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REVIEW

Targeting the redox neuroinflammatory nexus: insights into Alzheimer's and Parkinson's diseases

Loganathan Chandramani Priya Dharshini[1] · Kunnathur Murugesan Sakthivel[2] · K. Gilbert Ross Rex[3] · Rajan Radha Rasmi[1]

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Abstract
Neurodegenerative diseases, including Alzheimer's and Parkinson's, are characterized by the progressive deterioration of neuronal structure and function within the central and peripheral nervous systems. Among the multifactorial mechanisms implicated in their pathogenesis, oxidative stress and chronic neuroinflammation have emerged as pivotal contributors. An imbalance in redox homeostasis, marked by excessive generation of reactive oxygen species (ROS) and impaired antioxidant defenses, leads to sustained activation of inflammatory pathways and exacerbation of neuronal injury. This intricate interplay, known as the redox–neuroinflammatory nexus, constitutes a central axis in the onset and progression of neurodegeneration. This review underscores the critical role of redox imbalance in neurodegenerative processes and provides a comprehensive analysis of the oxidative stress and inflammation crosstalk in Alzheimer's and Parkinson's diseases, offering insights into potential therapeutic targets.

Keywords Neurodegenerative disease · Alzheimer's disease · Parkinson's disease · Oxidative stress · Inflammation

Introduction

Neurodegenerative diseases (NDDs) are a heterogeneous group of age-associated disorders marked by the selective and progressive loss of neuronal populations. Classification is typically based on clinical features (e.g., dementia, motor neuron disease), anatomical regions of degeneration (e.g., extrapyramidal systems, spinocerebellar degenerations), or key molecular abnormalities. The most prevalent forms include amyloidoses, tauopathies, α-synucleinopathies, and transactivation response DNA-binding protein 43 (TDP-43) proteinopathies (Dugger and Dickson 2017). With the global rise in the elderly population (Heemels 2016), the prevalence of NDDs, particularly Alzheimer's disease, Parkinson's disease, Huntington's disease (HD), Amyotrophic lateral sclerosis (ALS), and frontotemporal lobe dementia (FTD) has increased significantly. Reports stated that these conditions account for 3% of the total global burden of disease (Vellingiri 2024). These disorders manifest in a spectrum of neurological impairments ranging from cognitive decline, motor dysfunction, speech deficits, and respiratory failure (Abeliovich and Gitler 2016; Wyss-Coray 2016). Despite etiological heterogeneity, a convergence of molecular mechanisms, such as pathological protein aggregation, calcium buildup, mitochondrial dysfunction, oxidative stress, and neuroinflammation, ultimately culminates in neuronal death (Gan et al. 2018). While each of these diseases presents with unique molecular signatures, they all converge on the hallmark feature of chronic inflammation (Mayne et al. 2020).

Among the myriad pathogenic mechanisms implicated in ND, oxidative stress (OS), and neuroinflammation have emerged as central and interconnected drivers of disease progression. OS is recognized as a pivotal contributor in dementia development, defined by aberrant protein buildup and progressive neuronal degeneration. This causes an imbalance in redox homeostasis, reflected by dysregulation

✉ Rajan Radha Rasmi
rashmiffrajan@gmail.com

[1] Department of Biotechnology, PSG College of Arts and Science, Civil Aerodrome Post, Coimbatore, Tamil Nadu 641014, India

[2] Department of Biochemistry, PSG College of Arts and Science, Civil Aerodrome Post, Coimbatore, Tamil Nadu 641014, India

[3] Department of Biotechnology, Vivekanandha College of Engineering for Women (Autonomous), Tiruchengode, Namakkal, Tamil Nadu 637205, India

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of key OS markers, such as malondialdehyde (MDA), glutathione peroxidase (GSH-Px), protein carbonyls (PC), etc., culminating in ROS overproduction. The excessive ROS burden induces structural and functional damage, concurrently initiating chronic neuroinflammation (Wang et al. 2014).

Intriguingly, increased GSH-Px levels have been associated with a deceleration in cognitive decline, whereas paradoxically increased GSH activity accelerated cognitive deterioration, possibly due to higher OS and impaired GSH-Px activity. Moreover, OS promotes the formation of stress granules (SGs), causing neuronal function disruption by sequestering essential proteins and mRNAs, thereby impairing synaptic function and cellular resilience. The brain's heightened susceptibility to oxidative insults is largely attributable to its elevated metabolic demand and intrinsic vulnerability to neuroinflammatory signaling, predominantly mediated by microglial activation in response to oxidative injury. This neuroinflammatory milieu not only amplifies cellular and tissue damage but also serves as a key driver of disease progression (Dash et al. 2025). Table 1 summarizes the pathology, mechanism, and drugs in Alzheimer's and Parkinson's disease (AD and PD). This review focuses on the interrelation between oxidative stress and inflammation in Alzheimer's and Parkinson's disease, offering insights into their redox neuroinflammatory nexus.

Redox imbalances in neurodegeneration

In NDD, early stage mitochondrial dysfunction and OS are intricately linked in a self-perpetuating cycle that severely compromises neuronal viability. Owing to their high metabolic demands and limited regenerative capacity, neurons are particularly susceptible to deficits in mitochondrial energy metabolism and redox imbalance. Mitochondria, the central hubs of cellular energy production, are structurally defined by a selectively permeable outer mitochondrial membrane (OMM) and an impermeable inner mitochondrial membrane (IMM) that is tightly folded into cristae, encapsulating the matrix of mitochondria (Osellame et al. 2012). Embedded within the IMM is the electron transport chain (ETC), a series of protein complexes (I–IV) that facilitate oxidative phosphorylation by transferring electrons derived from nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide ($FADH_2$) generated through the tricarboxylic acid (TCA) cycle, to form molecular oxygen. This electron flow drives the translocation of protons from the matrix into the intermembrane space, establishing the electrochemical gradient required for ATP synthesis. Proper assembly and spatial organization of these complexes within the cristae are essential for maintaining mitochondrial integrity and bioenergetic efficiency (Zhao et al. 2019).

Table 1 Summarizing the known pathology, mechanism, and drugs in AD and PD

Pathological feature	Alzheimer's disease	Parkinson's disease
Underlying mechanism	Type 2 diabetes mellitus (T2DM), marked by insulin resistance, has been implicated in the AD pathogenesis. Chronic inflammation and OS associated with T2DM accelerate amyloid-β (Aβ) plaques and neurofibrillary tangles (NFTs), exacerbating mitochondrial dysfunction, contributing to the onset and progression of AD (Verdile et al. 2015)	OS in PD arises from both internal and external factors. Neuroinflammation is driven by pro-inflammatory mediators crossing the blood–brain barrier (BBB). A study demonstrated that lipopolysaccharides induced chronic inflammation and rotenone triggered ROS, which synergistically caused dopaminergic neuron loss, α-synuclein aggregation, and Lewy body formation, causing PD (He et al. 2020)
Protein aggregation	Amyloid-β, tau (Ross and Poirier 2004)	α-synuclein (Ross and Poirier 2004)
Mitochondrial complex dysfunction	Complexes I, II, III, IV, and V (Hroudova et al. 2014)	Complexes I, IV, and V (Golpich et al. 2016)
Key contributors to oxidative stress	Amyloid-β, tau, mitochondrial dysfunction, impaired neutrophil activity (Costa et al. 2012)	α-synuclein, mitochondrial dysfunction, impaired neutrophil activity (Hattingen et al. 2009)
Glial cell dysfunction	Astrocytes, microglia (Hanslik et al. 2021)	Astrocytes, microglia, oligodendrocytes (Hanslik et al. 2021)
Calcium homeostasis dysfunction	Aβ-induced pore formation, mitochondrial abnormalities, reduced expression of calcium-buffering proteins (Zundorf and Reiser 2011)	α-synuclein-induced pore formation, mitochondrial abnormalities, reduced expression of calcium-buffering proteins (Zundorf and Reiser 2011)
Proteins affecting mitochondrial function	Amyloid precursor protein (APP), presenilin (PSEN1, PSEN2), Aβ, tau (Hashimoto et al. 2003)	Tau, α-synuclein, parkin (Hashimoto et al. 2003)
Current pharmacological interventions	Donepezil, rivastigmine, galantamine, tacrine, memantine, aducanumab (Alhazmi and Albratty 2022)	Levodopa, Carbidopa, Tolcapone, entacapone, amantadine, safinamide, istradefylline, pimavanserin (Sivanandy et al. 2021)

Under physiological conditions, approximately 1–2% of the total oxygen consumed escapes ETC and forms reactive oxygen species (ROS), causing oxidative stress (Cadenas and Davies 2000). OS arises when ROS production surpasses the intrinsic antioxidant defense systems, such as superoxide dismutase (SOD), glutathione peroxidase, and catalase, leading to widespread oxidative injury (Duracková 2010). Mitochondria by themselves are both sources and targets of ROS, with at least eight distinct enzymatic sites contributing to their generation, notably complexes I, II, and III. Excessive ROS initiates lipid peroxidation, protein carbonylation, and mitochondrial DNA (mtDNA) damage, thereby compromising mitochondrial functionality and further amplifying ROS output (Jurcau 2021). This deleterious feedback loop disrupts cellular homeostasis and accelerates synaptic dysfunction, ultimately contributing to the progressive neuronal degeneration characteristic of NDDs (Phaniendra et al. 2015).

These ROS inflict oxidative damage on biomolecules, including DNA, proteins, and lipids, resulting in genomic instability, protein dysfunction, membrane disruption, and ultimately neuronal apoptosis or necrosis (Chang et al. 2011; Wang et al. 2004). Many of these triggers converge on redox imbalance, creating a self-perpetuating cycle wherein ROS inflict cellular damage and potentiate inflammatory signaling. Oxidized proteins, such as peroxiredoxin-2 (PRDX2), function as redox-sensitive danger signals that activate innate immune pathways, thereby forging a mechanistic link between oxidative injury and neuroimmune activation (Berlett and Stadman 1997; Salzanoa et al. 2014).

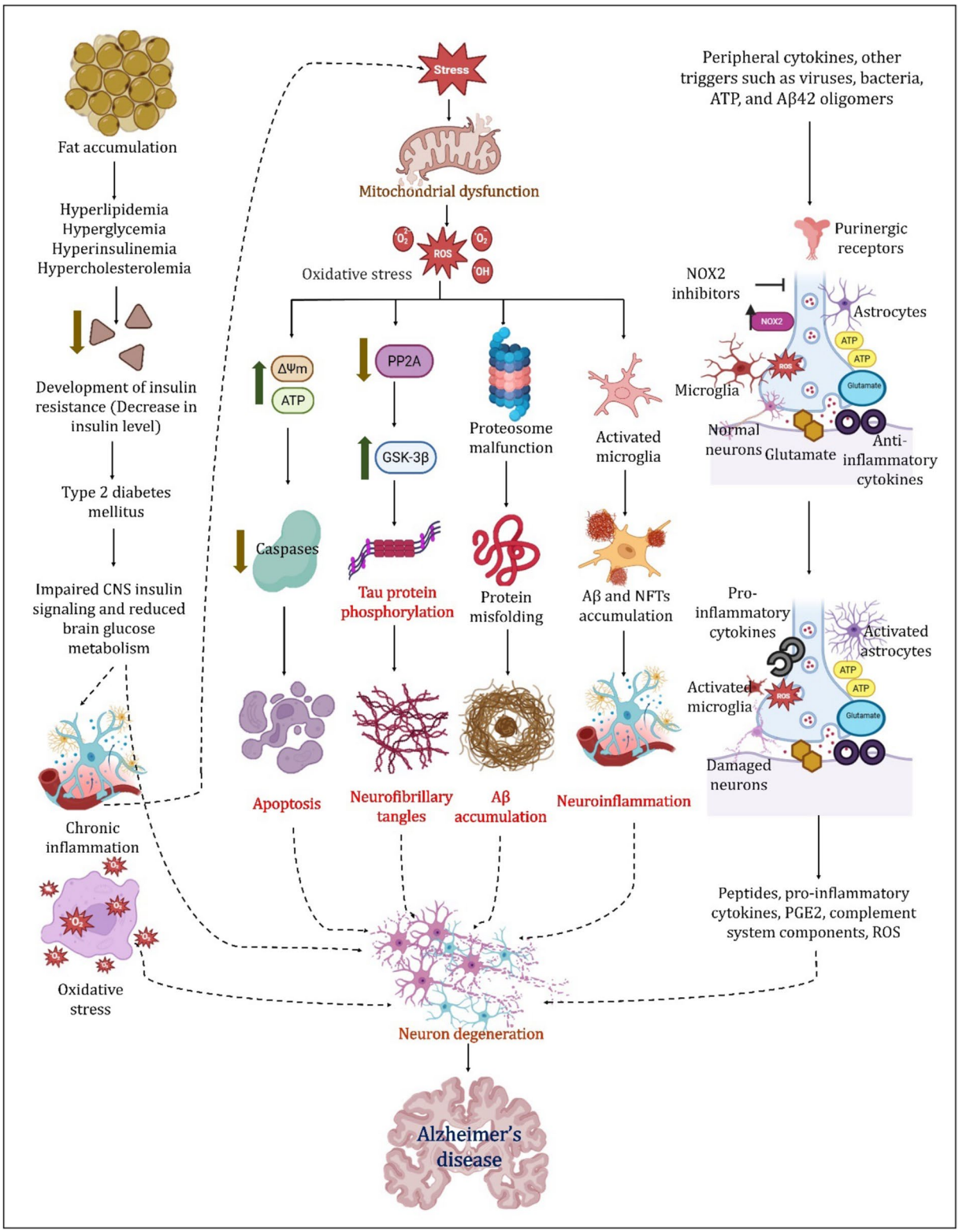
Within the cerebral parenchyma, ROS are predominantly generated as byproducts of mitochondrial oxidative metabolism, primarily via complexes I (NADH dehydrogenase) and III (ubiquinone cytochrome c reductase) of the ETC. In addition, several mitochondrial enzymes, such as monoamine oxidase (MAO), glycerol phosphate dehydrogenase, and α-ketoglutarate dehydrogenase, substantially contribute to ROS production. The rate of ROS production is tightly regulated by metabolic parameters, including the mitochondrial membrane potential (MMP) ($\Delta\Psi m$), the NADH/NAD^+ redox ratio, and mitochondrial calcium levels, all of which modulate the electron flux and redox state within the mitochondria. ROS also originates from NADPH oxidase (NOX), and the MAO isoforms A or B. Additionally, peroxisomal enzymes, such as xanthine oxidase, D-aspartate oxidase, acyl CoA oxidases, D-amino acid oxidase, urate oxidase, or L-α-hydroxy oxidase, are implicated in the non-mitochondrial generation of ROS (Jurcau et al. 2022). The convergence of these diverse enzymatic pathways creates a complex redox landscape in the brain, wherein dysregulation of ROS homeostasis plays a pivotal role in the pathogenesis of neurodegenerative diseases.

Redox-neuroinflammatory nexus in AD and PD progression

Alzheimer's disease

AD is a complex, multifactorial NDD predominantly associated with age-related dementia and is characterized by profound neuronal loss, especially in the hippocampus, amygdala, entorhinal, and neocortex regions (Johns 2014; Chakrabarti et al. 2013). AD is categorized based on onset in individuals, such as early onset AD (EOAD, < 65 years) and late-onset AD (LOAD, ≥ 65 years) (Dai et al. 2017). Genetic analyses have identified mutations in specific genes responsible for aberrant protein aggregation, particularly in the early onset of AD (EOAD). Notably, these mutations are in the APP on chromosome 21, and PSEN 1 and 2 genes on chromosomes 14 and 1, respectively, all of which drive amyloidogenic processing, leading to increased Aβ peptides (Christen 2000; Dai et al. 2017). All three genes encode essential components of the γ-secretase catalytic core, the enzyme complex responsible for Aβ production (Mendez 2017). These Aβ peptides accumulate extracellularly to form plaques, while hyperphosphorylated tau forms intracellular NFTs, leading to mortality typically within 3–9 years post-diagnosis. Clinically, AD presents with insidious to rapidly advancing cognitive deficits, including memory loss, executive dysfunction, language impairments, and eventual motor and functional decline (Holtzman et al. 2011).

Beyond its classical pathological hallmarks, AD is now widely recognized as a disease fundamentally driven by a redox–neuroinflammatory nexus. Reports from diseased brain models demonstrated that substantial damage due to brain atrophy, chronic inflammation, oxidative stress, and extracellular and intracellular deposition of Aβ and NFTs, respectively, leads to neurodegeneration (Ittner and Gotz 2011). Substantial evidence from postmortem analyses, in vivo imaging, and transgenic animal models has established that oxidative damage and mitochondrial dysfunction activate microglial cells, causing neuroinflammation, which constitutes a central axis of disease progression. In the AD brain, an essential endogenous antioxidant named glutathione, the decrease in its levels alongside a higher ratio of polyunsaturated fatty acids in neuronal membranes, renders neurons extremely vulnerable to ROS-mediated injury (Packer and Prilipko 2012). As this neuronal oxidative burden increases, the biological macromolecules undergo oxidative modifications in the brain and cerebrospinal fluid of AD patients, evidenced by several markers. A few such markers are (1) lipid peroxidation markers-malondialdehyde, 4-hydroxynonenal, F2-isoprostanes, (2) protein oxidation markers-protein



carbonyls, nitrotyrosine, and (3) DNA oxidation markers-8-hydroxy-2′-deoxyguanosine (Yao et al. 2004).

Importantly, ROS generation in AD is multifactorial, arising from mitochondrial dysfunction, transition metal-catalyzed redox reactions involving iron and copper bound to Aβ (Butterfield et al. 2014), and activation of the NOX system in microglia (Cheignon et al. 2018). OS in the neurons interacts with any of the biomolecule causing

◂**Fig. 1** Role of inflammation and OS in Alzheimer's disease progression- AD is critically driven by chronic inflammation and OS, which mutually reinforce each other to accelerate neurodegeneration. Metabolic factors such as obesity and insulin resistance promote type 2 diabetes, impairing brain glucose metabolism and fostering a pro-inflammatory, oxidative environment. Concurrently, peripheral cytokines, microbial elements, ATP, and Aβ42 oligomers activate microglia and astrocytes via NOX2 upregulation, triggering neuroinflammation and ROS production. This cascade leads to elevated levels of pro-inflammatory cytokines, neurotoxic mediators, and Aβ, amplifying neuronal stress. Sustained OS disrupts redox balance, alters signaling, dysregulates cell cycles, and impairs enzymatic activity, culminating in Aβ 1–42 accumulation, tau pathology, mitochondrial dysfunction, ER stress, and synaptic loss. These events collectively drive AD progression

oxidative stress to proteins. It breaks down the metabolism process, proteostasis, and redox motion in the brain by stimulating various stress-related protein kinases namely JNK, mitogen-activated protein kinase (p. 38), and ERK1/2 or brings about oxidative modifications in redox-sensitive transcription factors (Butterfield et al. 2014; Su et al. 2008). NOX2, a critical isoform upregulated in response to Aβ42, serves as a major enzymatic source of superoxide production. Once activated, microglia shift toward a pro-inflammatory state, releasing cytokines, such as IL-6, TNF-α, and chemokines, which exacerbate neuronal injury and synaptic dysfunction through sustained oxidative and inflammatory signaling (Ganguly et al. 2021).

The *TREM2* gene, implicated in sporadic AD, encodes a cell surface receptor expressed predominantly on microglia. The knockdown of *TREM2* gene expression in senescence-accelerated mouse prone-8 (SAMP8) brain models results in cognitive impairment followed by the elevated levels of pro-inflammatory cytokines (IL-6 and TNF- α) and a concomitant reduction in the anti-inflammatory cytokines namely IL-10. *TREM2* interacts with its intracellular adaptor protein DAP12, which is essential microglial survival, proliferation, chemotaxis, and phagocytosis (Zheng et al. 2017). Microglia, the resident immune cells of the central nervous system (CNS), play a critical role in maintaining CNS homeostasis during stress, injury, and disease, as well as in the remodeling of neuronal circuits (Tian et al. 2017; Ransohoff and El Khoury 2015; Tay et al. 2017]. Under physiological conditions, microglia clear amyloid-β (Aβ) via phagocytosis, thereby exerting neuroprotective effects. However, impaired *TREM2*-DAP12 signaling or dysfunctional microglia compromise this clearance mechanism, leading to excessive Aβ accumulation, persistent inflammation, synaptic loss, and neuronal degeneration (Perry and Homes 2014; ElAli and Rivest 2016). Additionally, failure to eliminate Aβ activates pro-inflammatory pathways, exacerbating oxidative stress and contributing to AD pathogenesis (Piirainen et al. 2017; Lee and Landreth 2010). Figure 1 illustrates the role of oxidative stress and inflammation in Alzheimer's disease.

Parkinson's disease

Parkinson's disease (PD) is a progressive neurodegenerative disorder marked by selective degeneration of pigmented dopaminergic neurons in the substantia nigra pars compacta and the accumulation of Lewy bodies, eosinophilic cytoplasmic inclusions comprising aggregates of α-synuclein. Clinically, PD presents with a constellation of motor symptoms, including akinesia (difficulty initiating voluntary actions), bradykinesia (slowness of movement), and extrapyramidal rigidity (muscle stiffness), as well as a spectrum of non-motor features (Deumens et al. 2002). The multifactorial etiology of PD includes environmental toxins, genetic factors, and oxidative stress. Oxidative damage is particularly detrimental in dopaminergic neurons due to their inherently high oxidative metabolism and vulnerability to ROS (Whitton 2007). Mitochondrial dysfunction is a well-established feature of PD; for instance, the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) induces Parkinsonian symptoms by inhibiting complex I of the ETC, thereby disrupting ATP production and enhancing ROS generation. Similarly, tetrahydrobiopterin, an endogenous compound, has been shown to inhibit mitochondrial complexes I and IV, causing mitochondrial malfunction and ROS accumulation (Sherer et al. 2002).

Dopaminergic neurons are particularly susceptible to OS-induced damage due to dopamine metabolism, which generates reactive intermediates such as dopamine quinones and hydrogen peroxide (H_2O_2). Through redox cycling in the presence of iron or oxygen, these intermediates produce hydroxyl radicals (•OH), causing irreversible damage to proteins, lipids, and DNA (Emamzadeh and Surguchiv 2018). Dopamine quinones covalently modify cysteine residues on proteins, depleting essential sulfhydryl groups and impairing mitochondrial function, contributing to neuronal degeneration (Gautam & Zeevalk 2011; Ma et al. 2015; Farzan et al. 2020). Accumulated ROS further destabilize the mitochondrial membrane potential, triggering apoptotic pathways (Vatansever et al. 2013). Environmental toxins like rotenone, a known mitochondrial complex I inhibitor, have also been implicated in sporadic PD and recapitulate many pathological hallmarks of the disease in animal models (Tanner et al. 2011).

Neuroinflammation is another critical contributor to PD pathology, predominantly mediated by activated microglia—the resident immune cells of the central nervous system. Activated microglia have been observed not only in the substantia nigra but also in regions such as the basal ganglia and brainstem (Filiano et al. 2015; Lecours et al. 2018; Subramaniam and Federoff 2017). These microglia adopt polarized phenotypes that are of two extremes, namely, M1 pro-inflammatory (classically activated) and M2 anti-inflammatory (alternatively activated) phenotypes

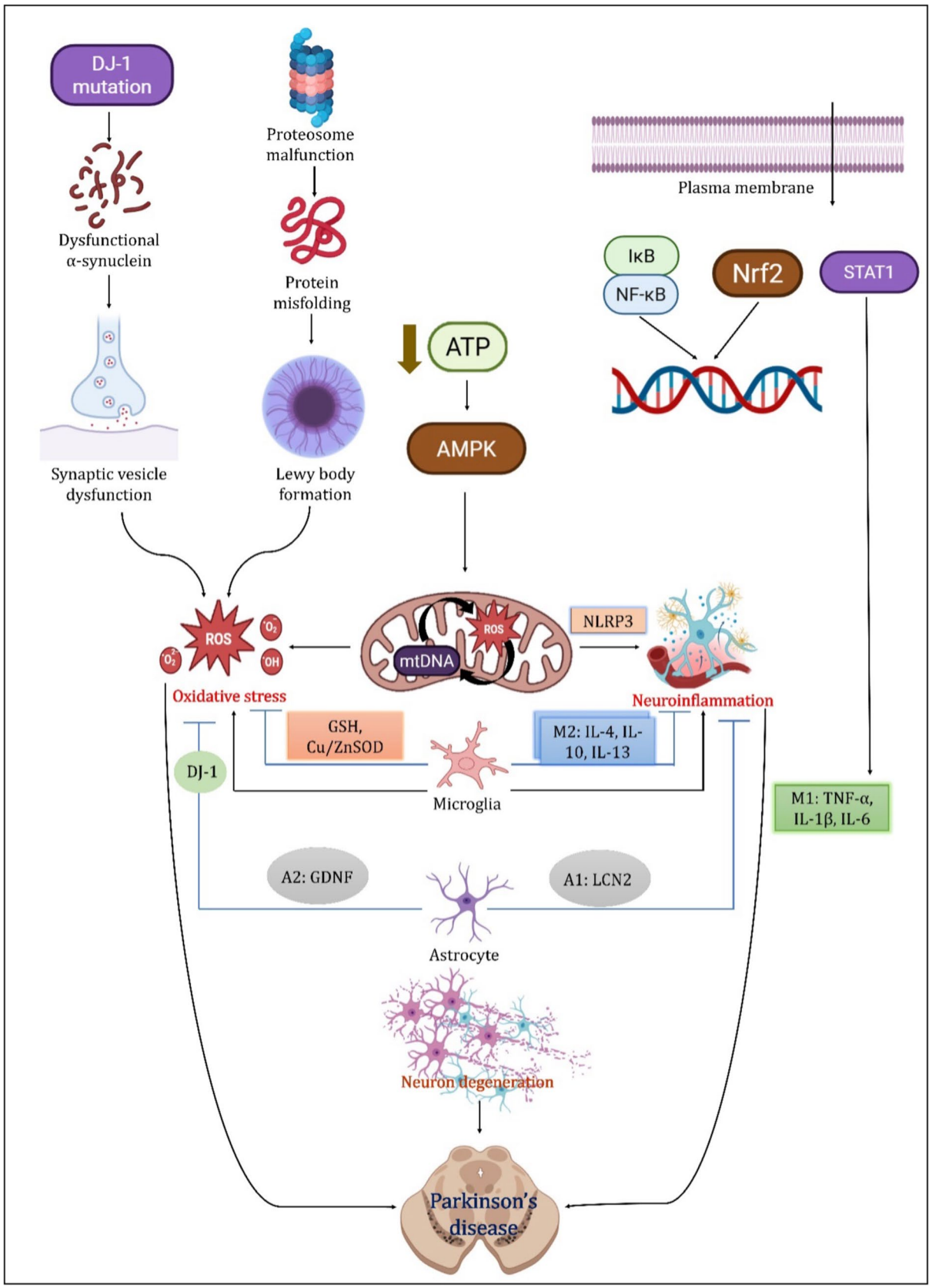


Fig. 2 Inflammation and oxidative stress in Parkinson's disease (PD) progression

Table 2 Clinical trials of drugs in Alzheimer's and Parkinson's disease linked with oxidative stress and inflammation

Official title	Clinical trials ID	Intervention/treatment	Sponsor	Phase	Recruitment status
Alzheimer's disease					
Glutathione, brain metabolism and inflammation in Alzheimer's disease	NCT04740580	• Dietary supplement: Glycine, N-acetyl-cysteine, Alanine	Baylor College of Medicine	Early phase I	Recruiting
Randomized, double-blind, placebo-controlled trial evaluating efficacy and safety of dimethyl fumarate in brain atrophy reduction, synaptic functional connectivity, cognitive functions, quality of life, and activity of daily living improvement among patients with mild cognitive impairment and dementia due to Alzheimer's disease	NCT06850597	• Drug: dimethyl fumarate	Medical University of Lodz	Phase II	Recruiting
Double blind crossover clinical trial of nabilone for agitation in frontotemporal dementia	NCT05742698	• Drug: Nabilone	Simon Ducharme, MD	Phase II	Recruiting
Effects of orally administered nicotinamide riboside on bioenergetic metabolism, oxidative stress and cognition in mild cognitive impairment and mild Alzheimer's dementia	NCT04430517	• Drug: Nicotinamide riboside	Mclean Hospital	Early phase I	Recruiting
Assessment of foralumab safety and modulation of microglial activation evaluated by PET imaging in patients with early symptomatic Alzheimer's disease	NCT06489548	• Drug: Foralumab TZLS-401 50 µg and 100 µg	Brigham and Women's Hospital	Phase II	Not yet recruiting
A phase II clinical trial of interleukin-2 (IL-2) in patients with mild-to-moderate Alzheimer's disease	NCT06096090	• Drug: Interleukin-2	The Methodist Hospital Research Institute	Phase II	Recruiting
MCLENA-2: A phase II clinical trial for the assessment of lenalidomide in patients with mild cognitive impairment due to Alzheimer's disease	NCT06177028	• Drug: Lenalidomide 10 mg	St. Joseph's Hospital and Medical Center, Phoenix	Phase II	Not yet recruiting
Randomized, double-blind, placebo-controlled, efficacy and safety study of sulforaphane in patients with prodromal to mild Alzheimer's disease	NCT04213391	• Drug: Sulforaphane	Second Affiliated Hospital, School of Medicine, Zhejiang University	Not Applicable	Unknown status
Parkinson's disease					
Phase II: Physiological effects of nutritional support in patients with Parkinson's disease	NCT04459052	• Dietary supplement: N-acetyl cysteine • Drug: [F-18] Fluorodopa Positron Emission Tomography	Thomas Jefferson University	Phase II	Active, not recruiting

Table 2 (continued)

Official title	Clinical trials ID	Intervention/treatment	Sponsor	Phase	Recruitment status
The effect of cilostazol on the clinical outcome of patients with Parkinson's disease	NCT06612593	• Drug: Cilostazol	Ain Shams University	Phase II	Not yet recruiting
TALLman family energizes research to help alleviate neuroinflammation in Parkinson's disease—"TALLER THAN PD." A Phase 2 futility study to evaluate the efficacy, safety and tolerability of hydroxychloroquine in subjects with early treated Parkinson's disease	NCT06816810	• Drug: Hydroxychloroquine (HCQ)	Ottawa Hospital Research Institute	Phase II	Not yet recruiting
Effect of folic acid on motor aspects of daily living and oxidative stress in Levodopa treated Parkinson's disease patients: A randomized, double-blind, placebo-controlled trial	NCT05959044	• Drug: Folic acid tablet	Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh	Phase II	Recruiting
Effects of propofol on brain function in patients with Parkinson's disease	NCT05895019	• Drug: Propofol	Beijing Tiantan Hospital	Not mentioned	Recruiting
A multicenter, randomized, double-blind, placebo-controlled study of idebenone in the treatment of early stage Parkinson's disease with motor and non-motor symptoms	NCT03727295	• Drug: Idebenone	Second Affiliated Hospital of Soochow University	Phase IV	Unknown status
A 6-month study to evaluate sulforaphane effects in treatment of cognition impairment of PD patients	NCT05084365	• Drug: Sulforaphane	Central South University	Phase II	Recruiting

Data were collected as of 12th of May 2025 from https://clinicaltrials.gov/

(McWhorter et al. 2015). M1 is morphologically altered and discharges numerous inflammatory components [TNF-α, IL-1, IL-6, and nitric oxide (NO)], leading to DA neuronal loss in PD patients (Ho 2019). M2 synthesizes anti-inflammatory cytokines (IL-4, IL-13, IL-10, and TGF) via phagocytic effects that reduce inflammation and repair the inflammatory response, thereby microglia-mediated neuroinflammation plays both a positive and negative role in PD progression (Cherry et al. 2014; Angeloni et al. 2015). Microglia-mediated oxidative stress operates via two key mechanisms: activation of NADPH oxidase (NOX) leading to extracellular ROS overproduction, and intracellular ROS accumulation, both of which trigger transcription of pro-inflammatory genes. Consequently, the synergistic interaction between oxidative stress and neuroinflammation forms a pathological feed-forward loop that amplifies DA neuron loss and accelerates PD progression (Verdile et al. 2015). Figure 2 depicts the role of oxidative stress and inflammation in Parkinson's disease.

PD is driven by a feedback loop of oxidative stress (OS) and neuroinflammation. DJ-1 mutations and proteasomal dysfunction trigger OS by disrupting synaptic vesicle function and promoting Lewy body formation. Persistent ROS exposure damages mtDNA and impairs mitochondria, activating the NLRP3 inflammasome and cytokine release. Key signaling pathways—NF-κB, Nrf2, and STAT3—mediate inflammatory responses: NF-κB and Nrf2 translocate to the nucleus to upregulate inflammation-related genes, while STAT3 enhances microglial activation. Microglia polarize into M1 (pro-inflammatory) and M2 (anti-inflammatory) phenotypes. M1 releases TNF-α, IL-6, and NO, promoting neuronal loss, whereas M2 supports antioxidant defense via GSH and Cu/Zn SOD. DJ-1-overexpressing astrocytes shift from the neurotoxic A1 to protective A2 phenotype, secreting GDNF to support dopaminergic neurons. The interplay of OS and inflammation accelerates PD pathogenesis.

Therapeutic approaches targeting oxidative stress and inflammation in AD and PD

Conventional pharmacological treatments for Alzheimer's and Parkinson's diseases primarily offer symptomatic relief and are often associated with considerable side effects, limited efficacy in halting disease progression, and poor long-term outcomes. These challenges have prompted a paradigm shift toward identifying disease-modifying strategies, particularly those targeting the redox–inflammatory axis implicated in neurodegeneration.

A growing body of research has focused on the neuroprotective potential of phytochemicals in the context of Parkinson's disease and Alzheimer's disease. Studies have observed that dietary intake of phytochemical-rich sources, such as tea, coffee, fruit, and vegetables, is associated with a reduced risk of neurological impairment and the onset of pathologically related conditions (Venkatesan et al. 2015). Another study highlighted that various bioactive molecules present in dietary sources, such as vanillin, ferulic acid, thymoquinone, epigallocatechin-3-gallate, theaflavin, and other antioxidant phytochemicals, exhibited significant neuroprotective effects across diverse experimental models. These naturally derived molecules modulate oxidative stress pathways, suppress pro-inflammatory mediators, and attenuate neuronal damage, thereby offering a multifaceted neuroprotective strategy (Limanaqi et al. 2020). Table 2 provides an overview of pharmacological agents currently under clinical investigation for Alzheimer's and Parkinson's diseases, specifically those targeting oxidative stress and neuroinflammation, underscoring a growing emphasis on disease-modifying therapeutics.

Conclusion

Oxidative stress and inflammation represent two fundamental and interlinked hallmarks of neurodegenerative diseases. This review explores the intricate association between these pathological processes and their synergistic role in driving neuronal dysfunction and degeneration. Under sustained oxidative stress, reactive oxygen species (ROS) act as critical signaling mediators, perpetuating the activation of redox-sensitive pathways. This persistent activation promotes the expression of pro-inflammatory mediators and disrupts the regulation of the immune response, leading to chronic neuroinflammation. The crosstalk between ROS and pro-inflammatory cytokines underscores a self-amplifying cycle that accelerates cellular damage and neurodegeneration. By examining this redox–inflammatory interplay, the review highlights its central role in the pathophysiology of neurodegenerative disorders.

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Declarations

Competing interests The authors declare that they have no competing interests.

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