REVIEW PAPER

The Multifaceted Role of SIRT1 in Parkinson's Disease: Therapeutic Implications and Mechanisms

Mr Navinkumar Malligarjunan[1], Mrs Sangeetha saravanan[2], Dr Gomathy Subramanian[3*]

Department of Pharmaceutical Chemistry, JSS College of Pharmacy, Ooty, Nilgiris-643001, Tamil Nadu, JSS Academy of Higher Education & Research

***Corresponding Author**

Email: gomathy@jssuni.edu.in

Received: 1st August, 2026; **Revised:** 5th August, 2026; **Accepted:** 7th August, 2026; **Available Online:** 31st August, 2026

ABSTRACT

Sirtuins (SIRTs), a highly conserved family of NAD^+-dependent histone deacetylases, play pivotal roles in various cellular processes. SIRT1, a key member, is involved in chromatin remodeling and gene transcription through histone deacetylation, influencing processes like mitochondrial function, metabolism, and inflammation. SIRT1's deacetylation activity is regulated by NAD^+ levels and post-translational modifications. In Parkinson's disease (PD), SIRT1 demonstrates potential therapeutic benefits by modulating autophagy, reducing α-synuclein toxicity, and enhancing mitochondrial function and neuronal survival. SIRT1 activation promotes autophagy, crucial for degrading misfolded proteins, and regulates heat shock factors to mitigate α-synuclein aggregation, a key pathological feature of PD. Furthermore, SIRT1 modulates apoptosis by targeting p53 and Bcl-2 family proteins, thereby enhancing neuroprotection. It also regulates mitochondrial function and oxidative stress via the SIRT1/PGC-1α pathway, improving antioxidant defence and mitochondrial biogenesis. Neuroinflammation, a contributor to PD pathology, is suppressed by SIRT1 through deacetylation of NF-κB, reducing pro-inflammatory cytokine production. Activators of SIRT1, such as resveratrol, exert neuroprotective effects by crossing the blood-brain barrier and reducing oxidative stress, inflammation, and α-synuclein aggregation across various PD models. Despite promising preclinical findings, the clinical efficacy of SIRT1 activators remains controversial, necessitating further trials to confirm their therapeutic potential. Additionally, exercise-induced neuroprotection in PD may involve SIRT1 activation, highlighting the multifaceted role of SIRT1 in PD treatment. Overall, targeting SIRT1 offers a multi-target approach addressing mitochondrial dysfunction, oxidative stress, neuroinflammation, and protein homeostasis, making it a compelling candidate for developing PD therapies. In this review, we aim to explore the various roles of SIRT1 with regard to PD.

Keywords: Deacetylation; oxidative stress; Parkinson's disease; sirtuins; SIRT1.

How to cite this article: Navinkumar Malligarjunan, Sangeetha saravanan, Gomathy Subramanian. The Multifaceted Role of SIRT1 in Parkinson's Disease: Therapeutic Implications and Mechanisms. Int J Drug Deliv Technol. 2026;16(78s):1469-1478. DOI: 10.25258/ijddt.16.78s.200.Source of support: Nil.

Conflict of interest: Nil.

INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative condition characterised by degeneration of dopaminergic neurons in the striatum and the formation of Lewy bodies, mostly composed of α-synuclein proteins [1][2]. Although the actual causation of PD is uncertain, ageing is commonly recognised as a major contributor to its progression [3][4][5][6][7]. Degeneration of dopaminergic neurons in PD is associated with aberrant protein aggregation, changes in microtubule dynamics, oxidative and nitrative stress, inflammation, and defective autophagy [7][8][9]. Many treatment techniques have focused on increasing dopaminergic activity while decreasing cholinergic activity. However, the limited effectiveness of existing therapies emphasises the need for new therapeutic techniques. One intriguing technique might be to target age-related degeneration, as ageing has a considerable influence on many of the pathophysiological processes linked with PD.

Sirtuins (SIRTs) are a group of NAD^+-dependent class III histone deacetylases [10]. In mammals, seven SIRT homologs, SIRT1-SIRT7, have been discovered, each with a unique role in regulating critical metabolic processes [11]. C-terminal and N-terminal domains of SIRTs differ greatly in length and sequence, which contributes to their different cellular localization. While SIRT3, SIRT4, and SIRT5 are only present in mitochondria, SIRT1 and SIRT2 are found in both the nucleus and the cytoplasm [12][13]. Though their ability to deacetylate lysine in a NAD^+-dependent manner is well-known, SIRTs may also remove acyl groups from other substances, including succinyl, malonyl, and long-chain fatty acyl groups [14][15][16][17]. These enzymes serve crucial roles in a wide range of biological processes, including cell survival, proliferation, ageing, longevity, senescence, apoptosis, DNA repair, and responses to calorie restriction. [18][19][20]. As possible therapeutic targets for a variety of illnesses, such as neurodegenerative, cardiovascular disorders and neoplastic, SIRTs have lately attracted attention.

SIRT modulators have demonstrated potential for the treatment of cancer, rheumatoid arthritis, type II diabetes, and other age-related illnesses [21].

The first SIRT to be identified, SIRT1, is a deacetylase that may be found in the cytoplasm and nucleus. Out of the seven SIRTs, it has been researched and understood the best. Numerous neurological conditions and cancers, including as AML, melanoma, glioma, lung adenocarcinoma, and cancers of the colon, prostate, ovary, and breast, have been connected to SIRT1 [22]. Resveratrol activates SIRT1 in Alzheimer's disease, inhibiting NF-κB and reducing the neurotoxic effects of Aβ in microglia [23]. Additionally, it has been shown that SIRT1 activity slows the progression of neurodegenerative diseases such PD and amyotrophic lateral sclerosis (ALS) via increasing autophagy [24]. Another potential therapeutic target for decreasing p53's involvement in neurodegenerative illnesses is SIRT1 [25].

SIRT2, a deacetylase present in both the nucleus and cytoplasm, is linked to neurodegenerative disorders and gliomas. SIRT3, another deacetylase located in mitochondria, has been linked to neurological illnesses and several cancers, including B-cell chronic lymphocytic leukemia, breast and stomach cancer. SIRT4, also recognized as mitochondrial ADP-ribosyltransferase, is implicated in breast and colorectal cancer. SIRT5, which is found in mitochondria and functions as a malonyl, succinyl, and glutaryl deacetylase, has been linked to non-small cell lung carcinoma, pancreatic and breast cancer. SIRT6, located in the nucleus, is unique among SIRTs because of its various enzymatic activities, which include deacetylase, ADP-ribosyltransferase, and long-chain fatty acyl deacylase functions. SIRT7, principally a nuclear deacetylase, has been linked to malignancies of the liver, spleen, thyroid, testis, and breast [26].

In this review, we provide current research and offer an in-depth analysis of SIRT1's involvement in PD, emphasizing its potential as a therapeutic target for this condition.

Parkinson's disease

PD first described by James Parkinson in his 1817 book "Essay on the Shaking Palsy," is marked by fundamental symptoms such as rest tremor, stiffness, bradykinesia, and postural instability, as well as a number of other motor and non-motor symptoms [27–29]. As the world population increases and lifespans lengthen, scientists are becoming increasingly interested in age-related illnesses such as PD. Neurological disorders are currently the largest cause of disability globally, with PD being the most rapidly developing of these ailments [30]. A potential 'PD pandemic' is indicated by the Global Burden of Disease Study, which predicts that the incidence of PD cases would double from around 7 million in 2015 to 13 million by 2040 [31]. This prediction highlights the huge socioeconomic ramifications that PD and other neurological illnesses may have, even though it is based on predicted population increase and is still only an estimate.

Traditionally, the most common form of parkinsonism seen in clinical settings has been referred to as "idiopathic" PD. The classification of PD necessitates ongoing review due to the identification of monogenic forms of the disease that may clinically resemble the idiopathic form, the clinical diversity of the illness, and overlaps with other conditions such as dementia with Lewy bodies, PD dementia, and other types of parkinsonism [32, 33].

The cardinal symptoms of PD include tremor (often initiating in one hand and most noticeable at rest), bradykinesia (slowness of movement, significantly impairing everyday tasks), rigidity (stiffness and inflexibility of limbs and trunk), and postural instability (resulting in balance issues and an elevated risk of falls). Additional non-motor symptoms comprise insomnia, constipation, depression, cognitive impairment, and autonomic dysfunction [34].

There is currently no cure for PD, however several therapies can help control the symptoms. Pharmacological therapy is the primary mode of treatment, with levodopa being the most effective medicine. The brain converts levodopa to dopamine, refilling depleted neurotransmitter levels. Other medications include MAO-B inhibitors, dopamine agonists, and COMT inhibitors. Individuals with severe PD who do not respond well to medication might consider surgical therapies such as deep brain stimulation (DBS). DBS involves implanting electrodes in certain brain regions to modulate abnormal neural activity. Non-pharmacological therapies, such as physical, occupational, and speech therapy, are also important in controlling PD. These therapies assist to maintain mobility, enhance quality of life, and treat particular symptoms such as speech and swallowing issues [35].

Pathways Involved in PD

The nigrostriatal dopaminergic system, which consists of dopamine-producing neurons extending from the substantia nigra pars compacta (SNc) to the striatum, is the primary target of PD. Degeneration of these neurons disrupts the direct and indirect pathways of the basal ganglia, which are essential for motor control, and results in a significant decrease in dopamine levels in the striatum [36].The basal ganglia, which include the striatum, globus pallidus (internal and exterior portions), subthalamic nucleus (STN), and substantia nigra, are crucial for motor control. The basal ganglia circuitry is separated into direct and indirect circuits. Facilitates movement. Dopamine from the SNc stimulates the striatal neurons in this pathway via D1 receptors, leading to increased activity in the motor cortex. Dopamine inhibits movement by acting on D2

receptors in the striatal neurons of this pathway, thereby reducing inhibitory output to the motor cortex. The balance between the basal ganglia's direct and indirect pathways is upset in PD by dopamine depletion. Due to this disturbance, the direct pathway is correspondingly under activated and the indirect pathway is overactivated, which contributes to the characteristic motor symptoms of PD [37]. The corticostriatal pathway involves projections from the cortex to the striatum. Glutamatergic neurons from various cortical regions modulate striatal activity. In PD, alterations in cortical input to the striatum contribute to the dysregulation of the basal ganglia circuitry [38]. This pathway connects the thalamus to the cortex and is crucial for motor function. In PD, abnormal output from the basal ganglia to the thalamus results in decreased excitatory input to the motor cortex, contributing to bradykinesia [39]. The PPN is involved in gait and posture control. Degeneration of PPN neurons in PD contributes to postural instability and gait difficulties [40].

Molecular and Cellular Targets

Alpha-synuclein is a protein implicated in PD pathogenesis. Abnormal aggregation of alpha-synuclein forms Lewy bodies, a hallmark of PD. These aggregates are toxic to neurons and contribute to neurodegeneration. Targeting alpha-synuclein aggregation and promoting its clearance are potential therapeutic strategies [41]. Dysfunction in the lysosomal and autophagy pathways leads to impaired degradation of cellular waste, including alpha-synuclein aggregates. Enhancing these pathways could help clear toxic protein aggregates and protect neurons [42]. Mitochondrial dysfunction is a significant factor in PD. Impaired mitochondrial function leads to increased oxidative stress and neuronal death. Therapeutic strategies aim to protect mitochondrial function and reduce oxidative stress [43]. Chronic neuroinflammation contributes to the progression of PD. Activated microglia release pro-inflammatory cytokines that can damage neurons. Targeting neuroinflammatory pathways to reduce microglial activation and cytokine production is a promising approach [44]. Several genes, including SNCA (encoding alpha-synuclein), LRRK2, PARK2 (parkin), PINK1, and DJ-1, are associated with familial variants of PD as represented in figure 1. These genes are involved in processes related to oxidative stress, mitochondrial activity, and protein breakdown. Potential therapies include gene therapy and small compounds that target these genetic pathways [45].

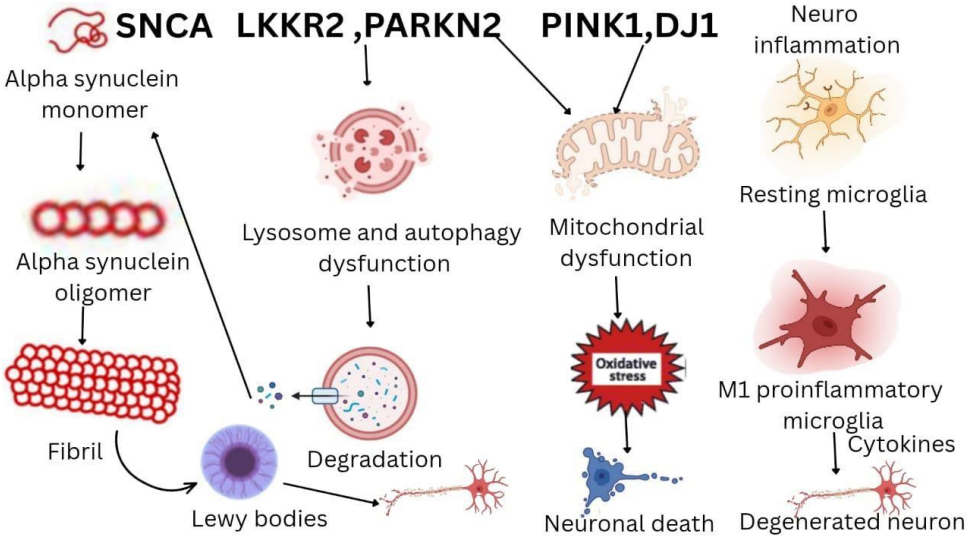

Fig:1 Molecular and Cellular Targets

Therapeutic Strategies

The primary treatment for PD symptoms involves dopaminergic therapies to replenish dopamine levels or mimic its action [46]. These include:

- **Levodopa**: Dopamine's precursor, levodopa, enters the brain across the BBB and transforms into dopamine. It is still the best drug for reducing the motor symptoms brought on by PD.
- **Dopamine Agonists**: Compounds that directly stimulate dopamine receptors.
- **MAO-B Inhibitors**: The mechanism by which monoamine oxidase B (MAO-B) inhibitors increase dopamine availability in the brain is by blocking the enzyme that breaks down dopamine. DBS is a surgical treatment involving the implantation of electrodes in the brain, typically in the STN or globus pallidus. Electrical stimulation of these areas can significantly reduce motor symptoms and improve quality of life [47]. Research is focused on developing neuroprotective therapies to slow or halt disease progression. These include antioxidants to reduce oxidative stress, anti-inflammatory agents, and compounds targeting mitochondrial dysfunction [48]. Gene therapy approaches aim to deliver functional copies of genes or silence mutated genes

involved in PD. For example, viral vectors can deliver genes encoding neurotrophic factors to support neuron survival [49]. Strategies to reduce alpha-synuclein aggregation include small molecules, immunotherapy (using antibodies to clear aggregates), and enhancing the autophagy-lysosomal pathway to degrade alpha-synuclein [50]. For PD patients to manage their symptoms and enhance their quality of life, physical therapy, occupational therapy, and exercise are essential. Comprehensive therapy for PD must also include dietary modifications and treatment of non-motor symptoms such depression and sleep disturbances [51].

PD remains a challenging condition to treat, with current therapeutic approaches often limited by significant disadvantages such as poor efficacy, off-target effects, and the inability to reverse established neuronal damage. The pathways and targets involved in PD are complex and interconnected, making it difficult to develop therapies that address all aspects of the disease.

Targeting SIRTs offers several potential advantages over existing therapies. Their neuroprotective effects, ability to regulate alpha-synuclein aggregation, anti-inflammatory properties, and role in maintaining mitochondrial function and energy metabolism make them promising candidates for PD treatment [52].

Sirtuins

The sirtuin family has been extensively studied for its functions in epigenetics and metabolism. Numerous studies have connected numerous SIRTs to lifespan in many animals, with their reduction being recognised as a sign of ageing [53]. As a result, tiny compounds that activate SIRT are actively being investigated in human anti-aging studies [54]. SIRTs, on the other hand, have a fascinating dual character in cancer, acting as tumour suppressors or oncogenes depending on the situation [55].

One distinctive feature of SIRT is they vary from other proteins in their enzymatic process, however they do use NAD^+ as a cofactor. They utilise the nicotinamide group that is separated from the ADP-ribose unit as an acceptor for the acyl group that is extracted from lysine residues, as opposed to breaking down NAD^+ [56] (Figure 1). SIRTs are directly in competition with other NAD^+-dependent enzymes due to this special mechanism. Poly ADP-ribose polymerases, for instance, have the ability to suppress SIRT activity and hence impede activities such as mitophagy if they consume a significant amount of NAD^+ [57/58].

Therefore, it is crucial for cellular health to maintain appropriate SIRT homeostasis. SIRT homeostasis is dependent on construction and disassembly, folding, refolding, and degradation activities, just as the larger proteome [59]. However, the mechanisms underlying the degradation of dysfunctional or excessive SIRTs remain poorly characterized [60].

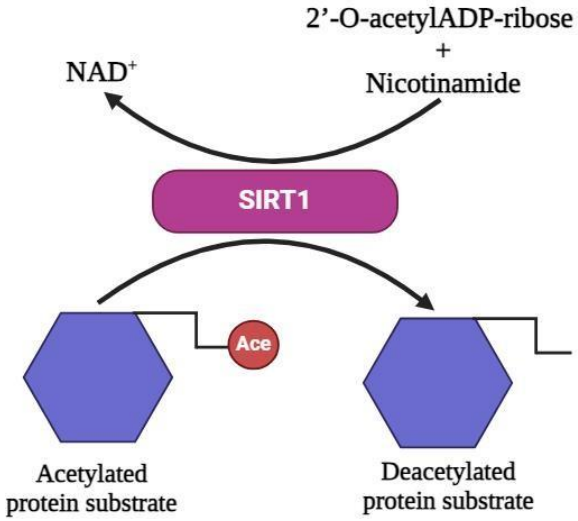

Figure 2 NAD^+-dependent SIRT1 deacetylase reaction.

The SIRT Family

The family of SIRTs demonstrates remarkable conservation, both in structure and function, across various life forms, including archaea, eubacteria, and eukaryotes. They play essential roles in chromatin and histone regulation [61]. Initially discovered in Saccharomyces cerevisiae, the SIRT family now comprises seven recognized members classified into four classes: Class I (SIRT1, SIRT2, and SIRT3), Class II (SIRT4), Class III (SIRT5), and Class IV (SIRT6 and SIRT7) [62] (see Table 1).

Table 1 displays the intracellular and chromosomal location, classifications, molecular weights, amino

acids, enzymatic activities, and interactions with targets for the known mammalian SIRTs up to the present [63].

Gene name	Classes	Intracellular localization	Chromosomal location	Activity	Molecular weight	Amino acids	Interactions
SIRT1	Ia	Nucleus, cytoplasmic	10q21.3	Deactylase	81.7	747	PGC-1α, FOXOs, p53, NF-κB, Ku-70, PPAR-γ, p300, pRB, LXR, NBS-1, BCL-6, USP-22, UCP-2, TORC2
SIRT2	Ib	Cytoplasmic	19q13.3	Deactylase	43.2	389	α tubulin, FOXO, histone H4, Phosphoenolpyruvate carboxykinase1 (PEPCK1), H3K18, Keratin-8, RIP1, p300, CDC20
SIRT3	Ib	Mitochondrial Nucleus	11p15.5	Deactylase	43.6	399	GDH complex I, AcCS2, , PGC-1α, OPA1, Ornithine transcarbamylase, IDH2, HMGCS2, LCA, Mitochondrial proteins, JNK2, OGG-1, CypD, Hsp10, KGDHC, LCAD, ATP synthase, NMNAT2, MPC-1, LKB-1, MnSOD
SIRT4	II	Mitochondrial matrix	12q	ADP-ribosyl-transferase	35.2	314	GDH, IDE, ANT
SIRT5	III	Mitochondrial	6p23	Deactylase	33.9	310	Carbamoyl phosphate synthetase 1 (CPSI), SOD1
SIRT6	IV	Nucleus	19p13.1	ADP-ribosyl-transferase	39.1	355	DNA polymerase β, PARP-1, Hif1α, Histones, TNFα, General control non-repressed protein 5, TRF2
SIRT7	IV	Nucleolus	17q25	Deactylase	44.8	400	RNA polymerase type 1, Hif1α, Hif2α, Histones, p53

SIRT1's mechanism of action

The importance of these enzymes that alter proteins is demonstrated by the great degree of conservation of the SIRT family of enzymes in bacteria, archaea, and eukaryotes. SIRTs function as class III NAD^+-dependent histone deacetylases (HDACs) and are widely expressed in a range of organs. They are essential for many different biological activities, including the transcription of DNA, the control of the cell cycle, inflammation, and cellular survival. The functional variety of SIRT enzymes is highlighted by their distinct N- and C-terminal sections, conserved catalytic domains, NAD^+ binding domains, and substrate specificities [64]. Encoding a protein of 747 amino acid residues, the human SIRT1 gene is made up of nine exons and eight introns and is found on chromosome 10q22.1. Its nuclear localization signal (KRKKRK), which indicates its location within the nucleus, and its conserved catalytic core are both present. Compared to other SIRT family members, SIRT1's N and C terminals are much larger, which may account for some of its increased catalytic activity [65]. Two NAD^+ binding domains: a big Rossman fold and a smaller domain made up of a helical module and a Zn^{2+} binding modules are part of SIRT1's conserved catalytic core [66, 67].

Similar to other class III histone deacetylases (HDACs), SIRT1 deacetylates both histone and non-histone proteins to neutralise the effects of

acetyltransferases. Within these two domains, an acetylated protein residue and NAD^+ engage to initiate the catalytic activity. During the deacetylation procedure, nicotinamide (NAM), 2'-O-acetylADP-ribose, 1'-O-acetyl-ADP-ribose, and 3'-O-acetyl-ADP-ribose are formed when the acetyl group is transferred onto the ribose component of NAD^+ [68]. Cellular NAD^+ levels, SIRT1-binding proteins, its end product NAM, and a variety of post-translational changes like ubiquitination, nitrosylation, sumoylation, glycosylation, phosphorylation, and glutathionylation all directly affect SIRT1 function. DNA methylation and a number of transcription factors and cofactors, including as E2F1, HIC1, p53, c-Myc, and FoxO3a, and regulate the expression of SIRT1 [69, 70]. Furthermore, inflammatory circumstances have an impact on SIRT1 expression. By deacetylating histones linked to inflammatory cytokines and modifying signalling pathways including HIF1a, AP-1, NF-kB, and P38MAPK, it controls inflammation [69].

SIRT1 regulates chromatin remodelling and gene transcription by deacetylating certain lysine residues on histones, including H3 lysine 9, H4 lysine 16, H1 lysine 26, and H3 lysine 56. Moreover, acetyl-CoA synthetase and cortactin are among the proteins that cytoplasmic SIRT1 deacetylates, controlling activities including fatty acid production and cytoskeleton changes during cell migration [71, 72]. There has been much discussion on how SIRT1 regulates peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PGC-1α) and how this regulates metabolism, mitochondrial biogenesis, and turnover [73]. Although SIRT1 is known to affect mitochondrial activity, how much depends on the kind of cell or the physiological setting. SIRT1 and PGC-1α interact with transcription factor A (TFAM) and mitochondrial DNA (mtDNA). SIRT1's alteration of PGC-1α emphasises how SIRT1 affects longevity and healthspan [70]. SIRT1 has been shown by Imperatore et al. to improve macrophage proliferative ability and self-renewal in both in vitro and in vivo settings [74]. Furthermore, it has been demonstrated that SIRT1 inhibition suppresses E2F1, a protein essential for cell cycle progression, the G1/S transition, and the stress responses Myc and FoxO [75].

It has been shown that SIRT1 deacetylates DNA damage repair enzymes as APE1, XPC, XPA, and WRN, which helps to stop tumour development by blocking NF-kB [76]. On the other hand, by deacetylating tumour suppressors such HIC1, p73, p53, Rb, FoxO, and E2F1, SIRT1 might encourage the growth of tumours [77]. In the control of nuclear receptors, cofactors, and oncogenes, such as PPARγ, oestrogen receptors (ER), androgen receptors (AR), c-Myc, HIF-1α, AMP-activated protein kinase (AMPK), and N-Myc, SIRT1 has both positive and negative effects. The mechanisms behind SIRT1's participation in diseases are complex because of its dual roles in tumour growth and suppression, as well as its dose-dependent influence on several cellular processes [78, 79].

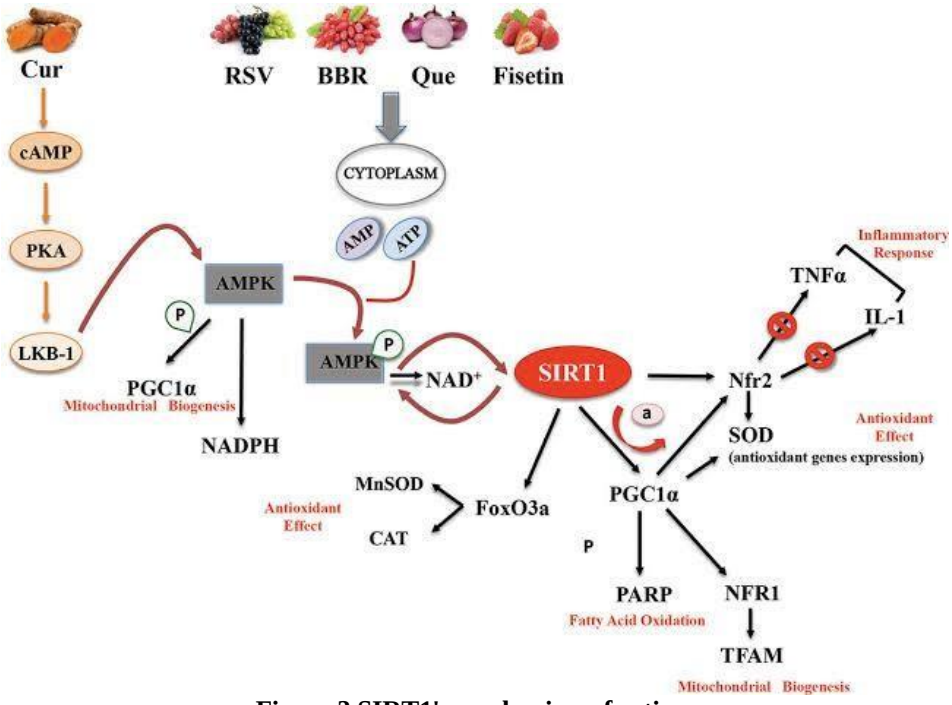

Figure 3 SIRT1's mechanism of action

Benefits of PD SIRT Targeting

Targeting SIRTs offers several potential advantages in the treatment of PD [80]:

SIRTs influence multiple pathways implicated in PD, including mitochondrial function, oxidative stress, neuroinflammation, and protein homeostasis. This multi-target approach can address the complex and multifactorial nature of PD.

Neuroprotection: By enhancing cellular defence mechanisms and promoting neuronal survival, SIRTs offer a neuroprotective strategy that could slow disease progression and preserve motor and cognitive functions.

Epigenetic and transcriptional programme modification: SIRTs act as epigenetic regulators, modulating the expression of genes involved in neuroprotection, metabolism, and stress responses. This could lead to sustained beneficial effects at the molecular level.

Reduction of α-Synuclein Toxicity: SIRTs, particularly SIRT1 and SIRT2, can reduce the aggregation and toxicity of α-synuclein, addressing one of the central pathological features of PD.

Anti-Inflammatory Effects: By inhibiting pro-inflammatory signaling pathways, SIRTs can mitigate chronic neuroinflammation, which is a significant contributor to PD pathology.

Improvement of Protein Clearance and Autophagy: By encouraging autophagy, SIRTs help remove misfolded proteins from the body and stop their harmful build-up. This process may lessen the burden that protein aggregation cause in PD.

Role of SIRT1 on PD

SIRT1 reduces α-synuclein accumulation by modulating autophagy and deacetylation levels of heat shock factor 1 in PD

Figure 4 shows the multiple mechanism of SIRT1 on PD. Abnormal α-synuclein aggregation in cells is a known contributor to PD. Preventing or lowering α-synuclein formation and increasing its removal may postpone disease development, making it a possible treatment option for PD. Upregulating autophagy offers therapeutic potential for PD by reducing aberrant α-synuclein buildup [81]. Autophagy is essential for a variety of cellular activities, including cell tolerance to starvation, misfolded protein elimination, senescence delay, and intracellular homeostasis [82]. By encouraging autophagy, SIRT1 can slow down the deterioration of human nucleus pulposus cells, according to recent studies on neurological disorders [83, 84]. Furthermore, it has been shown that SIRT1 promotes autophagy, which lessens the neurotoxicity caused by the prion protein fragment (106–126) [85]. Resveratrol, a naturally occurring agonist of SIRT1, was shown in a recent research to both increase the expression of the autophagy marker LC3-II and decrease the accumulation of α-synuclein in PC12 cells that overexpress it [86]. According to our research, resveratrol stimulates SIRT1, which facilitates LC3's movement from the nucleus to the cytoplasm. Increased LC3-II synthesis and enhanced autophagic clearance of α-synuclein and p62 were the outcomes of this stimulation in dopaminergic neurons. On the other hand, blocking SIRT1 with EX527 resulted in the build-up of α-synuclein and p62, inhibited the nuclear-cytoplasmic translocation of LC3, and prevented the decrease in acetylated LC3 levels [87].

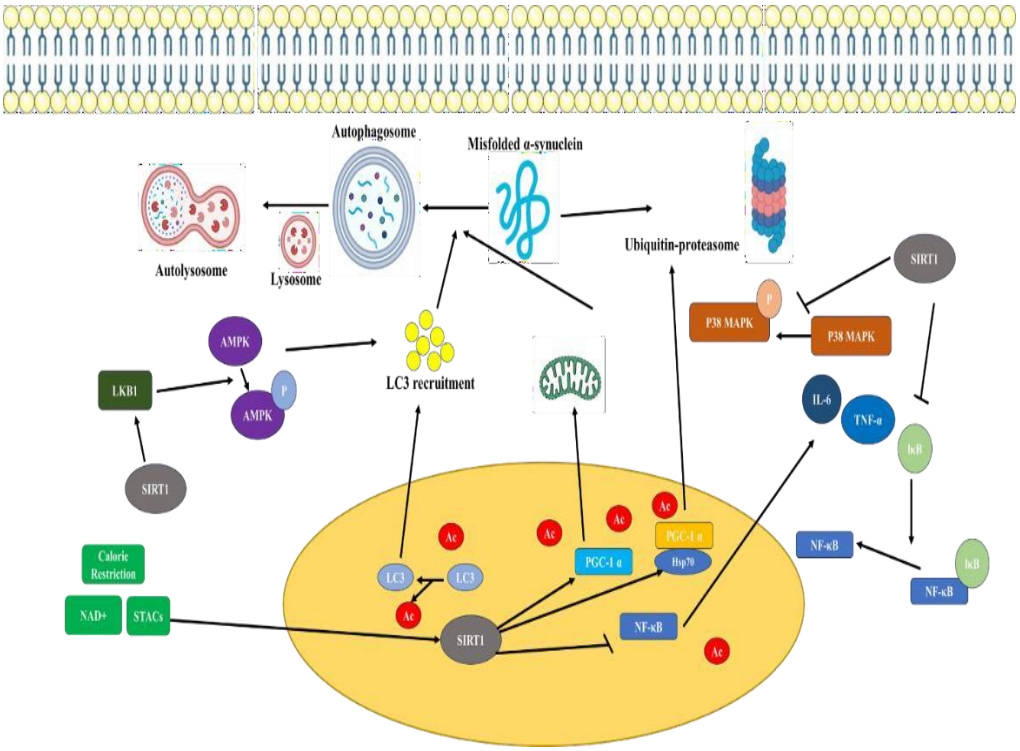

Figure 4. Neuroprotective role of SIRT1 against PD through multiple mechanisms

AMPK, often known as the "metabolic sensor protein" or the "energy monitor" of cells, is a crucial controller of energy metabolism. The main factor regulating AMPK activity is the AMP/ATP ratio. In order to control autophagy and protein breakdown, AMPK is essential [88]. SIRT1 activates the primary AMPK kinase, liver kinase B1 (LKB1) [89]. On the other hand, AMPK inhibitors dramatically lower SIRT1 expression and autophagy. Autophagy is probably largely regulated by the reciprocal regulation of SIRT1 and AMPK [90]. Prior studies have shown that resveratrol increases SIRT1 expression and stimulates AMPK phosphorylation and activity [91]. Therefore, targeting the SIRT1/AMPK pathway could potentially serve as an effective therapeutic approach for PD.

By influencing the tuberous sclerosis 2 (TSC2)-mammalian target of rapamycin (mTOR)-ribosomal protein S6 kinase 1 (S6K1) pathway, which in turn triggers autophagy, SIRT1 enhances neuronal survival in cerebral ischemic tissue [92]. Moreover, studies have demonstrated the role that SIRT1 plays in the deacetylation of forkhead transcription factor 1 (FOXO1), which initiates starvation-induced autophagy [93, 94]. Furthermore, it has been demonstrated that RelA/p65 deacetylation by SIRT1 partly promotes autophagy [95, 96]. Thus, it is hypothesised that SIRT1 might promote autophagy to increase α-synuclein breakdown, which could have a major impact on stopping or slowing the course of PD. The body of research suggests that SIRT1 is essential for controlling autophagy via a variety of pathways, albeit it is yet unclear how important each of these routes is in relation to the other, both established and undiscovered.

Besides autophagy, molecular chaperones are pivotal in clearing misfolded proteins. Their function involves facilitating the formation of native protein conformations, which is a crucial posttranslational modification for most proteins. Molecular chaperones serve a dual role: they assist in protein folding and stabilize protein structures, while also maintaining polypeptide chain components in a loosely folded state to facilitate their passage through organelle membranes [97]. Molecular chaperones enhance the transfer of misfolded monomers to the ubiquitin-proteasome system or encourage chaperone-mediated autophagy by particularly recognising their hydrophobic surface. Through this procedure, misfolded proteins' cytotoxicity is successfully reduced by avoiding their accumulation in the cytosol [98]. Molecular chaperones, which efficiently eliminate toxic protein monomers and oligomers and maintain protein homeostasis, are regulated by heat shock transcription factors (HSFs) and other cofactors [99, 100]. Heat shock transcription factors (HSFs) exhibit a highly conserved structure and function, with significant similarity among them. Among these factors, HSF1 is particularly representative.

Apart from phosphorylation, SIRT1-mediated deacetylation keeps HSF1 in a deacetylated state that encourages DNA binding, which can activate HSF1 in stressful situations [101, 102]. On the other hand, heat shock gene transcription is hampered by the use of small interfering RNAs to decrease SIRT1 expression. Research has indicated that the production of α-synuclein aggregates is decreased when SIRT1 is overexpressed [103]. α-synuclein oligomers are not, however, directly decreased by SIRT1. Rather, it sustains HSF1 in a deacetylated form, which makes it capable of binding DNA and extending HSF1's association with the heat shock promoter of heat shock protein 70 (Hsp70). By encouraging Hsp70 transcription, this approach improves cell viability and breaks down α-synuclein oligomers [104, 105].

SIRT1 controls apoptosis in PD

Apoptosis of dopaminergic neurons is a crucial factor in neuronal loss in PD and may constitute the ultimate common mechanism leading to their degeneration. SIRT1 has been shown in studies to reduce neurodegenerative disease damage by controlling brain cell death. As a result, addressing neuronal apoptosis shows promise as an effective technique for treating neurodegenerative illnesses. In a prior study, resveratrol dramatically reversed reductions in SIRT1 expression and protein kinase B (Akt) phosphorylation produced by rotenone, demonstrating an evident neuroprotective benefit against rotenone-induced neurotoxicity. Moreover, resveratrol's neuroprotective impact against rotenone-induced neurotoxicity was considerably diminished upon suppression of the SIRT1/Akt1 signalling pathway, indicating that SIRT1 and Akt1 may mediate neuroprotection and function as possible molecular targets for intervention [106]. p53 interacts with B-cell lymphoma 2 (Bcl-2) family members during apoptosis, namely Bcl-2, an anti-apoptotic protein. Furthermore, p53 facilitates the oligomerization of Bcl-2 homologous antagonist/killer (BAK), which causes cytochrome C to be released quickly, the permeabilization of the mitochondrial membrane, and ultimately cell death. Prior studies have demonstrated that resveratrol guards against neurotoxicity through a SIRT1-dependent mechanism. SIRT1 decreases p53 expression and enhances neuroprotection by changing the transcriptional level of the p53 gene expression and specifically targeting the H3K9 histone [91]. Researchers have discovered that SIRT1 deacetylates the C-terminal residues of the p53 ubiquitination main site under physiological stress circumstances. By doing this, p53 is stabilised and protein breakdown is stopped [107]. Moreover, it has been noted that SIRT1 enhances DNA repair activity in tumour and retinal cells via deacetylating Ku70. Furthermore, Bcl-2-associated X protein (Bax) in the cytoplasm may interact with SIRT1 to decrease apoptosis and increase cell survival [108–

110]. To completely comprehend the importance of the SIRT1/Ku70 pathway in the neurological system, more research is necessary.

SIRT1 regulates oxidative stress and mitochondrial activity in PD

Studies have indicated that oxidative stress and mitochondrial dysfunction have a role in dopaminergic toxicity and PD. Brain tissue exhibits high rates of oxygen consumption but lacks adequate antioxidant protection systems to counteract oxidative damage. Recent studies propose that in PD, an initial rise in oxygen free radicals might stimulate the striatal antioxidant enzyme system as a compensatory response, potentially mitigating oxidative stress-induced damage. However, as the disease develops, the production of free radicals increases, and the body's compensatory reaction fails to reduce the damage. Consequently, there is a disruption in the balance between the striatal pro-oxidant and antioxidant systems, leading to the death of neurons and apoptosis [111]. PGC-1α activates several nuclear receptors and transcription factors [112]. Experiments show that PGC-1α boosts antioxidant enzyme activity and protein levels, reducing cell death. Superoxide dismutase 1 (SOD1), SOD2, and catalase (CAT) were significantly reduced in mutant animals lacking PGC-1α compared to normal mice [113]. Many of PGC-1α's lysine residues may be directly acetylated by the histone acetyltransferase complex, which would lower the protein's antioxidative and transcriptional effects [114].

SIRT1 activation can result in PGC-1α deacetylation, which raises protein levels and increases antioxidant activity [115]. Nicotinamide, an inhibitor of SIRT1, reduces antioxidative capabilities in wild-type cells but not in cells that overexpress PGC-1α because PGC-1α operates downstream of SIRT1.The findings indicate that PGC-1α expression is upregulated by SIRT1 in response to oxidative stress, highlighting the possible significance of the SIRT1/PGC-1α pathway in the management and prophylaxis of PD.

SIRT1 controls PD's inflammatory responses

Studies reveal that microglial cells may change from their resting to their active states [116]. According to recent research, activation of microglia can affect dopaminergic neurons by increasing the production of proinflammatory cytokines and oxidative stress, which can set off an inflammatory cascade [117]. According to some researchers, neuroinflammation has a role in the DA neurons' degradation and eventual death in the substantia nigra (SN) of people with PD [118]. On the other hand, conflicting results from many studies imply that neuroinflammation could also protect the central nervous system (CNS) [119]. Whether neuroinflammation causes DA neuron loss directly or as a response to neuronal death is still a mystery in PD. However, neuroinflammation surely affects how PD advances [120]. According to recent research, SIRT1 may help PD via deacetylating and inhibiting NF-κB transcription [121]. Resveratrol has been demonstrated to inhibit the generation of inducible nitric oxide synthase (iNOS), p38 mitogen-activated protein kinases, and the degradation of IκB induced by lipopolysaccharide (LPS) in N9 microglial cells. Moreover, SIRT1 deficiency in microglia has been associated with age-related cognitive decline and neurodegeneration via the epigenetic regulation of interleukin-1β, corroborating previous findings [122]. Additionally, resveratrol significantly decreased the generation of nitric oxide and tumour necrosis factor-alpha in LPS-activated microglial cells, according to a research by Xiu Li Bi and colleagues [123]. All of these results point to SIRT1's possible involvement in controlling neuroinflammation and PD development by demonstrating that it suppresses microglial proinflammatory responses.

SIRT1 activators and PD neuroprotective effects

Polyphenolic substance resveratrol, a SIRT1 activator, is present in a variety of plants and foods, such as peanuts and grape skins. Resveratrol is well-known for its pleiotropic and multitargeted qualities. It can cross the blood-brain barrier and has been shown to have protective benefits against a variety of neurodegenerative illnesses, including PD. [123, 125]. Resveratrol has been demonstrated in studies to lessen oxidative stress and decrease α-synuclein (A30P) aggregation in SK-N-BE neuroblastoma cells [126]. Furthermore, resveratrol has been demonstrated to mitigate dopamine-induced oxidative stress in SH-SY5Y cells and avert MPP+-induced cerebellar granule cell death [127–129]. By adjusting the amounts of the pro-apoptotic protein Bax and the anti-apoptotic component Bcl-2, resveratrol has been shown to lessen MPP+-induced PC12 cell death [129]. Furthermore, resveratrol can mitigate rotenone-induced PC12 apoptosis by upregulating the expression of heme oxygenase-1, which in turn induces autophagy [130]. Experimental investigations using PD models on animals have demonstrated that resveratrol improves the activity of antioxidant enzymes, including glutathione peroxidase, glutathione reductase, and catalase. In the MPTP animal model of PD, it concurrently reduces the levels of phospholipase 2, protein carbonyls, and thiobarbituric acid reactive compounds, which lessens the death of dopaminergic neurons [131–133]. Resveratrol's antioxidant and anti-inflammatory qualities have been linked to protective benefits against 6-hydroxydopamine hydrobromide (6-OHDA)-induced PD in rat models [134]. Furthermore, in fibroblasts generated from patients with early-onset PD who possess mutations in the PARK2 gene, resveratrol has been shown to reduce oxidative stress, improve mitochondrial biogenesis, and control energy metabolism [135]. It

has been demonstrated that resveratrol inhibits rotenone-induced apoptosis in SH-SY5Y cells [91] and reduces α-synuclein accumulation in α-synuclein-overexpressing PC12 cells [86]. Additionally, resveratrol has shown promise in ameliorating degenerative changes and motor deficits in rats treated with MPTP. Notably, the positive effects of resveratrol were somewhat offset by EX527's suppression of SIRT1. These results emphasise how crucial it is to carry out more research on resveratrol's neuroprotective qualities and clarify the underlying processes. New approaches to the prevention and treatment of PD may result from this research.

Although resveratrol has been shown in recent studies to have neuroprotective qualities, its potential as a medicine is still up for discussion. Determining the ideal dietary dose of resveratrol to produce therapeutic benefits is a significant difficulty because different levels have been shown in both in vitro and in vivo investigations. However, research indicates that a 60-kg person may safely take 450 mg of resveratrol per day [136]. It is important to understand that resveratrol has anti-inflammatory and neuroprotective actions in addition to antioxidant ones that contribute to its health advantages. More study should look at different ways to administer it or pharmacological formulations like nanoencapsulation to increase resveratrol tissue concentration in order to optimise its therapeutic efficacy in PD.

In neuropharmacology, one of the primary goals is to develop drugs that can both directly activate SIRT1 and boost its bioavailability. The finding of the first SIRT-activating compounds (STACs) in 2003 was a significant advancement in the field. Since then, efforts in medicinal chemistry and extensive high-throughput screening have led to the identification of over 14,000 STACs across several chemical classes. Together with synthetic STACs like imidazothiazoles (e.g., SRT1720), thiazolopyridines (e.g., STAC-2), benzimidazoles (e.g., STAC-5), and bridging ureas (e.g., STAC-9), plant-derived STACs include stilbenes (e.g., resveratrol), chalcones (e.g., butein), and flavones (e.g., quercetin) [137, 138]. These varied substances provide viable paths for regulating SIRT1 and investigating its therapeutic uses in neurodegenerative illnesses such as PD.

Stilbenes, a subclass of polyphenols, have emerged as particularly promising in the numerous research that have examined the effect of phenolic compounds on PD. These chemicals, which are particularly rich in grapes and products made from them, provide a plethora of health advantages. In a recent study, the effects of three stilbenes (ampelopsin A, piceatannol, and isohopeaphenol) isolated from vine stalks on α-synuclein fibrillation were examined. It has been shown that piceatannol can prevent α-synuclein fibrillation, which causes soluble, non-toxic α-synuclein/polyphenol oligomers to form in neuronal PC12 cells [141]. This demonstrates stilbenes' potential as therapeutic agents to slow the course of PD.

Numerous STACs have been studied in animal models of various disorders, such as fatty liver disease, atherosclerosis, neurodegeneration, ageing, osteoporosis, infection, and type 2 diabetes. In vitro effectiveness of synthetic STACs, which are in their sixth generation now, is more than 1000 times greater than that of resveratrol. As a result, there is great treatment potential for PD with these new synthetic drugs. SRT1720, SRT2014, SRT3025, SRT2183, and SRT1460 are a few of these small molecule SIRT1 activators. Moreover, E6155, a member of the piperazine 1,4-diamide family, has been identified as a novel small molecule SIRT1 activator by recent studies using optimised high-throughput screening. The study's findings suggest that E6155 may be a useful treatment for diabetes and insulin resistance.

The hypothesis that STACs directly activate SIRT1 has been widely debated. Although it has been demonstrated in vitro that naturally occurring STACs, like resveratrol, can activate SIRT1 by lowering its peptide Michaelis constant (KM) and causing pharmacological changes linked to SIRT1 activation, there is still disagreement regarding how directly STACs affect SIRT1. Resveratrol and synthetic STACs like SRT1720 and SRT2014, but not SIRT1 knockouts, increased mitochondrial mass and ATP content in wild-type myoblasts, according to Hubbard et al. Furthermore, the effects of STACs on mitochondrial mass and ATP levels were diminished in myoblasts harbouring the E230K SIRT1 mutation. Through a variety of biochemical assays using native substrates and biophysical studies using nuclear magnetic resonance, surface plasmon resonance, and isothermal titration calorimetry, it was demonstrated by Pacholec et al. that SRT1720, SRT2183, SRT1460, and resveratrol do not directly activate SIRT1 [150]. These chemicals are exceedingly promiscuous, making them inappropriate as pharmacological tools for researching SIRT1 pathways, according to their rigorous selectivity testing against over 100 targets, including ion channels, transporters, enzymes, and receptors. As a result, there is currently little consistent and clear data from clinical studies. In order to confirm the neuroprotective advantages of STACs and clarify any possible mechanisms of action, we advise completing more clinical trials.

SIRT1 activation may have a role in the neuroprotection exercise induces in PD

Numerous studies have demonstrated that exercise protects nigral dopamine neurons and slows the progression of PD [151, 152]. Physical activities that improve neuroprotection include weight training and treadmill use, as shown by Tuon et al. Activating SIRT1, which deacetylates NF-κB and controls

mitochondrial function and neuroinflammation, may provide neuroprotective advantages as a result of exercise [153]. Thus, SIRT1 activation may operate as a mediator between physical exercise and its neuroprotective effects [154].

Conclusion

The most recent studies showing SIRT1's favourable benefits in reducing neuroinflammation and neurodegenerative disorders are included here. One of the most researched SIRTs, SIRT1 affects several biological processes, including apoptosis, stress management, inflammation, metabolism, cancer, and DNA repair. While modulating SIRT1 expression stands as a potential therapeutic avenue, comprehending the exact molecular mechanisms guiding its function necessitates deeper exploration. Furthermore, compounds like resveratrol and chemically distinct synthetic STACs, which have demonstrated therapeutic potential in other neurodegenerative conditions, present hopeful prospects for PD treatment in the future. Further research is necessary since the benefits of SIRT1 agonists in the treatment of PD are still up for dispute. The data from clinical research establishing the anti-inflammatory and neuroprotective benefits of SIRT1 is still lacking, despite certain clinical experiments highlighting the neuroprotective capabilities of the SIRT1 activator resveratrol. Therefore, more thorough investigations into SIRT1's specific targets are necessary since they can greatly influence the creation of therapeutic approaches for illnesses linked to neuroinflammation.

Reference

1. Bhatt V, Tiwari AK. Sirtuins, a key regulator of ageing and age-related neurodegenerative diseases. International Journal of Neuroscience. 2023;10: 1167-1192.
2. Jurcau A. Insights into the pathogenesis of neurodegenerative diseases: Focus on mitochondrial dysfunction and oxidative stress. International Journal of Molecular Sciences. 2021; 21:11847.
3. Collier TJ, Kanaan NM, Kordower JH. Ageing as a primary risk factor for Parkinson's disease: evidence from studies of non-human primates. Nature Reviews Neuroscience. 2011; 6: 359-366.
4. Dexter DT, Jenner P. Parkinson disease: from pathology to molecular disease mechanisms. Free Radical Biology and Medicine. 2013; 62: 132-144.
5. Pringsheim T, Jette N, Frolkis A, Steeves TD. The prevalence of Parkinson's disease: a systematic review and meta-analysis. Movement disorders. 2014; 13: 1583-1590.
6. Beilina A, Cookson MR. Genes associated with Parkinson's disease: regulation of autophagy and beyond. Journal of neurochemistry. 2016; 139: 91-107.
7. Pellegrini L, Wetzel A, Grannó S, Heaton G, Harvey K. Back to the tubule: microtubule dynamics in Parkinson's disease. Cellular and Molecular Life Sciences. 2017; 74: 409-434.
8. Hirsch EC, Vyas S, Hunot S. Neuroinflammation in Parkinson's disease. Parkinsonism & related disorders. 2012; 18: S210-2.
9. Lynch-Day MA, Mao K, Wang K, Zhao M, Klionsky DJ. The role of autophagy in Parkinson's disease. Cold Spring Harbor perspectives in medicine. 2012; 4: a009357.
10. Bai X, Yao L, Ma X, Xu X. Small molecules as SIRT modulators. Mini reviews in medicinal chemistry. 2018; 13: 1151-1157.
11. Houtkooper RH, Pirinen E, Auwerx J. Sirtuins as regulators of metabolism and healthspan. Nature reviews Molecular cell biology. 2012; 4: 225-238.
12. Huang JY, Hirschey MD, Shimazu T, Ho L, Verdin E. Mitochondrial sirtuins. Biochimica et Biophysica Acta (BBA)-Proteins and Proteomics. 2010; 8: 1645-1651.
13. Vaquero A, Scher MB, Lee DH, Sutton A, Cheng HL, Alt FW, Serrano L, Sternglanz R, Reinberg D. SirT2 is a histone deacetylase with preference for histone H4 Lys 16 during mitosis. Genes & development. 2006; 10: 1256-1261.
14. Parker CG, Pratt MR. Click chemistry in proteomic investigations. Cell. 2020; 4: 605-632.
15. Dai H, Sinclair DA, Ellis JL, Steegborn C. Sirtuin activators and inhibitors: Promises, achievements, and challenges. Pharmacology & therapeutics. 2018; 188: 140-154.
16. Ji Z, Liu GH, Qu J. Mitochondrial sirtuins, metabolism, and aging. Journal of Genetics and Genomics. 2022; 4: 287-298.
17. Kumar S, Lombard DB. Functions of the sirtuin deacylase SIRT5 in normal physiology and pathobiology. Critical reviews in biochemistry and molecular biology. 2018; 3: 311-334.
18. Green CL, Lamming DW, Fontana L. Molecular mechanisms of dietary restriction promoting health and longevity. Nature Reviews Molecular Cell Biology. 2022 Jan;23(1):56-73.
19. Guan Y, Wang SR, Huang XZ, Xie QH, Xu YY, Shang D, Hao CM. Nicotinamide mononucleotide, an NAD+ precursor, rescues age-associated susceptibility to AKI in a sirtuin 1–dependent manner. Journal of the American Society of Nephrology. 2017; 8: 2337-2352.
20. Chen C, Zhou M, Ge Y, Wang X. SIRT1 and aging related signaling pathways.

Mechanisms of ageing and development. 2020; 187: 111215.
21. Wu QJ, Zhang TN, Chen HH, Yu XF, Lv JL, Liu YY, Liu YS, Zheng G, Zhao JQ, Wei YF, Guo JY. The sirtuin family in health and disease. Signal transduction and targeted therapy. 2022; 1: 402.
22. Alves-Fernandes DK, Jasiulionis MG. The role of SIRT1 on DNA damage response and epigenetic alterations in cancer. International journal of molecular sciences. 2019; 13: 3153.
23. Gambini J, Inglés M, Olaso G, Lopez-Grueso R, Bonet-Costa V, Gimeno-Mallench L, Mas-Bargues C, Abdelaziz KM, Gomez-Cabrera MC, Vina J, Borras C. Properties of resveratrol: in vitro and in vivo studies about metabolism, bioavailability, and biological effects in animal models and humans. Oxidative medicine and cellular longevity. 2015; 1: 837042.
24. Song Y, Wu Z, Zhao P. The protective effects of activating Sirt1/NF-κB pathway for neurological disorders. Reviews in the Neurosciences. 2022; 4: 427-438.
25. Wang J, Zheng B, Yang S, Zhou D, Wang J. Olmesartan prevents oligomerized amyloid β (Aβ)-induced cellular senescence in neuronal cells. ACS Chemical Neuroscience. 2021; 7: 1162-1169.
26. Carafa V, Rotili D, Forgione M, Cuomo F, Serretiello E, Hailu GS, Jarho E, Lahtela-Kakkonen M, Mai A, Altucci L. Sirtuin functions and modulation: from chemistry to the clinic. Clinical epigenetics. 2016; 8: 1-21.
27. Jankovic J. Parkinson's disease: clinical features and diagnosis. Journal of neurology, neurosurgery & psychiatry. 2008; 4: 368-376.
28. Obeso JA, Stamelou M, Goetz CG, Poewe W, Lang AE, Weintraub D, Burn D, Halliday GM, Bezard E, Przedborski SJ, Lehericy S. Past, present, and future of Parkinson's disease: A special essay on the 200th Anniversary of the Shaking Palsy. Movement disorders. 2017; 9: 1264-1310.
29. Armstrong MJ, Okun MS. Diagnosis and treatment of Parkinson disease: a review. Jama. 2020; 6: 548-560.
30. Dorsey ER, Bloem BR. The Parkinson pandemic—a call to action. JAMA neurology. 2018; 1: 9-10.
31. Dorsey ER, Elbaz A, Nichols E, Abbasi N, Abd-Allah F, Abdelalim A, Adsuar JC, Ansha MG, Brayne C, Choi JY, Collado-Mateo D. Global, regional, and national burden of Parkinson's disease, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. The Lancet Neurology. 2018; 11: 939-953.
32. Marras C, Lang A, van de Warrenburg BP, Sue CM, Tabrizi SJ, Bertram L, Mercimek-Mahmutoglu S, Ebrahimi-Fakhari D, Warner TT, Durr A, Assmann B. Nomenclature of genetic movement disorders: Recommendations of the International Parkinson and Movement Disorder Society task force. Movement disorders: official journal of the Movement Disorder Society. 2017; 5: 724-725.
33. Deng H, Wang P, Jankovic J. The genetics of Parkinson disease. Ageing research reviews. 2018; 42: 72-85.
34. Jiménez-Jiménez FJ, Alonso-Navarro H, García-Martín E, Agúndez JA. The relationship between Parkinson's disease and essential tremor: review of clinical, epidemiologic, genetic, neuroimaging and neuropathological data, and data on the presence of cardinal signs of parkinsonism in essential tremor. Tremor and Other Hyperkinetic Movements. 2012; 2.
35. Zahoor I, Shafi A, Haq E. Pharmacological treatment of Parkinson's disease. Exon Publications. 2018; 129-144.
36. Lang AE, Obeso JA. Challenges in Parkinson's disease: restoration of the nigrostriatal dopamine system is not enough. The Lancet Neurology. 2004; 5: 309-316.
37. Simonyan K. Recent advances in understanding the role of the basal ganglia. F1000Research. 2019; 8.
38. Campanelli F, Natale G, Marino G, Ghiglieri V, Calabresi P. Striatal glutamatergic hyperactivity in Parkinson's disease. Neurobiology of Disease. 2022; 168: 105697.
39. Galvan A, Devergnas A, Wichmann T. Alterations in neuronal activity in basal ganglia-thalamocortical circuits in the parkinsonian state. Frontiers in neuroanatomy. 2015; 9: 5.
40. Chambers NE, Lanza K, Bishop C. Pedunculopontine nucleus degeneration contributes to both motor and non-motor symptoms of Parkinson's disease. Frontiers in Pharmacology. 2020; 10: 486278.
41. Parihar A, Parihar P, Solanki I, Parihar MS. Alpha synuclein and Parkinson's disease. Pathology, prevention and therapeutics of neurodegenerative disease. 2019: 1-4.
42. Sepúlveda D, Cisternas-Olmedo M, Arcos J, Nassif M, Vidal RL. Contribution of autophagy-lysosomal pathway in the exosomal secretion of alpha-synuclein and its impact in the progression of Parkinson's disease. Frontiers in Molecular Neuroscience. 2022; 15: 805087.

43. Moon HE, Paek SH. Mitochondrial dysfunction in Parkinson's disease. Experimental neurobiology. 2015; 2: 103.
44. Liu CY, Wang X, Liu C, Zhang HL. Pharmacological targeting of microglial activation: new therapeutic approach. Frontiers in cellular neuroscience. 2019; 13: 514.
45. Nuytemans K, Theuns J, Cruts M, Van Broeckhoven C. Genetic etiology of Parkinson disease associated with mutations in the SNCA, PARK2, PINK1, PARK7, and LRRK2 genes: a mutation update. Human mutation. 2010; 7: 763-780.
46. Lang AE, Marras C. Initiating dopaminergic treatment in Parkinson's disease. The Lancet. 2014; 9949: 1164-1166.
47. Charles D, Konrad PE, Neimat JS, Molinari AL, Tramontana MG, Finder SG, Gill CE, Bliton MJ, Kao C, Phibbs FT, Hedera P. Subthalamic nucleus deep brain stimulation in early stage Parkinson's disease. Parkinsonism & related disorders. 2014; 7: 731-7.
48. Krishnamurthy PT, Kumari M, Byran G, Gangadharappa HV, Garikapati KK. Neuroprotective approaches to halt Parkinson's disease progression. Neurochemistry International. 2022; 158: 105380.
49. Pignataro D, Sucunza D, Rico AJ, Dopeso-Reyes IG, Roda E, Rodríguez-Perez AI, Labandeira-Garcia JL, Broccoli V, Kato S, Kobayashi K, Lanciego JL. Gene therapy approaches in the non-human primate model of Parkinson's disease. Journal of Neural Transmission. 2018; 125: 575-589.
50. Fields CR, Bengoa-Vergniory N, Wade-Martins R. Targeting alpha-synuclein as a therapy for Parkinson's disease. Frontiers in molecular neuroscience. 2019; 12: 299.
51. Multimodal Complex Treatment improves motor symptoms, depression and quality of life. Journal of neurology. 2020; 4: 954-965.
52. Chojdak-Łukasiewicz J, Bizoń A, Waliszewska-Prosół M, Piwowar A, Budrewicz S, Pokryszko-Dragan A. Role of sirtuins in physiology and diseases of the central nervous system. Biomedicines. 2022; 10: 2434.
53. Tian X, Firsanov D, Zhang Z, Cheng Y, Luo L, Tombline G, Tan R, Simon M, Henderson S, Steffan J, Goldfarb A. SIRT6 is responsible for more efficient DNA double-strand break repair in long-lived species. Cell. 2019; 3: 622-638.
54. Bonkowski MS, Sinclair DA. Slowing ageing by design: the rise of NAD+ and sirtuin-activating compounds. Nature reviews Molecular cell biology. 2016; 17: 679-690.
55. Zhao E, Hou J, Ke X, Abbas MN, Kausar S, Zhang L, Cui H. The roles of sirtuin family proteins in cancer progression. Cancers. 2019; 12: 1949.
56. Imai SI, Guarente L. NAD+ and sirtuins in aging and disease. Trends in cell biology. 2014; 8: 464-471.
57. Fang EF, Bohr VA. NAD+: The convergence of DNA repair and mitophagy. Autophagy. 2017; 2: 442-443.
58. Fang EF, Scheibye-Knudsen M, Brace LE, Kassahun H, SenGupta T, Nilsen H, Mitchell JR, Croteau DL, Bohr VA. Defective mitophagy in XPA via PARP-1 hyperactivation and NAD+/SIRT1 reduction. Cell. 2014; 4: 882-896.
59. Hartl FU, Bracher A, Hayer-Hartl M. Molecular chaperones in protein folding and proteostasis. Nature. 2011; 7356: 324-332.
60. Xu C, Wang L, Fozouni P, Evjen G, Chandra V, Jiang J, Lu C, Nicastri M, Bretz C, Winkler JD, Amaravadi R. SIRT1 is downregulated by autophagy in senescence and ageing. Nature cell biology. 2020; 10: 1170-1179.
61. Vassilopoulos A, Fritz KS, Petersen DR, Gius D. The human sirtuin family: evolutionary divergences and functions. Human genomics. 2011; 5: 1-2.
62. Sosnowska B, Mazidi M, Penson P, Gluba-Brzózka A, Rysz J, Banach M. The sirtuin family members SIRT1, SIRT3 and SIRT6: Their role in vascular biology and atherogenesis. Atherosclerosis. 2017; 265: 275-282.
63. Khan H, Tiwari P, Kaur A, Singh TG. Sirtuin acetylation and deacetylation: a complex paradigm in neurodegenerative disease. Molecular Neurobiology. 2021; 58: 3903-3917.
64. Michan S, Sinclair D. Sirtuins in mammals: insights into their biological function. Biochemical Journal. 2007; 1: 1-3.
65. Pan M, Yuan H, Brent M, Ding EC, Marmorstein R. SIRT1 contains N-and C-terminal regions that potentiate deacetylase activity. Journal of Biological Chemistry. 2012; 4: 2468-2476.
66. Lakshminarasimhan M, Curth U, Moniot S, Mosalaganti S, Raunser S, Steegborn C. Molecular architecture of the human protein deacetylase Sirt1 and its regulation by AROS and resveratrol. Bioscience Reports. 2013; 3: e00037.
67. Jiao F, Gong Z. The beneficial roles of SIRT1 in neuroinflammation-related diseases. Oxidative medicine and cellular longevity. 2020; 1: 6782872.

68. Tanner KG, Landry J, Sternglanz R, Denu JM. Silent information regulator 2 family of NAD-dependent histone/protein deacetylases generates a unique product, 1-O-acetyl-ADP-ribose. Proceedings of the National Academy of Sciences. 2000; 26: 14178-14182.
69. Yang Y, Liu Y, Wang Y, Chao Y, Zhang J, Jia Y, Tie J, Hu D. Regulation of SIRT1 and its roles in inflammation. Frontiers in immunology. 2022;13: 831168.
70. Tang BL. Sirt1 and the mitochondria. Molecules and cells. 2016; 2: 87-95.
71. Hallows WC, Lee S, Denu JM. Sirtuins deacetylate and activate mammalian acetyl-CoA synthetases. Proceedings of the National Academy of Sciences. 2006; 27: 10230-10235.
72. Zhang Y, Zhang M, Dong H, Yong S, Li X, Olashaw N, Kruk PA, Cheng JQ, Bai W, Chen J, Nicosia SV. Deacetylation of cortactin by SIRT1 promotes cell migration. Oncogene. 2009; 28: 445-460.
73. Nemoto S, Fergusson MM, Finkel T. SIRT1 functionally interacts with the metabolic regulator and transcriptional coactivator PGC-1α. Journal of Biological Chemistry. 2005; 16: 16456-16460.
74. Imperatore F, Maurizio J, Vargas Aguilar S, Busch CJ, Favret J, Kowenz-Leutz E, Cathou W, Gentek R, Perrin P, Leutz A, Berruyer C. SIRT1 regulates macrophage self-renewal. The EMBO journal. 2017; 16: 2353-2372.
75. Jalgaonkar MP, Parmar UM, Kulkarni YA, Oza MJ. SIRT1-FOXOs activity regulates diabetic complications. Pharmacological Research. 2022; 175: 106014.
76. Uhl, M., Csernok, A., Aydin, S., Kreienberg, R., Wiesmüller, L. and Gatz, S.A., 2010. Role of SIRT1 in homologous recombination. *DNA repair*, 4, 383-393.
77. Chen LF, Mu Y, Greene WC. Acetylation of RelA at discrete sites regulates distinct nuclear functions of NF-κB. The EMBO journal. 2002.
78. Garcia-Peterson LM, Li X. Trending topics of SIRT1 in tumorigenicity. Biochimica et Biophysica Acta (BBA)-General Subjects. 2021; 9: 129952.
79. Shen P, Deng X, Chen Z, Ba X, Qin K, Huang Y, Huang Y, Li T, Yan J, Tu S. SIRT1: a potential therapeutic target in autoimmune diseases. Frontiers in Immunology. 2021; 12: 779177.
80. Donmez G. Sirtuins as possible targets in neurodegenerative diseases. Current Drug Targets. 2013; 6: 644-647.
81. Ghavami S, Shojaei S, Yeganeh B, Ande SR, Jangamreddy JR, Mehrpour M, Christoffersson J, Chaabane W, Moghadam AR, Kashani HH, Hashemi M. Autophagy and apoptosis dysfunction in neurodegenerative disorders. Progress in neurobiology. 2014; 112: 24-49.
82. Moulis M, Vindis C. Autophagy in metabolic age-related human diseases. Cells. 2018; 10: 149.
83. Jiang W, Zhang X, Hao J, Shen J, Fang J, Dong W, Wang D, Zhang X, Shui W, Luo Y, Lin L. SIRT1 protects against apoptosis by promoting autophagy in degenerative human disc nucleus pulposus cells. Scientific reports. 2014; 1: 7456.
84. Miyazaki S, Kakutani K, Yurube T, Maeno K, Takada T, Zhang Z, Kurakawa T, Terashima Y, Ito M, Ueha T, Matsushita T. Recombinant human SIRT1 protects against nutrient deprivation-induced mitochondrial apoptosis through autophagy induction in human intervertebral disc nucleus pulposus cells. Arthritis Research & Therapy. 2015; 17: 1-2.
85. Jeong JK, Moon MH, Lee YJ, Seol JW, Park SY. Autophagy induced by the class III histone deacetylase Sirt1 prevents prion peptide neurotoxicity. Neurobiology of aging. 2013; 1: 146-156.
86. Wu Y, Li X, Zhu JX, Xie W, Le W, Fan Z, Jankovic J, Pan T. Resveratrol-activated AMPK/SIRT1/autophagy in cellular models of Parkinson's disease. Neurosignals. 2011; 3: 163-174.
87. Guo YJ, Dong SY, Cui XX, Feng Y, Liu T, Yin M, Kuo SH, Tan EK, Zhao WJ, Wu YC. Resveratrol alleviates MPTP-induced motor impairments and pathological changes by autophagic degradation of α-synuclein via SIRT1-deacetylated LC3. Molecular nutrition & food research. 2016; 10: 2161-2175.
88. Li SJ, Liu CH, Chang CW, Chu HP, Chen KJ, Mersmann HJ, Ding ST, Chu CH, Chen CY. Development of a dietary-induced metabolic syndrome model using miniature pigs involvement of AMPK and SIRT 1. European journal of clinical investigation. 2015; 1: 70-80.
89. Lan F, Cacicedo JM, Ruderman N, Ido Y. SIRT1 modulation of the acetylation status, cytosolic localization, and activity of LKB1: possible role in AMP-activated protein kinase activation. Journal of Biological Chemistry. 2008; 41: 27628-27635.
90. Maiese K. Targeting molecules to medicine with mTOR, autophagy and neurodegenerative disorders. British journal of clinical pharmacology. 2016; 5: 1245-1266.
91. Feng Y, Liu T, Dong SY, Guo YJ, Jankovic J, Xu H, Wu YC. Rotenone affects p53

transcriptional activity and apoptosis via targeting SIRT 1 and H3K9 acetylation in SH-SY 5Y cells. Journal of neurochemistry. 2015; 4: 668-676.
92. Wang P, Guan YF, Du H, Zhai QW, Su DF, Miao CY. Induction of autophagy contributes to the neuroprotection of nicotinamide phosphoribosyltransferase in cerebral ischemia. Autophagy. 2012; 1: 77-87.
93. Bánréti Á, Sass M, Graba Y. The emerging role of acetylation in the regulation of autophagy. Autophagy. 2013; 6: 819-829.
94. Maiese K. Forkhead transcription factors: formulating a FOXO target for cognitive loss. Current neurovascular research. 2017; 4: 415-420.
95. Elbaz EM, Senousy MA, El-Tanbouly DM, Sayed RH. Neuroprotective effect of linagliptin against cuprizone-induced demyelination and behavioural dysfunction in mice: a pivotal role of AMPK/SIRT1 and JAK2/STAT3/NF-κB signalling pathway modulation. Toxicology and applied pharmacology. 2018; 352: 153-161.
96. Yang SR, Wright J, Bauter M, Seweryniak K, Kode A, Rahman I. Sirtuin regulates cigarette smoke-induced proinflammatory mediator release via RelA/p65 NF-κB in macrophages in vitro and in rat lungs in vivo: implications for chronic inflammation and aging. American Journal of Physiology-Lung Cellular and Molecular Physiology. 2007; 2: L567-L576.
97. Kubota H. Quality control against misfolded proteins in the cytosol: a network for cell survival. Journal of biochemistry. 2009; 5: 609-616.
98. Twohig D, Nielsen HM. α-synuclein in the pathophysiology of Alzheimer's disease. Molecular neurodegeneration. 2019; 1: 23.
99. Jacob P, Hirt H, Bendahmane A. The heat-shock protein/chaperone network and multiple stress resistance. Plant biotechnology journal. 2017; 4: 405-414.
100. Huang C, Wu J, Xu L, Wang J, Chen Z, Yang R. Regulation of HSF1 protein stabilization: An updated review. European journal of pharmacology. 2018; 822: 69-77.
101. Wang N, Zhang F, Yang L, Zou J, Wang H, Liu K, Liu M, Zhang H, Xiao X, Wang K. Resveratrol protects against L-arginine-induced acute necrotizing pancreatitis in mice by enhancing SIRT1-mediated deacetylation of p53 and heat shock factor 1. International journal of molecular medicine. 2017; 2: 427-437.
102. Zelin E, Freeman BC. Lysine deacetylases regulate the heat shock response including the age-associated impairment of HSF1. Journal of molecular biology. 2015; 7: 1644-1654.
103. Singh P, Hanson PS, Morris CM. SIRT1 ameliorates oxidative stress induced neural cell death and is down-regulated in Parkinson's disease. BMC neuroscience. 2017; 18: 1-3.
104. Raynes R, Leckey BD, Nguyen K, Westerheide SD. Heat shock and caloric restriction have a synergistic effect on the heat shock response in a sir2. 1-dependent manner in Caenorhabditis elegans. Journal of Biological Chemistry. 2012; 34: 29045-29053.
105. Westerheide SD, Anckar J, Stevens Jr SM, Sistonen L, Morimoto RI. Stress-inducible regulation of heat shock factor 1 by the deacetylase SIRT1. Science. 2009; 5917: 1063-1066.
106. Wang H, Dong X, Liu Z, Zhu S, Liu H, Fan W, Hu Y, Hu T, Yu Y, Li Y, Liu T. Resveratrol suppresses rotenone-induced neurotoxicity through activation of SIRT1/Akt1 signaling pathway. The Anatomical Record. 2018; 6: 1115-1125.
107. Liu T, Ma X, Ouyang T, Chen H, Lin J, Liu J, Xiao Y, Yu J, Huang Y. SIRT1 reverses senescence via enhancing autophagy and attenuates oxidative stress-induced apoptosis through promoting p53 degradation. International journal of biological macromolecules. 2018; 117: 225-234.
108. Zhang W, Wu H, Yang M, Ye S, Li L, Zhang H, Hu J, Wang X, Xu J, Liang A. SIRT1 inhibition impairs non-homologous end joining DNA damage repair by increasing Ku70 acetylation in chronic myeloid leukemia cells. Oncotarget. 2016; 12: 13538.
109. Yu W, Li L, Wang G, Zhang W, Xu J, Liang A. KU70 inhibition impairs both non-homologous end joining and homologous recombination DNA damage repair through SHP-1 induced dephosphorylation of SIRT1 in adult T-cell leukemia-lymphoma cells. Cellular Physiology and Biochemistry. 2018; 6: 2111-2123.
110. Anekonda TS, Adamus G. Resveratrol prevents antibody-induced apoptotic death of retinal cells through upregulation of Sirt1 and Ku70. BMC Research Notes. 2008; 1: 1-8.
111. Ortiz GG, Moisés FP, Mireles-Ramírez M, Flores-Alvarado LJ, González-Usigli H, Sánchez-González VJ, Sánchez-López AL, Sánchez-Romero L, Díaz-Barba EI, Santoscoy-Gutiérrez JF, Rivero-Moragrega P. Oxidative stress: love and hate history in central nervous system. Advances in protein chemistry and structural biology. 2017; 108: 1-31.

112. Lv J, Jiang S, Yang Z, Hu W, Wang Z, Li T, Yang Y. PGC-1α sparks the fire of neuroprotection against neurodegenerative disorders. Ageing research reviews. 2018; 44: 8-21.
113. Uldry M, Yang W, St-Pierre J, Lin J, Seale P, Spiegelman BM. Complementary action of the PGC-1 coactivators in mitochondrial biogenesis and brown fat differentiation. Cell metabolism. 2006; 5: 333-341.
114. Lerin C, Rodgers JT, Kalume DE, Kim SH, Pandey A, Puigserver P. GCN5 acetyltransferase complex controls glucose metabolism through transcriptional repression of PGC-1α. Cell metabolism. 2006; 6: 429-438.
115. Gerhart-Hines Z, Rodgers JT, Bare O, Lerin C, Kim SH, Mostoslavsky R, Alt FW, Wu Z, Puigserver P. Metabolic control of muscle mitochondrial function and fatty acid oxidation through SIRT1/PGC-1α. The EMBO journal. 2007; 7: 1913-1923.
116. Kaur K, Gill JS, Bansal PK, Deshmukh R. Neuroinflammation-A major cause for striatal dopaminergic degeneration in Parkinson's disease. Journal of the neurological sciences. 2017; 381: 308-314.
117. Wang Q, Liu Y, Zhou J. Neuroinflammation in Parkinson's disease and its potential as therapeutic target. Translational neurodegeneration. 2015; 4: 1-9.
118. Holmes S, Singh M, Su C, Cunningham RL. Effects of oxidative stress and testosterone on pro-inflammatory signaling in a female rat dopaminergic neuronal cell line. Endocrinology. 2016; 7: 2824-2835.
119. Wee Yong V. Inflammation in neurological disorders: a help or a hindrance?. The Neuroscientist. 2010; 4: 408-420.
120. Leszek J, E Barreto G, Gasiorowski K, Koutsouraki E, Aliev G. Inflammatory mechanisms and oxidative stress as key factors responsible for progression of neurodegeneration: role of brain innate immune system. CNS & Neurological Disorders-Drug Targets (Formerly Current Drug Targets-CNS & Neurological Disorders). 2016; 3:329-336.
121. Ye J, Liu Z, Wei J, Lu L, Huang Y, Luo L, Xie H. Protective effect of SIRT1 on toxicity of microglial-derived factors induced by LPS to PC12 cells via the p53-caspase-3-dependent apoptotic pathway. Neuroscience letters. 2013; 553: 72-77.
122. Cho SH, Chen JA, Sayed F, Ward ME, Gao F, Nguyen TA, Krabbe G, Sohn PD, Lo I, Minami S, Devidze N. SIRT1 deficiency in microglia contributes to cognitive decline in aging and neurodegeneration via epigenetic regulation of IL-1β. Journal of Neuroscience. 2015; 2: 807-818.
123. Bi XL, Yang JY, Dong YX, Wang JM, Cui YH, Ikeshima T, Zhao YQ, Wu CF. Resveratrol inhibits nitric oxide and TNF-α production by lipopolysaccharide-activated microglia. International immunopharmacology. 2005; 1: 185-1893.
124. Wang Q, Xu J, Rottinghaus GE, Simonyi A, Lubahn D, Sun GY, Sun AY. Resveratrol protects against global cerebral ischemic injury in gerbils. Brain research. 2002; 2: 439-447.
125. Robb EL, Stuart JA. trans-Resveratrol as a neuroprotectant. Molecules. 2010; 3: 1196-1212.
126. Albani D, Polito L, Batelli S, De Mauro S, Fracasso C, Martelli G, Colombo L, Manzoni C, Salmona M, Caccia S, Negro A. The SIRT1 activator resveratrol protects SK-N-BE cells from oxidative stress and against toxicity caused by α-synuclein or amyloid-β (1-42) peptide. Journal of neurochemistry. 2009; 5: 1445-1456.
127. Lee MK, Kang SJ, Poncz M, Song KJ, Park KS. Resveratrol protects SH-SY5Y neuroblastoma cells from apoptosis induced by dopamine. Experimental & molecular medicine. 2007; 3: 376-384.
128. Alvira D, Yeste-Velasco M, Folch J, Verdaguer E, Canudas AM, Pallas M, Camins A. Comparative analysis of the effects of resveratrol in two apoptotic models: inhibition of complex I and potassium deprivation in cerebellar neurons. Neuroscience. 2007; 3: 746-756.
129. Bournival J, Quessy P, Martinoli MG. Protective effects of resveratrol and quercetin against MPP+-induced oxidative stress act by modulating markers of apoptotic death in dopaminergic neurons. Cellular and molecular neurobiology. 2009; 29: 1169-1180.
130. Lin TK, Chen SD, Chuang YC, Lin HY, Huang CR, Chuang JH, Wang PW, Huang ST, Tiao MM, Chen JB, Liou CW. Resveratrol partially prevents rotenone-induced neurotoxicity in dopaminergic SH-SY5Y cells through induction of heme oxygenase-1 dependent autophagy. International journal of molecular sciences. 2014; 1: 1625-1646.
131. Anandhan A, Tamilselvam K, Vijayraja D, Ashokkumar N, Rajasankar S, Manivasagam T. Resveratrol attenuates oxidative stress and improves behaviour in 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) challenged mice. Annals of neurosciences. 2010; 3: 113.

132. Blanchet J, Longpré F, Bureau G, Morissette M, DiPaolo T, Bronchti G, Martinoli MG. Resveratrol, a red wine polyphenol, protects dopaminergic neurons in MPTP-treated mice. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2008; 5: 1243-1250.
133. Lu KT, Ko MC, Chen BY, Huang JC, Hsieh CW, Lee MC, Chiou RY, Wung BS, Peng CH, Yang YL. Neuroprotective effects of resveratrol on MPTP-induced neuron loss mediated by free radical scavenging. Journal of agricultural and food chemistry. 2008; 16: 6910-6913.
134. Wang Y, Xu H, Fu Q, Ma R, Xiang J. Protective effect of resveratrol derived from Polygonum cuspidatum and its liposomal form on nigral cells in Parkinsonian rats. Journal of the neurological sciences. 2011; 1-2: 29-34.
135. Ferretta A, Gaballo A, Tanzarella P, Piccoli C, Capitanio N, Nico B, Annese T, Di Paola M, Dell'Aquila C, De Mari M, Ferranini E. Effect of resveratrol on mitochondrial function: implications in parkin-associated familiar Parkinson's disease. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease. 2014; 7: 902-915.
136. Smoliga JM, Vang O, Baur JA. Challenges of translating basic research into therapeutics: resveratrol as an example. Journals of Gerontology Series A: Biomedical Sciences and Medical Sciences. 2012; 2: 158-167.
137. Howitz KT, Bitterman KJ, Cohen HY, Lamming DW, Lavu S, Wood JG, Zipkin RE, Chung P, Kisielewski A, Zhang LL, Scherer B. Small molecule activators of sirtuins extend Saccharomyces cerevisiae lifespan. Nature. 2003; 6954: 191-196.
138. Milne JC, Lambert PD, Schenk S, Carney DP, Smith JJ, Gagne DJ, Jin L, Boss O, Perni RB, Vu CB, Bemis JE. Small molecule activators of SIRT1 as therapeutics for the treatment of type 2 diabetes. Nature. 2007; 7170: 712-716.
139. Kasiotis KM, Pratsinis H, Kletsas D, Haroutounian SA. Resveratrol and related stilbenes: their anti-aging and anti-angiogenic properties. Food and Chemical Toxicology. 2013; 61: 112-120.
140. Riviere C, Pawlus AD, Merillon JM. Natural stilbenoids: distribution in the plant kingdom and chemotaxonomic interest in Vitaceae. Natural product reports. 2012; 11: 1317-1333.
141. Temsamani H, Krisa S, Decossas-Mendoza M, Lambert O, Mérillon JM, Richard T. Piceatannol and other wine stilbenes: a pool of inhibitors against α-synuclein aggregation and cytotoxicity. Nutrients. 2016; 6: 367.
142. Nishida K, Matsushita T, Takayama K, Tanaka T, Miyaji N, Ibaraki K, Araki D, Kanzaki N, Matsumoto T, Kuroda R. Intraperitoneal injection of the SIRT1 activator SRT1720 attenuates the progression of experimental osteoarthritis in mice. Bone & Joint Research. 2018; 3: 252-262.
143. Opal SM, Ellis JL, Suri V, Freudenberg JM, Vlasuk GP, Li Y, Chahin AB, Palardy JE, Parejo N, Yamamoto M, Chahin A. Pharmacological SIRT1 activation improves mortality and markedly alters transcriptional profiles that accompany experimental sepsis. Shock. 2016; 4: 411-418.
144. Mitchell SJ, Martin-Montalvo A, Mercken EM, Palacios HH, Ward TM, Abulwerdi G, Minor RK, Vlasuk GP, Ellis JL, Sinclair DA, Dawson J. The SIRT1 activator SRT1720 extends lifespan and improves health of mice fed a standard diet. Cell reports. 2014; 5: 836-843.
145. Miranda MX, Van Tits LJ, Lohmann C, Arsiwala T, Winnik S, Tailleux A, Stein S, Gomes AP, Suri V, Ellis JL, Lutz TA. The Sirt1 activator SRT3025 provides atheroprotection in Apoe−/− mice by reducing hepatic Pcsk9 secretion and enhancing Ldlr expression. European heart journal. 2015; 1: 51-59.
146. Gräff J, Kahn M, Samiei A, Gao J, Ota KT, Rei D, Tsai LH. A dietary regimen of caloric restriction or pharmacological activation of SIRT1 to delay the onset of neurodegeneration. Journal of Neuroscience. 2013; 21:8951-8960.
147. Liu P, Feng T, Zuo X, Wang X, Luo J, Li N, Han X, Zhu N, Xu S, Xu Y, Jin ZG. A novel SIRT1 activator E6155 improves insulin sensitivity in type 2 diabetic KKAy mice. Biochemical and biophysical research communications. 2018; 3: 633-639.
148. Zhang LX, Li CX, Kakar MU, Khan MS, Wu PF, Amir RM, Dai DF, Naveed M, Li QY, Saeed M, Shen JQ. Resveratrol (RV): A pharmacological review and call for further research. Biomedicine & pharmacotherapy. 2021; 143: 112164.
149. Hubbard BP, Gomes AP, Dai H, Li J, Case AW, Considine T, Riera TV, Lee JE, E SY, Lamming DW, Pentelute BL. Evidence for a common mechanism of SIRT1 regulation by allosteric activators. Science. 2013; 6124: 1216-1219.
150. Pacholec M, Bleasdale JE, Chrunyk B, Cunningham D, Flynn D, Garofalo RS, Griffith D, Griffor M, Loulakis P, Pabst B, Qiu X. SRT1720, SRT2183, SRT1460, and Resveratrol Are Not Direct Activators of

SIRT1♦. Journal of Biological Chemistry. 2010; 11: 8340-8351.
151. Santos D, Mahoney JR, Allali G, Verghese J. Physical activity in older adults with mild parkinsonian signs: a cohort study. The Journals of Gerontology: Series A. 2018; 12:1682-7.
152. Hou L, Chen W, Liu X, Qiao D, Zhou FM. Exercise-induced neuroprotection of the nigrostriatal dopamine system in Parkinson's disease. Frontiers in aging neuroscience. 2017; 9: 358.
153. Tuon T, Souza PS, Santos MF, Pereira FT, Pedroso GS, Luciano TF, De Souza CT, Dutra RC, Silveira PC, Pinho RA. Physical training regulates mitochondrial parameters and neuroinflammatory mechanisms in an experimental model of Parkinson's disease. Oxidative medicine and cellular longevity. 2015; 1: 261809.
154. Xu H, Liu YY, Li LS, Liu YS. Sirtuins at the crossroads between mitochondrial quality control and neurodegenerative diseases: structure, regulation, modifications, and modulators. Aging and Disease. 2023;13: 794.