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LETTERS

Small-molecules against Oxidative stress mediated Neurodegenerative diseases

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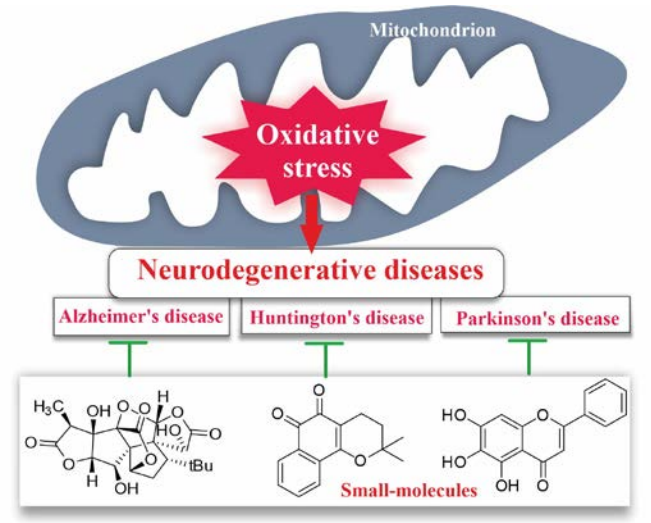
Review

ABSTRACT

Neurodegenerative diseases, marked by the gradual deterioration of neuronal structure and function, impose a significant burden on global healthcare systems. Oxidative stress, resulting from an imbalance between reactive oxidant production and cellular antioxidant defense, is believed to play a significant role in the development of various neurodegenerative disorders, including Alzheimer's disease, Parkinson's disease, and Huntington's disease. Recently, there has been a growing interest in exploring small compounds as potential therapeutic agents to counteract oxidative stress. In addition to highlighting the potential of small molecules to prevent oxidative stress-mediated neuronal damage, this article provides an overview of the function of oxidative stress in neurodegenerative illnesses. Targeting numerous oxidative stress-related pathways, a number of small molecules, including both natural and synthetic antioxidants, have shown promise for neuroprotective benefits. These substances neutralise reactive oxidants, boost endogenous antioxidant defences, reduce inflammation, alter mitochondrial function, and encourage neurotrophic growth.



Keywords: Small molecules, Oxidative stress, Alzheimer's disease, Parkinson's disease, Huntington's disease

INTRODUCTION

Neurodegenerative diseases comprise a collection of chronic and progressive conditions that have detrimental effects on both the central and peripheral nervous systems.[1-13] These disorders include Alzheimer's (AD), Parkinson's (PD), Huntington's (HD), and others.[13-15] In neurodegenerative diseases, certain neuronal populations deteriorate, and abnormal protein aggregates accumulate in the brain and/or spinal cord. These disorders have a significant impact on individuals, with millions of people worldwide affected by them. Neurodegenerative diseases rank among the leading causes of disability and mortality, resulting in substantial burdens on healthcare systems and society as a whole.[6]

Neurodegenerative disorders share a common characteristic, namely oxidative stress, which refers to an imbalance between the production of reactive oxidants and nitrogen species and the body's antioxidant defense mechanisms.[8-10] Oxidative stress can harm a number of cellular components, including lipids, proteins, DNA, and mitochondria, impairing cellular function and ultimately causing cellular death. The expression and activity of genes, enzymes, receptors, and signalling pathways implicated in the pathogenesis of Neurodegenerative disorders can also be altered by oxidative stress. Additionally, oxidative stress can worsen the neurodegenerative process by interacting with other elements like inflammation, excitotoxicity, metal dyshomeostasis, and dysfunctional autophagy. As a result, reducing oxidative stress is an effective way to prevent and manage Neurodegenerative disorders. However, the development of efficient antioxidant therapies has been difficult because of a number of factors, including the complexity of oxidative stress mechanisms, the heterogeneity of Neurodegenerative disorders aetiology and progression, the challenge of delivering antioxidants across the blood-brain barrier, and the potential negative side effects of antioxidants on physiological redox signalling.

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Current research on small molecules against oxidative stress-mediated neurodegenerative diseases is limited by insufficient clinical evidence, complex disease mechanisms, challenges in blood–brain barrier (BBB) penetration, a lack of specificity, and potential toxicity. Further efforts are needed to develop safe and effective treatments that address the multifactorial nature of these diseases and demonstrate disease-modifying effects in clinical settings.

Apart from emphasizing the potential of small molecules as therapeutic interventions, the article aims to present an overview of how oxidative stress plays a role in the development of neurodegenerative disorders. This article gives information on different small compounds that have demonstrated potential neuroprotective benefits by increasing natural antioxidant defences, scavenging reactive oxidants, and altering inflammation and mitochondrial function. For the development of efficient therapeutics for neurodegenerative illnesses, understanding the processes underlying oxidative stress-mediated neurodegeneration and investigating the therapeutic potential of small molecules in reversing this process offer enormous promise. This article can open the door for novel treatment approaches that could lessen the burden of neurodegenerative illnesses and enhance the lives of those who are affected by them by clarifying the role of small molecules in attenuating oxidative stress.

Role Oxidative stress in neurodegenerative diseases

Oxidative stress is closely linked to the development of several diseases, particularly neurodegenerative diseases. Free radicals, possessing unpaired electrons, tend to accept electrons from other molecules, leading to oxidation. An imbalance in oxidation-reduction processes results in an excess of Reactive Oxygen and Nitrogen Species (RONS), causing oxidative stress at different intensities. In response to the detrimental impact of RONS, a range of antioxidant defense mechanisms are present to counteract their effects. Enzymatic antioxidants like catalase (CAT), superoxide dismutase (SOD), glutathione reductase (GR), and glutathione peroxidase (GPx) convert reactive species into harmless substances. Non-enzymatic antioxidants such as thioredoxin (Trx), glutathione (GSH), vitamins A, E, and C, selenium, retinoic acid, carotenoids, and flavonoids also play vital roles in neutralizing oxidative damage. Due to its high oxygen consumption and elevated content of polyunsaturated lipids, the brain is highly vulnerable to oxidative damage. RONS can target polyunsaturated fatty acids in neuronal membranes, resulting in lipid peroxidation and the creation of stable products

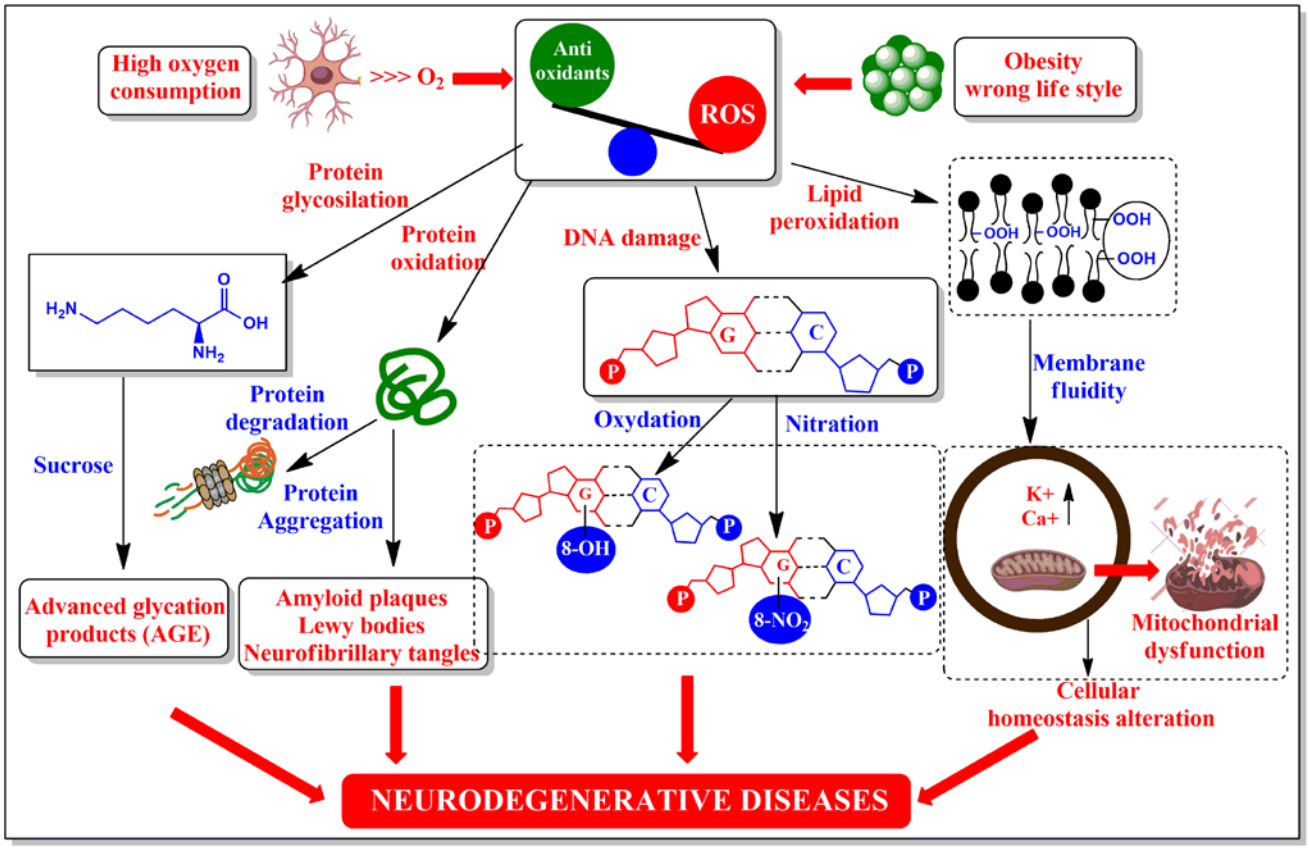


Figure 1. At the cellular level, the brain's intensive oxygen consumption stimulates the generation of reactive oxygen species (ROS). These highly reactive molecules cause an elevation in oxidative stress, which in turn promotes several processes: (i) glycosylation and oxidation of proteins, leading to the formation of advanced glycation products (AGE) or loss of protein function; (ii) DNA damage through oxidation or nitration of guanine bases; (iii) lipid peroxidation, which reduces membrane fluidity and increases cell permeability, ultimately affecting cellular homeostasis. These interconnected factors can collectively contribute to the development of neurodegenerative diseases.[1]

such as malondialdehyde (MDA) and 4-hydroxy-2-nonenal (HNE). This affects membrane fluidity, increases permeability, and disrupts cellular processes. Carbohydrates can also be influenced by RONS, leading to the formation of advanced glycation products (AGE) implicated in neurodegenerative disorders. Additionally, RONS can alter DNA and RNA bases, particularly guanine, in diseases like PD and AD. Neurodegenerative disorders share common characteristics, such as aggregated protein accumulation and mitochondrial dysfunction, indicating an oxidative stress status. Neurodegeneration is significantly influenced by reactive species, including hydrogen peroxide (H_2O_2), superoxide anion (O_2^-), and the highly reactive hydroxyl radical ($HO^\cdot$), which have a profound impact on protein structure and function. Nitric Oxide (NO) also plays a crucial role in neurological disorders, exhibiting both neuroprotective and neurotoxic effects. Its concentration determines its physiological activity. NO at controlled levels may have a protective effect, but excessive NO production can lead to neuroinflammation and neuronal degeneration. Lifestyle factors like obesity, sedentary habits, and an unbalanced diet contribute to the RONS generation, increasing the risk of developing neurodegenerative disorders. [30,] A well-balanced diet abundant in natural antioxidants plays a crucial role in providing essential protection against neurodegenerative diseases by addressing the central role of oxidative stress[32,33] Figure 1 depicts the oxidative stress theory and its cellular ramifications, which ultimately contribute to the onset of neurodegenerative diseases.[1]

ALZHEIMER's DISEASE

The field of neuroscience is deeply interested in the role of oxidative stress in Alzheimer's disease (AD).[34,35] When the equilibrium between reactive oxidant production and removal is disrupted, oxidative stress arises, leading to cell damage.[11]

In AD, the majority of neurons' components, such as lipids, proteins, and nucleic acids, can undergo oxidation due to factors like mitochondrial dysfunction, increased metal levels, inflammation, and β-amyloid (Aβ) peptides. The brain is particularly susceptible to oxidative stress compared to other organs. Oxidative stress is implicated in AD's development by promoting Aβ deposition, tau hyperphosphorylation, and the subsequent loss of synapses and neurons.[36,] Given the connection between oxidative stress and AD, antioxidants have been considered for potential therapeutic use. Oxidative stress is considered a critical element of the pathogenic process in AD, [39,40] and several studies have identified direct physical connections between many proteins associated with AD pathogenesis and mitochondria or mitochondrial proteins (Figure 2).[34,41]

Small molecules are substances that have the ability to interact with a wide range of biological targets, including proteins, enzymes, receptors, and genes. By modifying the activity or functionality of certain targets, they can have therapeutic effects. Small compounds can be used to treat various disease pathologies in AD, including amyloid-beta (Aβ) aggregation, tau phosphorylation, oxidative stress, inflammation,

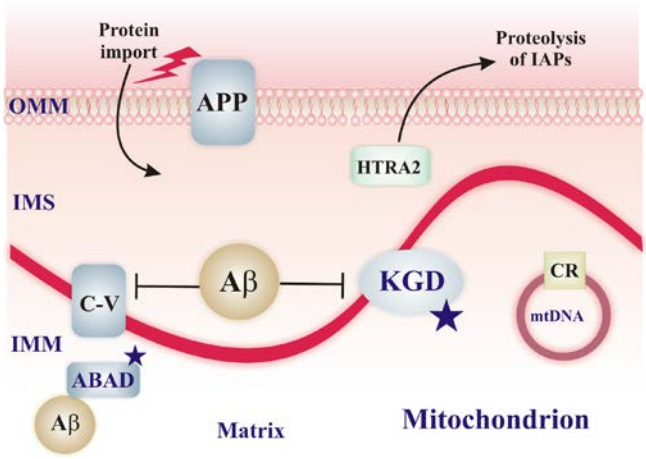
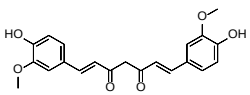
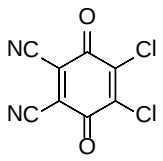
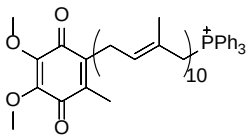
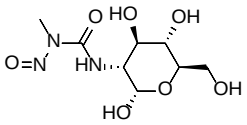
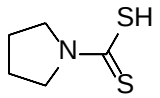
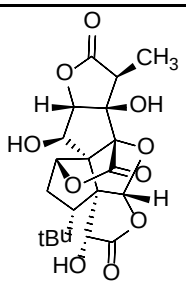
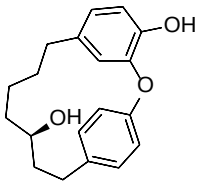
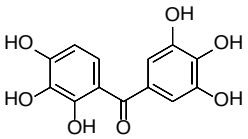
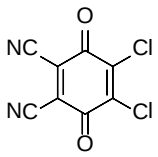


Figure 2. Role of mitochondria in Alzheimer's disease. In AD, mitochondrial dysfunction leads to the increased production of reactive oxidants, resulting in elevated levels of Aβ in cells and transgenic mice. Aβ interacts with mitochondria, causing dysfunction. The Aβ-binding alcohol dehydrogenase (ABAD) and complex IV and α-ketoglutarate dehydrogenase (KGD) are inhibited by Aβ, leading to the generation of reactive oxidants (indicated by blue stars). Additionally, amyloid precursor protein (APP) has been proposed to target the outer mitochondrial membrane (OMM) and act as a protein import inhibitor. It has been suggested that mitochondria contain active γ-secretase complexes responsible for cleaving APP to generate Aβ, and presenilin 1 enhances HTRA2's proteolytic activity towards IAPs. AD patients typically exhibit more somatic mutations in the mtDNA control region compared to controls.

and mitochondrial dysfunction. [42,43] Table 1 shows a summary of small molecules and their mechanisms of action for the treatment of AD.

Table: 1 Small molecules in Alzheimer's disease

Compounds	Mode of action in Alzheimer's disease
 **Curcumin**	In humans, curcumin inhibits amyloid-β aggregation (IC_{50} = 0.8 µM), penetrates the blood-brain barrier (BBB), and shields neurons from numerous toxic insults caused by ageing and amyloid-β. In mouse models of AD, curcumin also lessens cognitive decline and enhances synaptic functioning. [44,45]
 **DDQ**	At a concentration of 250 nM, DDQ effectively curtails excessive mitochondrial fragmentation, promotes mitochondrial fusion and biogenesis, boosts synaptic activity, reduces the levels of Aβ42, and shields neurons affected by AAD from Aβ-induced damage to both mitochondria and synapses.[46]

 **MitoQ**	The accumulation of excess mitoQ within mitochondria leads to the conversion of H_2O_2 into H_2O and O_2, thereby reducing the harmful effects of free radical damage. This protective effect on neurons, which safeguards them against mitochondrial damage associated with aging and/or disease, is achieved at a dosage of 1μM. Ultimately, this reduction in mitochondrial damage contributes to the mitigation of AD.
 **Streptozotocin**	The administration of 3 mg/kg of Streptozotocin (STZ) directly into the brain's ventricles (ICV) suppresses the Akt/PKB signaling molecule, the insulin receptor (IR) signaling molecule and induces insulin resistance. These alterations caused by STZ can be utilized to study the fundamental molecular and pathophysiological mechanisms involved in sporadic AD. Furthermore, they provide a platform for investigating therapeutic interventions aimed at developing drugs that target AD pathology.
 **Pyrrolidine dithiocarbamate**	In astrocytes specifically, the strong induction of Nrf2 signaling by pyrrolidine dithiocarbamate (PDTC) is observed, highlighting the crucial role of Nrf2 in the defense against oxidative stress mediated by PDTC. The control of this induction appears to be regulated by Keap1 and glycogen synthase kinase 3. Furthermore, the presence of Aβ amplifies the induction of endogenous protective mechanisms by PDTC, suggesting that PDTC may possess significant Nrf2-inducing capabilities in the context of Alzheimer's disease. Finally, it is demonstrated that the administration of PDTC at a dose of 20 mg/kg leads to the enhancement of brain copper levels, the expression of glial heme oxygenase-1, and the reduction of lipid peroxidation *in vivo*, thereby creating an environment that is more favorable for antioxidants.
 **Ginkgolide B**	Ginkgolide B (GB) was found to enhance cognitive function in SAMP8 mice through the Morris water maze and novel object recognition test. This improvement was associated with a decrease in oxidative stress, inflammation, and ferroptosis, which were regulated by the nuclear factor erythroid 2-related factor 2/glutathione peroxidase 4 (GPX4) pathways. Additionally, when the GPX4 inhibitor and ferroptosis inducer Ras-selective Lethal Small Molecule 3 were administered, they hindered the cognitive benefits induced by GB in SAMP8 mice. These findings suggest that GB alleviates cognitive impairments in AD by reducing oxidative stress, neuroinflammation, and ferroptosis.
 **Acerogenin A**	The activation of the PI3K/Akt and Nrf2 pathways is essential for acerogenin A to exert its neuroprotective effect against glutamate-induced oxidative damage. Acerogenin A, administered at a dose of 30 μM, induces the production of HO-1 through these pathways, which plays a crucial role in defending HT22 cells. The findings of this study provide evidence supporting the ability of acerogenin A to activate Nrf2-mediated HO-1 expression, underscoring its potential as a neuroprotective agent.
 **Exifone**	Exifone, with an EC_{50} value of 0.163 μM, enhances the relative maximal rate of deacetylation catalyzed by HDAC1. It acts as a mixed activator of HDAC1, and its binding occurs with both the free enzyme and the enzyme bound to the substrate. Through biolayer interferometry experiments that involve kinetic and selectivity profiling, it has been shown that Exifone directly interacts with HDAC1. Notably, HDAC1 is preferentially targeted by Exifone compared to other class I HDACs and the kinase CDK5, which are also implicated in AD.
 **DDQ**	At a concentration of 250 nM, DDQ effectively curtails excessive mitochondrial fragmentation, promotes mitochondrial fusion and biogenesis, boosts synaptic activity, reduces the levels of Aβ42, and shields neurons affected by AAD from Aβ-induced damage to both mitochondria and synapses.

PARKINSON's DISEASE

Parkinson's disease (PD) is characterized by the loss of pigmented neurons in the substantia nigra and the presence of Lewy bodies, unique cytoplasmic inclusions that contain α-synuclein and ubiquitin. [53] Clinical manifestations of PD include increasing stiffness, bradykinesia, and tremor. Mitochondria were first linked to PD when abusers of the drug MPTP

developed Parkinsonism due to its metabolite MPP+ blocking complex I of the mitochondrial electron-transport chain. [55-57] This model has been replicated in lab animals using rotenone or MPTP, both complex I inhibitors, which result in nigral degeneration and the appearance of cytoplasmic inclusions with α-synuclein and ubiquitin immunoreactivity, leading to a Parkinsonian phenotype. [58,] The toxicity mechanism in these complex I inhibition models is likely related to oxidative stress. Further evidence of complex I insufficiency and glutathione depletion was found in the substantia nigra of patients with idiopathic PD and those with pre-symptomatic PD, demonstrating the relevance of complex I inhibition and oxidative stress in naturally occurring PD. [60-62] Figure 3 illustrates the role of mitochondria in PD.

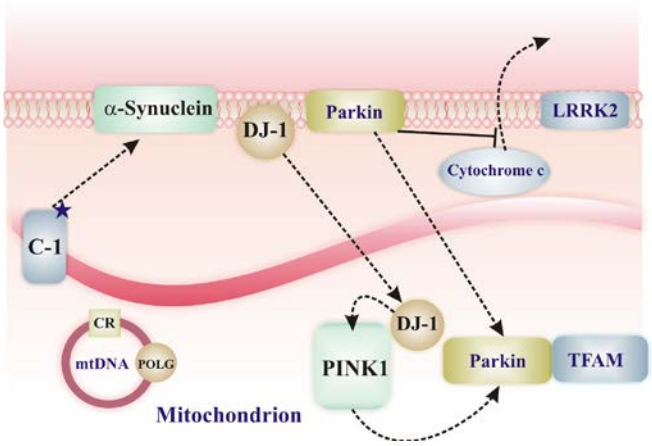
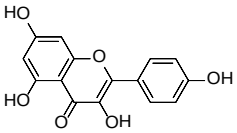
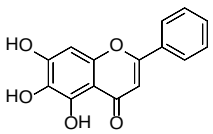
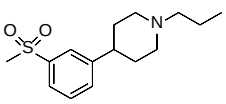
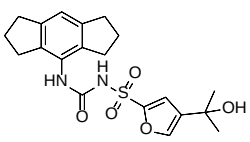
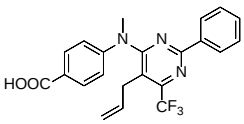
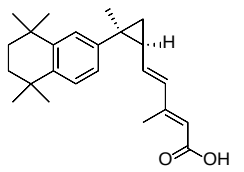
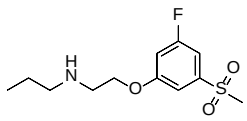
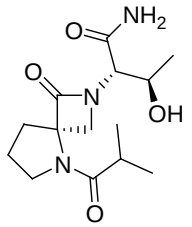
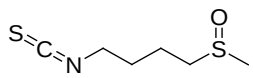
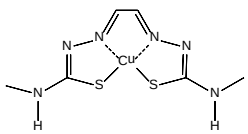


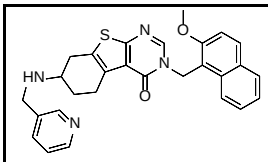
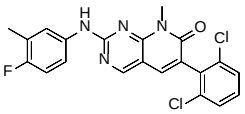
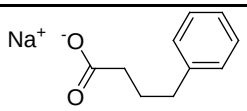
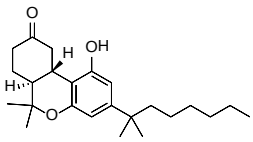
FIGURE 3. Role of mitochondria in Parkinson's disease. In Parkinson's disease (PD), the activity of complex I is decreased, and Parkinsonism can be induced by suppressing complex I using MPTP or rotenone. Mutations in complex I subunits encoded by mtDNA, 12SrRNA, and POLG can also lead to Parkinsonism. Additionally, numerous PD-related genes have been linked to mitochondria in the disease's pathophysiology. In mice overexpressing A53T α-synuclein, degenerating mitochondria show α-synuclein immunostaining. Overexpression of α-synuclein reduces mitochondrial efficiency and increases the toxicity of MPTP. Parkin interacts with the outer mitochondrial membrane (OMM) and inhibits the release of cytochrome c. It may also interact with TFAM to promote mitochondrial biogenesis. DJ-1 translocates to mitochondria (IMS and matrix) to protect the cell from oxidative stress-induced cell death. It downregulates the PTEN tumor suppressor and also translocates to mitochondria. PD-related mutations or kinase inactivation diminish the protective effect of the mitochondrial kinase PINK1 in apoptosis. Physical connections have been observed between DJ-1 and α-synuclein, DJ-1 and parkin, and DJ-1 and PINK1, with genetic data supporting their sequential function in the same pathway. Around 10% of LRRK2's total mass is localized to mitochondria, and PD-related mutations increase its kinase activity. Approximately 1% of individuals with sporadic Parkinson's disease have a mutation in the HTRA2 gene. Overexpression of the mutant reduces the normal HTRA2 protease activity, and HTRA2 deficiency leads to striatal degeneration and Parkinsonism.

Small molecules are substances that have a low molecular weight and can pass across the blood-brain barrier to get to the brain's cells. For PD, they have been investigated as potential treatments. It has been demonstrated that some tiny compounds can control how alpha-synuclein aggregates and lessen its toxicity. Activating the Smad1, 3, and 5 signalling pathway has been reported to improve the survival and neurite outgrowth of dopaminergic neurons. These compounds may have a dual role in PD, fostering both neuroprotection and bone growth. Different small molecules are shown in Table 2 along with how they work to treat PD.

Table: 2 Small molecules in Parkinson's disease

Compound	Mode of action in Parkinson's disease
 **Kaempferol**	Treatment with kaempferol demonstrated a reduction in behavioural impairments and lipid droplet (LD) toxicity in an animal model of PD. These effects were found to be dependent on autophagy. Kaempferol also reduced the loss of dopaminergic (DA) neurons. At a dose of 50 mg/kg, kaempferol stimulated autophagy, leading to a decrease in the accumulation of oxidized LDs, production of mitochondrial reactive oxygen species (mtROS), and mitochondrial damage in DA neurons. This reduction in mtROS production and alleviation of mitochondrial damage contribute to mitigating LD toxicity and the associated pathology of PD.
 **Baicalein**	Baicalein, administered at a dose of 100 mg/kg, inhibits the accumulation of α-synuclein (α-syn) in a mouse model of PD. This effect is attributed, at least in part, to its ability to prevent the formation of α-syn oligomers.
 **Pridopidine**	By encouraging functional neurorestoration in the injured nigrostriatal system and working through the sigma-1 receptor, pridopidine at a dose of 0.3 mg/kg prevents PD.
 **MCC950**	At an IC_{50} value of 7.7 nM, MCC950 provides protection to the brains of mice with PD by preventing the accumulation of hyperphosphorylated α-synuclein aggregates. Additionally, it safeguards against nigrostriatal dopaminergic degeneration and alleviates motor impairments in these mice.

 **BRF110**	In preclinical models of PD, the oral administration of the synthetic small chemical BRF110 at a daily dose of 10 mg/kg has shown a specific ability to activate the NURR1-RXR heterodimer. This activation offers protection to dopaminergic neurons from α-synuclein and leads to the restoration of dopamine production.
 **IRX4204**	IRX4204, a synthetic RXR ligand, can cross the blood-brain barrier and specifically activate the NURR1-RXR heterodimer. Oral administration of IRX4204 at a dose of 10 mg/kg per day successfully alleviates motor symptoms in PD and reverses the decline of dopaminergic neurons. Furthermore, IRX4204 promotes the expression of molecules that play a role in dopamine production.
 **IRL790**	In preclinical studies, the oral administration of IRL790, with an approximate ED_{50} value of 4 mg/kg, demonstrated the ability to alleviate dyskinesia and psychosis without negatively impacting normal dopamine transmission and motor function. As a result, IRL790 therapy holds promise for enhancing the quality of life for PD patients experiencing dyskinesia and psychosis.
 **NYX-458**	After administering NYX-458 at a dose of 0.5 mg/kg, significant and long-lasting improvements in attention, working memory, and executive function were observed. Notably, levodopa's effectiveness in alleviating antiparkinsonian effects, dyskinesia, and motor symptoms of PD remained unaffected by the dose levels that were found to be beneficial in enhancing cognitive function.[72,]
 **Sulforaphane**	At a dosage of 5 mg/kg, sulforaphane effectively prevents PD induced by MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine). This prevention is achieved by inhibiting the overexpression of Nrf2 or by knocking down of Keap1 using siRNA.[74]
 **Cu (II) ATSM**	After oral administration of copper (II) ATSM at a dose of 30 mg/kg, a set of genes associated with brain and cognitive development, neuroplasticity, regulation, and cellular response exhibited a reemergence of their expression in mice with PD.

 **ICL-SIRT078**	In a lactacystin-induced model of Parkinson's neuronal cell death using the N27 cell line, ICL-SIRT078 exhibited a potent neuroprotective effect with an IC_{50} value of 3.96 ± 0.87 µM. This neuroprotection was achieved by inhibiting SIRT2.
 **PD180970**	At a concentration of 10 µM, PD180970 induces autophagy in cell lines from the midbrain of mice, mitigating the toxicity caused by α-synuclein. Importantly, this autophagy promotion occurs in a manner independent of mTOR (the mammalian target of rapamycin). Additionally, PD180970 demonstrates anti-neuroinflammatory properties by reducing TLR-4 (Toll-like receptor 4)-mediated NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) activation. This leads to the inhibition of the release of proinflammatory cytokines such as IL-6 (interleukin-6) and MCP-1 (monocyte chemoattractant protein-1).
 **Sodium phenylbutyrate**	Sodium phenylbutyrate (NaPB) at a dosage of 200 mg/kg body weight per day hinders the activation of p21ras and the activity of p21rac, which leads to the suppression of glial activation of NF-κB and a decrease in the generation of reactive oxidants.
 **Nabilone**	Two clinical studies were carried out to assess the effectiveness and safety of nabilone, a synthetic analogue of tetrahydrocannabinol, in managing non-motor symptoms in patients with PD. The results of these trials indicate that nabilone, administered at a dosage of 0.75 mg, has beneficial effects on sleep outcomes in PD patients who experienced sleep problems at the beginning of the trials. [63,]

HUNTINGTON'S DISEASE

Another neurodegenerative condition that affects movement, cognition, and behaviour, Huntington's disease (HD), also has oxidative stress as a contributing factor. [32,80] An aberrant protein known as mutant huntingtin (mHTT) is produced as a result of a genetic mutation in the huntingtin (HTT) gene, which causes HD. [80,81] mHTT can gather into aggregates that disrupt several cellular functions and result in the malfunction and demise of neurons. [80] The mitochondria, which are organelles that provide energy for cells, are one of the main targets of mHTT . Reduced energy production, increased reactive oxidant generation, and altered calcium homeostasis are all consequences of mHTT's ability to affect mitochondrial structure, function, and dynamics. Other cellular mechanisms involved in HD pathogenesis, such as

autophagy, apoptosis, inflammation, and transcriptional regulation, can also be impacted by mitochondrial malfunction and oxidative stress, according to studies.[80,] For instance, oxidative stress can prevent autophagy, a process that breaks down damaged proteins and organelles and causes more mHTT and reactive oxidants to accumulate. [82] Additionally, oxidative stress can activate transcriptional mechanisms that change gene expression, inflammatory pathways that cause neuroinflammation, and apoptotic pathways that cause cell death. As a result, oxidative stress is a significant cause of HD's clinical symptoms and neuronal damage, as well as a possible target for therapeutic intervention. Clinical trials using antioxidant medications have, however, thus far only demonstrated little efficacy, similar to AD, probably because of difficulties with administration, bioavailability, specificity, and timing. To effectively modify the disease process, new antioxidant techniques that are more effective at reducing oxidative stress and redox signalling in HD must be developed. Fig-4 represents the role of the mitochondrion in HDs.

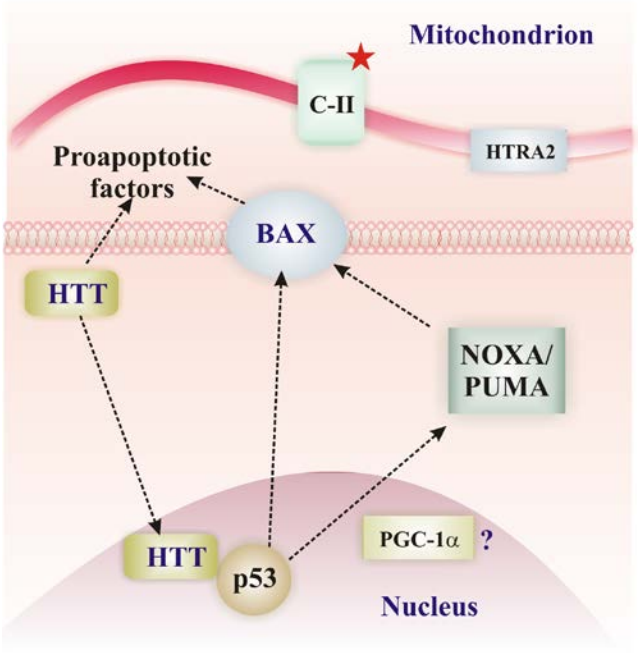
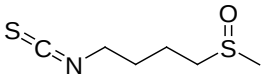
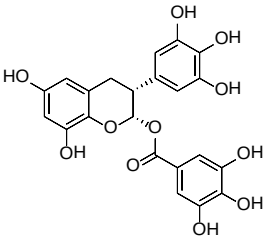
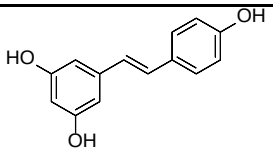
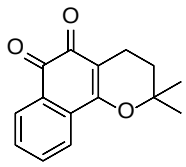
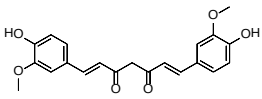
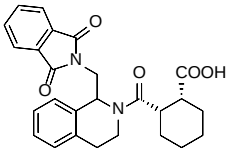
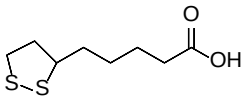
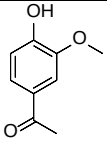
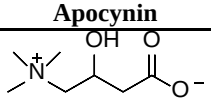
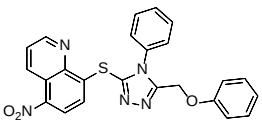
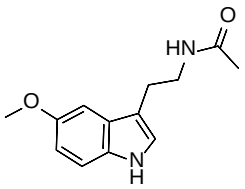
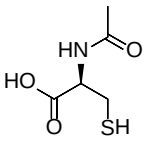
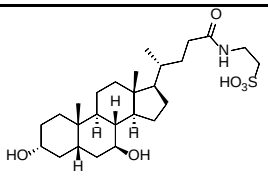
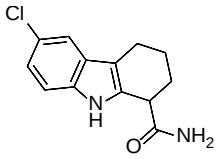


FIGURE 4. Role of mitochondria in Huntington's disease. The compound 3-nitropropionic acid, which inhibits complex II, leads to striatal degeneration and mobility impairments in both rats and primates. In individuals with Huntington's disease (HD), there is a notable decline in complex II activity in the brain. However, in striatal neurons expressing mutant HTT, augmenting the expression of complex II subunits mitigates cell death. Mutant HTT also interacts with the outer mitochondrial membrane (OMM) to enhance sensitivity to calcium-induced cytochrome c release. Moreover, in the nucleus, mutant HTT translocates and binds to p53, increasing its concentration and transcriptional activity. p53 activates the pro-apoptotic protein BAX either by upregulating the expression of BH3-only Bcl-2 family members PUMA and NOXA or by directly activating BAX. Striatal atrophy and involuntary movements are observed in mice with Pgc-1α knockout or missense mutations in Htra2.

Small molecules are compounds capable of modifying the behavior of proteins or other molecules within living cells. They have potential applications as therapeutic agents for various diseases, including HD, a neurodegenerative disorder caused by an abnormal expansion of CAG repeats in the huntingtin gene (HTT). Small compounds that target the CAG repeat RNA can stop it from interacting with other proteins or generating harmful structures. For instance, it was found that the powerful small chemical naphthyridine-azaquinolone inhibited HD pathogenesis by interacting with the AA mismatch in the RNA of the CAG repeats and lowering the expression of the mutant HTT protein. As a result, small molecules are crucial in HD because they control various symptoms of the condition, including protein aggregation, DNA damage, and RNA toxicity. They present a promising route for creating brand-new treatments for HD and other associated conditions. A few small compounds and their mechanisms of action have been discussed in this section (Table 3).

Table: 3 Small molecules in Huntington's disease

Compound	Mode of action in Huntington's disease
 **Sulforaphane**	At a dose of 5 mg/kg, sulforaphane protects against HD by increasing the levels of glutathione, glutathione reductase, and glutathione peroxidase while reducing oxidized proteins, mitochondrial dysfunction, striatal degeneration, and circling behavior induced by 2,3-Pyridine-dicarboxylic acid (quinolinic acid) that causes HD.
 **(-)-Eepigallocatechin-3-gallate**	(-)-Epigallocatechin-3-gallate (EGCG), a polyphenol found in green tea, effectively and dose-dependently inhibits the aggregation of mutant htt exon 1 protein with an IC_{50} of approximately 2 µM. In vitro experiments using dot-blot assays and atomic force microscopy show that EGCG modifies the misfolding and oligomerization of mutant htt exon 1 protein, indicating its impact on the initial stages of the aggregation process. Furthermore, in a yeast model of HD, EGCG significantly reduces polyQ-mediated htt protein aggregation and cytotoxicity, demonstrating its potential therapeutic effect.
 **Resveratrol**	In the presence of resveratrol, a dietary polyphenol with antioxidant and pro-autophagic properties, HD exhibits neuroprotective effects. At a concentration of 100 µM, resveratrol effectively inhibits the production of reactive oxygen species (ROS), increases the level of ATG4 (an

	autophagy-related protein), allows LC3 (a protein involved in autophagy) to undergo lipidation, accelerates the degradation of polyQ-Htt aggregates, and protects cells from the detrimental effects of dopamine.
 **β-lapachone**	HD is defined by the buildup of an enlarged form of the Huntingtin (Htt) protein due to polyglutamine (polyQ) expansion. In human neuroblastoma SH-SY5Y cells, β-lapachone at a concentration of 30 nM reduces the intracellular levels of polyQ aggregates and their associated cytotoxicity by activating Sirt1.
 **Curcumin**	To treat or prevent HD, curcumin at a concentration of 20 µM acts on various processes. These include exhibiting antioxidant and anti-inflammatory properties, chelating metal ions, inducing transcriptional changes, and upregulating the activity of molecular chaperones and heat shock proteins (HSPs).
 **(SRS)-5**	SRS-5 demonstrated comparable effects in inducing the expression of genes regulated by NRF2 in neurons and astrocytes from wild-type rat, wild-type mouse, and zQ175 (an HD mouse model) embryos. Notably, SRS-5 exhibited a distinct and clean profile, indicating minimal off-target effects. Additionally, SRS-5 effectively shielded cells from oxidative damage by preserving the ATP content and mitochondrial potential of primary astrocytes. These findings support the hypothesis that SRS-5's ability to enhance the innate antioxidant response can limit neurotoxicity induced by oxidative stress.[90]
 **Lipoic acid**	α-lipoic acid, when given at a dosage of 100 mg/kg/day, provides substantial protection against HD by significantly enhancing survival rates in both R6/2 and N171-82Q transgenic mouse models of the disease.[92]
 **Apocynin**	Apocynin, functioning as a NADPH oxidase inhibitor, effectively safeguards against HD when administered at a dose of 5 mg/kg i.p. by converting molecular oxygen into a superoxide radical.
 **L-carnitine**	L-carnitine treatment at a dosage of 250 mg/kg bodyweight significantly reduced the loss of neurons and the number of intranuclear aggregates in neurons. This therapy proves effective in preventing HD by reducing oxidative damage within HD.
 **MIND4**	MIND4, administered at a dosage of 60 mg/kg, protects against HD in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) mouse model by preserving NRF2 activation and decreasing oxidative damage.
 **Melatonin**	In the kainic acid animal model of neurodegeneration, melatonin has shown neuroprotective effects at a dose of 1 mg/kg body weight administered intraperitoneally per day. It reduces DNA damage and enhances neuronal survival. Similarly, in the 3-nitropropionic acid model of HD, melatonin treatment significantly reduces the increase in lipid peroxidation, protein carbonyls, and superoxide dismutase (SOD) activity in the striatum.
 **N-acetylcysteine (NAC)**	The administration of N-acetylcysteine (NAC) at a dosage of 100 mg/kg intraperitoneally to rats before exposure to 3-nitropropionic acid (3-NP) provided protection against oxidative damage, as evidenced by Electron Paramagnetic Resonance (EPR) and protein carbonyl analyses on a Western blot. Moreover, NAC treatment before 3-NP exposure significantly reduced the extent of striatal lesions.
 **Tauroursodeoxycholic acid**	Tauroursodeoxycholic acid (TUDCA) is a hydrophilic bile acid rich in antioxidants. In a 3-NP rat model of HD, TUDCA at a concentration of 50 mM effectively decreased striatal degeneration and improved locomotor and cognitive deficits.
 **Selisistat**	Selisistat, a small molecule inhibitor of sirtuin 1 deacetylase (SirT1), has shown promising results in treating Huntington's disease (HD) in both cellular models at a concentration of 10 µM and preclinical models at a dosage of 5 mg/kg. By preventing the toxicity of mHTT (mutant huntingtin protein), Selisistat significantly improved the motor function and lifespan of the treated mice. Its potent inhibitory effects on mHTT aggregation contribute to its therapeutic efficacy in HD.

CONCLUSIONS

In conclusion, Identifying and creating small compounds that target oxidative stress has become a potential strategy for treating neurodegenerative illnesses. These small compounds have a variety of modes of action, including scavenging reactive oxygen species, boosting endogenous antioxidant defences, and regulating important pathways causing neurodegeneration brought on by oxidative stress. Although problems with target specificity and blood-brain barrier penetration still exist, current research and creative approaches give promise for overcoming these restrictions. The possibility of improving the lives of those affected by neurodegenerative disorders and lessening the burden of these conditions globally lies in ongoing efforts to improve our understanding of oxidative stress-mediated neurodegeneration and optimise the therapeutic potential of small molecules.

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