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Review Article

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Modern Pharmacological Treatment of Parkinson's Disease: Reviving Known Drugs and New Perspectives

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ABSTRACT

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by motor symptoms such as tremor and rigidity, along with non-motor symptoms such as cognitive decline and depression. Current dopaminergic therapies offer symptomatic relief but fail to halt disease progression, underscoring the urgent need for novel, disease-modifying therapies. This review explores the potential of repurposed drugs from different therapeutic categories—including immunomodulatory, cardiometabolic, and anti-infective agents—as promising therapeutic strategies for PD. Immunomodulatory agents such as c-Abl inhibitors (imatinib, nilotinib) and sargramostim have shown potential in reducing α-synuclein aggregation and neuroinflammation, although clinical outcomes have been mixed. Cardiometabolic drugs, particularly glucagon-like peptide-1 agonists like exenatide, have shown improvements in motor and cognitive symptoms, with ongoing phase III trials evaluating their disease-modifying potential. Anti-infective agents, including doxycycline and rifampicin, exhibit neuroprotective effects through anti-inflammatory and anti-aggregating effects. While some concerns regarding efficacy and toxicity persist, these repurposed drugs offer valuable insights into novel therapeutic approaches for PD. In addition, emerging strategies such as gene therapy, enzyme replacement, and advanced drug delivery systems are discussed for their potential to address underlying disease mechanisms. Despite the lack of definitive disease-modifying therapies to date, advances in drug repurposing and innovative therapeutic approaches provide hope for future breakthroughs. Further large-scale clinical trials are necessary to confirm the efficacy and safety of these treatments.

Keywords: *Parkinson's disease, Neurodegeneration, Drug repurposing, Immunomodulatory therapies, Disease-modifying treatments*

INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative disorder primarily resulting from the loss of dopaminergic neurons in the substantia nigra (SN). These neurons play a crucial role in motor control, coordination, and various cognitive functions by producing dopamine. The depletion of dopamine leads to the hallmark motor symptoms (MS) of PD, which include tremors, increased muscle tone (rigidity), bradykinesia (slowness of movement), and postural instability, contributing to difficulties in gait and balance. In addition, PD progression varies significantly between individuals, and while the onset is often gradual, the disease inevitably worsens over time. Despite ongoing research, there is no disease-modifying treatment available for PD. However, symptomatic therapies and various interventions can alleviate MS and enhance the quality of life (QoL) for patients [1, 2].

In addition to the well-known MS, PD is also associated with a broad spectrum of non-motor symptoms (NMS), which can be equally, if not more, debilitating for patients. These NMS include dysarthria (speech difficulties), dysphagia (swallowing difficulties), depression, anxiety, sleep disturbances, and cognitive impairments such as memory loss and executive dysfunction. Other prevalent NMS include autonomic dysfunctions such as constipation and seborrheic skin disorders [3-6]. The severity and manifestation of these symptoms vary widely among patients, with not all experiencing the full spectrum of NMS. These deficits have a substantial impact on patient outcomes and make clinical management of PD more difficult.

PD affects approximately 1 million individuals in the United States alone, with an average age of onset around 60 years [7]. The annual incidence rate in the U.S. is estimated at 60,000 new cases [8]. Moreover, the prevalence increases with age, affecting 1-2% of individuals over 60 years old, and rising to nearly 4% in individuals over 80 years old [9]. The disease is more prevalent in men than in women, with a male-to-female ratio of about 1.5 to 1 [10]. Additionally, PD is more common among white populations compared to other racial or ethnic groups [11]. Globally, the burden of PD is expected to rise as the population ages, making it a significant public health challenge [12, 13].

Given the current limitations in treating PD and the anticipated rise in its global prevalence, there is an urgent need to explore new therapeutic fields. Recent research has started to investigate the potential repurposing of drugs from other medical fields, such as cardiology and immunology, for PD treatment. This approach involves targeting new molecular pathways and mechanisms that may help alleviate symptoms or slow disease progression. In this review, we have synthesized the latest findings in this area, particularly focusing on repurposed medications such as immunosuppressants and cardiovascular drugs. Our objective is to enhance understanding of these emerging therapies and discuss their potential to open new frontiers in PD management, aiming to improve patient outcomes and QoL.

RESULTS AND DISCUSSION

Background and disease pathology

At the molecular level, PD is thought to be related to a combination of abnormal protein accumulation, inflammation, and the generation of reactive oxygen species (ROS), all of which contribute to the degeneration of neurons in the SN **(Figure 1)**. A hallmark of PD is the formation of abnormal protein aggregates known as Lewy bodies (LBs) within the nerve cells of the SN, which are primarily composed of alpha-synuclein, a protein expressed throughout the brain [14]. These aberrant protein aggregates cause neurons' regular functions to be disrupted, which eventually results in their death. Beyond PD, LBs are also a feature of other neurodegenerative illnesses, like multiple system atrophy (MSA) and dementia with LBs, where their existence is associated with both motor and cognitive symptoms [15].

The role of alpha-synuclein in the development of LBs has been extensively studied. Alpha-synuclein is a 140 kDa protein encoded by the SNCA gene, and it is suggested to regulate neurotransmitter release and maintain the presynaptic cytoskeleton, as well as facilitate vesicular transport within cells [16-18]. Although its exact function remains unclear, alpha-synuclein is believed to play a critical role in maintaining neuronal integrity and modulating ion channel activity [18]. Furthermore, studies suggest that alpha-synuclein is involved in the regulation of oxidative stress and apoptosis [19, 20]. Research indicates that alpha-synuclein may promote apoptosis through interactions with mitochondria, which are essential for both energy production and the regulation of cell death [21, 22]. Genetic factors, including mutations in the SNCA gene and other related genes, have been implicated in the formation of LBs and the development of familial PD, though this form of the disease is rare [23, 24]. These genetic mutations are thought to increase susceptibility to PD and other alpha-synucleinopathies, highlighting the potential influence of heritable factors in what has traditionally been considered a sporadic or idiopathic disease [24].

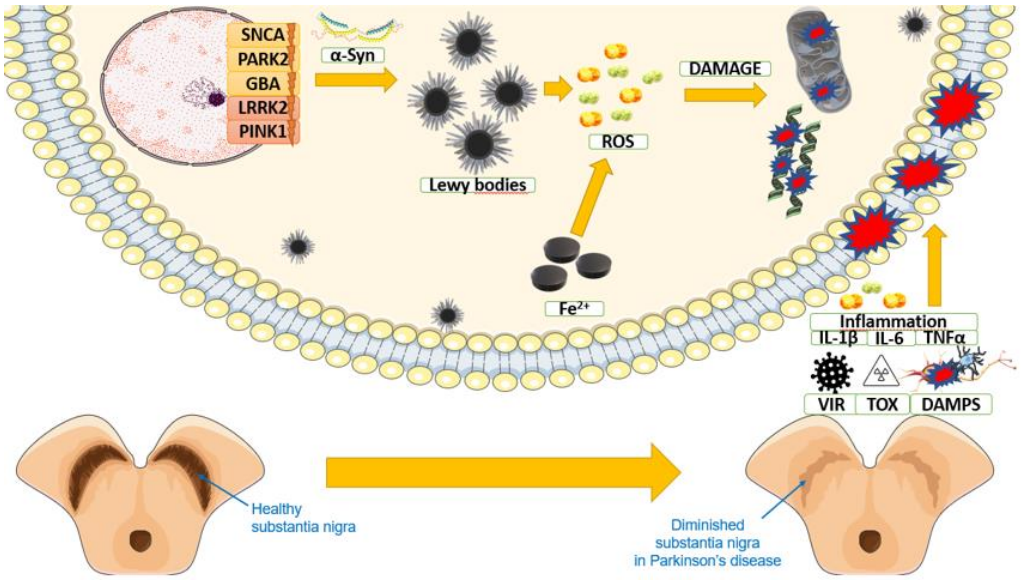

Figure 1. The pathophysiology model of PD. Abbreviations: SNCA, Synuclein Alpha Gene; PARK2, Parkin Gene; GBA, Glucocerebrosidase Gene; LRRK2, Leucine-Rich Repeat Kinase 2 Gene; PINK1, PTEN-induced kinase 1; α-Syn, Alpha-Synuclein; ROS, Reactive Oxygen Species; Fe^{2+}, Iron ions (Ferrous); IL-1β, Interleukin-1 Beta; IL-6, Interleukin-6; TNFα, Tumor Necrosis Factor Alpha; VIR, Viruses; TOX, Toxins; and DAMPS, Damage-Associated Molecular Patterns.

LBs are not exclusive to the SN; they can also be found in other regions of the brain, such as the amygdala, hippocampus, hypothalamus, and brainstem nuclei like the locus coeruleus, nucleus basalis of Meynert, and dorsal motor nucleus of the vagus nerve. They may also appear in the neocortex and amygdala in some cases of PD. Research by Braak and Tredici further revealed that LBs can extend beyond the central nervous system (CNS) to peripheral and enteric nervous systems, suggesting a broader involvement of these aggregates in PD pathology.
In addition to alpha-synuclein, LBs are composed of other proteins such as tau, ubiquitin, and neurofilaments, which may contribute to their formation and stability [25]. Other proteins, including 14-3-3, DJ-1, parkin, and LRRK2, have also been detected in LBs, though their precise roles remain unclear and warrant further investigation [25, 26]. Understanding the function of these proteins within LBs, as well as their contributions to the pathogenesis of neurodegenerative disorders like PD, is critical for developing potential therapeutic interventions targeting this molecular pathology.

Repurposed drugs for PD treatment- results

- *Immunomodulatory and anti-neurodegenerative therapies*

Abelson tyrosine kinase inhibitors

Abelson Tyrosine Kinase (c-Abl): Abelson tyrosine kinase (c-Abl) is a non-receptor tyrosine kinase crucial for cellular stress response. Studies on animal models of PD suggest that the activation of c-Abl contributes to the accumulation of α-Synuclein (α-Syn) and neuronal degradation, making c-Abl a potential target for disease-modifying therapies [27].
Imatinib, the first identified c-Abl inhibitor, has been used successfully in the treatment of Chronic Myeloid Leukemia (CML) and gastrointestinal stromal tumors. Research in MPTP-induced mouse models of PD demonstrated the neuroprotective effects of Imatinib. Administering 30 mg/kg of Imatinib significantly reduced c-Abl tyrosine phosphorylation and protected dopaminergic neurons from degeneration [28].
Nilotinib is a second-generation c-Abl inhibitor with higher selectivity and better brain penetration compared to other inhibitors. Several clinical trials have assessed its efficacy in PD patients. In a phase 2, double-blind, placebo-controlled study with 63 participants, nilotinib was shown to be safe with no significant adverse effects. However, no meaningful clinical improvements in MS were observed [29, 30]. Another study confirmed nilotinib's safety but did not show significant motor or non-motor outcome improvements compared to the placebo group [31]. Nevertheless, nilotinib has been shown to alter dopamine metabolism by increasing the levels of

DOPAC and homovanillic acid (HVA), indicating potential neurochemical effects that warrant further research [31].

Sargramostim

Sargramostim is a recombinant human granulocyte-macrophage colony-stimulating factor (GM-CSF) that stimulates immune function by activating neutrophils, macrophages, and myeloid dendritic cells. Given the involvement of mitochondrial and peripheral immune dysfunction in PD, sargramostim has emerged as a potential long-term therapeutic option [32, 33]. Sargramostim was well tolerated in PD patients, according to a phase 1 randomized, placebo-controlled research. Adverse events included injection site reactions and mild bone discomfort [34]. In addition, sargramostim increased regulatory T-cell (Treg) subsets and improved MDS-UPDRS Part III scores after six to eight weeks of treatment. A subsequent phase 1b study with reduced sargramostim dosing (3 mg/kg/day) showed fewer adverse events without worsening MS, though larger studies are necessary to determine its therapeutic efficacy [35].

Rapamycin (Sirolimus)

Rapamycin, an mTOR (mammalian target of rapamycin) inhibitor, has been used as an immunosuppressant to prevent organ transplant rejection. In PD models, mTOR inhibition by rapamycin has been shown to activate autophagy, which helps clear α-Syn aggregates, reduce oxidative stress, and alleviate dopaminergic neuronal damage [36]. Studies on mice with parkin and PINK1 mutations indicate that rapamycin improves PD-related pathology by reducing muscle and mitochondrial degeneration [37]. However, more human trials are required to validate these results and assess rapamycin's therapeutic potential in individuals with PD.

Isoalantolactone

Isoalantolactone is a bioactive sesquiterpene lactone known for its anti-inflammatory and anti-tumor properties. Research has shown that IAL can prevent Amyloid β-induced toxicity and ameliorate MPTP-induced PD symptoms in mouse models [38, 39]. The neuroprotective effects of IAL are thought to be mediated through its activation of antioxidant pathways, specifically by stimulating the nuclear factor erythroid 2–related factor 2 (Nrf2) signaling pathway [40]. IAL treatment has also been shown to preserve dopaminergic neurons and reduce neuroinflammation, making it a promising candidate for PD treatment. However, further research is needed to elucidate its molecular mechanisms and therapeutic potential.

Interferon beta

IFN-β is a polypeptide drug widely used in the treatment of relapsing multiple sclerosis (MS). Recent studies indicate that IFN-β can reduce neuroinflammation and prevent neurodegeneration in PD models. IFN-β has been shown to promote α-Syn degradation and protect dopaminergic neurons by modulating mitochondrial dynamics through the STAT5-PGAM5-Drp1 pathway [41, 42]. In vivo models of PD have demonstrated that IFN-β prevents neuronal loss and oxidative damage. However, more research is needed to fully understand the neuroprotective mechanisms of IFN-β and its potential for PD therapy.

- *Cardiological and metabolic (anti-diabetic) drugs*

Glucagon-like peptide 1 (GLP-1) agonists

Exenatide, a GLP-1 agonist, has emerged as one of the most studied drugs for potential repurposing in PD treatment. An open-label study showed a clinically significant improvement in both motor and cognitive symptoms in patients with moderate PD, with a mean improvement of 2.7 in the MDS-UPDRS scale compared to a decline of 2.2 in the control group ($P = 0.037$). Weight loss was the only notable adverse effect [43, 44]. Exenatide also showed the potential to slow down disease progression, as demonstrated in another clinical trial, where participants exhibited a mean improvement of 1.0 in MDS-UPDRS after 60 weeks of treatment (95% CI = -2.6 to 0.7) [45, 46]. Exenatide is currently completing phase III trials, and more research is being done on its neuroprotective, anti-apoptotic, anti-inflammatory, and antioxidative qualities [47]. Other GLP-1 agonists, including liraglutide and lixisenatide, are in phase II trials [48]. Semaglutide has shown potential by improving motor dysfunction, reducing α-Syn aggregation, and increasing glial cell line-derived neurotrophic factor (GDNF) expression in PD mouse models [43].

Insulin

The relationship between type 2 diabetes mellitus (T2DM) and PD has been recognized since the 1960s. A meta-analysis of seven population-based cohort studies reported a 38% increased risk of developing PD among diabetic patients [49, 50]. Studies have shown widespread insulin resistance and impaired insulin signaling in the brains of PD patients [47]. Observational studies indicate that PD patients have lower fasting plasma insulin levels and a higher fasting plasma amylin/fasting plasma insulin ratio (FPAIR), with FPAIR showing a modest correlation with NMS (NMSS scale) [51]. Insulin has neuroprotective effects through the PI3K pathway, which may protect dopaminergic neurons from the harmful effects of hyperglycemia [52]. Research on intranasal insulin in rats has demonstrated encouraging outcomes in terms of promoting neurogenesis and warding off inflammation and ROS [53]. Nevertheless, intranasal insulin did not show appreciable functional or cognitive advantages in phase II/III trials for Alzheimer's disease and moderate cognitive impairment [54].

Statins

Among statins, simvastatin has garnered the most attention due to its superior blood-brain barrier permeability compared to other statins like pravastatin and rosuvastatin. Preclinical studies in PD mouse models (6-OHDA and MPTP-induced) demonstrated simvastatin's neuroprotective effects [55]. Although cohort studies suggested that simvastatin may reduce PD risk, other retrospective case-control studies provided conflicting results [56]. A randomized controlled trial (RCT) in the UK enrolled 235 patients to assess simvastatin’s disease-modifying potential in PD. Despite the trial’s rigorous design, the results did not support simvastatin as a disease-modifying agent, and further trials were not pursued [57].

Metformin

Metformin, a widely used antidiabetic drug, has shown promising neuroprotective effects in vitro and in vivo. These include the inhibition of α-Syn phosphorylation and aggregation, the alleviation of oxidative stress, the prevention of mitochondrial dysfunction, the modulation of autophagy through the AMPK pathway, and the inhibition of glial cell hyperactivation [58, 59]. Despite these promising preclinical findings, recent meta-analyses suggest that metformin use in humans does not correlate with reduced PD risk and may even increase the risk, particularly in monotherapy [60]. Issues with metformin’s bioavailability in the brain and potential adverse effects from long-term use may explain these contradictions. New stratification criteria for identifying PD patients who could benefit from metformin are being explored, including studies on patients with idiopathic REM sleep behavior disorder, a group at high risk for PD [61, 62].

Sodium-glucose cotransporter-2 (SGLT2) inhibitors

The pathogenesis of both PD and T2DM shares mechanisms such as mitochondrial dysfunction and oxidative stress. SGLT2 inhibitors (flozins) may offer neuroprotective effects through their glucose excretion properties, lowering glycated hemoglobin, and reducing ROS production by inhibiting NADPH oxidase activity. These actions protect mitochondrial function and reduce inflammation [63]. In a murine model of PD, dapagliflozin improved motor dysfunction reduced oxidative stress, and attenuated ROS-dependent apoptosis [64]. A large population-based study comparing SGLT2 inhibitors with dipeptidyl peptidase-4 inhibitors (DPP4i) found a lower risk of PD in the SGLT2 group (HR = 0.28; 95% CI: 0.09 to 0.91; p = 0.0349) [65].

Deferiprone

Ferroptosis, an iron-dependent form of cell death, has been implicated in PD pathology, with increased iron accumulation observed in the brains of PD patients. Deferiprone, an iron chelator, has shown efficacy in reducing oxidative stress, improving motor activity, and preserving dopamine levels in preclinical PD models [55, 66]. Positive results from small-scale human studies also prompted the start of larger RCTs, such as the 372-participant FAIR PARK II experiment. Regretfully, further findings revealed that deferiprone was linked to worse parkinsonism scores among PD patients who had not yet started dopaminergic therapies, undermining the drug's potential as a therapeutic intervention [67, 68].

Antihypertensive drugs

Calcium channel blockers (CCBs)

Epidemiological studies suggest that CCBs, particularly isradipine, may reduce PD risk. However, the STEADY-PD phase III RCT, involving 336 patients, failed to demonstrate isradipine’s efficacy in slowing PD progression [56, 69]. While a modest impact on delaying the need for antiparkinsonian treatments was observed, the study

highlighted dosage limitations as a potential issue [70]. Computational analysis using IBM Watson identified nifedipine as another potential candidate, though it has been associated with Parkinsonism syndromes in some reports [71, 72].

Angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs)

Preclinical evidence supports the role of the renin-angiotensin system (RAS) in neuroinflammation and oxidative stress in PD, making ACE inhibitors and ARBs attractive therapeutic options. Studies have shown that drugs such as captopril and losartan can enhance L-DOPA effects without inducing dyskinesias and reduce PD risk in clinical populations [56, 73-77]. However, the quality of evidence remains low, and further trials are necessary to validate these findings [72].

- *Anti-infective drugs in PD therapy*

Minocycline

Minocycline, a second-generation tetracycline antibiotic, exhibits efficacy against both gram-positive and gram-negative bacteria. Owing to its lipophilicity, it can easily cross the blood-brain barrier (BBB) and accumulate in the cerebrospinal fluid (CSF) and CNS. This allows minocycline to be used in the treatment of CNS diseases, including PD. Minocycline exerts neuroprotective effects by inhibiting proinflammatory molecule production, reducing mitochondrial dysfunction, and preventing microglial activation, which are key processes in the etiopathogenesis of PD [78]. Preclinical studies in rotenone-induced PD rat models have demonstrated that minocycline can slightly alleviate motor deficits, although it has not shown significant improvements in motor function in clinical studies involving early PD patients [79].

Doxycycline

Doxycycline, another second-generation tetracycline antibiotic, is commonly used for bacterial infections. Recent studies highlight its ability to inhibit α-Syn aggregation and reduce mitochondrial-derived ROS [80]. In an experiment involving human α-Syn A53T transgenic mice, doxycycline treatment (10 mg/kg daily for 30 days) significantly improved motor function, including gait stability and muscle strength [81]. This suggests that doxycycline could be a potential therapeutic option for addressing both MS and neuropathological changes in PD. A randomized, double-blind, placebo-controlled trial is currently recruiting PD patients to further assess doxycycline's effects on motor performance and cognitive function in individuals receiving levodopa (NCT05492019).

Geldanamycin

Geldanamycin is an ansamycin antibiotic originally developed as an anticancer drug. It inhibits the function of Heat Shock Protein 90 (Hsp90) and upregulates Heat Shock Protein 70 (Hsp70). Hsp70 is known to prevent α-Syn misfolding and reduce amyloid aggregation [82]. Inhibition of Hsp90 by geldanamycin has shown protective effects against MPTP-induced dopaminergic neurotoxicity in PD models, due to the induction of Hsp70, which counters neurotoxicity and mitochondrial stress [83]. Despite these promising results, the toxicity of geldanamycin limits its clinical application. However, structural analogs of geldanamycin, such as 17-AAG, 17-DMAG, IPI-493, and retaspimycin, are currently being evaluated in clinical trials as potential treatments for PD [84].

Rifampicin

Rifampicin, an ansamycin antibiotic primarily used to treat mycobacterial infections, has demonstrated anti-inflammatory, anti-aggregating, and antioxidant properties, making it a potential therapeutic candidate for neurological disorders like PD [84]. Rifampicin has been shown in experimental tests to lessen neuroinflammation and neurodegeneration brought on by fibrillary aggregates of α-Syn [85]. Rifampicin reduced apoptosis in zebrafish models of PD caused by rotenone through the reduction of pro-inflammatory cytokines such as IL-1β and IL-6 and the mitigation of mitochondrial oxidative stress [86]. These results suggest that rifampicin could modulate neuroinflammation and reduce mitochondrial dysfunction in PD, though further evaluation in clinical settings is needed.

Ceftriaxone

Ceftriaxone, a third-generation cephalosporin antibiotic, can cross the BBB and has shown neuroprotective effects in CNS disorders by upregulating excitatory amino acid transporter 2 (GLT-1) expression [87]. Chronic

administration of ceftriaxone (200 mg/kg) in MPTP-induced PD rat models resulted in significant improvements in motor function and reduced oxidative damage. Furthermore, ceftriaxone downregulated neuroinflammation markers such as glial fibrillary acidic protein (GFAP) and Toll-like receptor 4 (TLR4) while reducing pro-inflammatory cytokines (IL-1β, TNF-α, and IL-6) [88]. A phase II randomized, double-blind, placebo-controlled trial is underway to assess the efficacy and safety of ceftriaxone in patients with PD dementia (NCT03413384).

Niclosamide

Niclosamide, an antihelminthic drug, has been recognized for its ability to modulate mitochondrial phosphorylation and influence various signaling pathways, including mTOR and JAK/STAT3 [89]. Niclosamide has shown promise in activating PINK1, a kinase involved in protecting against mitochondrial dysfunction, which is particularly relevant in autosomal recessive PD [90]. Niclosamide also promotes neurite growth in dopaminergic neurons and protects against α-Syn-induced neurodegeneration through the BMP-Smad pathway [91]. Although niclosamide shows potential as a neuroprotective agent, further research in vivo PD models is required to determine its effectiveness and safety.

CONCLUSION

This study highlights the potential of repurposed drugs for PD, focusing on immunomodulatory, cardiometabolic, and anti-infective agents. Immunomodulators like c-Abl inhibitors (imatinib, nilotinib) show neuroprotective effects by targeting α-Syn aggregation and cellular stress pathways, though clinical efficacy remains inconclusive. Cardiometabolic drugs, particularly GLP-1 agonists such as exenatide, demonstrate promising results in motor and cognitive symptom improvement, with potential disease-modifying effects. Anti-infective agents (minocycline, doxycycline, rifampicin) offer neuroprotection through anti-inflammatory and anti-aggregating actions, though clinical translation is limited by mixed results and toxicity concerns.

While these drugs offer promising therapeutic strategies, further large-scale trials are necessary to confirm their efficacy and safety. A deeper understanding of their molecular mechanisms in PD could guide the development of optimized treatment approaches.

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