Review

Cognitive impairment in Parkinson's disease: an updated overview focusing on emerging pharmaceutical treatment approaches

Yildiz Degirmenci , Efthalia Angelopoulou , Vasiliki Epameinondas Georgakopoulou , Anastasia Bougea *

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Cognitive impairment in Parkinson's Disease: An Updated Overview Focusing on Emerging Pharmaceutical Treatment Approaches

YildizDegirmenci [1,2], Efthalia Angelopoulou[3], Vasiliki Epameinondas Georgakopoulou [4] and Anastasia Bougea [3,*]

[1] Istanbul Health and technology University, School of Medicine, Department of Neurology, Istanbul, Turkey; ydegir@gmail.com
[2] Sisli Kolan International Hospital, Neurology Clinic, Parkinson' s Disease and Movement Disorders Unit, Istanbul, Turkey
[3] 1st Department of Neurology, Medical School, National and Kapodistrian University of Athens, Eginition Hospital, 11528 Athens, Greece; angelthal@med.uoa.gr, annita139@yahoo.gr
[4] Department of Infectious Diseases-COVID-19 Unit, Laiko General Hospital, 11527 Athens, Greece; vaso_georgakopoulou@hotmail.com
* Correspondence: annita139@yahoo.gr

Abstract: Cognitive impairment in patients with Parkinson's disease (PD), which may occur in various severities, represents one of the commonest and most disabling non-motor manifestations during the course of the disease, causing a negative impact on patients' quality of life. Eventually, it becomes a burden for the family members and/or the caregivers of patients, as it progresses to PD dementia. Current pharmacological treatments for cognitive impairment in PD exhibit partial efficacy, while novel effective therapeutic strategies are required. Accumulating preclinical and clinical evidence shows that several agents may provide beneficial effects on patients with PD and cognitive impairment, including ceftriaxone, ambroxol, intranasal insulin, nilotinib, atomoxetine, mevidalen, blarcamesine, prasinezumab, SYN120, ENT-01, NYX-458, GRF6021, fosgonimeton, INT-777, Neuropeptide S, silibinin, osmotin, cordycepin, huperzine A, fibroblast growth factor 21, Poloxamer 188, ginsenoside Rb1, thioredoxin-1, tangeretin, istradefylline, and Eugenia uniflora. Potential underlying mechanisms include the inhibition of a-synuclein aggregation, improvement of mitochondrial function, regulation of synaptic plasticity, impact on gut-brain axis, modulation of neuroinflammation, upregulation of neurotrophic factors, as well as cholinergic, dopaminergic, serotoninergic and norepinephrine neurotransmission. In this overview, we aim to cover the clinical aspects of PD associated cognitive impairment, highlighting recent evidence on emerging treatment approaches that are currently under investigation at a preclinical and clinical level.

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1. Introduction

Parkinson's disease (PD) is a progressive and disabling neurodegenerative disorder, characterized by both motor and non-motor manifestations during the course of the disease [1]. Non-motor symptoms occur as the initial presentation in about 2 % of the patients with PD (pwPD) [2]. There is a wide spectrum of non-motor symptomatology in pwPD, including sensory disturbances, mood changes, pain and sleep problems, autonomic system disorders, as well as cognitive impairment [2,3].

Cognitive impairment represents one of the most debilitating non-motor symptoms of PD that eventually has a great impact on patients' quality of life. The underlying pathophysiology is considered to involve the impaired dopaminergic circuits in the basal ganglia, as well as the disruption of cholinergic neurotransmission in the forebrain of pwPD. The affected cognitive domains in pwPD at the first place include executive and visuospatial functions, verbal fluency,

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processing speed as well as complex attention. Memory impairment may also occur in due course of the disease [4].

Several risk factors have been shown to be related with cognitive impairment in pwPD, including male sex, mood disorders, comorbidities such as Alzheimer's disease (AD), REM sleep behaviour disorder (RBD), hypertension, diabetes, cardiovascular diseases, hyperuricemia, labil blood pressure, environmental factors like trauma and pesticide exposure, as well as genetic factors, such as APOE ε4, MAPT H1/H1, and e G196A (Val66Met) polymorphism [5–9]. Alves and colleagues have also revealed an association between low cerebrospinal fluid amyloid-β 42 levels with a higher risk of cognitive decline in pwPD [10].

Cognitive decline can occur in both early and advanced stages during the course of the disease, characterized by heterogeneity in its symptomatology and severity. The clinical spectrum includes subjective cognitive decline (SCD), mild cognitive impairment (MCI), and Parkinson's disease dementia (PDD) [4,11,12].

Given the recent growing evidence on novel potential treatment approaches, herein, we provide a brief updated overview on the spectrum of cognitive impairment in PD, focusing on the emerging therapeutic implications, as indicated by recent clinical and preclinical evidence.

The introduction should briefly place the study in a broad context and highlight why it is important. It should define the purpose of the work and its significance. The current state of the research field should be carefully reviewed and key publications cited. Please highlight controversial and diverging hypotheses when necessary. Finally, briefly mention the main aim of the work and highlight the principal conclusions. As far as possible, please keep the introduction comprehensible to scientists outside your particular field of research. References should be numbered in order of appearance and indicated by a numeral or numerals in square brackets—e.g., [1] or [2,3], or [4–6]. See the end of the document for further details on references.

2. The Clinical Spectrum of Cognitive Impairment in Parkinson's Disease

2.1. Subjective Cognitive Decline (SCD)

SCD can be considered as an intermediate condition between age-related cognitive decline and MCI. In particular, it refers to a self-reported decline in cognitive functions, whilst the neuropsychological test results are within the normal limits, reflecting normal cognitive function among age matched populations. These subtle, self-reported difficulties may manifest as bradyphrenia, slowed thinking and processing in pwPD, and are considered to be associated with anxiety, stress and depression [13]. However, the frequency of subjective cognitive decline in pwPD have not been well documented. The complaints of the patients should be monitored during the course of the disease, as they may eventually evolve into MCI with objective deficits [12–14].

2.2. Mild Cognitive Impairment (MCI)

MCI could be considered as a transition stage of cognitive decline between normal aging and dementia, which occurs with a prevalence of 6.7%-25.2% in the elderly [15]. It has been reported that MCI prevalence among pwPD is up to 40%, and it represents an important risk factor for the development of PDD during disease course [11,16].

The major neuropathological characteristics of MCI in PD is Lewy body deposition in the neocortex and limbic system of pwPD. However, AD-associated neuropathology has also been associated with PD-MCI, and it may play an important role as a contributing factor [17].

The factors associated with a higher risk of MCI in pwPD have been reported to be older age, male gender, lower education status, comorbid metabolic syndrome, akinetic rigid phenotype, and the co-occurence of non-motor features such as anxiety, autonomic dysfunction, depression, and sleep behaviour disorders [18–20].

Literature evidence has shown that brain atrophy in pwPD with MCI is more likely to occur in the fronto-temporo-parietal regions, and the basal forebrain [21].

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The best neurophysiological assessment tools suggested for PD-MCI are trail making test, symbol digit modalities test, clock drawing test, intersecting pentagons, judgement of line orientation, Boston naming test, animal naming test, figural memory, and free and cued selective reminding tests [22].

Neuroimaging studies have demonstrated that MCI in PD is associated with cortical atrophy that involves the left prefrontal and insular, right anterior temporal, and right parietal and occipital areas in particular, and eventually the subcortical regions during the course of the pathology [23]. Moreover, hypoactivity in the occipital areas has been reported by Wang and colleagues to be associated with cognitive impairment in early PD with MCI [24].

Management strategies of PD-MCI include non-pharmacological and pharmacological approaches. Physical activity, and cognitive exercises have been demonstrated to be effective in enhancing global cognitive function and mental flexibility in pwPD [25,26]. However, there is currently no effective pharmacotherapy that has been clearly shown to improve cognition in PD-MCI. Hinson and colleagues reported that atomoxetine, a selective presynaptic serotonin reuptake inhibitor, might be beneficial in improving executive functions in PD-MCI [27]. Rivastigmine, as a cholinesterase inhibitor has been also indicated to improve cognitive function in pwPD [28]. Memantine, as a well-known N-Methyl-D-aspartate (NMDA) receptor inhibitor may also be useful for cognitive and behavioral symptoms in pwPD [29].

2.3. Parkinson' s Disease Dementia (PDD)

PDD is one of the most disabling and challenging non-motor symptoms, affecting about 30 % of pwPD [16]. Older age at the disease onset and advanced stage of PD are the most common risk factors for the development of PDD, as well as akinetic-rigid subtype, severe motor symptoms, atypical parkinsonian features such as symmetrical onset and early autonomic dysfunctiton, poor response to levodopa, male gender, low education level, vascular comorbidities such as hypertension and diabetes, RBD, presence of depression and hallucinations, and genetic factors, including GBA gene mutations, multiplications in the α-synuclein gene (SNCA) and H1 haplotype of the MAPT gene [30,31]. Xu and colleagues also reported that the history of smoking may be associated with a 2-fold increased risk of PDD [30].

The suggested underlying pathology in PDD is thought to involve deficits in the monoaminergic cholinergic and mesocortical dopaminergic system, as well as the disruption of the thalamic components of the limbic system [32,33]. PDD is characterized by degeneration of subcortical nuclei, cortical cell death, Lewy body-type pathology (dopaminergic neuronal loss in the substantia nigra and aberrant α-synuclein deposition in Lewy bodies), and AD-type pathology defined as the accumulation of extracellular β-amyloid and intracellular tau [32–34].

The treatment strategies for the management of PDD include rivastigmine, as it has been shown to improve cognitive and behavioural symptoms [35]. Despite the insufficient evidence, donepezil and galantamine are also considered as "possible useful" in PDD [35,36].

4. Novel Pharmaceutical Treatments under Investigation

4.1. Ceftriaxone

Ceftriaxone, an old, third-generation widely used cephalosporin antibiotic, has been demonstrated to exert beneficial neuroprotective effects in preclinical models of several neurological diseases [37]. Ceftriaxone can supress glutamatergic neuronal excitotoxicity, promote the expression of glutamate transporter-1, and enhance the reuptake of glutamate. In addition, it can bind to α-synuclein and supress its polymerization, regulate the expression of amyloid beta-related genes, and improve neurogenesis [37]. Given the fact that glutamatergic excitotoxicity plays a pivotal role in the pathophysiology of PDD, it has been hypothesized that it could mitigate cognitive and behavioural deficits in animal models of PD *in vivo*. Indeed, ceftriaxone could reverse behavioural deficits and enhance neurogenesis in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced rat models of PDD, since it was able to improve motor function, prevent working memory and object recognition

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deficits, and promote neurogenesis in the hippocampal dentate gyrus and substantial nigra of the animals [38]. Interestingly, another study has indicated that ceftriaxone exerted synergistic effects with erythropoietin on the behavioural impairment and neuronal alterations of MPTP-induced rat models of PD, in terms of memory deficits, as well as the degeneration of nigrostriatal dopaminergic projections and the CA1 area of the hippocampus [39]. Given these promising preclinical results, a double-blinded, randomized, placebo-controlled Phase II clinical trial is investigating the safety and efficacy of the use of ceftriaxone in patients with mild and moderate PDD (NCT03413384).

4.2. Ambroxol

Glucocerebrosidase (GBA1) gene variants are present in approximately 10-15% of patients with PD, constituting the most common genetic risk factor for PD. Ambroxol has been widely used against hyaline membrane disease and airway mucus hypersecretion in newborns, and it has been demonstrated to act as a chaperone of glucocerebrosidase (GCase), a lysosomal enzyme that is implicated in the glucosylceramide metabolism [40]. Ambroxol has been demonstrated to enhance the activity of GCase and decrease GCase substrates in GBA1-mutated macrophages, and it can penetrate the brain resulting in higher GCase levels in the cerebrospinal fluid of patients with PD carrying or not GBA1 mutations [40]. Although the exact underlying mechanism of its action is unclear, it is considered to involve the increased lysosomal clearance of a-synuclein [40]. Ambroxol could increase the activity of GCase activity, and reduce the levels of α-synuclein and tau in GBA1-mutated cholinergic neurons [40], suggesting that it could exert neuroprotective effects against PDD. A phase II randomized clinical trial is investigating the effects of ambroxol on mild and moderate PDD (NCT02914366).

4.3. Intranasal Insulin

Repurposing antidiabetic drugs has been emerged as a novel therapeutic strategy against neurodegenerative disorders, including AD and PD. Insulin plays a crucial role in the metabolism of glucose in the central nervous system, and it displays significant neurotrophic, neuromodulatory and neuroprotective properties [41]. Intranasal insulin has been previously indicated to enhance working memory in patients with MCI and AD. Preclinical evidence has shown that intranasal insulin may also ameliorate cognitive deficits in 6-hydroxylase dopamine (6-OHDA)-induced rat models of PD by regulating Akt/Glycogen Synthase Kinase 3 Beta (GSK3β) signaling pathway [42]. A double-blinded placebo-controlled pilot clinical trial has indicated that intranasal insulin was associated with better verbal fluency among patients with PD, although further larger studies are needed to clarify its efficacy in PD-related cognitive impairment [41].

4.4. Nilotinib

Discoidin domain receptors (DDRs) represent receptor tyrosine kinases, which have been found in higher levels in the midbrain of PD patients. Pharmacological inhibitors of DDRs, such as nilotinib, have been shown to elevate the levels of dopamine, as well as decrease α-synuclein and hyper-phosphorylated tau in preclinical studies [43].Nilotinib can also suppress microglia-mediated neuroinflammatory processes, thereby acting neuroprotectively against dopaminergic neuronal loss in PD models, by decreasing the generation of pro-inflammatory factors, such as cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS), tumor necrosis factor alpha (TNF-α), interleukin-1β (IL-1β) and IL-6 [44]. Nilotinib is a potent tyrosine kinase inhibitor that is already approved for the treatment of Philadelphia chromosome positive chronic myeloid leukemia. An open-label study has indicated that nilotinib administration was not associated with alteration in cognition in the Montreal Cognitive Assessment (MoCA) of PD patients [43].

4.5. Atomoxetine

PDD has been shown to be associated with neuronal cell death in the locus coeruleus (LC) in post-mortem studies of PD patients [45]. LC is the major norepinephrine generator in the brain that

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stimulates wakefulness, and its activation has been supposed to promote attention and cognitive function [46]. Atomoxetine, a serotonin norepinephrine reuptake inhibitor approved for attention deficit-hyperactivity disorder (ADHD), is hypothesized to enhance the function of the locus coeruleus. Except for norepinephrine, atomoxetine can also increase the levels of dopamine in the prefrontal cortex, since the uptake of dopamine in this brain area is mediated by norepinephrine transporters. Hence, it has been hypothesized that the potential beneficial effects of atomoxetine on cognitive performance in PD might be additionally linked to the increased noradrenergic or dopaminergic tone in the frontal brain regions [47]. A pilot open-label clinical trial indicated that atomoxetine was effective in improving the executive deficits of PD patients without dementia [48]. Another study demonstrated that although atomoxetine was not associated with clinical outcomes on depressive symptoms, it could improve global cognition of patients with PD [47].

4.6. Mevidalen

Mevidalen (LY3154207), a selective positive allosteric modulator (PAM) of the dopamine D1 receptor, acts by enhancing its tone and affinity for dopamine, thereby increasing the response to dopamine [49]. Mevidalen can improve cognitive function by promoting dopaminergic neurotransmission in frontal regions, activating cortical neuronal cells, increasing synaptic neuroplasticity, and enhancing the D1-induced release of acetylcholine [50]. However, a phase II, randomized, placebo-controlled clinical trial (NCT03305809) has recently demonstrated that mevidalen was not able to improve cognitive performance of patients with Lewy body dementia [51].

4.7. Blarcamesine

Sigma-1 receptors act as molecular chaperones, which are located at the mitochondria-associated endoplasmic reticulum membrane [52]. In preclinical models of PD, sigma-1 receptor activation has been associated with improved mitochondrial function, reduced microglial activation, decreased dopaminergic cell loss, and enhancement of brain-derived neurotrophic factor (BDNF) and glial cell line-derived neurotrophic factor (GDNF) [52]. Blarcamesine (ANAVEX2-73) is intracellular sigma-1 protein agonist that is clinically investigated in PDD in a phase II randomized placebo-controlled clinical trial (NCT03774459) in PDD patients.

4.8. Prasinezumab

Prasinezumab (RO7046015/PRX002) is an anti-α-synuclein monoclonal antibody (mAb) that has shown promising results in terms of cognitive function in preclinical models of PD. Prasinezumab is able totarget both insoluble and soluble forms of aggregated of α-synuclein [53]. Its murine parent monoclonal antibody 9E4 can ameliorate α-synuclein neuropathology, improve both motor and cognitive impairment, as well as protect against neurodegeneration in α-synuclein transgenic mouse models of PD [53]. Intravenous administration of prasinezumab has demonstrated good safety in healthy individuals [53], as well as in patients with PD [54]. A randomized, double-blind, placebo-controlled, phase II clinical trial is currently investigating the efficacy of prasinezumab in PD, and the secondary outcomes include its effects on cognitive function, as evaluated by alterations in MoCA (NCT03100149).

4.9. SYN120

Dysregulation of serotoninergic neurotransmission is critically related to PD pathophysiology, including the underlying mechanisms of non-motor manifestations such as depression and cognition. SYN120 is a dual serotonin receptor (5-HT6/5-HT2A) antagonist that has been proposed to exert beneficial effects in cognitive function in PD patients. A randomized, placebo-controlled clinical trial has recently demonstrated that SYN120 administration did not improve cognitive performance of patients with PDD [55].

4.10. ENT-01

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Squalamine is an antimicrobial aminosterol, which has been shown to displace a-synuclein via an electrostatic mechanism from membranes and inhibits the nucleation and aggregation of a-synuclein monomers into oligomers that display neurotoxic properties [56]. ENT-01 is a synthetic salt of squalamine, which has been investigated for the treatment of constipation in PD, and it has been also hypothesized to be beneficial for the cognitive function. In this regard, a multicenter, open label clinical trial (NCT03938922) intends to potentially resume in 2024 in order to investigate the efficacy and tolerability of ENT-01for patients with PDD.

4.11. Other Agents in Clinical Trials for PDD

NYX-458 is a NMDA receptor (NMDAR) modulator that improves synaptic neuroplasticity. A preclinical study has demonstrated that NYX-458 is able to improve cognitive performance in terms of working memory, attention, and executive function in a primate MPTP-induced model of PD [57]. A phase II clinical trial is also investigating the effects of NYX-458 on patients with MCI or mild dementia associated with PD, prodromal or manifest Lewy body dementia (NCT04148391). GRF6021 is an intravenously administered plasma-derived product, and its tolerability and safety has been also investigated in a randomized, double-blind, placebo-controlled trial for PD with cognitive impairment (NCT03713957). Fosgonimeton (ATH-1017) regulates hepatocyte growth factor (HGF)/MET, which affects neurite outgrowth and synaptogenesis [58]. This compound is also being investigated for PDD and Lewy body dementia in a randomized, placebo-controlled clinical trial (NCT04831281).

4.12. Agents for PDD under Investigation: An Update on Preclinical Evidence

Emerging preclinical evidence has revealed the therapeutic potential of several novel candidates for the treatment of cognitive impairment in PD. Gut microbiota and bile acid metabolism has been indicated to play an important role in PD and cognitive impairment in PD in particular [59]. In this context, a recent study has shown that INT-777, a 6α-ethyl-23(S)-methyl derivative of cholic acid (S-EMCA), which acts as a Takeda G protein-coupled receptor-5 (TGR5) agonist could exert neuroprotective properties in MPTP-induced mouse models of PD in terms of cognitive and motor deficits, at least partially via the regulation of neuroinflammation and mitochondrial function in microglia [60].

Neuropeptide S (NPS) and NPS receptor (NPSR) has been indicated to play a crucial role in PD pathophysiology. More specifically, NPS can enhance the release of dopamine release, inhibit oxidative damage, and suppress the dopaminergic neuronal loss in preclinical animal models of PD [61]. NPS was able to improve memory function in MPTP-induced mouse models of PD [62], suggesting its promising potential for PD-related cognitive impairment.

BDNF is neurotrophic factor critically involved in the molecular pathogenesis of neurodegenerative diseases, including AD and PD. A recent study indicated that BDNF overexpression via adeno-associated viruses (AAV) with BDNF gene injection was associated with improved cognitive performance in MPTP-induced mouse models of PD, which was accompanied by restoration of mitochondrial function and inhibition of dopaminergic neuronal loss [63].

Furthermore, another study has shown that silibinin, a flavonoid that is derived from milk thistle (Silybum marianum) with hepatoprotective, antioxidative and neuroprotective properties, was able to attenuate cognitive deficits in MPTP-induced mouse models of PD. These effects were associated with reduced cellular apoptosis and a-synuclein aggregation in the hippocampus, as well as decreased oxidative stress and improved mitochondrial function [64]. Hence, this agent represents another potential therapeutic candidate against PDD, which deserves further investigation.

Oral consumption of probiotics has been associated with improved both motor and non-motor symptoms in PD, such as constipation, depression and anxiety, via their implication in gut-brain axis regulation [65]. Interestingly, the administration of the probiotic *Bifidobacterium breve* could restore the abnormal synaptic plasticity in the hippocampus and facilitatate fear extinction in MPTP-induced mouse models of PD [66]. In addition, the administration of the probiotic formulation SLAB51 could improve behavioral deficits and prevent dopaminergic neuronal loss in the substantia nigra pars

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compacta and striatum in 6-hydroxydopamine (6-OHDA)-induced mouse models of PD [67], further supporting the role of probiotics in attenuating cognitive deficits in PD.

Another agent, osmotin, a adiponectin homolog that modulates the phosphorylation of 5' adenosine monophosphate-activated protein kinase (AMPK) through the adiponectin receptor 1 (AdipoR1), has been found to exert neuroprotective properties in preclinical models of PD. In particular, osmotin treatment was associated with better cognitive performance in a-synuclein transgenic and MPTP-induced mouse models of PD. The underlying mechanisms might involve the inhibition of α-synuclein accumulation via the upregulation of the AMPK/mammalian target of rapamycin (mTOR) signaling pathway and modulation of autophagy, as well as the regulation of neuroinflammation through its implication in mitogen-activated protein kinase (MAPK) pathway [68].

Cordycepin, a small molecule derived from cordyceps sinensis, is also able to regulate neuroinflammation in MPTP-induced models of PD, by downregulating Toll-like receptor (TLR)/nuclear factor kappa light chain enhancer of activated B cells (NF-κB) pathway [69]. It has also been demonstrated that cordycepin might exert beneficial effects on cognitive function in MPTP-induced models of PD, by modulating the adenosine A2A receptors andreversing the suppression of synaptic neurotransmission in the hippocampus [70].

Moreover, administration of huperzine A, a plant-derived lycopodium alkaloid acting as a natural acetylcholinesterase inhibitor, was able to improve memory and learning ability of MPTP-induced murine models of PD, which was accompanied by prevention of dopaminergic degeneration, and modulation of inflammatory and apoptotic mechanisms [71].

Fibroblast growth factor 21 (FGF21) has been shown to display several biological properties, such as anti-oxidant, anti-inflammatory and anti-apoptotic. FGF21 could prevent dopaminergic neuronal loss in the substantia nigra pars compacta, improve mitochondrial function and inhibit microglia activation in MPTP-induced mouse models of PD. Potential underlying mechanisms involved the upregulation of the AMPK/Peroxisome proliferator-activated receptor-gamma coactivator 1 alpha (PGC-1α) pathway [72]. A recent study revealed that FGF21 treatment was associated with better motor and cognitive performance of MPTP-induced mouse models of PD, possibly by re-structuring the profile of gut microbiota, thus preventing the PD-related metabolic alterations in the gut [73].

It has been indicated that Poloxamer 188, an amphipathic synthetic polymer, protects against MPTP-induced dopaminergic neuronal loss. Recently, this agent was also shown to exert beneficial effects against cognitive deficits in maneb- and paraquat-induced mouse models of PD, potentially by supressing inflammatory responses and microglia activation, and restoring hippocampal synaptic density [74].

Ginsenoside Rb1, the active ingredient of *Panax ginseng*, has been previously shown to attenuate motor impairment and prevent dopaminergic degeneration in MPTP-induced mouse models of PD, by upregulating the glutamate transporter GLT-1 and inhibiting glutamate excitotoxicity [75]. In addition, Ginsenoside Rb1 could improve memory and spatial learning ability and enhance long-term potentiation (LTP), by upregulating the expression of postsynaptic density-95 (PSD-95) [76].

Thioredoxin-1 (Trx-1), a redox protein, could also ameliorate memory and learning impairment in MPTP-induced mouse models of PD, by regulating dopamine D1 receptor expression and modulating the NMDAR/extracellular signal-regulated kinase (ERK1/2)/cAMP-response element binding protein (CREB) signaling pathway in the hippocampus [77].

Tangeretin, a citrus flavonoid, has also been demonstrated to suppress neurodegeneration and neuroinflammation responses in MPTP-induced cognitive impairment in rat models. In particular, in this study, tangeretin could reduce neuronal cell death in the hippocampus, as well as the pro-inflammatory IL-1β, IL-6 and IL-2, and these effects were accompanied by improved memory function [78].

Istradefylline, an antagonist of adenosine A2A receptor, shows promising effects on patients with advanced PD experiencing motor complications, in terms of reducing OFF episodes [79]. Although the exact underlying mechanism of action is unclear, it is considered that A2A receptor

antagonism may exert its effects via the modulation of gamma-aminobutyric acid (GABA) neurotransmission in the basal ganglia [79]. Notably, apart from its impact on levodopa induced motor complications, istradefylline administration has been associated with both better motor and cognitive performance of MPTP-treated macaque models of PD, regarding attentional deficits and working memory [80].

Eugenia uniflora, an extract of Brazilian purple cherry, has been associated with improved memory concerning short and long-term object recognition, social recognition and working memory of MPTP-induced rat models of PD [81]. These behavioral effects were accompanied by the modulation of the BDNF/tropomyosin receptor kinase B (TrkB)/$p75^{NTR}$ axis in the hippocampus, which is implicated in synaptic plasticity and neurotransmission. Hence, its clinical efficacy in PDD should be further explored in the future.

5. Conclusions

Cognitive decline in pwPD, which may occur in various severities, is one of the most disabling and challenging non-motor manifestations during the course of the disease that has a negative impact on the patients' quality of life. Thus, increasing the awareness, and enhancing the knowledge about non-motor symptoms in PD including cognitive decline, as well as further research with larger cohorts should be a global health priority to establish an effective coping strategy and proper management with the development of new treatments options. The emerging preclinical and clinical evidence on novel therapeutic agents against PDD further pave the way for the development of novel effective pharmaceutical strategies for this disabling non-motor symptom of PD.

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