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A Comprehensive Review of Parkinson's Disease: Insights into Pathogenesis, Clinical Features, and Herbal Treatment Strategies

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Abstract

Parkinson's disease (PD) is a debilitating and progressive neurodegenerative disorder that primarily targets the motor system. It is characterized by the gradual loss of dopaminergic neurons in the substantia nigra region of the brain, resulting in a wide array of motor and non-motor symptoms. In recent years, significant advancements in PD research have deepened our understanding of its pathogenesis and provided insights into potential therapeutic targets. The accumulation of alpha-synuclein protein aggregates (Lewy bodies) in dopaminergic neurons is considered a key pathological hallmark of PD. This, along with mitochondrial dysfunction, oxidative stress, and inflammation, contributes to the progressive degeneration of dopaminergic neurons. In recent years, there has been a growing interest and shift towards herbal drugs and natural remedies as an alternative or complementary approach to conventional allopathic drugs. Herbal drugs, also known as herbal medicines or phototherapeutics, are derived from plant sources and have been used for centuries in traditional medicine systems worldwide. Plants like Curcuma (turmeric), *Withania somnifera* (ashwagandha), Trifolium (red clover), and Tripterygium (thunder god vine) are among the many botanicals that have gained attention for their potential therapeutic properties. Curcuma, for example, contains the active compound curcumin, known for its anti-inflammatory and antioxidant properties. *Withania somnifera*, commonly known as ashwagandha, has been studied for its adaptogenic and stress-reducing effects. Trifolium, or red clover, is rich in phytoestrogens and has been explored for its potential benefits in managing menopausal symptoms. Tripterygium has been investigated for its immunosuppressive properties and its potential in the treatment of autoimmune diseases.

Keywords: - Parkinson's disease (PD), dopaminergic neurons, herbal drugs, Curcuma,

1.INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disorder worldwide, affecting approximately 1-2% of individuals over the age of 65 [1]. It is characterized by the progressive degeneration of dopaminergic neurons in the substantia nigra, leading to the hallmark motor symptoms of bradykinesia, rigidity, resting tremor, and postural instability [2]. However, PD is a complex and heterogeneous disease that also involves a range of non-motor symptoms, including cognitive impairment, sleep disturbances, autonomic dysfunction, and psychiatric manifestations [3].

The etiology of PD remains multifactorial, involving a combination of genetic susceptibility and environmental factors [4]. The aggregation of α-synuclein protein and the formation of Lewy bodies are central pathological features of PD [5]. Additionally, mitochondrial dysfunction, oxidative stress, neuroinflammation, and impaired protein degradation have been implicated in disease progression [6].

While there is currently no cure for PD, several treatment strategies aim to alleviate symptoms and improve quality of life for patients. The gold standard pharmacological therapy is levodopa, a precursor of dopamine [7]. Other medications, such as dopamine agonists and monoamine oxidase-B inhibitors, are used either as monotherapy or in combination with levodopa [8]. Deep brain stimulation (DBS) is a surgical intervention that provides significant benefits for patients with motor complications [9].

Despite significant advancements in our understanding and management of PD, there are still several challenges to overcome. The development of disease-modifying therapies that can slow or halt disease progression remains a major unmet need. Additionally, the identification of biomarkers for early diagnosis and disease monitoring is crucial for the development of personalized treatment approaches.

In this review, we aim to provide a comprehensive overview of PD, discussing its pathogenesis, clinical features, and current treatment strategies including herbal. We will also explore emerging research areas and potential future directions in PD research.

2. PATHOGENESIS

The pathogenesis of Parkinson's disease (PD) involves a complex interplay of genetic and environmental factors, leading to the progressive degeneration of dopaminergic neurons in the substantia nigra. Several key mechanisms have been implicated in the pathogenesis of PD, including α-synuclein aggregation, mitochondrial dysfunction, oxidative stress, neuroinflammation, and impaired protein degradation as shown in figure no.1

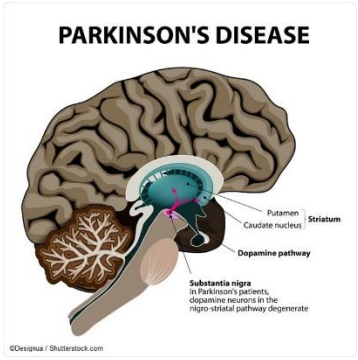

Figure No.1: Pathophysiology of Parkinson's disease

α-Synuclein Aggregation: The aggregation of α-synuclein protein and the formation of intracellular inclusions called Lewy bodies are central pathological features of PD [10]. Mutations in the α-synuclein gene (SNCA) and alterations in the protein's expression, folding, and clearance contribute to the aggregation process [11]. The accumulation of α-synuclein aggregates disrupts normal cellular function, leading to neuronal dysfunction and cell death.

Mitochondrial Dysfunction: Mitochondrial dysfunction plays a crucial role in the pathogenesis of PD. Impaired mitochondrial respiration, oxidative phosphorylation, and increased reactive oxygen species (ROS) production contribute to neuronal damage [12]. Mutations in genes associated with mitochondrial function, such as PINK1 and Parkin, have been linked to familial forms of PD [13]. Dysfunction of the mitochondrial quality control mechanisms, including mitophagy, further exacerbates mitochondrial abnormalities in PD.

Oxidative Stress: Oxidative stress, characterized by an imbalance between ROS production and antioxidant defenses, is a prominent feature of PD pathology [14]. Dopaminergic neurons are particularly vulnerable to oxidative stress due to their high metabolic activity and dopamine's propensity for auto-oxidation [15]. Oxidative stress leads to DNA damage, lipid peroxidation, and protein modifications, contributing to neurodegeneration in PD.

Neuroinflammation: Neuroinflammation, involving activated microglia and astrocytes, is observed in the brains of PD patients [16]. Chronic inflammation contributes to the progressive degeneration of dopaminergic neurons through the release of pro-inflammatory cytokines, chemokines, and reactive oxygen and nitrogen species [17]. Inflammatory processes further propagate α-synuclein pathology and neurodegeneration in PD.

Impaired Protein Degradation: Impaired protein degradation pathways, including the ubiquitin-proteasome system and autophagy-lysosomal pathway, have been implicated in PD pathogenesis [18]. Dysfunction in these clearance mechanisms leads to the accumulation of misfolded proteins, including α-synuclein, impairing cellular homeostasis and promoting neurodegeneration.

3. CLINICAL FEATURES

Parkinson's disease (PD) is characterized by a wide range of motor and non-motor symptoms that significantly impact the quality of life of affected individuals. The clinical features of PD can vary among patients and may change as the disease progresses. Here, we provide an overview of the key clinical manifestations observed in PD [19].

Motor Symptoms: Motor symptoms are the hallmark features of PD and include the following:

Bradykinesia: Slowness and difficulty in initiating and executing voluntary movements.

Rigidity: Increased muscle tone, resulting in stiffness and resistance to passive movement.

Resting Tremor: Typically, a pill-rolling tremor that occurs at rest and decreases with voluntary movement.

Postural Instability: Impaired balance and coordination, leading to a higher risk of falls.

These motor symptoms primarily result from the degeneration of dopaminergic neurons in the substantia nigra and the subsequent depletion of dopamine in the basal ganglia [20].

Non-Motor Symptoms: PD is also associated with various non-motor symptoms that can significantly impact patients' quality of life. Some of the common non-motor symptoms include:

Cognitive Impairment: PD patients may experience difficulties with memory, attention, executive functions, and visuospatial abilities [21].

Sleep Disturbances: Sleep disorders, such as insomnia, excessive daytime sleepiness, restless legs syndrome, and rapid eye movement sleep behavior disorder, are common in PD [22].

Autonomic Dysfunction: Dysautonomia can manifest as orthostatic hypotension (low blood pressure upon standing), urinary problems, constipation, and sexual dysfunction [23].

Psychiatric Manifestations: Depression, anxiety, apathy, and psychosis (hallucinations and delusions) are common psychiatric symptoms in PD [24]. These non-motor symptoms can occur at different stages of the disease and may precede the onset of motor symptoms in some cases.

4. DIAGNOSIS

The diagnosis of Parkinson's disease (PD) is primarily based on clinical assessment, as there are no definitive diagnostic tests available. The diagnostic process involves evaluating the patient's medical history, conducting a thorough neurological examination, and considering supportive investigations to rule out other conditions. Here are the key aspects of the diagnostic approach for PD.

Clinical Assessment: The clinical assessment focuses on identifying the cardinal motor symptoms of PD, including bradykinesia, rigidity, resting tremor, and postural instability. The presence and progression of these symptoms, along with the patient's response to dopaminergic medications, are crucial in establishing a diagnosis of PD [25]. Additionally, a comprehensive evaluation of non-motor symptoms, such as cognitive impairment, sleep disturbances, and autonomic dysfunction, helps support the diagnosis [26].

Diagnostic Criteria: The most widely used diagnostic criteria for PD are the UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria [27]. These criteria require the presence of bradykinesia along with at least one of the following: rigidity, resting tremor, or postural instability. These motor symptoms should be asymmetric, progressive, and not caused by other identifiable causes. Supportive criteria, such as a positive response to dopaminergic therapy or the presence of olfactory loss, can further strengthen the diagnosis.

Neuroimaging: Neuroimaging techniques are not typically required for routine PD diagnosis but may be helpful in certain cases. Dopamine transporter imaging using single-photon emission computed tomography (SPECT) or positron emission tomography (PET) can assess the integrity of the nigrostriatal dopaminergic system and aid in differentiating PD from other parkinsonian syndromes [28]. Imaging findings in PD often reveal reduced dopamine transporter uptake in the striatum.

Biomarkers: Biomarkers that can aid in the diagnosis and monitoring of PD are an active area of research. Several potential biomarkers, including cerebrospinal fluid (CSF) markers, blood-based biomarkers, and imaging markers (such as alpha-synuclein imaging), are being investigated [29]. However, currently, there are no validated biomarkers for routine clinical use in PD diagnosis.

5. TREATMENT STRATEGIES

The management of Parkinson's disease (PD) involves a multidisciplinary approach aimed at alleviating symptoms, improving quality of life, and minimizing functional impairments. The treatment strategies for PD can include medication, surgical interventions, and supportive therapies. Here are the key treatment modalities commonly employed in PD management.

Medications:

a. Levodopa: Levodopa is the most effective and commonly used medication for PD. It is converted to dopamine in the brain, replenishing the depleted dopamine levels. Levodopa improves motor symptoms, such as bradykinesia, rigidity, and tremor. However, long-term use may be associated with motor complications, such as dyskinesias and motor fluctuations [30].

b. Dopamine Agonists: Dopamine agonists mimic the action of dopamine in the brain and can be used as monotherapy or in combination with levodopa. They provide symptomatic relief and may delay the onset of levodopa-related motor complications. Examples include pramipexole, ropinirole, and rotigotine [31].

c. **Monoamine Oxidase-B (MAO-B) Inhibitors:** MAO-B inhibitors, such as rasagiline and selegiline, increase dopamine availability by inhibiting the enzyme responsible for dopamine breakdown. They are used as adjunctive therapy to levodopa and can help reduce motor fluctuations [32].

Deep Brain Stimulation (DBS): DBS is a surgical intervention used in advanced PD cases with motor complications not adequately controlled by medication. It involves implanting electrodes in specific brain regions, such as the subthalamic nucleus or globus pallidus, and delivering electrical stimulation to modulate abnormal neural activity. DBS can improve motor symptoms, reduce medication requirements, and enhance quality of life [33].

Supportive Therapies: a. Physical Therapy: Physical therapy, including exercises targeting strength, balance, and flexibility, can help improve mobility and reduce gait and balance problems in PD [34].

b. Speech Therapy: Speech therapy focuses on improving speech and swallowing difficulties commonly associated with PD. It involves exercises to strengthen muscles involved in speech production and techniques to enhance communication and swallowing function [35].

c. Occupational Therapy: Occupational therapy helps individuals with PD maintain independence in daily activities. It involves strategies to improve fine motor skills, adaptive techniques, and modifications to the home environment to enhance functionality [36].

d. Psychosocial Support: Psychological counselling, support groups, and education programs can provide emotional support, address mental health issues, and offer coping strategies for individuals and their families living with PD [37].

Disease-modifying Approaches:

Disease-modifying approaches in Parkinson's disease (PD) aim to slow down or alter the underlying neurodegenerative processes, potentially altering the course of the disease. While there is currently no definitive disease-modifying therapy for PD, several strategies are being investigated. Here are some of the key disease-modifying approaches that have shown promise in research:

Glucocerebrosidase (GBA) Activators: Mutations in the GBA gene are a significant risk factor for PD. GBA encodes an enzyme involved in the breakdown of certain fats in cells. Enhancing GBA activity has been explored as a potential disease-modifying strategy. Preclinical studies have shown that GBA activators can reduce abnormal protein accumulation and improve motor symptoms in PD models [38].

Immunotherapies: Immunotherapies aim to target abnormal protein aggregates, such as α-synuclein, which are a pathological hallmark of PD. Different approaches, including active immunization (vaccines) and passive immunization (monoclonal antibodies), are being

explored to enhance the immune system's ability to clear abnormal protein deposits. Several clinical trials investigating immunotherapies in PD are currently underway [39].

Neurotrophic Factors: Neurotrophic factors are proteins that support the growth, survival, and function of neurons. These factors, such as glial cell line-derived neurotrophic factor (GDNF), have shown potential in promoting the survival and function of dopamine neurons in preclinical studies. Clinical trials evaluating the efficacy and safety of neurotrophic factor therapies in PD are ongoing [40].

Anti-inflammatory Agents: Neuroinflammation is implicated in the pathogenesis of PD. Modulating inflammatory processes through the use of anti-inflammatory agents has been investigated as a potential disease-modifying strategy. Nonsteroidal anti-inflammatory drugs (NSAIDs) and other immunomodulatory agents have shown some promise in preclinical models, although further research is needed [41].

Mitochondrial-targeted Therapies: Mitochondrial dysfunction plays a role in PD pathogenesis. Targeting mitochondria with specific compounds, such as coenzyme Q10, creatine, and nicotinamide adenine dinucleotide (NAD+) precursors, has been investigated as a disease-modifying approach. These compounds aim to enhance mitochondrial function and reduce oxidative stress, potentially slowing down disease progression [42].

6. PERSONALIZED MEDICINE IN PARKINSON'S DISEASE

Personalized medicine, also known as precision medicine, involves tailoring medical treatment to individual patients based on their specific characteristics, including genetic, environmental, and lifestyle factors. In Parkinson's disease (PD), personalized medicine approaches aim to optimize treatment strategies, predict disease progression, and identify individuals at higher risk of developing PD. Here are some key areas where personalized medicine is being explored in PD:

Genetic Profiling: Genetic factors play a significant role in PD susceptibility and disease progression. Genetic profiling involves identifying specific gene variants associated with PD to better understand an individual's risk and response to treatment. Genetic tests, such as screening for mutations in genes like LRRK2, PARKIN, and GBA, can help guide treatment decisions and identify individuals who may benefit from targeted therapies [43].

Pharmacogenomics: Pharmacogenomics examines how an individual's genetic makeup influences their response to medications. In PD, pharmacogenomic studies aim to identify genetic variants that affect drug metabolism, efficacy, and side effects. This information can be used to guide medication selection and dosing, optimizing treatment outcomes and minimizing adverse reactions [44].

Biomarkers: Biomarkers are measurable indicators that can provide information about disease presence, progression, or response to treatment. In PD, researchers are actively investigating various biomarkers, including imaging markers (e.g., dopamine transporter imaging), cerebrospinal fluid (CSF) markers (e.g., alpha-synuclein, tau, and amyloid-beta), and blood-based markers (e.g., inflammatory markers), to aid in early diagnosis, disease monitoring, and treatment response assessment. These biomarkers can potentially help guide personalized treatment decisions [45].

Wearable Devices and Digital Health: Advancements in wearable devices and digital health technologies offer new opportunities for personalized management of PD. These technologies can provide continuous monitoring of motor symptoms, medication adherence, sleep patterns, and other relevant parameters. The data collected can help clinicians optimize treatment plans, track disease progression, and enable early intervention strategies [46].

Lifestyle and Environmental Factors: Personalized medicine also takes into account individual lifestyle and environmental factors that may impact PD risk and progression. Modifying lifestyle factors, such as diet, exercise, and exposure to toxins, may have a beneficial impact on PD outcomes. Tailoring interventions based on individual circumstances and risk profiles can help optimize overall treatment strategies [47].

It is important to note that personalized medicine approaches in PD are still evolving, and their widespread clinical implementation requires further research, validation, and integration into clinical practice.

8. Herbal medicine used in Parkinson disease

While conventional medication remains the standard treatment for Parkinson's disease (PD), some individuals may seek complementary and alternative therapies, including herbal medicine. It is important to note that the use of herbal remedies for PD should be approached with caution, and consultation with a healthcare professional is advised. Here are some herbal medicines that have been explored in the context of PD:

Mucuna pruriens (Velvet Bean): Mucuna pruriens is a legume native to tropical regions and has been used in Ayurvedic medicine for various conditions, including PD. It is a natural source of levodopa, the main medication used to manage PD symptoms. Some studies have suggested that Mucuna pruriens may provide similar benefits to synthetic levodopa, with potentially fewer side effects. However, standardized formulations and rigorous clinical trials are needed to establish its efficacy and safety [48].

Ginkgo biloba: Ginkgo biloba extract, derived from the leaves of the Ginkgo tree, is a popular herbal supplement with antioxidant and anti-inflammatory properties. It has been investigated for its potential neuroprotective effects in PD. Some studies suggest that Ginkgo biloba may improve cognitive function and motor symptoms in PD patients. However, results have been mixed, and further research is needed to determine its efficacy and optimal dosage [49].

Curcumin (Turmeric): Curcumin is the active compound found in turmeric; a spice commonly used in Indian cuisine. It exhibits antioxidant and anti-inflammatory properties and has been studied for its potential neuroprotective effects in various neurodegenerative diseases, including PD. Preclinical studies have shown promising results, indicating its ability to reduce oxidative stress and protect against dopaminergic neuron degeneration. Clinical trials are ongoing to evaluate its therapeutic potential in PD [50].

Green Tea: Green tea contains polyphenols, particularly epigallocatechin gallate (EGCG), which possess antioxidant and anti-inflammatory properties. Green tea extract has been studied for its neuroprotective effects in PD models, showing potential in reducing oxidative stress and protecting against neurodegeneration. However, more research is needed to determine its effectiveness in human subjects [51].

It is crucial to emphasize that the use of herbal medicines in PD should be discussed with a healthcare professional, as they may interact with conventional medications and have potential side effects. Additionally, the quality and purity of herbal products can vary, so obtaining them from reliable sources is important, which is showing in table no.1

Table no.1 : List of herbal plants used in Parkinson's disease

Plant Name	**Families**	**Mechanism of action**	**Plant Part**	Active	**Ref**
Chrysanthemum indicum	*Asterceae*	Inhibitory actions both on neuronal apoptosis and neuroinflammatory NF-κB/IκB-α signaling pathway	Whole plant	luteolin, apigenin, acacetin	[52-53]
Withania sominifera	*Solanaceae*	GABA mimetic effect	Root	Withanolides, somniferine anaferine kaempferol quercetin	[53-55]
Acanthopanax senticosus (Siberian ginseng)	*Araliceae*	protecting mice against MPTP-induced mitochondrial dysfunction and structural damage	root & rhizome	Eleutheroside B and E, are considered	[56-57]
Curcuma longa	*Zingiberaceae*	Curcumin has been shown to protect against oxidative stress-induced neurodegeneration in 6-OHDA PD by stimulating the Wnt/β-catenin pathway, which consequently leads to improving cell viability, survival, and reducing neuronal apoptosis	Rhizome	Curcumin	[58-59]
Polygala tenuifolia	*Polygonaceae*	protect dopaminergic neurons from oxidative stress and reduce neuroinflammation	Rizome	Tenuifolin, Senegenin, polygalasaponins	[60-61]
Trifolium pratense	*Fabaceae*	rescued the loss of dopaminergic neurons and the shortening of neurites in primary mesencephalic	Whole plant	isoflavones, including genistein, daidzein, and formononetin	[62-63]
Tripterygium wilfordii Hook F.(Thunder God Vine)	*Celastraceae*	protected dopaminergic neurons from LPS-induced degeneration in rat mesencephalic neuron-glia cultures	Root& bark	Triptolide, Celastrol, Wilforgine	[64-67]
Nardostachys jatamansi	*Valirenaceae*	reduce the motor and cognitive symptoms in the animal PD model by regulating DRD2 expression.	Root	nardosinone	[68]
Bacopa monnieri (Brahmi)	*Plantaginaceae*	both neuroprotective and neurorescue effects against MPTP-induced degeneration of the nigrostriatal dopaminergic neurons.	Seed, Whole plant	Bacopaside I and II	[69-70]
Mucuna pruriens	*Fabaceae*	Neuroprotective and dopaminergic	Seed	L-DOPA (Levodopa), Serotonin and 5-HTP	[71]
Gynostemma pentaphyllum (Thunb.) (Southern Ginseng)	*Cucurbitaceae*	demonstrated antioxidant and anti-inflammatory properties, which may help protect neurons from oxidative stress and inflammation	Leaves	Gypenosides,	[72-73]
Centella asiatica	*Apiaceae*	mitoprotective and antioxidative effects of CA may potentially be harnessed for the treatment of brain aging and neurodegenerative disease.	Whole plant	Asiaticoside, Madecassoside, Asiatic Acid, Centelloside	[74-76]
Plumbago scandens	*Plumbaginacea*	Not clear	Whole plant	Not reported	[77]
Ocimum sanctum (Holy Basil or Tulsi)	*Lamiaceae*	the loss of climbing ability and reduction in oxidative stress in the brain of PD model flies	Whole plant	Eugenol, Rosmarinic Acid, Ursolic Acid	[78-81]
Ginkgo biloba	*Ginkgoaceae*	reduction or inhibition of monoamine-oxidase activity	Whole plant	Ginkgolides, Bilobalide	[82-83]
Alpinia oxypylla	*Zingiberaceae*	the PI3K-AKT pathway might be part of the mechanism of neuroprotection of AOE.	Kernel extract	6-Shogaol, Kaempferide, Kaempferol, Quercetin	[84-86]
Panax ginseng (Asian ginseng)	*Araliaceae*	maintaining homeostasis, and anti-inflammatory, anti-oxidant, anti-	whole plant	Ginsenosides, Panaxynol and panaxydol	[87-89]

		apoptotic, and immune-stimulatory activities			
Cynodon dactylon (Bermuda grass or Durva grass)	*Poaceae*	Antioxidant, Flavonoids, Phenolic Acids, Alkaloids in Parkinson's disease and other movement disorders.	Plant extract	apigenin, luteolin, and quercetin, caffeic acid and ferulic acid, hordenine and gramine	[90-92]
Cassia Tora	*Fabaceae*	inhibited paraquat-dependent lipid peroxidation	Seed	chrysophanol, emodin, and rhein	[93-94]
Gastrodia elata	*Orchidaceae*	reduce the death of dopaminergic neurons, α-synuclein accumulation, and neuroinflammation in various PD models	Whole plant	Gastrodin, Parishin, Gastrodioside	[95-97]
Hypericum perforatum L. (St. John's Wort)	*Guttiferae*	increase the expression of brain-derived neurotrophic factor (BDNF), a protein that supports the survival and function of nerve cells.	Whole plant	Hypericin, Hyperforin	[98-100]
Clausena lansium (wampee or wampi)	*Rutaceae*	phenolic components depicted highly significant positive association ($p < 0.05$) with antioxidant activity.	Leaves	Coumarin, quercetin	[101-103]

9. FUTURE PROSPECTS

The future prospects of herbal drugs in the treatment of Parkinson's disease hold significant promise, as research and interest in alternative and complementary therapies continue to grow. Herbal drugs offer several potential advantages that may complement existing pharmacological treatments and enhance the overall management of Parkinson's disease (PD). As research progresses, an evidence-based integration of herbal remedies into conventional treatments could offer safer and more effective therapeutic options for individuals living with PD. However, it is essential to conduct rigorous clinical trials and establish standardized guidelines to ensure the safety, efficacy, and quality of herbal drug use in PD management.

10. SUMMARY AND CONCLUSION

A significant number of traditional herbal ingredients, i.e. herbs, have been identified for their successful role in autonomic dysfunction diagnosis and intervention. Some research has concentrated on herbs such as antioxidants, hepatoprotective, proinflammatory, and anti-apoptosis such as Hypericum, Gastrodia, Panax and specific ayurvedic varieties, Dopamine, flavonoids, alkaloids, and polyphenols are the other constituents contained in these plants against parkinsonism. One should look more closely at the pharmacological and phytochemical constituents of these plants, which can be useful for formulation preparation.

It is primarily because the bulk of traditional herbal items are sophisticated combinations of chemical components which have different phytochemical and pharmacological activities. The details gathered in this review on a wide range of herbal remedies and ingredients with beneficial results on laboratory animals of parkinsonism will be included in the quest for potential medication interventions from traditional medicines for this disease. The medicinal ingredients for which development and related and therapeutic potential are well defined may be prime candidates for further examinations and could eventually contribute to therapeutic intervention.

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