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Food derived SIRT1 activator: a deacetylation-driven new way to fight neurodegenerative diseases

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ABSTRACT: The primary characteristics of neurodegenerative diseases (NDs) are cognitive, motor and other dysfunctions resulting from the progressive loss of neurons, and the major mechanisms of NDs include abnormal aggregation of cytotoxic proteins, mitochondrial dysfunction, oxidative stress, and neuroinflammation. SIRT1 is a critical NAD⁺-dependent deacetylase and participates in widespread physiological processes, including energy metabolism, inflammation, and oxidation, which regulates the activity and function of multiple substrate proteins, thereby affecting intracellular signaling to ameliorate NDs. The signaling pathways involved in deacetylase SIRT1 mainly include the activation of AMPK, Akt and Nrf2 signals and the inhibition of NF-κB and NLRP3 inflammasome pathways, thereby alleviating mitochondrial dysfunction, oxidative stress, and neuroinflammation in NDs. Besides, microRNAs can adjust the activity of deacetylase SIRT1 to modulate the acetylation level of key molecular signals that influence the oxidative stress and neuroinflammation status in NDs. Notably, increasing evidence reveals natural food-derived deacetylase SIRT1 activators exhibit potential to fight NDs. This review primarily focuses on the role and underlying mechanism of SIRT1 on NDs, as well as the regulation of SIRT1 by microRNAs in NDs, and reveals the therapeutic effects of food sourced SIRT1 activators, especially bioactive ingredients from medicine food homology, so as to discover deacetylation-driven new therapeutic strategies for NDs.

Key words: deacetylase SIRT1, food derived activator, neurodegenerative diseases, energy metabolism, neuroinflammation, microRNAs

1. Introduction

Neurodegenerative diseases (NDs) are primarily characterized by a progressively loss of neuronal structure and function within different brain regions, resulting in cognitive, motor, sensory and other dysfunction (Figure 1). Beyond this, Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD) and other NDs also present with aberrant folding of cytotoxic proteins associated with degeneration and death of specific neurons, along with neuroinflammation and oxidative stress [1, 2]. Impaired function and degeneration of neurons and synapses have been shown to be one of the earliest pathological changes in NDs and ageing, such neurons and synapses are predominantly lost around mature, dense-core amyloid plaques and are cleared by glial cells, particularly microglia and astrocytes, through the

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classical complement pathway^[3, 4]. Deposited abnormal proteins, including amyloid β -protein (A β), Tau and α -synuclein, serve as damage-associated molecular patterns that bind to receptors like TLRs to activate surrounding microglia, thereby releasing large quantities of cytokines and chemokines, subsequently recruiting more glial cells^[5] to cause persistent chronic inflammatory response, finally leading to neurotoxicity^[6]. Moreover, in NDs, deficiency in autophagy, especially mitophagy, results in accumulation of impaired mitochondria that triggers extensive ROS production and exacerbates mitochondrial dysfunction, ultimately leading to neuronal death^[7]. Overall, NDs are linked to synaptic injury and neuronal loss caused by misfolding and aggregation of abnormal proteins, neuroinflammation, oxidative stress, and mitochondrial dysfunction, and amelioration of these abnormal changes could mitigate neurodegenerative lesions.

SIRT1, as a NAD⁺-dependent deacetylase, is mainly localized in nucleus and shuttles to cytosol under specific circumstances, which participates in a variety of physiological processes, such as metabolism and senescence, and is prevalently represented within all tissues, including brain^[8]. Through the deacetylation of modified lysine residues on histones and non-histones, including classic transcription factors PGC-1 α , NF- κ B, Nrf2, FoxO and p53, SIRT1 regulates gene transcription and translation to modulate cellular energy metabolism, inflammation, oxidation, autophagy, and senescence^[9]. Additionally, during neuronal development, SIRT1 has been shown to enhance axon elongation and dendritic branching, as well as adjust synaptic plasticity to facilitate memory formation. Brain-specific overexpression of SIRT1 extends lifespan and delays senescence in transgenic (Tg) mice during ageing. In addition to its essential role in normal brain ageing process, SIRT1 has been demonstrated to ameliorate multiple NDs, including AD and PD in animal models^[10]. In APP/PS1 mice, overexpression of SIRT1 decreases A β generation and A β plaques formation, while SIRT1 deletion up-regulates A β levels. SIRT1 overexpression rescued A β -induced microglia inflammation, senescence, and mitochondrial dysfunction by inhibiting NF- κ B signaling and promoting Nrf2 signaling^[11]. In addition, after spinal cord injury, overexpression of SIRT1 reduces endothelial ROS production and attenuates disruption of the blood-spinal cord barrier by deacetylating p66^{Shc}^[12]. Current therapies for NDs are not curative, thus targeting SIRT1 may hold promise for intervention in NDs.

Natural products from foods are a significant reservoir for developing drug candidates with specific biological activities to treat NDs and provide benefits as dietary supplements. There has been growing evidence that various natural compounds exhibit the capacity to slow down ageing and treat NDs, and exert multifaceted effects by modulating the production of neurotrophic factors, reducing oxidative stress, inhibiting apoptosis and ameliorating neuroinflammation^[13-15]. Furthermore, in recent years, natural compounds as SIRT1 activators for the treatment of NDs have garnered increasing attention and research from scholars. Consequently, this review focuses on the role of deacetylase SIRT1 in NDs, as well as the action of food-derived SIRT1 activators in NDs.

Neurodegenerative diseases

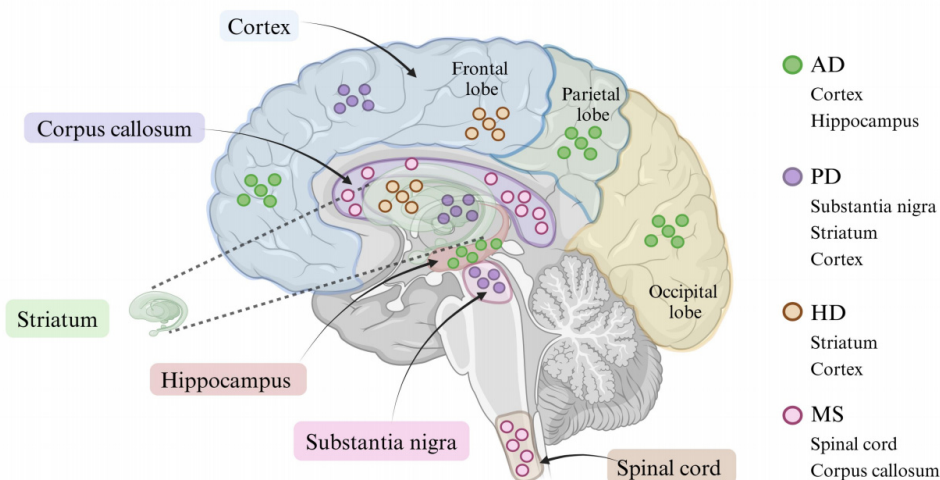


Figure 1. NDs in different brain regions with SIRT1 dysregulation. Generally, AD is mainly investigated in the hippocampus and cortex, PD is primarily explored in the substantia nigra, striatum and cortex, HD is principally discovered in the striatum and cortex, and MS is usually found in the spinal cord and corpus callosum.

2. Structure and biochemical feature of deacetylase SIRT1

SIRT1 is a class III histone deacetylase dependent on nicotinamide adenine dinucleotide (NAD^+), belonging to the mammalian sirtuin family, and is commonly expressed in various tissues and organs (Figure 2A). Acetylated proteins serve as substrates in the SIRT1-catalyzed reaction, where the acetyl group is transferred to the ribose portion of the NAD^+ cofactor, yielding the end products including deacetylated protein, niacinamide, and O-acetyl-ADP-ribose^[16]. The total length of SIRT1 is about 747 amino acids, which is composed of an N-terminal regulatory domain (NTD), a core catalytic domain (CAT) and a C-terminal regulatory domain (CTD) (Figure 2B). The CAT of SIRT1 ($\text{SIRT1}^{\text{CAT}}$) has 277 amino acids and consists of a larger Rossmann-folded NAD^+ binding subdomain, and a smaller subdomain consisting of helical module (residues 269-324) and a Zn^{2+} binding module (residues 362-419), both of which are insertions within the NAD^+ binding domain^[17]. The CTD regulates SIRT1 activity by influencing its interaction with the acetylation substrate, NAD^+ or the negative regulator, deleted in breast cancer-1 (DBC1)^[18], and is divided by a C-terminal regulatory segment (CTR) (residues 641-665) of 25 residues into a larger N-terminal region, followed by a shorter C-terminal extension, each of which interacts differently with CAT^[19]. In the presence of NAD^+ and peptide substrates, the heterodimer formed between $\text{SIRT1}^{\text{CAT}}$ and CTR binds to ADP ribose (ADPR), undergoing a conformation shift from the “open state” to the “closed state”. This transformation involves the smaller structural domains of $\text{SIRT1}^{\text{CAT}}$ and CTR, which rotate and fold over the larger structural domains, reducing the inter-domain distance for NAD^+ capture and forming a hydrophobic structure that locks the substrate peptide. In the closed state, a salt bridge is formed between Glu656 and Arg276 of the helical module located in the CTR (Figure 2C-D).

Biochemical analysis of the action of CTR on $\text{SIRT1}^{\text{CAT}}$ shows that CTR inhibits SIRT1 activity despite its stability. Compared to the $\text{SIRT1}^{\text{CAT}} \cdot \text{CTR}$ heterodimer, $\text{SIRT1}^{\text{CAT}}$ in isolation consistently

exhibits higher activity, suggesting an inhibitory effect of CTR, which is mediated by the 10 C-terminal residues of the CTR through the formation of a pseudo-substrate ^[19]. In addition, CTR mutants lacking the C-terminal extension or R276A and E656A mutants lose this inhibitory effect, suggesting that the salt bridge between these residues is a crucial determinant of CTR-mediated inhibition of SIRT1 activity ^[19]. Moreover, a small β -hairpin, known as the region essential for SIRT1 activity (ESA), has been identified in CTR. It has been demonstrated that SIRT1^{CTR} alters the affinity of the catalytic core for acetylated substrates through heterodimerization, and the ESA-deficient SIRT1 mutant is unable to interact with acetylated substrates, resulting in loss of activity ^[20]. The ESA region of CTR competes with the endogenous inhibitory protein DBC1 for binding to the CAT of SIRT1. DBC1 can form a stable complex with SIRT1, thereby inhibiting the deacetylase activity of SIRT1 and hindering its deacetylation of substrates. Genotoxic stress enhances the SIRT1-DBC1 interaction through ATM-mediated SIRT1 phosphorylation, while down-regulation of DBC1 expression increases SIRT1-dependent genotoxic stress-induced inhibition of apoptosis ^[18, 21, 22]. In addition, SIRT1 is also negatively regulated by ATP, which inhibits SIRT1 activity by binding to the ESA to disrupt the interaction of the CTR with the catalytic core characteristic of the active closed structure of SIRT1^[23]. Notably, activation of AMPK, an important cellular energy sensor, directly phosphorylates SIRT1 at T344, promoting SIRT1-DBC1 dissociation and subsequently leading to SIRT1 activation ^[24]. Activity regulator of SIRT1 (AROS) is a nuclear protein that directly interacts with the amino acids 114-217 of SIRT1^{NTD} to activate SIRT1 and enhance SIRT1-mediated p53 deacetylation, thus inhibiting p53-mediated transcriptional activity ^[25]. Besides, other studies have found physical interactions between SIRT1 and AROS, but the functional relationship between the two proteins is dependent on the biological context ^[26].

Overall, SIRT1 protein structure can be categorized into NTD, CAT and CTD three major functional domains, whose conformation directly affects the activity and substrate specificity, and SIRT1 is subject to regulation by multiple mechanisms, including the NAD⁺ level and interactions with regulatory proteins, such as DBC1 and AROS, all of which influence the biological function of SIRT1.

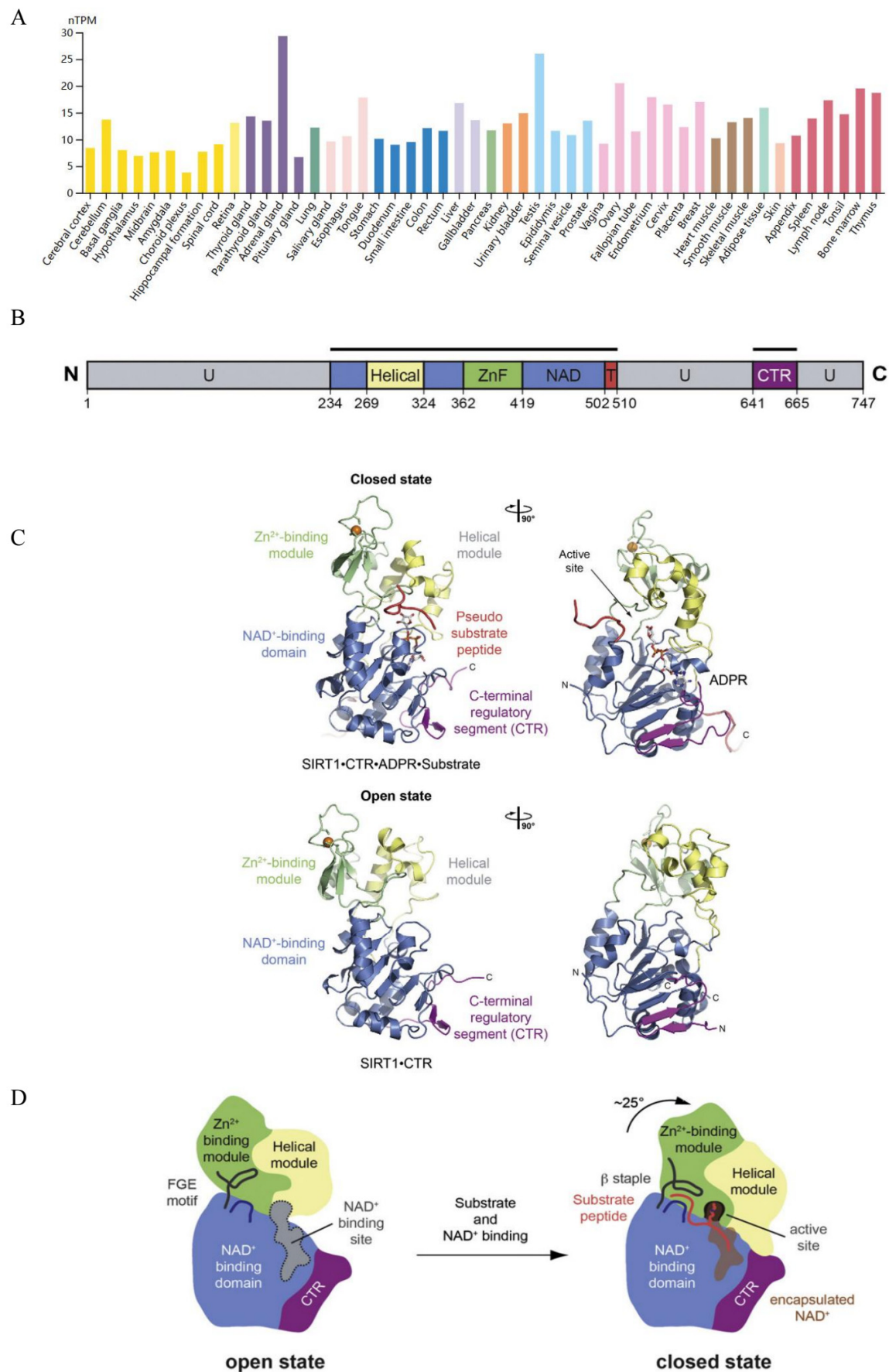


Figure 2. The expression and structure of SIRT1. (A) The level of SIRT1 in different tissues. Data from the Human Protein Atlas project (<https://www.proteinatlas.org/>). (B) Secondary structure of SIRT1 protein. (C, D) Structure of SIRT1. From ref. [25].

3. SIRT1 in neurodegenerative diseases

3.1 Energy metabolism-related signaling pathways and SIRT1

As key energy-sensing molecules in mitochondrial biogenesis, SIRT1 and AMPK regulate neuronal survival and energy homeostasis. In primary hippocampal neurons, A β ₂₅₋₃₅ suppresses the AMPK phosphorylation and SIRT1 expression, increases PGC-1 α acetylation levels, decreases mtDNA copy number, as well as inhibits the transcription and translation of mitochondrial biogenesis factors, such as Nrf1, Nrf2, and Tfam [27]. Therefore, inhibition of AMPK/SIRT1/PGC-1 α pathway and its downstream targets associates with impaired mitochondrial biogenesis in AD. Activation of SIRT1/PGC-1 α pathway by neural stem cell-derived exosomes enhances mitochondrial biogenesis and inhibits astrocyte activation in the brain of APP/PS1 mouse, whereas specific SIRT1 knockdown in nervous system further exacerbates AD [28]. Moreover, in APP/PS1 mice, glutamic-oxaloacetic transaminase (GOT) acting on SIRT1 alleviates cognitive and memory impairments, decreases neuronal loss and up-regulates neuronal synapses with decline of A β ₁₋₄₂ levels and mitochondrial damage, which effects are partially reversed by SIRT1 inhibitor EX527 [29]. The NAMPT-NAD⁺-SIRT1 axis is downregulated in the hippocampus of APP/PS1 mice. The NAMPT activator P7C3 enhances mitochondrial structure, function, and autophagic activity by promoting the NAD⁺-SIRT1 axis, thereby improving learning and memory, while the NAMPT inhibitor FK866 exacerbates A β plaque deposition in the hippocampus of AD mice [30]. Additionally, BPN14770, a allosteric inhibitor of phosphodiesterase-4D (PDE4D), improves scopolamine-stimulated memory and cognition impairments, increases Akt phosphorylation as well as SIRT1 and Bcl-2 expression, and reduces Bax expression in hippocampus, which are partially abrogated by cAMP, SIRT1, and Akt inhibitors [31]. Furthermore, the expression of SIRT1 and O-GlcNAcase (OGA) are decreased in the brains from AD patients. SIRT1 knockdown reduces OGA expression in primary cortical neuronal cells, and brain-specific SIRT1 knockdown increase Tau phosphorylation that relates to enhance Tau's O-GlcNAcylation, as a result of reduced OGA level and elevated OGT level. Besides, SIRT1 deletion also leads to the distribution of the specific site p-Tau in the synaptosomes, resulting in dendritic spine defects and synaptic dysfunction, leading to learning and memory deficits [32]. Collectively, SIRT1 suppresses Tau hyperphosphorylation and A β production via activating AMPK/PGC-1 α , GSK-3 β and cAMP/Akt pathways, thereby ameliorating mitochondrial dysfunction and oxidative stress, consequently reducing memory and cognitive deficits in AD (Figure 3).

There are many risk factors for AD, such as type 2 diabetes, traumatic brain injury (TBI) and ageing. A convergent point between type 2 diabetes and AD is thought to be dysfunctional energy metabolism. AMPK/SIRT1 signals show a downward trend in both APP/PS1 mice and streptozotocin (STZ)-induced mice, while overexpression of AMPK in bilateral hippocampal regions ameliorates spatial memory impairments and inhibits Tau hyperacetylation via promoting SIRT1 expression and activity [33]. Up-regulated S-nitrosylated (SNO) GAPDH in the cortex and hippocampus from TBI mice leads to SIRT1 inactivation and p300/CBP activation, which in turn causes increased acetylation of Tau in neurons and

mis-localization of Tau proteins. Activation of SIRT1 and inhibition of GAPDH SNO or p300/CBP all protect mice from Tau accumulation, neurodegeneration and neurobehavioral deficits [34]. Moreover, ageing is the predominant risk factor for AD. SIRT1 expression is decreased and the phosphorylation of Tau is increased in the cortex of SAMP8 mice. In D-gal-stimulated PC12 cells, D-gal stimulation increases SA- β -gal-positive cells and promotes age-related proteins expression including p21 and p16. The AMPK activator metformin and the direct precursor of glutathione, γ -glutamylcysteine (γ -GC), reverse D-gal-induced changes via increasing AMPK phosphorylation to facilitate GAPDH nuclear translocation and inhibit DBC1 nuclear translocation, leading to SIRT1 activation and p53 deacetylation in the nucleus. However, SIRT1 inhibitor EX527 partly reverses the effects of γ -GC [35]. Moreover, in β -galactose-induced senescent HT22 and BV2 cells, the interaction between NAMPT and SIRT1 become weakened, whereas nicotine, a metabolite of the NAD^+ metabolic pathway, facilitates their interaction. In senescent mice, SIRT1 and NAMPT expression are reduced and the acetylated NAMPT is increased, while nicotine ameliorates glucose metabolism hyperactivity through deacetylation of NAMPT by SIRT1 [36]. In general, SIRT1 could attenuate multiple risk factors for AD such as ageing by decreasing BACE1 expression, as well as Tau, NAMPT and p53 acetylation, and activating AMPK pathway (Figure 3).

Apart from AD, SIRT1 activation in other NDs, including PD, HD and MS, can also alleviate disease progression by modulating energy metabolism-related pathways. In SH-SY5Y cells, rotenone treatment induces mitochondrial dysfunction, oxidative stress, autophagy dysfunction and apoptosis, manifested by a decrease in mitochondrial membrane potential, an increase in the production of ROS and MDA, up-regulation of Bax and p62 expression and down-regulation of Bcl-2, LC3II and Beclin1 expression via suppressing the AMPK/SIRT1/PGC-1 α pathway. Ghrelin, a brain-gut peptide, reverses the above changes induced by rotenone, while Compound C and EX527 abolish the cyto-protection of ghrelin [37]. Besides, SIRT1 expression is not only reduced in primary neurons induced by the neurotoxin MPP^+ and in the substantia nigra pars compacta (SNpc) from MPTP-induced mice, which is also decreased in the Tg PD model. SIRT1 knockout exacerbates deterioration of motor function in MPTP-lesioned PD mice. Importantly, the ubiquitin-proteasome and Cdk5 are involved in the degradation of SIRT1 caused by MPP^+ , and the proteasome inhibitor MG132 and the Cdk5 inhibitor roscovitine can inhibit the decline of SIRT1 [38]. In MPTP-induced PD mice, SIRT1 could improve Parkinson's syndrome, while SIRT1 knockout further aggravates the PD phenotype. Mechanistically, SIRT1 deacetylates the pyruvate kinase M2 (PKM2) at K135 and K206, thereby reducing the activity of the PKM2 enzyme and the production of lactate, ultimately resulting in a decrease in glial activation in the brain [39]. Serving as a negative modulator of autophagy/lysosomal, GSK-3 is responsible for intracellular degradation and is essential for maintaining neuronal viability. In R6/2 HD mice, GSK-3 inhibitor L807mts reduces mHtt aggregation and increases the expression of autophagy and lysosomal markers. In addition, L807mts activates SIRT1 and promotes the phosphorylation of Akt, thereby increasing the production of related neurotrophic factors such as BDNF [40]. Furthermore, acetylated p53 levels increase in the half brain from models of SIRT1 knockout mice and HD

mice, suggesting the activity of SIRT1 is impaired. Abnormal phosphorylation of SIRT1 is observed in HD mice, especially in the striatum, where SIRT1 activity is weakened and age-dependent with increased p53 acetylation. In addition, there is an increased interaction between DBC1 and AMPK- α 1 and decreased mRNA expression of SIRT1, DBC1 and AMPK- α 1 [41]. As a risk factor for tauopathies, TSC1 is linked to age-related NDs, causing Tau deposition along with other pathologic changes in progressive supranuclear palsy (PSP). There are aberrant accumulation of acetylated Tau protein and reduced expression of SIRT1 in TSC1 haplotype-deficient neurons of mice and in the cortex of PSP patients harboring TSC1 risk variants. SIRT1 activator, p300 inhibitor and mTORC1/2 inhibitor all improve Tau accumulation and acetylation in TSC1 deficient neuronal cells [42]. Taken together, SIRT1 promotes Tau deacetylation, regulates energy metabolism-related pathways such as AMPK, Cdk5, Akt/GSK-3, and mTOR to enhance autophagy, and attenuate mitochondrial dysfunction, oxidative stress, and apoptosis, thus ameliorating NDs such as PD, HD, and MS (Figure 3).

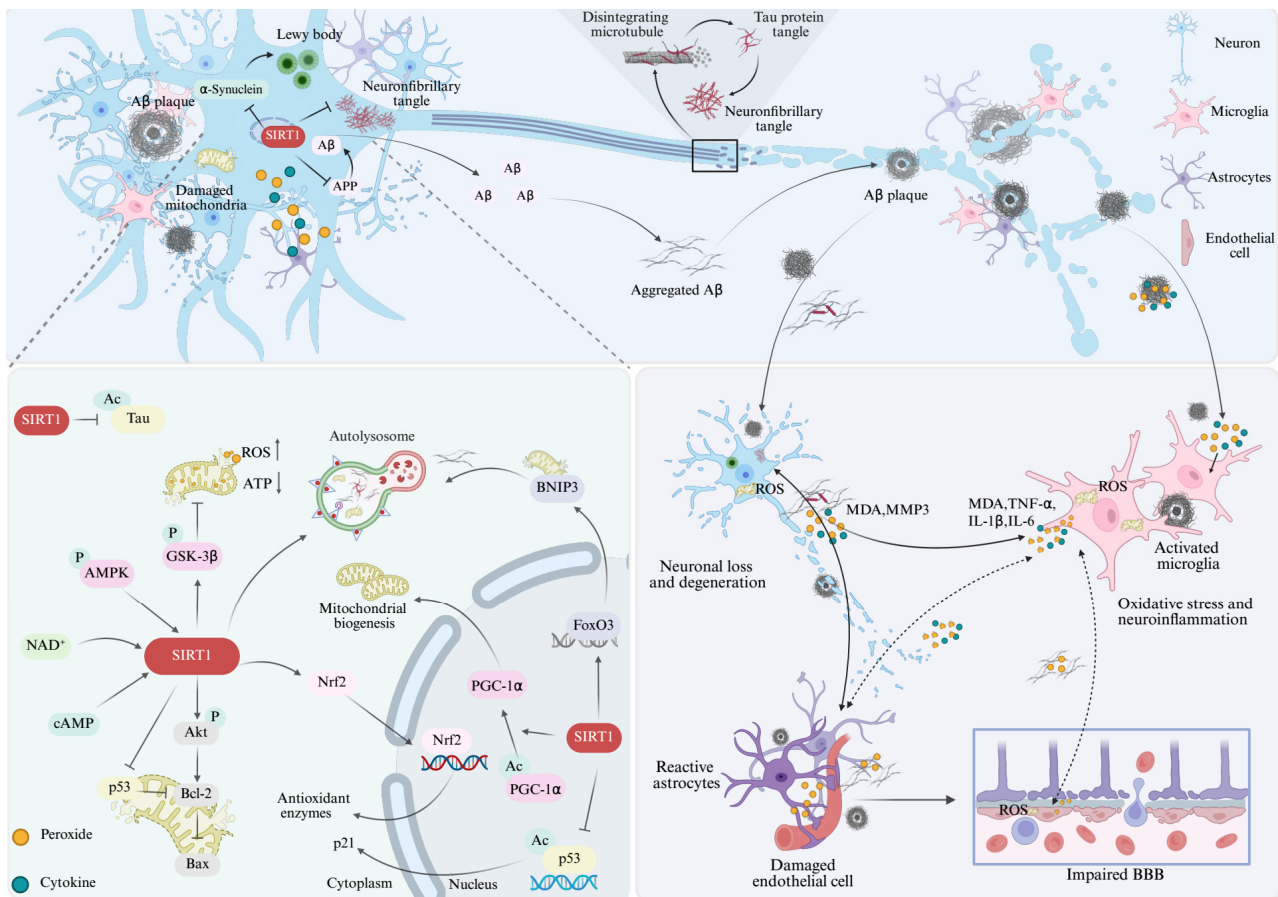


Figure 3. SIRT1 regulates energy metabolism and oxidative stress signaling in NDs. In a variety of cells in NDs, such as neurons, microglia and cerebrovascular endothelial cells, SIRT1 improves mitochondrial dysfunction and autophagy dysfunction, attenuates oxidative stress and apoptosis to mitigate NDs through the activation of energy-related pathways, such as AMPK/PGC-1 α , as well as oxidative-related pathways, such as Nrf2.

3.2 Oxidative stress-associated signaling pathways and SIRT1

A common feature of NDs is oxidative stress resulting from unregulated production of ROS that contributes to senescence and damage in a variety of cells, such as endothelial cells, microglia and neuron. In A β ₁₋₄₂-induced hCMEC/D3 cells, after withdrawing A β , SIRT1 levels return to normal, yet cell viability

remains unenhanced. Activation of SIRT1 and NAD⁺ supplementation alleviate cerebrovascular endothelial memory impairment, while SIRT1 inhibitor EX527 aggravates it [43]. A β ₁₋₄₂ not only induces oxidative damage in cerebral vascular endothelial cells, but also causes damage to microglia and neuron. In HMC3 cells, BV2, human induced pluripotent stem cells (iPSCs)-derived neural stem cells, SK-N-SH cells and SH-SY5Y cells, A β ₁₋₄₂ increases ROS generation, causes mitochondrial dysfunction, induces the expression of senescence-related genes and proteins by inhibiting SIRT1 expression, conversely, SIRT1 overexpression ameliorates the above changes caused by A β ₁₋₄₂ [44-46]. In addition, following entry of healthy mitochondria into A β ₁₋₄₂-induced SH-SY5Y cells and mice, autophagy is activated via SIRT1/FoxO3/BNIP3 axis, which results in scavenging of damaged mitochondria and A β proteins, reduces ROS and MDA production, and increases antioxidant enzyme activity, thereby improving cognitive performance in AD mice [47]. Besides, in primary neurons and cortex of mice, A β ₂₅₋₃₅ stimulation brings about neuronal over-oxidation and impaired autophagy via suppressing SIRT1/Nrf2 pathway, which results in mitochondrial and synaptic structural disarray with apoptosis, consequently leading to learning and memory impairments in mice [48]. There is a strong link between oxysterol and the advancement of brain diseases. In the course of AD, the level of 24-hydroxycholesterol (24-OHC) exhibits decreased in the cortex, which change is consistent with the expression of SIRT1, PGC-1 α and Nrf2 in AD patients. Interestingly, 24-OHC treatment activates antioxidant effects by up-regulating SIRT1 expression and activity and subsequently inhibiting acetylation of PGC-1 and Nrf2. And then Tau ubiquitination is triggered and degraded by the ubiquitin-proteasome system, resulting in the clearance of Tau proteins in SK-N-BE cells [49]. Furthermore, in the brains of AD people, A β plaques increase, while the expressions of SIRT1 and SOD1 gradually decrease with disease progression [46]. Regarding senescence, mesenchymal stem cells-derived exosomes (MSC-Exos) protect BV2 cells from H₂O₂-induced cellular senescence and decline in migration capacity. In the hippocampus of SAMP8 mice, MSC-Exos suppress astrocyte activation, attenuate excessive oxidative stress through activating SIRT1/Nrf2 pathway and modulate SIRT1/p53/p21 signals to retard brain ageing [50]. Furthermore, H₂O₂ also causes a reduction in Transendothelial electrical resistance and SIRT1 expression in mBMEC, which are reversed by SIRT1 activator. Downregulation of SIRT1 expression is accompanied by decreased expression of claudin-5 and ZO-1 in aged mice and aged human brain microvessels. In aged mice with SIRT1 overexpression and brain endothelium-specific SIRT1 knockout mice, it is further demonstrated that SIRT1 affects blood-brain barrier (BBB) integrity, prevents ageing-induced hyper-permeability of the endothelial barrier, and stabilizes claudin-5/ZO-1 interaction [51]. Moreover, diapocynin, a NADPH oxidase inhibitor, attenuates oxidative stress with an increase in GSH and GST and a decrease in gp91phox, inhibits neuroinflammation by inhibiting microglia and astrocyte activation and down-regulating iNOS and p65 expression, and mitigates apoptosis with a decrease in p53 and Bax and an elevation in Bcl-2 via regulating SIRT1/Nrf2/NF- κ B pathway in striatum of 3-nitropropionic acid -induced HD rats [52]. In short, SIRT1 attenuates excessive oxidative damage in diverse brain cells in NDs, mainly through activation of CysC/ADAM10, Nrf2, PGC-1 α signaling and inhibition of p53 and NF- κ B signaling (Figure 3).

3.3 neuroinflammation-associated signaling pathways and SIRT1

As a risk factor for neurodegeneration, hypoxia-reperfusion (H/R) injury not only causes neuroinflammation but also leads to amyloidosis changes in the pathologic development of AD. In HBMVECs, H/R increases endothelial permeability and induces HMGB1 acetylation, nuclear-cytoplasmic translocation and secretion by modulating intracellular SIRT1-HMGB1 binding. Overexpression of SIRT1 contributes to autophagy-mediated degradation of endogenous HMGB1, thereby inhibiting H/R-induced HMGB1 changes. More importantly, suppression of SIRT1 further exacerbates neuronal A β production caused by H/R-induced conditioned medium for HBMVECs (H/R-CM), whereas neutralizing HMGB1 in H/R-CM reverses this effect^[53]. In H₂O₂-induced and 27-hydroxycholesterol-stimulated SH-SY5Y cells, inhibition of SIRT1 is accompanied by NF- κ B signal activation, leading to increased transcription and translation of BACE1, which further brings about APP cleavage and A β production. Besides, in the cortex of 3 $\times$ Tg mice and HFC diet mice, the expression of BACE1 and APP is also up-regulated along with neuroinflammation and cognitive deficits^[54]. SIRT1 overexpression alleviates A β ₁₋₄₂-stimulated neuronal cells inflammation, senescence and ageing-associated DNA damage, as evidenced by a decrease in SA- β -gal-positive cells, IL-6 secretion, and levels of p21, PAI-1, MMP3, γ -H2AX and 8-OHdG^[55]. In Tau P301S mice, SIRT1 absence results in exacerbation of premature mortality, cognitive impairment, and synaptic loss, whereas SIRT1 overexpression reduces the acetylation of Tau protein, thereby attenuating the spread of Tau pathology^[56]. Moreover, GLP-1 agonist semaglutide accelerates autophagic flux by enhancing ACE2/SIRT1/FOXO1 signaling, thereby mediating microglial polarization to improve cognitive decline in P301S tauopathy Tg mice^[57]. In addition, in AlCl₃-induced AD rats, the expression of SIRT1 is decreased, accompanied by neuroinflammation and oxidative damage, and up-regulation of A β as well as phosphorylation of Tau, STAT3 and mTOR, which were reversed by mesenchymal stem cells^[58, 59]. Notably, the levels of SIRT1 and IL-6 are decreased, and the levels of A β ₁₋₄₂, p-Tau and T-Tau are increased in the serum of AD patients^[60]. Besides, in the cortex of early and late AD patients, SIRT1 expression progressively decreases with AD disease progression, accompanied by higher expression of pro-inflammatory mediators and increased cholesterol oxidation^[61]. Sum up, to improve AD, SIRT1 could mitigate neuroinflammation via inhibiting the acetylation of HMGB1, p65 and Tau as well as activating TFER, thereby enhancing autophagy to reduce A β production and aggregation as well as suppressing the activation of the NF- κ B and mTOR/STAT3 signaling (Figure 4).

SIRT1 expression and activity are reduced not only in multiple AD models, but also in models of ageing. With microglia senescence, SIRT1 expression decreases, and microglia SIRT1 deficiency causes cellular senescence and Tau-mediated memory defects by upregulating IL-1 β level in mice. SIRT1 deficiency activates IL-1 β transcription by inhibiting methylation of specific CpG sites on the IL-1 β proximal promoter^[62]. Cathepsin B (CatB), located in intracellular lysosomes, leaks into the cytoplasm in ageing microglia that has been linked to cognitive impairment. In the nuclei of L-leucyl-L-leucine methyl ester-induced microglia, the expression of SIRT1 decreases through CatB protein hydrolase activity.

Moreover, in CatB-deficient aged mice, the expression of SIRT1 in the cortex is further increased, in parallel with decreased production of pro-inflammatory mediators ^[63]. SIRT1 expression is reduced not only in senescent microglia but also in senescent neuronal cells, while 17 β -estradiol and β -hydroxybutyrate (BHBA) can ameliorate these changes. In D-gal-induced senescent SH-SY5Y cells, 17 β -estradiol inhibits nuclear translocation of p65 and p53 expression, and promotes Akt phosphorylation through an ER- α /SIRT1-dependent manner, whereas EX527 and Tamoxifen reverse these effects. 17 β -estradiol also activates ER- α /SIRT1 to inhibit NF- κ B and promote Nrf2/HO-1 signaling, thereby ameliorating senescence-induced neuroinflammation, oxidative stress and synaptic dysfunction, and reducing A β expression to improve AD-like pathology in D-gal-induced ageing mice ^[64]. Moreover, BHBA, a small endogenous molecule that can cross the BBB, has neuroprotective effects. In D-gal-induced HT22 cells and hippocampus from D-gal-induced mice, BHBA reduces IL-1 β , TNF- α , ROS and MDA secretion via SIRT1-dependent inhibition of NLRP3 inflammasome and activation of FoxO3, which are reversed by SIRT1 inhibitor EX527 and SIRT1 silencing ^[65]. Taken together, ageing induced microglia and neuronal inflammatory responses are improved by SIRT1-dependent activation of the FoxO3 and Nrf2 pathways and inhibition of the NF- κ B and NLRP3 inflammasome pathways (Figure 4).

In MPP⁺/ATP-induced BV2 cells and in the striatum and SN from MPTP-induced PD mice, SIRT1 expression is reduced, while NLRP3 inflammatory vesicles and NF- κ B signaling are activated, which are reversed by melatonin ^[66]. LPS rapidly multiplies microglial glycolysis and increases pro-inflammatory mediator production via inhibiting SIRT1 and activating NF- κ B signaling. Both 2-Deoxy-D-glucose (2-DG) and FGF21 ameliorate LPS-induced above changes, whereas SIRT1 inhibitor EX527 suppresses the effects of 2-DG and FGF21. Besides, in LPS-induced PD mice and MPTP-stimulated mice, 2-DG and FGF21 both inhibit microglia polarization, thereby ameliorating neuroinflammation ^[67, 68]. Additionally, SIRT1 deacetylates HSPA4 and promotes its nuclear translocation, thereby inhibiting pro-inflammatory cytokines production in LPS-induced microglia. And in MPTP-induced mice, SIRT1 overexpression reduces the activation of microglia and astrocytes and attenuates TH loss in SNpc and striatum ^[69]. Furthermore, the transcription and expression of SIRT1 are reduced in MS patient-derived peripheral blood mononuclear cells, accompanied by attenuation of the neurotrophic factors BDNF and NT-4, as well as an increase in the heat shock proteins HSP27 and HSP70 ^[70]. In conclusion, SIRT1 inhibits the pro-inflammatory polarization of microglia via facilitating the deacetylation of HSPA4, decreasing NLRP3 inflammasome activation, and inhibiting NF- κ B pathway, thus reducing neuroinflammation and ameliorating NDs (Figure 4).

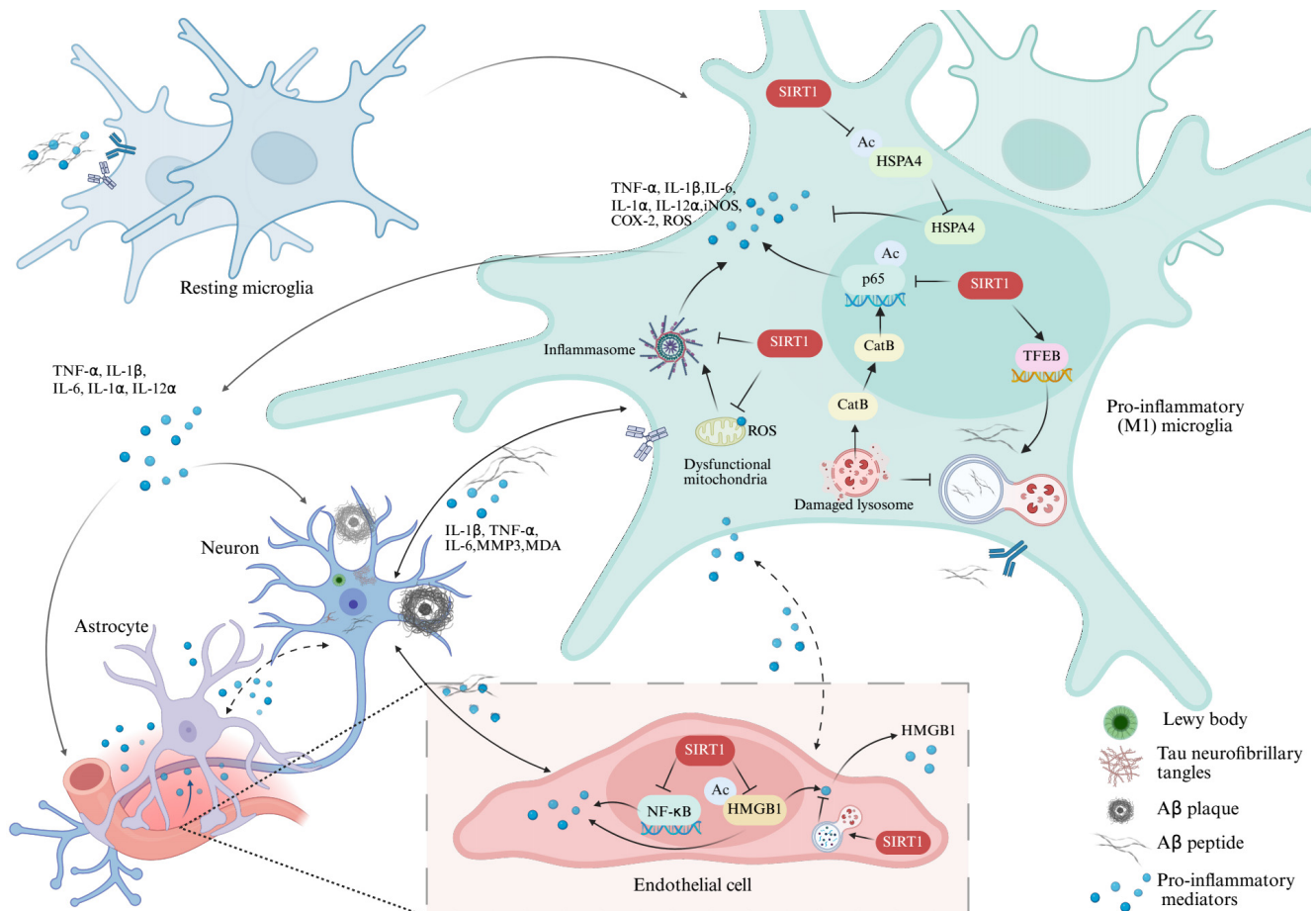


Figure 4. SIRT1 modulates inflammatory signaling pathways in NDs. Neuroinflammation is one of the pathological mechanisms of NDs. SIRT1 could inhibit pro-inflammatory polarization of microglia by suppressing the activation of the NF-κB signaling pathway and NLRP3 inflammasome, as well as enhancing autophagy, thus alleviating the damage caused by neuroinflammation to neurons and other cells to ameliorate NDs.

3.4 MicroRNAs and SIRT1

MicroRNAs (miRNAs), a kind of noncoding RNAs, play a critical role in regulation of target gene expression and exerts active against a large proportion of the transcriptome [71], and exert highly complex and dynamic regulatory effects on a variety of molecular processes that are relevant to nerve development, brain senescence, synaptic function, and cognitive capacity, contributing to processes involved in various aspects of the pathogenesis of NDs. With the emergence of a number of evidence demonstrate that miRNA mediates the post-transcriptional regulation of SIRT1 in NDs [72]. SIRT1 is a direct target of miR-138 in AD. In N2a co-transfected with APP and miR-138, SIRT1 overexpression suppresses Aβ production via up-regulation of ADAM10 and BACE1, and down-regulation of sAPPβ. Besides, miR-138 inhibition alleviates synaptic and cognitive impairments, suppresses microglia and astrocytes activation, and the production of Aβ via activation SIRT1 in APP/PS1 mice [73, 74]. The expression of miR-30a-5p is up-regulated in copper-induced SH-SY5Y APPswe cells, APP/PS1 mice and the plasma of AD patients. In SH-SY5Y APPswe cells, miR-30a-5p can directly bind to ADAM10 and SIRT1 to inhibit their expression, which promotes the production of Aβ₁₋₄₂ and leads to neuronal damage and apoptosis. Moreover, miR-30a-5p knockdown ameliorates cognitive deficits and neurodegenerative lesions in APP/PS1 mice via

upregulation of SIRT1^[75]. miR-30b levels are up-regulated in IL-1 β , TNF- α and A β ₄₂-induced hippocampal neurons and in the hippocampus of 5 $\times$ Tg AD mice and AD patients, while its directly targets including SIRT1, ephB2 and GluA2 are decreased along with NF- κ B signaling activation, resulting in synaptic and cognitive declines, but these effects are reversed by miR-30b knockout^[76]. The levels of miR-34a are increased in the brain of AD, and its overexpression results in suppression of SIRT1 expression with abnormal accumulation of intracellular A β and Tau hyperphosphorylation in the cortex, hippocampus and thalamus of doxycycline-induced mice, thus leading to cognitive impairment^[77]. Moreover, the rise of miR-132 and miR-212 generates decline of SIRT1 in the lymphoblastoid cells and hippocampus of AD patients^[78]. In A β ₂₅₋₃₅-induced PC12 cells and in APP/PS1 mice, miR-200a-3p levels are up-regulated that acts on SIRT1 and inhibits its expression, while miR-200a-3p inhibition and SIRT1 overexpression could reduce A β ₂₅₋₃₅-induced apoptosis^[79]. Overall, these abnormal increases in miRNA, including miR-138, miR-30, miR-34a, miR-200a-3p, miR-132 and miR-212, that lead to inhibit the expression and activity of SIRT1, thereby exacerbating synaptic dysfunction, neuroinflammation, oxidative damage, and the production and accumulation of abnormal proteins in AD (Figure 5).

Aging leads to increase of miR-142 that induces a decrease of SIRT1^[80]. As predicted by TargetScan, miR-9a, miR-34a, and miR-141 act directly at the 3'UTR of SIRT1 gene to reduce its expression. *In vitro*, MPP⁺ exposure significantly up-regulates the levels of miR-9, miR-34a, and miR-141 with subsequently down-regulation of SIRT1, inducing apoptosis and ROS overproduction in differentiated PC12 cells^[81]. Besides, in SH-SY5Y cells and primary astrocytes, miR-543 overexpression directly interacts with SIRT1 to inhibit its expression, this phenomenon is consistent with the white matter of early PD patients^[82]. By contrast, overexpression of miR-302 activates SIRT1/AMPK/PGC-1 α signals to attenuate neuronal cytotoxicity and enhances autophagy to protect mitochondrial function, thereby reducing mHtt aggregates in Huntington's disease^[83]. In general, SIRT1 is negative correlated with miRNA, like miR-9a, miR-34a, miR-141, miR-142, and miR-543, except miR-302, and its higher expression could attenuate neuroinflammatory and oxidative stress, and enhance autophagy to alleviate mitochondrial dysfunction in NDs, such as aging, PD and HD (Figure 5).

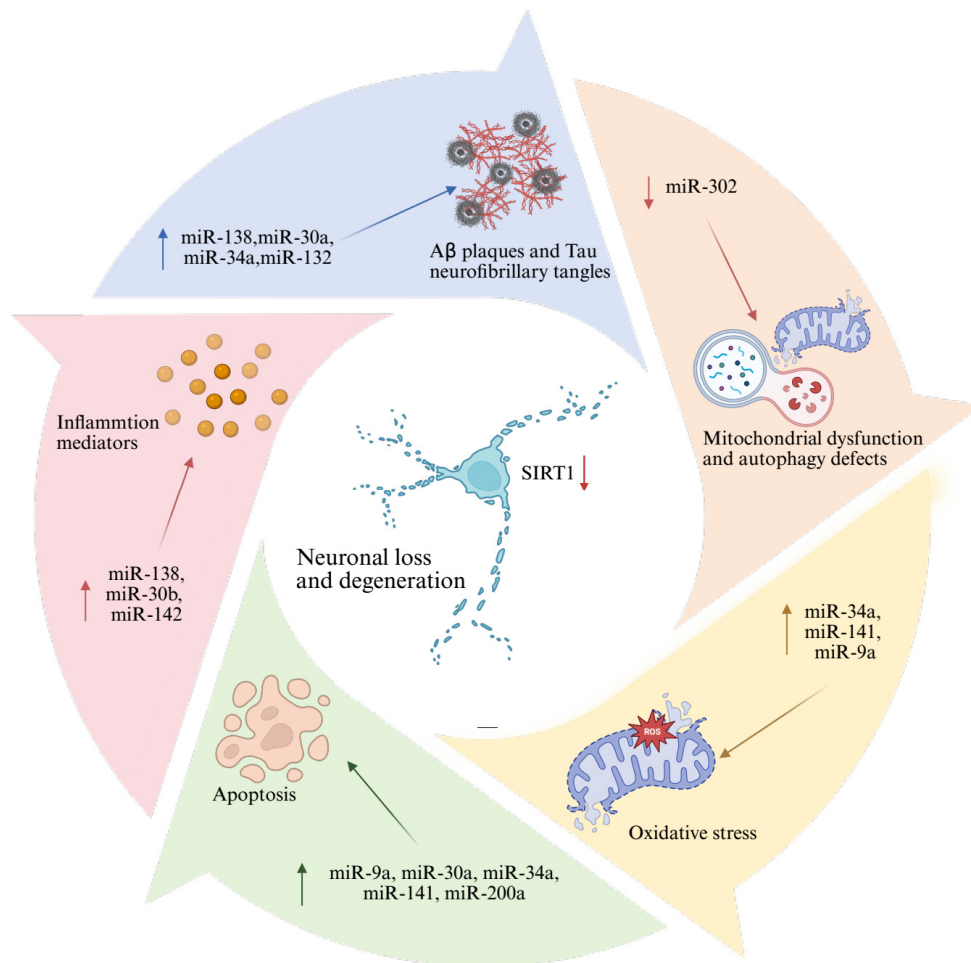


Figure 5. SIRT1 regulated by miRNAs in NDs. Generally, miRNAs negatively modulate the expression and activity of SIRT1, apart from some specific miRNA under certain condition, like miR-302 in HD, resulting in mitochondrial and autophagic dysfunction, excessive oxidative stress and neuroinflammation, apoptosis, and accumulation of abnormal proteins in NDs.

4. Food derived bioactive ingredients serve as SIRT1 activator in NDs

A variety of natural compounds such as phenols and flavonoids, are widely available in herbs and various dietary sources, and are able to modulate multiple pathways to alleviate NDs through activation of SIRT1. Therefore, understanding the mechanisms by which natural products act on SIRT1 in NDs is very valuable for developing nutritional guidelines and treatment strategies for NDs.

4.1 Phenols

As a natural plant polyphenol mainly from red grape skins and wine, resveratrol (RSV) (Figure 6A) has the ability to induce the activation of multiple neuroprotective pathways. In Aβ₁₋₄₂-induced cellular and animal models and in Tg AD model mice, RSV acts as a SIRT1 activator to activate AMPK/PGC-1α, CREB pathway and inhibit the acetylation of Tau, p53, which ameliorate Aβ pathology and Tau pathology changes, augment the activity of the ubiquitin-proteasome system, promote the neurotrophic factor production, consequently reducing oxidative stress and neuroinflammation [84-87]. In addition, it is very important to note that AD and diabetes mellitus frequently co-exist in patients as suffering from one increases the risk of developing the other. In the brain of STZ and Aβ₁₋₄₀-induced mice, RSV improves memory impairment and

alleviates oxidative stress and neuroinflammation through activating SIRT1^[88]. Hypoxia, a risk factor for AD, promotes extracellular and exosomal A β production. In hypoxia-induced overexpression of human wild-type APP695 cDNA SH-SY5Y cells, RSV reduces A β levels in the CM, exosome, and exosome-free CM via promoting SIRT1 expression with down-regulation of CD147. Interestingly, knockdown of SIRT1 and CD147 respectively promote A β expression and secretion, while administration of RSV reversed the alterations caused by CD147 knockdown. RSV also exerts above beneficial effects in hypoxia-induced mice^[89]. RSV ameliorates MPTP-caused motor and behavioral deficits, attenuates DA depletion, increases nigral TH-positive neurons and striatal TH protein expression, and reduces the expression of α -synuclein through activating SIRT1 to enhance deacetylation of LC3 to induce autophagy in striatum of PD mice, which are partly abolished by SIRT1 inhibitor EX527^[90]. Furthermore, in primary neurons from YAC128 mice and HD human lymphoblastoid cell lines, RSV enhances MMP and the rate of O₂ consumption, increases mitochondrial biogenesis, and suppresses histone H3 acetylation on lys9 (ac-H3K9). In addition, *in vivo*, RSV improves motor learning and coordination, promotes transcription of mitochondria-encoded genes in the cortex of YAC128 HD mice via activating SIRT1 to inhibit histone H3 acetylation^[91]. Furthermore, RSV also attenuates neurodegenerative lesions caused by ageing, aluminum and stress via activating SIRT1. Long-term RSV administration promotes glutamate metabolism, reduces the production of pro-inflammatory mediators via suppressing NLRP3 inflammatory vesicle and TLR4/NF- κ B pathway, and reduces oxidative stress through activating AMPK/SIRT1/Nrf2 pathway in primary hypothalamic astrocyte from aged rats^[92]. RSV attenuates inflammatory response via inhibiting TLRs/NF- κ B signaling pathway in LPS-induced hippocampal primary astrocyte from aged rats and hippocampal primary astrocyte from LPS-stimulated aged rats. In addition, RSV up-regulates the release of trophic factors, enhances glutamate metabolism, as well as prevents excessive oxidative stress via activating SIRT1/Nrf2/HO-1 signaling^[93]. Aluminum is a neurotoxic chemical contaminant in food, and its exposure is strongly associated with neurodegenerative diseases. Inactivation of NLRP3 inflammasome by RSV through activation of SIRT1 is accompanied by decreased IL-1 β and IL-18 levels, as well as down-regulation of DDX3X, NLRP3, ASC, Cleaved Caspase-1, and GSDMD expression in AlCl₃-induced BV2 cells. Furthermore, RSV also attenuates AlCl₃-induced cognitive deficits, increased BBB permeability, and activation of microglia and astrocytes via activating SIRT1 in the cerebral cortex of mice^[94]. Taken together, SIRT1 could be activated by RSV to activate AMPK/PGC-1 α , CREB, and Nrf2/HO-1 and suppress NF- κ B and NLRP3 inflammatory vesicles to reduce the production and accumulation of A β and Tau, attenuate mitochondrial dysfunction, neuroinflammation, and oxidative stress to improve NDs, which are specifically showed in Table 1.

Table 1. Effects of food-derived phenols on SIRT1 in NDs.

Compound	Dosage	Model	Disorder	Region and Index	Pathway
RSV	100mg/kg	3×Tg AD mice	AD	Hippocampus, ↓ (ac-Tau, ac-p53)	SIRT1/ac-p53 ^[84]
	200mg/kg,	Tg AD mice	AD	Hippocampus	SIRT1/ac-p53 ^[85]

	p.o.			pus, ↓ac-p53	
	20 μM	Aβ ₁₋₄₂ -induced primary rat neurons	AD	-	SIRT1/PGC-1α [86]
	20mg/kg	APP/PS1 mice		Hippocampus	
	p.o.			pus	
	0.02,0.2mg/kg,	Aβ ₁₋₄₂ -induced mice	AD	Hippocampus, cortex	AMPK/SIRT1/ PGC-1α [87]
	i.c.v.			Hippocampus	
	25 mg/kg,	STZ/Aβ ₁₋₄₀ -induced mice	AD	pus, cortex	SIRT1 [88]
	p.o.				
	25, 50 μM	Hypoxia-induced SH-SY5Y APP ⁶⁹⁵ cells	AD	-	SIRT1/CD147 [89]
	150,300 mg/kg	Hypoxia-induced mice		Hippocampus	
	100 mg/kg,	MPTP-induced mice	PD	Striatum,	SIRT1/ac-LC3 [90]
	p.o.			↓ac-LC3	
	5 μmol/L	HD human lymphoblastoid cell lines		-	
	1 mg/kg,	YAC128 mice	HD	Cortex, striatum,	SIRT1/ac-H3K9 [91]
	s.c.			↓ac-H3K9	
	1 μmol/L	primary astrocyte from aged rats	Ageing	-	SIRT1/AMPK/ PGC-1α [92]
	10 μmol/L	LPS-induced primary astrocyte from aged rats	Ageing	-	SIRT1/Nrf2/NF-κB [93]
	10 μmol/L	AlCl ₃ -induced BV2 cells		-	SIRT1/DDX3X /NLRP3 [94]
	100 mg/kg,	AlCl ₃ -induced mice	NDs	Cortex	
	p.o.				
Ligstroside	0.05 μmol/L	APP ₆₉₅ transfected SH-SY5Y cells	AD, Ageing	-	SIRT1/CREB [95]
	6.25 mg/kg	aged mice		Cortex	
6'-O-caffeoylarbutin	20, 60 mg/kg,	D-gal-induced ageing mice	Ageing	Brain	SIRT1/NF-κB [96]
	p.o.				
Salidroside	10, 20, 40 μmol/L	LPS-induced PC12 cells		-	AMPK/SIRT1, SIRT1/Nrf2/NF-κB [97]
	20, 40 mg/kg,	LPS-induced rats	NDs	Hippocampus	
	p.o.			pus	
Salidroside	20, 40 mg/kg,	D-gal-induced sub-acute ageing rats	Ageing	Hippocampus, ↓ac-p65	SIRT1/NF-κB [98]
	p.o.				
Schisanhenol	10,30,100 mg/kg,	scopolamine-induced cognitive impairment mice	NDs	Hippocampus	SIRT1/PGC-1α [99]
	i.p.			pus	
CAPE	10μmol/kg,	Cd-induced mice	AD	Brain	AMPK/SIRT1 [100]
	p.o.				
Curcumin	60 mg/kg,	MPTP-induced mice	PD	SNpc, striatum	SIRT1/Nrf2 [101]
	p.o.				
	200 mg/kg,	EAE-induced mice	MS	Brain	AMPK/SIRT1/CREB [102]
	p.o.				
Echinacoside	100 μmol/L	MPP ⁺ -induced PC12 cells		-	
	30 mg/kg,	MPTP-induced mice	PD	SNpc	SIRT1/PI3K/FoxO1 [103]
	p.o.				

Note: “↓” indicates inhibition.

In addition to RSV, other phenols such as Ligstroside and Salidroside (Figure 6A) may also ameliorate NDs by activating SIRT1. Ligstroside, a monophenol extracted from privet leaves, raises ATP levels via increasing respiratory chain complex capacity with up-regulation of SIRT1, CREB, complex I, and GPx1 expression in APP695 transfected SH-SY5Y cells. Moreover, *in vivo*, ligstroside also increases the levels of

cerebral ATP, expands the lifespan and enhances cognitive function in aged mice ^[95]. 6'-O-caffeoylarbutin is a phenolic compound mainly distributed in *Vaccinium species*. 6'-O-caffeoylarbutin alleviates D-gal-induced brain damage in aging mice by activating SIRT1 with inhibition of NF- κ B pathway, thus down-regulating inflammatory mediators and peroxides production^[96]. Neuroinflammation usually leads to cellular damage and cognitive deficits in NDs. Salidroside (Figure 6A) is one of the main active ingredients extracted from *Rhodiola rosea* L. In LPS-stimulated PC12 cells and cognitive deficits rats, salidroside reduces inflammatory response and oxidative stress via promoting SIRT1/AMPK signals, thus reducing cell apoptosis ^[97]. Besides, salidroside also promotes SIRT1 expression to attenuate neuroinflammation in D-gal-induced subacute senescent rats ^[98]. In scopolamine-induced cognitive disorder mice, schisanhenol (Figure 6A) derived from *Schisandra chinensis* improves cognitive impairment by up-regulating SIRT1/PGC-1 α signals with inhibition of Tau phosphorylation in hippocampus ^[99]. Caffeic acid phenethyl ester (CAPE) (Figure 6A), a polyphenol abundant in honey bee propolis, promotes the expression of A β -degrading enzyme NEP and reduces A β accumulation as well as the hyperphosphorylation of Tau through activating AMPK/SIRT1 pathway, thereby attenuating neuroinflammation and apoptosis to ameliorate cognitive impairment in Cd-induced mice ^[100]. Curcumin (Figure 6A) is a phenolic pigment extracted from the rhizome of turmeric. In MPTP-induced PD mice, curcumin reduces dyskinesia and dopamine neuron loss in the SNpc and striatum, and attenuates intestinal inflammation through activation of the SIRT1/Nrf2 pathway, which are partly reversed by Sirtinol ^[101]. Moreover, curcumin activates the AMPK/SIRT1 signaling pathway to inhibit JAK2/STAT3/NF- κ B pathway activation and increases antioxidant enzymes by promoting the expression of Nrf2, which attenuates the motor and cognitive deficits as well as pathological injuries caused by experimental autoimmune encephalomyelitis (EAE) in MS mice ^[102]. Echinacoside (Figure 6A), derived from the fleshy stems of Cistanches, attenuates neurotoxicity caused by MPP⁺ and could directly bind to SIRT1 to enhance its expression with increase of FoxO1, thus enhancing autophagy in neurons, while EX527 partly abolishes the effects^[103]. In conclusion, natural phenolic bioactive products could activate SIRT1 to regulate the activation or inhibition of various signaling pathways to alleviate NDs.

4.2 Flavonoids

Flavonoids are a class of natural compounds with 2-phenylchromone as the basic structural unit, widely found in herbs and various dietary sources, with neuroprotective effects. Quercetin (Figure 6B) is a natural flavonoid commonly found in a variety of fruits, vegetables and herbs such as apples, onions and ginkgo. In H₂O₂-induced SH-SY5Y cells, quercetin promotes SIRT1 to increase mitochondrial biogenesis to reduce ROS levels ^[104]. In the hippocampus of SAMP8 mice, quercetin ameliorates ageing-induced spatial learning and memory impairments, promotes neurotrophic factors production, and inhibits NLRP3 inflammasome activation by promoting SIRT1 expression ^[105]. Moreover, quercetin, silymarin and naringenin all enhances the cognitive and motor coordination decline caused by ageing, and increases noradrenaline and dopamine synthesis by up-regulating SIRT1 expression with reduction of p65 acetylation in hippocampus of aged rats

[106]. Fisetin (Figure 6B) is a flavonoid present in a variety of fruits and vegetables, such as mangoes, kiwi, beans and onions. Pb exposure increases cognitive deficits, apoptosis, neuroinflammation, and synaptic dysfunction, which could trigger or exacerbate NDs, and could be ameliorated by fisetin treatment through activating AMPK/SIRT1 signaling pathway [107]. In D-gal-induced mice, fisetin blocks ROS and LPO accumulation through activation of SIRT1/Nrf2/HO-1 pathway, thereby attenuating D-gal-induced oxidative stress in hippocampus and cortex. In addition, fisetin inhibits microglia and astrocyte activation via SIRT1/NF- κ B signaling, thereby attenuating D-gal-induced neuroinflammation [108]. Besides, A β ₁₋₄₂ oligomers induce AD-like behavioral and pathological changes accompanied by learning and memory impairments, neuronal loss and neuroinflammation in rats, while dihydromyricetin (DHM) (Figure 6B) ameliorates these symptoms by activating SIRT1/AMPK signaling pathway [109]. 5,6,7,4'-Tetramethoxyflavanone (TMF) (Figure 6B), a compound derived from *Chormolaela odorata*, ameliorated A β ₂₅₋₃₅-induced oxidative stress and apoptosis via activating SIRT1/Nrf2/HO-1 pathway in SK-N-SH cells. Besides, TMF also attenuates A β ₂₅₋₃₅-induced cellular senescence by regulating the SIRT1/P53/P21 pathway, thereby protecting synaptic plasticity [110]. Cyanidin-3-O-glucoside (Figure 6B) is a naturally occurring anthocyanin that attenuates hippocampal and cortical A β deposition and aberrant phosphorylation of Tau proteins, improves neuronal apoptosis and synaptic plasticity, enhances autophagy, and inhibits neuroinflammation and oxidative stress via inhibiting the MAPKs pathway and up-regulating the activation of AMPK/SIRT1 and PI3K/Akt in APP/PS1 mice [111]. In 6-hydroxydopamine (6-OHDA)-induced PD rats, baicalein (Figure 6B), existed in *Scutellaria baicalensis* Georgi, reduces neuronal apoptosis and activates autophagy in striatum, whereas autophagy inhibitor 3-MA partially abolishes the protective effects of baicalein. Furthermore, although miR-30b-5p increased in PD, baicalein reduces its transcription that promotes SIRT1 expression and AMPK phosphorylation. But, miR-30b-5p overexpression or SIRT1 inhibition abrogate the effects of baicalein on mitochondrial autophagy [112]. Furthermore, eriodictyol (Figure 6B), a flavonoid ubiquitously found in citrus fruits, attenuates LPS-caused mitochondrial dysfunction and improves antioxidant enzyme expression and activity via activating SIRT1/Nrf2 signaling in BV2 cells and brain of mice [113]. Kaempferol (Figure 6B) isolated from *Delphinium* and *Camellia* attenuates CdCl₂-induced cognitive deficits, hippocampal neuroinflammation, oxidative stress and apoptosis by inhibiting cytosolic PARP1 expression and promoting cytosolic SIRT1 activity, thereby inhibiting the acetylation of p65, p53 and FoxO1 in cognitive disorder rats [114]. Briefly, flavonoids including quercetin, fisetin and DHM could act as SIRT1 activators to attenuate mitochondrial dysfunction, neuroinflammation, oxidative stress, and abnormal protein accumulation in NDs (Table 2).

Table 2. Effects of food-derived flavonoids on SIRT1 in NDs.

Compound	Dosage	Model	Disorder	Region and Index	Pathway
Quercetin	2.5, 5, 7.5, 10 μ mol/L	H ₂ O ₂ -induced SH-SY5Y cells	AD	-	SIRT1/PGC-1 α [104]
	35, 70 mg/kg, p.o.	SAMP8 mice	Ageing	Hippocampus	SIRT1/NLRP3 [105]
Quercetin Silymarin	20 mg/kg, i.p.	Ageing rats	Ageing	Hippocampus, $\downarrow$ ac-p65	SIRT1/NF- κ B [106]

Naringenin	25, 50 mg/kg, p.o.	Pb-induced mice	AD	Brain	AMPK/SIRT1/NF- κ B ^[107]
Fisetin	20 mg/kg, i.p.	D-gal-induced mice	Ageing	Hippocampus, cortex	SIRT1/Nrf2/NF- κ B ^[108]
DHM	100, 200 mg/kg, i.p.	A β ₁₋₄₂ -induced rats	AD	Hippocampus	AMPK/SIRT1 ^[109]
TMF	0.1, 1, 10 μ M	A β ₂₅₋₃₅ -induced SK-N-SH cells	AD	-	SIRT1/Nrf2/p53 ^[110]
Cyanidin-3-O -glucoside	30 mg/kg, p.o.	APP/PS1 mice	AD	Hippocampus, cortex	AMPK/SIRT1 ^[111]
Baicalein	100 mg/kg, i.p.	6-OHDA-induced rats	PD	Striatum	miR-30b/SIRT1/AMPK/ mTOR ^[112]
Eriodictyol	25,50,200mg/kg, p.o.	LPS-induced mice	NDs	Brain	SIRT1/Nrf2 ^[113]
Kaempferol	50 mg/kg, i.p.	CdCl ₂ -induced rats	NDs	Hippocampus, $\downarrow$ ac-p65	SIRT1/NF- κ B/FoxO1 ^[114]

Note: “ $\downarrow$ ” indicates inhibition.

4.3 Terpenoids

Terpenoids are a class of bioactive chemical substances found in all living organisms, especially green plants and flowering plants have a much greater variety and overall quantity of terpenoids compared to other species^[115]. Patchouli alcohol (Figure 6C) is a natural tricyclic sesquiterpene isolated from *Pogostemon cablin* (Blanco) Benth. In the hippocampus from STZ-induced sporadic AD rats, patchouli alcohol activates SIRT1 to inhibit neuroinflammation and AD-like pathology, thus attenuating cognitive impairment^[116]. Linalool (Figure 6C), a natural monoterpene isolated from *Camellia sinensis* (L.) Kuntze, reduces MPP⁺-induced oxidative damage and apoptosis in neuronal cells by activating the SIRT1/Nrf2/HO-1 pathway and inhibiting the Bcl-2/Caspase-3 pathway. Meanwhile, motor behavioral deficits caused by MPTP as well as dopamine neuron loss are inhibited by linalool in PD mice^[117]. Ginsenoside Rg1 (Figure 6C) is a class of triterpenoid saponins isolated from the root of ginseng. In neural stem cells and mouse hippocampal tissues, ginsenoside Rg1 ameliorates D-gal-induced cellular and brain tissue senescence through activation of the SIRT1/Nrf2 pathway, manifested by increasing the expression of mitochondrial marker as well as suppressing the transcription of pro-inflammatory and senescence genes^[118]. Furthermore, in A β ₁₋₄₂-induced AD mice, ginsenoside Rg1 alleviates cognitive impairment and hippocampus neuronal injury through activating SIRT1-related autophagy^[119].

4.4 Quinones

Quinones, a family of natural neuroprotective agents characterized by a fully conjugated cyclic unsaturated diketone structure, are usually used as indicator for changes in physical properties, such as color changes^[120]. Tanshinone IIA (Figure 6C) is a fat-soluble quinone extracted from *Salvia miltiorrhiza* Bge, which acts on SIRT1 to attenuates A β ₁₋₄₂-induced endoplasmic reticulum stress in bEnd.3 cell and APP/PS1 mice. In addition, tanshinone IIA promotes endothelial A β transport via up-regulating LRP1 and down-regulating RAGE thereby reducing A β accumulation and subsequent oxidative stress, apoptosis and synaptic damage. In contrast, the SIRT1 inhibitor EX527 reversed the effects of Tanshinone IIA^[121]. β -Lapachone (Figure 6C) derived from *Tabebuia avellanedae* ameliorates mitochondrial superoxide levels in

neuronal stem cells from R6/2 HD mice through promoting SIRT1 expression with inhibition of PGC-1 α acetylation, thereby ameliorating behavioral deficits in R6/2 HD mice ^[122]. Moreover, acetylshikonin (Figure 6C), an active quinone extracted from *Lithospermum erythrorhizon* Siebold & Zucc., attenuates D-gal-induced cognitive deficits by promoting SIRT1 to reduce the acetylation of p53, thus mitigating neuroinflammation and oxidative stress in AD subacute ageing mice ^[123].

4.5 Vitamins

Generally, vitamins are clearly classified into fat-soluble vitamins (A, D, E and K) and water-soluble vitamins (B complex and C) according to their absorption properties as well as their different physiological feature ^[124]. Vitamin C (Figure 6C) ameliorates the inhibition of cell proliferation, neuronal differentiation, and neuronal maturation by activating SIRT1 to improve cognitive performance in D-gal-induced mice ^[125]. Besides, vitamin D (Figure 6C) can also promote SIRT1 expression to activate Nrf2/HO-1 pathway and inhibit NF- κ B signaling in D-gal-induced mice, which in turn inhibits neuroinflammation and A β accumulation, and up-regulates pre-synaptic and post-synaptic proteins expression, thereby ameliorating cognitive deficits ^[126]. In addition, vitamin D ameliorates cognitive impairment and inhibits neuroinflammation and oxidative stress via up-regulating the expression of CAMMK2 to facilitate the activation of the AMPK/SIRT1 pathway in hippocampus of AD rats ^[127].

4.6 Others

In addition to phenols, flavonoids, terpenoids, quinones, vitamin, other natural active products, such as alkaloids, aldehydes, indoles, phytohormone and peptide, also promote SIRT1 expression and activity to mitigate NDs. Tetramethylpyrazine (Figure 6C) is one of the main active ingredients of *Ligusticum chuanxiong*. In the hippocampus of mice with AD-like pathological changes induced by STZ, tetramethylpyrazine attenuates A β accumulation as well as microglia and astrocytes activation and aggregation, and ameliorates synaptic dysfunction and aberrant oxidative stress in the mitochondria through activation of the SIRT1/Nrf2/HO-1 pathway ^[128]. Moreover, in AD mice, betaine ameliorates cognitive deficits caused by A β _{25–35} by promoting SIRT1 expression ^[129]. Astaxanthin (Figure 6C), a carotenoid in shrimp, enhances SIRT1, PGC-1 α , BDNF and synaptophysin expression in the hippocampus, thereby ameliorating cognitive dysfunction in A β _{25–35}-induced mice, and its effects are partially inhibited by SIRT1 inhibitor nicotinamide ^[130]. Besides, trans-cinnamaldehyde (Figure 6C), a primary active ingredient in cinnamon, regulates the expression of BACE1 by promoting the expression of SIRT1, PGC1 α , and PPAR γ thereby inhibiting the formation of A β plaques to improve cognitive impairment in 5 $\times$ FAD Tg mice ^[131]. Furthermore, indole-3-carbinol (Figure 6C) is a naturally occurring compound found primarily in cruciferous vegetables. Indole-3-carbinol ameliorates rotenone-mediated motor dysfunction and neurodegeneration, increases striatal DA content as well as midbrain and striatal TH expression, and decreases α -synuclein expression in PD rats. Mechanistically, the neuroprotective effects of indole-3-carbinol are attributed in part to its anti-neuroinflammatory and anti-apoptotic effects via the activation of SIRT1/AMPK pathway and the inhibition of NF- κ B and p53 signals ^[132]. Absciscic acid (Figure

6C) is a phytohormone with several biological activities. In D-gal-induced subacute senescent mice, abscisic acid acting on SIRT1 increases SOD, CAT and AChE activities, decreases MDA levels to reduce oxidative injury, and inhibits apoptosis via inhibiting p53/Bcl-2/Bax signaling and promoting AMPK and PI3K/Akt pathway [133]. Black bean peptide is derived from hydrolyzed black bean protein. BSP1 down-regulates BACE1 and APP expression, inhibit Tau phosphorylation, and reduce A β ₁₋₄₂ deposition by phosphorylating LKB1 and AMPK, inhibiting mTOR signaling and activating AMPK/SIRT1 pathway[134].

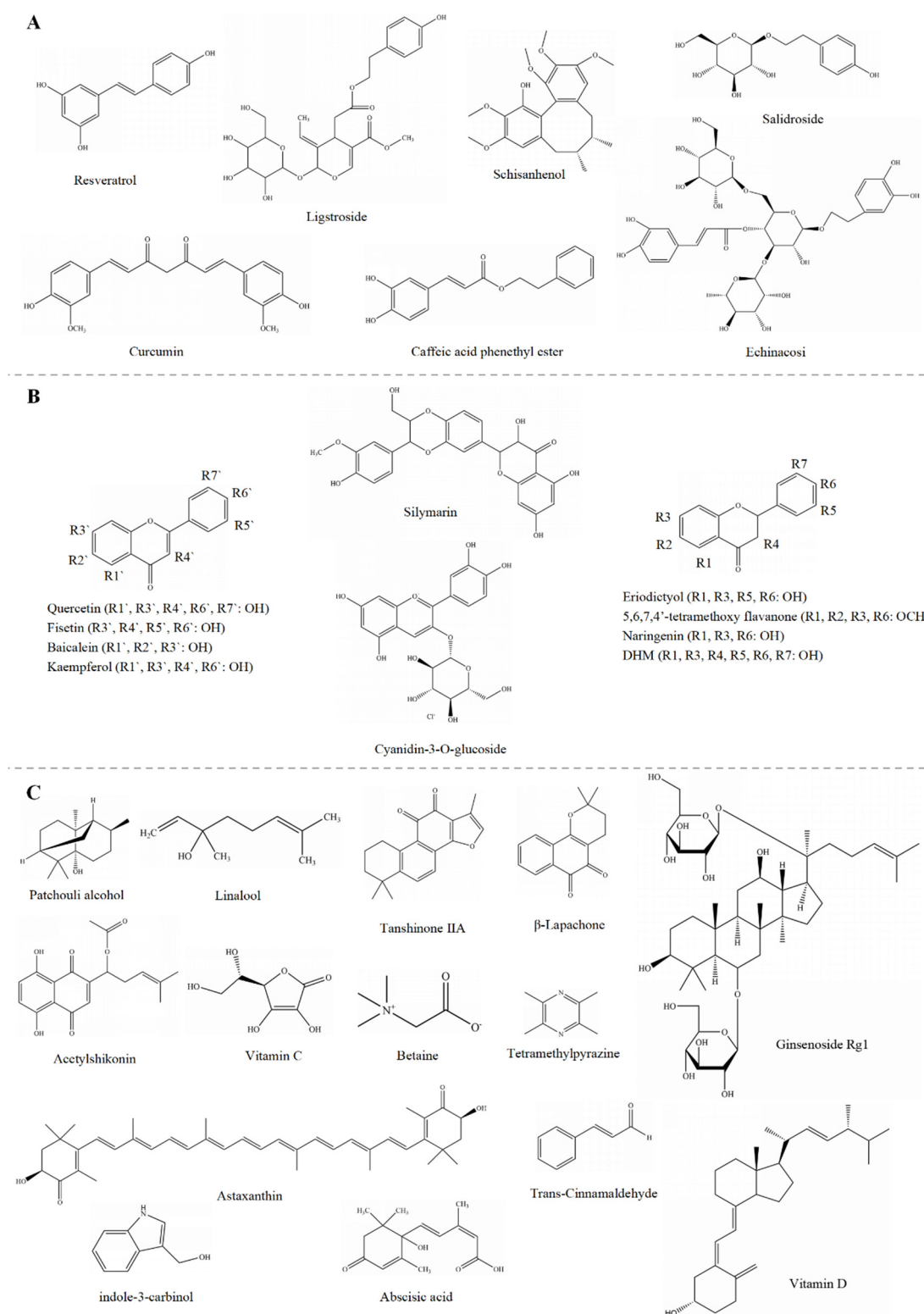


Figure 6. The chemical category and structures of natural SIRT1 activators in NDs, mainly including phenols, flavonoids, terpenoids, quinones, vitamins, etc., which promote SIRT1 to mitigate NDs.

Overall, natural food derived bioactive products might serve as SIRT1 activator to reduce neuroinflammation and oxidative stress, and inhibit cellular senescence and apoptosis, thereby reducing synaptic and neuronal loss and ameliorating behavioral deficits in NDs (Table 3).

Table 3. Effects of food-derived terpenes, quinones, alkaloids and others natural bioactive products on SIRT1 in NDs.

Compound	Dosage	Model	Disorder	Region and Index	Pathway
Terpenes					
Patchouli alcohol	25,50mg/kg p.o.	STZ-induced rats	AD	Hippocampus, ↓ac-Tau, ↓ac-p65	SIRT1/NF-κB [116]
Linalool	1, 10 nmol/L 12.5, 25 mg/kg, p.o.	MPP ⁺ -treated neurons MPTP-induced mice	PD	- SNpc	SIRT1/Nrf2/HO-1 [117]
Ginsenoside Rg1	2.5, 5, 10, 20, 40, 80 mg/mL 40 mg/kg, i.p.	D-gal-induced primary neural stem cells D-gal-induced mice	Ageing	- Hippocampus	SIRT1/Nrf2 [118]
	40 mg/kg, i.g.	Aβ ₁₋₄₂ -induced mice	AD	Hippocampus	SIRT1 [119]
Quinones					
Tanshinone IIA	20 μM 10, 20 mg/kg, p.o.	Aβ ₁₋₄₂ -induced bEnd.3 cells APP/PS1 mice	AD	- Hippocampus, cortex	SIRT1/BIP/PERK/ IRE-1 [121]
β-Lapachone	70 mg/kg, p.o.	R6/2 mice	HD	Brain, ↓ac-PGC-1α	SIRT1/CREB/PG C-1α [122]
Acetylshikonin	270,540,1080 mg/kg, p.o.	D-gal-induced mice	Ageing	Hippocampus, ↓ac-p53	SIRT1/p53 [123]
Vitamins					
Vitamin C	150 mg/kg/d, p.o.	D-gal-induced mice	Ageing	Hippocampus	SIRT1/ caveolin-1 [125]
Vitamin D	100 μg/kg 500 IU/kg, p.o.	D-gal-induced mice AlCl ₃ and D-gal-induced rat	Ageing Ageing	Brain Hippocampus	SIRT1/Nrf-2/NF-κ B [126] AMPK/SIRT1/PG C-1α [127]
Alkaloids					
Betaine	0.163 mmol/kg, s.c.	Aβ ₂₅₋₃₅ -induced mice	AD	Hippocampus	SIRT1 [129]
Tetramethylpyrazine	0.2 μg/μL, i.c.v.	STZ-induced mice	AD	Hippocampus	SIRT1/Nrf2/HO-1 [128]
Carotenoids					
Astaxanthin	10 mg/kg, p.o.	Aβ ₂₅₋₃₅ -induced mice	AD	Hippocampus	SIRT1/PGC-1α [130]
Aldehyde					
Trans-Cinnamaldehyde	30 mg/kg, i.p.	5×FAD Tg mice	AD	Brain	SIRT1/PGC1α/PP ARγ [131]
Indoles					
indole-3-carbinol	25, 50, 100 mg/kg, p.o.	Rotenone-induced rats	PD	Striatum, midbrain	SIRT1/AMPK [132]
Hormones					
Abscisic acid	20, 40 mg/kg, i.p.	D-gal-induced subacute ageing mice	Ageing	Brain	AMPK/SIRT1 [133]

Note: “↓” indicates inhibition.

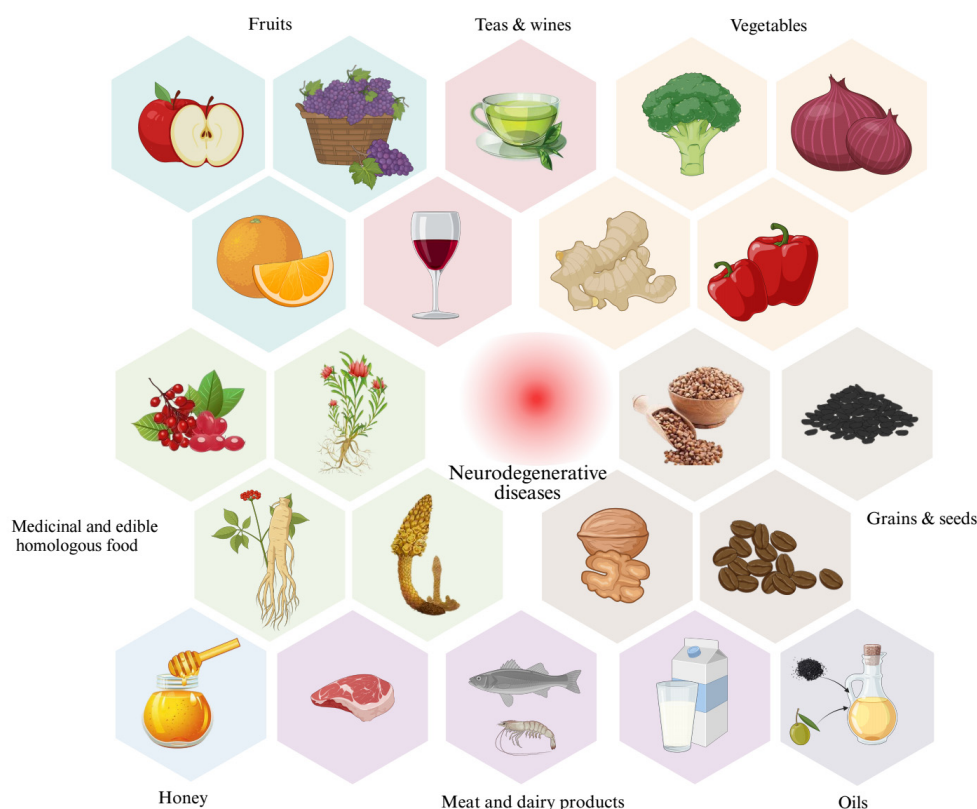


Figure 7. Sources of natural food-derived SIRT1 activators in NDs, widely existing in fruits, vegetables, grains, meat, dairy products, medicinal and edible homologous food.

5. Conclusion and perspective

SIRT1 activation ameliorates NDs primarily through deacetylation of the critical signals to modulate energy metabolism, oxidative stress, and neuroinflammation. SIRT1 is ubiquitously expressed in the mammalian brain, especially in regions associated with NDs, such as cortex and hippocampus. As a critical NAD^+ -dependent deacetylase, SIRT1 and AMPK, an AMP-dependent protein kinase, are at the pinnacle of metabolic and are key cellular energy sensors for the regulation of biological energy metabolism, from yeast to humans. In NDs, especially AD, SIRT1 regulates energy metabolism pathways mainly through interaction with AMPK, but also with cAMP, GAPDH and Cdk5, thereby promoting mitochondrial biogenesis, recovering mitochondrial dysfunction and autophagy influx, as well as reducing oxidative stress, neuroinflammation and apoptosis. Specifically, SIRT1 affects the deacetylation of downstream targets including histones, PGC-1 α , p53 and NAMPT, and regulates the activities of GOT, Akt, GSK-3 β and OGA, thereby inhibiting the hyperacetylation and phosphorylation of Tau protein isoforms, thus attenuating mitochondrial impairment caused by A β and ageing, and mitigating neuronal loss and synaptic damage to improve cognitive and motor behavioral disorders. Mitochondria, the center of energy metabolism, its dysfunction brings abundant ROS production are considered to be a precipitating factor of NDs [135]. Enhanced SIRT1 activity promotes nuclear transcription of Nrf2 and deacetylated state of PGC-1 α , thereby promoting biogenesis of mitochondria and its autophagy, and inhibiting cellular ageing and apoptosis, leading to rebalance redox state in NDs. Furthermore, signals in oxidative stress and neuroinflammation are

common pathways associated with neuronal abnormalities and the development of NDs, which are interconnected and influential. The primary characteristic of neuroinflammation is the activation of a wide range of immune cells, especially microglia and astrocytes release the massive production of inflammatory mediators ^[136]. In NDs, including AD, PD and MS, SIRT1 promotes the deacetylation of HMGB1, p65, HSPA4 and Tau, inhibits activation of NLRP3 inflammasome, NF- κ B and STAT3 signals, suppresses transcription and translation of senescence-related genes, and activates Nrf2 and autophagy pathways, which in turn enhance the degradation of A β to inhibit the formation of amyloid plaques, restrain microglia and astrocytes pro-inflammatory polarization, resulting in alleviating cerebrovascular endothelial cell damage, neuronal loss and synaptic dysfunction. More importantly, in the central nervous system, except miR-302 in HD, miRNAs negatively regulate the expression and activity of SIRT1 in general that generates aberrant protein aggregation and hyper-oxidation with neuronal loss and synaptic structural abnormalities, thereby aggravating the dysfunction of energy metabolism and inflammatory response, which might play a critical role in the pathophysiological mechanisms of NDs.

Moreover, as far as cells are concerned, current studies mainly involve neurons, microglia, brain microvascular endothelial cells and astrocytes, with neurons and microglia being more studied. The effects of SIRT1 on mitochondria, autophagic vesicles, as well as expression and aggregation of aberrant proteins are mainly explored in neurons. The modulatory effects of SIRT1 on pro-inflammatory polarization, migration and phagocytosis capacity are concerned in microglia. Additionally, the effects of SIRT1 on BBB permeability in NDs are most widely investigated on cerebrovascular endothelial cells. However, at present, there are only a few literatures have reported microglia effects on synaptic structure and neuronal apoptosis, and the effects of endothelial cells on A β production in neuronal cells. Therefore, in the process of the occurrence and development of NDs, the connections and interactions among these different cell types needs to be further explored in depth.

Natural products from food source, including phenols, flavonoids, terpenes, and alkaloids, etc. could promote the expression and activity of SIRT1 to treat NDs (Figure 7). Phenols, especially resveratrol, and flavonoids, such as quercetin, baicalein and fisetin, act as SIRT1 activators to promote the deacetylation of multiple transcription factors and histone H3, mainly through activating energy, antioxidant and autophagy pathways, and inhibiting inflammation and apoptosis signals, resulting in an increase of neurotrophic factors generation, repairment of mitochondrial function and cellular senescence and apoptosis, decrease of oxidant and pro-inflammatory mediator production, enhance autophagy and synaptic plasticity, promotion of aberrant proteins degradation, prevents activation of microglia and astrocytes, alleviates neuronal loss and restores neuronal function, thus reducing cognitive impairment. In addition to phenols and flavonoids, there are a few literature reports on the therapeutic effects of other categories of natural compounds on NDs through activation of SIRT1. Therefore, there are not enough research to support the analysis of the structure-activity relationship of these bioactive food-derived compounds on SIRT1.

Although these natural products are served as activators of SIRT1 to treat NDs, their application in clinical practice still faces many challenges such as bioavailability, stability, and delivery mechanisms limitations. As shown in Table 4, the maximum plasma concentration ($C_{\max}$) and the area under the plasma concentration–time curve (AUC) of these natural products after a single administration are low in rats, indicating low bioavailability, which mainly due to the poor water solubility and significant first-pass metabolism [137–140]. Improving the solubility and stability of natural products effectively enhance the bioavailability by loading them into the carrier materials. Curcumin-loaded lipopolysaccharide nanocarriers remarkably increase oral bioavailability in rats as evidenced by the increase of the $C_{\max}$ from (9.582 ± 0.391) ng/ml to (1004.177 ± 48.553) ng/ml^[139]. Thus, focusing on improving the bioavailability, stability, and safety of natural products can accelerate their application in clinical practice, with the aim of providing new candidate drugs for NDs treatment.

Table 4. The pharmacokinetic parameters of food-derived SIRT1 activators.

Compound	Dosage (mg/kg)	Pharmacokinetic parameters				
		$T_{\max}$ (h)	$C_{\max}$ ($\mu\text{g/mL}$)	$\text{AUC}_{(0-t)}$ ($\mu\text{g}\cdot\text{h/L}$)	$\text{AUC}_{(0-\infty)}$ ($\mu\text{g}\cdot\text{h/L}$)	CL (L/h/kg)
RSV [142, 143]	50	1.0	0.0767	-	1350	-
	100	-	-	-	6519 ± 1592	1.76 ± 0.49
	150	1.0	0.847	-	2,580	-
Curcumin [137–139]	50	0.5 ± 0.0	0.009582 ± 0.000391	23.225 ± 0.477	-	-
	100	0.5	0.03013 ± 0.00047	25.20 ± 11.01	40.88 ± 7.05	-
	500	0.7 ± 0.17	0.0027 ± 0.00060	4.1 ± 0.78	-	68.70 ± 12.560
Quercetin [144, 145]	10	0.083	0.2	-	60	-
	100	0.3 ± 0.1	842.1 ± 508.4	1580000 ± 583000	1600000 ± 590000	0.8 ± 0.3
Silymarin [146]	144	1.33 ± 0.29	7.54 ± 0.79	99970 ± 7730	-	0.82 ± 0.087
	10.5	2.50 ± 1.27	0.187 ± 0.114	518 ± 207	541 ± 216	25.1 ± 18.1
	21	3.00 ± 1.41	0.539 ± 0.487	1680 ± 1140	1710 ± 1150	18.4 ± 12.5
Naringenin [147]	42	3.30 ± 1.34	1.08 ± 0.745	4160 ± 3800	4220 ± 3780	18.7 ± 16.6
	168	5.70 ± 2.31	1.83 ± 0.858	11300 ± 4240	11500 ± 4260	19.6 ± 17.3
	10	2.05 ± 0.14	0.08358 ± 0.00373	396.03 ± 14.62	-	-
Kaempferol [148]	10	6.5	0.0956 ± 0.0456	-	1288.33 ± 270	0.131 ± 0.145
	200	7	0.339 ± 0.267	-	2500 ± 1282.67	0.118 ± 0.096
Astaxanthin [140]	200	7	0.339 ± 0.267	-	2500 ± 1282.67	0.118 ± 0.096
indole-3-carbinol [149]	50	0.5	16.06 ± 3.33	-	15850 ± 4210	3.05 ± 0.45

Despite widespread studies on the therapeutic role of SIRT1 activation in NDs and ageing, some limitations remain in the current research. First of all, the role of SIRT1 in AD has attracted more researchers, whereas it has been less studied in other NDs, such as PD, HD, and MS, which needs further research. Secondly, current reports have focused on neurons and microglia, with fewer studies on other important brain cells, such as cerebrovascular endothelial cells and astrocytes. In addition, there are fewer studies on the correlative interactions between cells, and only a few papers have reported the effects of CM derived from microglia and cerebrovascular endothelial cells on neurons, and the interactions between other cells need to be further investigated. Thirdly, the current studies suggest that the mechanisms by which SIRT1 improves NDs mainly include activation and inhibition of pathways related to energy metabolism, oxidative stress, and neuroinflammation, and it remains to be further investigated whether SIRT1 improves NDs through other pathways. Furthermore, apart from miRNAs, other non-coding RNAs, including long

non-coding RNAs (lncRNAs) and circular RNAs (circRNAs), are little investigated on the regulation of SIRT1, for example, only two circRNAs (circLPAR1, circHDAC9) have been reported to be able to influence the SIRT1^[73, 141], and there has been no study regarding the lncRNAs on SIRT1 in NDs, which requires further in-depth study. As a consequence, these evidences demonstrate that development of therapeutic agents specifically activating deacetylase SIRT1 will serve as a new way to fight NDs.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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