targeted by resveratrol in PD

usually appear between the ages of 30–50 years and worsen with chronological ages (Ajitkumar and Jesus 2023).

Studies have shown that SIRT1 activity plays a neuroprotective role in HD mouse models. However, the mechanisms that cause changes in SIRT1 activity have not been clarified. Ho et al. (2010) conducted a study to investigate the effects of resveratrol preparations (SRT501-M) on HD transgenic mice. The results revealed that administering SRT501-M led to an increase in the expression of PGC-1α, along with its downstream targets nuclear respiratory factor-1 (Nrf-1) and uncoupling protein-1 in brown adipose tissue. Nevertheless, no significant changes were observed in the expression of PGC-1α, Nrf-1, or the mitochondrial transcription factor in the striatum. A previous study indicated that the striatum-specific phosphorylation-dependent regulatory mechanism of SIRT1 induction under normal physiological conditions is impaired in HD (Li et al. 2016). In addition, the study also demonstrated that SIRT1 activity is attenuated in the brains of two complementary HD mouse models, providing insights into the regulation of SIRT1 activity for the possible development of novel therapeutic strategies.

Previous studies have indicated that SIRT1 deacetylase activity directly targets neurons to mediate neuroprotection from mHTT. SIRT1 activates CREB-regulated transcription coactivator 1 (TORC1) by promoting its dephosphorylation and interaction with cAMP-response element binding protein (CREB) to induce brain-derived neurotrophic factor (BDNF) transcription in models of HD (Jeong et al. 2011). Moreover, SIRT1 can control many physiological and pathological processes by regulating the activity of multiple targets, such as FoxO3a, phospho-tropomyosin receptor kinase B (p-TrkB), and p53, to mediate neuroprotection in HD models (Fig. 7) (Jiang et al. 2011). However, studies have indicated that SIRT1 mRNA levels are increased, whereas SIRT1 protein levels are decreased in postmortem HD brains and specific transgenic HD models (Baldo et al. 2018; Salamon et al. 2020). The possible hypotheses are that the SIRT1 protein is degraded via protein degradation pathways, such as the ubiquitin−proteasome pathway, in HD models or via posttranscriptional mechanisms that are correlated with the inhibition of SIRT1 mRNA translation. Through network pharmacology, the top 20 items with p values ≤ 0.01 were screened via KEGG analysis (Fig. 8). At present, further studies on resveratrol in HD are needed, and the results of the network pharmacology analysis suggest that the Ras signaling pathway, the MAPK signaling pathway, the phosphoinositide 3-kinase (PI3K)-AKT signaling pathway, and the Rap1 signaling pathway may play important roles in the effects of resveratrol in the treatment of HD.

Conclusion and perspectives

Multiple studies have emphasized the remarkable protective effects of SIRT1 in neurodegenerative diseases. Resveratrol, a potent activator of SIRT1, has demonstrated promising potential for treating these conditions. The clinical and economic significance of resveratrol has garnered widespread attention, resulting in its inclusion in numerous clinical trials. These trials have confirmed that resveratrol can be

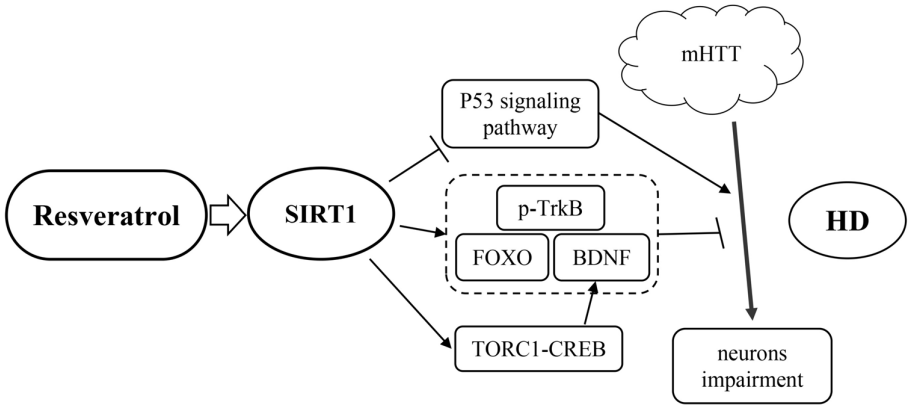

Fig. 7 The role of resveratrol and SIRT1 in HD. (→ indicates promotion; ┤ indicates inhibition)

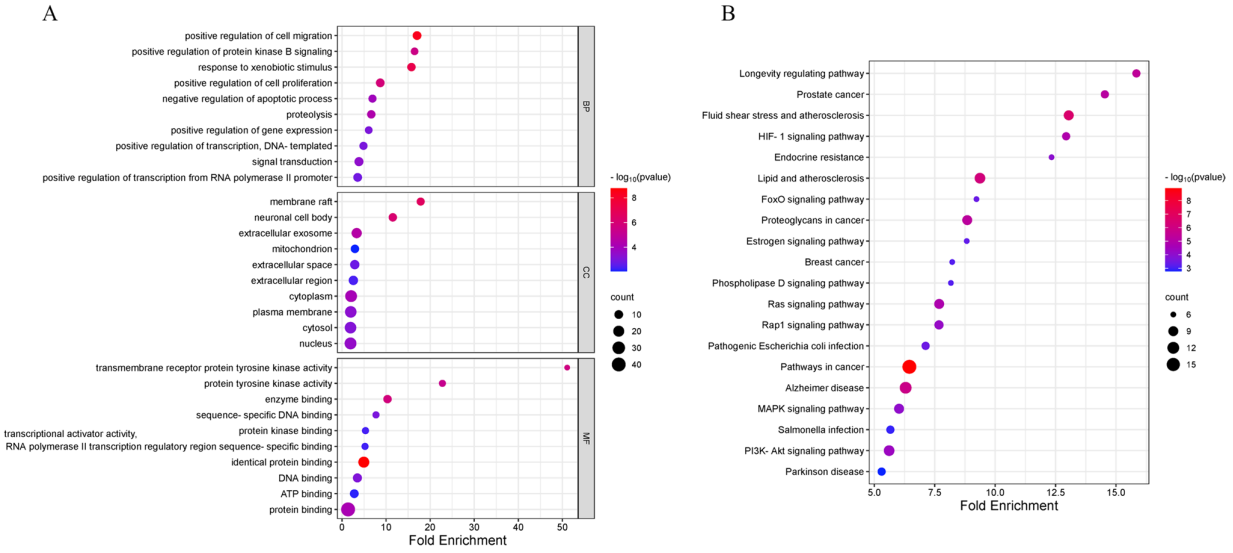

Fig. 8 GO (**A**) and KEGG (**B**) analyses of gene-encoding proteins targeted by resveratrol in HD

detected in both plasma and cerebrospinal fluid (CSF) following oral administration (Turner et al. 2015). Furthermore, oral intake of resveratrol has been shown to increase SIRT1 expression in the peripheral blood mononuclear cells of individuals with type 2 diabetes mellitus and in the muscles of obese individuals (Bo et al. 2018; Hoseini et al. 2019; Timmers et al. 2011). These findings provide strong support for the clinical use of resveratrol in the treatment of neurodegenerative diseases by targeting SIRT1.

Furthermore, clinical research has confirmed that the use of resveratrol enhances cognition and cerebrovascular function among non-HD patients (Evans et al. 2017; Huhn et al. 2018; Moran et al. 2018; Moussa et al. 2017; Thaung Zaw et al. 2021). Additionally, it reduces the levels of Aβ40 and Aβ42 in CSF and plasma, mitigates the decline in Mini-Mental Status Examination scores and changes in Activities of Daily Living scores, and regulates neuroinflammation in AD patients with minimal adverse effects (Bo et al. 2018; Turner et al. 2015). These findings collectively underscore the therapeutic potential of resveratrol as a novel drug for patients with neurodegenerative diseases. Future research will aim to comprehensively investigate the therapeutic effects and mechanisms of resveratrol in neurodegenerative diseases.

The research on resveratrol in the treatment of neurodegenerative diseases has shown promise. Despite current challenges, such as low bioavailability and insufficient clinical evidence, its diverse biological activities make it a potential therapeutic candidate. Future research should focus on overcoming these challenges, optimizing the delivery methods of resveratrol, and exploring its synergistic effects with other therapeutic approaches to provide new hope for patients with neurodegenerative diseases.

Authors contributions All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Lin Zhu, Lehao Fan, Miaomiao Yang, Qiuying Yan and Lifeng Zhang. The first draft of the manuscript was written by Lin Zhu, Ping Mu and Fangjin Lu and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript. The authors confirm that no paper mill and artificial intelligence was used.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Ethical approval Not applicable.

Conflict of interest The authors declare no competing interests.

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