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REVIEW ARTICLE

Neuroprotective Agents: Implications for Parkinson's Disease Treatment

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Abstract: Parkinson's disease (PD) is a multifaceted neurodegenerative condition marked by the progressive loss of dopaminergic neurons, leading to impairments in movement and cognition. This study offers an in-depth examination of the pathophysiological pathways associated with PD, emphasising the roles of oxidative stress, mitochondrial dysfunction, and neuroinflammation. The study examines the interaction between genetic and environmental factors in the development of PD, highlighting the significance of oxidative stress, mitochondrial dysfunction, and excitotoxicity in the degeneration of dopaminergic neurons. It also looks into the impact of neuroinflammation and microglial activation on the causes of PD. Despite considerable progress in research, there remains a lack of effective treatments that can modify the course of the disease, highlighting the pressing need for new therapeutic approaches that address mitochondrial malfunction, oxidative stress, and neuroinflammation. This study assesses the neuroprotective efficacy of various substances, notably natural agents like resveratrol, curcumin, ginsenoside, and melatonin, for managing PD. Although these natural chemicals show promise, further robust clinical trials are needed to confirm their effectiveness and safety, as well as to investigate their potential incorporation into conventional PD treatment.

Keywords: Neuroprotective agents, Parkinson's disease (PD), reactive oxygen species (ROS), substantia nigra pars compacta (SNpc), bradykinesia, mitochondrial dysfunction.

1. INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by the selective loss of dopaminergic neurons in the substantia nigra. This loss results in motor symptoms, such as tremors, bradykinesia, and rigidity, as well as non-motor symptoms, including cognitive decline. The development of PD involves a combination of factors, including oxidative stress, mitochondrial dysfunction, neuroinflammation, and genetic susceptibility. Despite advances in understanding these mechanisms, current treatments primarily focus on managing symptoms, with no available therapies that effectively halt or reverse disease progression. This highlights the need for novel neuroprotective strategies that target key pathological processes to slow the progression of the disease. In recent years, there has been a growing interest in neuroprotective agents, particularly natural compounds, such as resveratrol, curcumin, ginsenosides, and melatonin, which have exhibited positive effects in preclinical and early clinical studies. These compounds provide neuroprotection by modulating oxidative stress, mitochondrial function, and neuroinflammatory pathways. However, further research is required to validate their efficacy, determine the best dosages, and assess their long-term safety in clinical settings. To provide a comprehensive and up-to-date analysis, this review adopts a systematic approach to collect relevant literature. Peer-reviewed studies were identified through major scientific databases such as PubMed, Scopus, and Web of Science, using keywords such as "Parkinson's disease," "neuroprotection," "oxidative stress," "mitochondrial dysfunction," and "natural compounds." The selection criteria prioritized recent studies, particularly those published within the last decade, as well as seminal research that has had a significant impact on the field. This review is structured to initially discuss the fundamental pathological mechanisms of PD, followed by an evaluation of potential

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neuroprotective agents and their mechanisms of action. It will also address the current research limitations and suggest future directions for integrating neuroprotective strategies into clinical practice. By synthesizing recent findings and evaluating emerging therapeutic approaches, this review aims to contribute to the ongoing search for disease-modifying treatments for PD, ultimately bridging the gap between experimental research and clinical application.

1.1. Overview of PD

PD is the second most common neurodegenerative disorder associated with aging, impacting approximately 5% of individuals aged 65 and above. The primary motor symptoms include tremors, bradykinesia (slow movement), and muscle rigidity. PD symptoms result from the progressive loss of dopaminergic cells in the Substantia Nigra Pars Compacta (SNpc) [1]. Currently, there is no known cure for PD. Levodopa is considered the most effective approach for managing symptoms and is widely regarded as the best treatment option. Following a diagnosis of PD, it is estimated that approximately 30% of dopaminergic neurons have already degenerated, along with 50–60% of their axon terminals [2]. Therefore, extensive efforts have been made in recent decades to uncover the fundamental mechanisms and identify potential chemicals that could protect dopaminergic neurons from the complex destructive process. The reason for this is that current PD therapies only provide symptom relief in the early stages of the disease, and their efficacy declines as the condition progresses. PD is rapidly becoming more prevalent as a neurological disorder associated with aging. The neuropathology of this disorder is complex and characterised by two main features: the specific degeneration of dopaminergic neurons in the SNpc and the presence of clusters of fibrillar aggregates known as Lewy bodies (LBs), primarily composed of α-synuclein. These manifestations give rise to both motor and non-motor symptoms [3]. Braak's notion proposes that the progressive accumulation of LBs, which are rich in α-synuclein, starts in the medulla oblongata and anterior olfactory areas. Subsequently, it progresses in a discernible sequence, starting from lower regions and advancing towards the neocortex [4].

Despite extensive preclinical research and postmortem investigations, a single mechanism has not been discovered to fully explain the process of neurodegeneration and the precise pathogenic processes in PD, as it is the result of a complex interplay of various disease-causing pathways. The causes of this illness include mitochondrial dysfunction, oxidative stress, protein aggregation, abnormal protein breakdown due to alterations in proteostasis mechanisms, neuroinflammation, and aging [5]. At present, there are no proven medicinal therapies that can successfully prevent or alter the progression of PD. The current clinical approach places a higher emphasis on addressing and managing symptoms. The failure may be ascribed to the complex neurobiology involved in the progression of PD and the absence of precise animal models for research translation. Moreover, the clinical diagnosis of PD relies on the appearance of motor symptoms, which often occur after substantial nerve damage has already occurred. Several factors may hinder the development of neuroprotective therapeutics for PD. Motor problems, dementia, and balance issues primarily cause long-term impairment.

Additionally, patients frequently experience neuropsychiatric and cognitive symptoms, autonomic dysfunction, pain, social isolation, and sleep disturbances. There is a necessity for more efficient symptomatic therapies for these issues, as well as a therapeutic strategy to halt the progression of the illness. The absence of a continuous treatment pathway, delayed interventions for severe symptoms, and the lack of measures to halt or slow disease progression pose considerable challenges for healthcare providers, patients, and caregivers. Usually, by the time of clinical diagnosis, the patient has already lost 60% or more of the neurons in the SNpc.

PD was initially identified by James Parkinson in 1817. It is a worldwide health concern affecting 3% of the elderly population and 4-5% of individuals over the age of 85. It is more common in men and is influenced by the aging process. While the exact cause of PD remains unknown, recent research indicates that environmental factors and genetic susceptibility are the main contributing factors. Several factors, such as oxidative stress, mitochondrial malfunction, and inflammation, have been linked to the onset of PD. More than one million instances have been recorded in the United States, with a higher incidence in males, occurring about 1.5 times more often than in females. Developed countries have experienced a higher prevalence of PD, mainly due to the aging demographic [6]. PD is primarily influenced by the natural aging process, resulting in a lower occurrence in individuals under 40 and a higher prevalence among those in their 70s and 80s [7]. Most instances of PD are of unknown origin (idiopathic). Recent data suggest that environmental factors and genetic susceptibility are the primary contributors to PD. Genetic variations account for less than 5% of cases, while oxidative stress, mitochondrial dysfunction, and inflammation play significant roles in the disease progression.

1.2. Importance of Neuroprotective Agents in PD Treatment

1.2.1. Slowing Disease Progression

Neuroprotective agents aim to address the root cause of PD, which is neurodegeneration, by preserving neuronal function and integrity. By slowing down neuronal loss, these agents can delay the onset of more severe symptoms, offering patients a higher quality of life for an extended period. Agents, such as rasagiline, a monoamine oxidase B (MAO-B) inhibitor, have shown promise in slowing the progression of the disease by protecting neurons from oxidative stress [8].

1.2.2. Targeting the Mechanisms of Neurodegeneration

Neuroprotective agents target the mechanisms that contribute to neuronal death in PD, such as oxidative stress, mitochondrial dysfunction, and inflammation. For instance, neuroprotective agents, such as creatine and coenzyme Q10,

are being studied for their antioxidant properties to combat oxidative stress, a key factor in the development of PD. However, the clinical effectiveness of these agents remains inconclusive due to the complexities in translating preclinical success into patient outcomes [9].

1.2.3. Delaying Motor and Non-Motor Symptoms

The gradual degeneration of neurons in PD not only leads to motor impairment but also affects cognitive and non-motor functions. Using neuroprotective agents to mitigate neuronal death could potentially delay the onset of these disabling symptoms. For example, dopamine agonists, such as pramipexole, have demonstrated neuroprotective effects by stimulating dopamine receptors and providing early support to the dopaminergic system, potentially delaying both motor and non-motor symptom progression [10].

1.2.4. Potential to Modify Disease Course

Although no neuroprotective agent has yet been proven to conclusively modify the course of PD, clinical trials involving agents like rasagiline and selegiline suggest that early intervention with these drugs may alter the disease's trajectory. The delayed-start trial design, which distinguishes between symptomatic and neuroprotective effects, has shown promising results, especially with rasagiline demonstrating potential for disease-modifying effects [11].

1.2.5. Bridging the Gap Between Preclinical and Clinical Success

The development of neuroprotective therapies also has the potential to bridge the gap between preclinical successes and clinical applications. Many promising agents have demonstrated protective effects in animal models; however, only a few have proven effective in human trials. Improved clinical trial designs, better biomarkers, and a deeper understanding of PD's pathogenesis are crucial for identifying neuroprotective drugs suitable for practical use [12].

2. PATHOPHYSIOLOGY OF PD

2.1. Molecular Mechanisms Leading to Neuronal Degeneration

PD primarily affects the substantia nigra, pars compacta (SNpc), a crucial part of the basal ganglia in the brain which is composed of neurons that secrete dopamine (DA), a vital monoamine acting as an inhibitory neurotransmitter. DA is essential in controlling the responsiveness of striatal neurons in a healthy brain, which are responsible for coordinating physical actions. The reduction in DA levels leads to decreased inhibition of striatal neuron activity, causing them to fire excessively. Patients with PD experience difficulties in movement control, resulting in tremors, muscle rigidity, and reduced mobility. These motor symptoms are often associated with PD [13, 14].

The primary factors contributing to the progression of PD encompass the buildup of misfolded protein clumps, dysfunctional protein removal processes, mitochondrial injury, oxidative stress, excitotoxicity, neuroinflammation, and genetic alterations. The pathology of PD is marked by the buildup of Lewy bodies in the dopaminergic neurons of the substantia nigra pars compacta, which are made up of aggregated misfolded alpha-synuclein and related proteins. Molecular, genetic, and biochemical studies reveal that post--mortem brains of individuals with mixed dementia with Lewy bodies (DLB) and PD with dementia (PDD) frequently show a combination of misfolded protein aggregates, including p-tau, Aβ, and SNCA. Gomperts and his team conducted research on the brains of PD patients and discovered a combination of amyloid deposits. This relationship points to cognitive deficits, excluding dementia, implying that amyloid may contribute to cognitive decline over time but does not affect motor decline. In animal and cell culture models, increased SNCA expression resulted in the accumulation of SNCA aggregates in mitochondria, significant disruptions in mitochondrial movement, and a decrease in mitochondrial membrane potential. Animals lacking SNCA exhibited irregularities in mitochondrial lipids and disturbances in the electron transport chain, along with reduced vulnerability to mitochondrial toxins. The A53T transgenic mouse model of PD exhibited mitochondrial degeneration in the brain, an increase in SNCA-containing mitochondria, and a notable reduction in complex IV activity. Individuals with PD showed signs of oxidative stress, impaired respiratory chain function, mitochondrial DNA damage, and the presence of SNCA inclusions in human dopaminergic neurons [15] (Fig. **1**).

2.2. Role of Oxidative Stress and Mitochondrial Dysfunction

The brain uses approximately 20% of the body's oxygen, despite accounting for only 2% of total body weight. When the antioxidant capacity is exceeded, oxidative stress can occur, leading to the production of reactive oxygen species (ROS) due to excessive oxygen intake [16]. ROS molecules are inherently unstable due to the presence of one or more unpaired electrons in their outermost shell [17]. These molecules include superoxide (O_2-), hydroxyl ($OH-$), peroxyl (RO_2-), alkoxyl ($RO-$) radicals, and covalent complexes, such as H_2O_2. ROS can damage the cell membrane, proteins, and DNA. The brain's sensitivity to damage induced by ROS is heightened by the presence of high levels of fat in its cell membranes and myelin sheath. The imbalance between ROS production and antioxidant defense is attributed to a reduced amount of antioxidant enzymes in this anatomical location [18]. ROS can cause significant harm, leading to impaired brain function, a weakened blood-brain barrier, disrupted mitochondrial respiration, and changes in tubulin organisation [16]. Studies have shown that ROS can enhance the release of the excitatory neurotransmitter glutamate outside of cells, which can activate several receptors, especially NMDA receptors, causing anoxic depolarization. Additionally, ROS can impact gene expression, promote apoptotic pathways, and ultimately decrease neuronal survival (Fig. **2**).

Mitochondria play a key role in generating energy within cells, and when these organelles malfunction, they can significantly contribute to neurodegeneration. Mitochondria are crucial intracellular organelles characterized by their

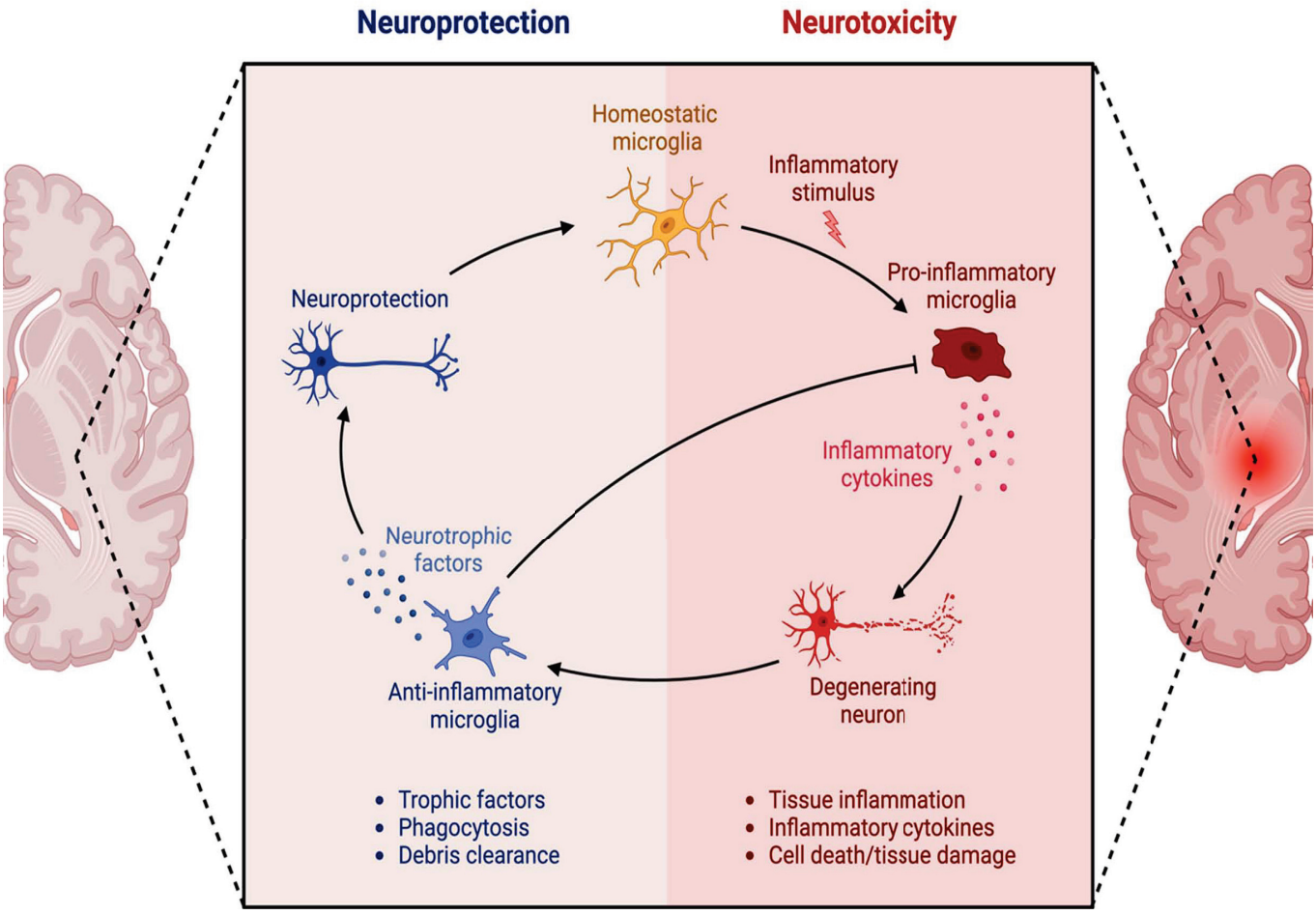

Fig. (1). Neurotoxicity and the possible action of neuroprotective agents. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

highly dynamic nature, which involves frequent processes of fission and fusion. Maintaining a balance between fission and fusion is crucial for optimal mitochondrial function, and neurons rely heavily on proper mitochondrial activity [19].

Age and environmental variables could potentially interact to induce cellular stress, which leads to the failure of compensatory mechanisms and ultimately results in clinical Parkinsonism characterized by persistent neuronal dysfunction [20].

Oxidative stress (OS) is a significant mechanism in the aging process that causes direct damage to the central nervous system (CNS) and is highly important in PD research, as well as other age-related neurodegenerative illnesses. This notion highlights the role of mitochondria in degenerative processes, as abnormal complex-I activity in mitochondria has been linked to PD, leading to impaired cellular ATP synthesis and ultimately cell death [21].

Free radicals play important roles in host defense, gene transcription, regulation of neuronal plasticity, and apoptosis [22]. However, OS arises when ROS surpasses the cellular antioxidant capacity. This results in the accumulation of cytotoxic substances, causing protein destabilization, enzyme malfunction, lipid degradation, and ultimately cell demise in several types of neurons, including dopamine-neuronal tissue [23].

2.3. Genetic Factors Contributing to PD

PD is influenced by a combination of hereditary and non-genetic factors, including environmental influences. A key abnormality in PD is the accumulation of LBs within dopamine neurons in the SNpc, which are aggregates of misfolded protein. Mutations in the SNCA gene, such as A53T, A30P, E46K, and H50Q, are responsible for familial PD, which is characterized by an early onset, rapid progression, and a high risk of developing dementia. Excessive phosphorylation of tau can lead to the formation of twisted filaments known as neurofibrillary tangles (NFT), a hallmark of several neurodegenerative diseases [4, 24, 25].

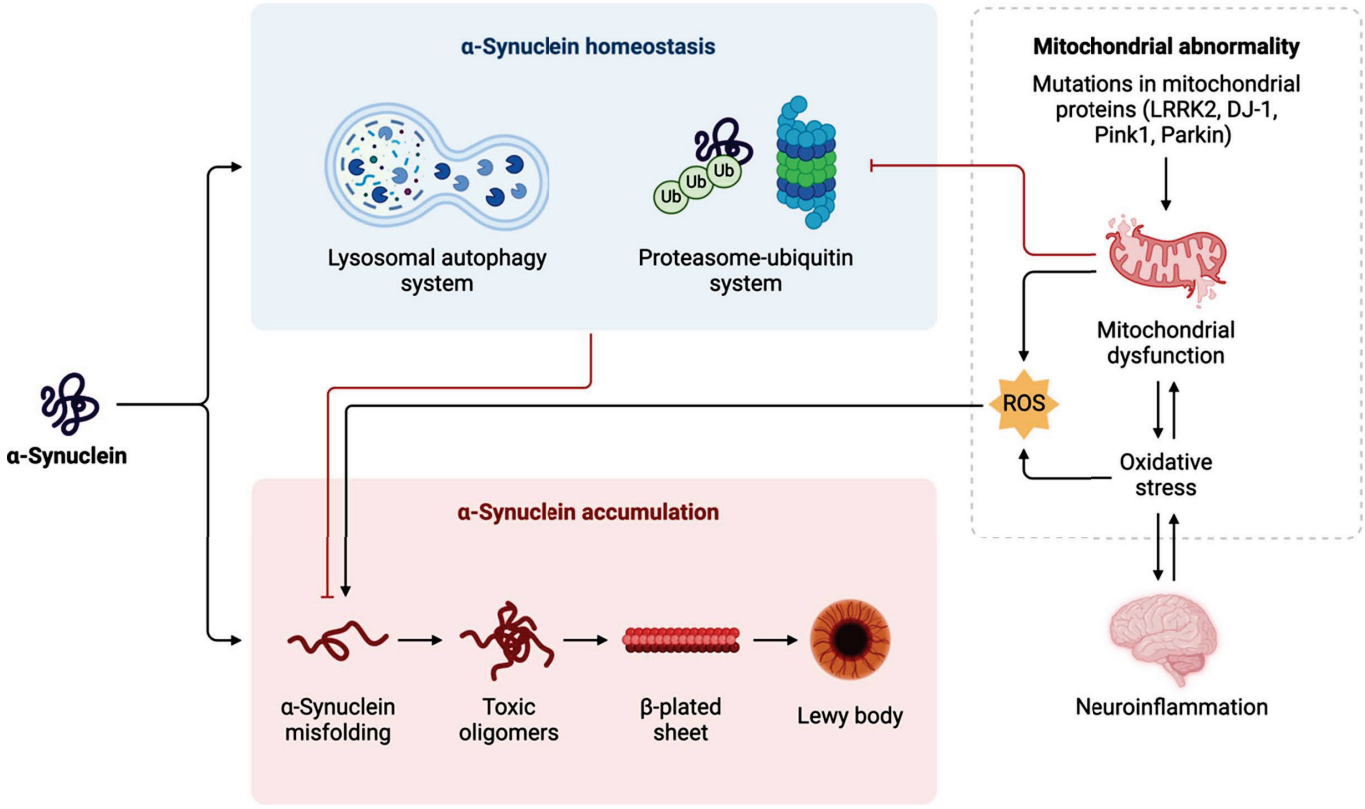

Fig. (2). The link between mitochondrial dysfunction, ROS, neuroinflammation, and alpha-Synuclein. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

The discovery of gene mutations in familial or hereditary forms of PD suggests that 5-10% of late-onset cases are associated with genetic factors. The primary genes linked to PD include SNCA, parkin, DJ-1, and PINK1 [26]. Research indicates that specific chromosomes, such as chromosome 6, are associated with an increased risk of PD. The parkin gene on chromosome 6 is associated with early-onset Parkinson's. Additionally, individuals with specific genes on chromosome 9 may not respond well to L-DOPA treatment for PD [27, 28].

3. MECHANISMS OF NEUROPROTECTION IN PD

3.1. Mitochondrial Stabilization

Genetic mutations in PINK1, Parkin, and DJ-1 that affect mitochondrial function are associated with familial forms of PD. Mitochondrial failure leads to oxidative stress, reduced ATP synthesis, and the release of pro-apoptotic proteins, ultimately contributing to neuronal demise. Neuroprotective methods targeting mitochondria include [29, 30]:

• Improving mitochondrial biogenesis through the use of substances like coenzyme Q10 and resveratrol.

• Utilizing antioxidants, such as vitamin E and N-acetylcysteine, to reduce oxidative damage.

• Maintaining the integrity of mitochondria by preserving the potential of the mitochondrial membrane and reducing the production of ROS.

3.2. Modulation of Inflammatory Pathways

Chronic neuroinflammation is a well-established factor in the development of PD, leading to ongoing neuronal damage. Neuronal damage is exacerbated by pro-inflammatory cytokines, such as TNF-α, IL-1β, and IL-6, which are released by activated microglia, the immune cells in the brain. To counteract this activation, anti-inflammatory medications, such as nonsteroidal anti-inflammatory drugs (NSAIDs) and inhibitors of inflammatory pathways, including those targeting NF-κB, can be used. Moreover, controlling cytokine release with substances like minocycline or curcumin, a natural anti-inflammatory compound, can help inhibit microglial activation [31, 32].

3.3. Enhancing Neurotrophic Support

Neuronal loss in PD is attributed to the depletion of neurotrophic factors, such as glial cell-derived neurotrophic factor (GDNF) and brain-derived neurotrophic factor (BDNF), which are essential for repairing and preserving neurons. Administering GDNF has shown potential in preserving dopaminergic neurons in PD animal models. Meanwhile, increasing the production of endogenous neurotrophic factors

through medications like antidepressants or activities like exercise, which boost BDNF production, are methods to improve neurotrophic support [33, 34].

3.4. Diminished Protein Accumulation

The primary pathogenic feature of PD is the formation of alpha-synuclein aggregates, which leads to the development of Lewy bodies in the brain. Presynaptic proteins, such as alpha-synuclein, can cause neurotoxicity and cellular malfunction when they aggregate. One strategy to reduce protein aggregation in PD is to target chaperone proteins, such as Hsp70, which assist in refolding misfolded proteins or directing them towards degradation pathways.

Increasing the removal of aggregated proteins through proteasomal breakdown and autophagy, substances like rapamycin can reduce the formation of harmful protein aggregates by inducing autophagy. Additionally, small molecules and peptides can be designed to directly bind and inhibit the aggregation of alpha-synuclein [35, 36].

3.5. Maintaining Calcium Homeostasis and Preventing Excitotoxicity

Excitotoxicity, resulting from excessive glutamate release and disruption of calcium homeostasis, is the primary cause of neuronal death. Dopaminergic neurons are particularly vulnerable due to the high expression of L-type calcium channels. Drugs that target these mechanisms can protect neurons in PD by preventing excitotoxicity and excess calcium.

Isradipine is a calcium channel blocker that has shown promise in preclinical research for reducing neuronal death. Glutamate receptor antagonists, such as memantine, can also prevent excitotoxic damage by reducing excessive glutamatergic signaling [37, 38].

4. CLASSIFICATION OF NEUROPROTECTIVE AGENTS

Neuroprotective drugs are substances that can delay or prevent the processes that lead to neuronal degeneration, injury, or apoptosis. These processes are commonly seen in neurodegenerative diseases like Huntington's disease, PD, and Alzheimer's disease. These substances target various pathological processes, including inflammation, protein aggregation, oxidative stress, mitochondrial dysfunction, and synaptic dysfunction. The mechanisms of action of these agents enable them to be classified accordingly.

4.1. Dopaminergic Agents

These remedies aim to maintain or increase dopamine levels in the brain, with Levodopa being the most effective medication for symptom treatment. However, prolonged use of Levodopa may lead to motor issues.

Dopamine agonists, such as pramipexole and ropinirole, mimic dopamine's effects and provide neuroprotection by reducing oxidative stress associated with dopamine metabolism [39].

Recent research supports the use of DA agonists as initial or adjunct therapy to levodopa in advanced PD. However, a more cautious approach to their use is emerging due to the complexity and potential side effects. The therapeutic management of PD and the availability of new DA agonists with improved safety and efficacy profiles may rely on assessing individual risk factors for side effects and adjusting DA agonist usage accordingly [40].

It has been demonstrated that dopamine receptor agonists can prevent neuronal degeneration in both *in vitro* and animal models. One such D2 receptor agonist is pramipexole, which has the ability to act as an antioxidant due to its chemical structure. Recently, a couple of relatively large studies have investigated the use of dopamine receptor agonists to evaluate their ability to protect neurons by using neuroimaging techniques in human PD subjects. It appears that dopamine receptor agonists are neuroprotective. These dopamine receptor agonists were proposed for use earlier than neuroprotectants and work by interacting with D2 receptors, which are commonly found in the terminals of dopamine-synthesizing neurons in the midbrain substantia nigra [41].

Eckol, a phlorotannin found in brown algae, exhibits a wide range of biological activities. It acts as an agonist for dopamine D3 and D4 receptors by affecting G-protein-coupled receptors (GPCRs), the largest superfamily of cell surface proteins encoded by the human genome, and are valuable molecular targets for drug discovery. These receptors are crucial targets for drug discovery, as they play a role in human pathophysiology and can be pharmacologically traced. This makes Eckol a promising candidate for the treatment of neurodegenerative diseases, especially PD [42].

4.2. Monoamine Oxidase-B (MAO-B) Inhibitors

These substances inhibit the MAO-B enzyme, preventing the breakdown of dopamine. This leads to increased dopamine levels and potential neuroprotection due to their antioxidant properties. Since the 1970s, patients with PD have had success with MAO-B inhibitors, starting with selegiline (L-(-)-deprenyl), followed by rasagiline, and most recently, safinamide. Studies have shown that using MAO-B-I inhibitors like selegiline, rasagiline, or safinamide alone can be beneficial in early PD. There is a growing body of evidence indicating that MAO-B inhibitors may offer neuroprotection through various pathways unrelated to MAO-B inhibition [43].

Rasagiline is a selective and potent propargylamine MAO-B inhibitor that reduces MPTP and 6-OHDA toxicity in PC12 and SH-SY5Y cells, and exhibits neuroprotective effects *in vivo.* Pretreatment with Rasagiline prevents nigrostriatal damage induced by MPTP in primates. Chronic administration of Rasagiline increases DA neuron survival in lesioned SNpc and improves motor impairments. It also increases the expression of the neurotrophins BDNF, GDNF, and NGF and reduces the long-term progression and symptoms in PD in humans. In a recent promising study, Rasagiline delayed the need for antiparkinsonian drugs, and pa-

tients had lower scores on the PD rating scale in a Phase III study.

Rasagiline inhibits mitochondrial apoptosis by blocking caspase-3 and nuclear poly (ADP-ribose) polymerase 1 (PARP-1) activation, preventing the translocation of glyceraldehyde-3-phosphate dehydrogenase (GAPDH), inhibiting the opening of the MPT, and reducing DNA fragmentation. It also upregulates the expression of anti-apoptotic proteins Bcl-2 and B-cell lymphoma-extra-large (Bcl-XL) through the PKC pathway, while downregulating the pro-apoptotic Bcl-2-associated death promoter (Bad) and Bcl-2-associated X protein (BAX).

Minocycline is a second-generation tetracycline with anti-inflammatory and antioxidant properties. It inhibits microglia activation and reduces inflammatory cytokine synthesis by blocking the p38 MAPK cascade. In animal studies on rodents, Minocycline prevented the degeneration of DA neurons in the SNpc induced by MPTP, thus preserving striatal DA levels and their metabolites. It also suppressed the expression of inducible NO synthase mediated by MPP+ *in vivo* and effectively prevented NO-induced neurotoxicity *in vitro*. Minocycline demonstrated potent DA neuroprotection in a Drosophila model of PD. Additionally, it decreased the number of apomorphine-induced rotations in 6-OHDA-lesioned rats, reduced the loss of TH-positive cells, and increased the size and fiber density of the remaining nigral cells.

Although Minocycline inhibits microglial activation, other studies have shown that it significantly exacerbates MPTP-induced damage to DA neurons in both *in vitro* and *in vivo* settings. Similarly, Minocycline treatment of monkeys and mice resulted in more severe and rapid Parkinsonism, behavioral deficits, and greater loss of nerve endings. The lack of neuroprotection was attributed to Minocycline's inability to abolish the activation of TNF-α and its receptors after MPTP administration. In a phase II clinical trial, Minocycline was found to be effective in slowing the progression of PD in patients. Furthermore, the combination of its neuroprotective effects with creatine demonstrates additive benefits in reducing PD progression in patients and is currently being evaluated in clinical trials [44].

Many studies have shown that MAO-B inhibitors are both effective and safe for patients with early and advanced PD. This medication can significantly improve patients' motor and non-motor symptoms, reduce "OFF" time, and potentially offer neuroprotective benefits. Additionally, several new MAO-B inhibitors with enhanced selectivity, safety, and neuroprotection are currently under development. It is anticipated that through continued research, MAO-B inhibitors will provide even greater benefits to patients with neurodegenerative diseases, such as PD [45].

Inhibitors of monoamine oxidase B (MAO-B) are used to alleviate symptoms by reducing the degradation of dopamine catalyzed by monoamine oxidase, thereby preserving functional levels of dopamine. The first MAO-B inhibitor used therapeutically was selegiline, followed by rasagiline, which has superior efficacy and selectivity. Both can be used as monotherapy or in combination with other anti-Parkinson drugs. Safinamide, a reversible MAO-B inhibitor that utilizes both dopaminergic and non-dopaminergic mechanisms, was recently approved by the European Medicines Agency (EMA) in 2015 and the U.S. FDA in 2017 as an add-on therapy for patients with mid- or late-stage PD. Furthermore, MAO-B inhibitors are associated with potential neuroprotective and disease-modifying effects [46].

There is also evidence supporting the benefit of type-B monoamine oxidase inhibitors on non-motor symptoms of PD, such as mood fluctuations, cognitive impairment, sleep disturbances, and fatigue. Preclinical studies suggest that type-B monoamine oxidase inhibitors possess strong neuroprotective potential in PD and other neurodegenerative diseases by reducing oxidative stress and stimulating the production and release of neurotrophic factors, particularly glial cell line-derived neurotrophic factor, which supports dopaminergic neurons. Additionally, safinamide, a new generation type-B monoamine oxidase inhibitor, may interfere with neurodegenerative mechanisms by counteracting excessive glutamate overdrive in the basal ganglia motor circuit and reducing excitotoxicity-induced cell death. Due to its dual mechanism of action, safinamide is garnering interest in other neurological pathologies, and numerous preclinical studies support its potential use in epilepsy, Duchenne muscular dystrophy, multiple sclerosis, and particularly ischemic brain injury.

Strong preclinical data suggest that MAOB inhibitors may help treat PD and other neurological conditions through mechanisms other than the typical increase in dopamine neurotransmission. These medications stimulate the production of neurotrophic factors and gene products that can alter neuronal survival, as well as possess antioxidant and possibly neuroprotective properties, which may underlie their disease-modifying effects. Furthermore, the dual mechanism of action of recent MAOB inhibitors may offer additional symptomatic and non-symptomatic benefits by combining dopaminergic stimulation with blocking the effects of excessive glutamatergic activity [47].

4.3. Antioxidants

Oxidative stress is a condition in which ROS damages lipids, proteins, DNA, and other cellular components, significantly impacting neurodegenerative disorders. Antioxidants help to neutralize ROS and prevent oxidative damage. Fig. (**3**) illustrates the classification of various antioxidants.

4.3.1. Vitamin D, Beta-carotene, and Riboflavin

Vitamin D, beta-carotene, and riboflavin are essential nutrients for supporting healthy brain function. Vitamin E, particularly α-tocopherol, serves as a fat-soluble antioxidant that protects cell membranes from oxidative damage, reduces iron accumulation, prevents microglial cell activation, removes oxygen radicals, and stops lipid peroxidation. It promotes the production of interleukin-1α and TNF-α, while inhibiting the p38 MAPK and NF-κB pathways. A deficiency in Vitamin E can result in increased oxidative stress in the brain, which can be mitigated by taking Vitamin E supplements [48, 49].

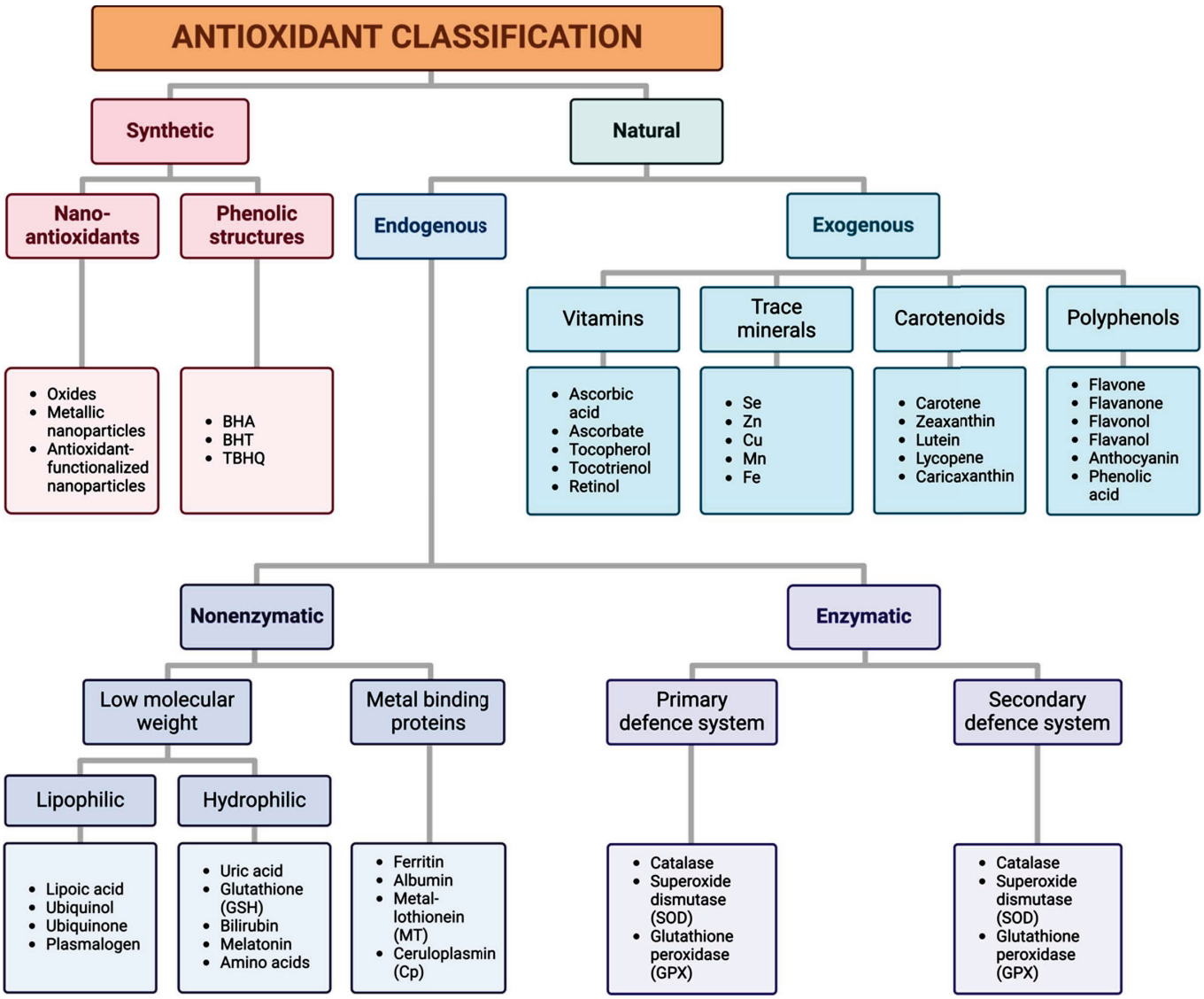

Fig. (3). Classification of different antioxidants. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

Vitamin C, also known as ascorbate, is found in high levels in the CNS and is principally linked to the functioning of glutamatergic neurons. This suggests that it might be beneficial as a neuroprotector or neuromodulator [50].

The occurrence of vitamin D insufficiency is common among individuals with PD [51]. Vitamin D receptors (VDR) are primarily located in dopaminergic neurons in the SNpc [52]. An imbalance in the regulation of Ca^{2+} levels speeds up the degeneration of dopaminergic neurons in the SNpc [53]. Conversely, the activation of GDNF can alleviate symptoms of PD in both primates and humans [54].

Vitamin D has anti-inflammatory properties, regulates the expression of GDNF, and maintains calcium (Ca^{2+}) homeostasis, as evidenced by numerous previous studies [49]. Additionally, the expression of VDR mRNA in the blood can be a valuable risk marker for identifying patients with PD, as demonstrated by Gill *et al.* in 2007 [55].

Furthermore, a study demonstrated that vitamin D increased locomotor activity in mice with PD [56]. However, a study comparing cases and controls in humans discovered a higher risk of PD associated with high vitamin D intake [57]. These findings indicate that consuming a moderate amount of vitamin D through food may help protect individuals from the progression of PD.

A research study in epidemiology, however, discovered a reduction in the risk of developing PD in individuals who consumed foods high in carotenoids and beta-carotene, which are forms of vitamin A [58]. The precursor to Vitamin A, beta-carotene, has the potential to provide neuroprotective benefits by inhibiting lipid peroxidation [59].

Patients with PD have lower levels of riboflavin compared to both healthy individuals and disease controls, indicating that consuming riboflavin supplements may have potential benefits [60]. Research has shown that riboflavin, unlike other B vitamins, can reduce the risk of developing PD [43].

4.3.2. Turmeric Possesses Potent Neuroprotective Properties

Research in epidemiology suggests that the consumption of turmeric/curcumin among Indians may explain the reduced incidence of Alzheimer's disease and Parkinson's disease in India compared to Caucasians. A study examining the effects of race and age on the prevalence of PD found that Indian brains have approximately 40% fewer melanized nigral neurons than Caucasian brains [61]. Moreover, the Asian-Indian demographic showed no decline in the number of nigral neurons with aging [62]. Thus, the lower incidence of PD in India, despite having fewer nigral neurons, suggests the presence of protective mechanisms likely associated with dietary habits. Recent studies have shown that long-term consumption of turmeric provided neuroprotection in a mouse model of PD exposed to toxins [63].

The antioxidant properties of curcumin in living beings may be supported by antioxidant enzymes such as superoxide dismutase, catalase, and glutathione peroxidase, along with its Michael acceptor characteristics, allowing it to interact with GSH and thioredoxin. Research indicates that curcumin exhibits antioxidant properties that are at least 10 times greater than those of vitamin E [64]. However, curcumin has limited use in treatment due to its low bioavailability, resulting from its water insolubility, slow absorption rate, rapid metabolism, and rapid systemic clearance [65].

Additional evidence of curcumin's potential neuroprotective role in PD comes from its interaction with α7-nACh receptors. Additionally, *in vivo* and *in vitro* investigations on PD models have shown that curcumin and its derivatives have limited reported toxicity and a high safety profile. Thus, enhancing our understanding of curcumin's neuroprotective properties could have significant therapeutic implications [66, 67].

4.3.3. N-acetylcysteine (NAC)

It is an antioxidant that is sold as a dietary supplement in the US and has been approved by the Food and Drug Administration (FDA) for treating paracetamol overdose. There is a belief that NAC, a precursor to endogenous glutathione, may have potential for treating PD by altering its progression. Preclinical studies have shown that NAC can protect against MPTP and rotenone-induced dopaminergic cell death in PD models. A study by Mursaleen *et al.* demonstrated that within 5-7 weeks of treatment, NAC was effective in protecting transgenic mice from harmful alpha-synuclein aggregation and in raising glutathione levels. Although evidence suggests that NAC is capable of crossing the blood--brain barrier (BBB) and influencing CNS oxidative stress, further large-scale, placebo-controlled trials are needed to validate its clinical efficacy and long-term safety in the context of PD [68].

4.4. Mitochondrial Neuroprotective Agents

Mitochondria are responsible for energy production in cells, and dysfunction in these organelles is a major contributor to neurodegeneration. Mitochondrial protective agents aim to stabilize mitochondrial function, prevent energy failure, and reduce oxidative stress from mitochondrial sources. The following are a few examples of mitochondrial neuroprotective medications used to treat PD.

4.4.1. Mitoquinone, or MitoQ

It is synthesized from CoQ10 as a mitochondria-targeted antioxidant. It has been found to have neuroprotective effects in experimental models of PD by reducing oxidative stress in dopaminergic neurons and preserving mitochondrial integrity [69].

4.4.2. Sulforaphane

This substance enhances mitochondrial function and reduces oxidative stress by activating the antioxidant defence system through the Nrf2/ARE signaling pathway. In preclinical models of PD, it has shown neuroprotective effects [70].

4.4.3. Antidiabetic Drugs

4.4.3.1. SGLT2 Inhibitors

Recent research suggests that SGLT2 inhibitors, commonly used to treat diabetes, may enhance mitochondrial function and offer protective benefits against PD [69]. A recent meta-analysis of prospective cohort studies revealed a low risk of developing PD in individuals with diabetes [70]. Those who have both type 2 diabetes mellitus (T2DM) and PD experience more severe motor symptoms, higher cognitive impairment, and an earlier onset of motor issues compared to individuals with PD but without diabetes [71].

Several research groups have investigated the potential impact of anti-diabetic drugs on the progression of PD. For example, the use of thiazolidinediones has been linked to a decreased risk of developing PD in individuals with diabetes, as well as a reduction in neurodegeneration and neuroinflammation in animal studies [72]. Exenatide, a drug that mimics incretin (an adjunct treatment for T2DM patients), may provide some level of neuroprotection in functional models of PD. Exenatide has shown effectiveness in reducing dopaminergic cell death, improving motor and cognitive function, decreasing neuroinflammation, and alleviating mitochondrial dysfunction [73]. Metformin has pleiotropic effects that extend beyond its anti-diabetic properties. It can slow down the aging process by directly influencing mitochondrial metabolism and insulin signaling [74]. Recent studies have shown that metformin can swiftly penetrate the blood-brain barrier, protecting the brain against stroke, cognitive deterioration, Huntington's disease, and possibly even preventing dementia [75].

Additionally, metformin can lower the phosphorylation and aggregation of α-synuclein, affecting cellular mechanisms associated with age-related conditions, such as inflammation and autophagy [76]. Metformin impacts mitochondria by altering the activities of the respiratory chain and decreasing ROS levels. This functional significance suggests that metformin can protect dopaminergic neurons from MPP+ toxicity in laboratory experiments by mitigating mitochondrial dysfunction and oxidative stress, as evidenced in research findings [77].

4.5. Anti-Inflammatory Agents

Damage to neurons is caused by long-term neuroinflammation, which is triggered by the activation of microglia and the synthesis of cytokines. Anti-inflammatory substances, including non-steroidal anti-inflammatory drugs (NSAIDs) such as Ibuprofen and diclofenac, have been studied to improve symptoms related to PD by promoting the production of neurotrophic factors or interfering with neuronal apoptosis. Research using both laboratory and animal models has demonstrated that certain NSAIDs, such as aspirin, can protect dopaminergic neurons and alleviate symptoms of the disease [78].

Human clinical trials have demonstrated that regular use of NSAIDs can reduce the risk of developing PD by approximately 45%. Furthermore, a follow-up study by the same researchers indicated that ibuprofen may have neuroprotective properties [79].

4.5.1. Statins

Statins have been used for several decades to lower cholesterol levels and can also prevent inflammation linked to PD by inhibiting the production of pro-inflammatory cytokines and free radicals [80].

4.5.2. Minocycline

Minocycline is a tetracycline antibiotic with anti-inflammatory properties, as it inhibits microglia activation and the release of cytokines.

4.6. Neurotrophic Factors

Neurotrophins are growth factors that play an important role in the differentiation and development of the mammalian nervous system. The neurotrophic factor hypothesis suggests that the presence or absence of neurotrophins impacts neuronal survival or death. Kania and Percival's research indicates that NTFs and related families are interconnected and function through multiple pathways. The neurotrophin family consists of Ciliary neurotrophic factor (C-NTF), Brain-derived neurotrophic factor (BDNF), Neurotrophin-4 (NT4), Neurotrophin-3 (NT3), Nerve growth factor (NGF), and Glial-derived neurotrophic factor (GDNF). Additionally, this family includes cerebral dopamine neurotrophic factor (CDNF) and Mesencephalic astrocyte-derived neurotrophic factor (MANF).

One hypothesis is that altered or malfunctional trophic factors may trigger the apoptotic death of neurons or lead to a general loss of dopaminergic neurons that underlie PD. The lack of neurotrophin effect does not definitively implicate neuronal death or decreased levels of neurotrophin as the cause of PD or other neurodegenerative diseases in humans. Neurotrophins may have therapeutic value in treating PD, regardless of the disease's etiology, as they can promote the development of dopaminergic neurons and inhibit neurotoxicity. They are clinically relevant to neuronal health, but not all neurodegenerative and related diseases result from changes in neurotrophic factors or alterations in receptors. Increased levels of NTFs have revealed proline neurotrophic features, protecting neurons against oxidative stress, toxin exposure, and programmed cell death. Additionally, the NGF family and its receptors are present in melanin-positive neurons in the SNpc. It has also been reported that reductions in the levels of BDNF and ING are common occurrences in PD [81].

4.7. Glutamate Antagonists (Anti-Excitotoxic Agents)

Glutamatergic transmission is crucial for the normal functioning of the brain's motor activity-modulating systems, particularly the basal ganglia. This transmission is significantly affected in pathological conditions like PD, leading to the alterations associated with this disorder. Glutamatergic hyperactivity plays a role in the neurotransmitter changes in both the direct and indirect nigro-striatal pathways that occur in PD. According to some theories, this hyperactive pattern serves two purposes: first, it triggers excitotoxic events that facilitate the neurodegenerative process; second, it contributes to the pathophysiology of motor fluctuations and dyskinesias associated with long-term levodopa (L-DOPA) use. While L-DOPA remains the primary treatment that significantly improves Parkinsonian symptoms, its long-term use has been linked to the development of motor fluctuations and dyskinesias. Therefore, it is important to design new therapies that target different mechanisms than the classic dopaminergic ones. Lately, there has been a growing interest in the development of new anti-glutamatergic drugs (AGD), such as amantadine and memantine [82].

4.8. Calcium Channel Blockers (CCBs)

The flux of calcium ions has the ability to regulate gene expression, muscle contraction, neurotransmitter release, and hormone secretion, all of which are crucial to the pathophysiology of PD. While previous research has yielded mixed results, CCBs have shown promise as a potential pharmacological target for neuroprotective treatment in PD. Some studies suggest that the use of CCBs can considerably lower the risk of developing PD, while others have not found a clear connection. One study indicated that CCB use may lower the mortality risk in PD patients, while another study found that it was associated with improved long-term cognitive function in PD patients. In PD, excess intracellular calcium levels contribute to neuronal death, and calcium channel blockers may provide neuroprotection by preventing this calcium excess [83]. Isradipine, a calcium channel blocker used to treat hypertension, has been shown in animal studies to have a neuroprotective effect [84].

4.9. Iron Chelators

According to recent research, high levels of iron may play a major role in the onset and progression of neurodegenerative diseases by inducing oxidative stress and other mechanisms. Furthermore, abnormalities in iron metabolism have been found to be a key factor in the onset and advancement of neurodegenerative diseases. The interaction between iron and melanin has been shown to accelerate the loss of dopaminergic neurons in PD patients. Furthermore, the SN of PD patients exhibited significantly higher levels of iron compared to healthy individuals, and these iron levels were also correlated with the severity of the patients' clinical symptoms. Numerous studies have confirmed that an iron-overloaded brain is closely linked to the accumulation of α-synuclein, oxidative stress, mitochondrial dysfunction, neuroinflammation, and disruption of the ubiquitin protease system, all of which contribute to the death of DA neurons in PD. A recently identified pattern of cell death, known as ferroptosis, is triggered by the accumulation of lipid peroxides, which iron chelators can prevent. Ferroptosis, distinct from other types of cell death in terms of biochemistry and morphology, occurs due to a significant buildup of intracellular ROS in the absence of mechanisms to counteract iron-related damage [85].

4.10. Other Agents with Multi-neuroprotection Mechanisms

4.10.1. Creatine or Coenzyme Q10 [CoQ10]

Creatine and Coenzyme Q10 (CoQ10), which are located in the mitochondria, have potential as neuroprotective agents in PD and other neurodegenerative disorders due to their involvement in the mitochondrial electron transport chain (METC) and their antioxidant properties. CoQ10 has been shown to protect nigrostriatal dopaminergic neurons in mice treated with MPTP. Long-term treatment with CoQ10 in individuals with PD slows the progression of the disease without causing any adverse consequences [86, 87]. In PD patients, the combination of creatine and CoQ10 has demonstrated encouraging neuroprotective benefits [88].

4.10.2. Caffeine and Nicotine

Numerous epidemiological studies indicate that consuming caffeinated beverages is associated with a lower risk of developing PD due to their brain-protective properties. Long-term administration of caffeine in mice has been shown to protect dopamine-producing cells from the harmful effects of paraquat and maneb [89]. Both acute and chronic caffeine consumption in mice reduced the impact of 6-hydroxydopamine (6-OHDA) and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) on dopamine depletion in the striatum, resulting in reduced motor deficits and increased dopamine levels. Moreover, the administration of caffeine significantly increased the levels of noradrenaline, dopamine, 3,4-dihydroxyphenylacetic acid, and homovanillic acid, along with their metabolites, in rats with 6-OHDA-induced lesions. Nonetheless, serotonin levels decreased, while the levels of its metabolite, 5-hydroxyindoleacetic acid, remained unchanged. The protective effects of theophylline and paraxanthine, which are metabolites of caffeine, contribute to extending the beneficial effects of caffeine in treatment. A significant advantage of caffeine is that it does not easily lead to tolerance, even with prolonged use. In a separate study, both male and female mice were treated with estrogen and caffeine after MPTP treatment, resulting in a lack of neuroprotection in all observed animals [90]. The beneficial effects of caffeine seem to be limited to males and post-menopausal females not undergoing hormone-replacement therapy.

Nicotine, an alkaloid, is the primary component in cigarettes, known for its rapid absorption and efficient penetration of the circulation and the BBB. It reduces oxidative stress linked to the progression of PD by neutralising free radicals produced by monoamine oxidase-B, an enzyme that breaks down dopamine [91]. Nicotine also boosts neurotrophic factor levels and enhances the expression of cholinergic receptors [92]. Both epidemiological research and animal studies have demonstrated the positive impact of nicotine, separate from caffeine, in lowering the risk of PD. The administration of nicotine at modest dosages (0.1 mg/kg s.c.) *in vitro* resulted in a reduction of dopamine depletion induced by MPTP and 6-OHDA treatments [93]. Long-term administration of nicotine to monkeys treated with MPTP facilitated the restoration and maintenance of dopamine function, while also delaying cell death in the SNpc. Additionally, short-term nicotine administration in humans has been shown to enhance cognitive processing and comprehension in individuals with PD who experience challenges in regulated semantic processing [94]. Nicotine is currently in Phase II studies focused on dose refinement and sample size expansion.

4.10.3. Neuroprotective Properties of Extracts Derived from Onion and Garlic Roots

Consuming a substantial amount of antioxidant-rich foods, such as garlic (*Allium sativum* L.) and onions (*Allium cepa*), can reduce the risk of developing neurodegenerative diseases. Hence, there is a growing trend towards using natural substances to combat such disorders due to their potent antioxidant properties, minimal side effects, and improved safety profile. The antioxidant properties of natural polyphenols are expected to protect against brain diseases [95]. Quercetin, catechins, kaempferol, and naringenin are significant flavonoids known for their potent antioxidant properties. These flavonoids are found in onions, vegetables, and citrus fruits [96]. According to research, onions have been shown to have positive benefits for neurological illnesses, as they significantly enhance learning and memory abilities in an animal model of ischemia [97]. Multiple studies have demonstrated that consuming flavonoids from onions, particularly quercetin, can protect brain tissues from the effects of aging by preventing apoptosis, which is responsible for brain degeneration [98]. Onions are rich in flavonoid components, including quercetin, kaempferol, and gallic acid, which contribute to the antioxidant effects of onions and can

also prevent apoptotic pathways and safeguard against neural damage [99, 100].

Allium sativum, commonly known as garlic, belongs to the Alliaceae family and is packed with vitamins, minerals, sulphur compounds, essential oils, phenols, and free amino acids. Garlic contains various bioactive components, including allicin, allyl sulfides, alliin, ajoenes, and 1,2-vinyldithiin. These compounds possess therapeutic properties, acting as antioxidants, anti-inflammatory agents, cardioprotective agents, antibacterial agents, anticancer agents, and immunomodulatory agents [101]. Garlic extracts contain active chemicals that have neuroprotective properties against neurotoxicity [100]. Moreover, garlic extracts are effective against aflatoxins (AFs), which are toxins produced by the fungus *Aspergillus flavus*, that can lead to chronic neurotoxicity in male rats. Consequently, garlic and onions are highly regarded for their notable antifungal properties [101, 102].

4.10.4. Therapeutic Benefits of Honey in PD

Honey consists of approximately 200 components, mainly carbohydrates, with sugars accounting for over 90% of its solid content. The main sugars found in honey are glucose, sucrose, maltose, fructose, melezitose, isomaltose, maltulose, turanose, nigerose, melibiose, panose, and maltotriose. Water is the second most important element in honey. In addition to carbohydrates and water, honey contains enzymes, vitamins, minerals, flavonoids, and polyphenols. Honey contains a variety of important vitamins, such as riboflavin (Vitamin B2), niacin (Vitamin B3), pantothenic acid (Vitamin B5), pyridoxine (Vitamin B6), folate (Vitamin B9), and ascorbic acid (Vitamin C). Potassium is the main mineral; however, substantial quantities of calcium, magnesium, sodium, sulfur, and phosphorus are also present. The main enzymes present in honey include invertase (saccharase), diastase (amylase), and glucose oxidase. Honey also contains non-enzymatic proteins, such as glycoprotein, MRJP1, and apalbumin-1, although in very small amounts [103].

Honey contains a high concentration of flavonoids and phenolic acids, which act as antioxidants to reduce oxidative stress and repair related damage. It has been shown to inhibit monoamine oxidase (MAO), an enzyme linked to decreased activity of free radical scavengers that can cause oxidative damage in neurodegenerative diseases like PD. A recent study indicates that individuals with PD may benefit from consuming pollen and honey from bees that primarily feed on Vicia faba L. blossoms. This particular honey has a notable amount of L-DOPA, a commonly prescribed drug for managing PD. Quercetin, a flavonoid found in most types of honey, has demonstrated protective benefits against neuronal degeneration in the substantia nigra and increased dopamine levels in MitoPark mice. Moreover, it activates multiple kinases, including PDK1 and Akt, which are crucial for the survival of neuronal cells. Furthermore, it boosts BDNF expression, rectifies mitochondrial dysfunction, and amplifies mitochondrial energy production. Quercetin enhances the restoration of antioxidant enzyme functions and reduces cognitive deficits associated with PD in the 6-hydroxydopamine-induced model [104].

Myricetin, a unique type of flavonoid, is highly regarded for its therapeutic effects in combating PD. Reports suggest that it not only increases dopamine levels in a dosage-dependent manner but also prevents the deterioration of dopaminergic neurons in the transgenic Drosophila model of PD. Previous research has shown that myricetin provides significant neuroprotection to dopaminergic neurons by inhibiting inflammation. It improves motor function impairments caused by PD and prevents neuronal death by reducing the activation of microglia. Additionally, it decreases the levels of inflammatory cytokines (IL-1β, TNF-α, and IL-6) and inhibits signaling pathways, such as MAPK and NF-κB [105, 106].

Chrysin, a flavonoid found in honey in large quantities, has been extensively researched for its role in PD. Studies have shown that it has a neuroprotective effect against the death of dopaminergic neurons caused by MPTP in mice. This effect is achieved by boosting the expression of the survival factor MEF2D through the AKT/GSK3β/MEF2D pathway, and also by suppressing MAO-B activity [107].

4.10.5. Urate, Uric acid, and Creatine Potential as Neuroprotective Agents

Uric acid (UA) is an antioxidant that mitigates oxidative stress by scavenging free radicals and chelating iron. Research has shown that it can inhibit oxidative stress and avert the death of dopaminergic cells in rats [108]. Studies suggest that individuals who consume a diet that increases urate levels may have a lower risk of developing PD. In the early stages of PD, individuals with higher levels of UA in their plasma, serum, and cerebrospinal fluid (CSF) tend to have slower disease progression. Treatment with urate has also been shown to reduce the risk of PD, with the effectiveness depending on the dosage administered [109].

4.10.6. Edible Bird's Nest (EBN)

Asians, particularly the Chinese, consume Edible Bird's Nest (EBN) for its nutritional value and purported medicinal benefits in accordance with the traditional medicine of Southeast and East Asian nations. EBN is produced by Swiftlet birds (Collocalia species) using their saliva.

EBN is chemically abundant in carbohydrates, such as sialic acid, galactose, glucosamine, galactosamine, and N-acetylneuraminic acid. Sialic acid has been shown to play a crucial role in mammalian brain development and intelligence, potentially enhancing learning and memory abilities through long-term potentiation in the hippocampus [110].

EBN contains lactoferrin and ovotransferrin, glycoproteins categorized as transferrins, which exhibit neuroprotective properties by scavenging free radical species in SH-SY5Y cells [111]. Recent studies by various experts have investigated EBN and its neuroprotective properties. Miranda *et al.* examined the neuroprotective effects of EBN extracts in HNS cells. EBN reduced apoptosis induced by 6-hydroxydopamine (6-OHDA) in HNS cells, as assessed through nu-

clear staining and morphological analysis. The digestion of the EBN extract led to a notable enhancement in cell viability compared to the EBN water extract. EBN water extract demonstrated significant effects in inhibiting caspase-3 cleavage, thereby reducing the initial apoptotic impact on phosphatidylserine externalization and facilitating neuronal recovery in the presence of reactive oxygen species (ROS) [112]. Sialic acid, a key nutrient in EBN, enhances brain function by optimizing synaptic pathways and ganglioside distribution, thereby improving a child's intellect and cognitive performance. The administration of sialic acid as a dietary supplement results in the upregulation of numerous genes associated with cognitive development within the physiological system [113]. Brain-derived neurotrophic factor (BDNF) is a crucial protein involved in learning and memory, particularly relevant for memory tasks associated with the hippocampus and parahippocampal regions. The administration of EBN to pregnant and lactating women resulted in increased concentrations of BDNF and sialic acid in the hippocampus. Hou *et al.* suggest that cognitive impairment linked to menopause may be mitigated through the use of EBN as a natural supplement. The results indicated that EBN substantially alleviated oestrogen deficiency and the decrease in gene expression associated with neurodegeneration in the hippocampus and frontal cortex. EBN functions as a therapeutic alternative with reduced harm compared to oestrogen, which has the potential to negatively impact the kidneys and liver in ovariectomised rats, notwithstanding its cognitive enhancement benefits. EBN may serve as an alternative treatment to improve neurological conditions following menopause [114].

4.10.7. Thymoquinone (TQ)

It is specifically known as 2-isopropyl-5-methylbenzo-1,4-quinone, the primary constituent found in the seeds of *Nigella sativa*, a plant commonly referred to as black cumin, fennel flower, or nutmeg flower. Alternative designations for *Nigella sativa* include Kalonji seeds and *Habbatu sawda* [115]. It belongs to the Ranunculaceae family and is a medicinal herb with religious significance, often referred to as the "remedy for all diseases except death" and "the Blessed Seed." The main medicinal components found in black cumin oil include tocopherols, phytosterols, polyunsaturated fatty acids, TQ, ρ-cymene, carvacrol, t-anethole, and 4-terpineol [116]. It has demonstrated effectiveness in treating various diseases, including neurodegenerative disorders, coronary artery disease, and conditions affecting the respiratory and urinary systems. Additionally, TQ has been proven to have antioxidant, anti-inflammatory, anticancer, antibacterial, antimutagenic, and antigenotoxic properties [117].

The research examined the therapeutic effects of TQ, administered orally at doses of 7.5 and 15 mg/kg, in alleviating symptoms of PD in animal models exposed to rotenone. Co-administering TQ with rotenone was shown to reduce symptoms of PD, such as movement impairment caused by rotenone. The findings suggest that TQ's ability to alleviate PD symptoms induced by rotenone may be associated with its neuroprotective and antioxidant properties [118]. The study findings indicate that TQ enhanced motor impairments in the animal model of PD due to its antioxidant properties. Additionally, it has demonstrated both antioxidant and anti-inflammatory effects in laboratory settings (*in vitro*) and in living organisms (*in vivo*). TQ acts as an antioxidant by neutralizing free radicals, protecting cells from oxidative damage caused by reactive substances. TQ also exhibited a significant protective effect on dopaminergic neurons, resulting in reduced LDH release and improved mitochondrial membrane potential. This study posits that TQ activates a lysosomal degradative mechanism in dopaminergic neurons, thereby mitigating cell death associated with mitochondria-mediated apoptosis. Neurodegenerative diseases, such as PD, Alzheimer's disease, and dementia with Lewy bodies, often involve synaptic degeneration. The study examined the neuroprotective effects of TQ on α SN-induced synaptic damage in rat hippocampal neurons and human-induced pluripotent stem cell (hiPSC)-derived neurons. Treatment with TQ (100 nM) protected cultured hippocampal neurons from synapse damage caused by α-SN. TQ also decreased synaptophysin levels and suppressed synaptic activity. In hiPSC-derived neurons, TQ preserved spontaneous firing activity and counteracted the inhibitory effects of the mutant P123H on synaptic vesicle recycling in hippocampal neurons [119-121].

4.10.8. Resveratrol

This polyphenolic molecule, found in red wine and grapes, exhibits various pharmacological properties, including anti-inflammatory, anti-apoptotic, antioxidant, antifungal, and anticancer effects [122]. Furthermore, it can cross the blood-brain barrier and is water-soluble. Recent studies by several research groups have extensively explored the use of resveratrol in treating PD, evaluating its therapeutic benefits from different angles [123]. Resveratrol significantly reduced the mRNA expression of two proinflammatory genes, interleukin 1-α (IL-1α) and tumor necrosis factor-α (TNF-α), in N9 microglial cells induced by lipopolysaccharide (LPS), which are associated with glial activation and neuroinflammation in the pathogenesis of PD. The administration of resveratrol also led to a significant decrease in the expression of cyclooxygenase-2 (COX-2) in the substantia nigra of rats with PD induced by 6-hydroxydopamine [124]. Resveratrol exhibits anti-apoptotic effects in rat and zebrafish brain synaptosomal fractions exposed to the neurotoxic compound rotenone, as determined by the MTT assay. Additionally, it improves antioxidant status and enhances neuroprotective potential in midbrain dopaminergic neurons subjected to various insults by MPP+ in rat models of PD [125].

4.10.9. Ginsenoside

It is a commonly used traditional Chinese medicine that contains several active components, including ginsenosides, polysaccharides, peptides, polyacetylenic alcohols, and fatty acids, all of which have therapeutic benefits. Ginsenosides can be classified into two main categories: protopanaxadiols (PPD), such as Ra, Rb, Rc, Rd, Rg3, and Rh2, and protopa-

naxatriols (PPT), including Re, Rf, Rg1, Rg2, and Rh1 [126]. Ginseng exerts neuroprotective effects by modulating synaptic plasticity, neuroinflammation, and neurotransmitter release. It has been shown to have pharmacological actions against neuroinflammation, cerebral oxidative stress, radical generation, and apoptosis, in both *in vitro* and *in vivo* studies [127]. Ginsenoside Re has demonstrated protective effects against MPTP-induced apoptosis in the nigral neurons of a PD model mouse. This effect may be attributed to the upregulation of Bcl-2 protein expression, downregulation of Bax and iNOS protein expression, and inhibition of caspase-3 activation [128]. Additionally, ginseng possesses antioxidant properties that inhibit ROS production.

4.10.10. The Neuroprotective and Therapeutic Functions of Melatonin in PD

Melatonin is a neurohormone produced by the pineal gland in the brain. It plays a crucial role in regulating circadian rhythm, protecting against oxidative stress, controlling energy metabolism, modulating the immune system, and delaying the aging process [129]. In addition to the pineal gland, other organs, such as the gut and skin, are primary sources of melatonin release. Other non-pineal sources include the retina, testes, ovaries, placenta, glial cells, and lymphocytes, which primarily function as antioxidant agents [130]. Nevertheless, melatonin produced by sources outside the pineal gland has minimal impact on the regular daily fluctuation of melatonin levels in the bloodstream. Studies have shown that removing the pineal gland disrupts the rhythmic pattern of melatonin secretion [131].

In 1958, dermatologist Lerner successfully extracted melatonin from powdered cow pineal glands. Melatonin gets its name from its ability to induce depigmentation in amphibians and fish. Recent research suggests that the effects of melatonin are not solely attributed to its production in the pineal gland at night, but also to melatonin produced by other sources outside the pineal gland [132]. Melatonin is found in a variety of dietary sources, including nuts, seeds, fruits, vegetables, and cereals. Its production occurs in pinealocytes through the conversion of the amino acid tryptophan into serotonin, which is then converted into melatonin in a four-step process [133]. Folate and vitamin B6 (pyridoxine) are essential for melatonin synthesis, as a deficiency of folate in rats results in reduced melatonin release [134]. Melatonin is metabolized in both the brain and liver [135], and its metabolites have strong antioxidant properties that can neutralize free radicals and initiate the free radical scavenging process.

Melatonin plays a crucial role in regulating Ca^{2+} by inhibiting the increase in intracellular calcium levels caused by acid. It also reduces the levels of parvalbumin and hippocampal calcium-binding protein, which are calcium-binding proteins in the cerebral cortex of rats. This contributes to the neuroprotective effect of melatonin against neuronal cell damage [135, 136].

In addition, research has shown that it can reduce the levels of glutamate outside cells in specific brain areas, such as the hippocampal sections, by reversing the release of glutamate in a rat ischemia model known as oxygen-glucose deprivation [137].

Administration of melatonin reduces the infiltration of macrophages in the brain during transient focal cerebral ischemia and middle cerebral artery occlusion (MCAO) in rats. This, in turn, inhibits the excessive release of inflammatory cytokines and the resulting inflammatory damage [138]. A study using RT-PCR revealed that administering melatonin led to a significant decrease in the production of interleukin-1 beta (IL-1β) and tumor necrosis factor alpha (TNF-α) in rats with MCAO. Melatonin also increases the concentration of antioxidant enzymes, such as catalase and superoxide dismutase in the nigrostriatal pathway in an animal model of PD [139].

4.10.11. The Role of Date Palm in PD

The date palm tree (*Phoenix dactylifera* L.) is a significant agricultural commodity cultivated in various countries, particularly in North Africa and the Middle East, including several nations within the GCC (Gulf Cooperation Council) region [140]. Date palm trees have thrived for 5,000 years in harsh climatic conditions, providing an excellent source of energy and nutrition through their fruits. Dates have been recognized for their significant health benefits since biblical times. Recent scientific research has provided evidence that supports the knowledge and discussions of ancient predecessors. Dates are primarily composed of sugars (81–88%), mainly fructose, glucose, and sucrose, and contain dietary fiber at approximately 5–8.5%. Additionally, they contain small quantities of protein, fat, and ash, as well as notable levels of phenols [141].

The date palm fruit has been used in traditional therapies for various infectious diseases and has immune-modulatory properties. Regular consumption of dates has been shown to provide protective effects against various types of cancer, including colon, prostate, breast, endometrial, lung, and pancreatic cancers. Dates are a significant source of energy, essential vitamins, and minerals. They are not only nutritionally valuable but also contain high levels of phenolic compounds and flavonoids, which can scavenge free radicals and act as antioxidants. Free phenolic acids found in dates include protocatechuic acid, vanillic acid, syringic acid, and ferulic acid. Bound phenolic acids in dates include gallic acid, protocatechuic acid, p-hydroxybenzoic acid, vanillic acid, caffeic acid, syringic acid, p-coumaric acid, ferulic acid, and coumaric acid [142].

Date fruit contains three powerful antioxidants: flavonoids, carotenoids, and phenolic acid, which provide various health benefits. For example, they can help reduce levels of interleukin-6 (IL-6), an inflammatory marker often elevated in neurodegenerative diseases [143]. Phenolic chemicals act as potent antioxidants, shielding cells from damage by neutralizing free radicals, which may help prevent age-related diseases [144]. Numerous studies have demonstrated the positive impact of dates on neurological disorders like Alzheimer's disease, attributed to their phenolic and

flavonoid compounds. Consequently, long-term consumption of date palm fruits has been associated with reduced oxidative stress and enhanced antioxidant enzyme activity in transgenic mouse models of Alzheimer's disease [145].

4.10.12. Mucuna Pruriens in MPTP-Intoxicated Models

Mucuna pruriens (MP), a leguminous plant rich in levodopa (L-DOPA), has emerged as a potential natural treatment for PD. In MPTP-intoxicated murine models, MP extract not only reinstates striatal dopamine concentrations but also alleviates motor impairments such as bradykinesia and stiffness [146]. In contrast to synthetic L-DOPA, MP contains cofactors such as NADH and glutathione, which enhance mitochondrial activity and reduce oxidative stress, potentially delaying the development of dyskinesia [147]. A 2022 study indicated that mice treated with MP showed a 40% increase in tyrosine hydroxylase (TH) expression in the substantia nigra compared to groups treated with synthetic L-DOPA, suggesting enhanced neurorestorative effects [148]. Nonetheless, further studies with extended dosages are required to evaluate its potential for translation into clinical use.

4.10.13. Ursolic Acid

Diverse Neuroprotective Properties: Ursolic acid (UA), a triterpenoid found in rosemary and apples, has anti-inflammatory and antioxidant properties in MPTP models. UA mitigates microglial activation by inhibiting NF-κB signalling, resulting in a 50–60% reduction in pro-inflammatory cytokines such as TNF-α and IL-6 [149]. Furthermore, UA elevates the expression of nuclear factor erythroid 2-related factor 2 (Nrf2), leading to increased glutathione production and protection of dopaminergic neurones from oxidative damage [150]. Significantly, UA can effectively cross the blood--brain barrier, as demonstrated by a 3-week pretreatment in rats showing a 70% preservation of nigral neurones after MPTP administration [151]. These results establish UA as a contender for both prophylaxis and therapy.

4.10.14. Chlorogenic Acid: Mitochondrial Rehabilitation

Chlorogenic acid (CGA), found in coffee, has been shown to alleviate MPTP-induced mitochondrial impairment. CGA enhances mitochondrial complex I function, preventing ATP depletion and excessive ROS generation [152]. *In vivo*, a dose of 50 mg/kg of CGA decreased α-synuclein aggregation by 30% and enhanced motor coordination in rotarod tests, similar to rasagiline [153]. Additionally, CGA's iron-chelating properties impede ferroptosis, a newly recognized process in PD [154]. Nonetheless, the challenge lies in its bioavailability; researchers are investigating nanoparticle-encapsulated CGA formulations to improve cerebral delivery.

4.10.15. Withania somnifera: Mechanisms of Anti-Apoptosis

In the Maneb and Paraquat (MB-PQ) models, Withania somnifera (WS) root extract has shown significant anti-apoptotic properties. MB-PQ triggers dopaminergic apoptosis by activating caspase-3 and downregulating the Bcl-2 protein. Treatment with WS therapy (100 mg/kg) reduced caspase-3 activity by 45% and increased Bcl-2 levels, protecting 60% of TH-positive neurones [155]. Withanolide A, a key bioactive compound in WS, inhibits the JNK/p38 MAPK pathways, diminishing oxidative stress and synaptic loss [156]. A 2023 study highlighted the synergistic effects of WS and coenzyme Q10 in enhancing mitochondrial biogenesis in dual-toxin models [157].

5. CLINICAL TRIALS AND EVIDENCE

Numerous clinical trials have been conducted or are ongoing to evaluate the effectiveness of various neuroprotective agents. Fig. (**4**) illustrates the drug discovery process, including preclinical and clinical trials. In this section, we provide a summary of the key completed and ongoing trials, as well as the challenges faced in translating preclinical successes into clinical applications.

5.1. Completed Trials of Neuroprotective Agents

A significant number of clinical trials have been conducted or are currently underway to assess the effectiveness of various neuroprotective drugs. The main completed and ongoing studies are outlined below, along with the difficulties encountered in converting preclinical research findings into clinical practice.

Many clinical trials conducted to assess the potential neuroprotective effects of various substances in PD have not yielded the expected results in terms of clinical efficacy. The lack of clinical efficacy of CoQ10 in PD is contrary to expectations based on compelling data linking oxidative damage and mitochondrial dysfunction to the disease's pathophysiology. Since mitochondrial oxidative damage may not be the main cause of dementia but rather a side effect of other pathogenic processes, blocking this pathway may not be recommended [158]. Similarly, the evaluation of creatine, which supports mitochondrial function and energy production, did not show significant benefits in slowing the progression of PD in patients with early-stage disease, leading to the early termination of the trial due to futility [159].

5.2. Ongoing Clinical Trials

Numerous neuroprotective medicines are presently being evaluated in active clinical trials for PD. These trials focus on novel compounds and interventions that target oxidative stress, inflammation, mitochondrial dysfunction, and protein aggregation. For instance, Ambroxol, a drug conventionally used as a mucolytic, has been shown to increase glucocerebrosidase (GCase) activity, a lysosomal enzyme essential for sphingolipid metabolism, and may reduce alpha-synuclein aggregation. Mullin *et al.* (2020) demonstrated that ambroxol holds promise as a therapeutic agent for targeting the glucocerebrosidase pathway in PD and enhancing GCase activity in the brain. These findings are consistent with cellular and animal models, suggesting that ambroxol treatment can regulate α-synuclein levels. This suggests its potential as a

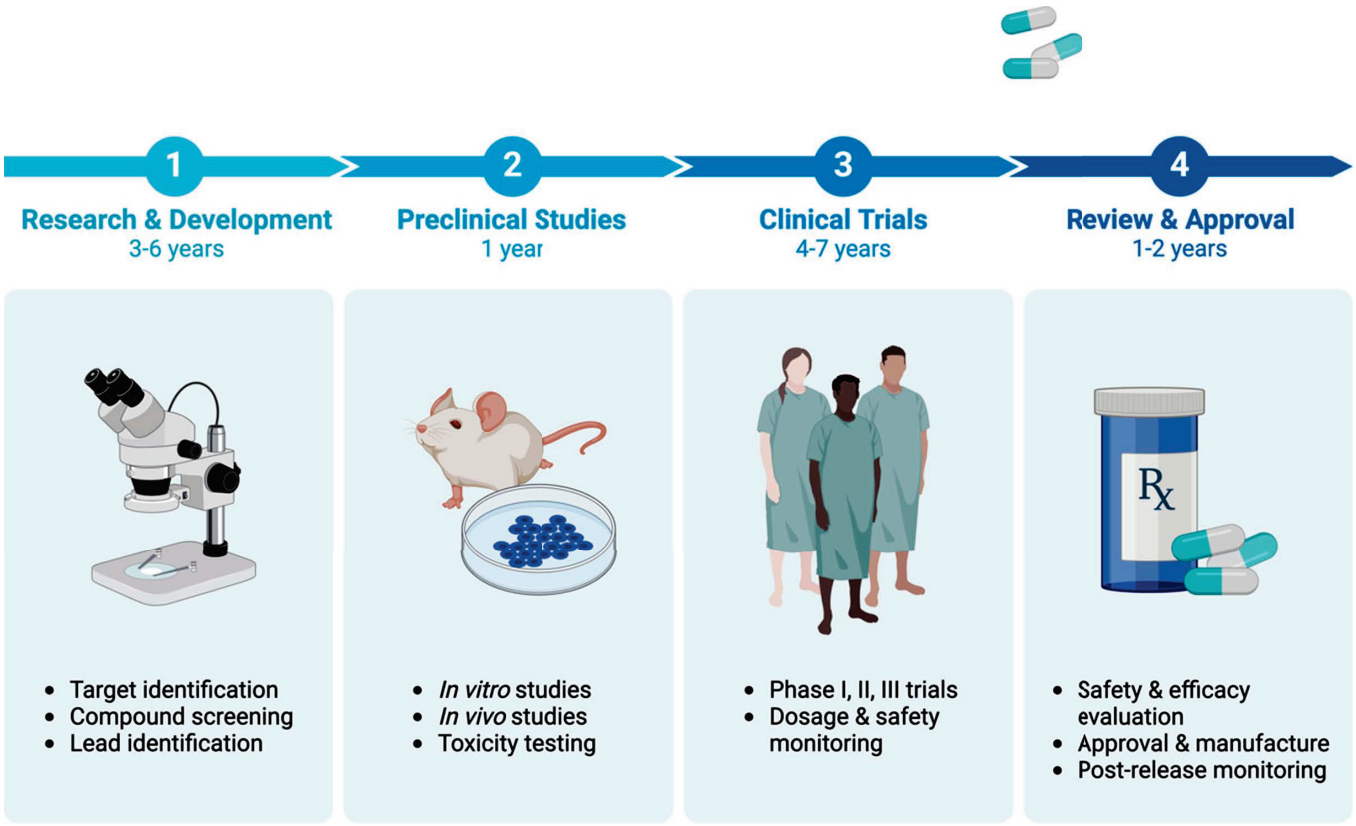

Fig. (4). The drug discovery process, including preclinical and clinical trials. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

therapeutic agent for improving outcomes, especially in individuals with PD who have a GBA1 mutation, and possibly in those without a GBA1 mutation. The expected conclusion of this investigation (phase II) was projected for 2024 [160].

5.3. Challenges in Translating Preclinical Success to Clinical Use

Despite significant progress in preclinical studies, translating neuroprotective agents to clinical success in PD has proven to be a challenging task. One of the main obstacles is the lack of disease models and agents that demonstrate efficacy in both animal models and humans. Many agents that show promise in animal models often fail in human trials due to a lack of biological and pathological relevance. The complexity of human PD is not fully replicated in animal models used in preclinical trials, such as rodent models. This is particularly evident in terms of progressive neurodegeneration and the variability of symptoms. For example, mouse DA neurons exhibit notable resistance to the overexpression of α-synuclein and LRRK2, as well as the absence of parkin, PINK1, or DJ-1. This resistance is thought to be due to the presence of intrinsic protective factors or other genetic modifications that mitigate toxic effects [161].

5.4. Long Disease Course and Heterogeneity

Despite the best modern treatments, such as Dopaminergic therapies, such as levodopa and surgical interventions, patients still experience disability due to the inability to control non-motor and non-dopaminergic features, such as freezing, falling, and dementia, effectively. If these symptoms are not managed properly, the disease will continue to progress in an increasingly intense manner.

PD is a slowly progressing disease, and its symptoms and progression vary widely among individuals, making it difficult to design trials that can effectively measure neuroprotection over a realistic timeframe. This is especially challenging because clinical endpoints often focus on motor symptoms rather than underlying neurodegeneration. Many clinical trials focus on symptomatic improvement rather than directly measuring neuroprotection, such as the preservation of dopaminergic neurons. Therefore, positive outcomes in animal models do not always translate into clinically meaningful results in humans [162].

6. CHALLENGES AND LIMITATIONS

Despite significant advancements in research on neuroprotective agents for PD, various challenges and limitations hinder the successful translation of preclinical findings to clinical practice. The complexity of the disease, as well as difficulties in drug development and trial design, are among the key issues.

6.1. Variability in Disease Progression and Patient Response

Clinically, PD is characterized by a variable duration, severity, and a combination of motor and non-motor features, resulting from genetic mutations in genes, such as LRRK2, PARK7, PINK1, and GBA, which are associated with specific forms of PD. These mutations can impact disease onset, progression, and response to treatment. Recent studies on PD have prioritized causation over clinical progression and long-term consequences. While recent results suggest that factors influencing the likelihood of developing PD may differ from those affecting clinical progression and outcomes, the factors influencing long-term clinical progression and outcomes in PD remain largely unclear. Prospective studies will be necessary to determine the variables that affect the course and outcomes of PD [163].

6.2. Challenges in Drug Delivery to the Brain

The efficient administration of neuroprotective agents to the brain is considerably hindered by the BBB, a protective barrier formed by the brain capillary endothelium that restricts the entry of numerous pharmaceuticals, completely excluding 100% of large-molecule neurotherapeutics and over 98% of small-molecule drugs. Only a small fraction of the prescribed medication reaches the brain, necessitating higher doses that may lead to various undesirable side effects. The BBB is the primary obstacle in the development of neurological pharmaceuticals and is the main factor limiting the progress of neurotherapeutics in the future. The development of new pharmaceuticals for neurological disorders poses a major challenge, as there are currently limited effective therapies available for most brain diseases. Numerous new treatments have been identified that could potentially help in treating brain disorders, provided that the issue of the blood--brain barrier is resolved. Nonetheless, if these pharmaceuticals are unable to traverse the blood-brain barrier, they will not be able to progress from the laboratory to clinical use. Drugs with high lipid solubility and a molecular mass below 400 Da can penetrate the blood-brain barrier and are often effective in treating specific central nervous system disorders, such as mood disorders, epilepsy, and chronic pain.

Recent advancements in drug delivery systems have the potential to enhance the efficacy of neuroprotective therapies by improving drug bioavailability, targeting specific brain regions, and minimizing side effects. One such method is intranasal administration, a non-invasive technique that allows drugs to bypass the blood-brain barrier through the olfactory and trigeminal nerves, delivering compounds directly to the brain. This approach is based on the notion that drugs can exit the submucous space of the nasal cavity, cross the arachnoid membrane, and enter the olfactory cerebrospinal fluid, provided that only lipid-soluble small molecules can penetrate the arachnoid membrane without disruption [164].

Nanomedicine is a field that integrates nanotechnology, chemistry, and medicine to develop potential therapeutic strategies for common neurological disorders like Alzheimer's disease, PD, frontotemporal dementia, amyotrophic lateral sclerosis, and Huntington's disease. Various drug delivery techniques based on nanomedicine are currently being studied to improve medication delivery to the brain [165].

There are three methodologies for administering medication to the brain using a nanomaterial-based blood-brain barrier technique: non-invasive, invasive, or identifying an alternative pathway. Non-invasive methods rely on biological mechanisms that facilitate the passage of drugs through the blood-brain barrier *via* transcellular routes. Larger proteins face challenges in using the olfactory route; therefore, macromolecules can be effectively administered with low cellular toxicity using cell-penetrating peptide (CPP)-based delivery systems. Invasive techniques involve Blood-Brain Barrier Disruption (BBBD) or directly delivering drugs to brain tissue through methods, such as intracerebral implants, intraventricular, intrathecal, and interstitial delivery, convection-enhanced delivery, osmotic BBBD strategies, biochemical strategies, and ultrasound-mediated BBBD strategies. The intranasal method is integrated with CPP-modified poly(lactic-co-glycolic acid) (PLGA) nanoparticles. This technique reduces endothelial cell size and disrupts tight junctions, allowing for the passage of molecules across the blood--brain barrier using magnetic fields, focused ultrasound, and hyperosmotic solutions. To enhance therapeutic benefits in CNS illnesses, biodegradable polymeric wafers containing medication are implanted for localized drug delivery. The introduction of substances, such as mannitol, fructose, or glycerol, into tight junctions compromises the integrity of the blood–brain barrier [166].

6.3. Side Effects and Safety Concerns

The safety and tolerability of neuroprotective drugs pose significant challenges, particularly since many of these molecules impact essential physiological functions, such as mitochondrial function and calcium homeostasis. While several drugs have shown neuroprotective effects in animal stroke models, they have not shown the same efficacy in clinical trials.

It is possible that these medications may have insufficient therapeutic ratios, resulting in the administration of ineffective doses and potentially leading to negative outcomes. The neuroprotective effectiveness was determined using an animal model of prolonged (24-hour) middle cerebral artery occlusion. The rotarod test was used to assess motor coordination and estimate potential side effects. The therapeutic ratio was calculated by dividing the minimal effective dosage (MED) for considerable neuroprotection by the MED for noticeable impairment in rotarod performance. It is possible that these medications may have inadequate therapeutic ratios, resulting in the administration of ineffective doses to prevent negative outcomes. Drugs like Ifenprodil, Cerestat, and Selfotel, which have not succeeded in clinical trials, had very low therapeutic ratios of ≤ 1, whereas molecules with more acceptable clinical side-effect profiles demonstrated higher therapeutic ratios. The ineffectiveness of some neuroprotectants in clinical studies may be attribut-

ed to their inadequate therapeutic ratios. Recent papers have discussed the reasons why robust neuroprotection shown in animal models has not translated into significant benefits for humans. These reasons include uncertainty about the reliability of stroke animal models, inadequacies in addressing the full spectrum of stroke pathology, shortcomings in clinical trial design, and delays in starting treatment. Since post-ischaemic cell loss occurs gradually, administering substances earlier can lead to greater protective effects. A significant factor contributing to the failure of neuroprotective drugs in clinical settings has been the onset of dose-limiting side effects, primarily impacting the cardiovascular or neurological systems, or both. This has resulted in a reduction in dosage to prevent adverse side effects [167]. Parkin and PINK1 are two mitochondrial proteins that have mutations associated with both cancer and PD, suggesting a common pathogenic mechanism between the two diseases. Mitochondria and autophagy/mitophagy are now being recognized as potential therapeutic targets for both PD and cancer. Mitochondria-targeted medicines have been shown to provide neuroprotection in preclinical mouse models of PD when administered early in the disease progression, and they also inhibit the growth of cancer cells. Consequently, it has been suggested that mitochondrial targeting can improve the preservation of cellular energy, which is crucial for neuronal cell survival, while hindering the growth of cancer cells by depriving them of the energy needed for their proliferation. These compounds have been shown to activate various cellular signaling pathways that affect immunomodulation, autophagy/mitophagy, and inflammation, all of which are associated with therapeutic options for PD and cancer [168].

Additional cerebral areas undergo non-dopaminergic degeneration, resulting in memory, affective, and olfactory impairments that precede the characteristic motor symptoms of PD. Caffeine has been shown to potentially impact the prevalence and progression of PD and provide neuroprotection against the death of dopaminergic neurons. Consistent epidemiological and preclinical evidence suggests that caffeine may offer neuroprotection against the degeneration of dopaminergic neurons and influence the progression and course of PD. The research suggests that coffee may enhance motor impairments in PD, while adenosine A2A receptor antagonists like istradefylline can reduce OFF time and dyskinesia linked to conventional dopamine replacement therapies. Additional experimental data also support the effectiveness of caffeine in addressing non-motor symptoms of PD that do not respond to existing dopaminergic medications. Overall, the reviewed trials provide compelling evidence that caffeine could be a viable therapeutic agent for PD, perhaps being the first substance to simultaneously alleviate both motor and non-motor early symptoms, along with its neuroprotective potential [169].

7. FUTURE PERSPECTIVES

7.1. Personalized Medicine Approaches in Neuroprotection

Approximately 80% of neurological illnesses are linked to genetic anomalies, epigenetic modifications (such as DNA methylation, histone/chromatin remodelling, and miRNA dysregulation), and environmental influences. The advent of novel sequencing technology and epigenomic analysis techniques has enabled the identification of predictive biomarkers for early diagnosis, thereby facilitating potential preventive therapies. Consequently, advancements in pharmacogenetics and pharmacoepigenomics facilitate personalized therapies tailored to individual patient profiles, taking into account the specific genetic and epigenetic mechanisms associated with the complexities of neurodegenerative diseases and the variability in patient responses to pharmacotherapy. This underscores the impact of genetic polymorphisms on the pharmacokinetics and pharmacodynamics of medications used in their treatment.

This research investigates genetic and genomic technologies to evaluate individual-specific drug metabolism for predicting and influencing medication response and related clinical effects. Additionally, it provides insights into the mechanisms of action of the medications under study and their potential effects on disease-modifying pathways [170].

More than 90% of pharmaceuticals fail to succeed in the final phase of human clinical trials due to ethical issues, exorbitant development expenses for animal models, and insufficient resemblance to human diseases, among other significant unresolved obstacles. A novel method utilizing induced pluripotent stem cells has been developed to overcome these limitations, offering a new perspective on clinical translational research and regenerative medicine. Human iPSCs were assessed and rated based on published research on PubMed for their role in the most common neurodegenerative disorders, such as PD, Alzheimer's disease, diabetic neuropathy, stroke, and spinal cord injury. PD exhibited the highest ranking, followed by AD. Moreover, recent breakthroughs in personalized medicine have been examined, including the concept of the "patient-on-a-chip," where Induced Pluripotent Stem Cells (iPSCs) are cultivated on three-dimensional matrices in microfluidic devices to develop an *in vitro* disease model for personalized treatment [171].

The effective primary prevention of chronic illnesses is a promising approach; hence, precision and personalized medicine are valuable tools for studying pathological processes before clinical symptoms appear and assisting physicians in selecting targeted treatments for patient care. Cardiovascular and neurodegenerative illnesses provide excellent examples for maximising the advantages of precision medicine technology throughout all stages of disease progression. Biomedical research has made substantial progress in understanding how genes, epigenetic modifications, aging, diet, drugs, the microbiome, and various environmental factors influence health and chronic disease [172].

7.2. Emerging Therapeutic Targets

By elucidating the aetiology, pathophysiology, and physical changes of the basal ganglia in PD, our understanding has advanced to a new level and provided the foundation for developing new drugs to address the emerging needs of this disease. While significant progress has been made in PD

treatments, current therapies primarily focus on symptom management rather than disease eradication. Therefore, a key clinical objective in PD is to develop disease-modifying treatments that target the underlying pathophysiologic processes responsible for slowing or halting disease progression and functional decline. Immunomodulation as a treatment approach is effective in managing PD patients, and ongoing stem cell trials are being conducted to explore additional treatment options.

In addition, recent preclinical investigations and phase II small clinical trials comparing new and established drugs have shown promising results in terms of their clinical utility. Molecular markers are also being developed for the early diagnosis of PD. Technological advancements in gene editing techniques, neuroimaging techniques, and software have contributed to these advances. Awareness of the limitations of previous research techniques in PD has led to the development of new pharmacological and non-pharmacological interventions that are currently being studied. Research advancements in biomarkers are also crucial because reliable, possibly multifactorial measures of PD etiology and progression are essential for implementing clinical trials aimed at delivering personalized, disease-altering treatments. Some current medications may have the capacity to alter disease progression, but estimating their moderate effects is problematic. In the advanced stages of PD, various non-motor symptoms are treated with nondopaminergic drugs to achieve motor therapeutic effects. These drugs include β-adrenergic and serotonergic agonists, as well as adenosine A2a antagonists. Recent studies have focused more on addressing the non-motor symptoms of PD, increasing the possibility of discovering interventions for these aspects of advanced PD. Additionally, recent trends in PD treatment have shifted towards molecular-structural-functional therapies targeting dopaminergic neurocircuits that are pathologically altered in PD over the last few years [173].

7.3. Potential of Combination Therapies

Current therapies for neurodegenerative disorders, such as PD and multiple system atrophy, primarily address the symptoms caused by the toxic accumulation of the protein alpha-synuclein (α-Syn) in neurons and glial cells. Utilizing drug combinations or multi-target drug strategies may improve treatment effectiveness compared to monotherapies. Synucleinopathies are complex conditions characterized by progressive stages, during which toxic α-syn aggregates exhibit prion-like properties, facilitating cell-to-cell transmission. This indicates that achieving meaningful and enduring effects in neurodegenerative diseases may necessitate advanced therapeutic approaches. Theoretically, medications, such as immunotherapy targeting α-Syn, which aim to reduce α-Syn accumulation and cell-to-cell transmission, could potentially have synergistic effects when combined with drugs that mitigate neuroinflammation. Reasoned therapy combinations, along with multi-target drugs, could offer a promising advancement in the treatment of synucleinopathies [174].

Matsunaga *et al.* (2017) found that zonisamide combination therapy effectively relieved motor symptoms in PD patients receiving antiparkinsonian treatment and demonstrated good tolerability in the Japanese population [175].

7.4. Critical Analysis of Findings

The neuroprotective efficacy of MP, UA, CGA, and WS in toxin-induced PD models underscores their multi-target mechanisms. The L-DOPA content of MP provides symptomatic relief, while its antioxidants address the pathogenesis, giving it a dual advantage over synthetic L-DOPA, which can exacerbate oxidative stress [149]. Similarly, UA and CGA modulate upstream pathways (NF-κB, Nrf2), offering disease-modifying potential. The anti-apoptotic effects of WS in MB-PQ models are consistent with its traditional use in neurodegeneration; however, its poor solubility may necessitate pharmaceutical optimization [159]. These findings corroborate prior studies on natural compounds but also reveal novel insights. For instance, the NADH content in MP explains its mitochondrial benefits, a feature absent in synthetic L-DOPA [151]. UA's Nrf2 activation parallels sulforaphane's effects but with greater BBB permeability [153]. Conversely, WS's efficacy in MB-PQ models contrasts with weaker effects in 6-OHDA models, suggesting toxin-specific mechanisms [159]. A key strength is the use of established toxin models that replicate the oxidative and inflammatory pathways of PD. However, most studies have employed acute toxin exposure, whereas chronic models better mimic human PD progression. Dosage variations (*e.g.,* UA at 10–50 mg/kg) complicate cross-study comparisons. Additionally, human trials are scarce, and the benefits of MP in Ayurvedic medicine lack rigorous clinical validation [150].

CONCLUSION

In this review, we emphasize the complexity of Parkinson's disease (PD) and the ongoing efforts to develop effective therapies. We also highlight the significance of specific chemical and natural compounds, such as anti-inflammatory substances, uric acid, curcumin, melatonin, and date palm, in offering potential neuroprotective and therapeutic benefits for PD.

To improve patient outcomes and quality of life, it is essential to continue efforts to understand the complex etiology and pathogenesis of PD. Future research should further explore the promising potential of natural compounds in managing PD, considering their efficacy and safety as adjunctive therapies. The importance of multidisciplinary approaches in PD management is also critical, as they integrate basic science research, clinical trials, and innovative therapeutic interventions aimed at targeting underlying mechanisms of neurodegeneration, such as mitochondrial dysfunction and oxidative stress. These efforts are crucial for developing treatments that not only alleviate PD symptoms but also have the potential to modify the course of the disease.

Although several neuroprotective agents have been investigated in clinical trials, many have failed to demonstrate significant benefits in PD management. Challenges in trans-

lating preclinical successes to clinical applications primarily stem from limitations in disease models, trial design, and outcome measures. Nevertheless, promising approaches, such as GLP-1 agonists and alpha-synuclein aggregation inhibitors, are currently under exploration.

Lastly, the limitations include the heterogeneity of the disease, difficulties with drug delivery across the blood--brain barrier, and the absence of reliable biomarkers. To overcome these limitations, personalized approaches, improved disease models, and innovative drug delivery systems should be considered to enhance the efficacy of neuroprotective therapies for PD.

AUTHORS' CONTRIBUTIONS

The authors confirm their contributions to the paper as follows: Draft manuscript: KRA and ARMFN; validation: MHMN and WM. All authors reviewed the results and approved the final version of the manuscript.

LIST OF ABBREVIATIONS

5-HT	=	Serotonin
6-OHDA	=	6-hydroxydopamine Hydrobromide
AD	=	Alzheimer's Disease
AFMK	=	N1-acetyl-N2-formyl-5-methoxykynuramine
Afs	=	Aflatoxins
AKT	=	Ak Strain Transforming
Alliin	=	S-allyl-l-cysteine Sulfoxide
AMPA	=	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic Acid
ATP	=	Adenosine Triphosphate
BBB	=	Blood-brain Barrier
BBBD	=	BBB Disruption
BDNF	=	Brain-derived Neurotrophic Factor
CBF	=	Cerebral Blood Flow
CNS	=	Central Nervous System
CoQ10	=	Coenzyme Q10
COX-2	=	Cyclooxygenase-2
CSF	=	Cerebrospinal Fluid
DA	=	Dopamine
DMT1	=	Divalent Metal Transporter 1
DLB	=	Dementia with Lewy Bodies
EBN	=	Edible Bird's Nest
FPN1	=	Ferroportin 1
FTDP	=	Frontotemporal Dementia with Parkinsonism
GABA	=	γ-Aminobutyric Acid
GDNF	=	Glial Cell Line-derived Neurotrophic Factor
GSH	=	Glutathione
GSK3β	=	Glycogen Synthase Kinase-3 beta
HG	=	High-glucose
hiPSC	=	Human Induced Pluripotent Stem Cell
IL	=	Interleukin
iNOS	=	Inducible Nitric Oxide Synthase
IRE	=	Irreversible Electroporation
IRPs	=	Iron-regulatory Proteins
LBs	=	Lewy Bodies
LBD	=	Lewy Body Dementia
L-DOPA	=	Levodopa
LPS	=	Lipopolysaccharide
LRRK2	=	Leucine-rich Repeat Kinase 2
MAO	=	Monoamine Oxidase
MAPK	=	Mitogen-activated Protein Kinase
MAPT	=	Microtubule-associated Protein
MCAO	=	Middle Cerebral Artery Occlusion
MEF2D	=	Myocyte Enhancer Factor 2D
METC	=	Mitochondrial Electron Transport Chain
MnSOD	=	Manganese Superoxide Dismutase
MPP+	=	1-methyl-4-phenylpyridinium
MPTP	=	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MRJP1	=	Major Royal Jelly Protein 1
MT	=	Melatonin
NA	=	Noradrenaline
NADPH	=	Nicotinamide Adenine Dinucleotide Phosphate
NbM	=	Basalis of Meynert
NFT	=	Neurofibrillary Tangles
NMDA	=	N-methyl-D-aspartate
NO	=	Nitric Oxide
NSAIDs	=	Non-steroidal Anti-inflammatory Drugs
OS	=	Oxidative Stress
PD	=	Parkinson's Disease
PDD	=	PD with Dementia
PDK1	=	Pyruvate Dehydrogenase Kinase 1
PGC-1α	=	Peroxisome Proliferator-activated Receptor Gamma Coactivator 1α
PINK1	=	PTEN-induced Kinase 1
PN	=	Peroxynitrite
PPARα	=	Peroxisome Proliferator Activating Receptor α
PPAR-γ	=	Peroxisome Proliferator-activated Receptor γ
PPD	=	Protopanaxadiols
PPT	=	Protopanaxatriols

PSP = Progressive Supranuclear Palsy
p-tau = Phosphorylated Tau
ROS = Reactive Oxygen Species
RSS = Reactive Sulphur Species
RT-PCR = Reverse Transcription Polymerase Chain Reaction
SERT = Serotonin Transporter
SHP2 = Src Homology 2-containing Protein Tyrosine Phosphatase 2
SN = Substantia Nigra
SNCA = Alpha-synuclein
SNpc = Substantia Nigra Pars Compacta
STN = Subthalamic Nucleus
T2DM = Type 2 Diabetes Mellitus
TBARS = Thiobarbituric Acid Reactive Substances
TCA = Tricarboxylic Acid
TNF-α = Tumor Necrosis Factor Alpha
TQ = Thymoquinone
TTP = α-tocopherol Transfer Protein
UA = Uric Acid
UCH-L = Ubiquitin Carboxyl-terminal Hydroxylase
VGCC = Voltage-gated Calcium Channels
α-SYOs = SNCA Oligomers

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