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# MULTIFACTORIAL NEURODEGENERATION IN PARKINSON'S DISEASE: DECODING MOLECULAR PATHOLOGY, MODEL SYSTEMS, AND HERBAL THERAPEUTICS

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## ABSTRACT

**Background:** Parkinson's disease (PD) is a progressive neurodegenerative illness characterized by both motor and non-motor symptoms. It is caused by a combination of environmental and genetic variables, oxidative stress, mitochondrial dysfunction, alpha-synuclein aggregation, dopaminergic neuron loss, poor proteostasis, and neurons. **Objective:** This study aims to give a comprehensive overview of the molecular and cellular mechanisms that underlie Parkinson's disease, talk about the important hereditary and environmental factors that play a role, and highlight new multi-targeted therapy approaches that try to change the condition. **Methods:** The contributions of mitochondrial failure, oxidative stress, alpha-synuclein aggregation, neuroinflammation, defective autophagy-lysosomal and ubiquitin-proteasome pathways, and changes in the gut-brain axis in Parkinson's disease pathogenesis were examined in a critical review of recent research. Research on new treatments that target these processes was also assessed. **Results:** Parkinson's disease is caused by a combination of environmental pollutants, mitochondrial malfunction, oxidative stress, proteostasis failure, neuroinflammation, gut microbiome alterations, and genetic abnormalities (SNCA, LRRK2, PINK1, GBA). Although dopaminergic treatments help with symptoms, they cannot stop neurodegeneration. Multi-targeted approaches are being developed to alter the course of disease, such as anti-inflammatory drugs and antioxidants derived from plants. **Conclusion:** Multiple pathogenic pathways must be targeted by integrative therapy due to the intricacy of Parkinson's disease. Novel approaches to disease-modifying treatments are presented by

developments in experimental models and molecular research. Personalized, multimodal techniques must be the focus of future efforts in order to effectively control and change the course of disease.

## ➢ INTRODUCTION

Parkinson's disease (PD) is a complicated neurological condition that is caused by cellular and molecular processes that are interrelated. α-synuclein misfolds and aggregates to produce Lewy bodies, which impair neuronal function, especially in the substantia nigra pars compacta (SNpc), and cause dopaminergic neurodegeneration.[1] This imbalance in the circuits of the direct and indirect basal ganglia causes the distinctive motor deficits.[2] Neuronal mortality is accelerated by mitochondrial failure, which is made worse by mutations in PINK1, Parkin, and DJ-1. This dysfunction impairs energy production and raises oxidative stress. In addition, malfunctioning protein degradation systems (such as the autophagy-lysosomal pathway and the ubiquitin-proteasome system) lead to the harmful buildup of misfolded proteins.[3] The damage is exacerbated by neuroinflammation, which is fueled by overactive microglia and an excess of pro-inflammatory cytokines. Meanwhile, new research indicates that the gut-brain axis, primarily the microbiome, influences the neurotransmission modulation of dopamine and acetylcholine in the brain, indicating that α-synuclein pathology may start in the gut and spread through the vagus nerve.[4] The daevelopment and susceptibility of disease are influenced by both genetic and epigenetic factors, including mutations in SNCA, LRRK2, and PINK1. PD's unrelenting neurodegeneration is caused by a combination of these pathogenic pathways, which emphasizes the necessity for multi-targeted therapy methods such as dopaminergic medicines, mitochondrial protectants, neuroinflammation inhibitors, and α-synuclein-targeting medications.[3]

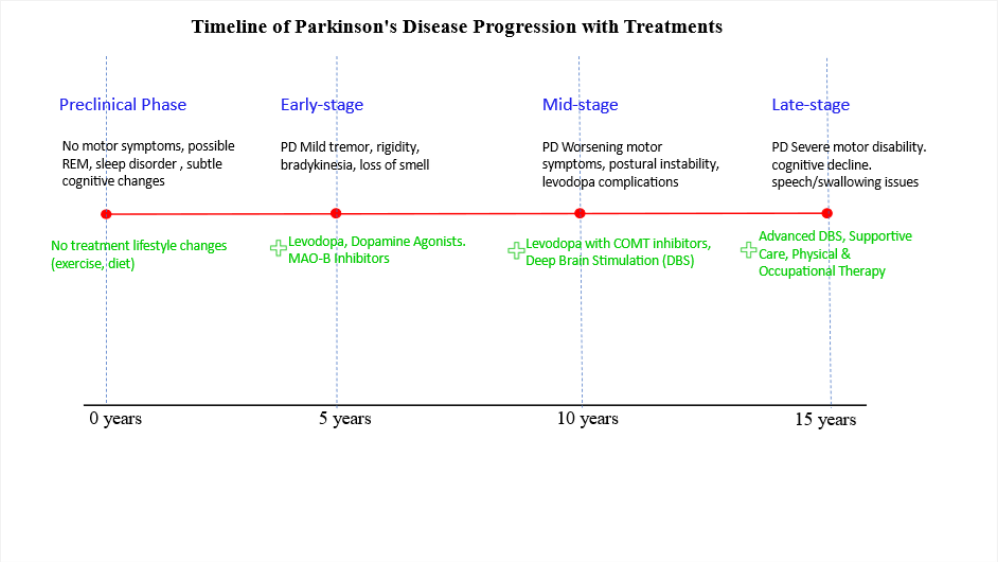


**Figure 1- Timeline of Parkinson's Disease Progression with Treatments.**

The most prevalent neurodegenerative movement disorder is Parkinson's disease (PD), which is typified by a variety of non-motor symptoms in addition to growing motor impairment. According to regional study, the reported frequency in India is between 6 and 53 per 100,000, with higher rates observed in urban and older populations. However, there are few nationwide incidence numbers available, and the range is between 6 and 14 per 100,000 people annually. In Europe, there are between 108 and 257 cases of Parkinson's disease for every 100,000 persons, with an estimated 11 to 19 new cases per 100,000 each year. These figures illustrate the disease's significant impact on public health.[5] The current definition of Parkinson's disease includes bradykinesia accompanied by stiffness, rest tremor, or both. The clinical presentation, however, is complex and includes a number of non-motor symptoms. Prognostic guidance is guided by knowledge of disease subtypes. A possibly protracted prodromal stage precedes the development of Parkinson's disease. Detecting prodromal parkinsonism will probably have consequences once disease-modifying drugs are available, but at the moment, prodromal symptoms have no therapeutic significance beyond symptom suppression.[6]

Tremor is often the first symptom, and it might be followed by bradykinesia and rigidity. Postural instability can significantly affect quality of life and is often identified late in the disease. It's also important to remember that some people may experience autonomic symptoms before motor problems. The majority of patients are diagnosed based on their clinical presentation and medical history. SPECT scans can be used to rule out other neurological conditions or in cases of uncertainty.

A degenerative neurological disorder, Parkinson's disease has a high morbidity and fatality rate. Most people discuss their Parkinson's disease symptoms with their primary care physician before consulting a specialist. Although motor symptoms are the main diagnostic markers of Parkinson's disease, the condition can also include nonmotor symptoms such autonomic dysfunction, depression, and hallucinations, which can make the first diagnosis difficult.[6]

Visual hallucinations, advanced age, biomarker changes including cortical shrinkage, Alzheimer-like changes on functional MRI and in cerebrospinal fluid, slowness and frequency variation on EEG, and other risk factors for early dementia progression are also included. Nevertheless, little is known about the mechanisms behind cognitive decline in Parkinson's disease. In Lewy body and Alzheimer-type illnesses, cortical involvement is significant, albeit multiple processes are probably at play.[7]

- **Parkinson's Disease Pathophysiological Mechanisms: An Interconnected System of Integrated Factors**

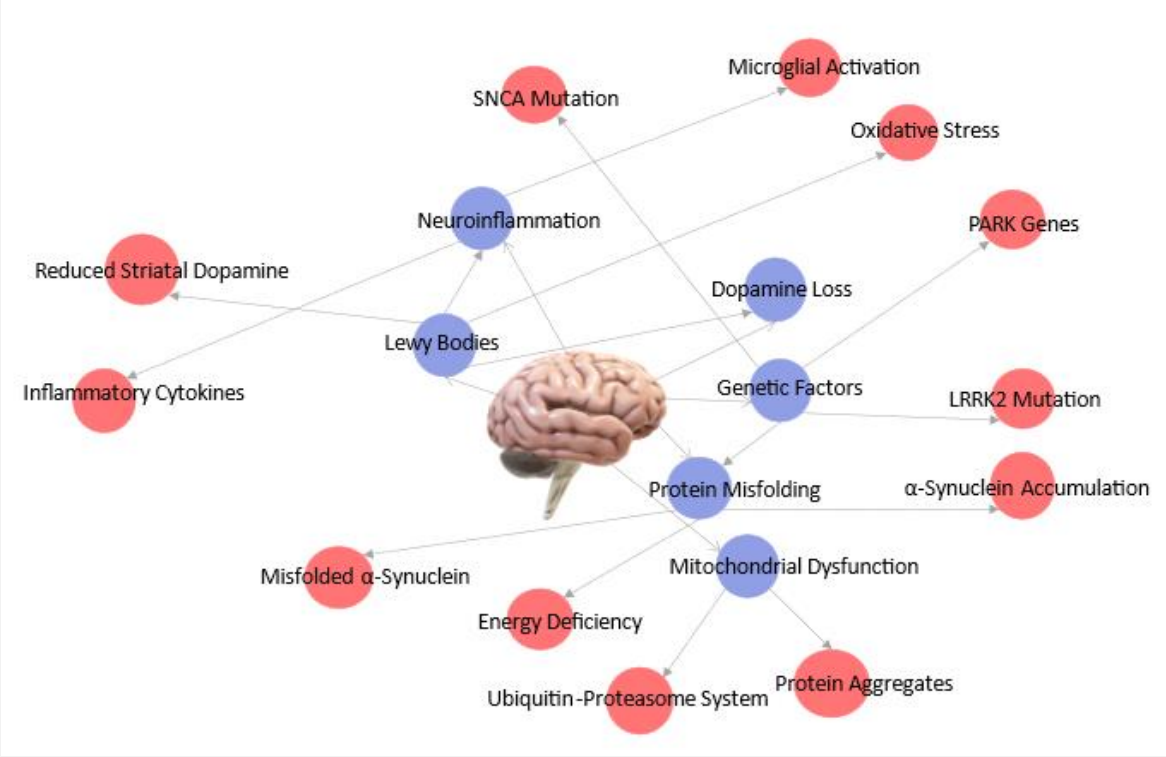


**Figure 2 - Parkinson's Condition Pathophysiological Mechanisms: An Integrated System of Linked Elements.**

The figure highlights the interrelated processes that lead to dopaminergic neurodegeneration and depicts the intricate pathophysiology of Parkinson's disease (PD). The progressive death of dopaminergic neurons, mostly in the substantia nigra pars compacta, is a key component of the disease process and results in dopamine deficit in the striatum[8] Critical initiators include genetic mutations like SNCA, LRRK2, and PARK gene changes, which encourage the buildup of misfolded α-synuclein and the development of Lewy bodies in neurons.[9] Intracellular protein aggregates caused by defective protein degradation processes, such as malfunctioning ubiquitin-proteasome systems, further aggravate this pathogenic protein aggregation.

The resulting energy deficit and mitochondrial malfunction further increase oxidative stress levels, resulting in a hazardous intracellular environment. Chronic neuroinflammation results from the release of pro-inflammatory cytokines from microglial activation brought on by α-synuclein aggregation and oxidative damage[10] These agents of inflammation promote synaptic dysfunction and neuronal damage. The cardinal motor symptoms of Parkinson's disease are the clinical manifestation of decreased striatal dopamine levels caused by the convergence of these processes. Further linking systemic factors to the development of disease, new research also points to a gut-brain axis involvement, where misfolded α-synuclein may travel from the enteric nervous system to the brain through the vagus nerve[11]

- **Recent advancements**

over the past five years have included the identification of genetic subtypes and a growing number of genetic variants linked to the risk of Parkinson's disease, the validation of clinical diagnostic criteria, and the introduction and testing of research criteria for prodromal Parkinson's disease. The development of diagnostic biomarkers has advanced significantly, and imaging and genetic tests are now routinely included in clinical practice regimens. Other tissue and fluid indications are now being researched. Early diagnosis, the identification of discrete subgroups with different prognoses, and the creation of novel disease-modifying medications are all made possible by Parkinson's disease's shift from a clinical to a biomarker-supported diagnostic entity.[12]

Public health attempts to prevent cardiovascular diseases and some types of cancer have appropriately led to an increase in focus to chronic neurological illnesses like dementia and Parkinson's disease. Multifaceted preventative strategies are required to address high-risk focused secondary prevention, population-based primary prevention, and tertiary prevention

treatment for Parkinson's disease. Triangulating the results of basic, applied, and epidemiological research will require future international collaborations in order to advance Parkinson's disease knowledge and prevention worldwide.

PD genetics provides a significant insight into the disease's process by revealing unique molecular pathways and their impact at the cellular level. This section outlines the complicated genetics of Parkinson's disease, focusing on the genes that have been most thoroughly studied.

Changes in NF-κB expression, a crucial regulator of cellular responses, have been linked to PD processes. PD disease is characterized by buildup of alpha-synuclein, which activates NF-κB in neurons and promotes death through many mechanisms.[13] Misfolded alpha-synuclein produced by degenerated neurons triggers signaling pathways in glial cells, leading to NF-κB activation and pro-inflammatory cytokine production, exacerbating neurodegenerative processes. However, NF-κB activation can be both beneficial and detrimental to neuronal survival. NF-κB activation is essential for mitochondrial function, and c-Rel deficiency can lead to DA neuron death through many routes. NF-κB plays a dual role in Parkinson's disease. However, strategically changing its processes and pathways can reduce DA neuron loss and PD.[14]

The etiology of sporadic Parkinson's disease is still unknown; however, the interplay of extrinsic and intrinsic variables may play an important role in the illness's genesis and progression. Animal models and human postmortem tissue have revealed unique cellular and molecular alterations in the sick brain, implying intricate interactions between different glial cell types and molecular pathways. Small changes in the expression of individual genes in one pathway or cell type may have an impact on others at the cellular and system levels.[15]

Our understanding of the etiology of Parkinson's disease has evolved significantly during the last several decades. Although more than 85% of patients with idiopathic or late-onset Parkinson's disease do not appear to have inherited the condition, a positive family history is connected with an increased risk of PD. The study of rare large families with clearly Mendelian inherited parkinsonism (<10%) identified several causative genes, indicating that mitochondrial or lysosomal dysfunctions, protein aggregation, the ubiquitin-proteasome system, and kinase signaling pathways all play a major role in the pathogenesis of PD.[16]

- **Current Treatment Landscape**

The goal of allopathic treatment for Parkinson's disease (PD) is to reduce symptoms using medications and dopaminergic therapy. To increase brain availability and reduce side effects, the most effective medication, levodopa, is combined with benserazide or carbidopa; nonetheless, prolonged use may result in motor fluctuations and dyskinesia.[17] While dopamine agonists (e.g., Pramipexole, Ropinirole) directly stimulate dopamine receptors, COMT inhibitors (e.g., Entacapone, Opicapone) and MAO-B inhibitors (e.g., Selegiline, Rasagiline) prolong dopamine effects. This helps with early or adjunct therapy, but it also carries risks like hallucinations and impulse control disorders. Anticholinergic medications, including trihexyphenidyl, reduce tremors but may have negative effects on cognition. Amantadine aids in the treatment of dyskinesias, while adenosine A2A receptor antagonists (such istradefylline) reduce "off" time.[18]

Antidepressants (such as SSRIs for depression), rivastigmine for dementia, pimavanserin for psychosis, and medications for orthostatic hypotension, constipation, and sleep issues are used to treat non-motor symptoms.[19] Emerging therapies that aim to postpone the onset of disease include alpha-synuclein-targeting drugs, gene therapy, and stem cell research.

- **An overview of the main features of several therapy for Parkinson's disease is provided in this comparative table**
- **Table 1: Comparative table of methods for treating Parkinson's disease that highlights the salient features of various treatments.**

| Treatment | Mechanism | Advantages | Limitations | Future Potential |
|---|---|---|---|---|
| Levodopa | Converts to dopamine in the brain | Most effective for motor symptoms | Long-term use causes fluctuations | Newer formulations for stability |
| Dopamine Agonists | Mimic dopamine action | Useful in early stages | Impulse control disorders possible | Personalized dosing improvements |
| MAO-B Inhibitors | Prevent dopamine breakdown | Mild symptom relief | Limited efficacy as monotherapy | Possible neuroprotective effects |
| Deep Brain Stimulation (DBS) | Electrical stimulation of brain regions | Reduces motor fluctuations | Requires brain surgery | Adaptive DBS with AI optimization |
| Gene Therapy | Modifies genes to enhance dopamine function | Potential long-term benefits | Experimental, limited trials | Disease-modifying potential |
| Stem Cell Therapy | Replaces lost neurons | Restores dopamine production | Ethical concerns, immune rejection | Ongoing research in neurodegeneration |

Dopamine agonists, levodopa, and MAO-B inhibitors are used to restore or mimic dopamine in Parkinson's disease, with differing advantages and disadvantages. Though they have drawbacks, cutting-edge alternatives like DBS, gene, and stem cell therapies seek to lessen symptoms or alter disease. Future priorities include regeneration, customisation, and stability.

- **Comparative table with specific drugs, success rates, and recent research updates**
- **Table 2: Table of comparisons with certain medications, success rates, and current study findings.**

| Treatment | Examples | Recent Research |
|---|---|---|
| Levodopa | Sinemet (Levodopa/Carbidopa), Rytary, Stalevo | Extended-release formulations like IPX203 in trials for more stable effects |
| Dopamine Agonists | Pramipexole (Mirapex), Ropinirole (Requip), Rotigotine (Neupro patch) | Newer formulations aim to reduce side effects |
| MAO-B Inhibitors | Rasagiline (Azilect), Selegiline (Eldepryl), Safinamide (Xadago) | Clinical trials assessing combination therapy benefits |
| COMT Inhibitors | Entacapone (Comtan), Tolcapone (Tasmar), Opicapone (Ongentys) | New formulations under review for longer efficacy |
| Deep Brain Stimulation (DBS) | Medtronic Activa, Abbott Infinity | Adaptive DBS (AI-controlled stimulation) in development |
| Gene Therapy | AAV-GAD, AAV2-neurturin (CERE-120) | Trials on GDNF & neurturin gene therapy ongoing |
| Stem Cell Therapy | IPSC-derived dopaminergic neurons | Clinical trials underway using IPSC (Induced Pluripotent Stem Cells) |
| Immunotherapy (Vaccines) | PD01A, AFFITOPE | New trials exploring active & passive immunization |
| Gut Microbiome Therapy | Probiotics, Fecal Microbiota Transplant (FMT) | AI-driven microbiome research accelerating discoveries |

Extended-release medication formulations, AI-optimized deep brain stimulation, and novel gene, stem cell, and microbiome therapies are examples of recent developments in the treatment of Parkinson's disease. These developments seek to improve symptom management, reduce adverse effects, and provide possible benefits for disease modification.

- **Non-Pharmacological Interventions**

Recent advancements in radiation therapy offer encouraging non-invasive options for managing Parkinson's disease (PD), especially for patients who are not candidates for surgery or who have symptoms that are not responsive to medication. The subthalamic nucleus (STN)

and globus pallidus internus (GPi), two deep brain structures, receive high-precision radiation from Gamma Knife Radiosurgery (GKS), which gradually lessens tremors and rigidity. A promising substitute for Deep Brain Stimulation (DBS) is Focused Ultrasound (FUS) with MRI guidance, which creates precise brain lesions and provides quick symptom relief without the need for surgeries or implants. Radiation-based methods offer long-lasting yet non-invasive therapies, while DBS is still the gold standard and requires the surgical implantation of electrodes for personalized symptom management.

Furthermore, although it is still in the experimental stage, proton beam therapy (PBT) is being investigated for altering the brain circuits implicated in Parkinson's disease. These radiation treatments, in contrast to DBS, remove the possibility of surgical infections and hardware issues, but they are not adjustable after the lesion has been created. These developments give PD patients new treatment options, including safer and easier ways to manage their symptoms, even if further study is required.

- **From Asanas to Antioxidants: A Natural Path to Parkinson's Disease Management.**

Yoga and other non-pharmacological therapies can improve mobility, balance, cognitive function, and general well-being, which can help manage Parkinson's disease (PD). Asanas, or poses, including Tree Pose (Vrikshasana) and Warrior Pose (Virabhadrasana), strengthen muscles and improve postural stability, which reduces the risk of falling.[20] Yoga is an ancient mind-body practice that enhances flexibility, stability, and mental resilience. Stretching exercises help people become less stiff and rigid, and mindful movements and breath control (Pranayama) improve motor coordination. In addition to lowering stress, anxiety, and despair, meditation and deep breathing also promote emotional stability and relaxation, both of which are critical for managing Parkinson's disease.[21]

Respiratory muscles, which may deteriorate as a result of the disease, are further strengthened by breathing exercises like Kapalabhati and Anulom Vilom[22] In addition to yoga, additional non-pharmacological treatments including physical therapy and fitness regimens like Pilates, tai chi, and resistance training aid to improve mobility, preserve muscular strength, and lessen bradykinesia, or slowness of movement[23] For voice modulation and swallowing issues that may develop in later stages of Parkinson's disease, speech therapy—including Lee Silverman Voice Treatment (LSVT)-is helpful[24] Focus, emotional resilience, and cognitive decline can all be improved with cognitive training and mindfulness exercises. Nutrition and food are also important; a Mediterranean diet high in fiber, omega-3 fatty acids, and antioxidants

supports brain function and helps with digestive problems that are typical in Parkinson's disease.

When combined with traditional treatments, these non-pharmacological methods can greatly enhance mental, emotional, and physical health, which will ultimately improve the quality of life for those with Parkinson's disease.

In experimental Parkinson's disease, phytochemicals may offer neuroprotection by reducing oxidative stress and mitochondrial dysfunction and by triggering autophagy to break down harmful α-synuclein molecules. The neuroprotective properties and modes of action of recently discovered naturally occurring phytochemicals that target oxidative stress and neurodegeneration at the cellular and molecular levels throughout the progression of Parkinson's disease are described in this study. Furthermore, we study pharmacological routes associated with autophagy signaling and Nrf2/ARE.[25]

In Parkinson's disease, plant extracts seem to inhibit the oligomerization and fibrillation of α-syn, a novel therapeutic target. In experimental models of Parkinson's disease, plant extracts that have been shown to be neuroprotective target pathogenic stages of α-syn conformations, such as fibrillation and oligomerization.[26] α-syn has been demonstrated to be targeted by plant extracts in Parkinson's disease models, frequently in vitro. Nevertheless, it is unknown which bioactive components are involved in this effect. In Parkinson's disease caused by A53T α-syn in Caenorhabditis elegans, *Bacopa monnieri* prevents neurodegeneration.[27]

In addition to reducing proinflammatory cytokines (such as prostaglandin E2, interleukin-6, interleukin-1β, and nuclear factor-κB), phytochemicals also inhibit apoptosis, reduce dopaminergic neuronal loss and depletion, and alter nuclear and cellular inflammatory signaling[28] In the treatment of Parkinson's disease, natural chemicals produced from plants may be employed as adjuvants or as pharmaceutical drugs in the future, in addition to conventional therapy approaches, to increase effectiveness and reduce psychological adverse effects. To evaluate phytochemicals' potential as future drugs for the treatment of neurodegenerative diseases, well-designed clinical trials are necessary to determine their healing and preventative benefits.[29]

Although the underlying mechanism is yet unknown, cumulative data has shown that phytochemicals as nutraceuticals can enhance the status of NDs. One study claim that

phytochemicals' anti-oxidative and radical-scavenging properties help to ameliorate the disease Although phytochemicals' exact biological targets are unknown, it is hypothesized that they may be triggering stress response pathways that the cells will use as a defence because they are unable to carry out their function by just altering gene expression and enzyme metabolism.[31]

According to an alternative idea, phytochemicals function as ligands, binding to particular receptors on the nucleus or cell membranes before functioning in a downward signal transduction cascade and exhibiting their antioxidant properties.[32]

The use of dopamine agonists and levodopa to treat motor symptoms in Parkinson's disease at any stage is well supported by research(31). While clozapine works well for hallucinations, dopamine agonists and dopamine metabolism inhibitors are better for motor disorders.[33] Pramipexole, cholinesterase inhibitors, and antidepressants may help reduce the symptoms of dementia.[34] It's unclear how well different therapies work for both motor and nonmotor traits.[35]

Nowadays, numerous drugs are formulated using nanoparticles (NP), which offers a number of benefits over traditional therapies.[34] Because of its size and makeup, this type of multifunctional carrier interacts differently with biological systems, which can reduce its ability to cross the blood-brain barrier, target drug delivery, boost bioavailability at the site of action, reduce dosage, and cause side effects.[36]

NP enhances therapeutic efficacy and biodistribution, reduces drug toxicity, conceals physicochemical characteristics, increases bioavailability, and provides controlled drug release. Analysing prolonged-release systems and the NP's transit into the brain is also essential for PD in order to determine whether a formulation actually crosses the blood-brain barrier, is deposited in the brain, and releases the drug or merely adheres to the lumen.[37]

No scientifically proven treatments exist to stop or prevent the progression of the condition.[38] For early Parkinson's disease, non-ergot dopamine agonists, oral levodopa formulations, selegiline, and rasagiline are clinically advantageous when used as monotherapy.[39] For early or stable Parkinson's disease, zonisamide, rasagiline, and non-ergot dopamine agonists are clinically effective adjuvant therapies. While physiotherapy is clinically valuable, rivastigmine may be useful as an adjuvant therapy in optimized

Parkinson's disease for general or specific motor symptoms, including gait; structured patterned exercises and exercise-based movement strategy training may also be helpful.[40]

Regarding the prevention or delay of motor disorders, no new research has been conducted, and the findings have not been altered.[41] For motor fluctuations, the majority of non-ergot dopamine agonists, including pergolide, levodopa ER, levodopa intestinal infusion, entacapone, opicapone, rasagiline, zonisamide, safinamide, bilateral STN, and GPi DBS, are clinically helpful. Dyskinesia can be effectively treated with amantadine, clozapine, bilateral STN DBS, and GPi DBS.[42]

Parkinson's disease is a complicated condition that can progress quickly or slowly. Both pharmaceutical (often levodopa formulations taken with or without other medications) and nonpharmacologic (exercise and physical, occupational, and speech therapies) treatments are used in treatment. Levodopa-carbidopa enteral suspension with deep brain stimulation can help those with drug-resistant tremors, dyskinesias, and worsening symptoms when the medication wears off.[43]

- **Pathophysiological Models of Parkinson's Disease**

In order to comprehend the pathophysiology of Parkinson's disease (PD), test potential treatments, and track the disease's development, models are essential.[44] With their own advantages and disadvantages, these models can be generically divided into three categories: computational, cellular, and animal models. There are alpha-synuclein-based, genetic, and toxin-induced animal models. PD symptoms are mimicked by toxicity-induced models that preferentially destroy dopaminergic neurons, such as 6-hydroxydopamine (6-OHDA)(45), MPTP.[46] rotenone[47] and paraquat[48] however they frequently lack essential characteristics like Lewy bodies. Genetic models reproduce familial Parkinson's disease (PD) mutations, including SNCA (alpha-synuclein), LRRK2, PINK1, Parkin, DJ-1, and GBA.[49] These mutations impact dopamine neurons through different ways, such as protein aggregation or mitochondrial failure. The spread of alpha-synuclein pathology is mimicked by other models, including viral vector models and preformed fibril (PFF) models.

Cellular models provide controlled settings for molecular research; organoids or 3D cultures offer more physiologically relevant systems; dopaminergic neuron cultures offer straightforward but efficient platforms for toxicity screening; and induced pluripotent stem cells (iPSCs) enable patient-specific studies.[50] Simulating brain activity, genetic

relationships, and pharmacological responses, computational models including neural network models, systems biology models, and pharmacokinetic/pharmacodynamic (PK/PD) models help create new treatments.[51] A combination of these methods is frequently required for a thorough grasp of Parkinson's disease pathogenesis and treatment options, as each model captures distinct facets of the condition.

While each model of Parkinson's disease offers distinct insights, none of them accurately depicts the illness. Computational models enhance medication development and predictive knowledge, cellular models provide molecular insights, and animal models aid in the study of neurodegeneration and motor impairments. In order to thoroughly investigate Parkinson's disease and create efficient treatments, a multi-model approach is necessary.

- **Different models used in PD**

**1. Animal Models**

To better understand neurodegeneration and possible therapies, researchers use animal models that replicate the pathology and symptoms of Parkinson's disease. Toxin-induced models, genetic models, and alpha-synuclein models are the three primary types.[52]

**A. Toxin-Induced Models**

In these models, elements of Parkinson's disease are replicated by selectively damaging dopaminergic neurons using neurotoxins.[53]

**1. 6-Hydroxydopamine (6-OHDA) Model**

Among the most popular and well-established experimental models for researching Parkinson's disease (PD), the 6-hydroxydopamine (6-OHDA) model focuses on the nigrostriatal dopaminergic pathway's degradation. Due to its active absorption by dopamine and norepinephrine transporters, 6-OHDA, a hydroxylated analog of dopamine, shows preferential toxicity toward catecholaminergic neurons. When 6-OHDA is injected intracerebrally, usually into the striatum, medial forebrain bundle (MFB), or substantia nigra pars compacta (SNc), it produces a lot of reactive oxygen species (ROS), which leads to oxidative stress, mitochondrial malfunction, and eventually the death of dopaminergic neurons. This specific neurodegeneration closely resembles the bradykinesia, stiffness, and postural instability that are motor deficits seen in Parkinson's disease.[45]

Rapid onset and reproducibility are two of the 6-OHDA model's main benefits, which enable researchers to quickly and carefully examine motor dysfunctions. Additionally, the site and injection dose can be used to fine-tune the severity of the lesion, giving the option to imitate partial or complete dopaminergic denervation. Assessing the effectiveness of dopaminergic replacement treatments like L-DOPA, testing neuroprotective drugs, and examining the part oxidative stress plays in the pathophysiology of Parkinson's disease are all common uses for the animal.[54]

**2. 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) Model**

The 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) model is one of the most established experimental systems for investigating Parkinson's disease (PD), especially dopaminergic neurodegeneration. MPTP is a lipophilic molecule that readily crosses the blood-brain barrier following systemic administration. Once in the brain, it is metabolized by monoamine oxidase-B (MAO-B) in glial cells to its toxic metabolite, 1-methyl-4-phenylpyridinium ion ($MPP^+$). $MPP^+$ is selectively taken up by dopaminergic neurons via the dopamine transporter (DAT), where it accumulates in mitochondria and inhibits complex I of the electron transport chain. This results in severe ATP depletion, oxidative stress, and ultimately dopaminergic neuronal death. The MPTP model effectively mimics the profound dopamine loss observed in PD and leads to motor symptoms such as bradykinesia, rigidity, and postural instability.[55]

**3. Rotenone Model**

The pathogenesis of Parkinson's disease (PD), specifically mitochondrial dysfunction and oxidative stress-induced neurodegeneration, can be replicated experimentally using the rotenone model. Naturally occurring rotenone is a lipophilic insecticide that easily penetrates the blood-brain barrier and specifically blocks dopaminergic neurons' mitochondrial complex I activity. This inhibition causes oxidative stress, mitochondrial malfunction, and ultimately neuronal death by interfering with the synthesis of ATP and increasing reactive oxygen species (ROS) levels. Chronic systemic or direct brain infusion of low doses of rotenone replicates important clinical aspects of Parkinson's disease (PD), such as the creation of intracellular α-synuclein aggregates that resemble Lewy bodies and the selective loss of nigrostriatal dopaminergic neurons.[56]

### 4. Paraquat and Maneb Models

Experimental methods for examining the role of the environment in the pathophysiology of Parkinson's disease (PD) include the paraquat and maneb models. Environmental pollutants such as the common herbicide paraquat and the fungicide maneb have been linked in epidemiological studies to the development of Parkinson's disease. Maneb mostly damages mitochondrial activity and antioxidant defences, whereas paraquat causes oxidative stress in animal models by producing reactive oxygen species (ROS). These substances, when taken separately or in combination, cause damage to specific dopaminergic neurons in the substantia nigra, which results in striatal dopamine depletion and motor dysfunctions. Particularly noteworthy is the synergistic impact of co-administration of paraquat and maneb, which results in increased neurotoxicity as compared to either drug alone.[57] The paraquat and maneb models' ability to accurately simulate environmental exposures that may be linked to Parkinson's disease (PD) and offer insights into how chronic toxin exposure may influence the start and course of the disease is one of its main advantages.[58]

## B. Genetic Models

Mutations associated with familial Parkinson's disease are replicated in genetic models.[59]

### 1. Alpha-Synuclein (SNCA) Models

The genetic models of Parkinson's disease (PD) that have been explored the most are alpha-synuclein (SNCA) models. The pathological aggregation of alpha-synuclein and the development of Lewy body-like inclusions are caused by either overexpression of wild-type alpha-synuclein or expression of mutant versions (such as A53T, A30P, or E46K alterations). Alpha-synuclein aggregation, a crucial molecular characteristic of Parkinson's disease, may be mimicked by SNCA models, which makes them useful instruments for researching early clinical alterations.[60]

### 2. LRRK2 Models

The most prevalent genetic cause of both familial and sporadic Parkinson's disease is mutations in the leucine-rich repeat kinase 2 (LRRK2) gene, namely the G2019S mutation. In most LRRK2 models, particular mutations are knocked in or mutant LRRK2 is overexpressed, resulting in dopaminergic dysfunction and altered neural signaling pathways. Because these models are relevant to human hereditary Parkinson's disease, they are extremely beneficial for drug development and therapeutic trials. However, LRRK2 transgenic mice frequently only exhibit inconsistent dopaminergic neuron loss and weak or

incomplete motor impairment, which limits their usefulness in accurately simulating the course of the illness. LRRK2 models are nevertheless essential for researching kinase inhibitors and other targeted treatments in spite of these difficulties.[61]

### 3. PINK1/Parkin/DJ-1 Models

Autosomal recessive early-onset Parkinson's disease is linked to the genes PINK1, Parkin, and DJ-1; models including these genes mostly concentrate on oxidative stress and mitochondrial malfunction. Mutations in DJ-1 decrease the cellular response to oxidative stress, while mutations in PINK1 or Parkin hinder mitophagy, all of which increase neuronal susceptibility. PINK1/Parkin/DJ-1 knockout animals successfully reproduce stress responses and mitochondrial defects associated with the pathophysiology of Parkinson's disease. However, there is frequently no discernible loss of dopaminergic neurons in these animals, and neurodegeneration is usually only mild or delayed. Therefore, they are less appropriate for reproducing the entire neurodegenerative profile of Parkinson's disease, even though they are very instructive for researching mitochondrial pathways.[62]

### 4. GBA Models (Glucocerebrosidase Mutations)

The lysosomal enzyme glucocerebrosidase is encoded by the GBA gene, and mutations in this gene are known to be important genetic risk factors for Parkinson's disease. GBA models link lysosomal dysfunction to the pathophysiology of Parkinson's disease by simulating decreased lysosomal function, which leads to the buildup of alpha-synuclein and other autophagic substrates. These models are especially helpful for investigating the relationship among neurodegeneration, autophagy, and alpha-synuclein clearance. However, a persistent drawback of GBA models is that they usually exhibit just a small amount of dopaminergic neuron loss, which restricts their capacity to mimic the progressive motor decline seen in PD patients. Nevertheless, they offer a crucial framework for creating treatments that target alpha-synuclein aggregation and lysosomal pathways.[63]

## C. Alpha-Synuclein Preformed Fibril (PFF) and Viral Models

### 1. Preformed Fibrils (PFF) Model

A potent method for simulating the pathophysiology of Parkinson's disease (PD) in experimental animals is the preformed fibrils (PFF) model. This method involves injecting synthetic alpha-synuclein fibrils into particular brain areas, which causes the endogenous alpha-synuclein to misfold, clump together, and spread like a prion throughout the nervous system. This model accurately replicates a number of important aspects of Parkinson's

disease, such as the loss of dopaminergic neurons and increasing alpha-synuclein pathology. The PFF model's capacity to replicate the temporal and spatial spread of PD pathology, closely mirroring the course of the disease in individuals, is one of its main advantages. The heterogeneity seen between species and even within strains, which results in irregularities in disease onset and severity, is one of its drawbacks. The PFF model is nevertheless very useful for researching the processes of illness progression and evaluating anti-aggregation treatments.[64]

### 2. Viral Vector Models

In viral vector models, human genes linked to Parkinson's disease, like wild-type or mutant alpha-synuclein, are delivered and expressed directly into specific neuronal populations via viruses, most frequently adeno-associated virus (AAV) vectors. These models are very versatile for researching gene-specific contributions to Parkinson's disease pathogenesis because they provide exact spatial and temporal control over gene expression. Viral vector models have a significant advantage in that they can cause strong and localized overexpression of pathogenic proteins, which results in the death of dopaminergic neurons and motor impairments that resemble the symptoms of Parkinson's disease in humans. However, a significant drawback is that viral-mediated overexpression can produce supraphysiological protein levels, which might not fairly represent the gradual, progressive character of sporadic Parkinson's disease.[65]

### 3. Cellular Models

For examining the molecular processes behind Parkinson's disease (PD) and for vetting possible treatment candidates, cellular models are essential resources. These models allow for controlled experimental manipulation by simulating particular characteristics of Parkinson's disease pathology using cultured neuronal or glial cells. Cellular models provide quick, inexpensive, and highly adaptable platforms for researching disease processes at the cellular and molecular levels, despite not having all the complexity of in vivo systems.[66]

### A. Induced Pluripotent Stem Cells (iPSCs)

Induced pluripotent stem cells (iPSCs) represent a groundbreaking advancement in modelling Parkinson’s disease. iPSCs are generated by reprogramming patient-derived somatic cells, such as skin fibroblasts or blood cells, into pluripotent stem cells, which can then be differentiated into dopaminergic neurons. This approach enables the creation of personalized disease models that reflect the genetic and molecular background of individual patients. A

major strength of iPSC-based models lies in their utility for drug screening, disease modelling, and understanding genetic contributions to PD. However, the process is both expensive and time-consuming, and variability in differentiation efficiency remains a significant technical challenge. Despite these limitations, iPSC technology holds great promise for advancing personalized medicine in Parkinson's disease.[67]

### B. Dopaminergic Neuron Cultures

The biology of Parkinson's disease is often studied using primary dopaminergic neuron cultures, which are usually produced from human stem cells or the embryonic ventral mesencephalon of rats. Under regulated circumstances, these cultures offer a rather easy-to-use and accessible method for examining neuronal function, neurotoxicity, and neuroprotection. For toxicological investigations including exposure to PD-associated poisons like MPTP or rotenone, they are very helpful. Dopaminergic neuron cultures provide several benefits, including cost-effectiveness, excellent repeatability, and ease of manipulation. The lack of the intricate brain microenvironment, which includes glial interactions and vascular components and is crucial to the pathophysiology of Parkinson's disease, is a significant drawback. Therefore, when extrapolating results from dopaminergic neuron cultures to the in vivo setting, care must be used.[68]

### C. Organoids and 3D Cultures

A major advancement in the creation of more physiologically accurate models of Parkinson's disease has been made with the creation of brain organoids and three-dimensional (3D) neuronal cultures. Organoids are stem cell-derived, miniature, self-organizing structures that can replicate features of the cellular variety and architecture of the brain. When compared to conventional two-dimensional cultures, these models provide a more realistic depiction of the cellular environment in vivo. They make it possible to investigate dopaminergic neuron loss, alpha-synuclein aggregation, and neural network creation in a more natural setting. However, the study of organoids is still in its infancy, and issues including batch variability, lack of vascularization, and uniformity make it difficult to use them widely. However, brain organoids and 3D cultures have a lot of potential for PD research and treatment trials in the future.[69]

## 4. Computational Models

In the study of Parkinson's disease (PD), computational models have emerged as useful instruments that offer platforms for simulating the course of the disease, neuronal dynamics,

and treatment approaches. Computational methods provide insights into the intricate mechanisms behind Parkinson's disease (PD) and aid in the creation of novel theories and therapeutic approaches by fusing biological data with mathematical frameworks. Computational models are becoming more and more crucial for improving experimental designs, forecasting results, and minimizing the need for lengthy animal testing, even if they cannot completely replace biological studies.[70]

### A. Neural Network Models

Neural network models mimic the activity of dopaminergic neurons and the larger circuits of the basal ganglia linked to Parkinson's disease by using mathematical formulas and computer algorithms. These models aid in forecasting how changes in neuronal firing patterns, motor dysfunction, and symptom manifestation may result from disturbances in dopamine signaling. Capturing dynamic neuronal interactions and testing the effects of different disease states or therapies in silico are two of neural network models' main advantages. One significant drawback, though, is that they frequently oversimplify the brain's cellular heterogeneity and extremely complicated biological processes, which could reduce the precision of their predictions. Neural network models, however, are useful for investigating theoretical therapy approaches and comprehending circuit-level dysfunctions.[53]

### B. Systems Biology Models

Systems biology models apply computational techniques to large-scale biological datasets, such as genomics, transcriptomics, proteomics, and metabolomics, to map and analyse the intricate networks of gene and protein interactions involved in Parkinson’s disease. These models enable researchers to identify critical molecular pathways, predict disease biomarkers, and uncover potential drug targets that may not be evident through traditional experimental approaches. A significant advantage of systems biology models is their ability to integrate multi-omics data, providing a holistic view of PD pathogenesis. However, these models require extensive, high-quality datasets, and their predictive power heavily depends on the completeness and accuracy of the input data. Despite these challenges, systems biology approaches are increasingly recognized for their potential to accelerate therapeutic discovery in PD.[71]

### D. Pharmacokinetic and Pharmacodynamic (PK/PD) Models

Essential computational tools for simulating how drugs are absorbed, distributed, metabolized, and excreted (pharmacokinetics) and how they affect disease symptoms

(pharmacodynamics) in the context of Parkinson's disease are pharmacokinetic and pharmacodynamic (PK/PD) models. The time-course of pharmacological efficacy and adverse effects is evaluated, therapeutic responses are predicted, and drug dosage schedules are optimized with the use of these models. The ability to improve personalized medicine tactics and refine clinical trial designs is one of PK/PD models' main advantages. However, precise experimental validation and thorough biological knowledge are prerequisites for their dependability. Therefore, in PD treatments, PK/PD modelling is an essential link between preclinical results and clinical translation.

- **Herbs as Hope: Implementing Plant-Based Therapeutics to Combat Parkinson's Disease**

In the quest for innovative PD treatments, herbal medicines have shown great promise. Medicinal plants, which are abundant in a variety of phytochemicals, including polyphenols, alkaloids, flavonoids, and terpenoids, have a range of pharmacological actions that can help with the intricate pathophysiology of Parkinson's disease.[72] Antioxidative, anti-inflammatory, anti-apoptotic, neurotrophic, and mitochondrial-protective properties are among them. Many herbs have been used historically in many traditional medical systems, and preclinical research has shown that they have neuroprotective qualities, indicating that they may be used as alternative or supplementary treatments for Parkinson's disease.[73]

Essential botanicals that have demonstrated encouraging outcomes in reducing oxidative stress, preventing neuroinflammation, safeguarding dopaminergic neurons, and enhancing motor functions in experimental models include *Mucuna pruriens* (natural source of L-DOPA), *Withania somnifera* (ashwagandha), *Curcuma longa* (turmeric), *Ginkgo biloba*, and *Bacopa monnieri*. Additionally, it has been proposed that certain herbal extracts may alter gut microbiome, a newly discovered therapeutic target in Parkinson's disease.

The clinical translation of herbal medicines is still in its infancy, despite the promising preclinical data. This calls for carefully planned trials, extract standardization, and pharmacokinetic analyses. However, botanicals' multi-targeted therapeutic potential makes them attractive options for the creation of integrative approaches to the treatment of Parkinson's disease.[74]

- **Botanical Neuroprotectants in Parkinson's Disease: Insights and Innovations.**
- **Table- 3 Botanical Neuroprotectant plants.**

| Scientific Name | Image | Common Name | Key Compounds | Therapeutic Benefits | Role in Parkinson's Disease |
|---|---|---|---|---|---|
| *Bacopa monnieri* |  | Brahmi | Bacosides | Neuroprotective, memory-enhancing, anti-inflammatory | Reduces oxidative stress and neuroinflammation, improves cognitive function |
| *Mucuna pruriens* |  | Velvet bean | Levodopa, antioxidants | Anti-inflammatory, enhances locomotion | Contains natural levodopa, improves motor functions in PD |
| *Withania somnifera* |  | Ashwagandha | Withanolides, alkaloids | Anti-anxiety, neuroprotective, anti-inflammatory | Increases glutathione (GSH) levels, reduces oxidative stress in PD models |
| *Curcuma longa* |  | Turmeric | Curcumin | Antioxidant, neuroprotective, anti-inflammatory | Enhances dopamine levels, prevents neuronal death |
| *Ginkgo biloba* |  | Ginkgo | Flavonoids, terpenoids | Neuroprotective, cognitive enhancer, anti-aging | Improves locomotion, muscle coordination, and decreases behavioral impairments |
| *Camellia sinensis* |  | Tea plant (Green & Black Tea) | Polyphenols, catechins, theaflavin | Antioxidant, neuroprotective, anti-inflammatory | Reduces risk of PD, black tea protects DA-ergic neurons, enhances TH expression in SN region |
| *Zingiber officinale* |  | Ginger | Gingerol, shogaol | Anti-inflammatory, neuroprotective, improves digestion | Reduces neuroinflammation and oxidative stress in PD models |
| *Vitis vinifera* |  | Grapeseed | Resveratrol, flavonoids | Antioxidant, neuroprotective, anti-aging | Protects neurons from oxidative damage, enhances mitochondrial function in PD models |
| *Centella asiatica* |  | Gotu Kola | Asiaticoside, madecassoside | Cognitive enhancer, neuroprotective, anti-inflammatory | Enhances neuronal survival, reduces oxidative stress and neuroinflammation in PD |

| | | | | | |
|---|---|---|---|---|---|
| *Citrus sinensis* |  | Orange Peel | Flavonoids, vitamin C | Antioxidant, anti-inflammatory, immune booster | Prevents neuronal damage by reducing oxidative stress and inflammation in PD |
| *Rosmarinus officinalis* |  | Rosemary | Carnosic acid, rosmarinic acid | Antioxidant, cognitive enhancer, neuroprotective | Enhances brain function, protects neurons from damage in PD models |
| *Panax ginseng* |  | Ginseng | Ginsenosides | Anti-inflammatory, cognitive enhancer, neuroprotective | Inhibits neurodegeneration, modulates neurotransmitter activity in PD |
| *Ocimum sanctum* |  | Holy Basil (Tulsi) | Eugenol, ursolic acid | Antioxidant, anti-inflammatory, neuroprotective | Reduces oxidative stress, prevents dopaminergic neuron loss in PD models |
| *Allium sativum* |  | Garlic | Allicin, sulfur compounds | Anti-inflammatory, antioxidant, neuroprotective | Protects neurons from oxidative damage, enhances mitochondrial function in PD |

*Brahmi*, also known as *Bacopa monnieri* (Bm), is a perennial plant that has antibacterial, anti-inflammatory, antioxidant, neuroprotective, and memory-boosting properties[75] In transgenic and toxin-induced models, Bm extract (BME) has anti-parkinsonian characteristics, suggesting that it may be used to treat Parkinson's disease (PD)[76]

Ayurveda has traditionally utilized the tropical bean *Mucuna pruriens* (Mp) to treat Parkinson's disease because of its high concentration of levodopa, which is thought to be the most effective treatment for the condition. In addition to levodopa, the other ingredients in Mp may also have therapeutic benefits, enhancing locomotor behaviour in humans and animal models.[77]

*Withania somnifera* (Ws), popularly referred to as ashwagandha, is a well-known nerve tonic that enhances memory and has anti-inflammatory and antioxidant qualities. By increasing the levels of glutathione (GSH) and glutathione peroxidase (GPx), Ws root extract restores oxidative stress in MPTP-induced Parkinson's disease rats.[78]

Turmeric, or *Curcuma longa* (Cl), includes curcumin, an antioxidant having antidepressant, neuroprotective, and anti-inflammatory properties. In animal models of Parkinson's disease, curcumin has been shown to increase striatal dopamine (DA) levels.[79]

In 6-OHDA-induced PD mice, *ginkgo biloba* (Gb), which possesses anti-aging, neuroprotective, and antioxidant qualities, has been demonstrated to increase muscular coordination and locomotor activity while also attenuating behavioural impairments.[75] The plant that produces black and green tea, Camellia sinensis (Cs), is rich in flavonoids and polyphenols, which have anti-inflammatory, antioxidant, and neuroprotective qualities.[80]

While *black tea* includes theaflavin, which protects dopaminergic neurons and enhances TH (Tyrosine Hydroxylase) expression in the substantia nigra (SN) of 6-OHDA-induced PD rats, green tea consumption reduces the incidence of Parkinson's disease. These plants may be used therapeutically to treat Parkinson's disease because of their exceptional neuroprotective qualities.[81]

Gingerol, shogaol, and zingerone are all found in *Zingiber officinale* (Zo), or ginger, and they all have anti-inflammatory, neuroprotective, and antioxidant qualities. By decreasing α-synuclein aggregation, blocking NF-κB signaling, and reducing microglia activation, phytochemicals can shield dopaminergic neurons from degeneration in Parkinson's disease. Additionally, Zo reduces intestinal dysbiosis and enhances mitochondrial function, both of which are connected to the advancement of Parkinson's disease.[82]

High concentrations of resveratrol, quercetin, catechins, and anthocyanins—all of which have neuroprotective, antioxidant, and anti-apoptotic properties- are found in *Vitis vinifera* (Vv), commonly referred to as grapevine. By activating SIRT1, resveratrol reduces oxidative stress and neuroinflammation while promoting mitochondrial biogenesis. Additionally, it prevents PD-associated neurotoxicity by protecting the integrity of the blood-brain barrier and inhibiting α-synuclein fibrillation.[83]

The chemicals asiaticoside, madecassoside, and centelloside, which are found in *Centella asiatica* (Ca), commonly referred to as gotu kola, have synaptogenic, neuroprotective, and cognitive-enhancing properties.[84] Through BDNF signaling, these phytochemicals enhance neurogenesis, inhibit pro-inflammatory cytokines (TNF-α and IL-6), and lessen oxidative

stress. Through its effects on dopamine metabolism, calcium has been shown to improve motor deficits in animals with Parkinson's disease.[85]

The flavonoids hesperidin and naringenin, limonene, and vitamin C found in *Citrus sinensis* (Cs), commonly referred to as sweet orange, have anti-inflammatory, antioxidant, and mitochondrial-protective qualities. By lowering oxidative stress-induced DA neuron loss, modifying Nrf2/HO-1 signaling, and preventing α-synuclein aggregations, these medications slow the progression of Parkinson's disease.[86]

Rosemary, or *Rosmarinus officinalis* (Ro), contains ursolic acid, carnosic acid, and rosmarinic acid, all of which have dopaminergic neuroprotective, mitochondrial, and anti-inflammatory properties. Ro is helpful in models of Parkinson's disease because it controls Nrf2 signaling, inhibits MAO-B activity (which degrades dopamine), and lowers neurotoxic glutamate excitotoxicity.[87]

Ginsenosides (Rg1, Rb1, Re) found in *Panax ginseng* (Pg), sometimes referred to as ginseng, have neuroprotective, anti-inflammatory, and antioxidant qualities(75). Pg increases dopamine release via protecting nigrostriatal neurons, inhibiting apoptosis through the PI3K/Akt pathway, and modulating NF-κB to decrease neuroinflammation. In animals with Parkinson's disease, it has been demonstrated in experiments to enhance motor performance and stop DA depletion.[88]

Eugenol, ursolic acid, and flavonoids- which are antioxidants, mitochondrial defenders, and dopaminergic enhancers—are found in *Ocimum sanctum* (Os), also referred to as holy basil (Tulsi). These medications increase dopamine production by controlling TH expression, decrease neuroinflammation by inhibiting COX-2, and stop α-synuclein aggregation.[89]

Allicin, S-allyl cysteine, and diallyl sulfide are components of *Allium sativum* (As), commonly referred to as garlic, and they have anti-inflammatory, detoxifying, and neuroprotective qualities. In order to prevent neurotoxicity linked to Parkinson's disease, Nrf2 activation reduces oxidative stress in DA neurons, inhibits α-synuclein aggregation, and increases glutathione (GSH) levels.[90]

Phytochemicals obtained from medicinal plants target several molecular pathways involved in the pathophysiology of Parkinson's disease (PD), exhibiting neuroprotective qualities. These include NF-κB and TNF-α signaling to reduce neuroinflammation, the Nrf2 pathway to

fight oxidative stress, the activation of SIRT1 and PGC-1α to restore mitochondrial function, and the regulation of dopamine metabolism enzymes like MAO-B and tyrosine hydroxylase (TH) to maintain dopaminergic signaling. According to these multi-targeted activities demonstrate the therapeutic potential of natural substances in the management of Parkinson's disease.[75]

## ➢ CONCLUSION

Parkinson's disease arises from the convergence of multiple pathological processes, including mitochondrial dysfunction, oxidative stress, neuroinflammation, impaired proteostasis, and dopaminergic neuronal loss. Genetic mutations, environmental factors, and gut-brain axis disruptions further exacerbate disease progression through interconnected molecular pathways. Advances in experimental models and molecular research have uncovered new therapeutic targets beyond dopamine replacement. Plant-derived bioactive compounds offer promising neuroprotective strategies by targeting oxidative and inflammatory cascades and stabilizing mitochondrial function. Although current animal models provide valuable mechanistic insights, limitations persist in replicating the full spectrum of human PD pathology. Moving forward, personalized, multi-targeted therapies integrating pharmacological agents, natural products, and lifestyle interventions hold the greatest promise for altering disease course and improving patient outcomes.

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## REFERENCES

1. DeLong MR, Wichmann T. Circuits and Circuit Disorders of the Basal Ganglia. Arch Neurol., 2007 Jan 1; 64(1): 20.
2. Stefanis L. -Synuclein in Parkinson's Disease. Cold Spring Harbor Perspectives in Medicine., 2012 Feb 1; 2(2): a009399–a009399.
3. Ulrich D, Bettler B. GABAB receptors: synaptic functions and mechanisms of diversity. Current Opinion in Neurobiology, 2007 Jun; 17(3): 298–303.

4. Romano MF. FKBPs: opportunistic modifiers or active players in cancer? Current Opinion in Pharmacology, 2011 Aug; 11(4): 279–80.
5. Balestrino R, Schapira AHV. Parkinson disease. Euro J of Neurology., 2020 Jan; 27(1): 27–42.
6. Armstrong MJ, Okun MS. Diagnosis and Treatment of Parkinson Disease: A Review. JAMA, 2020 Feb 11; 323(6): 548.
7. Aarsland D, Batzu L, Halliday GM, Geurtsen GJ, Ballard C, Ray Chaudhuri K, et al. Parkinson disease-associated cognitive impairment. Nat Rev Dis Primers., 2021 Jul 1; 7(1): 47.
8. Ni A, Ernst C. Evidence That Substantia Nigra Pars Compacta Dopaminergic Neurons Are Selectively Vulnerable to Oxidative Stress Because They Are Highly Metabolically Active. Front Cell Neurosci., 2022 Mar 4; 16: 826193.
9. Bhuvaneswari A, Legapriyadharshini N, Thirumaraikumari T, Rukmani Devi S, Pandiaraj S. Genetic Determinants of Parkinson's Disease: SNCA and LRRK2 in Focus. In: Kumar A, Ahuja S, Baliyan A, Anavatti S, Anand A, editors. Advances in Medical Technologies and Clinical Practice [Internet]. IGI Global, 2024 [cited 2025 May 2]; 199–214. Available from: https://services.igi-global.com/resolvedoi/resolve.aspx?doi=10.4018/979-8-3693-1115-8.ch011
10. Zhang QS, Heng Y, Yuan YH, Chen NH. Pathological α-synuclein exacerbates the progression of Parkinson's disease through microglial activation. Toxicology Letters., 2017 Jan; 265: 30–7.
11. Breen DP, Halliday GM, Lang AE. Gut–brain axis and the spread of α-synuclein pathology: Vagal highway or dead end? Movement Disorders., 2019 Mar; 34(3): 307–16.
12. Tolosa E, Garrido A, Scholz SW, Poewe W. Challenges in the diagnosis of Parkinson's disease. The Lancet Neurology., 2021 May; 20(5): 385–97.
13. Bellucci A, Bubacco L, Longhena F, Parrella E, Faustini G, Porrini V, et al. Nuclear Factor-κB Dysregulation and α-Synuclein Pathology: Critical Interplay in the Pathogenesis of Parkinson's Disease. Front Aging Neurosci., 2020 Mar 24; 12: 68.
14. Dolatshahi M, Ranjbar Hameghavandi MH, Sabahi M, Rostamkhani S. Nuclear factor-kappa B (NF-κB) in pathophysiology of Parkinson disease: Diverse patterns and mechanisms contributing to neurodegeneration. Eur J of Neuroscience, 2021 Jul; 54(1): 4101–23.

15. Zaman V, Shields DC, Shams R, Drasites KP, Matzelle D, Haque A, et al. Cellular and molecular pathophysiology in the progression of Parkinson's disease. Metab Brain Dis., 2021 Jun; 36(5): 815–27.
16. Corti O, Lesage S, Brice A. What Genetics Tells us About the Causes and Mechanisms of Parkinson's Disease. Physiological Reviews., 2011 Oct; 91(4): 1161–218.
17. Pandit AK, Vibha D, Srivastava AK, Shukla G, Goyal V, Behari M. Complementary and alternative medicine in Indian Parkinson's disease patients. Journal of Traditional and Complementary Medicine, 2016 Oct; 6(4): 377–82.
18. Marsili L, Marconi R, Colosimo C. Treatment Strategies in Early Parkinson's Disease. In: International Review of Neurobiology [Internet]. Elsevier, 2017 2025 Apr 29; 345–60. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0074774217300028
19. Mantovani E, Zucchella C, Argyriou AA, Tamburin S. Treatment for cognitive and neuropsychiatric non-motor symptoms in Parkinson's disease: current evidence and future perspectives. Expert Review of Neurotherapeutics, 2023 Jan 2; 23(1): 25–43.
20. Qureshi AR, Jamal MK, Rahman E, Paul DA, Oghli YS, Mulaffer MT, et al. Non-pharmacological therapies for pain management in Parkinson's disease: A systematic review. Acta Neurol Scand., 2021 Aug; 144(2): 115–31.
21. Suárez-Iglesias D, Santos L, Sanchez-Lastra MA, Ayán C. Systematic review and meta-analysis of randomised controlled trials on the effects of yoga in people with Parkinson's disease. Disability and Rehabilitation, 2022 Oct 9; 44(21): 6210–29.
22. Singh Bal B. Impact of Short-Term Training of Kapalbhati Pranayama on Components of Health-Related Fitness. IntJSCS., 2015 Jan 1; 3(13): 59–59.
23. Nikouei M. Non-pharmacological rehabilitation of Parkinson's disease through exercise therapy and music therapy: A narrative review. Chronic Diseases Journal, 2024 Nov 18; (12 No 4 (2024): 249–60.
24. Marchese MR, Proietti I, Longobardi Y, Mari G, Ausili Cefaro C, D'Alatri L. Multidimensional voice assessment after Lee Silverman Voice Therapy (LSVT®) in Parkinson's disease. Acta Otorhinolaryngol Ital., 2022 Aug; 42(4): 348–54.
25. Balakrishnan R, Azam S, Cho DY, Su-Kim I, Choi DK. Natural Phytochemicals as Novel Therapeutic Strategies to Prevent and Treat Parkinson's Disease: Current Knowledge and Future Perspectives. Buoso E, editor. Oxidative Medicine and Cellular Longevity, 2021 Jan; 2021(1): 6680935.

26. Limanaqi F, Biagioni F, Busceti CL, Ryskalin L, Polzella M, Frati A, et al. Phytochemicals Bridging Autophagy Induction and Alpha-Synuclein Degradation in Parkinsonism. IJMS, 2019 Jul 3; 20(13): 3274.
27. Javed H, Nagoor Meeran MF, Azimullah S, Adem A, Sadek B, Ojha SK. Plant Extracts and Phytochemicals Targeting α-Synuclein Aggregation in Parkinson's Disease Models. Front Pharmacol., 2019 Mar 19; 9: 1555.
28. Zahedipour F, Hosseini S, Henney N, Barreto G, Sahebkar A. Phytochemicals as inhibitors of tumor necrosis factor alpha and neuroinflammatory responses in neurodegenerative diseases. Neural Regen Res., 2022; 17(8): 1675.
29. Shahpiri Z, Bahramsoltani R, Hosein Farzaei M, Farzaei F, Rahimi R. Phytochemicals as future drugs for Parkinson's disease: a comprehensive review. Reviews in the Neurosciences, 2016 Aug 1; 27(6): 651–68.
30. Vo TTT, Chu PM, Tuan VP, Te JSL, Lee IT. The Promising Role of Antioxidant Phytochemicals in the Prevention and Treatment of Periodontal Disease via the Inhibition of Oxidative Stress Pathways: Updated Insights. Antioxidants, 2020 Dec 1; 9(12): 1211.
31. Forni C, Facchiano F, Bartoli M, Pieretti S, Facchiano A, D'Arcangelo D, et al. Beneficial Role of Phytochemicals on Oxidative Stress and Age-Related Diseases. BioMed Research International, 2019 Apr 7; 2019: 1–16.
32. Velmurugan BK, Rathinasamy B, Lohanathan BP, Thiyagarajan V, Weng CF. Neuroprotective Role of Phytochemicals. Molecules, 2018 Sep 27; 23(10): 2485.
33. Factor SA, Friedman JH. The emergin role of clozapine in the treatment of movement disorders. Movement Disorders, 1997 Jul; 12(4): 483–96.
34. Huang Z, Xiao D, Lao Y, Lai X, Huang W, Zhou D. The Significance of Psychological Support in Managing Depression in Parkinson's Disease: Combining Venlafaxine with Pramipexole and Psychological Care. Actas Esp Psiquiatr, 2025 Jan 5; 53(1): 19–25.
35. Connolly BS, Lang AE. Pharmacological Treatment of Parkinson Disease: A Review. JAMA, 2014 Apr 23; 311(16): 1670.
36. Hu K, Chen X, Chen W, Zhang L, Li J, Ye J, et al. Neuroprotective effect of gold nanoparticles composites in Parkinson's disease model. Nanomedicine: Nanotechnology, Biology and Medicine, 2018 Jun; 14(4): 1123–36.
37. Leyva-Gómez G, Cortés H, Magaña JJ, Leyva-García N, Quintanar-Guerrero D, Florán B. Nanoparticle technology for treatment of Parkinson's disease: the role of surface phenomena in reaching the brain. Drug Discovery Today, 2015 Jul; 20(7): 824–37.

38. Paolini Paoletti F, Gaetani L, Parnetti L. The Challenge of Disease-Modifying Therapies in Parkinson's Disease: Role of CSF Biomarkers. Biomolecules, 2020 Feb 19; 10(2): 335.
39. Cerri S, Blandini F. An update on the use of non-ergot dopamine agonists for the treatment of Parkinson's disease. Expert Opinion on Pharmacotherapy, 2020 Dec 11; 21(18): 2279–91.
40. Reilly S, Dhaliwal S, Arshad U, Macerollo A, Husain N, Costa AD. The effects of rivastigmine on neuropsychiatric symptoms in the early stages of Parkinson's disease: A systematic review. Euro J of Neurology, 2024 Feb; 31(2): e16142.
41. Blauwhospers C, Degraafpeters V, Dirks T, Bos A, Haddersalgra M. Does early intervention in infants at high risk for a developmental motor disorder improve motor and cognitive development? Neuroscience & Biobehavioral Reviews. 2007;31(8):1201–12.
42. Fox SH, Katzenschlager R, Lim S, Barton B, De Bie RMA, Seppi K, et al. International Parkinson and movement disorder society evidence-based medicine review: Update on treatments for the motor symptoms of Parkinson's disease. Movement Disorders., 2018 Aug; 33(8): 1248–66.
43. Srivastav S, Fatima M, Mondal AC. Important medicinal herbs in Parkinson's disease pharmacotherapy. Biomedicine & Pharmacotherapy, 2017 Aug; 92: 856–63.
44. Lewis SJG, Barker RA. A pathophysiological model of freezing of gait in Parkinson's disease. Parkinsonism & Related Disorders, 2009 Jun; 15(5): 333–8.
45. Blandini F, Armentero MT, Martignoni E. The 6-hydroxydopamine model: News from the past. Parkinsonism & Related Disorders, 2008 Jul; 14: S124–9.
46. Smeyne RJ, Jackson-Lewis V. The MPTP model of Parkinson's disease. Molecular Brain Research, 2005 Mar; 134(1): 57–66.
47. Sherer TB, Betarbet R, Testa CM, Seo BB, Richardson JR, Kim JH, et al. Mechanism of Toxicity in Rotenone Models of Parkinson's Disease. J Neurosci. 2003 Nov 26; 23(34): 10756–64.
48. Suntres Z. Role of antioxidants in paraquat toxicity. Toxicology. 2002 Oct 30; 180(1): 65–77.
49. Chia SJ, Tan EK, Chao YX. Historical Perspective: Models of Parkinson's Disease. IJMS. 2020 Apr 2; 21(7): 2464.
50. Alberio T, Lopiano L, Fasano M. Cellular models to investigate biochemical pathways in Parkinson's disease. The FEBS Journal, 2012 Apr; 279(7): 1146–55.

51. Derendorf H, Lesko LJ, Chaikin P, Colburn WA, Lee P, Miller R, et al. Pharmacokinetic/Pharmacodynamic Modeling in Drug Research and Development. The Journal of Clinical Pharma, 2000 Dec; 40(12): 1399–418.
52. Jackson-Lewis V, Blesa J, Przedborski S. Animal models of Parkinson's disease. Parkinsonism & Related Disorders, 2012 Jan; 18: S183–5.
53. Bové J, Prou D, Perier C, Przedborski S. Toxin-induced models of Parkinson's disease. Neurotherapeutics, 2005 Jul; 2(3): 484–94.
54. Smith MP, Cass WA. Oxidative stress and dopamine depletion in an intrastriatal 6-hydroxydopamine model of Parkinson's disease. Neuroscience, 2007 Feb; 144(3): 1057–66.
55. Meredith GE, Rademacher DJ. MPTP Mouse Models of Parkinson's Disease: An Update. Journal of Parkinson's Disease, 2011 Feb 1; 1(1): 19–33.
56. Cannon JR, Tapias V, Na HM, Honick AS, Drolet RE, Greenamyre JT. A highly reproducible rotenone model of Parkinson's disease. Neurobiology of Disease, 2009 May; 34(2): 279–90.
57. Qiu X, Wang Q, Hou L, Zhang C, Wang Q, Zhao X. Inhibition of NLRP3 inflammasome by glibenclamide attenuated dopaminergic neurodegeneration and motor deficits in paraquat and maneb-induced mouse Parkinson's disease model. Toxicology Letters, 2021 Oct; 349: 1–11.
58. Cicchetti F, Lapointe N, Roberge-Tremblay A, Saint-Pierre M, Jimenez L, Ficke BW, et al. Systemic exposure to paraquat and maneb models early Parkinson's disease in young adult rats. Neurobiology of Disease, 2005 Nov; 20(2): 360–71.
59. Lim KL, Ng CH. Genetic models of Parkinson disease. Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease, 2009 Jul; 1792(7): 604–15.
60. Delenclos M, Burgess JD, Lamprokostopoulou A, Outeiro TF, Vekrellis K, McLean PJ. Cellular models of alpha-synuclein toxicity and aggregation. Journal of Neurochemistry, 2019 Sep; 150(5): 566–76.
61. Yue Z. LRRK2 in Parkinson's disease: *in vivo* models and approaches for understanding pathogenic roles. The FEBS Journal, 2009 Nov; 276(22): 6445–54.
62. Dodson MW, Guo M. Pink1, Parkin, DJ-1 and mitochondrial dysfunction in Parkinson's disease. Current Opinion in Neurobiology, 2007 Jun; 17(3): 331–7.
63. O'Regan G, deSouza RM, Balestrino R, Schapira AH. Glucocerebrosidase Mutations in Parkinson Disease. JPD, 2017 Aug 8; 7(3): 411–22.

64. Polinski NK, Volpicelli-Daley LA, Sortwell CE, Luk KC, Cremades N, Gottler LM, et al. Best Practices for Generating and Using Alpha-Synuclein Pre-Formed Fibrils to Model Parkinson's Disease in Rodents. JPD, 2018 Jun 13; 8(2): 303–22.
65. Lundstrom K. Viral Vectors in Gene Therapy. Diseases., 2018 May 21; 6(2): 42.
66. Falkenburger BH, Saridaki T, Dinter E. Cellular models for Parkinson's disease. Journal of Neurochemistry, 2016 Oct; 139(S1): 121–30.
67. Ke M, Chong CM, Su H. Using induced pluripotent stem cells for modeling Parkinson's disease. WJSC, 2019 Sep 26; 11(9): 634–49.
68. Mastroeni D, Grover A, Leonard B, Joyce JN, Coleman PD, Kozik B, et al. Microglial responses to dopamine in a cell culture model of Parkinson's disease. Neurobiology of Aging, 2009 Nov; 30(11): 1805–17.
69. Chlebanowska P, Tejchman A, Sułkowski M, Skrzypek K, Majka M. Use of 3D Organoids as a Model to Study Idiopathic Form of Parkinson's Disease. IJMS, 2020 Jan 21; 21(3): 694.
70. Wiecki TV, Frank MJ. Neurocomputational models of motor and cognitive deficits in Parkinson's disease. In: Progress in Brain Research [Internet]. Elsevier; 2010 [cited 2025 May 1]. p. 275–97. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0079612310830146
71. Wood LB, Winslow AR, Strasser SD. Systems biology of neurodegenerative diseases. Integr Biol., 2015; 7(7): 758–75.
72. Srivastav S, Fatima M, Mondal AC. Important medicinal herbs in Parkinson's disease pharmacotherapy. Biomedicine & Pharmacotherapy, 2017 Aug; 92: 856–63.
73. Balakrishnan R, Azam S, Cho DY, Su-Kim I, Choi DK. Natural Phytochemicals as Novel Therapeutic Strategies to Prevent and Treat Parkinson's Disease: Current Knowledge and Future Perspectives. Buoso E, editor. Oxidative Medicine and Cellular Longevity, 2021 Jan; 2021(1): 6680935.
74. Balakrishnan R, Azam S, Cho DY, Su-Kim I, Choi DK. Natural Phytochemicals as Novel Therapeutic Strategies to Prevent and Treat Parkinson's Disease: Current Knowledge and Future Perspectives. Buoso E, editor. Oxidative Medicine and Cellular Longevity, 2021 Jan; 2021(1): 6680935.
75. Koppula S, Kumar H, More SV, Lim HW, Hong SM, Choi DK. Recent Updates in Redox Regulation and Free Radical Scavenging Effects by Herbal Products in Experimental Models of Parkinson's Disease. Molecules, 2012 Sep 26; 17(10): 11391–420.

76. Simpson T, Pase M, Stough C. *Bacopa monnieri* as an Antioxidant Therapy to Reduce Oxidative Stress in the Aging Brain. Evidence-Based Complementary and Alternative Medicine, 2015; 2015: 1–9.
77. Manyam BV, Dhanasekaran M, Hare TA. Neuroprotective effects of the antiparkinson drug *Mucuna pruriens*. Phytotherapy Research, 2004 Sep; 18(9): 706–12.
78. Kulkarni SK, Dhir A. Withania somnifera: An Indian ginseng. Progress in Neuro-Psychopharmacology and Biological Psychiatry, 2008 Jul; 32(5): 1093–105.
79. B. Mythri R, M. Srinivas Bharath M. Curcumin: A Potential Neuroprotective Agent in Parkinson's Disease, 2012 Jan 1; 18(1): 91–9.
80. Yu D, Zhang P, Li J, Liu T, Zhang Y, Wang Q, et al. Neuroprotective effects of Ginkgo biloba dropping pills in Parkinson's disease. Journal of Pharmaceutical Analysis, 2021 Apr; 11(2): 220–31.
81. Chaturvedi RK, Shukla S, Seth K, Chauhan S, Sinha C, Shukla Y, et al. Neuroprotective and neurorescue effect of black tea extract in 6-hydroxydopamine-lesioned rat model of Parkinson's disease. Neurobiology of Disease, 2006 May; 22(2): 421–34.
82. Angelopoulou E, Paudel YN, Papageorgiou SG, Piperi C. Elucidating the Beneficial Effects of Ginger ( *Zingiber officinale* Roscoe) in Parkinson's Disease. ACS Pharmacol Transl Sci., 2022 Oct 14; 5(10): 838–48.
83. Varadharajan V. In silico neuroprotective properties of volatile constituents of grape (Vitis vinifera L.) seed extract against Parkinson's disease. IJCBDD, 2021; 14(2): 87.
84. Pervin M, Unno K, Ohishi T, Tanabe H, Miyoshi N, Nakamura Y. Beneficial Effects of Green Tea Catechins on Neurodegenerative Diseases. Molecules, 2018 May 29; 23(6): 1297.
85. Wong JH, Barron AM, Abdullah JM. Mitoprotective Effects of Centella asiatica (L.) Urb.: Anti-Inflammatory and Neuroprotective Opportunities in Neurodegenerative Disease. Front Pharmacol, 2021 Jun 29; 12: 687935.
86. Palangasinghe PC, Liyanage WK, Wickramasinghe MP, Palangasinghe HR, Shih HC, Shiao MS, et al. Reviews on Asian citrus species: Exploring traditional uses, biochemistry, conservation, and disease resistance. Ecological Genetics and Genomics, 2024 Sep; 32: 100269.
87. Andrade JM, Faustino C, Garcia C, Ladeiras D, Reis CP, Rijo P. *Rosmarinus officinalis* L.: an update review of its phytochemistry and biological activity. Future Sci OA., 2018 Apr; 4(4): FSO283.

88. Kim KH, Lee D, Lee HL, Kim CE, Jung K, Kang KS. Beneficial effects of Panax ginseng for the treatment and prevention of neurodegenerative diseases: past findings and future directions. Journal of Ginseng Research, 2018 Jul; 42(3): 239–47.
89. Singh D, Chaudhuri PK. A review on phytochemical and pharmacological properties of Holy basil (Ocimum sanctum L.). Industrial Crops and Products, 2018 Aug; 118: 367–82.
90. Rakshit D, Nayak S, Kundu S, Angelopoulou E, Pyrgelis ES, Piperi C, et al. The Pharmacological Activity of Garlic ( *Allium sativum* ) in Parkinson's Disease: From Molecular Mechanisms to the Therapeutic Potential. ACS Chem Neurosci., 2023 Mar 15; 14(6): 1033–44.