Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(4), 145-158 | ISSN:2251-6727

A Review on Parkinson's Disease and its Management

Shivani Pandey[1], Kisalaya Mishra[2], Dharmendra Singh Rajput[3]

[1]Research Scholar, Department of Pharmacology, Hygia Institute of Pharmaceutical Education & Research, Lucknow, Uttar Pradesh

[2]Associate Professor, Department of Pharmacology, Hygia Institute of Pharmaceutical Education & Research, Lucknow, Uttar Pradesh

[3]Head of Department, Patel College of Pharmacy, MPU, Ratibad, Bhopal, Madhya Pradesh

(Received: 08 February 2024 Revised: 11 March 2024 Accepted: 08 April 2024)

KEYWORDS
Dopamine, Neuropathology, Lewy body, Bradykinasia neurodegeneration

ABSTRACT:

The preservation of neuronal structure and function against insults resulting from cellular damage caused by various agents or neurodegenerative disorders is known as neuroprotection. Amyotrophic lateral sclerosis, Parkinson's, Alzheimer's, and Huntington's are a few of the several NDs that impact millions of individuals worldwide. Primary risk factor for these diseases is growing older. Each of these illnesses has distinct clinical and molecular characteristics and affects certain neurons and/or brain areas. Consequently, a number of in vitro and in vivo experimental models that are unique to each illness have been used to investigate NDs in an effort to comprehend their fundamental processes and discover novel treatment approaches. Parkinson's disease is a complicated neurodegenerative disorder characterized by a progressive loss of function in the nigral dopaminergic neurons of the midbrain. A cure for Parkinson's disease that modifies the illness's pathophysiology is still undiscovered. Herbal remedies have been utilized for hundreds of years to treat neurological diseases throughout Asia, including China and India. This field of medicine has lately gained significant interest due to the development of pharmaceuticals that can cure Parkinson's disease. The pathogenic aspects of Parkinson's disease, proteins clumping together, oxidative stress, ion accumulation, mitochondrial malfunction, and neuroinflammation as well as the latest developments in the field, were originally outlined in this study.

1. Introduction

Parkinson's disease (PD) is a complicated neurological illness that worsens with time and is characterized by bradykinesia, tremor, and rigidity. Some people may also develop postural instability as the illness worsens. James Parkinson initially referred to it as a "shaking palsy" in 1817, and Jean-Martin Charcot went on to better characterize it. It is a progressive, long lasting disorder that usually affects motor functions and affects the central nervous system. [1]

Parkinson's disease (PD) is a neurological condition that is second most common after Alzheimer's disease (AD). Its frequency varies from 0.5-2 percent in individuals 65 to 69 years old to 1-3 percent in those 80 years of age and older. Parkinson's disease (PD) is expected to become more common and cause over 30% increase in incidence by 2030 due to the aging population. This will have direct and indirect consequences to the economy and society. [2]

A characteristic feature of the neuropathology of Parkinson's disease (PD) is the loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc). This loss is caused by a variety of factors, including inflammation, oxidative stress-mediated neuronal cell death, mitochondrial dysfunction, and environmental toxins. [3]

A neurological ailment that can affect both the motor and non-motor systems is called Parkinson's disease (PD). This is a progressive neurological disease that mainly affects the elderly, however it can also affect people much younger. It is the second most prevalent neurological condition. Idiopathic Parkinson's disease can resemble other neurodegenerative illnesses. hese include Dementia with Lewy Bodies (DLB), Multiple System Atrophy (MSA), Corticobasal Degeneration (CBD), and Progressive Supranuclear Palsy (PSP).

Although the exact cause of the illness is unknown, mutations in certain genes linked to familial Parkinson's

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(4), 145-158 | ISSN:2251-6727

disease may provide light on the functions of certain proteins and the processes behind the disorder's development. A complex combination of genetic, environmental, and epigenetic factors leads to Parkinson's disease (PD). Accordingly, the risk of Parkinson's disease (PD) was 1.3% for women and 2.0% for men (ratio = 1.5). [4]

Modifications in a multitude of additional genes were discovered by linkage analysis or a candidate gene approach, and were deemed PD-causative, in addition to the genes causing the six monogenic types of Parkinson's disease. Several genes, including UCHL1 [PARK5], PLA2G6 [PARK14], FBXO7 [PARK15], OMI/HTRA2 [PARK13], GYGYF2 [PARK11], and UCHL1 [PARK5], were even designated as "PARKI." Variants linked to a higher risk of developing Parkinson's disease (PD) have been found in several PARK-designated genes (SNCA, UCHL1, LRRK2, PARK 16, GAK) and a few other genes (MAPT, GBA, NAT2, INOS2A, GAK, HLA-DRA, and APOE).

Parkin, DJ-1, ubiquitin C-terminal hydrolase isozyme L1 (UCH-L1), nuclear receptor-related factor 1, and α-synuclein are among the genes linked to Parkinson or Parkinson-related disorders. With its rapid aggregation and production of the majority of Lewy bodies (LBs), α-synuclein stands out in particular. The proteasome is efficiently inhibited in its activity by the increasing α-synuclein's interaction with it. It's believed that proteasomal dysfunction plays a role in the pathogenesis of Parkinson's disease (PD) because of ubiquitin buildup in LBs and its interactions with parkin and UCH-L1, which impact the proteasomal system. Many studies suggest that neurotoxins may influence the onset of Parkinson's disease by interacting with proteins associated with the disorder, such as α-synuclein. [5]

1.1. Epidemiology

As people age, Parkinson's disease (PD) becomes more common and affects 1% of people those who are over 65 years of age. Early-onset Parkinson's disease (EOPD) is the term used to describe parkinsonian symptoms that start before the age of forty. 3–5% of all PD cases are accounted for by it. The conditions that it falls under include Young-onset PD (YOPD occurs within the age range of 21 to 40 years) and "juvenile" (occurs before age 21). "Late-onset" PD occurs after age of 60 years. In the majority of populations, men are twice as likely as women to have PD. Female sex hormones are shown to have a protective impact. [6] This male preponderance may be explained by gender-specific differences in exposure to environmental risk factors and the existence of gender-associated genetic pathways. The hereditary component accounts for only 5–10% of Parkinson's disease patients. When a patient presents with specific clinical symptoms (e.g., dystonia), the disease appears early, and there is a family history, suspicions about the patient having the genetic form of the illness develop. Over 10% of people with YOPD have a genetic basis, and if the disease appears before the age of thirty, the rate of genetically defined cases rises to over 40%. Numerous main genes, including DJ1 (PARK 7), alpha synuclein (SNCA-PARK1/PARK4), leucine rich repeat kinase 2 (LRRK2/PARK8), PTEN-induced putative kinase 1 (PINK1/PARK6), ubiquitin C-terminal hydrolase like 1 (UCH-L1), and Parkin (PARK2), have been associated to Parkinson's disease (PD). [7]

1.2. Neuropathology

The pathogenesis of Parkinson's disease (PD) involves the accumulation of Lewy bodies, which are abnormal intracellular aggregates containing proteins like ubiquitin and alpha-synuclein (α-Syn), as well as the degeneration or death of dopaminergic neurons in the substantia nigra pars compacta (SNpc). When symptoms occur, 60–70% of neurons in SNpc are destroyed. Studies have shown that, in addition to the dopaminergic neurons of the SNpc, the pathogenic process in Parkinson's disease (PD) involves parts of the central nervous systems and peripheral system. Lewy body pathology begins in neurons of the olfactory system and in the cholinergic and monoaminergic brainstem. As the disease progresses, limbic and neocortical brain regions are also affected. The initial loss of dopaminergic neurons in SNpc is subsequently expanded upon with the establishment of end-stage disease.

1.3. Symptoms of PD are-

Tremor- Tremor is linked to changes in two distinct circuits: the basal ganglia and the cerebella thalamocortical circuit. Parkinson's disease is primarily caused by dopamine depletion in the basal ganglia.

Bradykinesia- Bradykinesia may not be entirely explained by weakness, tremor, or rigidity. Bradykinesia results from a dysfunction in the basal ganglia's capacity to maintain the brain systems responsible for planning and

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(4), 145-158 | ISSN:2251-6727

executing motor orders. Midline motor regions have the greatest degree of the cortical impairment.

Rigidity- Parkinson's disease rigidity might be described as "cogwheel" or "lead pipe." Cogwheel rigidity, characterized by superimposed ratchet-like jerkiness, is commonly seen in upper extremity motions (e.g., flexion and extension of the wrist or elbow). There are several theories regarding the pathophysiology of Parkinson's disease (PD) rigidity, including the enhancement of stretch-evoked reflexes from segmental spinal or supraspinal activity, abnormalities in peripheral sensory inputs that may affect the response to muscle stretch, and modifications to the passive mechanical properties of joints, tendons, and muscles.

Motor fluctuation & Dyskinesia- Motor fluctuations have a complex etiology. Presynaptic neurons lose their capacity to store and release levodopa following its enzymatic conversion to dopamine as Parkinson's disease (PD) worsens and nigrostriatal dopaminergic neurons continue to deteriorate. Long-term Parkinson's disease makes it more difficult for the body to maintain a constant level of dopamine. Dopamine fluctuations could be a major factor in dyskinesia. Primary core mechanisms consist of:

a) The process of nigrostriatal degeneration leads to a decrease in the presynaptic vesicles' ability to store and release dopamine physiologically.

b) Increased levodopa conversion to dopamine and abnormal production of a fake neurotransmitter by serotonin neurons in the striatum.

c) Modifications brought about by plastic alterations in dopaminergic receptors.

d) Elevated striatal glutamatergic activity.

PD is associated with several autosomal dominant genes, including:

SNCA (Alpha- synuclein; PARK1): The long arm of chromosome 4q21 contains the gene alpha-synuclein, which has the missense mutation A53T. This mutation causes early onset Parkinson's disease (PD) as well as fast dementia and behavioral problems. Families with dominantly inherited Parkinson's disease have also been linked to four other mutations: A30P, E46K, G51D, and H5OQ.

LrrK2 (PARK8): With 51 exons, this gene is quite large. More than 80 mutations in this gene have been related to Parkinson's disease (PD) today, with 10% of cases being familial and a sizable percentage being sporadic. The development of lewy bodies and tau protein aggregation, which impairs neuronal function, are the primary processes linked to LrrK2.

Vps35 (PARK17): The late onset, autosomal dominant Parkinson disease (PD) is caused by the D620N mutation in this gene. With higher incidence of tremors, bradykinesia, and postural instability, the condition often manifests at age 51.

Parkin (PARK2): This gene is involved in the proteasome's process. Its function, which is for E3 ubiquitin ligase to ubiquitinate proteins, is lost when a mutation occurs. These lead to the buildup of harmful proteins. These play a critical part in the pathophysiology of Parkinson's disease (PD).

Pink1 (PARK6): Homozygous missense mutation PD has been linked to homozygous nonsense mutation W437X and G309D in this gene. Patients with PINK1 mutations have PD at a young age, it progresses slowly, and they frequently exhibit unusual symptoms such dystonia, anxiety, and depression. This gene functions as an upstream activator of parkin and participates in a common Parkin pathway that detects and removes damaged mitochondria from the mitochondrial network.

Dj-1 (PARK7): This gene offers defence against oxidative damage. This gene has been found to contain more than 10 mutations that can result in autosomal recessive juvenile Parkinson's disease. However, relatively few patients have been identified with Parkinson's disease (PD) caused by mutations in this gene. [8]

1.4. Symptoms

Fig 1: Symptoms of PD

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(4), 145-158 | ISSN:2251-6727

Motor Symptoms of Parkinson's Disease

Cardinal Motor Features ("Classical Triad")-

1. Bradykinesia - In between 80% and 90% of patients, reduced movement amplitude and slowness of motion.

2. Rigidity - The "cogwheel" phenomenon is frequently present, and when the limb is at rest, 80–90% of patients experience resistance to passive movement in the flexor and extensor muscles.

3. Tremor at rest - Initial symptoms are common (70–90% of patients), frequently go away with activity or sleep, and are mainly distal, affecting the hands but also the mouth, tongue, lips, chin, or legs.

4. Others -

Postural instability - Patient falls and injuries are predisposed to causes a loss of postural reflexes and manifests in the later stages of Parkinson's disease.

Dysarthria

Dystonia

Additional motor symptoms can include-

1. Blinking less frequently than usual: This is another sign of diminished facial muscle control.

2. Micrographia, or cramped or small handwriting, is a result of issues with muscle control.

3. Another sign of a loss of control over face muscles is drooling.

4. The mask-like facial expression known as hypomimia, in which there is little to no change in the expressions.

5. Dysphagia, or difficulty swallowing, is caused by a decrease in the control of the throat muscles. It raises the possibility of issues like choking and pneumonia.

6. Generally soft voice (hypophonia): This results from a lack of control over the muscles in the chest and throat. [9]

Nonmotor Symptoms of Parkinson's Disease

1. Autonomic Dysfunction - Orthostatic hypotension (noradrenergic sympathetic nervous system) and constipation (cholinergic parasympathetic nervous system) malfunction of the parasympathetic nerve system (cholinergic), The sympathetic nervous system is responsible for sweating, while the parasympathetic nervous system is in charge of urine retention.

2. Neuropsychiatric Symptoms – Fear, mild cognitive impairment dementia, Depression (such as apathy, suicidal thoughts, and dysphoria), problems of impulse control (such as obsessions, hypersexuality, compulsive buying, and binge eating), Anxiety disorders, psychosis (such as delusions and hallucinations)

3. Sensory Symptoms - Pain, paresthesias, and olfactory impairment (hyposmia)

4. Sleep Disturbance - Daytime drowsiness, sleep apnea, insomnia, restless legs syndrome, sleep attacks, and rapid eye movement

5. Other – Lethargy, diarrhea, and loss of weight [10]

1.5. Treatment

The first response to treatment for many Parkinson's patients may be remarkably favorable.

Still, even though symptoms are usually well controlled, the benefits of medicine tend to fade or alter over time. Medication helps treat movement, tremors, and walking disorders by increasing the quantity of dopamine in the brain. Some medications that are used to treat Parkinson's disease include the following ones:

1.5.1. Carbidopa with levodopa

Since its introduction in the 1960s, levodopa has been the gold standard pharmacological therapy for Parkinson's disease. Animals and plants both contain the organic substance levodopa. The nerve cells in the brain convert it from a precursor to dopamine. It may be possible to alleviate many of the debilitating symptoms of Parkinson's disease by increasing dopamine levels. [11]

Levodopa is a drug which enters the bloodstream through the intestines and travels to the brain where it is transformed into dopamine. It temporarily reduces the patient's symptoms by raising dopamine levels in the substantia nigra and striatum. Although serious adverse effects of Levodopa have been recorded, this medication is one of the main ones used to treat Parkinson's disease. It causes toxicity from free radical production, nausea, and dyskinesia. Carbidopa and L-dopa are administered together to lessen nausea symptoms. Levodopa starts converting to dopamine in the blood and intestines, which causes nausea. Only the conversion inside the brain is permitted by carbidopa, which inhibits it from occurring there. [12]

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(4), 145-158 | ISSN:2251-6727

Since dopamine cannot cross the blood-brain barrier, it cannot be employed as a therapeutic agent. Conversely, levodopa crosses this barrier, however only a very little quantity reaches the brain. To enhance the quantity of levodopa that enters the brain and decrease some of the side effects of this therapy, it is sometimes combined with other drugs, such as carbidopa. Early in the course of treatment, side effects from carbidopa-levodopa medication are usually not a major concern. But when the condition gets worse, the medication does become less reliable and constant. Consequently, dyskinesia may occur in certain people, frequently during the height of the drug's effects. The interval between each dose's effectiveness may start to diminish (wearing-off effect), necessitating more frequent administrations. Long-term carbidopa-levodopa medication may have an on-off effect that causes movement problems related to Parkinson's disease to appear and disappear suddenly and unpredictably. Two further potential side effects are orthostatic hypotension and hallucinations. Some patients may experience nausea when receiving carbidopa-levodopa therapy. [13]

1.5.2. Dopamine Agonists

Medication such as pergolide, bromocriptine, ropinirole and pramipexole acts as a chemical messenger in the brain, generating a dopamine-like response in neurons. They can be administered to prolong the duration of levodopa's effectiveness or in the early stages of the sickness. They can be recommended alone or in combination with levodopa. Before prescribing dopamine agonists to patients, clinicians consider the fact that these drugs typically greater adverse effects than levodopa. Possible adverse effects include fatigue, nausea, vomiting, dry mouth and light-headedness when standing. Although these are common adverse effects when starting a dopamine agonist, they usually disappear after a few days. Certain patients may have confusion, hallucinations, or psychosis as a result of dopamine agonists. [14]

1.5.3. Monoamine oxidase inhibitors

Selegiline and rasagiline are MAOIs that are mostly used in individuals with mild to moderate Parkinson's disease (PD), however, they are also helpful for patients with motor problems due to levodopa in moderately advanced Parkinson's disease (PD).

Selegiline-This medicine delays the breakdown of both naturally occurring dopamine and dopamine derived from levodopa by inhibiting the action of the enzyme monoamine oxidase B (MAO-B), which metabolizes dopamine in the brain. Selegiline may increase and prolong levodopa's effectiveness when taken together with the medication. Heartburn, nausea, dry mouth, and dizziness are possible side effects. Less frequently occurring symptoms like headaches, hallucinations, confusion, and nightmares should be reported to the doctor.

1.5.4. Inhibitors of catechol-O-methyltransferase (COMT)

Medication used to treat levodopa response variability includes entacapone and tolcapone. The COMT enzyme breaks down levodopa in the circulation. Treatment effectiveness is increased because more levodopa can enter the brain when COMT is blocked. Only those whose symptoms are not well controlled by other medications should be provided tolcapone due to the risk of severe toxic effects on the liver. To monitor liver function, patients on tolcapone need to have blood collected on a regular basis. Diarrhea and dyskinesias are possible side effects. [15]

1.5.5. Centrally acting Anticholinergics

Anticholinergics, such as procyclidine, biperiden, and trichyphenidyl and benztropine, inhibit the activity of acetylcholine at muscarinic receptors postsynaptic to striatal interneurons. They do not affect bradykinesia; instead, their main purpose is to lessen tremor. Acetylcholine antagonistic disorders can cause a wide range of negative symptoms, including dry mouth, constipation, impaired vision, disorientation, hallucinations, cognitive impairment, and urine retention. The effectiveness of anticholinergics as PD treatments is limited by these side effects. [16]

1.5.6. Amantadine

The only treatment for mild, early-stage Parkinson's disease is this antiviral drug. Amantadine may also be administered to carbidopa-levodopa-treated Parkinson's disease patients, especially if they have problems with the involuntary movements brought on by the drug (dyskinesia). Side effects include swelling in the ankles and purple spots on the skin. [17]

1.5.7. Coenzyme Q10

For cells to function correctly, mitochondria must synthesise compounds. Coenzyme Q10 is one of these

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(4), 145-158 | ISSN:2251-6727

molecules; it plays a role in the exchange of electrons during cellular respiration, the process by which cells obtain their oxygen-based energy. Parkinson's disease patients frequently have low levels of Coenzyme Q10, and research suggests that supplementing with Coenzyme Q10 may halt the disease's early course. [18]

1.6. Surgery

Surgery was a common treatment for Parkinson's disease in the past. Surgical techniques have been reevaluated, however, after Levodopa and other drug therapies became accessible. With advancements in electrical stimulation techniques and our growing understanding of basal ganglia physiology, there is an increasing availability of surgery for Parkinson's disease (PD). Stereotaxic thalamotomy is not currently a recommended treatment for tremor since the thalamus, in especially the ventral intermediate nucleus, is thought to be the most effective target for managing tremor but does not eliminate bradykinesia.

1.6.1. Stem cell therapy

One popular therapeutic and clinical option for the investigation and management of neurodegenerative diseases is stem cell technology. A range of stem cell therapies are being developed to treat neurodegenerative illnesses. Induced pluripotent stem cells (iPSCs), neural stem cells (NSCs), mesenchymal stem cells (MSCs), and embryonic stem cells (ESCs) are the most widely used instruments for regenerating brain cells in these therapies. In the substantia nigra pars compacta, dopaminergic (DA) neuronal cells are lost as a result of Parkinson's disease (PD). Stem cell-based therapies have the potential to be advantageous through various pathways, including but not limited to cell replacement, trophic effects, promoting remyelination, and inflammatory control. [19]

1.6.2. Acupuncture therapy

Nowadays, PD patients are increasingly receiving acupuncture treatments as an alternative because they have been shown to be successful. A study found that although acupuncture is a good complementary therapy, it does not completely cure PD patients—63% of patients in Korea and 25% of patients in Singapore utilize it. Patients' sleep and rest are improved but not their symptoms if treatment is administered as prescribed, such as applying acupuncture for one hour twice a week to body or scalp acupoints. Acupuncture to the Yanglinquan (GB34) acupoints has been proven in research using functional magnetic resonance imaging to stimulate the putamen and primary motor cortex, hence improving motor performance. Improvements in hemispheric regional blood flow and glucose metabolism are also outcomes of this therapy. In order to slow down the intellectual deterioration in PD patients, acupuncture is therefore essential. For further improvement, though, studies and reports are being prepared. [20]

1.6.3. Deep brain stimulation

Deep brain stimulation (DBS) involves the implantation of electrodes into a targeted brain region by means of magnetic resonance imaging (MRI) and, occasionally, recordings of brain activity while the surgery is being performed. An implanted generator in the chest, close to the collarbone, is attached to the electrodes. The generator may lessen Parkinson's disease symptoms by delivering electrical pulses to the brain.

During a second procedure, an impulse generator battery, or IPG for short, is implanted. An IPG is similar in size to a stopwatch and looks like a heart pacemaker. A controller is provided to patients undergoing DBS surgery so they can examine basic settings like battery life and turn the device on or off. [21]

1.6.4. Gene therapy

Gene therapy was first proposed as a means of recombining defective DNA with healthy DNA in 1972. While there are other methods, the most widely used one is the use of engineered non-replicating viral vectors, mainly lentivirus or adeno-associated virus (AAV), which are recombinant viruses of different serotypes. Non-disease modifying treatments try to correct the abnormal firing of GABA-producing or dopaminergic enzymes in the basal ganglia in order to alleviate the symptoms of Parkinson's disease (PD). Thus, gene therapy is anticipated to be among the most promising medicinal approaches. [22]

1.7. Drugs that should be avoided

Dopamine receptor-blocking medications can cause neuroleptic malignant syndrome, Parkinsonism, or a marked worsening of motor symptoms in Parkinson disease patients. Prochlorperazine and tetrabenazine are examples of neuroleptics; metoclopramide is an antiemetic; prochlorperazine and tetrabenazine are examples of antiemetics; and methyldopa is an example

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(4), 145-158 | ISSN:2251-6727

of an antihypertensive. If you take monoamine oxidase B inhibitors, stay away from meperidine. [23]

2. Plant-derived Anti-parkinsonian Compounds

Natural products made from fruits, vegetables, herbs, and spices have been shown to have neuroprotective properties against Parkinson's disease (PD). These properties include the presence of lycopene, thymocyanin, anthocyanins, flavonoids, ginsenosides, caffeine, ginkgolides, xanthones, oligosaccharide esters, isoflavonoids, catechins, S-allylcysteine, and thymoquinoflavones. The main polyphenol group of flavonoids is composed of aromatic rings that contain 3-OH and phenolic hydroxyl groups. These groups have strong antioxidant and iron-chelating properties. Flavonoids are categorized into flavones, flavanonols, flavanone, anthocyanidins, isoflavones, and anthocyanidins based on their patterns of alkylation, glycation, and hydroxylation. In addition to their antioxidant properties, flavonoids may also work via interacting with signaling cascades in neurons, including PI3K/Akt, MAPK, and protein kinase C, to decrease apoptosis and promote neuronal survival. Furthermore, flavonoids have a direct anti-inflammatory and neurotoxic effect on angiogenesis and neurogenesis. Flavonoids produce an antioxidant effect by scavenging reactive oxygen species (ROS) and free radicals. Increasing oxidative stress and excitotoxicity is a primary concern for neuroprotective compounds because it is thought that this is the primary cause of substantia nigra dopaminergic neuronal failure. There are important components in many medicinal plants that can help prevent Parkinson's disease.

2.1 Bacopa monnieri

Fig 2: *Bacopa monnieri*

Bacopa monnieri, a tiny perennial herb in the Schrophulariaceae family, is also referred to as Brahmi (in India). It features tiny, oblong leaves, plenty of branches, and purple or white blooms. Bacosides A and B are triterpenoid saponins that may serve as biomarkers, are the most significant bioactive components that have been identified and extracted from B. monnieri. By stopping dopaminergic neurodegeneration, blocking alpha-synuclein aggregation, and restoring lipid content in nematodes of pharmacological Caenorhabditis elegans models of Parkinson's disease, bacopa monnieri has been demonstrated to be a promising anti-Parkinsonian medication.

The anti-Parkinsonian effect of B. monnieri is due to its antioxidant and neuroprotective qualities, which also cause a reduction in the aggregation of alpha synuclein proteins and the selective degeneration of dopaminergic neurons. [24]

2.2 Camellia sinensis (Green tea)

Fig 3: *Camellia sinensis*

Famous for its health benefits, green tea is made from the dried and steamed green tea leaves of Cs. The results show that supplementing with Cs reduces the risks of Parkinson's disease. Catechins from the main ingredient of Camellia sinensis and epigallocatechin-3-gallate (EGCC), a part of Camellia sinensis extract, have been demonstrated to offer neuroprotection in the MPTP-induced PD mouse model due to their antioxidant and iron-chelating properties. Additionally, it was shown that the addition of Camellia sinensis polyphenols to a 6-OHDA induced Parkinson's disease rat model appeared to improve redox state, which in turn inhibits the ROS-NO pathway. It accomplishes this by treating dopaminergic neurons in the striatum and midbrain and by preserving the ability to scavenge free radicals. According to recent studies, EGCG protects mice's dopaminergic neurons from toxicity induce by MPTP in the PD mouse model. It tends to lessen oxidative stress by releasing some of the iron in the brain's nigral area. It is also evident that Camellia sinensis's neuroprotective qualities are frequently helpful for Parkinson's disease [25]

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(4), 145-158 | ISSN:2251-6727

2.3 Cassia obtusifolia L

Fig 4: ***Cassia obtusifolia L***

A common annual shrub in China and Korea, Cassia obtusifolia L is used to make roasted tea. It has been demonstrated that Cassiae semen (sicklepod) seed extract (CSE) protects against the MPTP-induced PD mice's substantia nigra and striatal dopaminergic neuronal degeneration as well as in vitro dopaminergic neurons. It has been shown that supplementing with CSE reduces cell damage, attenuates the formation of ROS, and attenuates the depolarization of the mitochondrial membrane in 6-OHDA-mediated PC12 cells. MPTP produces MPP+, a neurotoxic substance that causes dopaminergic neuronal death by blocking respiratory complex 1 activity in dopaminergic neuronal mitochondria.

2.4 Coffea arabica and Coffea canephora

Fig 5: Coffea arabica

Coffee beans, or Coffea arabica and Coffea canephora, are plants that is distributed throughout Africa and Asia. The Adenosine 2A receptor present in these plants is antagonistic to caffeine. Caffeine prevents the death of dopaminergic neurons in MPTP-induced Parkinson disease (PD) rats.

Additionally, in PD mouse models, coffee causes a reversal of motor deficit. It has been demonstrated that caffeine's behavioral and neurobiochemical effects result in less apomorphine-induced rotation and better motor control. It has also been demonstrated that the level of dopamine and its metabolites recovered following caffeine administration when dopaminergic neurotransmissions employing neurotoxic 6-hydroxydopamine (6-OHDA) were experimentally reduce.

Numerous mechanisms have been linked to caffeine's protective benefits, including the regulation of excitotoxicity and neurotoxicity as well as mitochondrial activity, the regulation of glutamatergic excitotoxicity, and the prevention of neuroinflammation via adenosine receptors. Caffeine increases locomotor activity in Parkinson's disease (PD) via acting as an adenosine A2 antagonist. Clinical studies have demonstrated that caffeine can improve Parkinson's disease patients' objective motor impairments. [26]

2.5. Curcuma longa (Turmeric)

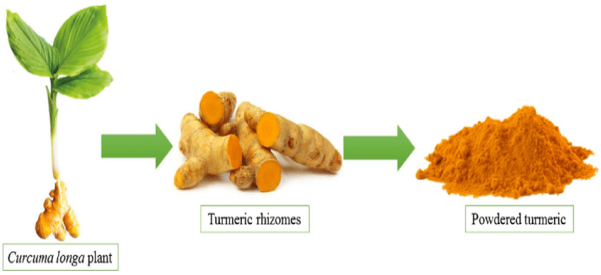

Fig 6: ***Curcuma longa*** **(Turmeric)**

Curcuma longa is a perennial herb whose rhizome was traditionally used to treat sprains and swelling following injuries, either in ancient times or later. The rhizomes of Curcuma longa include the anti-inflammatory and antioxidant compound curcumin. A study discovered that the aqueous extract of C. longa significantly reduced the mouse brain's monoamine oxidase A (MAOA), an enzyme that breaks down dopamine. Additionally, the C. longa extract decreased ROS produced by mitochondria, downregulated caspase 3 activity, and lessened the toxicity of salsolinol in human neuroblastoma cells (SH-SY5Y cells). Curcumin increased the concentration of monoaminergic neurotransmitters, such as dopamine and norepinephrine, in the tissue of the hippocampus. Additionally, it was evident that curcumin increased the expression of TrkB, phosphatidylinositide 3-kinases (PI3K), and derived neurotrophic factor (BDNF) in hippocampus tissue.

Curcumin treatment corrected mice's mitochondrial dysfunction and cognitive deficiencies. In rats undergoing ischemia reperfusion, an intraperitoneal dose of curcumin

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(4), 145-158 | ISSN:2251-6727

enhanced neurological deficits and increased the quantity of neurons tagged with NeuN. Research indicates that curcumin shields against neuronal abnormalities in the SN area of the brain in a 6-OHDA-induced rat model of Parkinson's disease. When taken orally, curcumin increased glutathione levels and decreased lipid peroxide levels. It has been demonstrated that extracts from Curcuma longa, such as calebin-A, demathoxycurcumin, bis-demethoxycumin, and curcumin, shield PC12 cells from β-amyloid damage. Curcumin decreases MDA levels while increasing SOD and GPx. Moreover, an upregulation of the DA and Ach levels was seen. Furthermore, it was noted that memory function had significantly improved.

Another research demonstrated that PQ exposed to PINK1, siRNA cells and curcumin pretreatment resulted in reduced apoptosis and enhanced mitochondrial membrane capacity. Thus, curcumin has a lot of potential for treating Parkinson's disease. [27]

2.6. Delphinium denudatum

Fig 7: ***Delphinium denudatum***

The medicinal plant known as Delphinium denudatum, or Jadwar, is Ranunculaceae family member and is also referred to as Nirvishi or Nirvisha. The bioactive components that were isolated from D. denudatum's roots include isotalatizidine, denudatine, panicutine, condelphine, and diterpenoid alkaloids. It aids in raising glutathione (GSH) levels, activating catalase (CAT), superoxide dismutase (SOD), elevating dopamine levels and lowering 3,4-Methylenedioxyamphetamine (MDA) levels. [28]

2.7. Fructus alpiniaoxyphylla

Fig 8: ***Fructus alpiniaoxyphylla***

Zingiberaceae, the family that includes ginger, has the genus Alpinia. It has been used in older systems of folk medicine, to treat turbid urine, spontaneous salivation, spermatorrhea, dyspepsia, gastralgia, polyuria, and renal asthenia with enuresis. More evidence has recently been discovered to support Fructus Alpinia oxyphylla's preventive properties against a range of neurological diseases. Fructus Alpinia oxyphylla alleviated a deficiency of locomotor activity, reversed dopaminergic (DA) neuron degeneration, and increased the viability of 6-OHDA-treated PC12 cells. [29]

2.8. Gingko Biloba

Fig 9: Gingko Biloba

The ginkgo tree also known as "The living fossil," is among the oldest living tree species on the planet. Ginkgo biloba contains two major bioactive components: ginkgolides and bilobalides. They are classified as the most powerful antioxidants originating from plants and include terpene, lactones, and flavonoids. Additionally, it is widely accessible as a nutraceutical for the prevention of neurological dysfunction, inflammation associated with kidney ailments, visual impairment, and cognitive decline. It functions as an anti-inflammatory, antioxidant, and platelet aggregation inhibitor in addition to regulating neurotransmitters and vasomotor action.

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(4), 145-158 | ISSN:2251-6727

A derivative of ginkgo biloba, ginkgolide B (GB) has potential therapeutic benefits for Parkinson's disease. PEG-PCL nanoparticles have been utilized to encapsulate GB and improve its brain concentration in Parkinson's disease treatment. Gingko can aid in the following ways to help people with Parkinson's disease:

1. It prevents the build-up of Lewy bodies.

2. Inflammation and oxidative stress in the brain might be reduced.

3. It guards both mood and cognitive abilities.

4. Neuroprotection is provided. [30]

2.9. *Juglandis semen*

Fig 9: ***Juglandis semen***

The seed of the Juglans regia L. plant, is a member of the Juglandaceae family, and it is known as Juglandis Semen (JS; walnut). It is both a popular food and spice. According to earlier research, JS-rich caffeine (caffeic acid) dramatically decreased the activity of MAO-B in rat C6 astrocyte cells and avoided Neuronal degeneration caused by 6-hydroxydopamine and its phenethyl ester derivative. [31]

2.10. Mucuna pruriens

Fig 10: ***Mucuna pruriens***

Mucuna pruriens, a plant belonging to the Fabaceae family, has been used in Indian traditional medicine to cure a variety of ailments, including Parkinson's disease. One of the primary ingredients of this plant is L-dopa. The therapeutic value of the tropical legume Mucuna pruriens (Mp) is well known. Analgesic, anti-inflammatory, anti-epileptic, anti-neoplastic, and antimicrobial qualities are claimed for them. Mucuna pruriens has a history in Parkinson's disease (PD) dating back to its usage as an ayurvedic drug for the management of Parkinson's disease symptoms. Long-term Parkinson's disease treatment with Mp appears to be superior than traditional L-DOPA medication, which overuse can result in severe dyskinesia. Significant neuroprotective qualities are present in the seed, leaf, and stem of MP. Seeds are frequently used as anti-PD medications because they contain higher levels of L-DOPA than other plant parts. [32]

2.11. *Panax ginseng*

Fig 11: ***Panax ginseng***

The dried roots of various Panax plant species are used to make ginseng. Ginseng and ginsenosides, a bioactive chemical ingredient, help Parkinson's disease by preventing the degradation of dopaminergic neurons. It boosts antioxidant defenses, decreases inflammation, speeds up the release of dopamine, and protects against neurotoxicity. This helps to strengthen both Parkinson's cognitive loss and motor impairments. The processes involved include AChE, signaling cascade, JNK, GDNF, BDNF, NGF, and brain network reconstruction. In earlier research, ginsenoside-Rg1 (G-Rg1) was shown to be able to slow down the death of dopaminergic neurons in animal models of Parkinson's disease (PD). [33]

2.12. Polygala

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(4), 145-158 | ISSN:2251-6727

Fig 12: Polygala

Polygala root extract (PRE) has been shown to have a neuroprotective impact on dopaminergic neurons and to cause neurotoxicity when exposed to 6-OHDA in Parkinson disease (PD) models that are both in vivo and in vitro. PRE is composed of xanthones, saponins, and esters of oligosaccharides. Reduced nitric oxide (NO) and ROS generation as well as changed caspase-3 activity are likely the route of action. Pre-oligosaccharide derivatives also counteract clinical depression by attaching to norepinephrine transporter proteins. Additionally, PRE's 3,4,5-trimethoxycinnamic acid (TMCA) reduces stress by suppressing norepinephrine.

2.13. Polygonum cuspidatum

Fig 13: *Polygonum cuspidatum*

The perennial herb Polygonum cuspidatum is mostly used in traditional Chinese medicine and other Asian cultures. In mice induced with 6-OHDA, recent research has shown the neuroprotective properties of resveratrol (RES) derived from P. cuspidatum. Its antiapoptotic properties and antioxidant decrease have a protective impact. In a different study, male Wistar rats treated with RES before 6-OHD injection showed no reduction in dopaminergic neuronal death or neurobehavioral abnormalities. The alleviation of DA deficiency and the elevation of antioxidant enzyme status can be the cause of this effect. [34]

2.14. Uncariarhynchophylla

Fig 14: Uncariarhynchophylla

Uncariarhynchophylla is a traditional medication used to treat hypertension, tremors, and convulsive seizures. The primary flavonoids are epicatechin and catechin, whereas the principal alkaloids are hirsutine, corynoxeine, corynantheine, and rhynchophylline. Each was demonstrated to have cytoprotective properties. Uncariarhynchophylla extract (URE) enhanced dopaminergic neuronal failure and apomorphine induced rotation in rats with diminished DA activity using 6-OHDA. In the meantime, caspase 3 activity and ROS production were clearly reduced, and PC12 neurotoxic cells demonstrated remarkably preserved GSH levels and cell viability. [35]

2.15. Withania somnifera (Indian ginseng Ashwagandha)

Fig 15: Withania somnifera

Withania somnifera (WS), a member of the Solanaceae family of medicinal plants, is also referred to as poison gooseberry or winter cherry. India has long utilized Withania somnifera as a medicinal plant, dating back thousands of years. Research indicates that Ws roots tents to normalize oxidative stress induce PD model in MPTP (1-mthyl-4-phenyl-1,2,3,6-tetrahydropyridine) by raising glutathione peroxidase (GPx) and glutathione (GSH)

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(4), 145-158 | ISSN:2251-6727

levels. Researchers found that Ws extract stabilizes the antioxidant stage, which reduces oxidative stress and promotes TH expression in a rat model of Parkinson's disease driven by 6-hydroxydopamine (6-OHDA). An further analysis of Maneb-PQ on the PD mouse model indicates that ws ethanol extract decreases iNOS expression and increases locomotor activity. Consequently, experiments using PD models in mice and rats clearly show that Ws has the ability to prevent PD. [36]

3. SUMMARY & CONCLUSION:

Plants are an endless source of molecules that can be added to food, spices, and herbs to enhance human health. However, a single plant can contain hundreds or even thousands of secondary, bioactive metabolites; it is this chemical diversity that encouraged plants to successfully adapt to their changing environment and ultimately contributed to their evolutionary success. From this angle, it would be inaccurate and premature to credit a single molecule or class of components for the health advantages of a medicinal herb or plant diet. It's likely that a number of phytochemicals work in vivo in additive or synergistic ways that boost, diminish, or inhibit their activity. Herbal treatments are not only seen to be safe, but many people in developing countries cannot afford the exorbitant costs of prescription drugs. Many rely on them as a result. As throughout human history, plant medicines may still be a valuable source of lead compounds, given the lack of effective treatments for the growing number of complex metabolic and neurological illnesses in western countries. It has been demonstrated that the interplay between oxidative stress and inflammation in neurodegenerative illnesses is crucial for the processes that result in the death of neuronal cells. The fact that the natural products used in this communication have several uses may be their most noteworthy quality. Among other things, their multifunctionality appears to offer the compounds considerable potency through mechanisms such as antioxidant and anti-inflammatory effects. The additional pathological characteristics of NDs that connect to these pathways include oxidative stress and uncontrolled inflammation caused by protein precipitation or aggregation, which are linked to neuronal deletions in particular brain regions.

REFERENCES

[1] Dong-Chen Xu, Yong Chen, Yang Xu, Chen-Yu Shen Tu, and Li-Hua Peng. (2023) "Signaling pathways in Parkinson's disease: molecular mechanisms and therapeutic interventions." Signal Transduction and Targeted Therapy 8, No. 73: 1–18.

[2] Aarsland Dag, Batzu Lucia, Halliday Glenda M., Geurtsen Gert J., Ballard Clive, Chaudhuri K. Ray, and Weintraub Daniel. (2021) "Parkinson disease-associated cognitive impairment." Nature Reviews Disease Primers 7, No. 1: 1-21.

[3] Dickson Dennis W. (2018) "Neuropathology of Parkinson disease." Parkinsonism and Related Disorders 46, No. Suppl. 1: S30–S33.

[4] Kouli A, Torsney KM, Kuan WL. (2018) Parkinson's disease: etiology, neuropathology, and pathogenesis. Exon Publications. 21:3-26.

[5] Rahman MM, Wang X, Islam MR, Akash S, Supti FA, Mitu MI, Harun-Or-Rashid M, Aktar MN, Khatun Kali MS, Jahan FI, Singla RK. (2022) Multifunctional role of natural products for the treatment of Parkinson's disease: at a glance. Frontiers in Pharmacology. 6;13:976385.

[6] Riboldi Giulietta M., Frattini Emanuele, Monfrini Edoardo, Frucht Steven J., and Fonzo Alessio Di. (2022) "A Practical Approach to Early-Onset Parkinsonism." Journal of Parkinsons disease 12, No. 1: 1-26.

[7] Radhakrishnan Divya M., and Goyal Vinay. (2018) "Parkinson's disease: A review." Neurolgy India 66: S26-35.

[8] Sinha PR, Charan AA. (2017) Parkinson's disease: A review article. The Pharma Innovation. 1;6(9, Part H):511.

[9] Sveinbjornsdottir Sigurlaug. (2016) "The clinical symptoms of Parkinson's disease." Journal of Neurochemistry 139, No. Suppl. 1:318–324.

[10] Stacy Mark. (2011) "Nonmotor symptoms in Parkinson's disease." International Journal of Neuroscience 121, No. SUPPL. 2: 9–17.

[11] Shaik Rahaman, Sreevani Basavaraju, Ravishanker K., Aparna T. Naga, Hemanth K., Kumar Rohit, and Sadik Jaffer. (2023) "Anti-Parkinsonian Effect Of Momordica Dioica On Haloperidol Induced Parkinsonism In Wistar Rats." Journal of Pharmaceutical Negative Results 14, No. 3: 69-81 .

[12] Charan Amit Alexander, and Sinha Priyansha Raj. (2017) " Parkinson's disease: A review article." The Pharma Innovation Journal 6, No. 9: 511–513.

[13] Carrarini Claudia, Russo Mirella, Dono Fedele, Pietro Martina Di, Rispoli Marianna G., Stefano Vincenzo Di, Ferri Laura, Barbone Filomena, Vitale

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(4), 145-158 | ISSN:2251-6727

Michela, Thomas Astrid, Sensi Stefano Luca, Onofrj Marco, and Bonanni Laura. (2019) "A stage-based approach to therapy in parkinson's disease." Biomolecules 9, No. 8: 1-32.

[14] Murakami Hidetomo, Shiraishi Tomotaka, Umehara Tadashi, Omoto Shusaku, and Iguchi Yasuyuki. (2023) "Recent Advances in Drug Therapy for Parkinson's Disease." Internal Medicine. 62, No. 1:33-42.

[15] Jankovic Joseph, and Tan Eng King. (2020) "Parkinson's disease: Etiopathogenesis and treatment." Journal of Neurology, Neurosurgery and Psychiatry 91, No. 8: 795–808.

[16] Brocks Dion R. (1999) "Anticholinergic drugs used in Parkinson's disease: An overlooked class of drugs from a pharmacokinetic perspective." J Pharm Pharmaceut Sci 2, No. 2: 39-46.

[17] Roger Butterworth. (2020) "Amantadine for the Treatment of Parkinson's Disease and its Associated Dyskinesias." Journal of Parkinson's disease & Alzheimer's disease, 7, No. 1: 1-7.

[18] Rauchová Hana. (2021) "Coenzyme Q10 Effects in Neurological Diseases." Physiological Research 70, No. Suppl. 4: 683–714.

[19] Chandra Suresh, Srivastav Mayank, and Chauhan Neelam. "Recent advances in Parkinson disease." Pharmaceutical And Biological Evaluations 4, No. 3 (2017): 141–147.

[20] Zhao Yadan, Zhang Zichen, Qin Siru, Fan Wen, Li Wei, Liu Jingyi, Wang Songtao, Xu Zhifang, and Zhao Meidan. (2021) "Acupuncture for Parkinson's Disease: Efficacy Evaluation and Mechanisms in the Dopaminergic Neural Circuit." Hindawi Neural Plasticity. 1-23

[21] Hariz Marwan, and Blomstedt Patric. (2022) "Deep brain stimulation for Parkinson's disease." J Intern Med. 292, No. 5: 764-778.

[22] Axelsen TM, Woldbye DP. (2018) Gene therapy for Parkinson's disease, an update. Journal of Parkinson's disease. 1;8(2):195-215.

[23] Rizek Philippe, Kumar Niraj, and Jog. Mandar S. (2016) "An update on the diagnosis and treatment of Parkinson disease." CMAJ 188, No.16:1157-1165..

[24] Fatima U, Roy S, Ahmad S, Ali S, Elkady WM, Khan I, Alsaffar RM, Adnan M, Islam A, Hassan MI. (2022) Pharmacological attributes of Bacopa monnieri extract: Current updates and clinical manifestation. Frontiers in nutrition. 18; 9: 972379.

[25] Chacko SM, Thambi PT, Kuttan R, Nishigaki I. (2010) Beneficial effects of green tea: a literature review. Chinese medicine.; 5:1-9.

[26] Bhusal CK, Uti DE, Mukherjee D, Alqahtani T, Alqahtani S, Bhattacharya A, Akash S. (2023) Unveiling Nature's potential: Promising natural compounds in Parkinson's disease management. Parkinsonism & Related Disorders. 10:105799.

[27] Fu W, Zhuang W, Zhou S, Wang X. (2015) Plant-derived neuroprotective agents in Parkinson's disease. American journal of translational research.; 7(7):1189.

[28] Navid RB, Karimi M, Ghojazadeh M, Araj-Khodaei SM, Bagherzadeh-karimi A, Dolati S. Jadwar (2020) (Delphinium denudatum Wall): a medicinal plant. Tradit Med Res; 5(6):487-97.

[29] Khazdair MR, Kianmehr M, Anaeigoudari A. (2021) Effects of medicinal plants and flavonoids on Parkinson's disease: a review on basic and clinical evidences. Advanced pharmaceutical bulletin;11(2):224.

[30] Yan YC, Xu ZH, Wang J, Yu WB. (2022) Uncovering the pharmacology of Ginkgo biloba folium in the cell-type-specific targets of Parkinson's disease. Frontiers in Pharmacology. 29;13:1007556.

[31] Choi JG, Park G, Kim HG, Oh DS, Kim H, Oh MS. (2016) In vitro and in vivo neuroprotective effects of walnut (Juglandis semen) in models of Parkinson's disease. International Journal of Molecular Sciences. 15;17(1):108.

[32] Rai SN, Birla H, Zahra W, Singh SS, Singh SP. (2017) Immunomodulation of Parkinson's disease using Mucuna pruriens (Mp). Journal of Chemical Neuroanatomy. 1;85:27-35.

[33] Van Kampen JM, Baranowski DB, Shaw CA, Kay DG. (2014) Panax ginseng is neuroprotective in a novel progressive model of Parkinson's disease. Experimental gerontology. 1;50:95-105.

[34] Yin R, Xue J, Tan Y, Fang C, Hu C, Yang Q, Mei X, Qi D. (2021) The positive role and mechanism of herbal medicine in Parkinson's disease. Oxidative medicine and cellular longevity.; (1):9923331.

[35] Khanam S, Subitsha AJ, Sabu S. 2021) Plants as a promising source for the treatment of parkinson disease: a systemic review. IP Int J Compr Adv Pharmacol.; 5:158-66.

[36] Zahiruddin S, Basist P, Parveen A, Parveen R, Khan W, Ahmad S. (2020) Ashwagandha in brain

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(4), 145-158 | ISSN:2251-6727

disorders: A review of recent developments. Journal of ethnopharmacology. 15;257:112876.