Neuroprotective Agents in Parkinson's Disease: Evaluating Natural Compounds and Novel Drugs

Deniz Guler *†

October 9, 2024

Abstract

Parkinson's Disease (PD) is a progressive neurodegenerative disorder characterized by the loss of dopaminergic neurons in the substantia nigra. Current treatments primarily focus on symptomatic relief rather than disease modification. This paper explores the potential of neuroprotective agents, encompassing both natural compounds and novel drugs, to prevent the worsening of the disease. This paper will discuss various natural compounds, including curcumin, resveratrol, ginkgo biloba, and green tea polyphenols, for their antioxidative, anti-inflammatory, and mitochondrial protective properties. Additionally, novel pharmacological agents such as nilotinib, istradefylline, and safinamide are examined for their innovative mechanisms targeting alpha-synuclein aggregation, dopamine receptor activation, and MAO-B inhibition. Through a comprehensive review of clinical trials, we assess the efficacy, safety, and future potential of these neuroprotective strategies in PD management.

1 Introduction

Parkinson's Disease (PD) is the second most common neurodegenerative disorder, affecting millions of people worldwide. Similar to Alzheimer's-type dementia, which is the most common human neurodegenerative disease, Parkinson's disease is a disorder predominantly of old age, and one that is becoming increasingly common as the global population ages. In stark contrast to Alzheimer's disease, however, Parkinson's disease benefits from robust and reliable drugs to target some of the most prominent and debilitating neurological symptoms resulting from neurodegeneration.Like Alzheimer's disease, there is yet no disease modifying therapy available.

*Student at Kabatas Erkek High School, Istanbul, Türkiye

†Advised by: Dr. Arij Daou, Visiting Assistant Professor of Neuroscience at the University of Chicago

Parkinson's disease (PD) was first described by Dr. James Parkinson in 1817 as a "shaking palsy." It is a chronic, progressive neurodegenerative disease characterized by both motor and nonmotor features. It occurs when brain cells that make dopamine stop working or die. Because PD can cause tremor, slowness, stiffness, and walking and balance problems, it is called a "movement disorder." In Parkinson's disease, the cells of the substantia nigra die, resulting in the production of less dopamine than normal. As Parkinson's disease progresses, over many years, brain cells in the substantia nigra continue to die and levels of dopamine slowly decline. The disease has a significant clinical impact on patients, families, and caregivers through its progressive degenerative effects on mobility and muscle control. While the motor symptoms of PD are attributed to the loss of striatal dopaminergic neurons, the presence of nonmotor symptoms supports neuronal loss in nondopaminergic areas as well. Thus, a major unmet medical need is the prevention of disease progression.

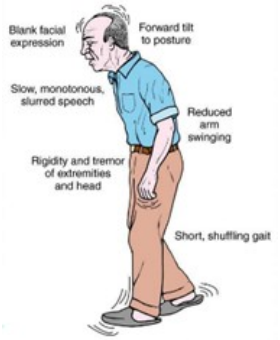

Figure 1: The Movement Symptoms of Parkinson's disease [Mis24]

The term *parkinsonism* is a symptom complex used to describe the motor features of PD, which include resting tremor, bradykinesia, and muscular rigidity. Gait and postural instability are also prominent motor features. The motor symptoms typically have an asymmetrical onset (starting on one side of the body) with symptoms typically manifesting initially in one upper limb. The contralateral side does eventually become involved, but a degree of asymmetry tends to persist throughout the disease course. Furthermore, bradykinesia is slowness of movement and is the most fundamental feature of parkinsonism, as its presence is required for a positive diagnosis of Parkinson's disease to be made. Patients might have loss of facial expression with masklike facies (hypomimia), and they may notice that their voice has become quieter and more monotonous (hypophonia). Bradykinesia can be examined clinically by asking the patient to perform rapid alternating movements such as tapping the forefinger and the thumb or opening and closing the hand repetitively. Rigidity is an involuntary increase in muscle tone with a feeling of stiffness or resistance when moving the patient's relaxed limb. Tremor is the involuntary rhythmic oscillatory movement of a body part. Tremor of body parts, such as the chin

and jaw, is frequently seen in Parkinson's disease.

While PD is the most common cause of *parkinsonism*, other secondary causes, including diseases that mimic PD and drug-induced causes, also exist. According to the Parkinson's Disease Foundation, approximately 1 million Americans currently have the disease, with an incidence of about 20 cases per 100,000 people per year, equating to roughly 60,000 new cases annually. The mean age of onset is close to 60 years. The prevalence of PD is reported to be approximately 1% in people aged 60 years and older, increasing to 1% to 3% in those over 80. Although it is primarily a disease of the elderly, individuals have developed PD in their 30s and 40s, but accounts for less than 5% of cases. Gender differences pertaining to the incidence of PD are reflected in a 3:2 ratio of males to females, with a delayed onset in females likely due to the neuroprotective effects of estrogen on the nigrostriatal dopaminergic system. There is, at present, no diagnostic test for Parkinson's disease.

The primary pathological hallmark of PD is the progressive loss of dopaminergic neurons in the substantia nigra pars compacta, leading to a substantial decline in dopamine levels in the striatum. Current therapeutic strategies mainly offer symptomatic relief, with limited efficacy in halting or reversing neurodegeneration. Research suggests that the pathophysiological changes associated with PD may start before the onset of motor features and include a number of nonmotor presentations, such as sleep disorders, depression, and cognitive changes. Evidence for this preclinical phase has driven the enthusiasm for research that focuses on protective or preventive therapies.

Neuroprotection (or the extraordinary competence of bioagents in preventing neuronal damage and secondary injuries by limiting oxidative stress, neuroinflammation, mitochondrial dysfunction, excitotoxicity, protein misfolding, disruptive autophagy and apoptosis) is currently leading the therapeutic strategy to slow disease progression. Neuroprotection in PD aims to preserve neuronal function and prevent cell death, thereby modifying the disease course. Natural compounds have garnered attention due to their multifaceted mechanisms, including antioxidative, anti-inflammatory, and mitochondrial protective effects. The main function of a reliable neuroprotective agent is to demonstrate experimentally, first in PD animal models and then in clinical trials, its effects on the preservation of functional nigral dopaminergic neurons, mainly by decreasing apoptotic cell death and activating the glutathione-dependent antioxidant systems which contribute to the reduction of motor dysfunction. Concurrently, advancements in drug development have introduced novel pharmacological agents targeting key pathogenic pathways in PD.

PD's variable but pronounced progression has a significant impact on patients, families, and society. Advanced and end-stage disease may lead to serious complications, including pneumonia, which is often associated with death.Current treatment is focused on symptomatic management. Evidence suggests that PD patients may also benefit from a multidisciplinary approach to care that includes movement specialists, social workers, pharmacists, and other health care practitioners.

Numerous risk factors and genetic mutations are associated with PD. Risk

factors for the disease include oxidative stress, the formation of free radicals, and exposure to several environmental toxins. Limited data support genetic associations with PD, with some gene mutations identified. Interestingly, an inverse relationship exists between cigarette smoking, caffeine intake, and the risk of developing PD. Inhibition of the enzyme monoamine oxidase (MAO), an enzyme which converts biogenic amines to their corresponding aldehydes, may explain the protective effects of tobacco smoking, whereas the benefits of caffeine may be related to its adenosine antagonist activity in which compounds block the proximal nephron site of sodium reabsorption by antagonizing the adenosine receptor, potentially leading to reduced sodium and water absorption in the kidneys. The variable prevalence of PD throughout the world suggests that environmental and genetic factors along with ethnic differences may all play roles in disease pathogenesis. Biomedical research in individuals with PD continues to identify additional risk factors and guide future prevention and treatment decisions.

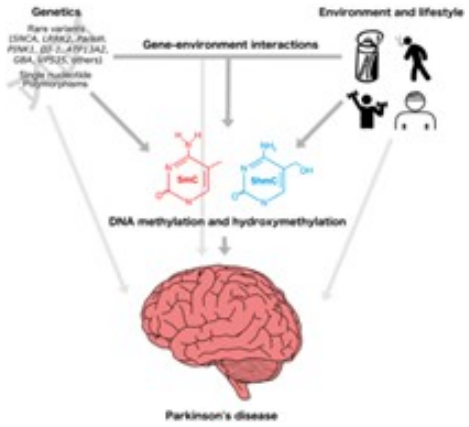

Figure 2: Genetic, environmental, and epigenetic underpinnings of Parkinson's disease [Sch22]

In this paper, we critically evaluate the neuroprotective potential of various natural compounds and novel drugs, scrutinizing their mechanisms of action, efficacy in preclinical and clinical studies, and safety profiles. This paper delves into the realm of neuroprotective agents, exploring both natural compounds and novel drugs that hold potential to provide therapeutic benefits beyond symptomatic management. Through this comprehensive analysis, we aim to highlight promising neuroprotective strategies and identify avenues for future research in the quest to improve outcomes for individuals with PD.

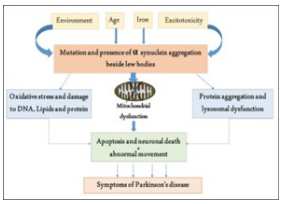

Figure 3: Genetic, environmental, and epigenetic underpinnings of Parkinson's disease [Sch22]

2 Pathophysiology of Parkinson's Disease

2.1 Overview of the Disease Mechanism

The pathogenesis of Parkinson's involves complex interactions between genetic and environmental factors, triggering a cascade of cellular events [Raz19]. Key mechanisms include mitochondrial dysfunction, which impairs energy production and increases oxidative stress, leading to cellular damage. Oxidative stress, in turn, contributes to the accumulation of reactive oxygen species, further damaging neurons and cellular components [DC21]. Protein aggregation, particularly of -synuclein, plays a central role in the formation of Lewy bodies, intracellular inclusions that are a hallmark of the disease [Raz19]. These aggregates interfere with normal cellular functions and can propagate throughout the brain in a prion-like manner. Additionally, neuroinflammation and impaired protein degradation pathways, such as the ubiquitin-proteasome system and autophagy, contribute to the progressive nature of the disease [DC21]. Understanding these interlinked processes is essential for identifying potential therapeutic targets and developing more effective treatment strategies.

2.2 Prion-like Hypothesis

An important advance in the understanding of PD pathogenesis and mechanisms that might contribute to disease progression is the emergence of evidence that a-synuclein aggregates can spread from one cell to another in a prion-like manner. According to the prion hypothesis, small amounts of fibrillar -synuclein act as seeds which can trigger the conversion of normal, soluble -synuclein into insoluble -synuclein Lewy bodies and Lewy neurites. Recent research has proposed the prion-like hypothesis as a central mechanism in the pathogenesis of PD. This hypothesis suggests that misfolded alpha-synuclein proteins can propagate from cell to cell, spreading pathological aggregates throughout the brain in a manner similar to prions. Alpha-synuclein is a presynaptic neuronal protein that, under pathological conditions, misfolds and forms insoluble fibrils that aggregate into Lewy bodies. The histological hallmark of Parkinson's disease (PD) is the presence of fibrillar aggregates called Lewy bodies (LBs). LB formation has been considered to be a marker for neuronal degeneration, because

neuronal loss is found in the predilection sites for LBs. These misfolded proteins are thought to induce the misfolding of native alpha-synuclein in neighboring cells, thereby perpetuating a cycle of neurodegeneration.

Several studies have demonstrated that alpha-synuclein can be transferred between cells via exosomes, direct cell-to-cell contact, or through the release of free-floating protein aggregates. This prison-like spread of alpha-synuclein pathology may explain the characteristic progression of PD symptoms from the lower brainstem to cortical regions as the disease advances. Understanding this prion-like mechanism opens new avenues for therapeutic interventions aimed at halting the spread of alpha-synuclein aggregates.

2.3 Epigenetics

Epigenetic modifications play a crucial role in the regulation of gene expression and have been implicated in the pathogenesis of PD. These modifications, such as DNA methylation, histone modification, and non-coding RNA expression, can influence neuronal function and survival by modulating the expression of genes involved in neuroprotection, inflammation, and oxidative stress. In PD, dysregulation of epigenetic mechanisms has been observed, leading to aberrant expression of genes that contribute to neuronal vulnerability. For instance, hypermethylation of the promoter region of the gene encoding the protein DJ-1, a known neuroprotective factor, has been associated with reduced DJ-1 expression and increased oxidative stress in dopaminergic neurons. Additionally, altered histone acetylation patterns have been linked to neuroinflammation and mitochondrial dysfunction in PD. Targeting epigenetic modifications presents a promising therapeutic strategy for PD. Agents that modulate DNA methylation, histone acetylation, or microRNA expression could potentially restore normal gene expression patterns and confer neuroprotection. Although research into epigenetic therapies is still in its early stages, the potential for developing disease-modifying treatments based on epigenetic modulation is substantial. The underlying pathophysiology involves complex mechanisms, including mitochondrial dysfunction, oxidative stress, neuroinflammation, and protein misfolding. Consequently, identifying molecular targets for neuroprotection has become a critical aspect of developing therapeutic strategies aimed at slowing or halting the progression of PD. There are several key molecular targets for neuroprotection including Deep Brain Stimulation (DBS) targets such as the subthalamic nucleus (STN), and the globus pallidus interna (GPi). Deep Brain Stimulation (DBS) is a surgical treatment that involves implanting electrodes in specific brain regions to modulate neural activity. It has provided remarkable benefits for people with a variety of neurological conditions. Stimulation of the ventral intermediate nucleus of the thalamus can dramatically relieve tremor associated with essential tremor or Parkinson disease (PD). Similarly, stimulation of the subthalamic nucleus or the internal segment of the globus pallidus can substantially reduce bradykinesia, rigidity, tremor, and gait difficulties in people with PD. Multiple groups are attempting to extend this mode of treatment to other conditions. Yet, the precise mechanism of action of DBS remains uncer-

tain. Such studies have importance that extends beyond clinical therapeutics. Investigations of the mechanisms of action of DBS have the potential to clarify fundamental issues such as the functional anatomy of selected brain circuits and the relationship between activity in those circuits and behavior. While primarily used to alleviate motor symptoms in PD, there is growing interest in exploring its neuroprotective potential. The Subthalamic Nucleus (STN) is one of the primary targets for DBS in PD. It is part of the basal ganglia circuitry and plays a crucial role in the regulation of motor function. In PD, the loss of dopaminergic input leads to overactivity of the STN, which contributes to the characteristic motor symptoms. DBS of the STN is thought to exert neuroprotective effects by normalizing the pathological activity within the basal ganglia circuitry. It may reduce excitotoxicity and oxidative stress, both of which contribute to neuronal degeneration. Additionally, STN-DBS has been shown to modulate neuroinflammatory responses and enhance the release of neurotrophic factors, which support neuron survival. STN-DBS not only improves motor symptoms but may also have long-term benefits in preserving cognitive function and slowing disease progression. However, the extent of its neuroprotective effects remains a topic of ongoing research. The Globus Pallidus Interna (GPi) is another major target for DBS in PD. Like the STN, the GPi is a critical component of the basal ganglia circuitry, and its activity is dysregulated in PD. GPi-DBS may provide neuroprotection by restoring the balance of excitatory and inhibitory signals within the basal ganglia. This can help prevent the downstream effects of abnormal GPi activity, such as excitotoxicity and inflammation. GPi-DBS may also reduce the energy demands on neurons, potentially protecting them from metabolic stress. GPi-DBS is particularly effective in reducing dyskinesias, a common side effect of long-term dopaminergic therapy in PD. Its potential neuroprotective effects are being investigated, with some studies suggesting that GPi-DBS may help preserve motor function over time.

3 Natural Compounds with Neuroprotective Effects

Numerous natural compounds have been investigated for their neuroprotective effects in PD. These compounds are derived from plants, fungi, and other natural sources.

3.1 Key Neuroprotective Mechanisms of Natural Compounds in PD

3.1.1 Antioxidative Properties

Oxidative stress is a phenomenon caused by an imbalance between production and accumulation of reactive oxygen species (ROS) in cells and tissues and the ability of a biological system to detoxify these reactive products. Superoxide radicals (O2), hydrogen peroxide (H2O2), hydroxyl radicals (OH), and singlet

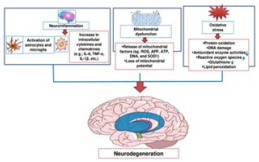

Figure 4: Different biological processes, including oxidative stress and neuroinflammatory and mitochondrial dysfunctions, have been involved in the development and pathogenesis of ND [Rah20]

oxygen (1O2) are commonly defined reactive oxygen species (ROS); they are generated as metabolic by-products by biological systems. Processes, like protein phosphorylation, activation of several transcriptional factors, apoptosis, immunity, and differentiation, are all dependent on a proper ROS production and presence inside cells that needs to be kept at a low level. ROS are mainly produced by mitochondria, during both physiological and pathological conditions. When ROS production increases, they start showing harmful effects on important cellular structures like proteins, lipids, and nucleic acids. Signs of oxidative stress are abundant in the substantia nigra of patients with PD. Mitochondrial complex I activity is depressed. Levels of intrinsic antioxidants, such as glutathione, are reduced, while oxidized products of proteins, lipids, and DNA increase significantly. Increasing levels of oxidative stress can eventually lead to apoptosis. Factors peculiar to midbrain DA neurons may enhance the risk of oxidative damage in SNc. Spontaneous autooxidation of DA produces reactive DA-quinone species and the superoxide anion (O2), as well as hydrogen peroxide (H2O2). When not sequestered in synaptic vesicles, DA can form complexes with cysteine that inhibit mitochondrial complex I. Glutamatergic activation of N-methyl-D-aspartate (NMDA) receptors on SNc neurons results in Ca2+ influx that may activate nitric oxide (NO) synthase (NOS), thereby increasing the availability of NO that could in turn combine with the superoxide anion to produce peroxynitrite (ONOO), which can cause nitrative damage to proteins, lipids, and DNA. Oxidative stress plays a vital role in the pathogenesis of PD [Dau03]. The substantia nigra is particularly vulnerable to oxidative damage due to elevated levels of iron, increased dopamine metabolism, and reduced antioxidant defenses. Natural compounds can exert antioxidative effects through various mechanisms, offering protection against this oxidative assault. Many natural compounds act as direct scavengers of reactive oxygen species (ROS) and reactive nitrogen species (RNS), neutralizing these harmful molecules before they can damage cellular components. This direct antioxidant action is often attributed to the chemical structure of these compounds, particularly the presence of hydroxyl groups that can donate electrons to stabilize free radicals. Beyond direct scavenging, numerous natural compounds have the ability to enhance the body's endogenous antioxidant defenses. They can upregulate the expression and activity of antioxidant enzymes such as superoxide dismutase (SOD), catalase, and glutathione peroxidase. This bolstering of the

cellular antioxidant machinery provides a more sustainable and comprehensive protection against oxidative stress. Another crucial mechanism by which natural compounds combat oxidative stress is through the activation of the Nrf2-ARE pathway. This pathway is a master regulator of cellular antioxidant responses, and its activation leads to increased expression of a wide array of antioxidant and detoxifying enzymes [Sar16]. Many natural compounds have been shown to activate this pathway, providing a powerful means of enhancing cellular resilience against oxidative damage.

3.1.2 Anti-inflammatory Effects

Neuroinflammation is a key feature of PD pathology, contributing to the progressive loss of dopaminergic neurons. Chronic activation of microglia and astrocytes leads to the release of pro-inflammatory cytokines, ROS, and RNS, creating a neurotoxic environment. The anti-inflammatory properties of natural compounds are therefore crucial in mitigating this aspect of PD pathogenesis [Rah20]. One of the primary ways natural compounds exert anti-inflammatory effects is through the inhibition of NF-kB, a transcription factor that plays a central role in regulating the inflammatory response. By suppressing NF-B activation, these compounds can reduce the expression of a wide range of pro-inflammatory genes, effectively dampening the inflammatory cascade. Natural compounds also demonstrate the ability to modulate microglial activation. Microglia, the brain's primary immune cells, can adopt different phenotypes ranging from pro-inflammatory (M1) to anti-inflammatory (M2). Many natural compounds have been shown to promote the shift towards the M2 phenotype, fostering a more neuroprotective environment. Furthermore, these compounds can directly suppress the production and release of pro-inflammatory cytokines from activated glia. By reducing levels of cytokines such as TNF-, IL-1, and IL-6, natural compounds can help mitigate the neurotoxic effects of chronic inflammation in PD.

3.1.3 Mitochondrial Protection

Mitochondrial dysfunction is a central feature of PD pathogenesis, contributing to energy deficits, increased oxidative stress, and ultimately neuronal death [Dau03]. The ability of natural compounds to protect and enhance mitochondrial function is therefore a crucial aspect of their neuroprotective potential in PD. Many natural compounds have been shown to enhance the activity of mitochondrial complex I, a key component of the electron transport chain that is often impaired in PD. By boosting complex I activity, these compounds can improve overall mitochondrial function, increasing ATP production and reducing the generation of ROS. Another important mechanism of mitochondrial protection is the reduction of mitochondrial oxidative stress. The mitochondrial genome is particularly vulnerable to oxidative damage, and many natural compounds can act as mitochondria-targeted antioxidants, protecting both mitochondrial DNA and proteins from oxidative insults. Natural compounds can

also modulate mitochondrial dynamics, including processes of fission, fusion, and mitophagy. These processes are crucial for maintaining a healthy population of mitochondria, and their dysregulation is implicated in PD pathogenesis. By promoting balanced mitochondrial dynamics, natural compounds can help ensure the removal of damaged mitochondria and the maintenance of a functional mitochondrial network.

3.2 Examples of Neuroprotective Natural Compounds

The most common neuroprotective natural compounds include curcumin, resveratrol, ginkgo biloba, and Green Tea Polyphenols. Initially, curcumin, the primary bioactive compound in turmeric, exemplifies the multi-faceted neuroprotective potential of natural compounds in PD. Its antioxidant properties stem from both direct ROS scavenging and the activation of cellular antioxidant defenses, particularly through the Nrf2 pathway (cellular defense against toxic and oxidative insults through the expression of genes involved in oxidative stress response and drug detoxification). Curcumin's anti-inflammatory effects are largely mediated through the inhibition of NF-B and the modulation of microglial activation. Additionally, curcumin demonstrates significant mitochondrial protective effects, enhancing complex I activity and reducing mitochondrial oxidative stress [Rah20]. Secondly, resveratrol, a polyphenol found in grapes and berries, has garnered significant attention for its neuroprotective potential in PD. Its antioxidant effects include direct ROS scavenging and the activation of SIRT1, a protein that enhances cellular stress resistance. Resveratrol's anti-inflammatory properties are evident in its ability to suppress microglial activation and reduce pro-inflammatory cytokine production. In terms of mitochondrial protection, resveratrol stands out for its ability to activate PGC-1, a master regulator of mitochondrial biogenesis, thereby promoting the generation of new, healthy mitochondria [Sar16]. Thirdly, Ginkgo Biloba contains powerful antioxidants, such as flavonoids and terpenoids, that may protect brain cells from oxidative stress and damage. Lastly, green tea polyphenols have strong antioxidant and anti-inflammatory properties, which may help reduce the oxidative damage that contributes to the degeneration of dopaminergic neurons. Both Ginkgo Biloba and Green Tea Polyphenols might help protect neurons from damage, which could slow the progression of Parkinson's. They may also improve cognitive function and reduce motor symptoms like tremors and rigidity [Fra17]. The exploration of natural compounds for neuroprotection in Parkinson's Disease reveals a promising avenue for therapeutic development. The ability of these compounds to simultaneously address multiple pathological mechanisms —including oxidative stress, neuroinflammation, and mitochondrial dysfunction— positions them as valuable candidates for further research and potential clinical application [Car19]. While the studies reviewed here demonstrate the significant potential of natural compounds, it is important to note that much of the current evidence comes from in vitro and animal studies. Translating these findings to effective treatments for PD patients will require rigorous clinical trials to establish efficacy and safety in humans. Future

research should focus on optimizing the delivery and bioavailability of these compounds, as well as exploring potential synergistic effects between different natural compounds or in combination with existing PD therapies. Additionally, a deeper understanding of the precise molecular mechanisms underlying the neuroprotective effects of these compounds will be crucial for their development as targeted therapeutics.

4 Novel Drugs and Their Mechanisms

4.1 Overview of Novel Drugs Developed for PD

Recent years have seen a surge in the development of novel drugs for PD, targeting various aspects of the disease pathology. These innovative therapies aim to not only alleviate symptoms but also potentially modify the course of the disease, addressing a critical need in PD management. The clinical trial pipeline for PD drugs is robust, with numerous compounds in various stages of development [McF23]. By diversifying the therapeutic landscape, researchers hope to provide more effective and personalized treatment options for PD patients.

4.2 Mechanisms of Action

Dopamine belongs to the catecholamine family of chemicals and consists of a simple aromatic ring structure with two hydroxyl groups (a catechol) modified with an amine group attached to an ethyl chain. In the brain, dopamine is derived from a precursor molecule, the amino acid levodopa, which also acts as the precursor for norepinephrine and epinephrine (also known as noradrenaline and adrenaline, respectively). Dopamine is degraded via several catabolic enzymes, notably by catechol-O-methyltransferase (COMT). Because of the importance of dopamine in PD, the metabolic pathways that generate and degrade this chemical, have been of critical importance in developing drugs that act to alleviate the symptoms of Parkinson's disease. A key consequence of the death of dopaminergic neurons in the substantia nigra pars compacta and the subsequent decrease in the levels of dopamine is the disruption of dopaminergic signaling passing out of the basal ganglia to the rest of the brain. Both excitatory (stimulating downstream action potentials) and inhibitory (suppressing downstream activity) dopaminergic signaling is perturbed in the parkinsonian brain, which has important consequences for therapeutic efforts targeting these networks.

4.2.1 Alpha-synuclein Aggregation Inhibitors

Alpha-synuclein aggregation is a hallmark of PD pathology, and novel drugs targeting this mechanism aim to prevent or reduce the formation of toxic alpha-synuclein aggregates. It is a presynaptic protein implicated in the pathogenesis of PD due to its propensity to misfold and form toxic aggregates known as Lewy bodies [Sar22]. Reducing a-synuclein aggregation, enhancing its clearance, or preventing its misfolding are potential strategies for neuroprotection.

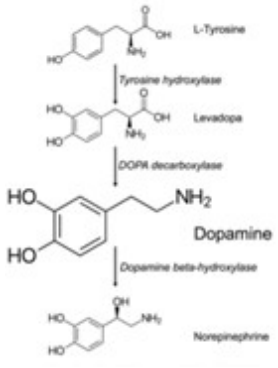

Figure 5: Dopamine metabolism showing the anabolic pathway from l-tyrosine through levodopa to dopamine [SG18]

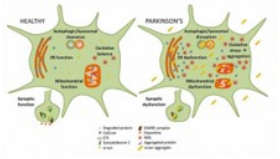

Figure 6: a-syn toxicity impairs cellular pathways [Res24]

Therapeutic approaches include small molecules, antibodies, and gene-silencing techniques that target a-synuclein. The normal physiological functions of a-Syn are involved in regulating synaptic vesicle dynamics at the nerve terminals and participating in synaptic functions such as plasticity and dopaminergic neurotransmission. These compounds work by interfering with the misfolding and aggregation of alpha-synuclein proteins, potentially slowing disease progression. This approach represents a shift from symptomatic treatment to potentially disease-modifying therapies. Examples of such compounds include NPT200-11 and ANLE138b, which have shown promise in preclinical studies [Jan20]. By targeting the fundamental process of protein aggregation, these drugs offer hope for not only managing symptoms but also altering the course of PD.

4.2.2 Dopamine Agonists

While dopamine agonists are not entirely novel in PD treatment, new formulations and delivery methods continue to be developed, expanding their therapeutic potential. These drugs stimulate dopamine receptors, mimicking the action of dopamine in the brain. By doing so, they aim to alleviate motor symptoms and potentially address some non-motor aspects of PD. Recent innovations in this class include Apomorphine sublingual film, which offers rapid relief for "off" episodes, and IPX203, an extended-release carbidopa-levodopa formulation de-

signed to provide more consistent symptom control throughout the day [McF23]. These advancements in dopamine agonist therapy demonstrate the ongoing efforts to refine and improve upon established treatment approaches.

4.2.3 MAO-B Inhibitors

Monoamine oxidase B (MAO-B) inhibitors represent another class of drugs with ongoing development and refinement. These compounds work by inhibiting the breakdown of dopamine, thereby increasing its availability in the brain. This mechanism not only helps manage motor symptoms but may also have neuroprotective effects. A notable example in this category is Safinamide, a novel MAO-B inhibitor with additional mechanisms of action. The continued research into MAO-B inhibitors underscores the importance of dopamine regulation in PD treatment and the potential for multi-modal approaches to therapy.

4.3 Examples of Novel Drugs

4.3.1 Nilotinib

Nilotinib, originally developed as a treatment for chronic myeloid leukemia, has emerged as a potential therapy for PD, exemplifying the concept of drug repurposing in neurodegenerative disease research. This compound acts as a c-Abl tyrosine kinase inhibitor, potentially reducing alpha-synuclein levels and neuroinflammation. By targeting these fundamental aspects of PD pathology, Nilotinib represents a novel approach to disease modification. Current research on Nilotinib in PD is ongoing, with Phase 2 clinical trials showing mixed results. Some studies have reported improvements in motor and cognitive symptoms, while others have yielded fewer promising outcomes [McF23]. The continued investigation of Nilotinib highlights the challenges and potential rewards of exploring new therapeutic targets in PD.

4.3.2 Istradefylline

Istradefylline represents a novel approach to PD treatment as an adenosine A2A receptor antagonist. This unique mechanism of action sets it apart from traditional PD therapies. By blocking adenosine A2A receptors, Istradefylline may enhance the effect of levodopa and improve motor function in PD patients. This synergistic effect with levodopa makes Istradefylline particularly valuable as an adjunctive therapy. The drug has gained approval in Japan and the United States as an adjunctive treatment to levodopa/carbidopa in PD patients experiencing "off" episodes [Jan20]. The success of Istradefylline demonstrates the potential of targeting non-dopaminergic systems in PD treatment and opens the door for further exploration of adenosine-related therapies.

4.3.3 Safinamide

Safinamide stands out among novel PD drugs due to its multiple mechanisms of action. Primarily acting as a MAO-B inhibitor, Safinamide also inhibits glutamate release and modulates sodium and calcium channels. This multi-modal approach allows Safinamide to address various aspects of PD pathology simultaneously. The drug has been approved in several countries as an add-on therapy to levodopa in mid-to-late-stage PD [McF23]. Safinamide's success highlights the potential benefits of drugs with multiple complementary mechanisms in managing the complex symptomatology of PD.

4.4 Emerging Therapies: Probiotics

Recent research has explored the potential of probiotics in PD treatment, highlighting the growing interest in the gut-brain axis in neurodegenerative diseases. This novel approach stems from increasing evidence linking gut microbiome dysbiosis to PD pathology. Probiotics may modulate the gut microbiome, potentially influencing neuroinflammation and alpha-synuclein aggregation. While still in early stages, studies have shown promising results in animal models and small clinical trials [Mir22]. The exploration of probiotics in PD treatment represents a paradigm shift, emphasizing the systemic nature of the disease and opening new avenues for therapeutic intervention. As research in this area progresses, it may lead to innovative combination therapies that address both central and peripheral aspects of PD. The field of PD therapeutics is rapidly evolving, with novel drugs targeting various aspects of the disease pathology. From alpha-synuclein aggregation inhibitors to innovative formulations of dopamine agonists, and from repurposed drugs like Nilotinib to multi-modal compounds like Safinamide, the landscape of PD treatment is becoming increasingly diverse. Moreover, emerging approaches such as probiotic therapies demonstrate the expanding scope of PD research. While challenges remain in translating preclinical promises to clinical efficacy, the diverse mechanisms of action represented by these new compounds offer hope for improved symptom management and potential disease modification in PD. As research continues, it is likely that future PD treatment strategies will involve combinations of these novel approaches, tailored to individual patient needs and disease characteristics.

5 Clinical Trials and Efficacy

Parkinson's disease remains a formidable challenge in neurology, with ongoing efforts to develop more effective treatments and potentially disease-modifying therapies. Clinical trials play a crucial role in advancing our understanding of PD and evaluating new therapeutic approaches.

5.1 Overview of Key Clinical Trials

The field of PD research has seen a surge in clinical trials over the past decade, spanning a wide range of therapeutic approaches. According to [McF22], the clinical trial pipeline for PD drug therapies is robust, with numerous compounds in various stages of development. These trials encompass traditional pharmacological approaches, novel drug candidates, gene therapies, and even alternative treatments such as acupuncture. One notable trend in recent years has been the focus on genetically targeted clinical trials. [Lon23] highlights that the PD field is learning from successes made in oncology, where genetic profiling has led to more personalized and effective treatments. For instance, trials targeting specific genetic mutations associated with PD, such as those in the LRRK2 or GBA genes, are becoming more common. These targeted approaches hold promise for developing therapies that may be more effective for specific subgroups of PD patients. In addition to pharmacological interventions, alternative therapies are also being rigorously studied. [Zha21] discusses clinical trials evaluating the efficacy of acupuncture in PD, exploring its potential effects on the dopaminergic neural circuit. These studies represent a growing interest in integrating traditional practices with modern medical approaches in PD treatment.

5.2 Evaluation of Efficacy

The evaluation of efficacy in PD treatments is a complex process, involving various outcome measures and considering both motor and non-motor symptoms. Clinical trials typically assess efficacy through standardized rating scales such as the Unified Parkinson's Disease Rating Scale (UPDRS), quality of life measures, and specific symptom assessments. When comparing natural compounds and novel drugs, the landscape becomes even more intricate. Natural compounds, including herbal extracts and nutritional supplements, have shown promise in some studies. For example, green tea polyphenols and curcumin have demonstrated neuroprotective effects in preclinical models. However, their efficacy in clinical settings often falls short of that seen with pharmaceutical interventions [McF22]. Novel drugs, on the other hand, are designed to target specific pathways involved in PD pathogenesis. These include compounds aimed at reducing alpha-synuclein aggregation, enhancing mitochondrial function, or modulating neurotransmitter systems beyond just dopamine. While many of these drugs show promise in early-phase trials, the challenge lies in translating these results into meaningful clinical benefits in larger, later-phase studies. The efficacy of genetically targeted therapies is an area of particular interest. [Lon23] notes that by focusing on specific genetic subgroups, these trials may yield more robust and meaningful results. This approach could lead to more personalized treatment strategies, potentially offering greater efficacy for patients with specific genetic profiles.

5.3 Side Effects and Safety Profiles

The evaluation of side effects and safety profiles is crucial in PD clinical trials, given the chronic nature of the disease and the need for long-term treatment. Traditional PD medications, such as levodopa and dopamine agonists, have well-documented side effect profiles, including motor fluctuations, dyskinesias, and impulse control disorders. Novel drugs often aim to improve upon these safety profiles. For instance, newer formulations of existing drugs or entirely new compounds may offer similar efficacy with reduced side effects. However, as [McF22] points out, unexpected safety issues can emerge in later-stage trials or post-marketing surveillance, highlighting the need for rigorous and long-term safety monitoring. Natural compounds are often perceived as having more favorable safety profiles, but this is not always the case. While many natural therapies do have good safety records, they can still interact with other medications or have their own side effects. The challenge lies in conducting sufficiently powered studies to detect less common adverse events. In the realm of genetically targeted therapies, safety considerations take on added dimensions. [Lon23] emphasizes the need for careful monitoring of potential off-target effects, especially with interventions that may have long-lasting or irreversible effects, such as gene therapies.

5.4 Emerging Trends and Future Directions

The landscape of PD clinical trials is continuously evolving. One emerging trend is the integration of digital health technologies and wearable devices in clinical trials. These tools offer the potential for more continuous and objective measurement of PD symptoms, potentially increasing the sensitivity of efficacy assessments. Another important direction is the focus on disease modification rather than just symptom management. Many ongoing trials are exploring compounds that may slow or halt the progression of PD, a holy grail in PD research. However, demonstrating disease modification remains a significant challenge, requiring long-term studies and potentially new assessment paradigms. The exploration of combination therapies is also gaining traction. Given the complex nature of PD, approaches that target multiple pathways simultaneously may offer synergistic benefits. This could involve combinations of pharmaceutical interventions, or integrations of drug therapies with non-pharmacological approaches like exercise or acupuncture [Zha21]. The field of PD clinical trials is dynamic and multifaceted, encompassing a wide range of therapeutic approaches from novel pharmaceuticals to alternative therapies. While significant progress has been made in developing more effective and targeted treatments, challenges remain in translating promising preclinical findings into clinical benefits. The comparison between natural compounds and novel drugs highlights the diverse landscape of PD therapeutics, with each approach offering unique benefits and challenges. As our understanding of PD pathophysiology deepens, and as clinical trial methodologies evolve, we can expect to see more personalized and potentially more effective treatment strategies emerge. The integration

of genetic profiling, digital health technologies, and a focus on disease modification are likely to shape the future of PD clinical trials. By carefully balancing efficacy with safety considerations, and by continuing to explore diverse therapeutic avenues, the field moves closer to the goal of not just managing PD symptoms, but potentially altering the course of the disease itself.

6 Challenges and Future Directions

6.1 Potential for Combination Therapies

As our understanding of PD's multifaceted nature grows, there is increasing interest in combination therapies that target multiple aspects of the disease simultaneously. These approaches may include combining pharmacological treatments with non-pharmacological interventions such as physical therapy, cognitive training, and lifestyle modifications [Els19]. One promising area of combination therapy involves the use of traditional dopamine replacement strategies alongside novel neuroprotective agents. For instance, researchers are exploring the potential of combining levodopa with antioxidants or anti-inflammatory compounds to not only alleviate symptoms but also slow disease progression [Poe17]. Another innovative approach is the combination of pharmacological treatments with non-invasive brain stimulation techniques, such as transcranial magnetic stimulation (TMS) or transcranial direct current stimulation (tDCS). These neuromodulation techniques, when used in conjunction with medication, have shown potential in improving motor symptoms and cognitive function in PD patients [Cho15]. Exercise-based interventions are also being increasingly recognized as valuable components of combination therapies. Studies have shown that combining traditional PD medications with tailored exercise programs can lead to improvements in both motor and non-motor symptoms, as well as overall quality of life [Blo15]. Furthermore, the integration of cognitive behavioral therapy (CBT) with standard PD treatments has shown promise in addressing the psychological aspects of the disease, such as depression and anxiety, which are often overlooked but can significantly impact patient outcomes [Dob11]. By addressing various aspects of PD pathology and symptoms concurrently, combination therapies hold promise for more effective management of the disease. However, more research is needed to determine the optimal combinations and timing of these interventions for different patient subgroups.

6.2 Global Collaboration

6.2.1 International Research Partnerships

The complexity of PD necessitates a global approach to research and treatment development. International collaborations can facilitate the sharing of expertise, resources, and diverse patient populations, leading to more robust and generalizable findings [Col19b]. One notable example of successful international collaboration is the Parkinson's Progression Markers Initiative (PPMI), a

landmark study involving multiple countries and research institutions. This initiative aims to identify biomarkers of PD progression and has already made significant contributions to our understanding of the disease [Mar18]. Another important collaborative effort is the Global Parkinson's Genetics Program (GP2), which brings together researchers from around the world to study the genetic basis of PD. By pooling genetic data from diverse populations, GP2 aims to accelerate the discovery of novel genetic risk factors and potential therapeutic targets [BC20]. International partnerships also play a crucial role in conducting large-scale clinical trials. The Parkinson Study Group (PSG), for instance, is an international network of researchers that collaborates on designing and implementing clinical trials for new PD treatments. Such collaborations enable faster recruitment of participants and more diverse study populations, leading to more generalizable results [Mes21].

6.2.2 Shared Data and Resources

Establishing global databases and biobanks for PD research can accelerate scientific discoveries and promote more efficient use of resources. These shared platforms can enable large-scale genetic studies, facilitate the identification of novel biomarkers, and support the development of AI-driven diagnostic and prognostic tools [Els19] . The Parkinson's Disease Biomarkers Program (PDBP), supported by the National Institute of Neurological Disorders and Stroke, is an excellent example of a shared resource initiative. This program collects and shares a wide range of biological and clinical data from PD patients and health controls, providing researchers with valuable resources for biomarker discovery and validation [Ros16]. Another significant development in data sharing is the establishment of the Accelerating Medicines Partnership Parkinson's Disease (AMP PD) program. This public-private partnership aims to identify and validate promising biological targets for PD therapeutics by integrating and analyzing data from multiple large-scale studies [Sul20]. The use of blockchain technology is also being explored to facilitate secure and efficient sharing of research data across international boundaries. This approach could potentially address concerns about data privacy and ownership while promoting more open collaboration [Ang17]. Furthermore, initiatives like the Global Parkinson's Disease Database (GPDD) are working towards creating standardized data collection protocols and shared databases that can be accessed by researchers worldwide. Such efforts can help overcome the challenges of data heterogeneity and incompatibility that often hinder large-scale analyses [Bhi20]. To sum up, global collaboration through international research partnerships and shared data resources is essential for advancing our understanding and treatment of Parkinson's Disease. By leveraging the collective expertise and resources of the global scientific community, we can accelerate progress towards more effective prevention, diagnosis, and treatment strategies for this complex neurodegenerative disorder.

7 Conclusion

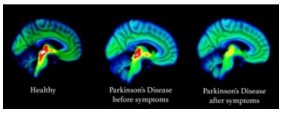

Figure 7: Parkinson's Disease Brain Malfunction Evident in Scans Potentially Years Before Symptoms [KKP21]

This comprehensive review of neuroprotective agents in Parkinson's Disease (PD) underscores the multifaceted approach required to address this complex neurodegenerative disorder. The exploration of both natural compounds and novel drugs reveals promising avenues for therapeutic intervention, potentially offering disease-modifying effects beyond mere symptomatic relief.

Our investigation into the pathophysiology of PD has yielded significant insights, particularly regarding the prion-like hypothesis of a-synuclein propagation. This mechanism has emerged as a central component in PD pathogenesis, offering new targets for therapeutic intervention. Moreover, the role of epigenetics in PD has come to the forefront, highlighting the potential for developing treatments that modulate gene expression patterns. These advancements in our understanding of PD's underlying mechanisms provide a foundation for more targeted and effective neuroprotective strategies. Building on this pathophysiological framework, the investigation of natural compounds has revealed a wealth of potential neuroprotective agents. Substances such as curcumin, resveratrol, Ginkgo biloba, and green tea polyphenols have demonstrated remarkable multifaceted properties. These compounds exhibit potent antioxidative, anti-inflammatory, and mitochondrial protective effects, addressing multiple pathological mechanisms simultaneously [Rah20] [Sar16] [Fra17]. The ability of these natural compounds to target various aspects of PD pathology positions them as valuable candidates for further research and potential clinical application.

Complementing the promise of natural compounds, innovative pharmacological agents have expanded the therapeutic landscape for PD. Novel drugs targeting a-synuclein aggregation, such as NPT200-11 and ANLE138b, represent a shift towards potentially disease-modifying therapies. Advancements in dopamine receptor activation, exemplified by new formulations like Apomorphine sublingual film and IPX203, offer improved symptom management. Additionally, the development of next-generation MAO-B inhibitors, such as Safinamide, demonstrates the ongoing refinement of established treatment approaches. The exploration of repurposed drugs like Nilotinib and novel compounds such as Istradefylline further diversifies the arsenal of potential PD treatments [Jan20] [McF23]. As our understanding of PD's systemic nature grows, emerging therapies are broadening the scope of treatment strategies. The exploration of probiotics, for instance, highlights the increasing recognition of the gut-brain axis in PD pathology. This innovative approach opens new avenues for systemic interventions that may complement traditional brain-centric

treatments [Mir22]. Furthermore, while primarily used for symptomatic relief, Deep Brain Stimulation (DBS) of the subthalamic nucleus (STN) and globus pallidus interna (GPi) has shown potential neuroprotective effects by modulating basal ganglia circuitry and reducing excitotoxicity.

The promising results observed in preclinical and early clinical studies underscore the critical need for continued research in neuroprotective agents for PD. Several key areas warrant further investigation to advance our understanding and treatment of this complex disorder. Translational research remains a priority, as the challenge of converting preclinical success to clinical outcomes persists. Many natural compounds and novel drugs show promise in vitro and in animal models, but rigorous clinical trials are essential to establish their efficacy and safety in humans.

Given the complex pathology of PD, future research should explore combination therapies that leverage the synergistic effects of multiple neuroprotective agents. This approach may offer more comprehensive treatment strategies, addressing various aspects of PD pathology simultaneously. Additionally, the heterogeneity of PD necessitates the development of personalized treatment regimens based on individual genetic profiles, environmental factors, and specific disease characteristics. Such personalized medicine approaches may enhance the efficacy of neuroprotective strategies and minimize side effects.

As PD is a chronic, progressive disorder, long-term studies are crucial to evaluate the sustained efficacy and safety of neuroprotective agents. This includes assessing their potential to slow or halt disease progression over extended periods. Parallel to these clinical investigations, the identification and validation of reliable biomarkers for early PD diagnosis and disease progression monitoring are essential. Such biomarkers would facilitate earlier intervention with neuroprotective agents and enable more accurate assessment of treatment efficacy.

To further refine our therapeutic approaches, deepening our understanding of the precise molecular mechanisms underlying the neuroprotective effects of both natural compounds and novel drugs is crucial. This knowledge will inform the development of more targeted and effective therapeutics. Additionally, research into optimizing the delivery and bioavailability of neuroprotective agents, particularly for natural compounds, is vital. This includes exploring novel drug delivery systems that can enhance the penetration of these agents across the blood-brain barrier. In conclusion, the field of neuroprotective agents in PD is rapidly evolving, offering hope for disease-modifying treatments that can significantly improve patient outcomes. Parkinson's Disease is a devastating degenerative neurological disorder, impacting most obviously motor performance, and is also now recognized to cause severe symptoms across a range of systems. The convergence of insights from natural compound research, drug development, and emerging therapies like probiotics presents a rich landscape for future investigation. Continued investment in this research area is essential to address the growing global burden of PD and improve the quality of life for millions of affected individuals worldwide. Although major strides have been made to understand the mechanisms leading to neurodegeneration in Parkinson's disease, the goal of developing disease-modifying treatments for this disorder remains,

at present, out of reach. The significant efforts now being directed toward clinical trials of compounds or approaches that directly address neurodegeneration in Parkinson's disease provide hope that treatments that slow or halt disease progression will become available over the coming years.

References

[Alt19] Muckenthaler M. U. Altamura, S. Iron toxicity in diseases of aging: Alzheimer's disease, parkinson's disease, and atherosclerosis. *Journal of Aging Disorders*, 2019.

[Ang17] Gibbs J. S. Angel M. Kosik I. Hickman H. D. Frank G. M.-Das S. R. Wheatley A. K. Prabhakaran-M. Leggat D. J. McDermott A. B. Yewdell J. W. Angeletti, D. Defining b cell immunodominance to viruses. *Nature Immunology*, 2017.

[BC20] Diez-Fairen M. Kim J. J. Singleton A. B. Bandres-Ciga, S. Genetics of parkinson's disease: An introspection of its journey towards precision medicine. *Neurobiology of Disease*, 2020.

[Bei14] J. M. Beitz. Parkinson's disease: A review. *Journal of Neurodegenerative Disorders*, 2014.

[Bhi20] Boonmongkol T.-Thongchuam Y. Phumphid S. Kantachadvanich N. Panyakaew P. Jagota P. Plengsri-R. Chokpatcharavate M. Phokaewvarangkul O. Bhidayasiri, R. Impact of disease stage and age at parkinson's onset on patients' primary concerns: Insights for targeted management. *PLoS One*, 2020.

[Blo15] de Vries N. M. Ebersbach G. Bloem, B. R. Nonpharmacological treatments for patients with parkinson's disease. *Movement Disorders*, 2015.

[Car19] Cacabelos R. Carrera, I. Current drugs and potential future neuroprotective compounds for parkinson's disease. *Journal of Parkinson's Disease Drug Therapies*, 2019.

[Car21] Landis H. E. Getachew B. Silva V. D. A. Ribeiro P. R.-Aschner M. Tizabi Y. Carvalho, F. V. Iron toxicity, ferroptosis, and microbiota in parkinson's disease: Implications for novel targets. *Journal of Neurotherapeutics*, 2021.

[Cho15] Turner J. A. Devine E. B. Hansen R. N. Sullivan S. D. Blazina-I. Dana T. Bougatsos C. Deyo-R. A. Chou, R. The effectiveness and risks of long-term opioid therapy for chronic pain: a systematic review for a national institutes of health pathways to prevention workshop. *Annals of Internal Medicine*, 2015.

[Col19a] GBD 2016 Neurology Collaborators. Global, regional, and national burden of neurological disorders, 1990-2016: a systematic analysis for the global burden of disease study 2016. *Lancet Neurology*, 2019.

[Col19b] GBD 2016 Neurology Collaborators. Global, regional, and national burden of neurological disorders, 1990–2016: A systematic analysis for the global burden of disease study 2016. *The Lancet Neurology*, 2019.

[Dau03] S. Dauer, W. Przedborski. Parkinson's disease: mechanisms and models. *Neuron*, 2003.

[DC21] Yong C. Yang X. Chen-Yu S. Li-Hua P. Dong-Chen, X. Signaling pathways in parkinson's disease: Molecular mechanisms and therapeutic interventions. *Neuroscience Research Reviews*, 2021.

[DM17] Goldman S. M. Miller-G. W. Greenamyre J. T. Dorsey-E. R. De Miranda, B. R. Preventing parkinson's disease: An environmental agenda. *Environmental Health Perspectives*, 2017.

[Dob11] Menza M. Allen L. A.-Gara M. A. Mark M. H. Tiu-J. Bienfait K. L. Friedman J. Dobkin, R. D. Cognitive-behavioral therapy for depression in parkinson's disease: a randomized, controlled trial. *American Journal of Psychiatry*, 2011.

[DP15] G. DeMaagd and A. Philip. Parkinson's disease and its management: Part 1: Disease entity, risk factors, pathophysiology, clinical presentation, and diagnosis. *PT*, 2015.

[Els19] J. D. Elsworth. Parkinson's disease treatment: Past, present, and future. *Parkinson's Disease Journal*, 2019.

[Fen20] Wang Z. Z. Yuan Y. H. Wang X. L. Sun H. M.-Chen N. H. Zhang Y. Feng, S. T. Dynamin-related protein 1: A protein critical for mitochondrial fission, mitophagy, and neuronal death in parkinson's disease. *Journal of Molecular Biology*, 2020.

[Fra17] Schmitz Y. Sulzer D. Cenci M. A. Francardo, V. Neuroprotection and neurorestoration as experimental therapeutics for parkinson's disease. *Journal of Parkinson's Research*, 2017.

[Jan20] Tan E. K. Jankovic, J. Parkinson's disease: Etiopathogenesis and treatment. *Journal of Neurology Psychiatry*, 2020.

[KKP21] T. Kantonen, T. Karjalainen, and L. et al. Pekkarinen. Cerebral - opioid and cb1 receptor systems have distinct roles in human feeding behavior. *the Nature*, 2021.

[Lon23] Chatzis L. G. Dal Pozzolo R. Peretti S. Fulvio G. La Rocca G.-Navarro Garcia I. C. Orlandi M. Quartuccio-L. Baldini C. Bartoloni E. Longhino, S. Sjögren's syndrome: one year in review 2023. *Clinical and Experimental Rheumatology*, 2023.

[Mar18] Jin J. Goode T. D. Giustino T. F. Wang Q. Acca G. M.-Holehonnur R. Ploski J. E. Fitzgerald P. J. Lynagh T. Lynch J. W. Maren S. Sah P. Marek, R. Hippocampus-driven feed-forward inhibition of the prefrontal cortex mediates relapse of extinguished fear. *Nature Neuroscience*, 2018.

[McF22] Rafaloff G. Baptista M. Mursaleen L. Fuest R. McFarthing, K. Parkinson's disease drug therapies in the clinical trial pipeline: 2022 update. *Journal of Parkinson's Research*, 2022.

[McF23] Buff S. Rafaloff G. Fiske B. Mursaleen L. Fuest R. Wyse R. K.- Stott S. R. W. McFarthing, K. Parkinson's disease drug therapies in the clinical trial pipeline: 2023 update. *Parkinson's Drug Trials*, 2023.

[Mes21] Macklin E. A. Ascherio A. Ferreira J. J. Lang A. E. Schwarzschild-M. A. Parkinson Study Group SURE-PD3 Investigators Mestre, T. A. Expectations of benefit in a trial of a candidate disease-modifying treatment for parkinson disease. *Movement Disorders*, 2021.

[Mir22] Sedighi S. Kouchaki E. Barati E. Dadgostar E. Tamtaji O. R. Mirzaei, H. Probiotics and the treatment of parkinson's disease: An update. *Gut Microbiome in Parkinson's Disease*, 2022.

[Mis24] Jena L. Mishra N. Chang H.-T. Mishra, S. Pd-detector: A sustainable and computationally intelligent mobile application model for parkinson's disease severity assessment. *Heliyon*, 2024.

[NIC15] Parkinson's disease in over 20s: diagnosis and management. *National Institute for Health and Care Excellence (NICE)*, 2015.

[Pal20] Wysocka A. Gasiorowska A. Chalimoniuk M. Niewiadomski-W. Niewiadomska G. Palasz, E. Bdnf as a promising therapeutic agent in parkinson's disease. *Brain Research Reviews*, 2020.

[Par02] J. Parkinson. An essay on the shaking palsy. *The Journal of Neuropsychiatry and Clinical Neurosciences*, 2002.

[Poe17] Seppi K. Tanner C. M. Halliday G. M. Brundin P. Volkmann J. Schrag-A. E. Lang A. E. Poewe, W. Parkinson disease. *Nature Reviews Disease Primers*, 2017.

[Rah20] et al. Rahman, M. M. Synthesis and investigation of dyeing properties of 8-hydroxyquinoline-based azo dyes. *Journal of the Iranian Chemical Society*, 2020.

[Raz19] Anjum R. Shakeel N. A. Raza, C. Parkinson's disease: Mechanisms, translational models and management strategies. *Parkinson's Research Management*, 2019.

[Res24] Biomarker organization in circulating extracellular vesicles: New applications in detecting neurodegenerative diseases, 2024. Scientific Figure on ResearchGate.

[Ros16] M. Rosenthal. Qualitative research methods: Why, when, and how to conduct interviews and focus groups in pharmacy research. *Currents in Pharmacy Teaching and Learning*, 2016.

[Sar16] Raymick J. Imam S. Sarkar, S. Neuroprotective and therapeutic strategies against parkinson's disease: Recent perspectives. *Journal of Parkinson's Therapeutics*, 2016.

[Sar22] Siwecka N. Galita G. Kucharska-Lusina A. Rozpedek-Kamińska W. Majsterek I. Saramowicz, K. Alpha-synuclein contribution to neuronal and glial damage in parkinson's disease. *Neurodegenerative Disease Research*, 2022.

[Sch15] Horsfall L. Walters K. et al. Schrag, A. Prediagnostic presentations of parkinson's disease in primary care: A case-control study. *The Lancet Neurology*, 2015.

[Sch22] Kobor M. S. Schaffner, S. L. Dna methylation as a mediator of genetic and environmental influences on parkinson's disease susceptibility: Impacts of alpha-synuclein, physical activity, and pesticide exposure on the epigenome. *Frontiers in Genetics*, 2022.

[SG18] T. B. Stoker and J. C. Greenland, editors. *Parkinson's Disease: Pathogenesis and Clinical Aspects*. Codon Publications, 2018.

[SJ14] Neely Sherwood and Jones. Parkinson's disease foundation statistics on parkinson's. *National Institute for Health and Care Excellence (NICE)*, 2014.

[Son19] Sung C. Y. Ke C. H. Yang F. Y. Song, W. S. Anti-inflammatory and neuroprotective effects of transcranial ultrasound stimulation on parkinson's disease. *Journal of Ultrasound Research*, 2019.

[Sul20] Antonini A. Leta V. Nordvig A. Smeyne R. J. Goldman J. E. Al-Dalahmah O. Zecca L. Sette A. Bubacco-L. Meucci O. Moro E. Harms A. S. Xu Y. Fahn S. Ray Chaudhuri K. Sulzer, D. Covid-19 and possible links with parkinson's disease and parkinsonism: from bench to bedside. *NPJ Parkinson's Disease*, 2020.

[Twe03] Perkins K. S. Counsell C. Twelves, D. Systematic review of incidence studies of parkinson's disease. *Movement Disorders*, 2003.

[Wan22] Liu J. Y. Yang C. B. Malampati S. Huang Y. Y. Li-M. X. Song J. X. Wang, Z. Y. Neuroprotective natural products for the treatment of parkinson's disease by targeting the autophagy–lysosome pathway: A systematic review. *Journal of Neuroprotective Research*, 2022.

[Zha21] Zhang Z. Qin S. Fan W. Li W. Liu J. Wang S. Xu-Z. Zhao M. Zhao, Y. Acupuncture for parkinson's disease: Efficacy evaluation and mechanisms in the dopaminergic neural circuit. *Journal of Integrative Neuroscience*, 2021.