Phytochemicals pharmacotherapy for Parkinson's disease: A comprehensive review on the current strategies

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***Abstract*- Parkinson's disease (PD) is a chronic neurodegenerative illness that affects motor skills and cognitive ability. It is the second most common neurodegenerative disease. Motor symptoms, including dystonia, rigidity, bradykinesia, and tremors, are uncontrollable movements brought on by severe forms of Parkinson's disease. Non-motor symptoms like hysteria, sadness, constipation, and sleeplessness are also brought on by Parkinson's disease. Motor symptoms in Parkinson's disease are primarily caused by disruption of dopaminergic and non-dopaminergic neuronal networks in the substantia nigra pars compacta. The intricacy of pharmaceuticals crossing the blood-brain barrier contributes to the complexity of Parkinson's disease treatment. For the treatment of Parkinson's disease (PD), a number of conventional therapeutic modalities have been developed that just manage symptoms. Hence, a variety of ongoing studies are centred on the pursuit of novel compounds that may offer therapeutic advantages to individuals with Parkinson's disease. The objective is to review phytochemicals that have been shown to have preventive or therapeutic effects in Parkinson's disease (PD) in-depth before concentrating on the neuropsychopharmacology processes behind these effects. the many subgroups of the most prevalent classes of phytochemicals with proven antiparkinsonian properties, flavonoids, phenolic acids, and anthocyanins. Numerous mechanisms of action enable phytochemicals to exert their antiparkinsonian effects. These mechanisms include the suppression of apoptosis (through the reduction of Bax/Bcl-2, caspase-3, and α-synuclein accumulation), the reduction of proinflammatory gene expression, the reduction of dopaminergic neuronal loss and dopamine depletion, the modulation of nuclear and cellular inflammatory signalling, the elevation of neurotrophic factors, and the improvement of antioxidant status. To increase their effectiveness and lessen or eliminate their negative psychological effects in the treatment of Parkinson's disease (PD), a variety of plant-derived natural compounds may be used as pharmaceutical medications in the future or as an adjuvant treatment alongside traditional therapeutic procedure. In the management of neurodegenerative illnesses, well-designed recent clinical trials are just as promising as upcoming medications. These trials are required to assess the protective and restorative properties of phytochemicals.**

Keywords: **Neurodegenerative, dystonia, rigidity, bradykinesia, tremors, hysteria.**

1. INTRODUCTION:

An Essay on the Shaking Palsy, published in 1817, is the publication that first detailed the symptoms of Parkinson's disease (PD), which bears the name of its English physician, James Parkinson. PD is a neurological condition that affects both motor and non-motor functions. It is sometimes referred to as shaking palsy and paralysis agitans [1]. Postural instability, tremor, stiffness, and bradykinesia are uncontrolled movements known as motor symptoms which are the hallmarks of Parkinson's disease (PD), a degenerative neurological condition. Non-motor symptoms of Parkinson's disease include hysteria, melancholy, constipation, and sleeplessness. The clinical syndrome known as "Parkinsonism" is a group of illnesses that may exhibit any or all of these symptoms. "Parkinsonian disorders" are conditions where Parkinsonism plays a major role [2]. It arises from the degeneration of substantia nigra neurons in the mesencephalon, a region of the midbrain, which causes DA levels to drop and the neuronal circuitry controlling movement to become disrupted. Unbalanced relay functions at the striatal level cause disruptions in sub corticocortical connections [3]. Degenerative, vascular, traumatic, and toxic etiologies are among the illnesses associated with Parkinsonism. Although a number of risk factors for Parkinson's disease have been identified, including as exposure to pesticides and other toxins, a family history of the condition, and oophorectomy, age remains the most important factor [4].

2. EPIDEMIOLOGY:

"Paralysis agitans," another name for Parkinson's disease, can occasionally be uncommon in young adults, especially those under 40. It is estimated that one million Americans suffer from Parkinson's disease (PD), of which about 60,000 new cases are recorded annually. Men are affected by Parkinson's disease (PD) 1.5 times more often than women; estimates place the number of affected individuals at 7–10 million globally. Medicare enrolees 65 and older had an average prevalence of PD of 1.6%, according to a population-based investigation [5].

3. PATHOGENESIS:

Many processes have been linked to the pathophysiology of Parkinson's disease (PD), with α-synuclein aggregation playing a key role in the disease's progression. Numerous other mechanisms are also believed to be involved; research has revealed a role for aberrant protein clearance, mitochondrial dysfunction, and neuroinflammation in the development and course of Parkinson's disease (PD). The connection between these pathways is still unknown, though[6]

3.1. α-SYNUCLEIN AGGREGATION AND MISFOLDING:

The majority of native α-synuclein in the brain is unfolded and lacks a clear tertiary structure. When PD develops, α-synuclein takes on an amyloid-like structure rich in β-sheets that is prone to aggregation. Indeed, 5–10 nm long filaments of misfolded α-synuclein are seen within Lbs.' The structural alterations that cause aberrant α-synuclein aggregation have been attributed to a number of processes, including ubiquitination, serine 129 phosphorylation, and C-terminal truncation[7]. Current research on rodents has revealed that the early oligomeric form of α-synuclein, as opposed to the mature insoluble fibrils, is the most neurotoxic type. In comparison to fibrillary α-synuclein, these oligomers were confirmed to be more hazardous by studies conducted on cells. Abnormal protein aggregation can be accelerated and "seeded" by α-synuclein oligomeric species[8].

3.2. MITOCHONDRIAL DYSFUNCTION:

One of the main theories for the aetiology of both familial and idiopathic Parkinson's disease is mitochondrial malfunction. In comparison to healthy subjects, PD patients' skeletal muscle and platelets also showed deficiencies in mitochondrial complex-I, an essential part of the electron transport chain. Subsequent research revealed that oxidized MPTP is absorbed by DA neurons, causing complex-I inhibition and power depletion that results in DA cell death and dopaminergic cell loss. In animals, and maybe in people as well, other chemicals and herbicides that disrupt mitochondrial complex-I activity, including as paraquat and rotenone, also result in DA cell loss and a Parkinsonian phenotype[9]. The route that controls the elimination of malfunctioning mitochondria is regulated by the engagement of two essential components, PINK1 and parkin (PARK2 and PARK6, respectively). Mitochondrial quality control is compromised by loss of function and mutations in both gene, resulting in autosomal recessive Parkinson's disease. α-synuclein has the ability to connect with the mitochondrial membrane and gather within the organelles. This results in complex-I activity damage, which in turn causes mitochondrial malfunction and elevated oxidative stress[10].

3.3. DYSFUNCTIONAL PROTEIN CLEARANCE SYSTEMS:

Damage to either of the two central protein clearance systems in cells—the autophagy-lysosome pathway and the ubiquitin-proteasome system (UPS)—contributes to the accumulation of defective proteins, specifically soluble misfolded α-synuclein, which is implicated in the pathogenesis of Parkinson's disease (PD)[11].

3.3.1. UBIQUITIN-PROTEASOME SYSTEM:

By "tagging" aberrant proteins with ubiquitin and transferring them to the proteasome for destruction, the UPS is principally in charge of breaking down abnormal proteins. When PD patients were compared to brains in good health, the UPS's catalytic activity was found to be significantly lower. In particular, parkin (PARK2; E3 ubiquitin ligase) and UCH-L1 (PARK5; Ubiquitin C-terminal hydrolase) are the proteins encoded by two of the PARK genes associated with monogenic PD. Along with lowering levels of the components of the 26S subunit and pharmacological suppression of the proteasome in wild-type rats, the toxin MPTP also reduced enzyme activity in the UPS, which results in the death of dopaminergic neurons. Protein turnover dysfunction may be a pathogenic mechanism for Parkinson's disease (PD) since it can lead to the death of neurons[12].

3.3.2. AUTOPHAGY-LYSOSOME SYSTEM:

Three components make up the autophagy-lysosome pathway: chaperone-mediated autophagy (CMA), micro autophagy, and macro-autophagy. PD brain nigral neurons had elevated levels of the autophagosome marker LC3-II, indicating a build-up of autophagic vacuoles. On the other hand, it was discovered that there was a decline in numerous molecular chaperones from the heat-shock protein family, including hsp35 and hsc70, as well as essential lysosomal membrane proteins like LAMP1 and LAMP2A point mutation in the lysosomal protein ATP13A2 (PARK9) gene, resulting in an autosomal recessive atypical Parkinsonian syndrome; GBA1 mutations, which cause the lysosome-autophagy system to malfunction; and PARK genes impair the function of either parkin (PARK2) (58) or PINK1 (PARK6) (60), both of which are involved in the autophagic turnover of mitochondria[10]

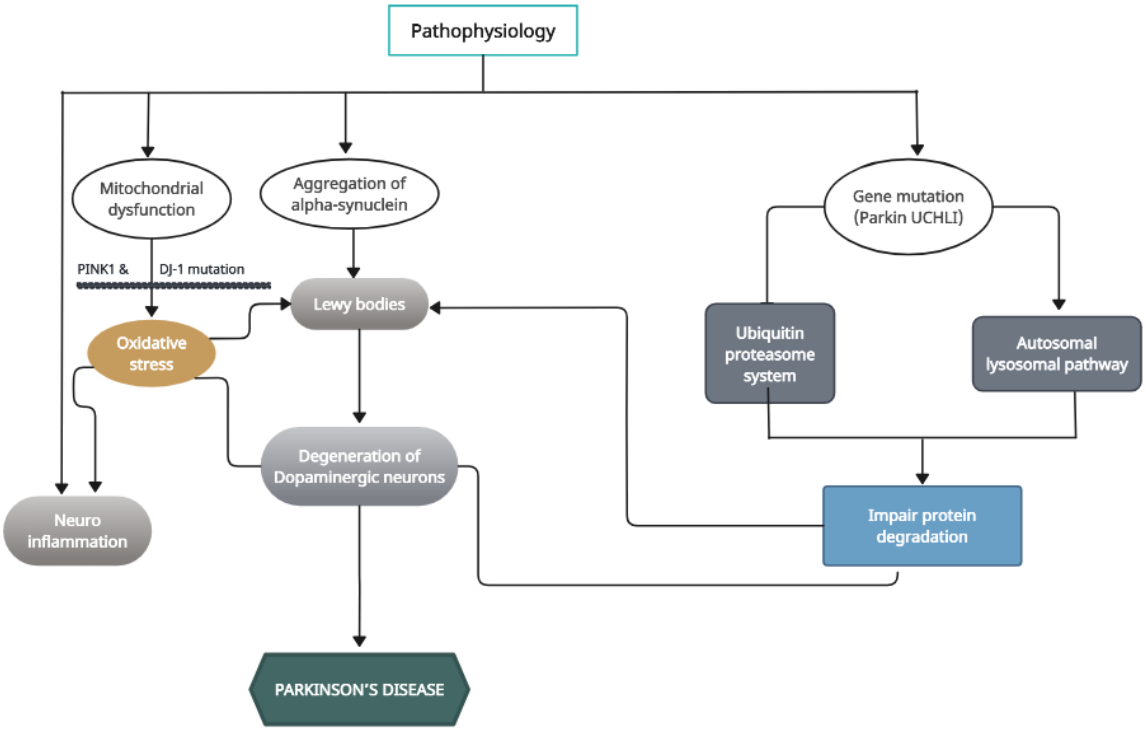
3.4. NEUROINFLAMMATION:

Neuronal cells that mediate immunological responses and lower oxidative stress, including microglia and astrocytes, are crucial for maintaining CNS homeostasis. To restore the equilibrium and heal injured cells, glial cells release cytokines when CNS regional homeostasis is upset. While this kind of reaction is normal and advantageous for neurons, it also causes chronic inflammatory stress when microglia and astrocytes are repeatedly activated. This can result in a significant rise in reactive oxygen species production and serious damage to neurons. Numerous research on humans, animals, and cells suggest that neuroinflammation plays a role in the etiology of Parkinson's disease[6].

4. CLINICAL DIAGNOSIS OF PARKINSON'S DISEASE:

A clinical diagnosis of Parkinson's disease is made by looking through the patient's medical history. Parkinson's disease can also be clinically diagnosed based on symptoms such as constipation, poor sleep, and loss of smell. In addition, the clinical diagnosis of Parkinson's disease is based on a patient's past and present medical history as well as any environmental exposure. Advanced Parkinson's disease patients frequently pass away or become care dependent. Parkinson's disease diagnosis is still based on the clinician's ability to identify the illness's distinctive symptoms, especially in the early stages. The precise origin of Parkinson's disease is still unknown, despite the fact that intricate interactions between inherited and environmental factors are thought to be involved. For example, early detection of Parkinson's disease using state-of-the-art technology like nano biosensors is essential to help doctors accurately diagnose the condition before irreversible harm is done[13].

Figure 1. Mechanism of action of PD



5. MANAGEMENT OF PARKINSON'S DISEASE:

Levodopa as a natural substance that the brain may readily absorb and convert to dopamine, levodopa serves as a dopamine replacement medication for the treatment of Parkinson's disease. Outside of specific brain areas, levodopa cannot be converted to dopamine due to the binding action of carbidopa. These medications are unable to lessen the harm that Parkinson's disease causes. Levodopa overdoses can also result in uncontrollable movements. Unlike

levodopa, dopamine agonists like Bromocriptine, Ropinirole, Pramipexole function in the brain like dopamine rather than being converted to dopamine. When it comes to treating Parkinson's disease symptoms, dopamine agonists are less effective than levodopa. Combining them with levodopa can lower the chance of experiencing irregular side effects because they have a longer half-life. A dopamine agonist called apomorphine is also used to treat the symptoms of Parkinson's disease. Moreover, MAO-B inhibitors like Entacapone, Tolcapone function by blocking the action of monoamine oxidase B, an enzyme involved in the breakdown of dopamine in the brain. In the brain, dopamine is metabolized by MAO-B[14]. When treating the movement symptoms of Parkinson's disease, dopamine agonists are used in place of dopamine to stimulate neurons in the brain that produce dopamine. Combining a dopamine agonist plus an MAO-B inhibitor inhibits the brain's ability to break down levodopa and dopamine. Other neurotransmitters, including DOPA, are broken down by catechol-O-methyltransferase (COMT). Two anticholinergics that are used to treat Parkinson's disease are benatropine and trihexyphenidyl. However, there are a number of adverse effects associated with these drugs, including constipation, dry mouth, hallucinations, memory loss, and urinary issues. For the most part, people with early-stage Parkinson's disease are prescribed amantadine. Delaying the need for L-dopa medication is possible with selegiline. When administered alongside L-dopa, it appears to extend and improve the L-dopa response. The degenerative nature of Parkinson's disease leads to a deterioration in the patient's responsiveness to medication, which can cause a variety of motor problems. Parkinson's disease has to be prevented by early detection before the repeated use of medications that may have several negative effects, since individuals receive therapy after the disease has advanced[15].

6. SURGICAL PROCEDURE FOR PARKINSON'S DISEASE:

Through surgery, people with Parkinson's disease can receive deep brain stimulation treatment (DBS), which stimulates the patients' brains. To treat the symptoms of Parkinson's disease, electrodes are inserted into specific brain regions during this procedure. Parkinson's disease is treated using DBS, a procedure that uses electrodes based on nanotechnology. To control the aberrant impulses brought on by Parkinson's disease, these electrodes generate electrical impulses in the brains. The Food and Drug Administration has approved this method as a treatment for cases of severe Parkinson's disease. Deep brain regions connected to motor regulation undergo surgery to cure involuntary movements caused by Parkinson's disease. Under local anaesthesia, a neurosurgeon performing this kind of surgery may implant a metal framework in the skull. Surgeons utilize diagnostic imaging to pinpoint specific brain regions and drill tiny holes the size of nickels. To alleviate Parkinson's disease symptoms, doctors can use high-frequency radio waves to make microscopic lesions in these structures. Patients with severe Parkinson's disease or those who do not respond well to pharmacological treatments may benefit from this method. Critical issues, such as which brain regions should be targeted and in which patients, persist despite the effectiveness and general acceptance of DBS. This treatment will be done only in the condition of unresponsiveness of medicinal therapy[16].

7. PHYTOCHEMICALS PHARMACOTHERAPY:

7.1. ICARIIN:

The main bioactive component *of Epimedium sagittatum*, icariin, is thought to have therapeutic potential for treating serious age-related illnesses. The nigrostriatal system's neuroprotective effects of icariin against MPTP-induced dopaminergic neuronal death in mice. Its mode of action may involve the signalling pathways MEK/ERK and PI3K/Akt. Icariin might offer an alternate line of defence against nigrostriatal system damage caused by neurotoxins[17]. Through SIRT3's mediation, Icariin regulates PGC-1α, improving mitochondrial activity and providing neuroprotection against ROT-induced DA neuronal cell death[18].Icariin has the potential to be a promising therapeutic for Parkinson's disease (PD). This is demonstrated by its ability to activate the NLRP3 inflammasome, reduce IL-1β secretion, inhibit neuroinflammation, reduce oxidative stress, improve mitochondrial function, and interact with BBB-related proteins[19].

7.2. BAICALIN:

The dry roots of *Labiatae Scutellaria* Linn, *Scutellaria baicalensis* Georgi are used to isolate and extract baicalin from flavonoids. Baicalin exhibits antimicrobial, antiviral, anti-inflammatory, anticancer, cardiovascular, and neuroprotective properties. Baicalin can stop the death of dopaminergic neurons in the SN by inhibiting apoptosis, controlling the release of monoamine neurotransmitters, and reducing oxidative stress in 6-OHDA-induced Parkinson's disease (PD) rats. Baicalin's primary mode of action might be through controlling the metabolism of glutamate and N-acetyl aspartate[20].Baicalin's capacity to break down α-synuclein oligomers shielded dopaminergic neurons from the damaging effects of α-synuclein oligomer-induced toxicity and stopped α-synuclein from gradually building up[21].Baicalin inhibits the mTOR/AKT/GSK-3β pathway directly, which protects the substantia nigra neurons from undergoing apoptosis in PD rats[22].Using the SIRT1/AMPK/mTOR pathway and miR-30b-5p to promote mitochondrial autophagy, baicalein rescued PD animals. Baicalin may, however, also mediate additional mechanisms of mitochondrial autophagy[23].Both in vitro and in vivo, baicalein inhibits MPTP-induced neurotoxicity. Reduced oxidative stress, iron

metabolism control, and inhibition of MAO-B activity may all contribute to baicalein's neuroprotective effects. Furthermore, ERK activation inhibition might potentially play a role in the mechanism of this neuroprotective action[24].The neuroinflammatory NLRP3/caspase-1/GSDMD pathway plays a role in the PD-like pathophysiology that MPTP induces, and blocking this route with baicalein has neuroprotective effects[25].Baicalin prevented the mice from suffering damage from 6-OHDA by preventing apoptosis and reducing oxidative stress through the p38 MAPK signalling pathway[26].

7.3. BIOCHANIN:

Red clover, peanuts, chickpeas, soy, and alfalfa sprouts are some of the foods that contain the isoflavone biochanin. The benefit of Biochanin on mice's neuroprotection against rotenone-induced neurotoxicity. The prevention of dopaminergic neuronal degeneration, the restoration of antioxidant capacity, and the downregulation of midbrain glial activity were indicative of this protective impact. Additionally, Biochanin increases the synthesis of beclin-1 and promotes PI3K/Akt/mTOR signalling, which improves autophagy[27].In a rat model of PD brought on by LPS, Biochanin reduced behavioural abnormalities, stopped the death of dopaminergic neurons, and stopped microglia activation. Furthermore, in the rat brain, Biochanin enhanced SOD and GPx activity while blocking NADPH oxidase activation and MDA synthesis. The suppression of NADPH oxidase and microglia activation may be linked to the neuroprotective action of Biochanin[28].In PC12 cells, biochanin A can offer defence against glutamate-induced apoptotic cell death. Biochanin's protective properties could be achieved by apoptosis suppression and antioxidant recovery[29].Redox equilibrium is maintained by biochanin, which may provide dopaminergic neuroprotection[30].

7.4. CHRYSIN:

Scutellaria baicalensis, honey, bee propolis, blue passion flowers (*Oroxylum indicum*, *Passiflora incarnata*, and *Passiflora caerulea*), mushrooms, and bee propolis are just a few fruits and vegetables that are rich in the phytochemical chrysin. the ability of chrysin to function as an MAO-B inhibitor, raise dopamine levels in the brain, and have potential neuroprotective, antioxidant, and anti-inflammatory effects in PD[31].Nucleolin and HO-1 are upregulated in response to chrysin. Both the inhibition of NF-κB signalling pathways and the activation of NRF2/HO-1 mediate the neuroprotective action of chrysin[32].Given its neuroprotective efficacy against the 6-OHDA-induced parkinsonian animal model, chrysin may present a unique therapeutic alternative for Parkinson's disease (PD). This neuroprotective effect is thought to be caused by their strong antioxidant potential, modulation of TH neurons in the striatum which subsequently preserved neurotransmitters like DA, DOPAC, and HVA as well as behavioural alterations and their inhibitory role on various critical events implicated in neuroinflammation and neurotrophic factor conservation[33].By protecting CGNs from MPP+-induced neurotoxicity in vitro, saving SNpc DA neurons from MPTP-induced death, and reducing the amount of dopamine and its metabolites in mice, the naturally occurring flavonoid chrysin may have multiple mechanisms of action, such as anti-neuronal apoptosis, neuroprotection through activating the AKT/GSK3β/MEF2D pathway, and suppression of MAO-B activity[34].

7.5. DIOSMIN:

A naturally occurring citrus flavone called diosmin (DM), also known as diosmetin 7-O-rutinoside, is derived from hesperidin which is obtained from citrus fruits (Rutaceae family), including orange (*Citrus sinensis*), grapefruit (*Citrus paradise*), tangerine (*Citrus reticulata*), lime *(Citrus aurantifolia*), and lemon (*Citrus limon*). Moreover, DM reduced TNF-α levels and the NF-κB expression increase brought on by rotenone. Additionally, DM prevented the Nrf2/HO-1 pathway from being overexpressed as a result of rotenone. As a result, the current study raises the possibility that DM could be a good option for controlling the neuropathological progression of Parkinson's disease[35].

7.7. FIESTIN:

Numerous fruits and vegetables are rich in the bioactive flavonoid fisetin. Fisetin works well as an enzyme inhibitor, scavenger of free radicals ,and metal chelating agent[36]. Fisetin has the ability to block a number of inflammatory and apoptotic pathways, which are crucial to the development and course of Parkinson's disease, according to a mechanisms study. Fisetin can promote neuroprotective effects and lower α-synuclein levels while providing some information about possible implicated signalling pathways[37].Fisetin may be able to prevent rotenone-induced apoptosis by maintaining antioxidant activity and oxidative stress. Fisetin reduced the toxicity caused by rotenone by down-controlling the expression of the caspase-3 protein, Bax, and up-controlling the Bcl-2, p38/JNK-MAPK and PI3K, Akt, and GSK-3β pathways' protein expression[38].Fisetin may lessen oxidative stress by increasing the activity of mitochondrial enzymes[39].

7.8. KARANJIN:

Pongamia pinnata (L.) Pierre is the primary source of karanjin (3-methoxy-2-phenylfuro[2,3-h]chromen-4-one), a furanoflavonoid (family: Fabaceae). Its numerous biological properties, such as those that are antioxidant, anti-

inflammatory, antidiabetic, anti-cancer, and anti-ulcer, are widely known[40].By modulating the molecular targets α-synuclein, monoamine oxidase B, β-site APP cleaving enzyme, and acetylcholinesterase implicated in the disease progression, karanjin has demonstrated potential against Parkinson's disease when compared to commercial standard medications[41].

7.9. DIOSCIN:

Dioscin, a steroidal saponin, is frequently employed in the manufacture of hormonal medicines. It is found in abundance in a number of medicinal plants, such as *Dioscorea nipponica* Makino and *Dioscorea rizhoma*. By focusing on GLP-1 signalling, dioscin changed the gut microbiota and controlled oxidative stress and neuroinflammation caused by bile acid. The results also suggested that Dioscin should be viewed as a strong contender because bile acid and gut microbiota would be intriguing targets for PD treatment[42].Dioscin exhibits superior effects on oxidative stress, metabolism, anti-inflammatory, and anti-cancer properties. Dioscin prevented Parkinson's disease (PD) via protecting neurons. In vitro and in vivo, dioscin inhibited oxidative stress by involving the DUSP6/ERK pathway. This resulted in the restoration of GSH and MDA levels, a decrease in ROS levels, improved motor behaviour, and TH levels[43].In the SH-SY5Y neuroblastoma cell line, dioscin reduces autophagic flux impairment, which may be related to its neuroprotective action against MPP+-induced cell death. Subsequent research showed that dioscin increases dopamine precursor TH and neurotrophic factors.

7.10. SCOPOLETIN:

Convolvulus pluricaulis, a nootropic herb long used as a brain stimulant, memory enhancer, and treatment for mental debility, yields scopoletin (Sp), a strong neuroprotective substance with robust antioxidant capabilities. Higher levels of reduced glutathione in the Sp-treated cells made them resistant to disruptions in the antioxidant system or the neurotoxic MPP+. Dopaminergic brain networks and motor capacities could recover as a result of Sp reestablishing the redox equilibrium, mitochondrial function, and preventing oxidative damage[44].*Morinda citrifolia* is another source of scopoletin (Sp). By increasing Nrf2's phosphorylation and nuclear translocation in a DJ-1-dependent manner, scopoletin the active component of MCE seems to be in charge of stabilizing the Nrf2/ARE pathway. It also inhibited α-synuclein aggregation by boosting Nrf2-antioxidant signalling and reducing oxidative stress[45].

7.11. SILYMARIN:

With cytoprotective, anti-inflammatory, antioxidant, and anticarcinogenic qualities, silymarin, a compound of flavonolignans, is extracted from the seeds of the *Silybum marianum* plant is an annual or a biennial plant and is a member of plant family Asteraceae. Because silymarin elevates superoxide dismutase, lowers glutathione levels, and scavenges free radicals, it functions as an antioxidant in the central nervous system. Beneficial effects of 100 mg/kg silymarin in a PD model caused by MPTP. Through preventing substantia nigra apoptosis and protecting dopaminergic neurons, silymarin preserved striatal dopamine levels[46].Moreover, it binds to estrogen receptor β in CNS areas with an affinity that reduces neurotoxicity and stops lipid peroxidation. Because of these benefits, silymarin is a wise option for treating neurodegenerative diseases like Parkinson's disease[47].Silymarin corrected MPTP-induced deficits in macro autophagy, CMA, and lysosome quality by restoring the antioxidant defence mechanism of dopamine-producing neurons in the nigrostriatal region[48].Silymarin corrected MPTP-induced deficits in macro autophagy, CMA, and lysosome quality by restoring the antioxidant defence mechanism of dopamine-producing neurons in the nigrostriatal region[49].

7.12. TRICIN:

Of the flavonoid class, tricin is an O-methylated flavone. Rice bran and sugarcane are two sources of it. ATG7- and AMPK-dependent pathways accelerated the breakdown of α-synuclein via enhancing autophagy, which was facilitated by the nontoxic flavonoid tricin. Furthermore, tricin protected transgenic PD mice by promoting dopamine release and autophagic breakdown of disease proteins. This led to an improvement in the animals' behaviour, learning, and memory while also reducing the overabundance of inflammatory cytokines being released[50].

7.13. PEONIDIN:

Peonidin, a main pigment found in plants, is an O-methylated anthocyanidin that is produced from Cyanidin. The highest concentrations of peonidin were shown to be most efficient in reducing the cytotoxicity of SH-SY5Y neuroblastoma cells by totally suppressing α-synuclein fibrillation[51].

7.14. PELARGONIDIN (PEL):

Plant pigments known as anthocyanidins, such as pelargonidin, provide food and industrial dyes their distinctive orange hue. Among the berries that contain pelargonidin are ripe raspberries, strawberries, blueberries, blackberries, cranberries, saskatoon berries, and chokeberries. Moreover, pomegranates and plums include it. Red radishes get their

colour from pelargonidin. Kidney beans have high levels of it. Reduced catalepsy time was one of the aberrant behaviours caused by reserpine that were reversed by the administration of pelargonidin (PEL). Furthermore, nitric oxide concentration decreased as PEL repaired brain glutathione. As a result of increased complex I activity and a decreased ADP/ATP ratio, it enhanced neuronal mitochondrial function. According to these results, the intrinsic apoptotic pathway is suppressed by PEL, as evidenced by the decreased production of cleaved PARP and cleaved caspase-3 proteins.In the future, PEL may be used to treat mitochondria-related neurological problems PD by regulating the continuing cascades of inflammation and degeneration[52].

7.15. EUROPINIDIN:

The plant species *Plumbago Europea* and *Ceratostigma plumbaginoides* yield europinidin, an o-methylated derivative of delphinidin that is a member of the Plumbaginaceae family. The perineal herb plumbago Europea is used medicinally to treat a wide range of illnesses, including scabies, cancer, hepatitis, dysmenorrhea, edema, and respiratory issues. The research findings indicate that the neuroprotective effect of europinidin in rotenone-induced Parkinson's disease is attributed to its capacity to reverse cognitive deficits and behavioural patterns, modify oxidative injury through the restoration of antioxidant enzymes, reduce neuroinflammation, and restore neurotransmitter levels[53].

7.16. VANILLIC ACID:

4-hydroxy-3-methoxybenzoic acid, or vanillic acid (VA), is a derivative of dihydroxybenzoic acid that is derived from a variety of plant extracts. It is mostly found in rice, rice roots, wine, wheat, vinegar, and barley. It results from the process wherein ferulic acid is transformed into vanillin.VA lessened the oxidative stress caused by rotenone that resulted in behavioural, physiological, neurochemical, and histological changes. The antioxidant capacity of VA, which lessened the oxidative damage caused by rotenone in the rats' brains, can be used to interpret these outcomes. In every parameter, the combination of VA at 50 mg/kg plus levodopa and carbidopa had the greatest results[54].

7.17. SYRINGIC ACID (SA):

One of the main active phenolic compounds found in a wide variety of plant materials, including fruits and vegetables, is syringic acid, also known as 4 hydroxy-3,5-dimethoxybenzoic acid. Significant improvements were made in motor dysfunction, reduced nigral dopamine release, higher nitrite/nitrate levels brought on by 6-OHDA, and enhanced iNOS expression after receiving SA therapy. Syringic acid increased TAS capacity and decreased TOS capacity in the SN of PD rats, while also dramatically improving the loss of nigral TH-positive cells. According to these findings, SA may be used as a therapeutic intervention to treat the 6-OHDA-induced PD model in rats. The neuroprotective, antioxidant, and anti-inflammatory properties of syringic acid slowed the advancement of Parkinson's disease (PD)[55].The defence mechanisms of SA against MPTP/p-induced nigrostriatal denervation in PD-affected mice. Raising DA and its metabolites in the ST may have protective effects because they raise the expression of dopaminergic markers and significantly lower the expression of inflammatory cytokines by preventing oxidative stress and enhancing behavioural dysfunctions[56].

7.18. FERULIC ACID (FA):

One phenolic antioxidant component that is present in wheat, oats, rice, peanuts, artichokes, and coffee is ferulic acid (4-hydroxy-3-methoxycinnamic acid, FA). Fruits containing FA, which is well-known for being a strong antioxidant that scavenges free radicals, include oranges, pineapples, and apples. Activating the Nrf2/ARE signalling pathway may be one way that FA's strong antioxidant qualities contribute to its antiparkinsonian action, as demonstrated by experimental data gained through the use of both in vitro and in vivo methods. The findings leave up the possibility that MPTP mice's rotarod performance deficiencies can be improved by a slight SIRT2 inhibition. The findings leave up the prospect that MPTP mice's deficiencies in rotarod performance could be improved by a slight SIRT2 inhibition[57].Results showed that FA had an antiapoptotic effect in the SNpc area by reducing MPP+ production and changing the Bax/Bcl2 ratio. When mice are given MPTP, their motor balance and coordination are improved by the combined antioxidant and antiapoptotic actions of FA[58].Induced nitric oxide synthase, cyclooxygenase-2, proinflammatory cytokines, and other inflammatory mediators were decreased after FA therapy. Attenuation of microglial and astrocytic activation is further suggested by the dramatic reduction of Iba-1 and GFAP hyperactivity.FA's antioxidant and anti-inflammatory qualities exert a protective influence on the nervous system, perhaps preventing degenerative alterations in Parkinson's disease[59].We found that FA enhanced the motor function in the rotenone-induced Parkinson's disease (PD) mouse model; this effect may have been caused by elevated Hsp70 expression and total hippocampal density[60].

7.19. CAFFEIC ACID:

Honey bee propolis contains phenethyl ester of caffeine. It has anti-inflammatory, ant-cancer, and immunomodulatory qualities. By suppressing microglia cells and downregulating inflammatory mediators such COX-2, iNOS, and NFκB,

caffeic acid reduced the inflammatory burden in the rotenone model of Parkinson's disease. These positive effects played a role in the neuroprotective action of caffeine as well as the improvements in locomotor activity that were observed[61].

7.20. P-COUMARIC ACID (pCA):

Camellia sinensis, Camellia reticulata, and other species naturally contain p-coumaric acid (pCA), also known as 4-hydroxycinnamic acid. The neuroprotective action of pCA in mice with rotenone-induced PD-like pathologies. Anti-lipid peroxidation, suppression of neurodegeneration, and anti-inflammation via TNF-α reduction are some of the advantages of pCA. It also has a nourishing effect on TH levels in the SNc and striatum, which mitigates motor deficits[62].

CONCLUSION:

Parkinson's disease is the second most prevalent chronic neurodegenerative illness. It primarily affects the dopamine-producing brain subregions, which in turn affects motor function and cognitive function. Clinically recognized symptoms of Parkinson's disease can be classified as either non-motor or motor. The brain, spinal cord, and the nerves that connect them are all part of the central nervous system, which is also impacted by Parkinson's disease. Parkinson's disease does not currently have a known treatment. In order to regulate the psychological side effects and effectiveness of Parkinson's disease (PD), different therapy techniques have been implemented thus far. But all these drugs do is treat the condition's symptoms. Deep brain simulation, which entails implanting electrodes in specific brain regions, is one of the alternative treatments for Parkinson's disease. An electrical impulse that controls brain activity is produced by these electrodes. But only when the illness has progressed are these costly operations performed. Many contemporary studies are therefore focused on finding innovative compounds that can both boost therapeutic advantages and lessen psychological side effects in patients with Parkinson's disease. This article highlights several phytoconstituents that are thought to play a critical role in the treatment of neurodegenerative diseases, such as Parkinson's disease. The efficiency of phytoconstituents in various PD models, whether cellular or animal models, has been examined in this paper based on available data. The current review also showed that, in order to reduce the negative psychological effects and increase the effectiveness of treating neurodegenerative diseases, such as Parkinson's disease (PD), plant-derived natural products can be used as an adjuvant treatment in conjunction with other conventional therapeutic approaches.

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