



## EXPLORING TRADITIONAL APPROACHES IN THE MANAGEMENT OF PARKINSON'S DISEASE

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**ABSTRACT** Parkinson's disease (PD) is a chronic, degenerative neurological disorder that affects over 5 million people globally. The likelihood of developing the disease rises with age. Sustained microglia activation and neuroinflammation are thought to play an important role in the mechanism of chronic dopaminergic neuronal loss in Parkinson's diseases. Oxidative stress, mitochondrial dysfunction, protein malfunction, inflammation, autophagy, apoptosis, and abnormal  $\alpha$ -synuclein deposition are among the pathogenic processes. In India, a patient spends around 16-41.7% of the income for medications. Though cost of treatment in India is lesser, it is still out of reach of many patients. To consider surgical options, when necessary, may be much more difficult in patients of lower socioeconomic status. In India, many patients seek alternative medicine, especially in chronic diseases. Ayurveda is the most common alternative medicine available in the country for PD. The systematic analysis of the publications demonstrates that the treatment of Parkinson's disease in Ayurveda requires a lot of research with its relevance and efficacy in building an Ayurvedic treatment regimen. More research is needed to better understand the condition in patients, both globally and in India based on Ayurveda. This review presents a brief overview of the Parkinson's disease and their current treatments, followed by a discussion of the natural compounds which have been studied as therapeutic agents and the mechanisms underlying the beneficial effects, in particular the decrease in oxidative stress.

**KEYWORDS :** Parkinson's disease, Pathophysiology, Neuroinflammation, Ayurveda, Natural Remedies

### INTRODUCTION:-

Parkinson's disease (PD) is a chronic, progressive, neurodegenerative disease with a multifactorial aetiology. Characterized by hallmark signs of bradykinesia, rigidity, tremor, and postural instability, it is superseded only by Alzheimer's disease as the most common neurodegenerative disorder.<sup>1-5</sup> PD is an extrapyramidal, slowly progressing motor neurodegenerative condition. It is a result of neurodegeneration, particularly in the region of the brain that regulates movement. This causes an imbalance of a neurotransmitter called dopamine, resulting in decreased motor responsiveness.<sup>6</sup>

The geriatric period is commonly thought to begin in the sixth decade and last until the tenth decade. The neurological disorders seen in this geriatric population are frequently degenerative in nature. "Parkinson's disease" is the second most common serious neurological condition after Alzheimer's disease. It is a slowly progressive neurodegenerative disease of late adulthood.<sup>7</sup>

James Parkinson described Parkinson's disease (PD) for the first time in the early nineteenth century. However, knowledge of PD has existed in India since ancient times. It is known as Kampavata in the ancient Indian medicinal system Ayurveda, and it is characterised by Kampa (Tremors), Stambha (Rigidity), Chesthahani (Akinesia), and Gativikriti (Gait disorders). If left untreated, the symptoms increase over time to end-stage disease, in which the patient is unable to move, breathe correctly, and dies primarily from chest infections and embolism.<sup>6,8,9</sup>

The main goal of effective Parkinson's disease treatment is to increase and replenish the brain's dopaminergic activity. As a result, therapy consists of drugs that either increase synaptic dopamine concentration and release or inhibit its degradation. The traditional pharmacological treatment of Parkinson's disease is based on dopamine replacement using dopamine precursors (levodopa, L-DOPA, L-3,4 dihydroxy phenylalanine), dopamine agonists (amantadine, apomorphine), and MAOB inhibitors (selegiline, rasagiline), which can be used alone or in combination. Currently available pharmaceutical treatments for Parkinson's disease do not alleviate the degeneration process of dopaminergic neurons fundamentally and have major side effects.

Environmental pollutants, medicines, pesticides, brain microtrauma, localised cerebrovascular injury, and genomic defects are all potential risk factors.<sup>6,9</sup>

In most cases, the initial symptoms appear later in life, at the age of 40 or older. To distinguish it from other types of Parkinsonism, Parkinson's disease is also referred to as primary Parkinsonism or idiopathic Parkinsonism. It is a common accelerative bradykinetic condition with a simple diagnosis. It is distinguished by severe loss in the motor portion of the pars compacta cell and  $\alpha$ -synuclein aggravation in certain brain stem, spinal cord, and cortical regions.<sup>11</sup>

### Epidemiology:-

James Parkinson originally described Parkinson's disease (PD) in 1817. In persons over the age of 65, the prevalence of Parkinson's disease is around 1%. It usually begins between the ages of 40 and 70, and it is extremely rare before the age of 20. If Parkinson's disease (PD) develops before the age of 20, it is referred to as young onset PD, which has a distinct aetiology than other varieties of PD, is frequently inherited, and is caused by Wilson's disease or Huntington's disease. Men are three times as likely than women to get Parkinson's disease.<sup>42</sup>

The prevalence of Parkinson's disease is roughly 160 persons per 100,000 people, while the incidence is around 20 people per 100,000 people. The disease's prevalence and incidence rise with age, so that by the age of 70, the prevalence is about 550 people per 100,000, and the incidence is 120 people per 100,000. Trauma, overwork, exposure to coldness, rigid personality, and stress are thought to be risk factors; however, this has yet to be definitely demonstrated.<sup>45</sup>

Though the prevalence of PD in India is less compared to other countries the total burden of PD is much higher as a result of large population. The prevalence rate in Europe is 1.8 per 100 in population above 65 years.<sup>9</sup>

### SYMPTOMS OF PARKINSON'S DISEASE:-

The basic symptoms of Parkinson's disease are four cardinal motor manifestations: (1) resting tremor, (2) bradykinesia (slowness of movement), (3) rigidity (stiffness of muscle) and (4) postural

instability (impairment of postural reflexes), which comes later in the disease.<sup>5,12</sup> Micrographia (abnormally small, cramped handwriting) and difficulties in other fine skills, such as button fastening, are symptoms experienced by patients when the dominant hand is implicated. Motor complaints typically begin asymmetrically but progress to the contralateral side over time.<sup>5,13</sup>

### (1) Resting tremor

A state in which the person's muscles relax, such as when the hands are hanging in resting condition. This typically affects the fingers or hands and is common in stressful situations. Tremor initially affects only one body region or half of the body in around 60-70% of cases, but becomes more severe over time.<sup>4,5,13,14</sup>

### (2) Rigidity

When a patient tries to move an arm, neck, or leg, they may experience stiffness or freezing. The muscles remain tight and constricted, and the person feels fragile and lacks grace or pace.<sup>4,5,13,14</sup>

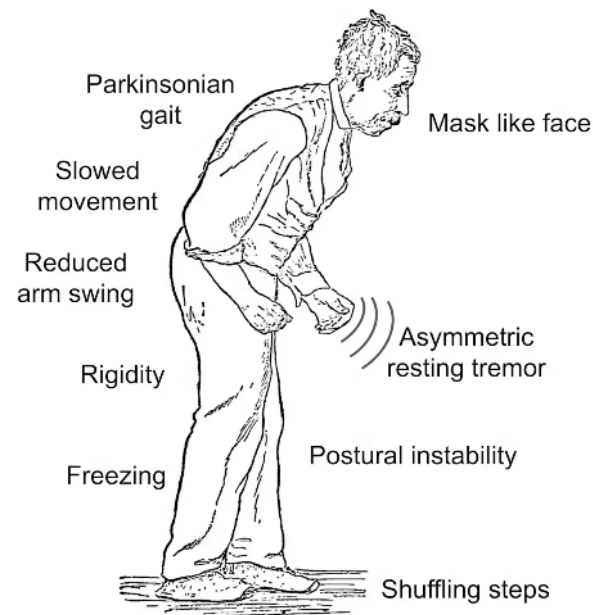
### (3) Bradykinesia

It is distinguished by an incapacity or slowness to initiate a movement. Reduced facial movement, shuffling stride, alteration in speech, and trouble with fine-fingered movements are examples of contributing flaws. The most difficult component of the condition for many sufferers is extreme frustration. The patient may even experience trouble and be unable to do fundamental daily duties such as writing, dressing, using utensils for eating and serving, and rising from chairs or bed.<sup>4,5,13,14</sup>

### (4) Postural reflexes impairment

Postural reflexes impairment, also known as posture instability, is the inability to balance the entire body with conditional synchronisation. Patients may take a backward or forward lean to balance and fall more readily, resulting in a stooped posture with modest hip and knee flexion, a bowed head, and rounding of the shoulders.<sup>4,5,13,14</sup>

**Secondary signs and symptoms:** - anxiety, stress, tension, constipation, swallowing difficulties, insomnia, slower blinking, low blood pressure after waking up, sweating, and a lack of body temperature regulation are all symptoms.<sup>4,5,13,14</sup>



**Figure: - 1.** Symptoms of Parkinson's disease

## AETIOLOGY OF PARKINSON'S DISEASE:-

### Idiopathic Parkinsonism:-

In 70-80% of cases, the physician is unable to identify the exact cause of Parkinson's disease, also known as idiopathic Parkinsonism. It was discovered that roughly 15% of cases had a link to disease occurrence, involvement of single gene mutations in genes like Alpha synuclein non A4 component of amyloid precursor (SNCA), Leucine-rich repeat kinase-2 (LRRK2), Parkin RBR E3 ubiquitin protein ligase (PARKIN), Parkinson protein 7 (DJ-1), PTEN induced putative kinase

1 (PINK1), and HtrA serine peptidase 2 (HTRA2) genes among others, have been linked to mitochondrial dysfunction, resulting in impaired electron transport chain (ETC) function, oxidative stress, and increased susceptibility to excitotoxicity in substantia nigra and the accumulation of damaged synuclein proteins are also generated and Apoptosis is also triggered.<sup>10</sup>

### Secondary Parkinsonism:-

"A group of disorders with recognised origins that are associated with basal ganglia functioning abnormalities as well as symptoms similar to Parkinson's." Underlying reasons such as metabolic disorders (hypothyroidism, hyperparathyroidism, Wilson's disease), viruses, drugs, toxins, tumours in basal ganglia, hydrocephalus, and vascular disease etc. are some predisposition factors associated with secondary Parkinsonism.<sup>10,20</sup>

### Environmental Factors

Epidemiological studies have shown that the following environmental factors are positively associated with the chance of getting Parkinson's disease.

### Pesticide exposure (Rotenone and Paraquat)

According to a NIEHS (National Institute of Environmental Health Sciences) assessment, rotenone and paraquat directly impair mitochondrial function. People who are exposed to these pesticides are 2.5 times more likely to develop disease than the non-exposed group. Trichloroethylene, manganese, carbon disulphide, carbon monoxide, cyanide, methanol, exposure to wood preservatives, and exposure to MPTP are all examples of industrial chemicals. Most of these environmental factors were assumed to be linked to mitochondrial dysfunction.<sup>15</sup>

## PATHOPHYSIOLOGY OF PARKINSON'S DISEASE:-

### Genetics

Until recently, most researchers believed that environmental factors were the only whole and sole cause of Parkinson's disease (PD), but investigations such as gene mutations in familial, inherited, or autosomal forms of PD have led to a global exposure in neurobiology research and the impaired function of the altered proteins encoded by these genes. Most people do not inherit PD, but the genes that cause the sporadic type of PD can use to better understand both inherited and non-hereditary instances of the disease. It has been discovered that the genes and proteins responsible for the inherited type of Parkinson's disease are the same as those responsible for the non-inherited form, but environmental chemicals or other risk factors also play a role.<sup>6,10</sup>

### Alpha-synuclein

Alpha-synuclein was the first gene discovered to be linked to Parkinson's disease. Several research on the genetic profiles of sporadic and non-sporadic cases were conducted, and it was discovered that the neurohistopathology of the disease was slightly associated to an impaired protein disposal mechanism of cells due to an alpha-synuclein mutation. These results support the role of alpha synuclein in the genesis of Lewy bodies (clumps of alpha-synuclein proteins). These findings revealed a potential link between non-sporadic and sporadic forms of the disease, allowing researchers to better understand the biomolecular and histopathological differences between the normal functioning of alpha synuclein and its debilitated effects caused by mutations in alpha-synuclein during normal cellular activity.<sup>17</sup>

It was later discovered that during the normal course of cellular activity inside the cell body, all of the individual molecules of alpha-synuclein protein form a spiral and coiled shape together, forming little protein fibres called fibrils; this process is known as fibrillization. However, the mutant alpha-synuclein gene inhibits this fibrillization process and causes protofibril build up, a transitory step during alpha-synuclein fibrillization. The structure of Proto fibrils is similar to that of bacterial and insect toxins, and it promotes membrane leakage and cell death. The mutant alpha synuclein-induced impaired fibrillization harms the cells usual housekeeping functions. The effects of this type of dysfunction include the accumulation of proteins to hazardous amounts.<sup>18</sup>

Lysosomal activity attacks alpha-synuclein in a typical protein disposal system. However, mutant alpha-synuclein prevents lysosomal processing of alpha synuclein as well as other proteins, resulting in 'trash' due to hazardous protein accumulation. The presence of alpha-synuclein in close proximity to cell membrane was

found in a post-mortem report of brain tissue from a diffuse Lewy body disease patient; it has been suggested that this may be related to clogging up the protein disposal mechanism of neurons and causing them to die. As a result of this type of dysfunction, proteins accumulate to hazardous levels.<sup>16,18</sup>

#### **Oxidative Stress, Mitochondria and Programmed Cell Death**

For many years, mitochondria, the cell's powerhouse, have been firmly linked to disease development. Mitochondria have their own DNA, which is known as mtDNA. This DNA is distinct from the genes located in the cell's nucleus. The majority of the researchers discovered Complex I (group of proteins) anomalies, the largest and most efficient energy processing component of mitochondria, appeared in Parkinson's disease. Mitochondria are a primary source of free radicals for the cell, which cause damage to its own components such as DNA, protein, and lipids through the process known as oxidative stress.<sup>6,15,21</sup>

Mitochondria are also involved in protein breakdown, Lewy body formation, neuron cell toxicity, and death. Toxins such as MPTP and rotenone disrupt mitochondrial complex I, causing an increase in free radicals that can cause alpha synuclein to aggregate or clump together to create microfibrils known as fibrils. According to studies, mitochondria, specifically striatal neurons, are more sensitive to complex I impairment due to specific genetic polymorphisms in mtDNA that raise the risk of Parkinson's disease, although other types of mtDNA changes support a lower risk.<sup>10,15,17,21</sup>

Another consequence was that in reaction to oxidative stress and mitochondrial toxins, mitochondria activate caspases, producing a chemical called cytochrome c, which activates these caspases and other cell death factors. Collectively, oxidative stress and mitochondrial triggered apoptosis are the controlling and definitive variables in neuronal loss, providing potential targets for therapeutic plan development.<sup>17,21</sup>

#### **Protein Degradation (Ubiquitin Proteasome System - UPS)**

The Ubiquitin Proteasome System (UPS) is the natural protein disposal system of cells. Researchers believe that failure of this disposal system increases the likelihood of poisons and other compounds building up to harmful toxic levels inside the cells, leading to cell cytotoxicity. Ubiquitin, which works as a regulatory protein as a tagging component in the UPS, targets specific proteins for breakdown by one of the primary intracellular devices known as proteasomes, as well as recycling of unneeded proteins. Proteasomes typically deal with endogenous proteins such as cyclins, as well as proteins encoded by viruses and other pathogens. In the UPS, several proteins, including parkin and UCH-L1, interact with one another. The interruption in the UPS pathway may supports the underlying mechanism through which mutations in these genes occurs and causes Parkinson.<sup>16,17,18</sup>

According to research, the UCH-L1 gene is important in the manufacturing of ubiquitin, and mutations in the parkin gene disrupt normal proteasomal activity. Toxin exposure produces mutations in alpha-synuclein, making it prone to apoptosis, which is accompanied by activation of death domains termed caspases and mitochondrial damage. Cyclosporine-A prevents apoptosis by preventing the production of substances that activate caspases. Proteasome inhibition causes the accumulation of molecules such as Bax, NFkB, and p53, which are contributing factors that help to promote apoptosis.<sup>16,17,18</sup>

#### **Excitotoxicity**

Excitotoxicity is defined as neuron hyperdepolarization that results in cell death. Excitotoxicity occurs when the brain becomes overly sensitive to glutamate, resulting in brain hyperactivity. Dopamine, on the other hand, works as both an excitatory and an inhibitory neurotransmitter depending on the type of receptor present. In this situation, a lack of DA induces excitation of sub-thalamic neurons, which may result in excitotoxic injury. According to research, parkin may play a protective role in Parkinson's disease excitotoxicity. The histology of DA neurons in Parkinson's disease patients revealed that cyclin E, a degradative protein, accumulates in neurons subjected to excitotoxicity and promotes neurodegeneration. However, as a defensive role, cyclin E is efficiently tagged by parkin, which effectively degrades it and so protects neurons from cyclin E degradation. In contrast, the mutant form of parkin was unable to stimulate the breakdown of cyclin E, resulting in the death of neuron cells. When neurons are exposed to excitotoxicity, a protein called cyclin E accumulates and causes neurodegeneration. In one study, it was discovered that when kainite was used to excessively excite

dopaminergic neurons, the increased level of parkin inhibited cyclin E function, preventing the neuronal cells from dying.<sup>17,19</sup>

#### **Neuroinflammation**

Neuroinflammation in Parkinson's disease patients is caused by an overactivation of specialised immune cells. Microglia are brain cells that produce non-antibody signalling proteins called cytokines. Regardless of inflammation, this can be harmful, however studies have shown that In vivo, activating immune cells can protect neuronal cells. In PD patients, the amount of the inflammatory enzyme COX-2 in dopaminergic neurons is higher than in non-PD individuals. The researchers also discovered an increased level of COX-2 in a mouse model of Parkinson's disease. Rofecoxib (COX-2 inhibitors) suppresses COX-2 while simultaneously increasing the amount of neurons that survive. The medicine, however, does not lower neuroinflammation and may instead protect neurons by reducing oxidative stress.<sup>12,17</sup>

#### **CURRENT TREATMENTS OF PARKINSON'S DISEASE:-**

##### **Dopamine replacement therapy:**

L-dopa was found 50 years ago in 1960, after James Parkinson described the disease in 1817, and is still regarded as a milestone in replacement therapy as 'Old is Gold.' Because of its high lipophilicity, it crosses the BBB and converts to dopamine, replenishing the shortage locally to improve motor impairment. L-dopa is usually given or recommended in conjunction with carbidopa (Atamet), since carbidopa (Atamet) inhibits the peripheral conversion of L-dopa into dopamine and so reaches the brain in L-dopa form. Thus, prevents some of the peripheral side effects of L-dopa and thus improves the midbrain deficiency of dopamine.<sup>4,9,12,22</sup>

##### **Dopamine Agonists:**

These medications do not convert to dopamine; instead, they imitate the impact of dopamine by attaching to the same receptor. Bromocriptine, pergolide, pramipexole, and ropinirole, among others, play a role similar to dopamine in the midbrain. Dopamine agonists stimulate the DA receptor, which is normally excited by dopamine. Overall, dopamine agonists can improve motor function when used alone in early Parkinson's disease and also help to postpone L-dopa therapy. Pramipexole and ropinirole are the newest agonists in this class that are better tolerated. To get the dopamine agonist into the body, the rotigotine transdermal device (Neupro patch) employs a different delivery method.<sup>4,9,12,22</sup>

##### **MAO-B antagonists:**

Monoamine oxidase is a type of enzyme that degrades neurotransmitters such as dopamine. Monoamine oxidase inhibitors are a type of medicine that inhibits the enzyme and prevents dopamine breakdown, resulting in more dopamine in the brain and less motor symptoms. When used with L-dopa, selegiline (Eldepryl, Zelapar) and rasagiline appear to increase the efficacy by boosting and extending the response of L-dopa.<sup>4,9,12,22</sup>

##### **Other medications:**

COMT inhibitors should never be used alone because they have no direct involvement in the treatment of Parkinson's disease. Instead, they should be used in conjunction with L-dopa to prevent the breakdown of L-dopa and route more and more dopamine to the brain. It has been discovered that with Parkinson's disease, the level of cholinergic neurotransmitter increases, resulting in extrapyramidal symptoms (EPS) so anticholinergics also play an important role in effective management of symptoms by controlling tremor and rigidity.<sup>4,9,12</sup>

#### **NATURAL REMEDIES FOR THE MANAGEMENT OF PARKINSON'S DISEASE:-**

Several essential parts of Parkinson's disease treatment found in these study articles have been summarised: In Parkinson's disease (PD), 40-70% of people used complementary and alternative medicine (CAM). CAM is used by over half of Parkinson's disease patients. CAM is used by 46 percent of Indian Parkinson's disease patients who visit a tertiary care teaching hospital in India. Ayurvedic therapy is the most generally used complementary and alternative medicine.<sup>29</sup>

Medicinal plants have long been recognised for their distinct and beneficial advantages around the world. In addition to their economic worth, research has demonstrated that these plants have a distinctive status in the health and well-being of many societies due to the antioxidant impact of phenolic chemicals found in them. As a result,

the overall strategy is to discover new plant species and their active components. Plants now play a vital part in illness therapy techniques and novel medications. As a result, the need for innovative oral treatments with no side effects remains high. The therapeutic benefits of medicinal plants and their constituents on the treatment of Parkinson's disease in vivo and in vitro were reviewed in this study. Despite the fact that the majority of herbal extracts and their active ingredients have been studied in PD models in vivo, some of them have so far been investigated only in cell models.<sup>36</sup>

*Hyoscyamus* species is one of four plants used in Ayurvedic medicine to treat Parkinson's disease (PD). Because L-DOPA levels in

*Hyoscyamus niger* were found to be insignificant, its neuroprotective potential was investigated. The methanolic extract of *Hyoscyamus niger* seeds protects mice against parkinsonism by inhibiting increased OH production in the mitochondria.<sup>32</sup>

Antiparkinsonian medicines are known to occur naturally in plants, including anticholinergics in *Datura stramonium*, levodopa in *Mucuna pruriens* and *Vicia faba*, dopamine agonist action in *Claviceps purpurea*, and MAO inhibitor activity in *Banisteria caapi*. HP-200, produced from *Mucuna pruriens*, was studied for its efficacy and tolerance. HP-200, created from an Ayurveda, an alternative medicine source, was discovered to be a successful treatment for Parkinson's disease patients.<sup>34</sup>

**Table: -1. Natural remedies for the management of Parkinson's disease<sup>33</sup>**

| Plant  | Used model   | Concentration        | Effects  |
|--|--|----------------------|--|
| <i>Tinospora cordifolia</i>  | Rat induced by 6-OHDA  | 200, 400 mg/kg       | 1. Increased the dopamine levels   |
|  |  |                      | 2. Decreased iron asymmetry ratio  |
|  |  |                      | 3. Decreased MDA levels  |
|  |  |                      | 4. Increased mitochondrial complex I activity  |
|  |  |                      | 5. Improved locomotor activity   |
| <i>Sesamum indicum</i> - seed oil (SO)                             | Mice induced by 6-OHDA   | SO, mix diet         | 1. Increased glutathione reductase (GR), glutathione-S-transferase (GST), glutathione peroxidase (GPx), catalase (CAT) and content of glutathione (GSH) and thiobarbituric acid reactive substance (TBARS) |
|  |  |                      | 2. INHIBIT the activation of Nox2 and Cox2   |
|  |  |                      | 3. Restored MnSOD expression   |
| <i>Carthamus tinctorius L.</i>                                     | (MPTP)-lesioned rat  | 70, 35mg/kg          | 1. Improve behavioural performances  |
|  |  |                      | 2. Suppression of $\alpha$ -synuclein overexpression or aggregation  |
|  |  |                      | 3. Suppression of reactive astrogliosis  |
| <i>Chaenomeles speciosa</i>  | In vitro and in vivo assays, Chinese hamster ovary (CHO) cells, rat induced by 6-OHDA (MPTP)-lesioned mice | 250, 500, 1000 mg/kg | 1. Increased tyrosine hydroxylase-positive neurons in the substantia nigra   |
|  |  |                      | 2. Increased D8 cell viability   |
|  |  |                      | 3. Time-dependently reduced abnormal turns in apomorphine-induced rotational turning   |
| <i>Portulaca oleracea</i>  | Rat induced by 6-OHDA  | 200, 400 mg/kg       | 1. Increase in crossings and rearing in open field test  |
| <i>Paeonia suffruticosa</i>  | (MPTP)-lesioned mice   | 25, 50 mg/kg         | 1. Increased movement distance in the open field test  |
|  |  |                      | 2. Increased total striatal dopamine   |
|  |  |                      | 3. Attenuated the loss of dopaminergic neurons   |
|  |  |                      | 4. Reversed down regulation Akt and the mitochondrial OXPHOS subunits  |
| <i>Mucuna pruriens</i>   | Rat induced by 6-OHDA  | 40, 80, 120 mg/kg    | 1. Reduced risk for drug-induced dyskinesias   |
|  |  |                      | 2. Increased nigrostriatal catecholamine content   |
| <i>Hyoscyamus niger seeds</i>                                      | Unilateral intrastriatal injection of rotenone in rat  | 125, 250, 500 mg/kg  | 1. Attenuated motor disabilities   |
| <i>Hibiscus asper leaves</i>                                       | Rat induced by 6-OHDA  | 50, 100 mg/kg        | 2. Increased level of GSH content and GPX, SOD and CAT activities  |
|  |  |                      | 1. Increased SOD, GPX and CAT activities, total GSH content  |
| <i>Gynostemma pentaphyllum</i>                                     | Rat induced by 6-OHDA  | 10, 30 mg/kg         | 2. Reduced MDA level   |
|  |  |                      | 1. Recovered the levels of dopamine, 3,4 dihydroxyphenylacetic acid, homovanillic acid and norepinephrine in striatum  |
| <i>Ginkgo biloba</i>   | Rat induced by 6-OHDA  | 50, 100, 150 mg/kg   | 2. Ameliorated the loss of TH-immunopositive neurons in substantia nigra   |
|  |  |                      | 1. Decreased rotation  |
|  |  |                      | 2. Improved locomotor activity and muscular coordination   |
|  |  |                      | 3. Increased GSH content   |
|  |  |                      | 4. Decreased generation of TBARS   |
|  |  |                      | 5. Increased SOD, CAT activities   |
| 6. Increase in the number of dopaminergic D2 receptors in striatum |  |                      |  |

|  |  |                              |   |
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| <i>Fructus alpinioxyphylla</i>         | Zebrafish and PC12 cell models                                   | 20% solution                 | 1. Restored dopaminergic (DA) neuron degeneration<br>2. Attenuated a deficit of locomotor activity<br>3. Increased the viability of 6-OHDA-treated PC12 cells<br>4. Attenuating cellular apoptosis  |
| <i>Delphinium denudatum</i>            | Rat induced by 6-OHDA  | 200, 400, 600 mg/kg          | 1. Decreased MDA levels<br>2. Increased GSH content<br>3. Increased SOD, CAT activities<br>4. Increased levels of dopamine  |
| <i>Bacopa monniera</i> Linn            | Rat induced by 6-OHDA  | 20, 40 mg/kg                 | 1. Decreased MDA levels<br>2. Increased GSH content<br>3. Increased SOD, CAT activities   |
| <i>Althaea officinalis</i> L.          | Rat induced by 6-OHDA  | 10 mg/kg                     | 1. Attenuated rotational behaviour<br>2. Decreased MDA levels   |
| <i>Albizia adianthifolia</i>           | Rat induced by 6-OHDA  | 150, 300 mg/kg               | 1. Improved working memory and reference memory<br>2. Attenuated the contralateral rotational asymmetry   |
| <i>Valeriana officinalis</i>           | Rotenone-induced apoptosis in human neuroblastoma SH-SY5Y cells  | 0.049, 0.098 and 0.195 mg/mL | 1. Increase in cell viability   |
| <i>Camellia sinensis</i> -Black tea    | Rat induced by 6-OHDA  | 1.50%                        | 1. Recovery in d-amphetamine induced circling behaviour and spontaneous locomotor activity<br>2. Recovery indopamine (DA)-D2 receptor binding, striatal DA and 3-4-dihydroxy phenyl acetic acid (DOPAC) level<br>3. Decreased MDA levels<br>4. Increased GSH content<br>5. Increased SOD and CAT activities<br>6. Increased TH protein level and TH mRNA expression in substantia nigra |
| <i>Panax ginseng</i>                   | Rat received $\beta$ -sitosterol $\beta$ -D-glucoside            | 100 mg/kg/d                  | 1. Reduced dopaminergic cell loss, microgliosis, and accumulation of $\alpha$ -synuclein aggregates   |
| <i>Carthamus tinctorius</i> -Safflower | Mouse induced with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine- | 35, 70 mg/kg/d               | 1. Reversed the decreased protein expression of tyrosine hydroxylase, dopamine transporter and DJ-1<br>2. Increased dopamine levels<br>3. Decreased acetylcholine levels  |
| <i>Hypericum perforatum</i>            | Rat induced by 6-OHDA  | 200 mg/kg/d                  | 1. Attenuated apomorphine-induced rotational behaviour<br>2. Decreased the latency to initiate and the total time on the narrow beam task<br>3. Decreased MDA levels<br>4. Increased catalase activity  |
| <i>Oxalis corniculata</i> l.           | C57 male mice MPTP administration                                | 250, 500 mg/kg               | 1. Decreased SOD activity<br>2. Increased catalase activity   |

#### ***Mucuna pruriens* extract (MPE): -**

The neuroprotective effects of L-dopa decreased *Mucuna pruriens* extract (MPE) in murine microglia BV-2 and neuroblastoma SH-SY5Y cells were investigated. MPE shown neuroprotective benefits in Parkinson's disease animals.<sup>23</sup> Mp contains L-DOPA as well as ursolic acid, which has anti-inflammatory properties. The results of several studies show Mp modulate the immune components like TNF- $\alpha$ , IL-6, IFN- $\lambda$ , IL-1 $\beta$ , iNOS and IL-2 in the CNS. It also influences the activity of the transcription factor NF-kB, which is involved in the course of Parkinson's disease. Mp therefore inhibits or slows the progression of Parkinson's disease via modulating these cytokines or transcription factors.<sup>25</sup>

#### ***Bacopa monnieri* (BM): -**

An ethanolic extract of *Bacopa monnieri* (BM) was tested for neuroprotection in a parkinsonian mouse model induced by MPTP. It was demonstrated to greatly improve motor behaviour (Rotarod, Grip Strength and Foot Printing test). Furthermore, on biochemical parameters, BM considerably improved Catalase, LPO, Nitrite, SOD, GR, and GPx parameters, while levels of Dopamine, DOPAC, and HVA were significantly increased. There was a considerable decrease in TH immunoreactivity in the substantia nigra (SN) in the MPTP-treated group, which was significantly recovered by the use of BM extract. BM also aided neuroprotection by establishing an anti-

apoptotic milieu, as seen by lower levels of apoptotic (Bax and caspase 3) and higher levels of anti-apoptotic (Bcl2) protein expression.<sup>24</sup>

*Bacopa monnieri* (BM), an ayurvedic medicinal plant, has caught the attention of researchers due to its unique neuropharmacological properties. Epidemiological studies have found a link between paraquat (PQ) exposure and an increased incidence of Parkinson's disease. The study looked at the ability of a standardised extract of BM to reduce acute PQ-induced oxidative damage, mitochondrial dysfunctions and neurotoxicity in prepubertal mouse brain areas.<sup>31</sup>

#### ***Withania somnifera* L. (Ashwagandha): -**

Withanolide A (steroidal lactone) is a significant ingredient of Ashwagandha, the most used herbal drug in Ayurvedic therapy. It has been discovered that Withanolide A mediates lifespan extension and promotes stress resistance via the insulin/insulin-like growth factor signalling pathway for the prevention or reversal of age-related ailments, as well as to improve the survival of Alzheimer's or Parkinson's disease patients.<sup>27</sup>

*Withania somnifera*, also known as 'Indian ginseng,' is a medicinal plant native to the Indian subcontinent with anti-microbial, anti-inflammatory, anti-tumour, anti-stress, neuroprotective, cardioprotective, and anti-diabetic properties, as well as a diverse phytochemical profile that allows it to have a wide range of biological implications.<sup>28</sup>

An ethanolic root extract of *Withania Somnifera* (Ws) was co-treated with the Maneb-Paraquat induced mouse model of Parkinson's disease and was shown to significantly rescue canonical indicators of Parkinson's disease such as impaired locomotor activity, decreased dopamine in the substantia nigra, and various aspects of oxidative damage.<sup>30</sup>

#### **Curcuma longa (Turmeric- an Indian spice):-**

Once relegated spice to the kitchen shelf, has made its way into the clinic and may be Curcumin or diferuloylmethane, a yellow pigment found in turmeric (curry powder), has been proven to have a variety of actions. Curcumin regulates inflammatory enzymes, cytokines, adhesion molecules, and cell survival proteins. Curcumin has anti-proliferative, anti-invasive, and anti-angiogenic properties; it can act as a mediator of chemoresistance and radio resistance; it can be used as a chemo preventive agent; and it can be used as a therapeutic agent in wound healing, diabetes, Alzheimer's disease, Parkinson's disease, cardiovascular disease, pulmonary disease, and arthritis.<sup>33</sup>

#### **Ginkgo biloba:-**

*Ginkgo biloba* is an ancient tree native to China and has been extensively used in traditional Chinese medicine to manage symptoms associated with dysfunctions of the heart and lungs. *G. biloba* usually contains three ingredients, which include flavonoids, terpenoids, and ginkgolide acid. Ginkgolides well-known plant extracts obtained from leaves from *G. biloba*, especially in the preparation EGB761, which contains ginkgolide B and bilobalide, have emerged as natural therapeutic compounds, in part due to their antioxidant activity. These effects have been observed in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine- (MPTP-) treated mouse model of PD, where chronic ingestion of EGB761 prevented MPTP-induced reduction in the dopaminergic nerve endings. In addition, EGB761 administered before or after MPTP treatment protected against MPTP induced dopaminergic neurotoxicity [10]. Moreover, EGB761 attenuated the neurotoxic effect of levodopa in the 6- hydroxydopamine (6-OHDA) model of PD, indicated that levodopa is neurotoxic and that EGB761 may decrease this toxicity. The neuroprotective effects of EGB761 were demonstrated in the 6-OHDA rat model, as indicated by the reduction in the behavioural deficit in the rat. Ultimately, the *G. biloba* extract treatment improved locomotor activity, decreased oxidative damage, maintained the dopamine homeostasis, and inhibited the development of PD in A53T  $\alpha$ -synuclein transgenic mice.<sup>44,45,46</sup>

#### **Valeriana officinalis:-**

*Valeriana officinalis* (Valerian) is a plant with sedative and antispasmodic effect, traditionally used in the treatment of insomnia, anxiety, and restlessness. The effects of valerian on rotenone-induced cell death in SHSY5Y cells have been demonstrated. Moreover, extract of valerian was effective in reducing the toxicity induced by rotenone in *Drosophila melanogaster*, as confirmed by the normalisation in the expression of SOD and catalase mRNAs, suggesting that the effects of valerian are, at least in part, associated with the antioxidant properties of the plant due to its phenolic and flavonoid constituents. *Valeriana wallichii*, also known as Indian valerian or Tagar-Ganthoda, belongs to the family Valerianaceae and is considered as an important Asian counterpart of the European valerian. Tus, valeriana wallichii treatment significantly recuperated the altered behaviour, striatal dopamine levels, increased GFAP expression, and the histopathological changes observed in mice treated with MPTP. Likewise, it ameliorated the increased levels of ROS, inflammatory cytokines and lipid peroxidation and also ameliorated the diminished levels of antioxidants.<sup>47,48</sup>

#### **Passiflora incarnata (Passion Flower):-**

Passion flower, commonly known as *Passiflora incarnata* (Passifloraceae), contains flavonoids, glycosides, alkaloids, and phenolic compounds. Also, it has been used for the treatment of anxiety, insomnia, epilepsy, muscular spasms, and other diseases. Therefore, the biological effects of passion flower have been investigated in PD. The extract of passion flower reduced the number of jaw movements induced by tacrine, which is a widely used animal model of PD tremors. In addition, the model showed cognitive improvement, with significantly reduced duration of haloperidol-induced catalepsy. The passion flower possesses antioxidant activity, as shown by its significant scavenging ability. *Passiflora cincinnata* is a Brazilian native species of passion flower and its possible biological effects have been investigated. Tus, in a model of PD induced by reserpine, *Passiflora cincinnata* extract prevented the decrease in TH in the SN induced by reserpine, delayed the onset of motor

impairments, and prevented the occurrence of increased catalepsy behaviour. However, the extract did not modify reserpine-induced cognitive impairments.<sup>49,50</sup>

#### **Hypericum Perforatum:-**

St. John's Wort. The use of St. John's wort, known as *Hypericum perforatum*, dates back to the time of the ancient Greeks. Active compounds of St. John's wort have been identified and include naphthodianthrones, phloroglucinols, and flavonoids (such as phenylpropanes, flavanol glycosides, and biflavones), as well as essential oils. Therefore, the active compounds provide antioxidant and neuroprotective effects. Two standardised extracts of St. John's wort have been tested on the neurodegeneration induced by chronic administration of rotenone in rats. Accordingly, St. John's wort reduced neuronal damage and inhibited the apoptotic cascade by decreasing Bax levels. Besides, intrastriatal 6-OHDA-lesioned rats were treated with the extract of St. John's wort and showed lowered striatal level of malondialdehyde, enhanced catalase activity, reduced GSH content, normalised expression of GFAP and TNF- $\alpha$ , lowered DNA fragmentation and prevention of damage to dopaminergic neurons.<sup>51,52</sup>

#### **Future Aspects:**

Despite the world's enormous variety of plants, only a small number of them have been researched for anti-Parkinsonian action, and so there are countless opportunities for future research on plants and their bioactive components. To date, a large number of medicinal plants and their active ingredients have been reported to prevent and treat PD. Most studies have focused on antioxidant, anti-inflammatory, antiapoptotic properties of these plants.<sup>37,38,39</sup>

At the moment, the pathogenesis of Parkinson's disease is attributed to the formation of ROS and the onset of oxidative stress, which leads to damage to the SN compacta, particularly changes in the iron content of the brain, mitochondrial dysfunction, changes in the antioxidant defence system (particularly reductions in superoxide dismutase and glutathione [GSH]), and oxidative damage to fats, proteins, and DNA. GSH deficiency is linked to Lewy body disease. GSH could be the most essential biochemical marker for nigral cell death. GSH depletion may not be the main cause of nigral neuron degeneration, although it may enhance susceptibility to toxic or free radical exposure.<sup>40</sup>

The majority of the medicinal plants and active compounds presented in this research raise glutathione, superoxide dismutase, and catalase levels in the brain, resulting in neuroprotective benefits. There is evidence that inflammation plays a role in the aetiology of Parkinson's disease. Active microglia increase in the striatum and SN of Parkinson's disease patients. Microglial cells, which are macrophages in the brain, respond to a variety of adverse situations by rapidly hypertrophic growth and the release of a number of cytokines. Active microglia increase the expression of cell surface markers including macrophage antigen complex 1 and release a number of pro-inflammatory cytokines. A variety of cytokines, including IL-1, IL-6, and TNF- $\alpha$ , contribute to inflammation.<sup>41</sup>

#### **CONCLUSION:-**

The goal of this study was to offer a summary of existing experimental evidence on the anti-Parkinsonian actions of medicinal plants and their active components. We discovered that numerous natural chemicals and herbal extracts have anti-Parkinsonian effects. Taken together, diverse Parkinson's disease neurotoxic models are an excellent foundation for developing anti-Parkinsonian medications, and herbal substances can be employed to produce new PD treatments. However, future empirical investigations should look into the efficacy of plant extracts and their active components in PD models. Furthermore, the active components and methods of action of herbal extracts have yet to be properly described.

**Conflict Of Interest:** The authors declare no conflict of interest.

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