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Review Article

Comprehensive Review on Parkinson's Disease: Insights into Prevalence, Pathophysiology, Diagnosis, and Multifaceted Treatment Approaches

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Abstract

Background: Parkinson's disease (PD), a prevalent neurodegenerative condition affecting more than seven million individuals globally, manifests through the loss of dopaminergic neurons, leading to diverse motor and non-motor symptoms. This comprehensive review aims to explore PD's multifaceted nature, covering its introduction, prevalence patterns, pathophysiology, diagnostic challenges, and varied treatment strategies. Genetic and environmental influences on prevalence, brain region degeneration, Lewy body formation, and early-stage diagnostic difficulties are key focus areas. The review emphasizes the necessity of personalized approaches, innovative clinical criteria-, and subtype categorizations for effective management.

Objective: This review aims to provide a holistic understanding of Parkinson's disease, contributing to improved insights for both individuals and healthcare professionals. By consolidating knowledge on PD's various facets, it seeks to facilitate informed decision-making for better management and enhanced quality of life.

Methods: A thorough review of research literature, including studies, trials, and historical perspectives, was done. It covers prevalence, causes, diagnosis, and treatment options, including both traditional and herbal remedies, alongside conventional approaches.

Results: The review reveals the complex interplay of genetic predisposition, environmental factors, and the neurodegenerative mechanisms underlying PD. It underscores the challenges of early-stage diagnosis and the wide array of treatment options available, emphasizing the need for personalized care.

Conclusion: Understanding Parkinson's disease in its entirety is crucial for effective management. By presenting a comprehensive overview, this review advocates for a holistic approach, integrating diverse treatments and individualized strategies, thereby offering valuable guidance for improved quality of life in PD patients.

Keywords: Parkinson's, neurodegeneration, DBS, Lewy bodies, motor & non-motor symptoms, diagnosis.

1. Introduction:

Parkinson's disease (PD) is the second most common neurodegenerative disorder, predominantly affecting individuals over the age of 55, but it can also manifest in younger adults and even children. PD is distinguished by the loss of 50-70% of dopaminergic neurons situated in the substantia nigra[1]. Parkinson's disease affects around 1 to 3 out of every 100 people who are over 60 years old worldwide[2,3]. Parkinson's disease also places significant burdens on caregivers, often leading to high levels of stress and strain[4]. Alongside motor symptoms, nonmotor symptoms and complications, including neuropsychiatric or neurobehavioral issues, autonomic dysfunction, and sensory problems, are also recognized as integral aspects of PD[5]. Common neuropsychiatric or neurobehavioral issues, including depression, anxiety, rapid eye movement sleep behaviour disorder, and dementia, often stem from neurodegenerative processes affecting diverse neurotransmitter systems within various brain regions in individuals with PD[6]. Parkinson's disease is a progressive condition with no known cure, and the pace of progression can vary significantly. The condition can be divided into four overlapping stages: diagnosis, maintenance, complex, and palliative[7].

Parkinson's disease primarily affects older individuals, with men at a somewhat higher risk than women. While there is a strong genetic component with numerous associated genetic

factors, environmental elements, such as exposure to pesticides and other factors like smoking, coffee consumption, exercise, and head trauma, also play a role in the disease's development. Although there have been significant advancements in understanding the disease's causes and epidemiology, the exact origin of Parkinson's disease remains unknown, and there are no known cures or preventive therapies. Recent years have seen the development of clinical diagnostic criteria, which aim to improve accuracy. However, diagnosing the condition remains challenging, especially in the early stages when symptoms may overlap with other neurodegenerative disorders. Identifying prodromal (early) stages of the disease is crucial because future disease-modifying therapies are most likely to succeed at this point. Additionally, there's a need to better categorize Parkinson's disease into subtypes based on clinical presentation, prognosis, and underlying mechanisms, allowing for more personalized treatment approaches. For instance, monogenic Parkinson's disease serves as a clear example, where subtype-specific therapies are currently undergoing clinical trials[8].

2. Search Methodology:

The search methodology for this comprehensive review on Parkinson's disease encompassed a thorough exploration of research resources. Multiple databases, including Research Scholar, Google Scholar, PubMed, NCBI, and ScienceDirect, were employed to ensure a broad search spectrum. A selection of carefully curated keywords, such as "Parkinson's Disease," "Risk factors associated with PD," "Symptoms of PD," "Treatment Approaches," "Herbs used to treat PD," "Allopathic treatment of PD," "Ayurvedic treatment," "Prevalence," "Pathophysiology," and "Role of dopamine," was used. Boolean operators refined the search queries, while inclusion criteria focused on articles published until 2023. After a rigorous screening process, articles were selected, and data were extracted for content synthesis. Quality assessments ensured the credibility of the selected sources, ultimately contributing to the comprehensive and up-to-date coverage of Parkinson's disease in this review.

3. Prevalence:

Multiple studies have gathered data on PD epidemiology. Yet, variations in research methods complicate direct prevalence estimate comparisons. The prevalence of Parkinson's disease (PD) generally ranges from 1 to 2 per 1000 in unselected populations, affecting about 1% of the population above 60 years. PD is rare before the age of 50 and becomes more prevalent, reaching 4% in the highest age groups. The annual incidence of PD per 100,000 inhabitants varies from less than 10 to more than 20 across different studies, largely due to methodological differences and diagnostic criteria. In Nordic countries with stable populations and well-organized healthcare systems, the incidence varies, but studies generally find low numbers of cases below the age of 50. The increasing prevalence of PD over time has been linked to the aging population, changes in smoking behaviour, and increased exposure to traffic-related air pollution. However, some studies do not support an increased risk of PD[9,10].

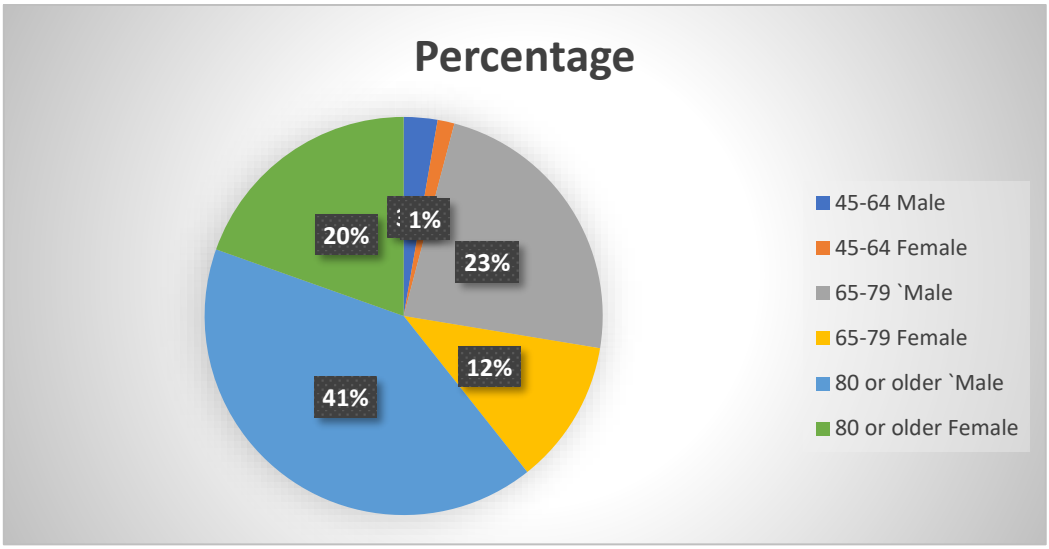

Figure 1: Percentage of prevalence of Parkinson's disease with different age groups.

4. Pathophysiology:

Parkinson's disease (PD) is a condition that affects the extrapyramidal system, specifically the motor components of the basal ganglia. It is defined by loss of dopaminergic function, resulting in reduced motor function and the emergence of clinical symptoms associated with disease. Research from the late 1950s highlighted that motor symptoms in PD are primarily linked to striatal dopamine depletion. However, the existence of non-motor features suggests the involvement of various other neurotransmitters, including those in the glutamatergic, cholinergic, serotonergic, and adrenergic systems, along with neuromodulators like adenosine and enkephalins. Further research provides evidence that PD may have its initial impact in the dorsal motor nucleus of the vagal and glossopharyngeal nerves, along with the anterior olfactory nucleus. This implies a disease progression pattern that starts in the brainstem and moves toward higher cortical levels. Histopathologically, PD is defined by the loss of pigmented dopaminergic neurons and the presence of Lewy bodies (LBs)[11].

In PD, the hallmark pathology involves the depletion of cells in the substantia nigra, especially in the ventral region of the pars compacta. At the point of death, this brain region exhibits a neuron loss of 50-70% when compared to the same area in individuals without the condition. The initial documented pathological alterations in PD have been noticed in the medulla oblongata/pontine tegmentum and the olfactory bulb. Patients in the pre-symptomatic phase are typically found in the early

stages, which include Braak stages 1 and 2. In the later stages, specifically Braak stages 3 and 4, the disease impacts the substantia nigra, midbrain regions, and basal forebrain. At the final stage, pathological changes manifest in the neocortex[12].

Mutations in genes that code for proteins within the central nervous system play a role in neuronal cell death. In particular, alpha-synuclein undergoes abnormal self-aggregation. Lewy Bodies, which are the hallmark of PD, predominantly consist of this aggregated and insoluble alpha-synuclein. Additionally, systems that are meant to degrade abnormal proteins, such as the ubiquitin-proteasome system, become compromised. Moreover, other impaired processes potentially relevant to PD involve mitochondrial dysfunction and abnormal oxidative stress caused by reactive oxygen species, ultimately leading to neuronal degeneration[13].

a) Role of dopamine agonists:

Dopamine agonists alleviate Parkinson's symptoms by directly stimulating dopamine receptors, resembling the brain's natural neurotransmitter. There are two types of dopamine agonists: ergoline and non-ergoline, both of which target dopamine D2-type receptors. Ergoline agonists include bromocriptine, pergolide, lisuride, and cabergoline, while ropinirole and pramipexole fall into the non-ergoline category. Apomorphine, an early dopamine agonist, improves Parkinson's symptoms by targeting both D1 and D2 receptors, but it requires subcutaneous administration[14].

b) γ-Aminobutyric Acid (GABA):

In Parkinson's disease, potential abnormalities in GABA (gamma-aminobutyric acid) neurons have been suggested based on decreased GABA receptor binding in the substantia nigra, where dopamine neurons are notably reduced nigral dopamine neurons or via interneuronal connections. However, GABA receptor changes were not observed in other brain regions studied. Similarly, experimental lesions in animal models did not result in alterations to striatal GABA receptors, affirming this localized effect within the substantia nigra in Parkinson's disease[15].

c) Glutamate:

In Parkinson's disease (PD), the loss of dopamine neurons in the substantia nigra pars compacta (SNc) and consequent denervation of the striatum lead to complex alterations in the basal ganglia circuitry. Glutamate, particularly in the striatum and subthalamic nucleus (STN), plays a crucial role in this process.

Within the striatum, a close interplay exists between glutamate and dopamine. Dopamine depletion or blockade of striatal dopamine receptors causes increased glutamate release in the striatum. This affects NMDA receptor downregulation without impacting AMPA receptors, with changes observed in NMDA receptor subunit mRNA in rodent PD models. Additionally, blocking NMDA receptors intensifies rotational behavior and the expression of c-fos in the striatum in rats with SNc lesions.

The STN, a key glutamatergic hub in the basal ganglia, becomes overactive in PD. Its increased activity affects the output nuclei, leading to reduced GABAergic projections to the motor thalamus. This ultimately diminishes motor thalamic output to the motor cortex, likely contributing to many PD clinical symptoms. The origin of STN overactivity is multifaceted, involving reduced inhibitory control by the external globus pallidus (GPe) over the STN and direct projections from the striatum and cortex. Furthermore, the impact of dopamine depletion on STN neurons needs consideration.

The intricacies of glutamate-dopamine interactions in the striatum and the overactivity of the STN, compounded by altered basal ganglia outputs, contribute to the motor dysfunctions observed in Parkinson's disease[16].

d) Serotonin:

While studies have hinted at possible involvement of serotonergic neurons in Parkinson's disease (PD), the exact role and alterations in serotonin receptors in the PD brain remain inconclusive. Suggestions indicate a functional contribution of serotonergic neurons to regulate motor behaviour and tremor, possibly interacting with dopamine and noradrenaline systems. Studies exploring changes in serotonin receptors in the PD brain have shown varied outcomes. Some research found no alterations in 3H-serotonin binding in the striatum or frontal cortex of PD patients. Neither levodopa treatment nor neuroleptics significantly affected 3H-serotonin binding. Specific findings observed a moderate decrease in serotonin receptors in the putamen but not in the caudate nucleus or pallidum. Additionally, recent studies revealed a decrease in both high and low affinity binding sites and an increase in 3H-serotonin affinity in the frontal cortex of PD patients. Overall, the evidence regarding alterations in serotonin receptors in Parkinson's disease is inconclusive, with differing results across different brain regions, indicating complexities and inconsistencies in the role of serotonergic neurons in the pathology of PD[17].

e) Acetylcholine:

In Parkinson's disease (PD), an imbalance between dopaminergic and cholinergic neurotransmitters occurs, with dopamine deficiency (via D2 receptors) and an excess of muscarinic cholinergic neurons (via M4 receptors). Scopolamine, a muscarinic cholinergic receptor antagonist, was used for a Parkinsonian patient unable to take oral medication. Dopaminergic and cholinergic neurons interact antagonistically, mediated by presynaptic GABAergic neurons (GABAA receptors) and glutaminergic neurons (NMDA receptors). However, nicotinic cholinergic (nAch) neurons partially activate dopaminergic neurons in the putamen via ß2 receptors, suggesting potential therapeutic value for ß2 nAch agonists in PD treatment. Additionally, dementia, which affects 40% of PD patients, may be linked to cholinergic loss in the nucleus basalis of Meynert, the origin of cerebral cortex inputs[18].

f) Norepinephrine:

The involvement of norepinephrine (NA) neuron degeneration in Parkinson's disease (PD) impacts mood changes and potentially links to postural instability and gait abnormalities. While dopamine-centered treatments show limitations in addressing these symptoms, medications targeting both dopamine and norepinephrine, like methylphenidate, show promise, albeit needing further study. Additionally, the involvement of the NA system in levodopa-induced dyskinesias (LID), as shown in trials with fipamezole, reveals a potential avenue for addressing these specific complications in PD. The complex mechanisms involving α2 receptors require deeper investigation, offering insights into understanding and potentially treating these facets of PD[19].

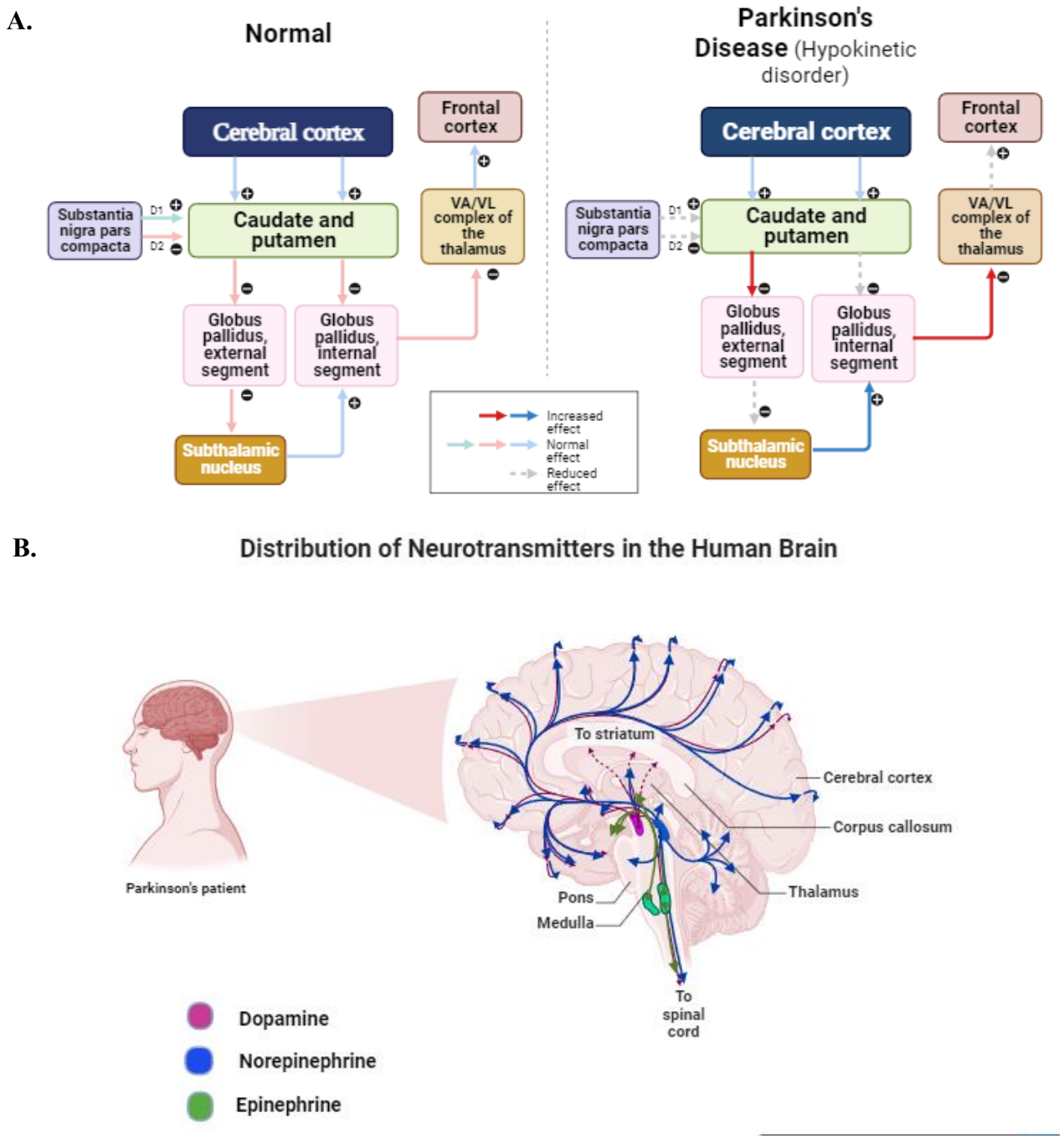

Figure 2(A): Pathophysiology of Parkinson's Disease Compared to a Normal Brain: A comparative illustration depicting the pathophysiology of Parkinson's disease (PD) in contrast to a normal brain. The figure provides a visual overview of key structural and biochemical changes associated with PD.

(B): Role of neurotransmitter in Parkinson's disease pathophysiology.

Illustration highlighting neurotransmitter imbalances in Parkinson's disease. Decreased dopamine levels in the substantia nigra lead to motor dysfunction, while disrupted acetylcholine and serotonin contribute to non-motor symptoms, underscoring the multifaceted neurotransmitter involvement in Parkinson's pathology.

5. Symptoms Of Parkinson's Disease:

Symptoms of Parkinson's disease are divided into two categories[20]:

A. Motor symptoms (MS)

B. Nonmotor symptoms (NMS).

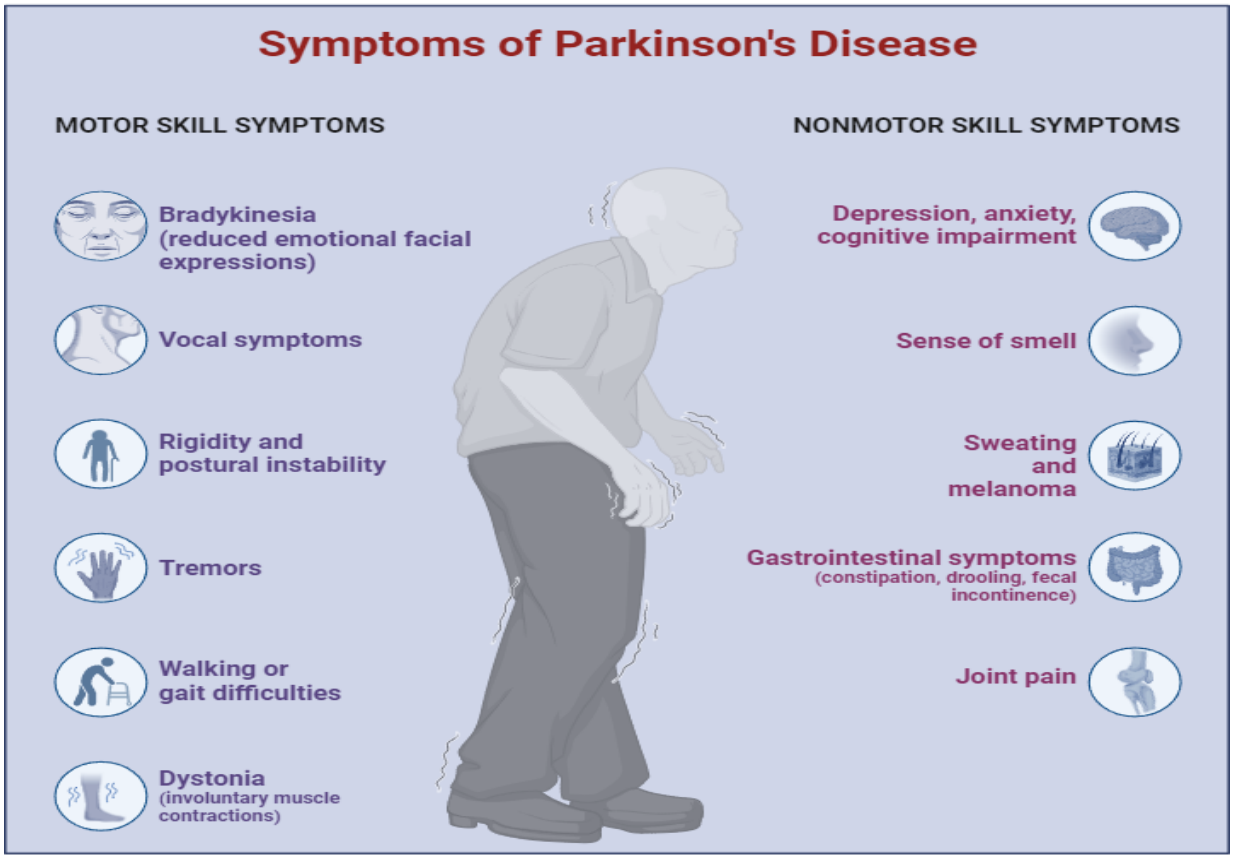

Figure 3: Symptoms of Parkinson's Disease: This figure outlining hallmark symptoms of Parkinson's disease, including tremors, bradykinesia, and postural instability, providing a concise visual representation of the clinical manifestations.

A. Motor symptoms:

Parkinson's disease (PD) brings about symptoms like a resting tremor (usually starting on one side), slow movements (bradykinesia), stiffness, a shuffling walk, and difficulty maintaining balance. It starts gradually, and people might initially think the symptoms are just a part of getting older. PD symptoms worsen over time, but the speed at which this happens can vary from person to person[21].

❖ Tremor:

In Parkinson's disease, a common type of tremor happens when the body is at rest or during movement. This tremor usually occurs at a rate of 4-7 times per second. Sometimes, in the early stages or when movements become very stiff, the tremor can be faster[22]. In Parkinson's disease, tremors can happen when at rest, while holding a posture, or sometimes a mix of both. These tremors can affect the arms and legs but are less common in the head. Unlike slow movements (bradykinesia), tremors may not be there all the time and might decrease as the condition progresses[23]. Postural tremor, often mistaken for Essential Tremor, can also be the initial sign of Parkinson's disease and may occur more frequently in relatives of PD patients. The focus on rest tremor in Parkinson's studies has overlooked action tremor, which, unlike rest tremor, directly correlates with motor disability, weakness, and slower movements, impacting the patient's functionality and quality of life[24].

❖ Bradykinesia:

In PD, bradykinesia stands out as the defining primary motor symptom, characterized by slow movement, reduced amplitude, and impaired fine motor control, all stemming from decreased neuronal density in the substantia nigra. Due to bradykinesia, patient struggle to supply enough energy to their muscles for quick movements, leading to difficulties in executing rapid actions. At the outset, symptoms include delayed reaction times and challenges in multitasking. Additionally, patients may experience difficulties with swallowing, reduced gesturing, and less frequent blinking[25]. The emotional state of PD patients can impact bradykinesia, necessitating stronger external stimuli to engage motor functions. Bradykinesia typically correlates well with the extent of dopamine deficiency[26].

❖ Rigidity:

Rigidity, the second most prevalent primary motor symptom in PD, is characterized by stiffness in the limbs, neck, or trunk. In contrast to bradykinesia, where movement speed is reduced, rigidity involves limited motion within a restricted range due to muscle stiffness and the inability to relax. The painful shoulders, a common symptom arising from rigidity in PD, are frequently mistaken for arthritis[27].

❖ **Postural Instability:**

Postural instability is the key indicator of lost postural reflexes and typically arises in the later stages of the disease. This symptom is the primary cause of most falls in PD patients, leading to subsequent hip fractures[28]. Postural instability does not typically respond to dopaminergic therapy, but promising results have been observed with deep brain stimulation[29].

❖ **Freezing:**

Freezing, also known as motor blocks, represents a type of akinesia (loss of movement) and is among the most incapacitating symptoms in PD[30]. Freezing typically impacts the legs during walking, although it can also affect the arms and eyelids[31]. Typically, it presents as a sudden and short-lived (usually less than 10 seconds) incapacity to move. This can involve hesitating when starting to walk (start hesitation) or experiencing a sudden inability to move the feet in specific situations, such as while turning, navigating narrow passages, crossing busy streets, or approaching a destination. Freezing has notable social and clinical effects on patients, resulting in significant outcomes. Especially, it often results in falls[32]. Freezing can be categorized into five subtypes: start hesitation, turn hesitation, hesitation in confined spaces, destination hesitation, and open space hesitation[33]. Episodes are more pronounced in the OFF state and improve with levodopa therapy. In addition, patients often create techniques to manage freezing episodes. These strategies involve following commands like marching, stepping over objects (such as a walking stick or cracks in the floor), walking to the rhythm of music or a beat, and shifting body weight[34–36].

B. Non-motor symptoms in PD:

The clinical representation of PD has been predominantly influenced by its motor symptoms. However, PD patients often encounter a variety of non-motor symptoms that may appear during different phases of the disease. Non-motor symptoms, which have gained increasing recognition over the past few decades, are now regarded as crucial components of the clinical spectrum. Non-motor symptoms that are frequently observed comprise sleep disturbances, anxiety, depression, constipation, fatigue, changes in smell perception, hallucinations, and a progressive decline in cognitive function, which can lead to dementia[37].

❖ **Autonomic dysfunction:**

Autonomic dysfunction can occur before diagnosis, become noticeable as the disease advances, or be induced by medication[38]. Autonomic dysfunction can have an impact on all aspects of function, with reported effects on the daily lives of over 50% of patients[39].

Autonomic dysfunctions in PD patients lead to a variety of systemic symptoms. These involve cardiovascular symptoms (orthostatic hypotension, cardiac arrhythmia), gastrointestinal issues (gastric dysmotility, indigestion, constipation, and regurgitation), urinary symptoms (frequency, urgency, or incontinence), sexual problems (impotence or hypersexual drive), and thermoregulatory dysfunctions (excessive sweating or intolerance to heat or cold). The pathophysiology of dysautonomia in PD is attributed to the degeneration and dysfunction of nuclei responsible for autonomic functions. These include the dorsal vagal nucleus, nucleus ambiguous, and several medullary centres such as the rostral ventrolateral medulla, ventromedial medulla, and caudal raphe nuclei. These nuclei exert differential control over sympathetic preganglionic neurons through descending pathways[40,41].

❖ **Sleep disturbances:**

Sleep problems are very common in people with Parkinson's disease. Men who have more severe disease, experience drug-related mental symptoms, or have difficulties with thinking have the highest chance of facing sleep issues[42]. In Parkinson's disease, sleep disorders are more prevalent compared to those without the condition. One common issue is REM sleep behaviour disorder, where individuals physically act out their dreams, moving and kicking during the night. This condition affects around 27-32% of people with established Parkinson's, but its symptoms can arise many years before the typical movement-related signs[43]. The link between early-stage Parkinson's and non-movement-related symptoms like smell and REM sleep behaviour could guide tests (like smell assessments and brain imaging for those with REM sleep behaviour disorder) for individuals without symptoms yet. This helps provide guidance and support, particularly for those with family members affected by Parkinson's, who already have a higher risk due to genetic factors[44]

❖ **Anxiety:**

Anxiety disorders are more common in PD patients compared to age-matched controls, but they are frequently underdiagnosed[45]. In PD patients, anxiety disorders are observed in 25-40% of cases and can take the form of panic attacks, generalized anxiety disorder, or different phobias[46]. Pharmacological treatments, including benzodiazepines, buspirone, and SSRIs, can be utilized to manage anxiety. Nevertheless, it is preferable to prioritize the control of PD motor symptoms due to the potential adverse side effects of these agents, particularly benzodiazepines[47].

❖ **Psychosis and Hallucination:**

Hallucinations are more common in the advanced stages of PD. Psychosis and visual hallucinations are frequently seen as side effects of anti-PD medications, and their occurrence is influenced by factors such as dosage, disease progression, and the presence of medical conditions[48]. The risk factors for hallucinations involve advancing age, the presence of dementia, and polypharmacy. Cognitive decline is commonly observed in patients who experience hallucinations. In addition, they experience a more unfavourable prognosis, linked to elevated mortality rates[49]. PD-related hallucinations are primarily visual, as opposed to the auditory hallucinations more commonly associated with schizophrenia[50].

Around 40% of people with Parkinson's may experience seeing things that aren't there, often harmless. But as the disease goes on, more serious issues like strong beliefs, paranoia, and confusion may become more common[51]. Hallucinations can also be linked to problems with thinking, but not necessarily to age, how long you've had the disease, or feeling down. One idea is that medication-related mental symptoms may start with sleep troubles, leading to intense dreams and then hallucinations and confusion[52].

6. Diagnosis:

Initially, Parkinson's disease was categorized as a motor disorder with three cardinal signs: tremor, rigidity, and bradykinesia. With time, postural changes, especially postural instability, came to be recognized as a fourth cardinal sign[53]. In the 1990s, it became evident that a significant number of individuals clinically diagnosed with Parkinson's disease did not meet the histopathological criteria for PD upon autopsy, even when assessed by highly experienced professionals[54,55]. The clinical diagnostic criteria for PD were recently updated[56]. In diagnosing Parkinson's disease, doctors rely on patient history and neurological exams. The International Parkinson and Movement Disorder Society's criteria, originally for

research, help clinicians in diagnosis. A positive response to dopaminergic therapy supports a PD diagnosis, with a higher levodopa dose if needed. Identifying 'red flags' indicating other conditions can speed up diagnosis, but no single flag guarantees a specific diagnosis[57]. Knowing all the red flags and their meanings is mainly needed by movement disorder specialists. For instance, a simple red flag is an unsteady, wide walking stance or difficulty in walking along a straight line for ten steps. This hints at a different kind of parkinsonism[58].

7. Herbal Treatment of Parkinson's Disease:

Below, we describe the herbs that exhibit a significant impact on treating parkinsonism.

Acanthopanax:

These are the dried roots and rhizomes of Acanthopanax senticosus (Rupr. et Maxim.) Harms. An 80% ethanol extract from the Araliaceae plant family exhibits protective effects on dopaminergic neurons in a PD mouse model induced by MPTP-HCl[59]. The stem bark of A. senticosus Harms shows effectiveness in an in vivo PD model. A mixed extract containing 100% ethanol, 50% ethanol, and hot water can serve as a preventive measure against MPTP-induced PD in rats. Additionally, it raises the levels of dopamine (DA) and noradrenaline (NA) in the PD rat model[60,61]. Sesamin, a component of A. senticosus Harms, prevents behavioural dysfunction in a rotenone-induced rat model. Additionally, sesamin, even at picomolar doses, safeguards neuronal PC12 cells against cellular death induced by MPP+[62,63].

Alpinia:

Alpiniae Oxyphyllae Fructus represents the dried, ripe seeds of Alpinia oxyphylla Miq. (Zingiberaceae). An 80% ethanol extract derived from these seeds provides protection against 6-OHDA-induced damage in PC12 cells and dopaminergic neurons in zebrafish[64]. Protocatechuic acid, found in Fructus Alpiniae Oxyphyllae, provides protection to C57BL/6J mice against dopaminergic neuronal damage induced by MPTP[65]. Additionally, it reduces cell death caused by hydrogen peroxide or sodium nitroprusside in PC12 cells and, in PC12 cells treated with MPP (+), inhibits apoptosis, decreases TH expression cytotoxicity, and mitigates abnormal aggregation of alpha-synuclein[66,67].

Camellia:

Camellia sinensis (Cs) is famous for its various tea products, such as green tea, black tea, oolong tea, and white tea. The major form is black tea, representing over 70% of the total tea production[68]. Green tea extracts have the capacity to reduce 6-OHDA-induced activation of nuclear factor-κB (NF-κB) and cell death in SH-SY5Y cells[69]. Polyphenolic catechins obtained from green tea exert protective effects on SH-SY5Y cells and a rat model of PD by inhibiting the ROS-nitrogen monoxide (NO) pathway[70,71]. Polyphenolic catechins consist of four main components: (−)-epigallocatechin-3-gallate, (−)-epicatechin gallate, (−)-epigallocatechin, and (−)-epicatechin. In terms of protective effects on PC12 cells, the order is as follows: (−)-epicatechin gallate > (−)-epigallocatechin-3-gallate > (−)-epicatechin > (−)-epigallocatechin[72]. In MPTP-induced PD mice, (−)-Epigallocatechin-3-gallate, a constituent of polyphenolic catechins, suppresses iNOS expression and prevents cell death. Additionally, it reduces cell death in iNOS expression and prevents cell death. Additionally, it reduces cell death in dopaminergic SHSY-5Y cells induced by dichlorodiphenyltrichloroethane[73,74].

Cassia:

Cassiae Seman is derived from the dried, ripe seeds of Cassia obtusifolia L. or Cassia tora L.(C.tora). One of its components, alaternin from C.tora, exhibits strong peroxynitrite-scavenging properties, which are associated with PD. It also reduces neuronal cell death induced by transient cerebral hypoperfusion in mice[75,76]. The extract of Cassiae Semen exhibits protective effects in PD models against neurotoxicity induced by 6-OHDA in PC12 cells, neuronal degeneration induced by MPTP in the mouse PD model, and in mouse hippocampal cultures[77,78].

Ginkgo:

Ginkgo Folium consists of the dried whole leaf of Ginkgo biloba L. In PD mice models, Ginkgo biloba 761 effectively reduces neurodegeneration in the nigrostriatal pathway caused by MPTP and also shows inhibitory effects against oxidative stress[79]. In PC12 cells, Ginkgo biloba extract demonstrates protective effects against paraquat-induced apoptosis. In rat models of PD, it exhibits dose-dependent protection against parkinsonism induced by 6-hydroxydopamine[80,81].

Gynostemma:

The dried entire herb of Gynostemma pentaphyllum (Thunb.) Makino (Cucurbitaceae) is known as Fiveleaf Gynostemma Herb. Ethanol extracts from this herb have been found to possess neuroprotective effects in a rat model of PD induced by 6-OHDA[82]. Gypenosides, derived from Gynostemma pentaphyllum, exhibit protective properties for dopaminergic neurons. This protection is observed in both primary cultures and within the substantia nigra of a mouse model of PD, guarding against oxidative injury caused by MPP+[83,84].

Hypericum:

The dried aerial part of Hypericum perforatum L. (Guttiferae), known as Hyperici Perforati Herba, contains a methanol extract that shows a neuromodulating effect in mice with PD induced by MPTP[85]. An extract containing high levels of flavonoids from Hypericum perforatum L. offers protection against H2O2-induced apoptosis in PC12 cells[86]. In a rat model of PD induced by rotenone, this extract reduces oxidative stress and enhances the expression of genes related to antioxidant enzymes[87].

Ligusticum:

Tetramethylpyrazine, found in Chuanxiong Rhizoma, offers neuroprotective benefits against MPTP-induced neurotoxicity in both in vivo and in vitro Parkinson's disease models. Additionally, it reduces oxidative damage in rats with PD induced by levodopa[88,89].

Mucuna:

Mucuna pruriens (Mp) seeds possess anti-inflammatory properties and are employed in the treatment of ulcers, helminthiasis, and nephropathy[90]. Mucuna pruriens (Mp) has a historical association with Parkinson's disease, as it has been utilized as an Ayurvedic remedy for providing symptomatic relief[91]. When evaluated in the 6-OHDA-induced rat model of Parkinson's disease, Mucuna pruriens exhibited greater anti-Parkinson activity in comparison to levodopa[92]. In the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) model of Parkinson's disease, Mucuna pruriens treatment demonstrated a superior ability to restore all the deficits induced by MPTP when compared to estrogen[93].

Nardostachys:

Nardostachys jatamansi is a flowering plant belonging to the Valerian family. In the 6-OHDA model of Parkinson's disease, the Nardostachys jatamansi extract exhibits neuroprotective properties, indicated by the elevated population of D2 receptors in the striatum and increased activities of antioxidant enzymes like SOD (superoxide dismutase) and CAT (catalase). Prior treatment with N. jatamansi significantly restores GSH

(glutathione) levels and enhances the density of TH-IR (tyrosine hydroxylase immunoreactivity) fibers[94].

Paeonia:

Paeoniae Radix Alba consists of the dried roots of Paeonia lactiflora Pall. Paeoniflorin, found in Paeoniae Radix Alba, helps protect PC12 cells from damage induced by MPP+ and acidity through the autophagic pathway[95]. In a Parkinson's disease model induced by MPTP, paeoniflorin reduces neuroinflammation and dopaminergic neurodegeneration by activating adenosine A1 receptors[96].

Panax:

Ginseng Radix Et Rhizoma, derived from Panax ginseng C. A. Mey, shows protective effects against MPP+-induced apoptosis in SH-SY5Y cells when used as a water extract[97]. G115, an extract from ginseng, exhibits neuroprotective effects in both MPTP-induced mouse models and MPP+-induced rat models of Parkinson's disease[98]. Ginseng inhibits MPP+ uptake in dopaminergic neurons, reduces oxidative stress from dopamine autooxidation, lessens MPP+-induced apoptosis, and enhances nerve growth factor (NGF). Ginsenosides block dopamine uptake in rat synaptosomes[99].

In rat models, ginsenoside Rg1 exhibits protective effects on dopaminergic neurons in two different models of Parkinson's disease: the ovariectomized rat model and the 6-OHDA-induced rat model. This protection occurs through the insulin-like growth factor-I receptor signaling pathway[100,101]. It also offers neuroprotection against rotenone toxicity[102].

Plumbago:

A study by L.C.S.L. Morais et al showed that the crude ethanolic extract (CEE) and total acetate fraction (TAF) of Plumbago scandens (at a dose of 1000 mg/kg, administered intraperitoneally) reduced locomotor activity, induced catalepsy, and led to palpebral ptosis, indicating their potential in countering parkinsonism[103].

Salvia:

Salviae Miltiorrhizae Radix Et Rhizoma is the dried root and rhizoma of Salvia miltiorrhiza Bge., a plant belonging to the Labiatae family[104]. Salvianolic acid and salvianolic acid B safeguard cells from damage caused by various factors. They shield against oxidative stress caused by H2O2 and help prevent cell death caused by substances like 6-OHDA and MPP+. Moreover, salvianolic acid B shields against cell damage triggered by H2O2 in PC12 cells[105–107].

Table 1: Various studies done on herbal plants for evaluation of their neuroprotective effect.

S.N.	Herbal Plant	Mechanism and uses	Study done on / type of study	Ref
1.	Curcuma (Turmeric)	Anti-inflammatory, antioxidant, neuroprotective	*In vitro, In vivo*	108
2.	Panax (Ginseng)	Neuroprotection, antioxidant, anti-inflammatory	*In vitro, In vivo*	109,110
3.	Mucuna	Boosts movement and behaviour, reduces stress caused by harmful molecules, helps remove metals from the body, improves the performance of cell powerhouses (mitochondria), and enhances communication between brain cells while also helping with TH (tyrosine hydroxylase) functions.	*In vitro, Clinical*	111
4.	Ginkgo	Neuroprotection, antioxidant	*In vitro, In vivo*	112,113
5.	Rhodiola	Neuroprotection, anti-inflammatory	*In vitro, In vivo*	114
6.	Valeriana	Neuroprotection, anxiolytic	*In vitro, In vivo*	115
7.	Uncaria	Anti-inflammatory, antioxidant	*In vitro, In vivo*	116
8.	Prunus dulcis	Reduced problems with behaviour and a lack of dopamine.		117

8. Ayurvedia Treatment of Parkinson's Disease:

Ayurveda, an ancient system of medicine, is based on the concept of Tridosha, which represents three bioentities: Vata, Pitta, and Kapha. These entities are responsible for various physical, physiological, and psychological functions in the human body. Neurological disorders in Ayurveda are often associated with an imbalance in Vata, which is considered the "life force." Parkinson's disease bears a resemblance to the Ayurvedic disorder known as "kampavata," characterized by tremors, stiffness, and depression.

The treatment for kampavata and similar conditions involves both internal and external administration of medicinal substances. General treatment measures include the use of medicated edible fats, sudation, enemas, oil massages, laxatives, and nasal instillation of medicated solutions. Various plant-based drugs, such as Ashwagandha, Atmagupta, Bala, and Paraseekayavanee, are utilized. Additionally, there are medicated oils, decoctions, and powdered drugs.

In recent years, there has been a resurgence of interest in herbal remedies within modern medicine. Research has shown that Mucuna pruriens seeds, known as the cowhage plant, can significantly improve the symptoms of Parkinson's disease, possibly due to their L-Dopa content and other constituents. This suggests a potential bridge between Ayurvedic knowledge and modern understanding of Parkinson's disease. While interpreting ancient Ayurvedic texts can be challenging, they provide evidence that Parkinson's disease has been recognized for thousands of years, with documented symptoms and remedies[118].

9. Allopathic Treatment of Parkinson's Disease:

Drug treatment typically begins when the patient's daily functioning is affected. In such cases, the choice between starting with levodopa or a dopamine agonist depends on the patient's age and symptom severity. As symptoms worsen, additional medications may be introduced. When these medications are no longer effective, surgical options become a consideration. Deep brain stimulation surgery can significantly improve a patient's quality of life and is one of the best available therapies, albeit expensive and not without risks[119].

Table 2. Various drugs used for the treatment of PD's with their mechanism of action, side effect and uses[120].

Treatment Type	Medication Name	Mechanism of Action	Common Side Effects	Usage and Dosage
Levodopa/Carbidopa	Sinemet	Increases dopamine levels in the brain	Nausea, dizziness, dyskinesias	Oral tablets, typically initiated at low doses and adjusted based on response
Dopamine Agonists	Pramipexole (Mirapex), Ropinirole (Requip)	Activates dopamine receptors directly	Nausea, dizziness, hallucinations	Oral tablets, dosage gradually increased
COMT Inhibitors	Entacapone (Comtan), Tolcapone (Tasmar)	Enhances the effects of levodopa by inhibiting COMT	Diarrhoea, orange urine (Entacapone), liver toxicity (Tolcapone)	Taken with each levodopa/carbidopa doses
MAO-B Inhibitors	Rasagiline (Azilect), Selegiline (Eldepryl)	Blocks the enzyme that breaks down dopamine	Insomnia, dizziness	Daily oral tablets
Anticholinergic Drugs	Benztropine (Cogentin), Trihexyphenidyl (Artane)	Helps control tremors and rigidity by balancing neurotransmitters	Dry mouth, confusion, constipation	Usually taken in divided doses
Amantadine	Symmetrel	Enhances dopamine release and reduces symptoms	Swelling, hallucinations, dry mouth	Daily oral tablets
Surgical Procedures	Deep Brain Stimulation (DBS)	Modulates abnormal nerve signals	Risk of infection, lead displacement	Implanted device adjusted as needed
Physical Therapy	N/A	Improves mobility and muscle control	N/A	Tailored exercise regimen

MAO-B: Monoamine oxidase B, N/A: Not Available

Levodopa Absorption and Metabolism in Parkinson's Disease Treatment:

Levodopa is absorbed in the small bowel through the LNAA transport system and undergoes rapid metabolism by AADC and COMT enzymes, resulting in a short plasma half-life. Gastric emptying speed and protein-rich meals can impact levodopa's entry into the brain. To counter AADC degradation, levodopa is administered with AADC inhibitors, and COMT inhibitors may also be introduced. Levodopa crosses the blood-brain barrier via the LNAA transport system, where other LNAAs may compete with it. The precise central mechanisms of levodopa's action are not fully understood, but it's believed to involve decarboxylation to dopamine, which may occur in various brain regions. Experimental and clinical evidence suggests that dopamine receptor antagonists can block levodopa's effects. Dopamine agonists, which directly activate postsynaptic dopamine receptors, are an alternative to levodopa but have not proven as effective, and the reasons for this remain unclear[121].

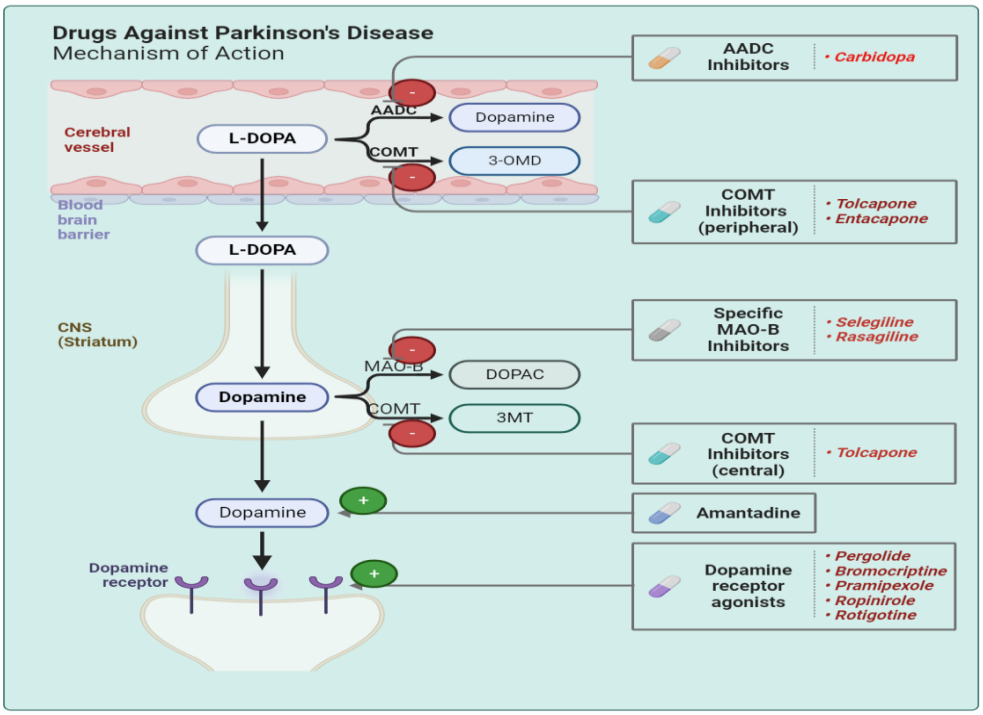

Figure 4: Mechanism of action of Varius Antiparkinsonian Drugs: Diverse Mechanisms Targeting Disease Pathology L-DOPA: Dopamine-Replenishing Agent in Parkinson's Disease[122].

The mechanisms of action of various antiparkinsonian drugs are diverse and aim to address different aspects of Parkinson's disease pathology. Levodopa, the mainstay of treatment, is converted to dopamine to replenish its reduced levels in the brain. Dopamine agonists like pramipexole and ropinirole directly stimulate dopamine receptors. MAO-B inhibitors such as rasagiline or selegiline work to block the breakdown of dopamine in the brain. COMT inhibitors like entacapone extend the effects of levodopa by preventing its breakdown. Amantadine exerts its effects by increasing dopamine release and blocking glutamate receptors, whereas anticholinergics like trihexyphenidyl reduce the activity of acetylcholine, aiming to rebalance the dopamine-acetylcholine equilibrium. Each drug or therapeutic approach targets specific aspects of the disease's neurochemistry to alleviate symptoms and improve the patient's quality of life. Actions of L-DOPA mediated by dopamine: L-DOPA's therapeutic effectiveness in Parkinson's disease is suggested to be related to its potential as a dopamine-replenishing agent in the brain. While its administration increases brain dopamine concentration, the correlation between the efficacy of L-DOPA and post-mortem brain dopamine levels in Parkinson's patients implies part of its beneficial effects are mediated by dopamine. Behavioural responses in animals also support this, evidenced by the inducement of locomotor hyperactivity in rodents and the delay of dopamine-mediated circling behaviour in rats using inhibitors of central DOPA decarboxylase[123].

10. Conclusion:

This review covers Parkinson's disease, emphasizing its growing prevalence, complex pathophysiology, challenging diagnosis, and diverse treatment approaches. Understanding its mechanisms and subtypes is vital for personalized treatment. Despite diagnostic challenges, recent criteria improvements aim to enhance accuracy, particularly in detecting prodromal stages. Treatment options range from Ayurvedic and herbal remedies to allopathic interventions like levodopa and deep brain stimulation. Overall, a multidimensional approach and ongoing research are crucial for improving patients' and caregivers' quality of life.

11. Future Perspectives:

In the future, the field of Parkinson's disease research is expected to witness several promising developments. These include the identification of new biomarkers for early diagnosis, the advancement of precision medicine tailored to individual patients, the exploration of neuroprotective treatments, and the development of innovative therapies such as gene-based interventions. Additionally, research will continue to delve into the underlying mechanisms of the disease, leading to more effective management and potential cures. Overall, the future of Parkinson's disease research holds hope for improved patient care and better quality of life.

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Conflicts Of Interests:

No conflicts of interest

List of Abbreviation:

PD: Parkinson's disease

LBs: Lewy bodies

GABA: Gamma-aminobutyric acid

SNc: Substantia nigra pars compacta

STN: Subthalamic nucleus

NMDA: N-Methyl-D-Aspartate

AMPA: α-amino-3-hydroxy-5-methylisoxazole propionic acid

c-fos: Cellular-feline osteosarcoma gene

NA: Norepinephrine

LID: Levodopa-induced dyskinesias

REM: Rapid Eye Movement

DA: Dopamine

Cs: Camellia sinensis

MPP+: 1-methyl-4-phenylpyridinium

MPTP: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine

iNOS: Inducible Nitric Oxide Synthase

6-OHDA: 6-hydroxydopamine

SOD: Superoxide dismutase

CAT: Catalase

GSH: Glutathione

TH-IR: Tyrosine hydroxylase immunoreactivity

NGF: Nerve growth factor

NF-κB: Nuclear factor-κB

CEE: Crude ethanolic extract

TAF: Total acetate fraction

DBS: Deep Brain Stimulation

COMT: Catechol-O-methyltransferase, MAO-B: Monoamine oxidase B

DOPA: Dihydroxyphenylalanine

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