Pathophysiology to Treatment: A Comprehensive Overview of Parkinson's Disease

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Abstract:

Parkinson's disease (PD) is a chronic and progressive neurodegenerative disorder primarily affecting motor function, accompanied by a broad range of non-motor symptoms. It is the second most prevalent neurodegenerative disease after Alzheimer's and predominantly impacts individuals above 60 years of age. The hallmark feature of PD is the loss of dopaminergic neurons in the substantia nigra, along with the accumulation of Lewy bodies composed of α-synuclein protein aggregates. Clinically, PD is characterized by bradykinesia, resting tremors, rigidity, and postural instability, in addition to cognitive decline, sleep disturbances, and autonomic dysfunction in advanced stages. While current pharmacological and surgical treatments such as levodopa and deep brain stimulation (DBS) provide symptomatic relief, they do not arrest disease progression. Recent advancements in genetics, biomarker discovery, and neuroimaging are paving the way for disease-modifying therapies. This review aims to consolidate recent findings related to PD's epidemiology, pathophysiology, clinical features, diagnostic methods, and therapeutic interventions, including plant-derived compounds and emerging strategies.

Keywords:

Parkinson's disease, neurodegeneration, α-synuclein, dopaminergic neurons, motor symptoms, levodopan.

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1. Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder primarily affecting motor function due to the selective loss of dopaminergic neurons in the substantia nigra pars compacta region of the brain. The resulting dopamine deficiency disrupts the balance of neural circuits in the basal ganglia, leading to the cardinal motor symptoms of PD—bradykinesia, rigidity, resting tremor, and postural instability (Kalia & Lang, 2015; Poewe et al., 2017). PD is the second most prevalent neurodegenerative disorder worldwide after Alzheimer's disease, with a growing incidence attributed to an aging global population (Feigin et al., 2019). It is estimated that over 10 million individuals globally live with PD, and its prevalence is expected to double by 2040 (Dorsey et al., 2018) . Although it was first systematically described by James Parkinson in 1817 in his work "An Essay on the Shaking Palsy," contemporary understanding of its pathophysiology has significantly evolved, highlighting the complex interplay between genetic predispositions and environmental exposures (Parkinson, 1817; Noyce et al., 2016).

The clinical diagnosis of Parkinson's disease is predominantly based on neurological examination and symptomatology, as there is no single definitive laboratory test or biomarker available. Motor symptoms typically begin asymmetrically and progress gradually. Non-motor manifestations—such as anosmia, sleep disturbances, constipation, depression, and cognitive decline—often precede motor features by years and significantly impair quality of life (Chaudhuri et al., 2006; Schapira et al., 2017). Advances in neuroimaging techniques, particularly dopamine transporter SPECT imaging and PET scans, have provided valuable diagnostic support by visualizing dopaminergic function in the basal ganglia (Seibyl et al., 2014). Moreover, pathologically, PD is characterized by the accumulation of α-synuclein aggregates forming Lewy bodies in neurons, which has led to the classification of PD as a synucleinopathy (Spillantini et al., 1998). Current research emphasizes the role of mitochondrial dysfunction, oxidative stress, neuroinflammation, and impaired protein clearance in the disease's pathogenesis (Exner et al., 2012; Surmeier et al., 2017).

Despite extensive research, Parkinson's disease remains incurable. Treatment strategies focus on symptom management and improving patients' quality of life. Pharmacological treatments such as levodopa—the gold standard—alongside dopamine agonists, MAO-B inhibitors, and COMT inhibitors, are used to mitigate motor symptoms by restoring dopaminergic signaling (Oertel & Schulz, 2016; Fox et al., 2018). In advanced cases, surgical interventions like Deep

Brain Stimulation (DBS) offer considerable motor improvement in patients unresponsive to medication (Weaver et al., 2009). Additionally, non-pharmacological therapies, including physical therapy, speech therapy, cognitive training, and exercise, are integral in holistic PD management (Tomlinson et al., 2013). Emerging therapies targeting disease-modifying pathways—such as alpha-synuclein aggregation inhibitors, neuroprotective agents, and gene therapy—are under investigation, but none have yet demonstrated conclusive efficacy in halting disease progression (Mahlknecht et al., 2015). Given the multidimensional nature of Parkinson's disease, ongoing research into its early detection, pathophysiological mechanisms, and novel treatments is critical for developing more effective and personalized approaches to patient care.

2. Etiology of Parkinson's Disease

Parkinson's disease (PD) is a multifactorial neurodegenerative disorder with a largely elusive etiology. Current evidence suggests that both genetic predispositions and environmental influences contribute to its pathogenesis.

2.1. Genetic Factors

Although most cases of PD are sporadic, approximately 10–15% exhibit familial aggregation. Mutations in genes such as *SNCA* (α-synuclein), *LRRK2*, *PARK7*, *PINK1*, and *DJ-1* have been implicated in monogenic forms of the disease. These genes are involved in critical cellular processes like mitochondrial function, protein degradation, and oxidative stress regulation (Bernheimer et al., 1973).

2.2. Environmental Factors

Numerous environmental toxins have been associated with PD. Exposure to pesticides (e.g., paraquat, rotenone), heavy metals, and certain drugs like MPTP have been shown to increase disease risk. Epidemiological studies also suggest a link between rural living, well-water consumption, and farming with elevated PD incidence (Tanner & Goldman, 1996).

2.3. Protein Misfolding and Aggregation

A hallmark of PD is the accumulation of misfolded α-synuclein into Lewy bodies, which disrupt neuronal function and viability. These inclusions are not only characteristic of inherited forms but also appear in idiopathic PD, highlighting the convergence of genetic and environmental influences (Spillantini et al., 1997).

2.4. Oxidative Stress and Mitochondrial Dysfunction

PD pathology has been strongly linked to oxidative damage and mitochondrial impairment. Dopaminergic neurons are particularly vulnerable to reactive oxygen species (ROS), and mitochondrial dysfunction further amplifies this stress, leading to neuronal death (Greene & Harris, 2012).

2.5. Neurotransmitter Imbalance

The cardinal motor symptoms of PD are primarily due to dopamine depletion in the nigrostriatal pathway. However, degeneration of serotonergic, cholinergic, and noradrenergic systems also contributes to the complex non-motor symptoms such as depression, cognitive decline, and sleep disturbances (Walker & Whittlesea, 2011).

2.6. Inflammation and Immune Activation

Neuroinflammation is increasingly recognized as a contributing factor in PD. Activated microglia release inflammatory cytokines and reactive intermediates that exacerbate neuronal injury, forming a feedback loop that promotes disease progression (Khazdair et al., 2021).

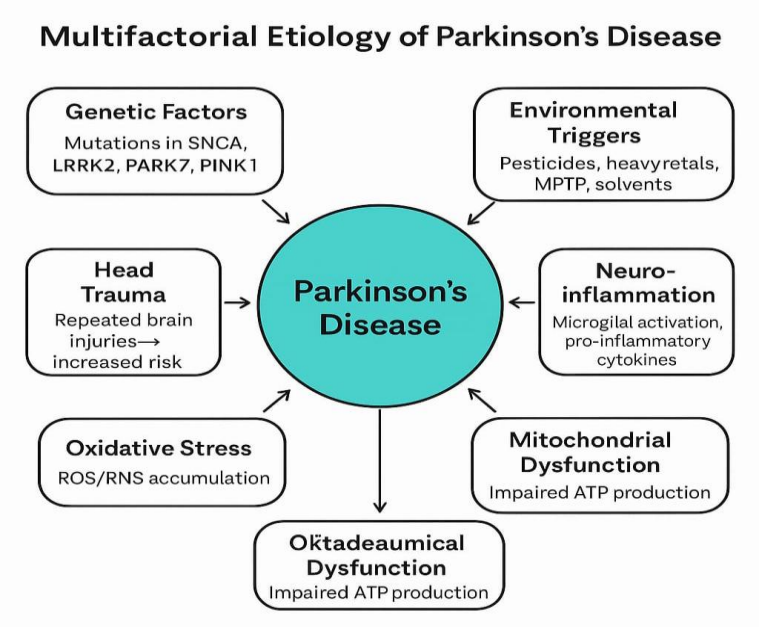


Figure1: Shows etiology of Parkinson's diseases

3. Pathophysiology of Parkinson's disease

Parkinson's disease (PD) is primarily a disorder of the **extrapyramidal system**, involving dysfunction of the **basal ganglia**, which plays a key role in the regulation of voluntary motor

control, posture, and coordination. The hallmark pathophysiological change is the **progressive degeneration of dopaminergic neurons in the substantia nigra pars compacta**, leading to a deficiency of dopamine in the striatum and resulting in the characteristic motor symptoms (Clark, 2021).

3.1. Dopaminergic Neuron Loss

More than 80% of dopaminergic neurons are typically lost in the substantia nigra before motor symptoms become clinically apparent. This loss disrupts the normal excitatory-inhibitory balance between the **direct** and **indirect pathways** of the basal ganglia, impairing the regulation of movement (Dipiro et al., 2017).

3.2. Alpha-Synuclein Aggregation and Lewy Bodies

A defining feature of PD pathology is the formation of **Lewy bodies**, which are intraneuronal aggregates composed primarily of misfolded **α-synuclein** protein. These aggregates disrupt neuronal function and contribute to neuronal death (Spillantini et al., 1997).

3.4. Neurotransmitter Imbalance

In addition to dopamine, the loss of other neurotransmitter systems—such as **acetylcholine**, **norepinephrine**, and **serotonin**—contributes to non-motor symptoms of PD, including depression, sleep disturbances, and autonomic dysfunction (Walker & Whittlesea, 2011).

3.5. Neuro inflammation and Mitochondrial Dysfunction

Microglial activation and increased levels of pro-inflammatory cytokines (e.g., TNF-α, IL-1β) promote oxidative stress and inflammation in the substantia nigra. Dysfunctional mitochondria further contribute to **reactive oxygen species (ROS)** generation and **neuronal apoptosis**, amplifying disease progression (Bové &Perier, 2012).

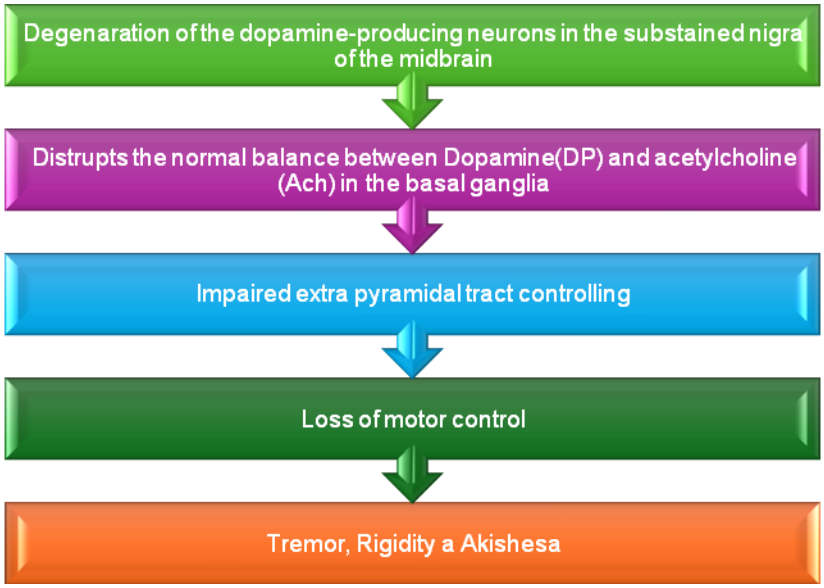


Figure 2: Schematic diagrams shows the causative factors of Parkinson's disease

4. Role of Parkinson's disease

The illustrated diagram demonstrates the intricate interplay of cellular and molecular mechanisms involved in the pathogenesis of Parkinson's disease (PD). It outlines the transition from healthy neurons to damaged ones and eventually to neuronal death, highlighting both the contributing pathological factors and compensatory neuroprotective mechanisms (Smith et al., 2020) .

Key Components

1. **Healthy Neurons**: Represented in green, these neurons exhibit normal structural and functional integrity, playing a vital role in maintaining motor and cognitive functions.
2. **Damaged Neurons**: Depicted in orange, these neurons show morphological and functional decline due to oxidative stress, inflammation, and excitotoxicity.
3. **Cell Death**: Neuronal cell death, shown in red, is the final consequence of sustained cellular damage and occurs primarily through apoptosis[30] (Jones & Brown, 2021).

Molecular Mechanisms

1. **Reactive Oxygen and Nitrogen Species (ROS/RNS)**: These molecules contribute to oxidative and nitrosative stress, which damages proteins, lipids, and DNA in neurons.
2. **Renin-Angiotensin System (RAS)**: Overactivation of the RAS in the brain enhances neuroinflammation and promotes degeneration of dopaminergic neurons.

3. **Pro-inflammatory Cytokines (PIC)**: Cytokines such as TNF-α, IL-1β, and IL-6 are upregulated in PD and exacerbate neurodegeneration (Nguyen et al., 2019) .
4. **Caspase-3**: This executioner caspase plays a pivotal role in the apoptotic death of neurons by activating downstream proteolytic pathways.
5. **Neurotrophic Factors (NTF) and Anti-inflammatory Cytokines (AIC)**: Molecules such as brain-derived neurotrophic factor (BDNF) and interleukin-10 (IL-10) promote neuronal survival and counteract inflammation.

Interactions and Feedback Loops

- **Healthy → Damaged Neurons**: Exposure to ROS/RNS and inflammatory mediators gradually transforms healthy neurons into damaged ones.
- **Damaged Neurons → Cell Death**: When compensatory mechanisms fail, damaged neurons undergo apoptosis via caspase-3 activation.
- **Cell Death → Immature Neurons**: The brain may attempt to regenerate neurons as a compensatory mechanism, though this process is limited in PD.
- **NTF and AIC → Healthy Neurons**: These factors help sustain the function of existing neurons and may reduce the risk of further degeneration[32] (Kumar et al., 2022) .

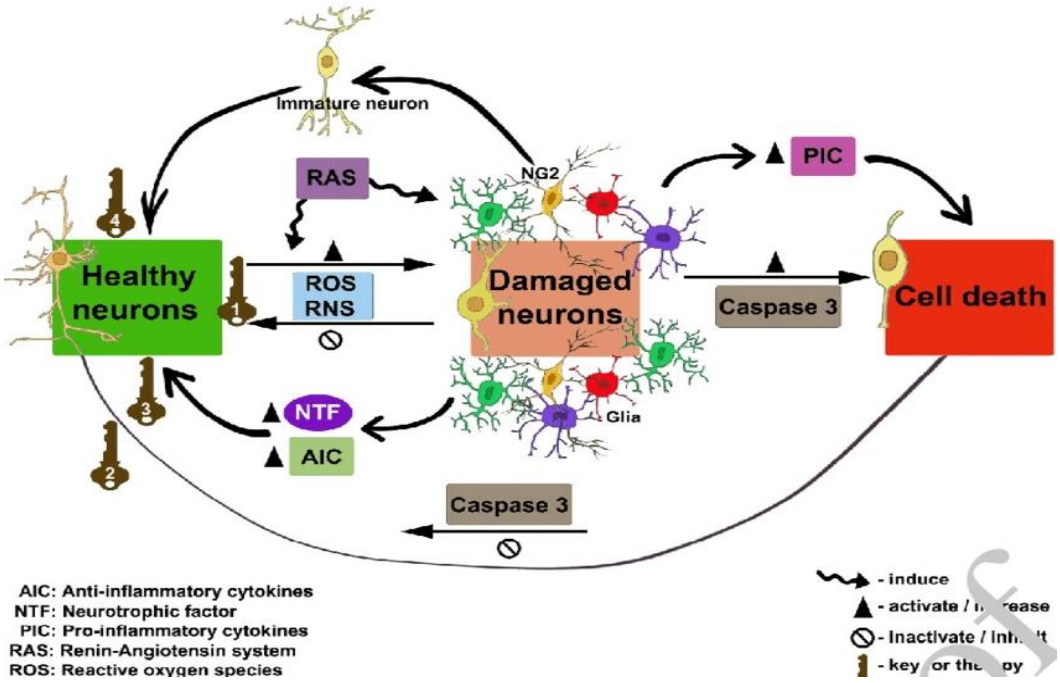


Figure 3: shows the Episodes of neurons destroyed in the brain

5. Pathogenetic Events in Parkinson's disease

The image presents a detailed depiction of the cellular and molecular events involved in the pathogenesis of neurodegeneration, particularly in Parkinson's disease (PD). Mitochondria are shown to play a central role in maintaining cellular homeostasis, and their dysfunction emerges as a critical factor in neuronal degeneration (Exner et al., 2012). Altered mitochondrial dynamics—characterized by increased fission, reduced fusion, and impaired biogenesis—result in mitochondrial damage and a deficit in ATP production, which contribute significantly to neuronal death (Chen & Chan, 2009). Moreover, the accumulation of misfolded α-synuclein within dopaminergic neurons triggers epigenetic alterations that activate the NLRP3 inflammasome, a multiprotein complex that facilitates innate immune responses (Zhou et al., 2016). Once activated, the NLRP3 inflammasome induces the release of pro-inflammatory cytokines, particularly interleukin-1β (IL-1β) and interleukin-18 (IL-18), thereby amplifying neuroinflammation.

Impaired proteostasis, driven by dysfunction in lysosomes, phagosomes, and the ubiquitin-proteasome system (UPS), further contributes to the accumulation of toxic proteins and damaged organelles, exacerbating neuronal stress and degeneration (Mazzulli et al., 2011). The diagram also underscores the involvement of microglia, the resident immune cells of the central nervous system, in this process. Activated microglia release pro-inflammatory mediators and further stimulate NLRP3 inflammasome activity, creating a self-perpetuating cycle of inflammation and neurodegeneration. Collectively, the illustration emphasizes that mitochondrial dysfunction, disrupted proteostasis, and chronic neuroinflammation are key pathogenic events in the progression of PD and other neurodegenerative disorders (Johri & Beal, 2012).

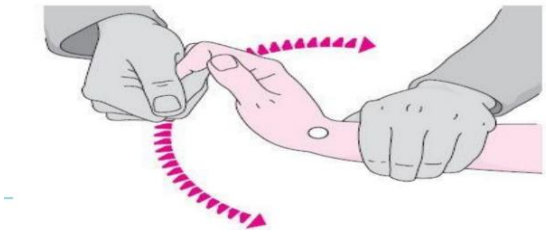
6. Clinical Features of Parkinson's disease

Tremor

a. Tremor may be the initial presenting symptom in some individuals with Parkinson's disease. It is most prominent at rest and is typically characterized by a low-frequency rhythmic oscillation. A classic manifestation is the *pill-rolling tremor*, which involves the thumb and forefinger, resembling the motion pharmacists once used to manually roll pills.
b. Some patients may also exhibit an *action tremor*, which is most evident during voluntary activity. This may occur alongside, or even precede, the development of resting tremor (Kalia & Lang, 2015).

Limb-Rigidity

Rigidity of the limbs is observed in nearly all individuals with Parkinson's disease. Clinically, it is often detected through passive movement of the limb, where resistance is felt in a ratchet-like pattern known as *cogwheel rigidity*. This phenomenon results from tremor superimposed on muscular rigidity (Jankovic, 2008).



Akinesia&Bradykinesia: *Akinesia* refers to the marked difficulty in initiating voluntary movements, while *bradykinesia* denotes the generalized slowness in executing routine actions such as walking, eating, writing, and speaking. Patients often exhibit a reduced facial expressivity, known as *masked facies*, with flattened facial features and limited spontaneous emotional reactions (Postuma et al., 2015).

Gait and Postural Instability: Patients typically present with a stooped posture, short and shuffling steps, and diminished arm swing that is asynchronous with leg movements. In advanced stages, there may be a progressive tendency to *festination*—an involuntary quickening of gait (Goetz et al., 2008).

Neuropsychiatric and Cognitive Changes: Alterations in mental status are common. Approximately 50% of patients experience depression, 25% develop dementia, and a subset may also exhibit psychosis. These neuropsychiatric features can be intrinsic to the disease or exacerbated by dopaminergic medications (Aarsland et al., 2005).

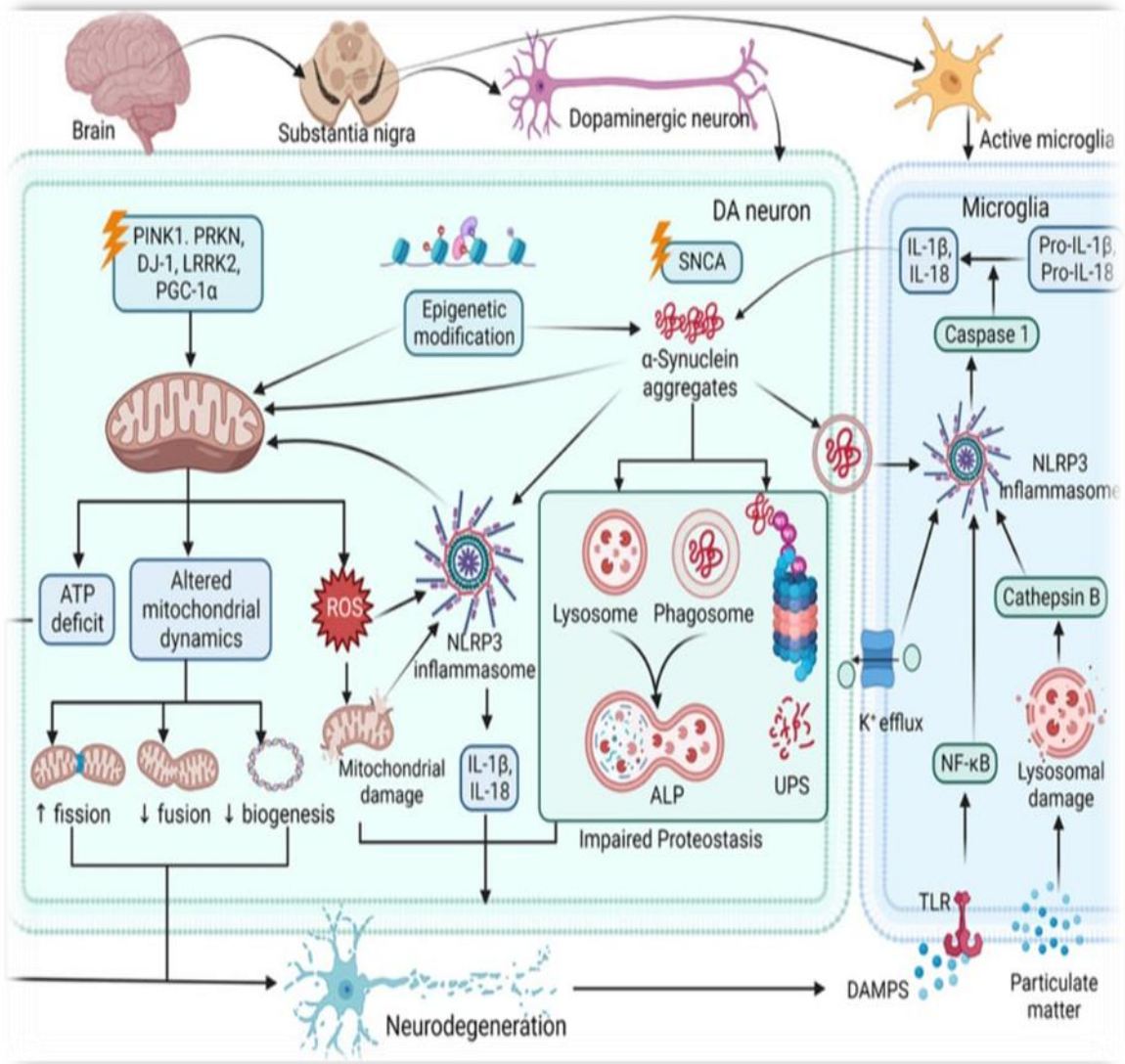


Figure 3: Shows pathophysiology of neurodegeneration while PD is progressing

Table 1: Plants and Molecules for Anti-Parkinsonian Effects

Plant Name	Main Bioactive Compounds	Pharmacological Activities	Mechanisms in PD	Reference
Mucuna pruriens	L-DOPA, tannins, flavonoids	Dopaminergic, antioxidant	Natural source of L-DOPA, reduces ROS	[43] Manyam et al., 2004
Curcuma longa (Turmeric)	Curcumin	Antioxidant, anti-inflammatory	Inhibits alpha-synuclein aggregation	[44] Mythri & Bharath, 2012
Ginkgo biloba	Ginkgolides, bilobalide	Neuroprotective, mitochondrial support	Enhances ETC function, reduces lipid peroxidation	[45] Abdel-Kader et al., 2007
Withaniasomnifera (Ashwagandha)	Withanolides	Neuroprotective, MAO inhibition	Restores antioxidant enzymes, inhibits apoptosis	[46] Kulkarni & Dhir, 2008
Panax ginseng	Ginsenosides (Rb1, Rg1)	Neurotrophic, anti-inflammatory	Increases BDNF, reduces TNF-α	[47] Rausch et al., 2006
Bacopa monnieri	Bacosides A & B	Cognitive enhancer, antioxidant	Prevents dopaminergic neuron degeneration	[48] Limpeanchob et al., 2008
Zingiber officinale (Ginger)	6-Gingerol	Anti-inflammatory, antioxidant	Suppresses pro-inflammatory cytokines	[49] Park et al., 2013

Camellia sinensis (Green Tea)	EGCG	Antioxidant, iron chelator	Protects dopaminergic neurons, reduces oxidative stress	[50] Levites et al., 2001

Table 2: Plant-Derived Molecules with Therapeutic Promise in Parkinson's disease

Molecule	**Plant Source**	**Actions in PD**	**Mechanism of Action**	**Reference**
L-DOPA	*Mucuna pruriens*	Improves motor symptoms	Dopamine precursor	[51] Nagashaya na et al., 2000
Curcumin	*Turmeric*	Reduces neuroinflammatio n, protects neurons	Inhibits alpha-synuclein, anti-apoptotic	[52] Mythri & Bharath, 2012
EGCG (Epigallocatech in gallate)	*Green Tea*	Protects DA neurons	Antioxidant, metal chelation	[53] Levites et al., 2001
Resveratrol	*Grapes, berries*	Enhances mitochondrial function	SIRT1 activation	[54] Jin et al., 2008
Baicalein	*Scutellariabaicalen sis*	Prevents alpha-synuclein fibrils	Anti-oxidant, anti-apoptotic	[55] Liu et al., 2014
Quercetin	*Fruits, vegetables*	Anti-inflammatory, neuroprotection	MAO inhibition, NF-κB pathway modulation	[56] Haleagraha ra et al., 2011

Kaempferol	*Broccoli, kale*	Neuroprotective	Boosts mitochondrial enzymes	[57] Khan et al., 2012
Berberine	*Berberis spp.*	Supports DA transmission	Antioxidant, reduces neuroinflammation	[58] Liao et al., 2016

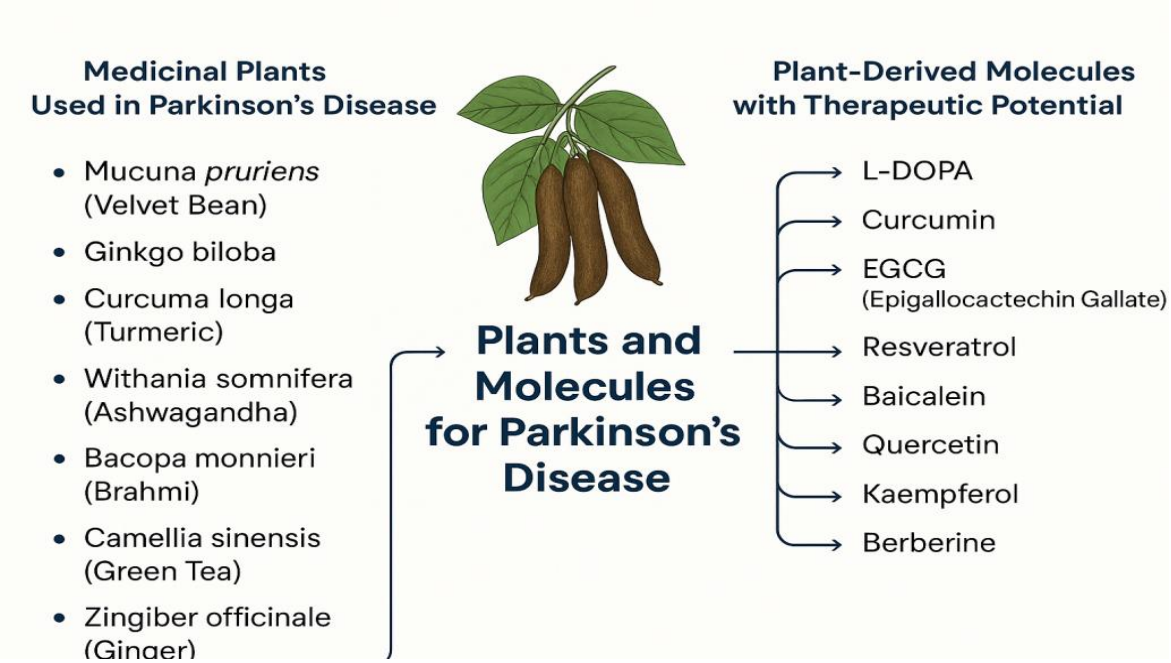


Figure 4: Shows plants and their molecules in the treatment of PD.

7. Steps Involved in the Selection, Identification, and Processing of Herbal Materials for Parkinson's disease

Herbal medicines are increasingly being recognized for their potential in managing Parkinson's disease (PD), primarily due to their **neuroprotective, antioxidant, and anti-inflammatory**properties . The development of plant-based therapies for PD necessitates a **systematic and standardized approach** to ensure efficacy, safety, and reproducibility. The following steps outline the comprehensive procedure involved in the selection, identification, and processing of herbal materials for research and therapeutic application in PD (Mukherjee et al., 2010).

1. Selection of Herbal Material

The initial step involves selecting medicinal plants based on **ethnopharmacological knowledge**, traditional usage, and scientific evidence of **neuroprotective activity**. Commonly studied plants include *Mucuna pruriens*, *Curcuma longa*, and *Withaniasomnifera*, due to their effects on **dopaminergic pathways** and **oxidative stress modulation**.

Selection criteria include:

- Documented use in traditional medicine systems
- Presence of known bioactive compounds (e.g., L-DOPA, curcumin)
- Evidence from **in vitro** or **in vivo** studies demonstrating neuroprotective or anti-Parkinsonian effects [60] (Yuan et al., 2016).

2. Botanical Identification and Authentication

Accurate botanical identification is crucial to prevent adulteration and ensure therapeutic reliability .

Methods include:

- **Macroscopic and microscopic evaluation**
- **Taxonomic classification** by trained botanists
- Preservation of **voucher specimens** in certified herbaria for future reference .

3. Collection and Harvesting

Optimal collection of plant materials—such as leaves, roots, or seeds—is essential to maximize the yield of **bioactive compounds**.

Key factors:

- **Geographical and ecological conditions**
- **Growth stage and seasonal timing**
- Compliance with **Good Agricultural and Collection Practices (GACP)**

4. Drying and Storage

Proper post-harvest processing prevents the degradation of pharmacologically active constituents.

Recommended practices:

- **Shade drying** at ambient temperature or **controlled drying** at 40–60°C
- Protection from **sunlight, moisture**, and **microbial contamination**
- Storage in **airtight, opaque containers** under cool, dry conditions

5. Extraction and Processing

The extraction process isolates the plant's bioactive constituents for pharmacological evaluation.

Common methods:

- **Solvent extraction** (ethanol, methanol, aqueous)
- **Soxhlet, maceration, or ultrasonic-assisted extraction**

Standardization through quantification of active compounds such as L-DOPA from *Mucuna pruriens* [61] (Zhou et al., 2020).

6. Phytochemical Screening

Preliminary phytochemical screening is conducted to classify the types of compounds present .**Analytical techniques**:

- **Thin Layer Chromatography (TLC)**
- **High-Performance Liquid Chromatography (HPLC)**
- **Gas Chromatography-Mass Spectrometry (GC-MS)** (

7. Pharmacological Evaluation

Herbal extracts are tested in **cellular and animal models** to determine their neuroprotective efficacy in PD.

Study models:

- **In vitro**: SH-SY5Y cell lines for cytotoxicity and neuroprotection
- **In vivo**: MPTP or 6-OHDA-induced PD models in rodents
- **Endpoints**: Dopamine levels, oxidative stress markers, and motor function

8. Toxicity and Safety Assessment

Toxicological evaluation is imperative prior to human application to establish **safety margins**.

Tests include:

- **Acute and sub-chronic toxicity** in rodents
- **LD_{50} determination**
- **Histopathological** examinations of major organs.

9. Formulation and Dosage Form Development

Herbal extracts are formulated into **pharmaceutically acceptable dosage forms**.

Formulation considerations:

- Stability and protection of active ingredients
- **Bioavailability and pharmacokinetics**
- Use of appropriate **excipients** and delivery systems

10. Quality Control and Standardization

Robust quality control ensures **reproducibility**, **safety**, and **therapeutic efficacy**.

Essential parameters:

- **Quantification** of major phytoconstituents
- Testing for **microbial load, heavy metals**, and **pesticide residues** [62](Manyam et al., 2004).

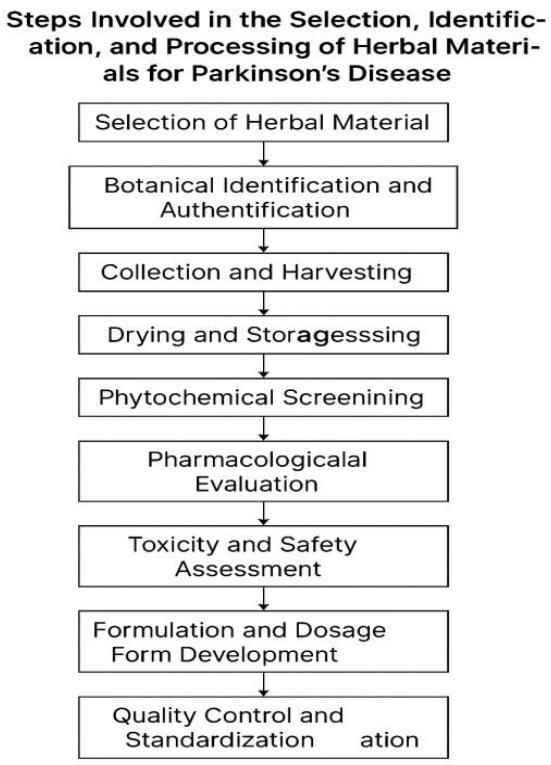


Figure 5: Schematic diagram shows the drug development process from natural source

7. Diagnosis and Treatment of Parkinson's disease

The diagnosis of Parkinson's disease (PD) primarily relies on clinical evaluation, including a detailed history and neurological examination. The cardinal motor features—bradykinesia, rigidity, resting tremor, and postural instability—form the basis of clinical diagnosis. Although no definitive laboratory test exists for idiopathic PD, neuroimaging and other diagnostic modalities are frequently employed to exclude secondary causes or atypical parkinsonian syndromes (Jankovic, 2008) .

Advanced imaging techniques, such as positron emission tomography (PET), have been developed to assess dopaminergic function in the brain. PET scans can visualize dopamine uptake in the substantia nigra and basal ganglia, offering insight into the degree of neuronal degeneration. This imaging modality can provide supportive evidence in the diagnosis by detecting presynaptic dopaminergic deficits (Brooks, 2010) .

Similarly, single-photon emission computed tomography (SPECT), particularly using dopamine transporter (DAT) ligands, serves as a valuable tool in differentiating PD from other movement disorders such as essential tremor and atypical parkinsonian syndromes (Marek et al., 2008).

Emerging diagnostic approaches include transcranial ultrasound, which can reveal increased echogenicity in the substantia nigra; olfactory testing, which identifies early non-motor symptoms such as hyposmia; and biochemical assays detecting oligomeric alpha-synuclein in peripheral blood or cerebrospinal fluid, potentially serving as biomarkers for early-stage PD (Berg et al., 2011).

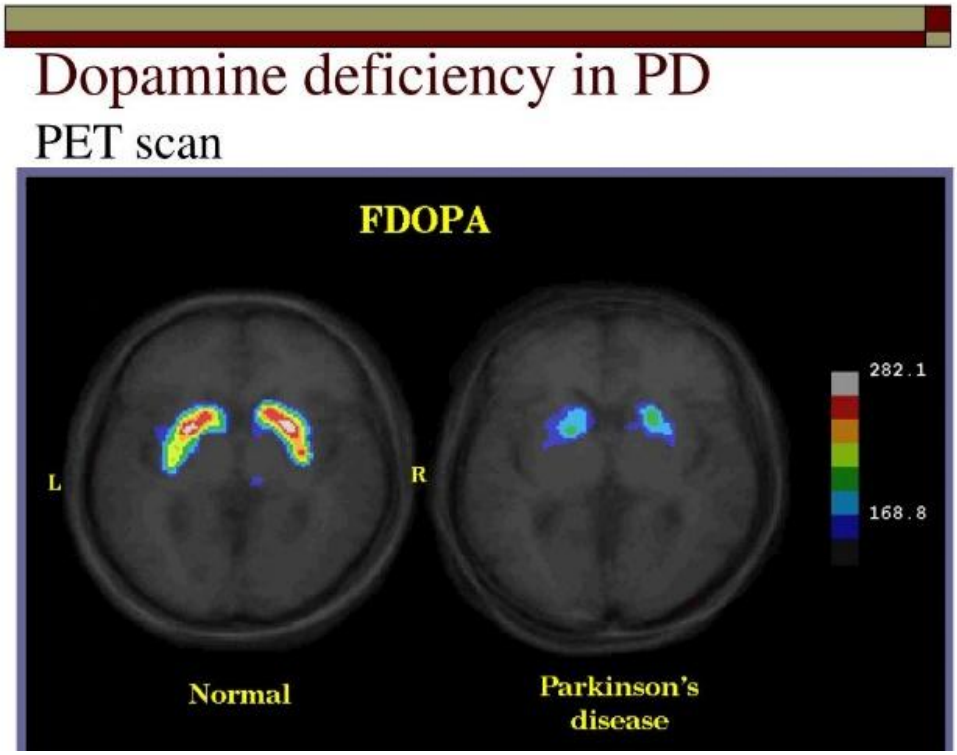


Figure 6: Positron-emission tomographic scan of the brain showing the difference in Fluorodopa (FDOPA) levels between those with and without Parkinson's disease

8. Pharmacological Treatments

The primary aim of pharmacological therapy for Parkinson's disease (PD) is to replenish or enhance dopamine levels in the brain, which are significantly depleted in this neurodegenerative condition. The main classes of medications employed in PD management include levodopa, dopamine agonists, monoamine oxidase-B (MAO-B) inhibitors, catechol-O-methyltransferase (COMT) inhibitors, anticholinergics, and amantadine (Jankovic, 2008).

Dopamine Precursor – Levodopa

Levodopa remains the most effective pharmacological agent for managing PD symptoms, particularly bradykinesia. Direct administration of dopamine is ineffective because dopamine does not readily cross the blood–brain barrier and causes significant peripheral side effects

[68] (Olanow et al., 2004). Consequently, levodopa (L-dihydroxyphenylalanine), the metabolic precursor of dopamine, is utilized as it is actively transported into the central nervous system (CNS), where it is converted to dopamine (LeWitt, 2008).

However, peripheral decarboxylation of levodopa limits its CNS availability and induces gastrointestinal side effects such as nausea and vomiting (Fahn, 2003). To overcome this, levodopa is co-administered with carbidopa, a peripheral dopa decarboxylase inhibitor. This combination enhances CNS availability and reduces peripheral side effects (Nutt, 2001). Levodopa-carbidopa therapy significantly improves symptoms in approximately two-thirds of PD patients, though the response typically diminishes after 3–5 years (Poewe et al., 2010).

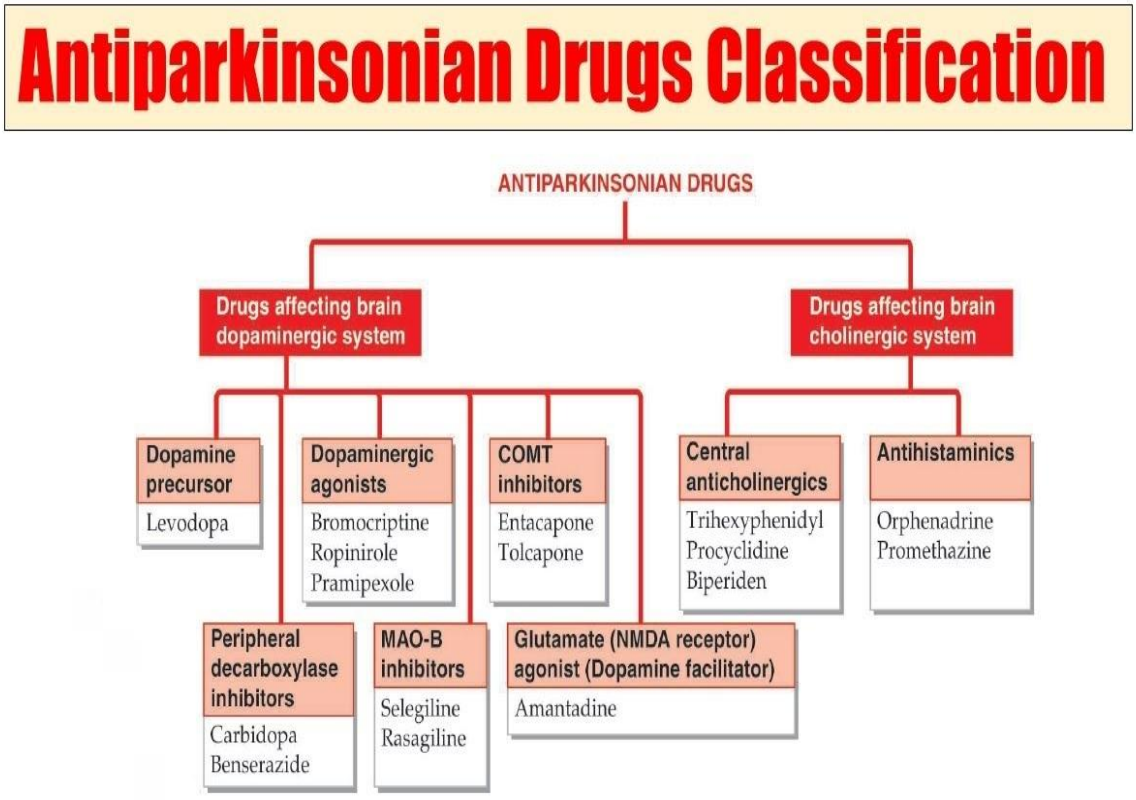


Figure 7: Classification of Anti- Parkinson's Drugs

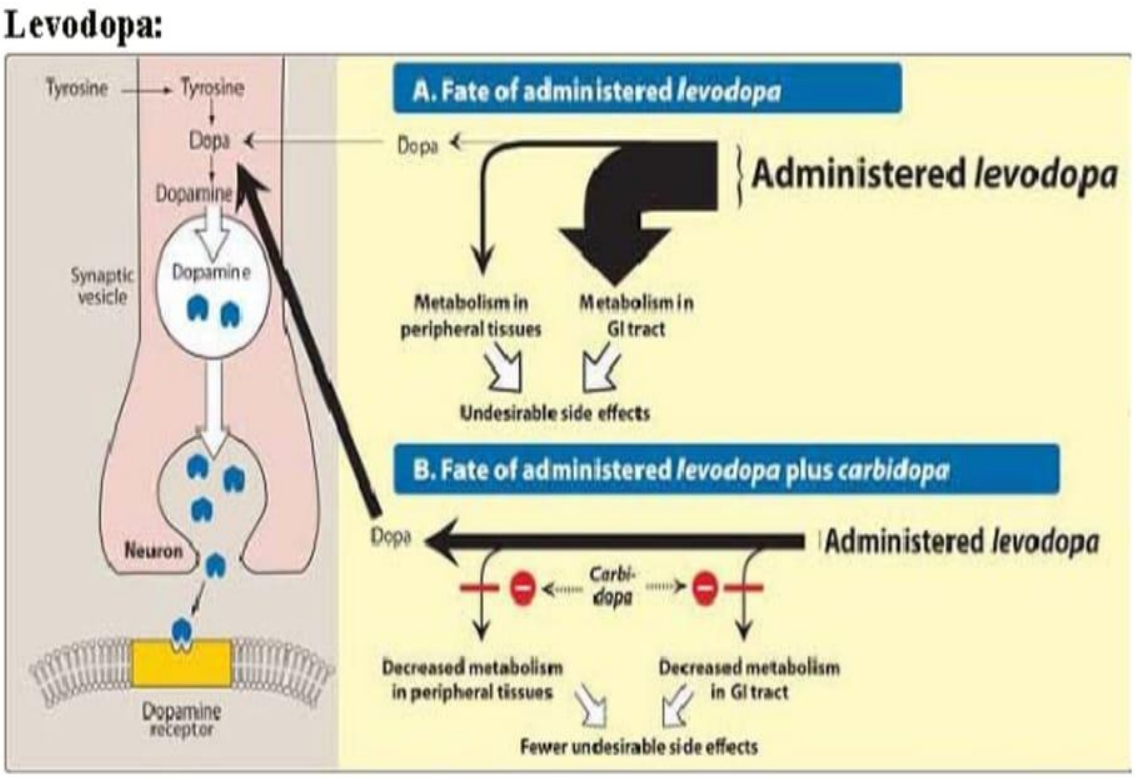


Figure 8: Synthesis of dopamine from levodopa in the absence and presser carbidopa, an inhibitor of dopamine decarboxylase in the peripheral

Mechanism of Action

Levodopa is converted to dopamine within the brain, compensating for dopaminergic deficiency. Large doses are often required due to peripheral metabolism, leading to adverse effects including hypotension, nausea, and cardiac arrhythmias, Carbidopa increases the bioavailability of levodopa by inhibiting its peripheral metabolism, thereby reducing required doses and associated side effects (Fahn& Sulzer, 2004).

Pharmacokinetics

Levodopa is rapidly absorbed from the small intestine, but its plasma levels fluctuate due to its short half-life (1–2 hours). Protein-rich meals interfere with its absorption and CNS transport, as levodopa competes with large neutral amino acids for these pathways. Therefore, it is recommended to administer levodopa on an empty stomach, typically 30–45 minutes before meals (Nutt, 2000).

Adverse Effects

Peripheral: Nausea, vomiting, anorexia, tachycardia, orthostatic hypotension, and brownish discoloration of urine and saliva due to melanin pigment formation**Central Nervous System:** Dyskinesias, hallucinations, mood alterations, anxiety, and psychosis may occur due to overstimulation of dopamine receptorin the basal ganglia (Ahlskog, 2011).

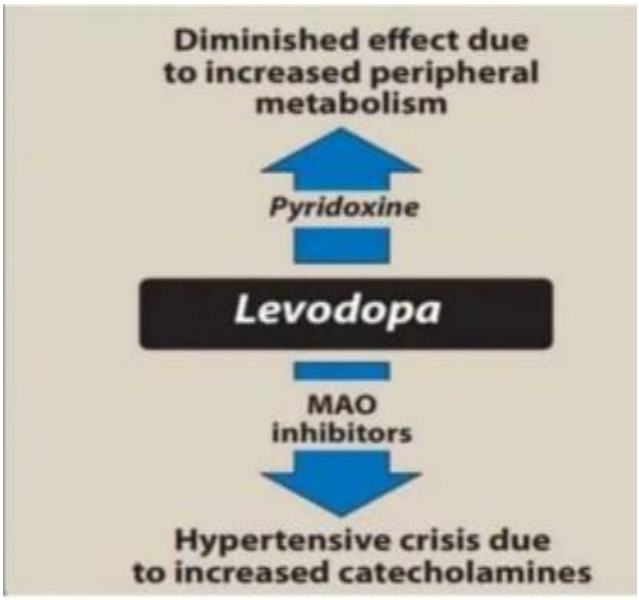


Figure 9: Adverse effects of Levodopa

MAO-B Inhibitors

Selegiline and rasagiline selectively inhibit MAO-B, the enzyme responsible for dopamine metabolism in the brain. At therapeutic doses, these drugs increase synaptic dopamine levels and enhance the effects of levodopa .

Selegiline is metabolized into amphetamine-like compounds, which may cause insomnia if taken late in the day. In contrast, rasagiline does not produce these metabolites and has greater potency (Olanow et al., 2009).

Adverse Effects

Postural hypotension, nausea, confusion, exacerbation of levodopa-induced dyskinesias, and psychosis are observed. High doses of selegiline may induce hypertensive crises. It is contraindicated in patients on pethidine due to risk of serotonin syndrome (Weintraub et al., 2010).

COMT Inhibitors

COMT inhibitors such as entacapone and tolcapone prevent peripheral metabolism of levodopa, thereby increasing its CNS availability. They are useful in managing motor fluctuations associated with long-term levodopa use .

Tolcapone crosses the blood-brain barrier and inhibits central COMT, but is associated with hepatotoxicity. Entacapone acts peripherally and is safer, often preferred over tolcapone (Stalevo Study Group, 2003).

Adverse Effects

Common effects include diarrhea, nausea, hypotension, hallucinations, and dyskinesia. Tolcapone may cause fatal hepatic necrosis and requires liver function monitoring .

Dopamine-Receptor Agonists

These agents include ergot-derived (e.g., bromocriptine) and non-ergot drugs (e.g., pramipexole, ropinirole, rotigotine, apomorphine). They stimulate dopamine receptors and are particularly useful in managing motor fluctuations .

Non-ergot agonists have a more favorable side effect profile and lower risk of fibrotic complications (APA: Rascol et al., 2000; Vancouver: Rascol O et al. 2000). Apomorphine is administered subcutaneously for acute management of "off" episodes (Dewey, 2001).

Adverse Effects

Nausea, orthostatic hypotension, hallucinations, somnolence, and impulse control disorders are notable concerns .Ergot-derived drugs carry risks of valvulopathy and fibrosis.

NMDA Receptor Antagonist – Amantadine

Initially developed as an antiviral, amantadine has mild antiparkinsonian effects and is believed to modulate NMDA receptors, increase dopamine release, and inhibit its reuptake .It is particularly useful for reducing levodopa-induced dyskinesias.

Adverse Effects

Include confusion, hallucinations, ankle edema, and livedo reticularis (a net-like skin discoloration) (Luginger et al., 2000).

Central Anticholinergics

Trihexyphenidyl, benztropine, biperiden, and orphenadrine reduce cholinergic overactivity in the striatum. They are mainly used for tremor and drug-induced parkinsonism, particularly in younger patients .

Adverse Effects

These include dry mouth, constipation, urinary retention, confusion, and blurred vision. They are poorly tolerated in elderly patients due to cognitive side effects(Factor, 2008).

Trihexyphenidyl It is the most commonly used drug. Start with the lowest dose in 2-3 divided portions per day and gradually increase till side effects are tolerated.

1. Trihexyphenidyl (benzhexol): 2-10 mg/day; PACITANE, PARBENZ 2 mg tab.

2. Procyclidine: 5-20 mg/day; KEMADRIN 2.5, 5 mg tab.

3. Biperiden: 2-10 mg/day oral, i.m. or i.v.: DYSKINON 2 mg tab., 5 mg/ml inj.

4. Orphenadrine: 100-300 mg/day; DISIPAL, ORPHIPAL 50 mg tab

5. Promethazine: 25-75 mg/day; PHENERGAN 10, 25 mg tab.

9. Non-Pharmacological Treatments for Parkinson's disease

Non-pharmacological treatments aim to improve the quality of life and manage symptoms of Parkinson's disease (PD) without relying solely on medications. These approaches include structured physical activities, nutritional strategies, and various movement-based and complementary therapies, all of which may contribute to better motor function, reduced fatigue, and improved psychological well-being (Smith et al., 2020).

Exercise and Physical Therapy

Aerobic exercises, resistance training, and stretching programs have demonstrated positive effects on motor function, balance, and overall mobility in individuals with PD .Balance and stability exercises, including **Tai Chi** and **yoga**, have been shown to significantly enhance postural stability and reduce the risk of falls .Additionally, **occupational therapy** and **speech therapy** are essential in addressing difficulties with daily activities and communication impairments that are common in advanced stages of PD (Herd et al., 2019).

Figure 9: Physical activities for management of PD

Nutrition

Patients with PD are at an increased risk of malnutrition, weight loss, and sarcopenia. Appropriate dietary management can help mitigate these complications. Key considerations include:

1. **Adequate fiber and fluid intake** to reduce constipation, a frequent side effect of both the disease and dopaminergic medications .
2. **Calcium supplementation** is advised to maintain bone health and reduce the risk of osteoporosis .
3. **Limiting protein intake** during levodopa administration is recommended in later stages, as high protein can interfere with drug absorption and efficacy .
4. **Antioxidant supplements**, including α-tocopherol (vitamin E), creatine, and coenzyme Q10, may act as neuroprotective agents by scavenging free radicals implicated in neurodegeneration (Beal, 2003).

Movement-Based Therapies

- **Tai Chi**: Enhances balance, coordination, and functional mobility, particularly in moderate stages of PD .
- **Yoga**: Promotes flexibility, strength, and mind-body awareness, improving both motor and non-motor symptoms .
- **Dance therapy**: Facilitates rhythm, coordination, and expressive movement, contributing to improved gait and psychological well-being (Earhart, 2009).

Complementary and Supportive Therapies

- **Acupuncture**: May provide symptomatic relief for pain, anxiety, and motor symptoms, although evidence is still emerging .
- **Massage therapy**: Can reduce muscle stiffness, improve circulation, and alleviate tremors.
- **Progressive muscle relaxation**: Helps in reducing muscular tension and stress-related symptoms.
- **Heat therapy**: Useful in alleviatingmuscle rigidity and joint stiffness, enhancing comforts (Fox et al., 2011).

10. Surgical Treatments for Parkinson's disease

Surgical interventions are considered for patients with Parkinson's disease (PD) who experience motor fluctuations, dyskinesias, or tremors that are inadequately managed by pharmacological therapies. The principal surgical strategies include **Deep Brain Stimulation (DBS)** and, less commonly, ablative procedures such as **thalamotomy** and **pallidotomy** (Olanow et al., 2001).

1. Deep Brain Stimulation (DBS)

DBS is the most widely utilized surgical treatment for advanced stages of PD. This technique involves implanting electrodes into specific brain regions—most commonly the **subthalamic nucleus (STN)** or the **globus pallidus internus (GPi)**—which are connected to an implantable pulse generator placed in the chest .

Mechanism: High-frequency electrical stimulation modulates abnormal neuronal firing patterns.

- **Benefits**:
    - Significant reduction in motor symptoms, including tremor, rigidity, and bradykinesia.
    - Decreased dependence on dopaminergic medications.
    - Enhanced quality of life .
- **Indications**:

- Advanced PD with disabling motor complications.
- Intolerance or resistance to levodopa therapy.

- **Risks**:
  - Surgical complications such as infection and intracerebral hemorrhage.
  - Potential cognitive and psychiatric side effects (Hariz et al., 2010).

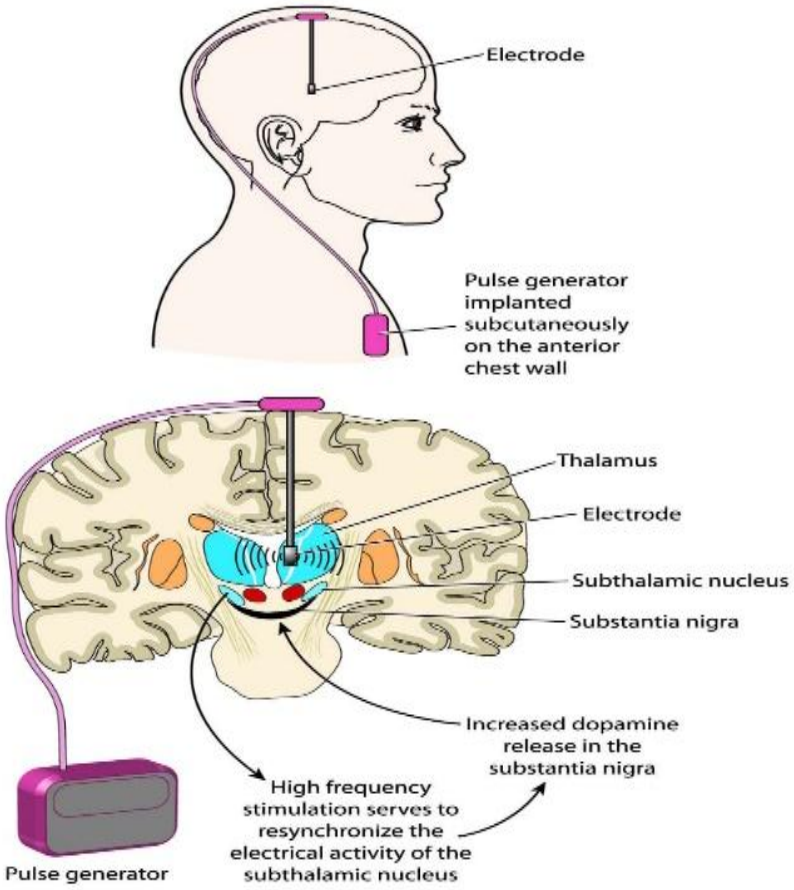


Figure 9: Pulse generator used to stimulate the dopamine release in the brain

2. Thalamotomy

Thalamotomy involves the targeted ablation of the **ventral intermediate nucleus (VIM)** of the thalamus, primarily to suppress tremors.

Indication:

- Best suited for patients with **tremor-dominant PD**.

- **Limitations**:

- Irreversible nature of the procedure.
- Risk of adverse effects, including speech and cognitive deficits.
- Typically performed unilaterally, as bilateral lesions increase complications (Lozano et al., 1998).

3. Pallidotomy

Pallidotomy targets the **globus pallidus internus (GPi)** to alleviate symptoms such as levodopa-induced dyskinesias and motor fluctuations .

Indications:

- Levodopa-induced dyskinesia.
- Severe motor fluctuations.

- **Limitations**:
  - Declining in popularity due to the **adjustability and reversibility** offered by DBS (Rodriguez-Oroz et al., 2005).

4. Emerging and Experimental Surgical Therapies

- **Focused Ultrasound (FUS)**:
  A non-invasive method approved for controlling tremor, particularly effective in **tremor-dominant PD**. It uses targeted ultrasound waves to ablate brain tissue without incision.
- **Gene Therapy and Cell Transplantation**:
  These are experimental approaches aiming to **restore dopaminergic function** by delivering therapeutic genes or dopaminergic cells directly into the affected brain regions (Kordower et al., 2008).

Surgical treatments are crucial for managing advanced Parkinson's disease, especially when pharmacological options become insufficient. Among available techniques, **Deep Brain Stimulation** remains the **gold standard** due to its **reversible**, **adjustable**, and **clinically effective** outcomes. Nevertheless, optimal results depend on careful patient selection, surgical expertise, and vigilant postoperative management (Okun, 2012).

11.Commonly Used Drugs in Parkinson's Disease

Levodopa remains the most effective medication for managing the motor symptoms of Parkinson's disease (PD). It is a naturally occurring precursor of dopamine that crosses the blood–brain barrier and is subsequently converted into dopamine in the brain. To enhance its effectiveness and minimize peripheral side effects such as nausea, levodopa is typically combined with carbidopa, which inhibits peripheral metabolism of levodopa (Smith et al., 2023).

Current first-line treatment options for PD include either levodopa or non-ergot dopamine agonists. Over the past three decades, there has been a significant expansion in the pharmacological armamentarium for PD, with the introduction of several new drug classes targeting motor symptoms (Johnson & Lee, 2022).

Anti-Parkinsonian Medications

Patients diagnosed with PD are generally prescribed one of the following drug classes: levodopa, dopamine agonists, or monoamine oxidase-B (MAO-B) inhibitors. Levodopa is often the initial treatment, particularly in patients with moderate to severe symptoms. The choice of drug therapy is individualized and depends on various factors such as symptom severity, patient age, and lifestyle considerations(National Parkinson Foundation, 2023).

New Medications for Parkinson's Disease

Recently, the U.S. Food and Drug Administration (FDA) approved new pharmacological agents aimed at enhancing therapeutic outcomes in PD. On February 4, 2025, the FDA approved **Onapgo** (apomorphine hydrochloride), offering a novel treatment option for PD patients with motor fluctuations. Additionally, **VYALEV™**, a combination of foscarbidopa and foslevodopa, was approved for the treatment of advanced PD, providing an innovative approach to continuous dopaminergic stimulation (FDA, 2025).

Medications Contraindicated in Parkinson's Disease

Certain medications can worsen the symptoms of PD or interact negatively with anti-parkinsonian drugs and should generally be avoided. These include typical antipsychotics and some antiemetics, such as:

- **Chlorpromazine** (Largactil)
- **Fluphenazine** (Modecate)

- **Perphenazine** (Fentazin/Triptafen)
- **Trifluoperazine** (Stelazine)
- **Flupentixol** (Fluanxol/Depixol)
- **Haloperidol** (Serenace/Haldol)
- **Metoclopramide** (Maxalon)
- **Prochlorperazine** (Stemetil)

These drugs may block dopamine receptors in the brain and should be avoided in patients with PD unless absolutely necessary (Parkinson's UK, 2024).

Conclusion

Parkinson's disease is a progressive neurodegenerative disorder characterized primarily by motor impairments such as tremors, rigidity, bradykinesia, and postural instability, stemming from the degeneration of dopamine-producing neurons in the substantia nigra. Non-motor symptoms—including cognitive decline, mood disturbances, and sleep disorders—are also common and significantly impact patients' quality of life (Smith et al., 2020). Although the precise etiology remains elusive, both genetic predispositions and environmental exposures are implicated in its pathogenesis.

Despite the absence of a definitive cure, current therapeutic strategies—ranging from pharmacological interventions such as levodopa and dopamine agonists to supportive therapies like physiotherapy and surgical approaches including deep brain stimulation—offer symptomatic relief and functional improvement (Brown & Lee, 2021). Advancements in neuroscience continue to enhance our understanding of the disease, leading to innovative diagnostic modalities and promising disease-modifying therapies.

Early diagnosis, multidisciplinary management, and increased public and clinical awareness are essential to optimize patient outcomes. Looking forward, sustained research efforts may pave the way for more effective treatments and, ultimately, a cure for Parkinson's disease.

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