REVIEW ARTICLE

RECORDS OF PHARMACEUTICAL AND BIOMEDICAL SCIENCES

Parkinson's Disease: Molecular Mechanisms and Treatment Strategies

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Abstract

Parkinson's disease (PD) is the second most common neurodegenerative disorder in the elderly, clinically manifested by bradykinesia, resting tremor, postural instability, and hypermyotonia. Key pathological mechanisms implicated in PD onset include neuroinflammation, autophagy impairment, alpha-synuclein aggregation, and mitochondrial dysfunction. However, the precise molecular pathways underlying these processes remain to be fully elucidated. Currently, dopamine replacement therapy using levodopa/carbidopa is established as the gold standard of treatment for PD. No drug has been proven to slow disease progression. Recent findings highlight the pivotal role of the high-mobility group box 1 (HMGB1)/ receptor for advanced glycation end products (RAGE) axis in PD pathogenesis through its involvement in neuroinflammation, autophagy modulation, apoptosis regulation, and gene transcription. Additionally, the AMP-activated protein kinase (AMPK)/ silent information regulator 1 (SIRT1)/ peroxisome proliferator-activated receptor-gamma coactivator-1α (PGC-1α) signaling axis has emerged as a crucial regulator of mitochondrial biogenesis and cellular energy homeostasis. Both HMGB1/RAGE and AMPK/SIRT1/PGC-1α pathways are gaining attention as promising therapeutic targets for developing interventions that could modify disease's course and slow the progression of PD.

Keywords: Parkinson's disease; AMPK/SIRT1/PGC-1α; HMGB1/RAGE.

1. Introduction

Parkinson's disease (PD) is a complex and progressive neurodegenerative disorder that results from the deterioration of brain cells responsible for producing dopamine. The latter is a neurotransmitter essential for coordinated muscle activity and movement control **(Dolgacheva et al., 2022)**. PD is marked by both motor symptoms, such as slowed movements, tremor, muscle stiffness, gait disturbances, and balance issues, and a variety of non-motor symptoms, including cognitive decline, psychiatric conditions, sleep disturbances, pain, and other sensory issues **(Kashif et al., 2022; Thangaleela et al., 2023)**. As the disease advances, these symptoms contribute to increasing disability and greater care needs. A significant number of individuals with PD eventually develop dementia **(Aarsland et al., 2021)**.

Parkinson's disease is the second most common neurodegenerative disorder after Alzheimer's disease (AD), affecting approximately 0.5–1% of people aged 65–69, with prevalence increasing to 1–3% in individuals over 80 years old **(Erkkinen et al., 2018)**. By 2030, the prevalence and incidence of PD are anticipated to grow by over 30%, largely because of population aging **(Khatib,**

2022), leading to significant social and economic burdens through both direct medical expenses and indirect costs **(Wanneveich et al., 2018)**. According to the Global Burden of Disease Study, the global number of people living with PD is expected to rise from around 7 million in 2015 to nearly 13 million by 2040, raising concerns about a potential PD pandemic **(Jankovic and Tan, 2020)**.

2. Diagnosis of Parkinson's disease

The diagnosis of PD relies on the presence of key motor symptoms, particularly bradykinesia and rigidity and/or resting tremors, alongside additional supporting and exclusion criteria **(Poewe et al., 2017)**. More specifically, multiple rating scales may be used to evaluate the stage of PD. The Hoehn and Yahr (H&Y) and Unified PD Rating Scale (UPDRS) are the two most utilized rating scales in clinics **(Aggarwal et al., 2021)**.

The H&Y scale classifies PD into several stages of progression. Briefly, stage I is characterized only by unilateral involvement, with low or no impairment in function. Stage II includes bilateral or midline deterioration, without disturbance of balance. During stage III, the first signs of decreased righting reflexes develop. Functionally, the patient's restriction is mild to moderate, and they can live individually. In stage IV, severe clinical disability has fully established, nonetheless, people can still work and stand without help, despite their significant disability. Finally, stage V is defined by restriction to a bed or wheelchair unless helped. However, certain patients might never reach stage five because of the associated mortality **(Templeton et al., 2022)**.

Furthermore, the most recent edition of UPDRS, supported by the Movement Disorders Society (MDS), called MDS-UPDRS, contains four aspects linked to cognitive function, daily activities, motor evaluation, and motor difficulties, respectively **(Terra et al., 2024)**. Patients are assessed in each section, with zero for no problems, one for minimal, two for mild, three for moderate, and four for severe issues **(Yosipovitch et al., 2019)**.

3. Pathogenesis of Parkinson's disease

The key neuropathological features of PD involve the degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNpc) of the midbrain, accompanied by the presence of Lewy bodies, cytoplasmic inclusions containing insoluble aggregates of α-synuclein **(Fukusumi et al., 2021)**. While our understanding of the pathophysiology of PD continues to grow, it is still primarily regarded as idiopathic. Previous studies suggested that interactions between genetic predisposition and environmental influences contribute to PD development. A small proportion of cases have a genetic basis, and research into genetic factors is ongoing **(Costa et al., 2023)**.

Various environmental influences such as head trauma from contact sports and exposure to toxins like pesticides, solvents, metals, and other pollutants may increase the risk of PD. Men are approximately 50% more likely to be affected than women, and the average age of onset is around 60 years **(Orozco et al., 2020)**.

Multiple mechanisms have been connected to the development of PD, with the aggregation of α-synuclein being a critical factor in the disease's progression. Several studies have suggested that unusual protein clearance, mitochondrial dysfunction, and neuroinflammation all have a role in the initiation and course of PD **(Figure 1) (Jankovic and Tan, 2020)**.

3.1. Neuroinflammation

Postmortem brain investigations have revealed activation of microglial and complement, T-lymphocyte infiltration, and higher levels of pro-inflammatory cytokines in the SNpc and striatum of PD patients compared to normal persons **(Muñoz-Delgado et al., 2023)**.

Inflammatory responses may play a direct role in the development of PD. Early research using rodent models of PD (such as rotenone, 6-hydroxydopamine (6-OHDA), and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) revealed that inhibiting microglial activation with minocycline significantly reduced dopaminergic cell death in the SNpc. This suggests that microglia-induced inflammation may contribute to the degeneration of these cells. Numerous studies showed that α-synuclein can activate microglia and trigger inflammation, with α-synuclein causing a dose-dependent activation of microglia in primary cultures **(Zheng and Zhang, 2021)**.

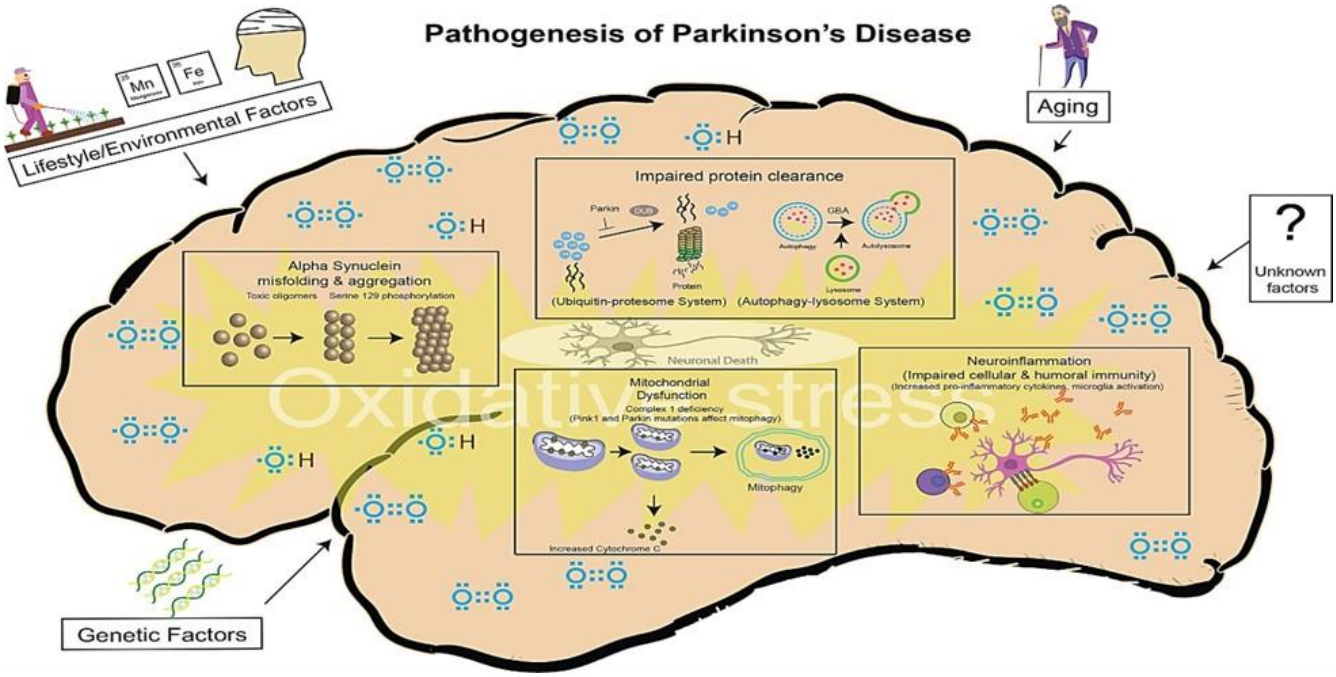

Figure 1: Pathogenesis of PD: a variety of cellular mechanisms on the background of oxidative stress, coupled with aging, lifestyle/environmental and genetic factors contribute to the PD- related neurodegeneration. PD, Parkinson's disease **(Jankovic and Tan, 2020)**.

3.1.1. Tumor necrosis factor-α (TNF-α)

Elevated levels of soluble TNF-α have been observed in the cerebrospinal fluid and post-mortem brain tissues of Parkinsonian patients, as well as in animal models exposed to dopaminergic neurotoxins like MPTP and 6-OHDA, which are commonly used to simulate nigral degeneration in rodents and non-human primates **(Han et al., 2019)**. The marked expression of TNF-α at sites of neurological damage indicates that this pro-inflammatory cytokine likely contributes to neuronal injury, making it a promising therapeutic target for PD **(Amin et al., 2022)**.

3.1.2. Interleukin-1β (IL-1β) and interleukin-6 (IL-6)

Several lines of evidence suggest that IL-1β and IL-6, pro-inflammatory cytokines, exhibit diverse biological effects both in the brain and in peripheral tissues **(Kany et al., 2019)**. These cytokines are involved in various neuroimmune and neurophysiological processes within the central nervous system (CNS) **(Kennedy and Silver, 2022)**. Elevated levels of IL-1β and IL-6 have been detected in the cerebrospinal fluid and post-mortem striatal tissue of individuals with PD **(Tanaka et al., 2020)**. Additionally, in PD models, increased expression of IL-1β and IL-6 mRNA has been observed in the degenerating SNpc following 6-OHDA administration **(Yan et al., 2020)**.

Additionally, it has been reported that astrocytes can also be activated by cytokines such as TNF-α, IL-1β, and IL-6 from microglia, leading to the production of reactive oxygen and nitrogen species **(Tanaka et al., 2020)**. A recent investigation using a co-culture model revealed that astrocytes amplify microglial inflammatory activity via nuclear factor kappa beta (NF-κB)-dependent pathway, resulting in increased dopaminergic cell toxicity **(Jurcau et al., 2023)**.

3.1.3. High-mobility group box 1 (HMGB1)

A growing body of evidence indicates that HMGB1 is one of the initial pro-inflammatory cytokines produced after injury, and it serves as the "master switch" of neuroinflammation. HMGB1 is a member of the high-mobility group (HMG) family, which is defined by quick electrophoretic mobility. Its subcellular distribution is regulated by acetylation and cellular activity status **(Mo et al., 2023)**. Nuclear HMGB1 is a functional chromatin protein that regulates genome stability by relaxing nucleosome compaction and making chromatin structure readily available **(Zhao et al., 2021)**. Furthermore, HMGB1 may improve the DNA-binding ability of various transcription factors,

including NF-κB **(Hiramoto et al., 2020)**.

Based on numerous stimuli, hyperacetylated HMGB1 can be translocated from the nucleus to the cytosol, stored in lysosomes, and released extracellularly **(Chen et al., 2022)**. Cellular necrosis causes HMGB1 to be released passively into the extracellular space, whereas inflammatory stimuli can prompt its active release from immune cells or astrocytes **(Behl et al., 2021)**. Several receptors, including receptor for advanced glycation end products (RAGE), toll-like receptors (TLRs) like TLR2, TLR4, and TLR9 can then interact with extracellular HMGB1. Upon binding to RAGE, HMGB1 can regulate cell growth, proliferation and migration via activation of (mitogen-activated protein kinase) MAPK and NF-κB pathways, while HMGB1-TLRs interaction mainly modulates inflammatory responses **(Xue et al., 2021)**.

Evidence strongly implicates HMGB1 in the pathogenesis of PD, as it appears to influence key processes such as neuroinflammation, autophagy, apoptosis, gene expression, and potentially mitochondrial dysfunction and oxidative stress **(Figure 2) (Angelopoulou et al., 2018)**.

3.2. Mitochondrial Dysfunction

Mitochondrial dysfunction is recognized as a key contributor to the development of both idiopathic and familial PD **(Malpartida et al., 2021)**. Earlier studies on SNpc in Parkinson's patients revealed a deficiency in mitochondrial complex I, a vital part of the electron transport chain. These findings were among the first to establish a direct connection between mitochondrial impairment and PD **(Muddapu and Chakravarthy, 2021)**. The complex I deficiency was also observed in the skeletal muscle and platelets of Parkinson's patients compared to healthy individuals **(Kverneng et al., 2025)**. Further evidence came from studies on the MPTP neurotoxin which causes permanent Parkinsonian symptoms. Postmortem analyses showed dopaminergic neuron loss, and experimental studies demonstrated that once MPTP is oxidized, it is absorbed by dopamine neurons, leading to complex I inhibition **(Akram et al., 2022)**.

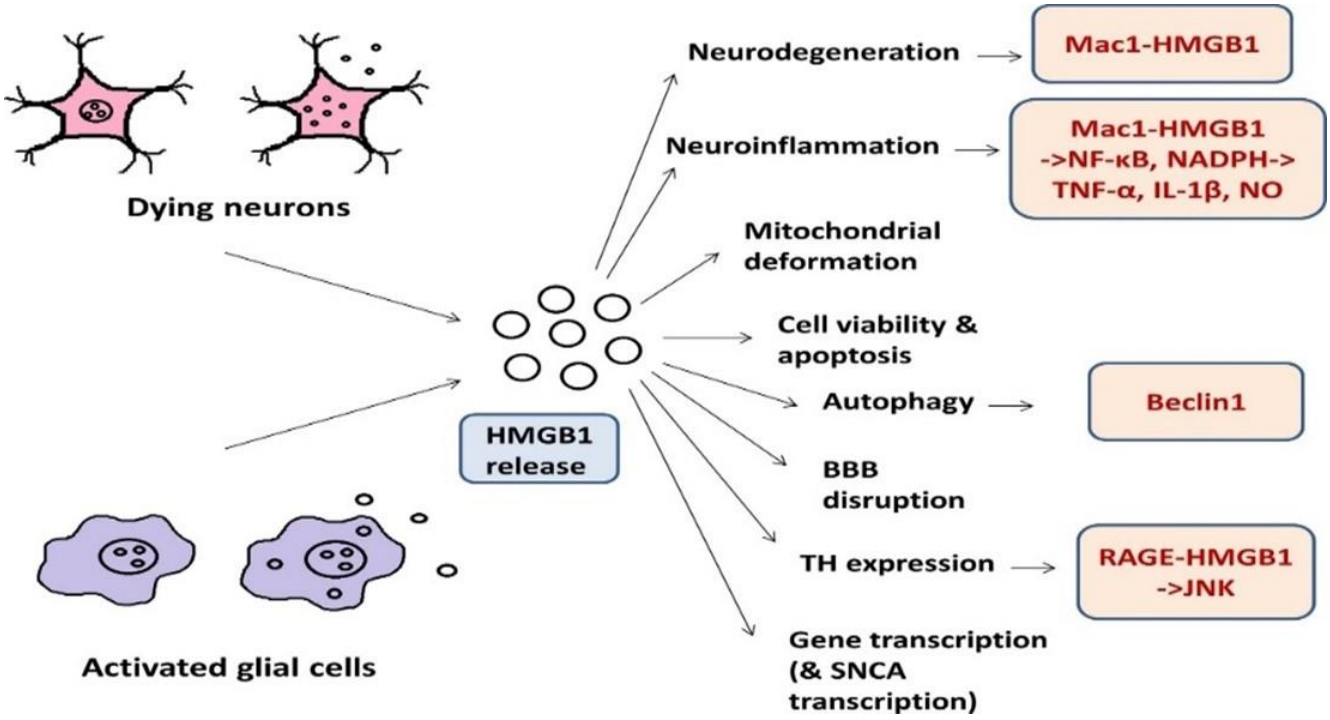

Figure 2: Molecular mechanisms of HMGB1 contribution to PD pathogenesis. Active HMGB1 secretion by inflammatory cells and passive release by dying neurons affects cell viability and apoptosis induces mitochondrial dysfunction and oxidative stress, regulates autophagy, modulates gene SCNA transcription and TH expression, and contributes to neuroinflammation and neurodegeneration associated with PD. BBB, blood-brain barrier; HMGB1, high mobility group box 1; IL-1β, interleukin-1β; JNK, Jun N-terminal kinase; Mac1, macrophage 1 antigen; NADPH, nicotinamide adenine dinucleotide phosphate oxidase; NF-κB, nuclear factor kappa beta: NO, nitric oxide: RAGE, receptor for advanced glycation end products; SNCA, α-synuclein **(Angelopoulou et al., 2018)**.

Several environmental toxins and herbicides, such as rotenone and paraquat, which disrupt complex I activity, have been shown to induce Parkinsonian symptoms and dopaminergic neuron death in both animal models and humans. Impairment of mitochondrial complex I may be a key factor in dopaminergic cell death due to energy depletion **(Epifane-de-Assunção et al., 2024)**.

3.2.1. AMP-activated protein kinase (AMPK)/ silent information regulator 1 (SIRT1)/ peroxisome proliferator-activated receptor-gamma coactivator-1α (PGC-1α) axis

In the early stages of PD, characterized by energetic stress, AMPK activates SIRT1 and phosphorylates PGC-1α, increasing its susceptibility to deacetylation by SIRT1. This modification enhances PGC-1α's capacity to stimulate mitochondrial biogenesis, improve mitochondrial function, and promote the expression of antioxidant proteins **(Rakshe et al., 2024)**. Numerous studies have demonstrated a significant reduction in the downstream signaling p-AMPK, SIRT1, and PGC-1α. As a result, the AMPK/SIRT1/PGC-1α pathway plays a crucial role in the progression of PD **(Safar et al., 2021)**. The AMPK/SIRT1/PGC-1α signaling pathway has been highlighted for its potential protective effects against these harmful processes **(Athari et al., 2023)**.

3.3. Oxidative stress

Overproduction of reactive oxygen species (ROS) in the brain promotes oxidative stress in PD patients. Evidence suggests that dopamine metabolism, mitochondrial dysfunction, and neuroinflammation lead to increased oxidative stress and dopaminergic neuronal loss in the brains of patients with PD **(Chang and Chen, 2020)**. Unstable and highly reactive, free radicals achieve stability by accepting electrons from nucleic acids, proteins, lipids, carbohydrates, and other nearby molecules **(Di Meo and Venditti, 2020)**, thus inducing cellular damage.

3.3.1. Lipid peroxidation products

Lipid peroxidation disrupts membrane structure and impairs the function of proteins and DNA **(Su et al., 2019)**. A variety of research findings reveal changed amounts of lipid peroxidation products, such as malondialdehyde (MDA), in the brain tissues of neurodegenerative patients **(Chang and Chen, 2020)**.

Malondialdehyde is the principal product of polyunsaturated fatty acid peroxidation and is considered as a biomarker of lipid peroxidation and oxidative stress **(Demirci-Cekic et al., 2022)**. MDA is formed by successive hydroperoxide formations and β-cleavage of the fatty acid chain to give a hydroperoxyl aldehyde **(Vandemoortele, 2020)**. MDA is then generated by β-scission or by reaction of the final acrolein radical with a hydroxyl radical **(Zhou et al., 2020)**.

3.3.2. Nicotinamide adenine dinucleotide phosphate oxidase (NADPH Oxidase or NOX)

The NOX enzyme family, located in the central nervous system, is recognized as a source of ROS in the brain. NOX, a superoxide-producing enzyme, is highly expressed in microglia **(Hou et al., 2018)**. The activation of NOX produces both extracellular and intracellular ROS, which play important roles in mediating chronic neuroinflammatory responses and related neuronal damage **(Hou et al., 2019)**.

4. Treatment of Parkinson's disease

Although the specific origin of PD remains unclear, therapy developments have been advancing **(Elsworth, 2020)**. There is no known cure for the disease, therefore treatments aim to control symptoms rather than prevent or stop the disease's progression **(Oertel, 2017)**. Medicines, surgery, behavioral therapy, or a combination of the three are all options for treatment **(Nemade et al., 2021)**.

4.1. Drug treatment

4.1.1. Dopaminergic medications

Dopaminergic medicines are typically used to treat motor symptoms in PD **(Mo et al., 2023)**. Dopaminergic drugs help to boost or mimic dopamine levels. L-DOPA, the most potent anti-Parkinsonian medication available today, remains the "gold standard" for PD treatment **(Bogetofte et al., 2020)**. Dopamine cannot easily penetrate the blood-brain barrier, whereas its precursor, L-DOPA, can **(Franco et al., 2021)**.

About 80% of people with idiopathic PD respond to L-DOPA, which reduces bradykinesia and rigidity. However, it is inefficient or inadequate in treating several significant PD symptoms including posture and gait abnormalities, difficulty speaking, freezing, autonomic dysfunction, cognitive impairment, mood disorders, and sleep issues **(Rizek et al., 2016)**.

Dopamine agonists can also be used to treat non-motor symptoms of PD, including depression. They are helpful and therapeutically useful for controlling depression and depressive symptoms for people with PD **(Seppi et al., 2019)**.

L-DOPA, despite being the "gold standard" for PD treatment, has long-term consequences **(Bogetofte et al., 2020)**. Wearing off, dyskinesias, and unpredictable "on-off" swings are the most significant consequences of chronic L-DOPA treatment **(Thanvi and Lo, 2004)**. The relief of PD symptoms by L-DOPA can also make it hard to reliably determine the patient's real health issues, making the disease progression harder to monitor **(Teymourian et al., 2022)**.

Continuous dopaminergic stimulation is required for patients with advanced PD, which can be supplied using levodopa carbidopa intestinal gel and deep brain stimulation as a replacement to oral L-DOPA (**Pirtošek et al., 2023)**. In contrast to oral L-DOPA, the intestinal gel shows fewer motor disturbances and dyskinesias, although they are not totally eliminated **(Antonini et al., 2021)**. A continuous dose of levodopa-carbidopa equals the oral L-DOPA dose provided by the gel that is injected into the jejunum **(Rizek et al., 2016)**.

4.1.2. Monoamine oxidase inhibitors, catechol O-methyltransferase inhibitors, and N-methyl D-aspartate receptor antagonists

Monoamine oxidase inhibitors (MAOIs) and catechol O-methyltransferase (COMT) inhibitors serve to prolong the effects of dopamine and L-DOPA by inhibiting their degradation **(De Beer, 2020)**. MAOIs decrease the amount of dopamine broken down in the synapse **(Ostadkarampour and Putnins, 2021)**. Moreover, COMT inhibitors stop COMT from rapidly converting L-DOPA to dopamine **(Fabbri et al., 2022)**. It lowers the peripheral loss of L-DOPA before it reaches the brain **(Rizek et al., 2016)**.

4.1.3. Anticholinergics

The earliest pharmacological medications utilized in PD therapy were anticholinergic drugs **(Lavrador et al., 2023)**. They suppress acetylcholine activity by working as antagonists at choline receptors, intending to restore the equilibrium between dopamine and acetylcholine levels that was altered by PD **(Lee and Yankee, 2021)**. These medications have mostly been substituted by L-DOPA and other centrally acting dopaminergic agonists, but they remain available for use in the treatment of PD **(Lane, 2019)**. Benztropine, biperiden, diphenhydramine, and ethopropazine are included in this therapeutic class of drugs **(LeWitt et al., 2024)**. Anticholinergic drugs play a larger role in tremor-predominant PD. They can be used alone in the early stages, but they are typically used in conjunction with L-DOPA or other prescription treatments **(Zahoor et al., 2018)**.

4.2. Behavioral therapy

Gait and balance training are among the most effective exercise therapies for PD (**Mak et al., 2017)**. Other forms of exercise include treadmill exercise **(Mehrholz et al., 2016)**, strength training, aerobic exercise **(Mak et al., 2017)**, and music- and dance-based approaches **(Zhang et al., 2017)**. Physiotherapy, occupational therapy, and speech therapy can also help with speech and swallowing **(Mak et al., 2017; Fox et al., 2018)**. Behavioral therapy approaches can assist in maintaining or enhancing motor symptoms, balance, gait, and function while also providing solutions for managing hypophonia and dysphagia. Referrals for interdisciplinary therapy consultations are an important component of quality care in PD **(Factor et al., 2016)**.

4.3. Surgical treatment

Deep brain stimulation involves surgical placement of unilateral or bilateral leads (wires) trans cranially in the subthalamic nucleus or the globus pallidus interna. These leads are attached to a battery in the chest, like a pacemaker battery. Following surgical recovery, individuals with deep brain stimulation attend programming visits to optimize stimulation parameters and medications. Deep brain stimulation is used to treat the effects of wearing off that involve motor symptoms, tremor, and dyskinesia **(Fox et al., 2018)**.

In tremor-predominant PD, some clinicians use the ventralis intermedius nucleus (thalamic) deep brain stimulation, MRI-guided focused ultrasound **(Bond et al., 2017)**, or, less commonly, traditional thalamotomy. The thalamic target is only for tremors, not other PD symptoms. Focused ultrasound uses highly focused ultrasound beams to burn the target (the thalamus) while using MRI to target and monitor the extent of the lesion. The resulting lesion improves on-medication tremor scores by 62% **(Bond et al., 2017)**. Still, it can only be performed unilaterally due to the risks of adverse events such as worsening speech and balance. Factors linked to worse deep brain stimulation outcomes include advanced age (75 years or older), cognitive decline—especially dementia—and symptoms that do not respond to levodopa, such as gait and balance issues **(Moro et al., 2016)**.

4.4. Emerging therapeutic strategies

Current research trends in PD increasingly prioritize personalized therapies that aim to restore molecular, structural, and functional integrity within disease-specific brain circuits **(Stocchi et al., 2024)**. A variety of non-dopaminergic therapies—such as β-adrenergic agents, serotonergic agonists, and adenosine A2A receptor antagonists are currently in late-stage development and may offer benefits for managing motor symptoms and associated complications. Additionally, the growing emphasis on non-motor symptoms in PD has the potential to accelerate the discovery of treatments targeting these key aspects of advanced disease (**Gouda et al., 2022)**.

Developing therapies that reduce α-synuclein accumulation and transmission while slowing or preventing the degeneration of dopaminergic neurons in PD remains a critical unmet medical need. Several key pathological mechanisms involved in PD can be modulated, at least partially, through the activation of AMPK **(Curry et al., 2018)**. With continued research and the advancement of more selective pharmacological agents, targeting AMPK-related pathways relevant to PD may become a promising approach to mitigating neurodegeneration and ultimately slowing disease progression **(Athari et al., 2023)**.

Therapies targeting HMGB1 could offer a promising approach for treating PD and may also be effective in other synucleinopathies, such as Lewy body dementia **(Tian et al., 2023)**. As neuroinflammation, disrupted autophagy, and mitochondrial dysfunction are common pathological features in several neurodegenerative conditions—including Alzheimer's disease and amyotrophic lateral sclerosis—HMGB1 is likely to play a role in these disorders as well **(Yoo et al., 2020)**.

Recent studies have increasingly highlighted the role of RAGE pathway in oxidative stress and neuroinflammation which contribute to neuronal death in PD **(Ray et al., 2016)**. The interaction between RAGE and its ligands such as advanced glycation end-products (AGEs) and S100B protein is strongly associated with the development of PD. Given RAGE's central role in neuroinflammation, targeting this receptor presents a promising therapeutic strategy for future interventions in PD **(Jiang et al., 2018)**.

Given that oxidative stress can lead to neuronal degeneration by triggering intracellular damage such as protein aggregation, mitochondrial impairment, and DNA fragmentation, targeting oxidative damage has emerged as a promising approach for Parkinson's disease treatment. In this context, the antioxidant activity of vitamins and their role in modulating gene expression may offer therapeutic benefits in managing PD. Existing clinical studies suggest that adequate intake of certain vitamins may help lower the risk of developing PD and alleviate symptoms in affected individuals. However, the safety of long-term or routine vitamin supplementation requires further attention. Overall, vitamin supplements hold promise as a supportive treatment option in PD management **(Zhao et al., 2019)**.

Nicotinamide plays a key role in the biosynthesis of nicotinamide adenine dinucleotide (NAD), which exists in both oxidized (NAD^+) and reduced (NADH) forms, through several metabolic pathways. NADH is a crucial cofactor that supports tetrahydrobiopterin in the activity of tyrosine hydroxylase, the enzyme responsible for converting tyrosine into dopamine **(Rehman et al., 2022)**. Notably, NADH deficiency is commonly observed in individuals with PD **(Mischley et al., 2023)**.

Moreover, it has been reported that vitamin C can enhance the synthesis of dihydroxyphenylalanine (DOPA), the direct metabolic precursor of dopamine. Vitamin C can improve the absorption of levodopa in elderly PD patients with poor levodopa bioavailability. Furthermore, it has been suggested that ascorbic acid can reduce the

required dosage of levodopa without compromising therapeutic effectiveness. This indicates that combining vitamin C with standard anti-Parkinsonian medications may yield improved symptom management **(Zhao et al., 2019)**.

Additionally, vitamin D3 has demonstrated a protective effect on dopaminergic neurons in models of 6-OHDA-induced PD and has been shown to enhance motor performance. These benefits are likely linked to vitamin D's ability to suppress oxidative stress and reduce the generation of reactive oxygen species and free radicals **(Da Costa et al., 2023)**.

Vitamin E has demonstrated neuroprotective effects in experimental models of PD, mainly through its antioxidant properties and ability to inhibit apoptosis. In animal models, such as those induced by 6-OHDA or rotenone, pretreatment with forms of vitamin E (e.g., D-alpha-tocopherol, γ-/δ-tocotrienol) has been shown to reduce behavioral abnormalities and dopaminergic neuron loss. Additionally, tocotrienols may exert protective effects via estrogen receptor beta (ERβ) and PI3K/Akt signaling pathways **(Zhao et al., 2019)**.

While some epidemiological studies also showed no clear association between vitamin E intake and reduced PD risk, other studies suggested that high dietary intake might lower disease incidence. Notably, high-dose vitamin E supplementation can increase cerebrospinal fluid levels, but its therapeutic significance is still uncertain. Overall, while preclinical findings are promising, further studies are needed to confirm whether vitamin E can serve as an effective adjunctive treatment for PD in humans **(Zhao et al., 2019)**.

5. Conclusion

PD remains a complex and progressive neurodegenerative disorder with multifaceted pathophysiological mechanisms and no definitive cure. This review highlighted key aspects of PD, from its clinical features and epidemiological burden to diagnostic approaches and underlying molecular mechanisms. Emerging evidence supports the pivotal roles of neuroinflammation, particularly involving TNF-α, IL-1β, IL-6, and the HMGB1/RAGE axis alongside mitochondrial dysfunction mediated by the AMPK/SIRT1/PGC-1α pathway, and oxidative stress linked to NADPH oxidase, in the pathogenesis of PD. Despite current therapeutic strategies offering symptomatic relief, they do not halt disease progression. Understanding these molecular underpinnings offers promising avenues for the development of more effective, disease-modifying interventions. Future therapeutic strategies targeting these molecular pathways may provide new hope in altering the course of PD and improving patients' quality of life.

Conflict of interest

The authors report no conflict of interest.

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