Int. J. Pharm. Investigation, 2026; 16(2):371-383.
https://www.jpionline.org

Review Article

Neuroprotection in Parkinson's Disease: No More Status Quo

Mary Brenda Ogwang*, Deepak Kumar Jha, Sandipan Chatterjee

Department of Pharmacology, Karnataka College of Pharmacy, Bengaluru, Karnataka, INDIA.

ABSTRACT

This study aims to evaluate and analyze the concept of neuroprotection in Parkinson's Disease (PD) by investigating the underlying mechanisms responsible for dopaminergic neuronal death. It explores how these pathological processes contribute to disease progression and identifies potential targets for therapeutic intervention. Apart from deciphering neuroprotection, once considered an elusive goal, to its definition, this study also points out how translational science has contributed to the understanding of not only PD but also other Neurodegenerative disorders, with the turn of the 20th century. A comprehensive review was conducted focusing on key pathological mechanisms involved in PD, including α-synuclein aggregation, mitochondrial dysfunction, oxidative stress, and neuroinflammation. The study found that the accumulation of misfolded α-synuclein impairs synaptic and mitochondrial functions, initiating neurodegeneration. Reduced mitochondrial complex activity and defective mitophagy were identified as central causes of mitochondrial impairment. Mitochondrial dysfunction, along with dysregulated iron metabolism, emerged as primary sources of oxidative stress, increasing the susceptibility of dopaminergic neurons. Widespread microglial activation, T-cell infiltration, and elevated pro-inflammatory cytokines were consistently observed. Glutamate-induced excitotoxicity via NMDA receptors, lysosomal dysfunction, and apoptosis were significant contributors to neuronal loss. Genetic mutations in *SNCA, LRRK2, PARKIN, PINK1*, and *GBA* were found to exacerbate these pathogenic processes. The findings underscore that PD results from a multifactorial interplay involving α-synuclein pathology, mitochondrial deficits, oxidative damage, and chronic neuroinflammation. These overlapping mechanisms converge to cause progressive dopaminergic neuron degeneration. Targeting these early molecular events presents an effective approach for neuroprotection and for slowing disease progression, with the aim of preserving neuronal function in Parkinson's disease.

Keywords: Parkinson's Disease (PD), Alpha-Synuclein, Mitochondrial Dysfunction, Oxidative Stress, Neuroinflammation, Apoptosis, Autophagy.

Correspondence:
Ms. Mary Brenda Ogwang
M. Pharmacy, Department of Pharmacology, Karnataka College of Pharmacy, Bengaluru, Karnataka, INDIA.
Email: ogwangmary@gmail.com
ORCID: 0009-0006-2143-327X

Received: 12-09-2025;
Revised: 03-10-2025;
Accepted: 24-12-2025.

INTRODUCTION

Neuroprotection, once poorly understood, has now become a key strategy in addressing neurodegenerative disorders, particularly Parkinson's Disease (PD). PD is the 2nd most common neurodegenerative disorder, has a significant and growing global impact. Its prevalence is approximately 160 per 100,000, but this increases markedly with age rising to around 1,000 per 100,000 in individuals over 60, about 550 at age 70, and up to 4,000 in those over 80 (Schapira 2008; Postuma *et al*., 2015; Driver *et al*., 2009; Lau *et al*., 2006). The incidence also escalates with age, from a general range of 8-20 per 100,000 per year to 120 per 100,000 at age 70. PD affects men more and the ratio of male to female i.e 3:2, possibly due to estrogen's neuroprotective role. Currently, there are an estimated 6 million PD cases globally, a number expected to double by 2040 due to aging populations. The disease imposes a heavy burden, accounting for 3.2 million DALYs and over 200,000 deaths annually (Tysnes *et al*., 2017) (refer to Figure 1).

Modern therapeutic approaches for PD have evolved beyond symptomatic relief to include Disease Modifying Therapies (DMTs) that target the underlying causes of disease progression. These strategies span across multiple therapeutic areas, including neurology, infectious diseases, metabolic and respiratory disorders, and microbiome-related interventions, recognizing the role of the gut-brain axis in PD. A key focus has shifted toward neuroprotective and neuro-rescue approaches, which seek to intervene before neuronal death occurs, particularly in dysfunctional but still viable neurons. Although the concept of neuroprotection has faced challenges, such as high clinical trial failure rates, and complex implementation. It refers to any intervention that delays or prevents disease progression through

OPEN ACCESS

Manuscript TECHNOMEDIA

DOI: 10.5530/ijpi.20260022

Publishing Partner : Manuscript Technomedia. [www.mstechnomedia.com]

neuronal protection, rescue, or restoration (Stocchi *et al.*, 2003). Ideally, neuroprotection provides long-term benefits by modifying disease etiology or pathogenesis, ultimately delaying onset or clinical decline (Biglan *et al.*, 2007).

This review attempts to cover studies that have been done over the last two decades related to PD and Neurodegeneration. It not only focuses on systematic reviews but also covers clinical studies. Topics addressed include pathophysiology of PD, genetic and environmental risk factors, limitations of current therapies with a mention on their respective clinical trials, emerging neuroprotective strategies and diagnostic biomarkers. Information involving secondary causes of PD, differential diagnosis that may interfere with correct diagnosis, different pre-clinical models and FDA approved drugs for management and treatment of PD are beyond the scope of this review. To help bridge the gap between the "unknown" to the "known" in the study of neurodegeneration. As initially submitted by American Academy of Neurology that concluded, "no treatment has been shown to be neuroprotective", researchers can now respectfully refute this claim with sufficient evidence from reputable studies. This review paper bright to our attention the stark contrast between prior knowledge and the current updates and may help in guiding future experimental work and clinical aspects.

METHODOLOGY

A comprehensive literature review was conducted to examine the key pathological mechanisms involved in Parkinson's disease. Relevant information was systematically collected from various scientific databases and sources, including Scopus, Web of Science, UGC CARE-listed journals, and other peer-reviewed scientific websites and publications. The collected literature was critically analyzed to identify consistent findings, emerging hypotheses, and recent advancements related to PD pathophysiology.

Key Findings

Pathophysiology of Parkinson's Disease

PD involves the gradual loss of dopaminergic neurons in the SNpc, which critically impairs dopaminergic transmission in the striatum and underlies the hallmark motor symptoms, such as rigidity, tremor, bradykinesia, and postural instability. It also affects non-dopaminergic neurons, including noradrenergic, serotonergic, and cholinergic neurons (Jellinger 2012 and Werner *et al.*, 2020). Additionally, the peripheral nervous system including the olfactory bulb, mesenteric nervous system, and autonomic nerves is involved. The accumulation of Lewy bodies, intracellular aggregates containing α-synuclein and other proteins, is a pathological hallmark (Braak *et al.*, 2000; Kovari *et al.*, 2009). With the advancement of neurodegeneration in PD, patients often experience diverse non-motor manifestations such as cognitive impairment, mood disorders, autonomic irregularities, sleep-related issues, and sensory deficits. PD is defined as a multifactorial syndrome**,** influenced by genetic predispositions and environmental triggers, with overlapping biological mechanisms such as apoptosis, autophagy, mitophagy, ferroptosis, necrosis, and parthanatos (Target of Rapamycin [*mTOR*] poly [ADP-ribose] [PAR] polymerase-1 [*PARP-1*]) contributing to neuronal loss (Del Tredici *et al.*, 2012; Olanow 2007). This complexity underscores the heterogeneous and syndromic nature of the disease.

PD risk is influenced by metabolic and environmental factors via peripheral insulin resistance, promoting brain pathology and dopaminergic neuron degeneration. Vitamin D deficiency (hypovitaminosis D) has also been associated with increased neurodegeneration risk, with higher serum 25-hydroxy vitamin D levels linked to reduced PD incidence. Mitochondrial dysfunction**,** including reduced ATP production, membrane depolarization, and increased oxidative stress, plays a central role. The generation of ROS by enzymes like NADPH oxidase, iNOS, and MPO contributes to oxidative damage in PD brains, particularly in the substantia nigra. Iron accumulation in the SNpC amplifies ROS production via Fenton reactions, further exacerbating neuronal injury. Elevated pro-inflammatory cytokines and enzymes like COX-2 in dopaminergic neurons suggest a prominent role for neuroinflammation (Refer to Table 1).

Genetic and environmental factors

Genome-Wide Association Studies (GWAS) have substantially enhanced insight into genetic predispositions underlying both idiopathic and familial PD. Mutations and polymorphisms in several key genes contribute to disease onset and progression (refer to Table 2) (Polymeropoulos *et al.*, 1997; Yasuda *et al.*, 2010; Rohn, 2012; Poole *et al.*, 2008; Schapira *et al.*, 1990 and Konnova *et al.*, 2018).

Epidemiological studies and/or environmental factors play a role in increasing the risk of PD (Anthony *et al.*, 2009). The former demonstrates that in calcium homeostasis, enhanced entry into Substantia Nigra pars Compacta (SNpC) neuronal cells have been associated with heightened oxidative damage, impaired mitochondrial function, and neurodegeneration (Sulzer *et al.*, 2013; Ilijic *et al.*, 2011). These studies, despite lacking definitive proof, also indicate overwork, exposure to coldness, inflexible personality, stress, trauma, rural living, well water consumption, and exposure to environmental toxins increase the risk of developing PD (Koller *et al.*, 1990) and these results validate the involvement of neuroinflammatory mechanisms in the advancement of PD.

Limitations of Current Therapies

L-Dopa is the primary symptomatic therapy since 1960s. Despite its limitations of the "wearing off" effect 5 years after initiation of treatment, which may occur in 30-40% of patients, and disabling dyskinesia in about 50% or the "on-off" phenomenon

with the development of other features that do not respond to it, like freezing, dementia, autonomic disturbances and postural instability, and 20%-30% of PD patients ceasing it as evidenced by drug intervention trials, it remains as the basis for dopaminergic symptomatic treatment as it is a DA precursor, and biochemically, degeneration of nigrostriatal neurons is associated with a decline in striatal DA. This is because a comparison was made with dopamine agonists, and it was found that L-Dopa has rich pharmacology and forms DA that stimulates D1-D5 receptors. Moreover, a portion of Dopamine (DA) is converted to Noradrenaline (NA). L-Dopa not only contributes to DA synthesis but may also displace serotonin (5-HT) from serotonergic neurons, influence glutamate release, and potentially function as an amino acid neuromodulator in its own right. In contrast, dopamine agonists such as ropinirole and pramipexole selectively target post-synaptic D2/D3 receptors. Interestingly, evidence suggests that while DA agonists may prime the basal ganglia for dyskinesia, the manifestation of dyskinetic symptoms typically emerges only after the introduction of L-Dopa (Biglan *et al.*, 2007). Supporting findings from clinical trials such as DATATOP, ELLDOPA, and TEMPO continue to affirm the cautious yet strategic initiation of L-Dopa therapy. Early restoration of basal ganglia function is believed to enhance compensatory mechanisms and potentially delay irreversible neurocircuitry alterations characteristic of Parkinson's disease progression. As such, L-Dopa remains a compelling therapeutic option, offering the potential for sustained clinical benefits when introduced at an appropriate stage of disease management.

Emerging Neuroprotective Strategies

Targeting Mitochondrial Dysfunction and Modulating Neuroinflammation

Neuroprotective strategies in PD target multiple mechanisms involved in dopaminergic neuronal loss. Monoamine oxidase B inhibitors like selegiline, safinamide, and rasagiline reduce dopamine catabolism, limit oxidative stress, and show anti-apoptotic properties independent of MAO-B inhibition. Dopamine agonists such as pramipexole, ropinirole, and apomorphine not only mimic dopamine action but may also reduce oxidative damage and excitotoxicity while providing symptomatic relief with fewer motor complications. Anti-apoptotic agents, including TCH346 and CEP-1347, prevent programmed neuronal death by stabilizing mitochondrial membrane potential and inhibiting key apoptotic mediators. Anti-excitotoxic agents like amantadine and memantine reduce glutamate-mediated excitotoxicity in overactive brain regions such as the subthalamic nucleus, helping to mitigate levodopa-induced dyskinesias. Strategies enhancing mitochondrial biogenesis and bioenergetics, such as the use of resveratrol, *PPAR-γ* agonists, creatine, and CoQ10, aim to restore mitochondrial function and energy production, vital for neuron survival (refer to Table 3) (McFarthing *et al.*, 2020 and Biglan *et al.*, 2007).

Alpha-synuclein Targeting Therapies

Therapeutic strategies targeting α-synuclein in PD aim to reduce its production, enhance its clearance, prevent its aggregation, and minimize chemical modifications that promote its toxic forms. One major approach is to reduce α-syn synthesis using gene interference technologies such as siRNAs or Antisense Oligonucleotides (ASOs), e.g. Ionis and Biogen's *ASOs, AmNA-ASO*, and Synucleozid, a compound modulating 5′ UTR

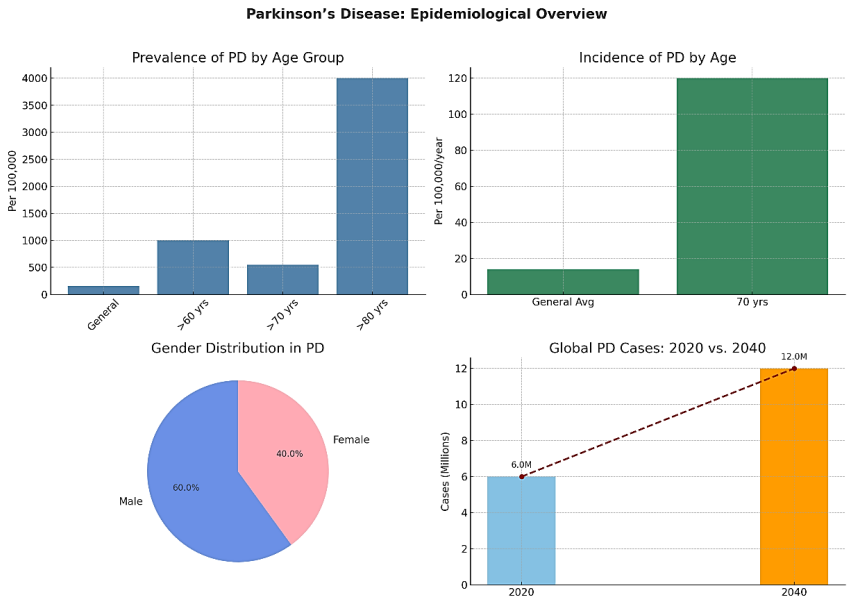

Figure 1: Parkinson's Disease Epidemiology and burden.

Table 1: Mechanism of pathogenesis and Risk Factors in PD.

Mechanism of Pathogenesis	Role and/ or effect
Alpha syn mutations (also hallmark for PD pathogenesis) (Jellinger 2012 and Konnova *et al.*, 2018)	- *SNCA* gene duplication/triplication causes familial PD. - Misfolding and aggregation form Lewy Bodies. - Defective clearance via endolysosomal system.
Neuroinflammation (Talene *et al.*, 2009)	- Involves microglial activation, astrogliosis, and T-cell infiltration. - Selective for nigrostriatal pathway. - Plays a role in disease initiation and progression.
Mitochondrial and lysosomal malfunctions (Alwena *et al.*, 2018; Haas 1995)	- Impaired mitochondrial biogenesis and ATP production. - Increased ROS, reduced calcium buffering. - Complex I and II/III deficiency observed in early PD.
Generation of Reactive Oxygen Species (ROS) (Schieber *et al.*, 2014; Finkel 2011)	- Accumulate due to dopamine metabolism and iron overload. - Reduced glutathione in SN. - Promote oxidative stress and neuronal damage.
Autophagy (Poehler *et al.*, 2014, Friedman *et al.*, 2012; Dagda *et al.*, 2009)	Impaired clearance of damaged organelles/proteins. - Linked to accumulation of dysfunctional mitochondria.
Defects in the mitophagy pathway (Gegg *et al.*, 2010 and 2011)	- Mutations in *PINK1* and PARKIN affect mitochondrial clearance. - Leads to build-up of damaged mitochondria.
Apoptosis (Tatton *et al.*, 2003, Allain *et al.*, 2008; Karbowski *et al.*, 2010; Verdin *et al.*, 2010; Wang *et al.*, 2009)	- Involves caspase activation and cytochrome C release. - Triggered by mitochondrial depolarization and oxidative stress.
Excessive glutamatergic excitotoxicity (Rodriguez *et al.*, 1998; Feger *et al.*, 1997)	- Excessive NMDA receptor activation increases Ca^{2+} influx. - Enhances ROS production and neuronal death. - STN overactivity reinforces SNpc degeneration. -Excitotoxicity susceptibility increases when mitochondrial deficits, induced by mitochondrial dysfunction, cause loss of ATP-dependent magnesium blockade of N-Methyl-D-Aspartate (NMDA) receptors.
Proinflammatory changes (Hunot *et al.*, 1999, Godoy *et al.*, 2008, Mogi *et al.*, 1994; Blum-Degen *et al.*, 1995)	That leads to the production of ROS and/or induces the expression of iNOS, which may occur through the combined action of cytokines such as Interferon γ, TNF α, and IL 1 beta. COX 2 may also generate ROS
Gene mutation and polymorphisms	-*mTOR* gene deletion induces autophagy; α-syn overexpression impairs it. Genetic polymorphisms may influence inflammatory responses and drug effectiveness.
Blood Brain Barrier (BBB) function and Brain Capillaries (Brochard *et al* 2009; Farkas *et al.*, 2000)	Infiltration of CD4+/CD8+ T cells near dopaminergic neurons. Increased endothelial cell density and microvascular changes. Microglia-derived ROS may trigger angiogenesis without BBB breakdown.
Viral Infections (Hisanaga *et al.*, 2001)	May initiate neuroinflammation (e.g., postencephalitic parkinsonism, influenza).
Elevated iron levels (Mandel *et al.*, 2003; Sian Hulsmann *et al.*, 2010)	- Excess iron in glial cells → mitochondrial stress, ferroptosis, Lewy body formation.
Reduced Neutrophic Factors (NFs) (Bothwell *et al.*, 2016; Siegel *et al.*, 2000)	↓ GDNF, CDNF, MANF, EPO, BDNF → dopaminergic neuron death. CDNF/MANF shown to protect and regenerate neurons in PD models.
Pre-synaptic Dysfunction (Nemani *et al.*, 2010; Khan *et al.*, 2023)	-α-syn disrupts synaptic vesicle recycling → early PD feature.

Mechanism of Pathogenesis	Role and/ or effect
Monoamine Oxidase B activity (Jellinger 2017; Heikkila RE *et al.*, 1984; Tong *et al.*, 2017)	Elevated MAO-B in astrocytes → ROS production → DA neuron death.
Altered Calcium ion homeostasis (Guzman *et al.*, 2010)	-Cav1.3 channels in DA neurons → excessive mitochondrial ROS → mtDNA damage. -
Loss of Glutathione (GSH) biomarker (Garrett *et al.*, 2018)	-GSH depletion → oxidative stress → increased PD risk and neuron vulnerability.
Growth Stimulating Hormone levels (Ceda GP; Sun *et al.*, 2005; Pellecchia MT *et al.*, 2014)	-↓ IGF-1 linked to worse prognosis; may have neuroprotective roles.
Signalling Pathways:	Insulin/IGF-1 Pathway (Aguirre *et al.*, 2016) Dysregulated in diabetes/metabolic syndrome; reduces neuroprotection. GH/IGF-1 Axis (Gubbi S *et al.*, 2018) Age-related decline → risk for PD, AD, ALS, etc. Neurotrophic Factor Signalling (via Akt) Requires α-syn function; reduced Akt → impaired IGF-1 response. Serotonin Pathway 5-HT-mediated GH release impaired in PD. Chaperone-Mediated Autophagy (CMA) CMA dysfunction → α-syn accumulation → Lewy body formation. Ubiquitin-Proteasome Pathway Dysfunction leads to α-syn aggregation; PARKIN and UCHL-1 essential for recovery (Desplats *et al.*, 2009). Fas-Fas Ligand Pathway T-cell-mediated neuronal apoptosis; Fas upregulated in PD (Ferrer *et al.*, 2002). JNK Pathway Inhibition protects DA neurons; linked to COX-2 in PD (Tieu K *et al.*, 2003). Gut-Brain Axis α-syn originates in gut, spreads via vagus nerve. Constipation, inflammation, and ↓ ghrelin linked to early PD (Fiszer *et al.*, 2010). Mesocorticolimbic and Cholinergic Pathways α-syn deposits affect cognition; ↓ NE in prefrontal cortex. Kynurenine Pathway (KP) TRP metabolism imbalance → neurotoxic (QUIN) vs. neuroprotective (KYNA) effects (Dhivya *et al.*, 2020).
Pathogenesis of decreased Motor Activity (George DeMaagd *et al.*, 2015)	-DA loss → GPi/SNpc overactivity → GABA inhibition → ↓ thalamocortical stimulation.
Olfactory Dysfunction (Siderowf *et al.*, 2005)	-Early Lewy pathology in olfactory bulb may signal PD onset.

of α-syn mRNA. To increase α-syn clearance, therapies focus on activating lysosomal or proteasomal degradation pathways. Agents like Cathepsin D, Ambroxol, and LTI-291 (a *GBA* stimulator) and Venglustat (a sphingolipid synthesis inhibitor) support lysosomal function. Enhancing chaperone activity through proteins like HSP70 and drugs like geldanamycin, or inhibiting SCD enzymes via YTX-7739, can further facilitate degradation.

Another key therapeutic direction is immunotherapy, which targets extracellular toxic α-syn species. This includes passive immunization (like *PRX002, BIIB-054, and MEDI-1341*) and active immunization (like PD01A, UB-312, or DNA-based vaccines like AV-1950D). These strategies aim to clear pathological α-syn and prevent its spread. Vehicles such as ApoB and glucan microparticles with rapamycin have been explored for delivery

across the blood-brain barrier. Further, therapies aim to disrupt membrane interactions or aggregation of α-syn using peptide inhibitors, chaperone-like proteins (e.g., 14-3-3, β-syn), or small molecule inhibitors such as UCB-0599, Anle138b, ENT-01, and CLR01 (refer to Table 4).

Neurotrophic Factors and Growth Agents

Gene and targeted therapies aim to correct mutations in genes like *PINK1*, PARKIN, and DJ-1, while restorative therapies involve neurotrophic factors such as GDNF and CDNF, and stem cell transplantation to regenerate dopaminergic neurons. Adenosine A2a receptor antagonists like Istradefylline enhance dopamine signalling and offer neuroprotection. Neuroimmunophilins, including Rapamycin and FK506, support neuronal growth by modulating protein synthesis. Other strategies target calcium homeostasis (e.g., Isradipine), iron overload (e.g., Deferiprone), and critical signalling pathways. These include insulin signalling through GLP-1 agonists, gut-brain axis modulation via ghrelin, kynurenine pathway adjustments for neurotransmission, and antioxidant defense via KEAP1-NrF2 activation.

Gene Therapy Approaches

In Gene Therapy, a possible source of treatment may come from overexpression of autosomal recessive genes, where loss of function is linked to PD, supported by a study reporting overexpression of PRKN via γAA2 vectors had protective effects

Table 2: Genetic Pathophysiology of Parkinson's Disease (PD).

Gene	Role / Effect of Mutations
SCNA	Encodes α-synuclein; mutations lead to aggregation and Lewy Body (LB) formation. Found in autosomal dominant PD (Greek, Italian families). Therapeutic target.
LRRK2	Identified in 2004 as a monogenic PD cause; impairs autophagy and lysosomal function. Autosomal dominant with variable penetrance.
PINK1	Mutations disrupt mitochondrial quality control, causing dopaminergic neuron dysfunction.
PARKIN (PRKN)	Regulates mitochondrial dynamics. Most common gene mutated in Early-Onset PD (EOPD). Accounts for 50% of familial, 20% of idiopathic EOPD cases.
DJ-1 (PARK7)	Functions as oxidative stress sensor. Mutations compromise cellular defense mechanisms.
GBA	Mutations cause Gaucher's disease. Strong PD risk factor due to impaired lysosomal function. Associated with mitochondrial dysfunction.
POLG1	Encodes mtDNA polymerase; mutations lead to mtDNA deletions, myopathy, neuropathy, and Parkinsonian features.
HMOX1	Encodes stress-response protein; variants linked to increased PD susceptibility under oxidative stress.
c-Abl	Tyrosine kinase; inactivates PARKIN via phosphorylation, promoting oxidative stress and impaired proteostasis.
JNK (c-Jun N-terminal Kinase)	Activates apoptosis in DA neurons; associated with COX-2 in PD pathology.
mTORC1	Senses nutrients/energy; promotes neuronal survival. Activation improves motor function in PD models.
Omi/HtrA2	Mitochondrial serine protease; mutations impair oxidative stress response, linked to sporadic PD.
Neuroinflammatory Genes	TNF-α (psn -308), IL-1β (psn -511), IL-6 (psn -174) variants increase PD risk via pro-inflammatory signalling.
EIF4G1	Enhances mRNA translation under oxidative stress; linked to sporadic and familial PD.
SOD2	Converts superoxide to H_2O_2; mutation reduces mitochondrial antioxidant capacity.
VPS35	Identified D620N mutation in autosomal dominant late-onset PD; involved in retromer trafficking.
PITX3	Transcription factor essential for dopaminergic neuron development. SNP rs2281983 linked to EOPD; rs4919621 more frequent in EOPD vs. LOPD.
Other Transcription Factors	Nurr1, EN1, SHH, c-Rel: regulate dopaminergic neuron development and survival.
ATG5 / ATG7	Key autophagy genes; mutations impair clearance of damaged proteins/organelles, contributing to PD.
Kynurenine Pathway (KP) Genes	Mutations in KMO and ACMSD affect TRP metabolism. ACMSD SNPs identified in both familial and sporadic PD (e.g., p.Trp26*, p.Glu298Lys).
Familial Mutations	Autosomal Dominant: *SNCA, LRRK2*, VPS35, RAB39B, TMEM230. Autosomal Recessive: *PARKIN, PINK1, DJ-1, ATP13A2, PLA2G6, FBXO7, DNAJC6, SYNJ1*. Also includes mitochondrial Complex I mutations.

Table 3: **Neuroprotective Strategies and Agents in Parkinson's disease.**

Category	Aim / Mechanism	Key Targets / Pathways	Examples
Monoamine Oxidase B Inhibitors (MAO-B-I)	Inhibit DA catabolism; reduce oxidative stress and prevent MPTP → MPP^+ conversion; anti-apoptotic effects.	MAO-B, ROS, SOD, Catalase, BCL-2, GAPDH	Selegiline, Rasagiline, Safinamide, Lazabemide, BTS 74-398.
Dopamine Agonists	Stimulate DA receptors; ↓ ROS and STN excitotoxicity; ↑ endogenous antioxidant defenses.	D1, D2, D3, Glutathione, SOD, Catalase, Iron, Lipid peroxidation.	Pramipexole, Ropinirole, Apomorphine, Pergolide, Bromocriptine, Cabergoline, Aplindore, Pardoprunox.
Anti-Apoptotic Agents	Prevent programmed cell death pathways; stabilize mitochondria; block nuclear GAPDH translocation.	BCL-2, SOD, GAPDH, Caspases, MLK pathway.	Selegiline, DMD, Rasagiline, TVP1022, TCH346, CEP-1347
Anti-Excitotoxic Agents	Block excitatory glutamate transmission (NMDA or mGluR); protect STN and downstream nuclei from overexcitation.	NMDA receptors, mGluRs, Na^+ channels (for glutamate release).	Amantadine, Memantine, Riluzole, Remacemide, Mavoglurant, AFQ-056
Mitochondrial Biogenesis and Bioenergetics	Enhance mitochondrial function and biogenesis through PGC-1α/SIRT1; restore energy metabolism via bioenergetics.	PGC-1α, SIRT1, PPAR-γ, NAD^+, Complex I, ATP synthesis.	Rosiglitazone, Pioglitazone, Bezafibrate, Resveratrol, MitoQ, Creatine, CoQ10, Nicotinamide.
Antioxidants	Scavenge ROS/RNS; protect cells via direct or indirect antioxidant activity.	ROS, RNS, SOD, Catalase, Selenium, Free Radicals, Uric Acid.	CoQ10, Vitamin E, Uric Acid, Inosine, Ginkgo Biloba, Lipoic acid, Acetyl-carnitine, Riboflavin.

Table 4: **Therapeutic strategies targeting α-synuclein.**

Category	Therapeutic Strategy	Mechanism	Example(s)
α-Synuclein Directed Therapies	a) Reduce α-syn Synthesis	Gene interference via siRNAs or ASOs	- Ionis/Biogen ASOs- Human *SNCA*-ASOs- AmNA-ASO
		Modulation of 5′ UTR of α-syn mRNA	- Synucleozid
		Drug repurposing	- Salbutamol (asthma drug)
	b) Enhance α-syn Clearance	Boost lysosomal/proteasomal activity	- Cathepsin D- Ambroxol- LTI-291- Venglustat
		Promote chaperone function	- HSP70- Geldanamycin
		PARKIN/UCH-L1 augmentation	Experimental
		Inhibit oleic acid and SCD activity	- YTX-7739
		Immunotherapy (active/passive)	- PD01A, PD03A- Prasinezumab (PRX002)- BIIB-054 (Cinpanemab)- UB-312- LuAF82422- MEDI-1341- AV-1950D
		Immunization with siRNA or antigenic peptide	- AFFITOPE-based vaccines
		Delivery systems to BBB	- ApoB-linked oligonucleotides- GP + Rapamycin
	c) Inhibit Aggregation	Peptide/small molecule inhibitors blocking self-association	- β-syn, 14-3-3 proteins- UCB-0599/ NPT200-11- ENT-01- Anle138b- EGCG (Epigallocatechin Gallate)- CLR01- PBT434
	d) Prevent Modifications	Antioxidants and Kinase inhibitors	Investigational

in the striatum of γ AAV-α-syn-treated Non-Human Primates. Gene therapy may lead to knowledge on "precision medicine" for subtypes of PD, and this may change treatment methods, allowing for new therapy approach, albeit constant revision of the methodology involved with criteria for efficacy and safety issues being addressed before application to humans like ability to drive expression of a therapeutic gene in adequate number of cells, maintenance of long-term expression and allow exogenous control over the transgene product with considerations that gene therapy may not replace symptomatic treatment (Pavese *et al.*, 2009). The vaccine paradigm is supported by evidence that general immune stimulation in the periphery can attenuate harmful microglial responses to neuronal injury, potentially exerting neuro-restorative effects (refer to Table 5).

Cell Replacement Therapies

Emerging cellular strategies such as iPSC-derived midbrain organoids and cell culture models provide robust, ethical, and personalized platforms to study PD pathology, such as dopaminergic degeneration and α-synuclein accumulation. Transplantation therapies, while promising in restoring dopamine function through implanted neurons, face safety issues like graft-induced dyskinesia and ethical controversies surrounding fetal tissue use. Adenosine A2a receptor antagonists offer symptomatic improvement and are generally safe, but they do not modify disease progression. Meanwhile, cell replacement therapies using stem cells (like MSCs or iPSCs) hold regenerative potential but are shadowed by risks of tumorigenesis, immune reactions, and ethical debate, particularly concerning embryonic sources (Lohle *et al.*, 2010) (refer to Table 6).

Table 5: Emerging Treatment and Management Strategies in Parkinson's Disease.

Therapeutic Approach	Target	Mechanism	Examples
1. Gene Therapy / Targeted Therapy	*PINK1* / *PARKIN*	*PINK1* activators (neo substrates), cell-permeable *PARKIN* protein.	9-Methyl Kinetin, CV-O6
	DJ-1	Pharmacological chaperone	CB101
	HMOX1	Inhibition of oxidative stress	AZ-001
	GBA gene	Linked to α-synuclein pathways	—
	AAV-Neurturin	Neurotrophic delivery	—
2. Restorative Therapy	Neurotrophic Factors (NFs)	Enhances DA neuron survival, gene therapy delivery.	GDNF (AGT-190, BT-13), CDNF (NCT03295786), EPO (AGT-115), BDNF (MP201), MANF (AMRS-001), SR57667B, AMG-474
	Transplantation	Neural stem cells to replace degenerated neurons.	Neural stem cells
3. Adenosine (A2a) Receptor Antagonists	A2a receptor blockade	Enhances DA signaling, neuroprotection in non-DA areas.	Istradefylline, Preladenant, V81444, Tozadenant, ST 1535, PBF-509, ST 4203
4. Neuroimmunophilins	FK-binding proteins	Modulate 4E-BP, reduce protein synthesis, DA neuron growth.	Rapamycin, Cyclosporine, FK506, GPI-1046, GPI-1485
5. Calcium Homeostasis	L-type Ca^{2+} channel blockade	Aimed at Cav1.3 channels, modulating cellular calcium.	Isradipine
6. Iron Overload	Iron chelation	Targets elevated iron in PD pathology.	Deferiprone, Phytic acid (IP6)
7. Signaling Pathways	Insulin Signaling	Repurposing T2DM drugs, activates neurotrophic pathways.	Exenatide (PT302), Lixisenatide, Liraglutide, Semaglutide
	Gut-Brain Axis	Elevate AG:UAG ratio, ghrelin crossing BBB and binding GHSR.	AG strategies to increase bioavailability
	Kynurenine Pathway	KYNA analogs, enzyme inhibitors modulating neurotransmission.	FK506, UPF648, Ro-61-8048
	KEAP1-NrF2 Pathway	Antioxidant defense and autophagy modulation.	KKPA4026

Note: DA=Dopaminergic, AG=Acyl-Ghrelin, UAG=Unacylated Ghrelin, BBB=Blood-Brain Barrier, T2DM=Type 2 Diabetes Mellitus.

Table 6: Emerging Cellular and Receptor-Targeted Strategies in Parkinson's Disease.

Strategy	Description / Discovery	Uses / Mechanism	Advantages	Limitations / Disadvantages	Safety and Ethical Challenges	Examples
Cell Culture Models and Midbrain Organoids	Use of patient-derived iPSCs to generate DA neurons and 3D midbrain organoids.	Models PD pathology, α-syn aggregation, neuron-glia interaction *in vitro*.	Human-specific models; cost-effective; avoids animal use; supports personalized research.	Protocol variability; lacks behavioral phenotype modeling; scalability concerns.	Generally safe; minimal ethical concerns due to use of patient-derived cells.	iPSC-derived DA neurons, midbrain organoids
Transplantation Therapy	Implantation of fetal nigral cells or stem cell-derived neurons into striatum.	Replace lost neurons, restore dopamine function, induce behavioral recovery.	Long-term DA production; reinnervation observed in animal/human trials.	Mixed clinical outcomes; off-medication dyskinesia; immunosuppression needed.	Ethical issues with fetal tissue; tumor risk with pluripotent cells; long-term rejection concerns.	Fetal nigral transplants, neural stem cells, ES cell-derived DA neurons
Adenosine A2a Receptor Antagonists	Target basal ganglia output to reduce overactive indirect pathway signaling.	Adjunct to L-Dopa; improve motor symptoms; reduce "off" time.	Oral agents; improve motor response without worsening dyskinesia.	No disease modification; psychiatric side effects in some patients.	Low ethical risk; adverse events like hallucinations or insomnia require monitoring.	Istradefylline
Cell Replacement Therapies	Transplantation of MSCs, iPSCs, or neural stem cells to replace lost DA neurons.	Regenerative strategy aimed at restoring DA circuits and function.	Self-renewal capacity; can be patient-specific (autologous); potential long-term benefit.	Graft variability; risk of uncontrolled growth or misdifferentiation.	Tumorigenesis, immune rejection; ethical debate with embryonic sources.	iPSC-derived neurons, MSCs, neural progenitor cells

Biomarkers and Early Diagnosis

Pre-synaptic dopaminergic imaging biomarkers are used to assess the functional integrity of the dopaminergic neurons, particularly within the nigrostriatal pathway. Among these, 6-[^{18}F]-Fluoro-L-Dopa (FD) PET is widely used to measure dopamine synthesis capacity. While FD PET is effective for tracking disease progression, it may underestimate neuronal loss in early-onset PD (EOPD) due to compensatory upregulation of enzymes like AADC. Dopamine Transporter (DAT) imaging using SPECT or PET is another sensitive technique for detecting early dopaminergic terminal loss. However, its diagnostic utility in EOPD may be confounded by compensatory DAT downregulation and pharmacological influences from treatment. Vesicular monoamine transporter 2 imaging using [^{11}C]-Dihydrotetrabenazine (DTBZ) PET provides a stable measure of presynaptic dopaminergic integrity and is less affected by acute pharmacological changes, though alterations in vesicular dopamine levels may influence binding. FMT PET is another tracer that behaves similarly to FD but is less metabolized and has limited availability.

Post-synaptic dopaminergic imaging markers are focused on dopamine receptor availability (D1, D2, D3) in the striatum and other brain regions. Commonly used tracers include [^{11}C]-raclopride for PET and [^{123}I]-IBZM for SPECT, which help assess receptor binding changes due to dopamine deficiency. In EOPD, an upregulation of D2 receptors is commonly observed, reflecting compensatory responses. However, receptor binding can vary with age, disease stage, and chronic dopaminergic therapy, which can complicate interpretation. Ligands like [^{18}F]-fallypride and [^{11}C]-FLB-457 allow for higher affinity imaging of extrastriatal receptors, offering more detailed insights into dopaminergic dysfunction.

Markers of neuroinflammation, such as [^{11}C]-PK11195 PET, target activated microglia and provide *in vivo* evidence of inflammatory processes contributing to PD pathogenesis. Elevated binding has been reported in the basal ganglia, pons, and cortical regions of PD patients (Star *et al.*, 2014; Song *et al.*, 2017).

Clinical Trials Landscape

In clinical research, ontology was introduced in neurodegenerative conditions to define reality and create standardized frameworks relevant to PD drug development (Lee *et al.*, 2021; Miranda *et al.*, 2012; Voss *et al.*, 2008). The lack of benefit of non-symptomatic drugs over placebo may not reflect absence of neuroprotection but rather failure to "readjust" basal ganglia compensation or translation gaps between preclinical and clinical studies (Devos *et al.*, 2020). Better understanding of dopamine system biology at behavioral and cellular levels could foster hypothesis-driven research and translational infrastructure integrating pathogenesis, epidemiology, and genetics. However, the brain's inaccessibility for *in vivo* neuronal counts limits clinical tools for monitoring neuroprotection, and no accepted criteria for disease-modifying effects exist (Lee *et al.*, 2000). Some reported benefits were confounded by symptomatic or pharmacological effects (Hart *et al.*, 2009). Patient selection is critical. Efforts to involve the PD community in clinical trials enhance awareness and participation (Lee *et al.*, 2021). Yet, early PD populations may already be too advanced, and differential diagnosis complicates inclusion of EOPD and other parkinsonisms. Prodromal markers and gene-positive carriers, such as *LRRK2* G2019S, may allow earlier or stage-specific trials assessing both motor and non-motor outcomes.

Trial design and sample size also pose challenges. Large cohorts are needed to detect modest effects and offset dropouts, though differential attrition complicates randomization. Delayed-start designs attempt to distinguish symptomatic from disease-modifying effects but face limitations, including wash-in/wash-out confounds and ethical concerns. The ADAGIO trial was the first to show a positive delayed-start result, though interpretation remained uncertain (Anthony *et al.*, 2009). Futility designs, adapted from cancer and stroke research, efficiently screen out ineffective agents with small samples, historical controls, and one-sided testing, but lack power to confirm disease modification. Outcome measures remain problematic: UPDRS is subjective and treatment-sensitive, while alternatives like composite outcomes, imaging biomarkers (FDOPA PET, β-CIT SPECT), and patient-reported scales (PDQ-39, MoCA, NMSS, DRS-2) each have limitations.

Further barriers include misdiagnosis (up to 15% with normal dopaminergic imaging), inconsistent statistical handling, and inadequate reporting transparency. Post-mortem studies show mixed neuroinflammation, while *in vivo* biomarkers support oxidative stress (3-nitrotyrosine). FD PET suggests a 6-year preclinical phase of dopaminergic loss. Initiatives like AMP-PD and PPMI aim to refine biomarkers and trial design. Novel designs, e.g., Multi-Arm, Multi-Stage (MAMS), allow simultaneous testing of multiple candidates. Lessons from transplantation trials, where off-medication dyskinesias emerged, highlight the need for rigorous placebo controls. Despite challenges, progress continues through repurposed therapies, cell-based approaches, and trial resources (Mirza *et al.*, 2000).

Rethinking the Paradigm: From Disease Modification to Prevention

There is a growing shift in PD research from focusing solely on disease modification to actively pursuing strategies for prevention. Central to this evolving paradigm is the identification of the prodromal phase of PD, an early window of opportunity where non-motor symptoms and biomarkers may precede clinical diagnosis by years. Intervening during this phase could delay or prevent the onset of motor symptoms. In parallel, lifestyle interventions such as regular physical activity and a neuroprotective diet rich in antioxidants and anti-inflammatory components have shown promise in slowing disease progression and reducing risk. Furthermore, modifying known risk factors, such as managing diabetes, correcting vitamin D deficiency, and restoring gut microbiome balance, offers potential avenues to reduce neurodegenerative vulnerability. Together, these strategies support a more proactive and preventive approach to PD, emphasizing early detection, personalized intervention, and holistic care.

Future Directions and Recommendations

Future directions in PD research and treatment emphasize the transition toward more personalized and integrative approaches. Precision medicine, guided by patient stratification based on genetic, molecular, and clinical profiles, offers the potential to tailor interventions for improved efficacy and reduced side effects. Alongside this, multi-targeted combination strategies are gaining prominence, aiming to simultaneously address various pathological mechanisms such as mitochondrial dysfunction, oxidative stress, neuroinflammation, and alpha-synuclein aggregation. Collaborative efforts across disciplines, including neurology, immunology, genomics, and biotechnology, are essential to drive innovation and translate laboratory findings into clinical applications. Furthermore, policy and funding reforms are crucial to support high-risk, high-reward research, enabling the development and implementation of transformative disease-modifying therapies. Together, these directions reflect a shift from managing symptoms to modifying disease progression and ultimately improving quality of life for individuals with PD.

CONCLUSION

This review not only explores neuroprotection in Parkinson's Disease (PD) but also highlights the significant milestones achieved in understanding and managing neurodegenerative disorders. What was once deemed an unattainable goal, disease modification is now increasingly viable, including in PD. Advances in research, clinical care, and health infrastructure have transformed the outlook for neurodegenerative diseases. Evidence supports that PD is heterogenous in nature with the

major factors causing neuronal loss aforementioned, from the major causes like alpha-synuclein accumulation, mitochondrial dysfunction, oxidative stress and chronic neuroinflammation amongst others and the availability of different treatment approaches. There are better ways to improve the livelihood of People living with Parkinsons (PwPs) who are now capable of understanding their situation and are in a better position to advocate for themselves, their caregivers may also be at a better position of understanding their needs and keen to notice changes and provide better care and medical staff being at a better position, especially in diagnosis of the prodromal phase without the assumption of normal aging, requesting for proper diagnostic procedure and giving proper advice as needed. The future no longer appears daunting. In the case of PD, patients, healthcare professionals, researchers, policymakers, and the pharmaceutical industry have all contributed to breaking the status quo. Today, we can move forward with renewed optimism and greater clarity and the stereotypical negative attitude towards aging can be changed and embraced with a more positive approach.

ACKNOWLEDGEMENT

The authors would like to acknowledge all the scientific websites, authors, and tools used to obtain and analyze the information in this study.

ABBREVIATIONS

PD: Parkinson's Disease; **UPDRS:** Unified Parkinson's Disease Rating Scale; **MDS-UPDRS:** Movement Disorder Society - Unified Parkinson's Disease Rating Scale; **FDA:** Food and Drug Administration; **CNS:** Central Nervous System; **CSF:** Cerebrospinal Fluid; **PET and MRI:** Positron Emission Tomography and Magnetic Resonance Imaging; **SPECT:** Single Photon Emission Computed Tomography; **DAT and VMAT2:** Dopamine Transporter and Vesicular Monoamine Transporter 2; **MAO-B:** Monoamine Oxidase B; **COMT:** Catechol-O-Methyltransferase; **MSA:** Multiple System Atrophy; **PSP:** Progressive Supranuclear Palsy, **CBD:** Corticobasal Degeneration; **DLB:** Dementia with Lewy Bodies; **NPH:** Normal Pressure Hydrocephalus; **α-syn:** Alpha-Synuclein; **LRRK2:** Leucine-Rich Repeat Kinase 2; **SNCA:** Synuclein Alpha; **PINK1:** PTEN-Induced Putative Kinase 1; **MPTP and 6-OHDA:** 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine and 6-Hydroxydopamine; **A2A:** Adenosine A2A Receptor; **NFs:** Neurotrophic Factors; **NfL:** Neurofilament Light Chain; **GWAS:** Genome-Wide Association Studies; **BBB:** Blood-Brain Barrier; **ADL:** Activities of Daily Living; **PWPs:** People living with Parkinsons; **SNpc:** Substantia Nigra pars Compacta; **DALYs:** Disability-Adjusted Life Years; **DMTs:** Disease Modifying Therapies; **EOPD:** Early-Onset Parkinson's Disease; **LOPD:** Late-Onset Parkinson's Disease; **AADC:** Aromatic L-amino acid decarboxylase; **DTBZ:** Dihydrotetrabenazine; **FMT:** Fluoro-Methyl-Tyrosine; **NMSS:** Non-Motor Symptoms Scale; **DRS-2:** Dementia Rating Scale-2; **MoCA:** Montreal Cognitive Assessment; **PDQ-39:** Parkinson's Disease Questionnaire-39; **MAMS:** Multi-Arm, Multi-Stage; **GSH:** Glutathione; **GH:** Growth Hormone; **IGF-1:** Insulin-like Growth Factor 1; **AD:** Alzheimer's Disease; **ALS:** Amyotrophic Lateral Sclerosis; **JNK:** c-Jun N-terminal Kinase; **COX-2:** Cyclooxygenase-2; **TRP:** Tryptophan; **QUIN:** Quinolinic Acid; **KYNA:** Kynurenic Acid; G**PI:** Globus Pallidus Interna; **ASOs:** Antisense Oligonucleotides; **siRNAs:** small interfering RNAs; **5-HT:** Serotonin; **NA:** Noradrenaline; PPAR: Peroxisome Proliferator-Activated Receptor; **AG:** Acyl-Ghrelin; **UAG:** Unacylated Ghrelin; **GHSR:** Growth Hormone Secretagogue Receptor; **T2DM:** Type 2 Diabetes Mellitus; **iPSCs:** induced Pluripotent Stem Cells; **ES cell:** Embryonic Stem cell; **MSCs:** Mesenchymal Stem Cells; **PARP:** poly (ADP-ribose) polymerase.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

REFERENCES

Aguirre, G. A., De Ita, J. R., de la Garza, R. G., & Castilla-Cortazar, I. (2016). Insulin-like growth factor-1 deficiency and metabolic syndrome. Journal of Translational Medicine, 14, Article 3. https://doi.org/10.1186/s12967-015-0762-z

Anthony, H. V. S. (2009). Neuroprotection in Parkinson's disease. Parkinsonism and Related Disorders, 15, 41–43.

Biglan, K. M., & Ravina, B. (2007). Neuroprotection in Parkinson's disease: An elusive goal. Seminars in Neurology, 27(2), 106–112. https://doi.org/10.1055/s-2007-971168

Blum-Degen, D., Müller, T., Kuhn, W., Gerlach, M., Przuntek, H., & Riederer, P. (1995). Interleukin-1 beta and interleukin-6 are elevated in the cerebrospinal fluid of Alzheimer's and de novo Parkinson's disease patients. Neuroscience Letters, 202 (1–2), 17–20. https://doi.org/10.1016/0304-3940(95)12192-7

Bothwell, M. (2016). Recent advances in understanding neurotrophin signaling. F1000Research. F1000 Faculty Rev-1885, 5. https://doi.org/10.12688/f1000research .7698.1

Braak, H., & Braak, E. (2000). Pathoanatomy of Parkinson's disease. Journal of Neurology, 247(Suppl. 2), 3–10.

Brochard, V., Combadière, B., Prigent, A., Laouar, Y., Perrin, A., Beray-Berthat, V., Bonduelle, O., Alvarez-Fischer, D., Callebert, J., Launay, J.-M., Duyckaerts, C., Flavell, R. A., Hirsch, E. C., & Hunot, S. (2009). Infiltration of CD4+ lymphocytes into the brain contributes to neurodegeneration in a mouse model of Parkinson disease. The Journal of Clinical Investigation, 119(1), 182–192. https://doi.org/10.1172/JCI36470

Ceda, G. P., Dall'Aglio, E. E., Maggio, M., Lauretani, F., Bandinelli, S., Falzoi, C., Grimaldi, W., Ceresini, G., Corradi, F., Ferrucci, L., Valenti, G., & Hoffman, A. R. (2005). Clinical implications of the reduced activity of the GH-IGF-I axis in older men. Journal of Endocrinological Investigation, 28(11)(Suppl. Proceedings), 96–100.

Dagda, R. K., & Chu, C. T. (2009). Mitochondrial quality control: Insights on how Parkinson's disease-related genes PINK1, parkin, and OMI/HtrA2 interact to maintain mitochondrial homeostasis. Journal of Bioenergetics and Biomembranes, 41(6), 473–479. https://doi.org/10.1007/s10863-009-9255-1

De Lau, L. M. L., & Breteler, M. M. B. (2006). Epidemiology of Parkinson's disease. The Lancet. Neurology, 5(6), 525–535. https://doi.org/10.1016/S1474-4422(06)70471-9

Del Tredici, K., & Braak, H. (2012). Lewy pathology and neurodegeneration in premotor Parkinson's disease. Movement Disorders, 27(5), 597–607. https://doi.org /10.1002/mds.24921

DeMaagd, G., & Philip, A. (2015). Parkinson's disease and its management part 1: Disease entity, risk factors, pathophysiology, clinical presentation, and diagnosis. P & T., 40(8), 504–532.

Desplats, P., Lee, H.-J., Bae, E.-J., Patrick, C., Rockenstein, E., Crews, L., Spencer, B., Masliah, E., & Lee, S.-J. (2009). Inclusion formation and neuronal cell death through neuron-to-neuron transmission of alpha-synuclein. Proceedings of the National Academy of Sciences of the United States of America, 106(31), 13010–13015. https:/ /doi.org/10.1073/pnas.0903691106

Devos, D., Hirsch, E., & Wyse, R. (2020). Seven solutions for neuroprotection in Parkinson's disease. Movement Disorders, 36(2), 306–316. https://doi.org/10.1002/ mds.28379

Dhivya Venkatesan, I., M., Narayanasamy, A., Sivad, K., & Vellingiri, B. (2020). Kynurenine pathway in Parkinson's disease-An update. eNeurologicalSci, 21, 1–10.

Driver, J. A., Logroscino, G., Gaziano, J. M. *et al.* (2009). Incidence and remaining lifetime risk of Parkinson's disease in advanced age. Neurology, 72, 32–38.

Farkas, E., De Jong, G. I., de Vos, R. A., Jansen Steur, E. N., & Luiten, P. G. (2000). Pathological features of cerebral cortical capillaries are doubled in Alzheimer's disease and Parkinson's disease. Acta Neuropathologica, 100(4), 395–402. https://doi.org/10.1007/s004010000195

Féger, J., Hassani, O. K., & Mouroux, M. (1997). The subthalamic nucleus and its connections: New electrophysiological and pharmacological data. Advances in Neurology, 74, 31–43.

Ferrer, I., Blanco, R., Cutillas, B., & Ambrosio, S. (2000). Fas and Fas-L expression in Huntington's disease and Parkinson's disease. Neuropathology and Applied Neurobiology, 26(5), 424–433. https://doi.org/10.1046/j.1365-2990.2000.00267.x

Finkel, T. (2011). Signal transduction by reactive oxygen species. The Journal of Cell Biology, 194(1), 7–15. https://doi.org/10.1083/jcb.201102095

Fiszer, U., Michałowska, M., Baranowska, B., Wolińska-Witort, E., Jeske, W., Jethon, M., Piaścik-Gromada, M., & Marcinowska-Suchowierska, E. (2010). Leptin and ghrelin concentrations and weight loss in Parkinson's disease. Acta Neurologica Scandinavica, 121(4), 230–236. https://doi.org/10.1111/j.1600-0404.2009.01185.x

Friedman, L. G., Lachenmayer, M. L., Wang, J., He, L., Poulose, S. M., Komatsu, M., Holstein, G. R., & Yue, Z. (2012). Disrupted autophagy leads to dopaminergic axon and dendrite degeneration and promotes presynaptic accumulation of α-synuclein and LRRK2 in the brain. The Journal of Neuroscience, 32(22), 7585–7593. https://doi.org/10.1523/JNEUROSCI.5809-11.2012

Garrett, T., Rachel, A., Ruoqiong, C., Karo, G., Hicret, I., Mariana, L. *et al.* (2018). Glutathione as a marker for human disease. Advances in Clinical Chemistry, 87, 1–19.

Gegg, M. E., Cooper, J. M., Chau, K.-Y., Rojo, M., Schapira, A. H. V., & Taanman, J.-W. (2010). Mitofusin 1 and mitofusin 2 are ubiquitinated in a PINK1/parkin-dependent manner upon induction of mitophagy. Human Molecular Genetics, 19(24), 4861–4870. https://doi.org/10.1093/hmg/ddq419

Gegg, M. E., & Schapira, A. H. V. (2011). PINK1-parkin-dependent mitophagy involves ubiquitination of mitofusins 1 and 2: Implications for Parkinson disease pathogenesis. Autophagy, 7(2), 243–245. https://doi.org/10.4161/auto.7.2.14332

Gubbi, S., Quipildor, G. F., Barzilai, N., Huffman, D. M., & Milman, S. (2018). 40 years of IGF1: IGF1: The Jekyll and Hyde of the aging brain. Journal of Molecular Endocrinology, 61(1), T171–T185. https://doi.org/10.1530/JME-18-0093

Guzman, J. N., Sanchez-Padilla, J., Wokosin, D., Kondapalli, J., Ilijic, E., Schumacker, P. T., & Surmeier, D. J. (2010). Oxidant stress evoked by pacemaking in dopaminergic neurons is attenuated by DJ-1. Nature, 468(7324), 696–700. https://doi.org/10.1038/nature09536

Haas, R. H., Nasirian, F., Nakano, K., Ward, D., Pay, M., Hill, R., & Shults, C. W. (1995). Low platelet mitochondrial complex I and complex II/III activity in early untreated Parkinson's disease. Annals of Neurology, 37(6), 714–722. https://doi.org/10.1002/ana.410370604

Hart, R. G., Pearce, L. A., Ravina, B. M., Yaltho, T. C., & Marler, J. R. (2009). Neuroprotection trials in Parkinson's disease: Systematic review. Movement Disorders, 24(5), 647–654. https://doi.org/10.1002/mds.22432

Heikkila, R. E., Manzino, L., Cabbat, F. S., & Duvoisin, R. C. (1984). Protection against the dopaminergic neurotoxicity of 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine by monoamine oxidase inhibitors. Nature, 311(5985), 467–469. https://doi.org/10.1038/311467a0

Hisanaga, K., Asagi, M., Itoyama, Y., & Iwasaki, Y. (2001). Increase in peripheral CD4 bright+ CD8 dull+ T cells in Parkinson disease. Archives of Neurology, 58(10), 1580–1583. https://doi.org/10.1001/archneur.58.10.1580

Hunot, S., Dugas, N., Faucheux, B., Hartmann, A., Tardieu, M., Debré, P., Agid, Y., Dugas, B., & Hirsch, E. C. (1999). FcεRII/CD23 is expressed in Parkinson's disease and induces, *in vitro*, production of nitric oxide and tumor necrosis factor-alpha in glial cells. The Journal of Neuroscience, 19(9), 3440–3447. https://doi.org/10.1523/JNEUROSCI.19-09-03440.1999

Ilijic, E., Guzman, J. N., & Surmeier, D. J. (2011). The L-type channel antagonist isradipine is neuroprotective in a mouse model of Parkinson's disease. Neurobiology of Disease, 43(2), 364–371. https://doi.org/10.1016/j.nbd.2011.04.007

Jellinger, K. A. (2012). Neuropathology of sporadic Parkinson's disease: Evaluation and changes of concepts. Movement Disorders, 27(1), 8–30. https://doi.org/10.1002/mds.23795

Jellinger, K. A. (2017). Brain monoamine oxidases in human parkinsonian disorders. Brain, 140(9), 2262–2264. https://doi.org/10.1093/brain/awx190

Karbowski, M. (2010). Mitochondria on guard: Role of mitochondrial fusion and fission in the regulation of apoptosis. In Advances in Experimental Medicine and Biology, 687, 131–142. https://doi.org/10.1007/978-1-4419-6706-0_8

Khan, E., Hasan, I., & Haque, M. E. (2023). Parkinson's disease: Exploring different animal model systems. International Journal of Molecular Sciences, 24(10), Article 9088. https://doi.org/10.3390/ijms24109088

Koller, W., Vetere-Overfield, B., Gray, C., Alexander, C., Chin, T., Dolezal, J., Hassanein, R., & Tanner, C. (1990). Environmental risk factors in Parkinson's disease. Neurology, 40(8), 1218–1221. https://doi.org/10.1212/WNL.40.8.1218

Konnova, E. A., & Swanberg, M. (2018) (Chapter 5). Animal models of Parkinson's disease. In T. B. Stoker & J. C. Greenland (Eds.),Parkinson's disease: Pathogenesis and clinical aspects (pp. 83–106). Codon Publications. https://doi.org/10.15586/codonpublications.parkinsonsdisease.2018.ch5

Kövari, E., Horvath, J., & Bouras, C. (2009). Neuropathology of Lewy body disorders. Brain Research Bulletin, 80 (4–5), 203–210. https://doi.org/10.1016/j.brainresbull.2009.06.018

Lee, C. S., Cenci, M. A., Schuler, M., & Björklund, A. (2000). Embryonic ventral mesencephalic grafts improve L-dopa-induced dyskinesia in a rat model of Parkinson's disease. Brain, 123(7), 1365–1379.

Lee, J. W., Song, Y. S., Kim, H., Ku, B. D., & Lee, W. W. (2021). Patients with scans without evidence of dopaminergic deficit (SWEDD) do not have early Parkinson's disease: Analysis of the PPMI data. PLOS One, 16(2), Article e0246881. https://doi.org/10.1371/journal.pone.0246881

Löhle, M., & Reichmann, H. (2010). Clinical neuroprotection in Parkinson's disease-Still waiting for the breakthrough. Journal of the Neurological Sciences, 289 (1–2), 104–114. https://doi.org/10.1016/j.jns.2009.08.025

Mandel, S., Grünblatt, E., Riederer, P., Gerlach, M., Levites, Y., & Youdim, M. B. H. (2003). Neuroprotective strategies in Parkinson's disease: An update on progress. CNS Drugs, 17(10), 729–762. https://doi.org/10.2165/00023210-200317100-00004

Mirza, B., Hadberg, H., Thomsen, P., & Moos, T. (2000). The absence of reactive astrocytosis is indicative of a unique inflammatory process in Parkinson's disease. Neuroscience, 95(2), 425–432. https://doi.org/10.1016/S0306-4522(99)00455-8

Mogi, M., Harada, M., Riederer, P., Narabayashi, H., Fujita, K., & Nagatsu, T. (1994). Tumor necrosis factor-alpha (TNF-alpha) increases both in the brain and in the cerebrospinal fluid from parkinsonian patients. Neuroscience Letters, 165 (1–2), 208–210. https://doi.org/10.1016/0304-3940(94)90746-3

Morgan, A. H., Rees, D. J., Andrews, Z. B., & Davies, J. S. (2018). Ghrelin mediated neuroprotection-A possible therapy for Parkinson's disease? Neuropharmacology, 136(B), 317–326. https://doi.org/10.1016/j.neuropharm.2017.12.027

Nemani, V. M., Lu, W., Berge, V., Nakamura, K., Onoa, B., Lee, M. K., Chaudhry, F. A., Nicoll, R. A., & Edwards, R. H. (2010). Increased expression of alpha-synuclein reduces neurotransmitter release by inhibiting synaptic vesicle reclustering after endocytosis. Neuron, 65(1), 66–79. https://doi.org/10.1016/j.neuron.2009.12.023

Olanow, C. W. (2007). The pathogenesis of cell death in Parkinson's disease-2007. Movement Disorders, 22(Suppl. 17), S335–S342. https://doi.org/10.1002/mds.21675

Pavese, N., Kiferle, L., & Piccini, P. (2009). Neuroprotection and imaging studies in Parkinson's disease. Parkinsonism and Related Disorders, 15(Suppl. 4), S33–S37. https://doi.org/10.1016/S1353-8020(09)70832-6

Pellecchia, M. T., Santangelo, G., Picillo, M., Pivonello, R., Longo, K., Pivonello, C., Vitale, C., Amboni, M., De Rosa, A., Moccia, M., Erro, R., De Michele, G., Santoro, L., Colao, A., & Barone, P. (2014). Insulin-like growth factor-1 predicts cognitive functions at 2-year follow-up in early, drug-naïve Parkinson's disease. European Journal of Neurology, 21(5), 802–807. https://doi.org/10.1111/ene.12137

Poehler, A.-M., Xiang, W., Spitzer, P., May, V. E. L., Meixner, H., Rockenstein, E., Chutna, O., Outeiro, T. F., Winkler, J., Masliah, E., & Klucken, J. (2014). Autophagy modulates SNCA/α-synuclein release, thereby generating a hostile microenvironment. Autophagy, 10(12), 2171–2192. https://doi.org/10.4161/auto.36436

Poewe, W., Seppi, K., Marini, K., & Mahlknecht, P. (2020). New hopes for disease modification in Parkinson's disease. Neuropharmacology, 171, Article 108085. https://doi.org/10.1016/j.neuropharm.2020.108085

Polymeropoulos, M. H., Lavedan, C., Leroy, E., Ide, S. E., Dehejia, A., Dutra, A., Pike, B., Root, H., Rubenstein, J., Boyer, R., Stenroos, E. S., Chandrasekharappa, S., Athanassiadou, A., Papapetropoulos, T., Johnson, W. G., Lazzarini, A. M., Duvoisin, R. C., Di Iorio, G., Golbe, L. I., & Nussbaum, R. L. (1997). Mutation in the alpha-synuclein gene identified in families with Parkinson's disease. Science, 276(5321), 2045–2047. https://doi.org/10.1126/science.276.5321.2045

Poole, A. C., Thomas, R. E., Andrews, L. A., McBride, H. M., Whitworth, A. J., & Pallanck, L. J. (2008). The PINK1/Parkin pathway regulates mitochondrial morphology. Proceedings of the National Academy of Sciences of the United States of America, 105(5), 1638–1643. https://doi.org/10.1073/pnas.0709336105

Postuma, R. B., Berg, D., Stern, M., Poewe, W., Olanow, C. W., Oertel, W., Obeso, J., Marek, K., Litvan, I., Lang, A. E., Halliday, G., Goetz, C. G., Gasser, T., Dubois, B., Chan, P., Bloem, B. R., Adler, C. H., & Deuschl, G. (2015). MDS clinical diagnostic criteria for Parkinson's disease. Movement Disorders, 30(12), 1591–1601. https://doi.org/10.1002/mds.26424

Pott Godoy, M. C., Tarelli, R., Ferrari, C. C., Sarchi, M. I., & Pitossi, F. J. (2008). Central and systemic IL-1 exacerbates neurodegeneration and motor symptoms in a model of Parkinson's disease. Brain, 131(7), 1880–1894. https://doi.org/10.1093/brain/awn101

Rodriguez, M. C., Obeso, J. A., & Olanow, C. W. (1998). Subthalamic nucleus mediated excitotoxicity in Parkinson's disease: A target for neuroprotection. Annals of Neurology, 44(3)(Suppl. 1), S175–S188. https://doi.org/10.1002/ana.410440726

Rohn, T. T. (2012). Targeting alpha-synuclein for the treatment of Parkinson's disease. CNS & Neurological Disorders Drug Targets, 11(2), 174–179. https://doi.org/10.2174/187152712800269678

Santos, C. M. M. (2012). New agents promote neuroprotection in Parkinson's disease models. CNS & Neurological Disorders Drug Targets, 11(4), 410–418. https://doi.org/10.2174/187152712800792820

Schapira, A. H. V. (2008). Progress in neuroprotection in Parkinson's disease. European Journal of Neurology, 15(Suppl. 1), 5–13. https://doi.org/10.1111/j.1468-1331.2008.02055.x

Schapira, A. H. V., Cooper, J. M., Dexter, D., Clark, J. B., Jenner, P., & Marsden, C. D. (1990). Mitochondrial complex I deficiency in Parkinson's disease. Journal of

Neurochemistry, 54(3), 823–827. https://doi.org/10.1111/j.1471-4159.1990.tb02325.x

Schieber, M., & Chandel, N. S. (2014). ROS function in redox signaling and oxidative stress. Current Biology, 24(10), R453–R462. https://doi.org/10.1016/j.cub.2014.03.034

Sian-Hülsmann, J., Mandel, S., & Youdim, M. B. (2010). The relevance of iron in the pathogenesis of Parkinson's disease. Journal of Neurochemistry, 118(6), 939–957.

Siderowf, A., Newberg, A., Chou, K. L., Lloyd, M., Colcher, A., Hurtig, H. I., Stern, M. B., Doty, R. L., Mozley, P. D., Wintering, N., Duda, J. E., Weintraub, D., & Moberg, P. J. (2005). [99mTc]TRODAT-1 SPECT imaging correlates with odor identification in early Parkinson disease. Neurology, 64(10), 1716–1720. https://doi.org/10.1212/01.WNL.0000161874.52302.5D

Siegel, G. J., & Chauhan, N. B. (2000). Neurotrophic factors in Alzheimer's and Parkinson's disease brain. Brain Research. Brain Research Reviews, 33 (2–3), 199–227. https://doi.org/10.1016/S0165-0173(00)00030-8

Song, N., Wang, W., Jia, F., Du, X., Xie, A., He, Q. *et al.* (2017). Assessments of plasma ghrelin levels in the early stages of Parkinson's disease. Movement Disorders, 0(0), 1–5.

Starr, B. W., Hagen, M. C., & Espay, A. J. (2014). Hydrocephalic parkinsonism: Lessons from normal pressure hydrocephalus mimics. Journal of Clinical Movement Disorders, 1, Article 2. https://doi.org/10.1186/2054-7072-1-2

Stocchi, F., & Olanow, C. W. (2003). Neuroprotection in Parkinson's disease: Clinical trials. Annals of Neurology, 53(Suppl. 3), S87–97; discussion S97. https://doi.org/10.1002/ana.10488

Sulzer, D., & Surmeier, D. J. (2013). Neuronal vulnerability, pathogenesis, and Parkinson's disease. Movement Disorders, 28(1), 41–50. https://doi.org/10.1002/mds.25095

Sun, L. Y., Al-Regaiey, K., Masternak, M. M., Wang, J., & Bartke, A. (2005). Local expression of GH and IGF-1 in the hippocampus of GH-deficient long-lived mice. Neurobiology of Aging, 26(6), 929–937. https://doi.org/10.1016/j.neurobiolaging.2004.07.010

Tatton, W. G., Chalmers-Redman, R., Brown, D., & Tatton, N. (2003). Apoptosis in Parkinson's disease: Signals for neuronal degradation. Annals of Neurology, 53(Suppl. 3), S61–70; discussion S70. https://doi.org/10.1002/ana.10489

Teismann, P., Tieu, K., Choi, D.-K., Wu, D.-C., Naini, A., Hunot, S., Vila, M., Jackson-Lewis, V., & Przedborski, S. (2003). Cyclooxygenase-2 is instrumental in Parkinson's disease neurodegeneration. Proceedings of the National Academy of Sciences of the United States of America, 100(9), 5473–5478. https://doi.org/10.1073/pnas.0837397100

Tong, J., Rathitharan, G., Meyer, J. H., Furukawa, Y., Ang, L.-C., Boileau, I., Guttman, M., Hornykiewicz, O., & Kish, S. J. (2017). Brain monoamine oxidase B and A in human parkinsonian dopamine deficiency disorders. Brain, 140(9), 2460–2474. https://doi.org/10.1093/brain/awx172

Tysnes, O.-B., & Storstein, A. (2017). Epidemiology of Parkinson's disease. Journal of Neural Transmission, 124(8), 901–905. https://doi.org/10.1007/s00702-017-1686-y

Verdin, E., Hirschey, M. D., Finley, L. W. S., & Haigis, M. C. (2010). Sirtuin regulation of mitochondria: Energy production, apoptosis, and signaling. Trends in Biochemical Sciences, 35(12), 669–675. https://doi.org/10.1016/j.tibs.2010.07.003

Voss, T., & Ravina, B. (2008). Neuroprotection in Parkinson's disease: Myth or reality? Current Neurology and Neuroscience Reports, 8(4), 304–309. https://doi.org/10.1007/s11910-008-0047-5

Wang, C., & Youle, R. J. (2009). The role of mitochondria in apoptosis*. Annual Review of Genetics, 43, 95–118. https://doi.org/10.1146/annurev-genet-102108-134850

Werner, P., Seppi, K., Marini, K., & Mahlknecht, P. (2020). New hopes for disease modification in Parkinson's disease. Neuropharmacology, 171, 1–11. (Duplicate; remove one instance.)

Yacoubian, T. A., & Standaert, D. G. (2009). Targets for neuroprotection in Parkinson's disease. Biochimica et Biophysica Acta, 1792(7), 676–687. https://doi.org/10.1016/j.bbadis.2008.09.009

Yasuda, T., & Mochizuki, H. (2010). The regulatory role of α-synuclein and parkin in neuronal cell apoptosis: Possible implications for the pathogenesis of Parkinson's disease. Apoptosis, 15(11), 1312–1321. https://doi.org/10.1007/s10495-010-0486-8

Cite this article: Ogwang MB, Jha DK, Chatterjee S. Neuroprotection in Parkinson's Disease: No More Status Quo. Int. J. Pharm. Investigation. 2026;16(2):371-83.