"EMERGING ROLE OF DIETARY POLYPHENOLS AND HERBS IN PARKINSON'S DISEASE"

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ABSTRACT:

Parkinson's disease (PD) is a slow-progressing neurodegenerative disease characterised by dopaminergic neuron loss in the nigrostriatal pathway. Despite decades of research, disease therapeutic options are severely limited, providing just symptomatic relief and failing to prevent progression of the disease. Moreover, the average drug treatment expenses and therapeutic surgical procedures are highly expensive. Besides that, the overall number of Parkinson's disease patients worldwide is increasing dramatically, which has a significant impact on individual and social lives of patients. As a result, herbal supplements for treating and preventing Parkinson's disease have received a lot of attention in past few decades. Herbal remedies, phytochemicals, and polyphenolic compounds derived from food supplements, fruits, vegetables, and spices can help to prevent, delay, or alleviate the symptoms of long-term neurological disorders, and also improve cognition, learning, and overall brain health and welfare. Innumerable plants and polyphenolic compounds have been recognised in recent scientific studies as having healing properties against neurological diseases including such Parkinson's disease and Alzheimer's disease. As a result, the aim of the review is to describe some of the most medicinally significant herbal supplements and polyphenols in terms of their neuroprotective potential, as well as to aid in the discovery of possible therapeutic interventions for Parkinson's disease.

KEYWORDS: Parkinson disease, Oxidative stress, Mitochondrial Dysfunction, Polyphenol, Flavonoids, Herbs.

INTRODUCTION:

Every day, modern life becomes more stressful. All stress-related diseases result in lack of physical action and psychological relaxation. Stress and restlessness impair both the physical

and mental health, particularly the central nervous system, which serves as the regulating system's midpoint.(1) Neurodegenerative disorders have emerged as one of the most serious global public health issues, described primarily by the progressive decline of neuronal cells and nervous system disorder related to aging. These diseases can lead neurons to malfunction, leading to cell death.(2,3) Neurological diseases disease that kills a huge number of people all over the world. As per latest statistics, the overall mortality rate in the twenty-first century is 8% (1)

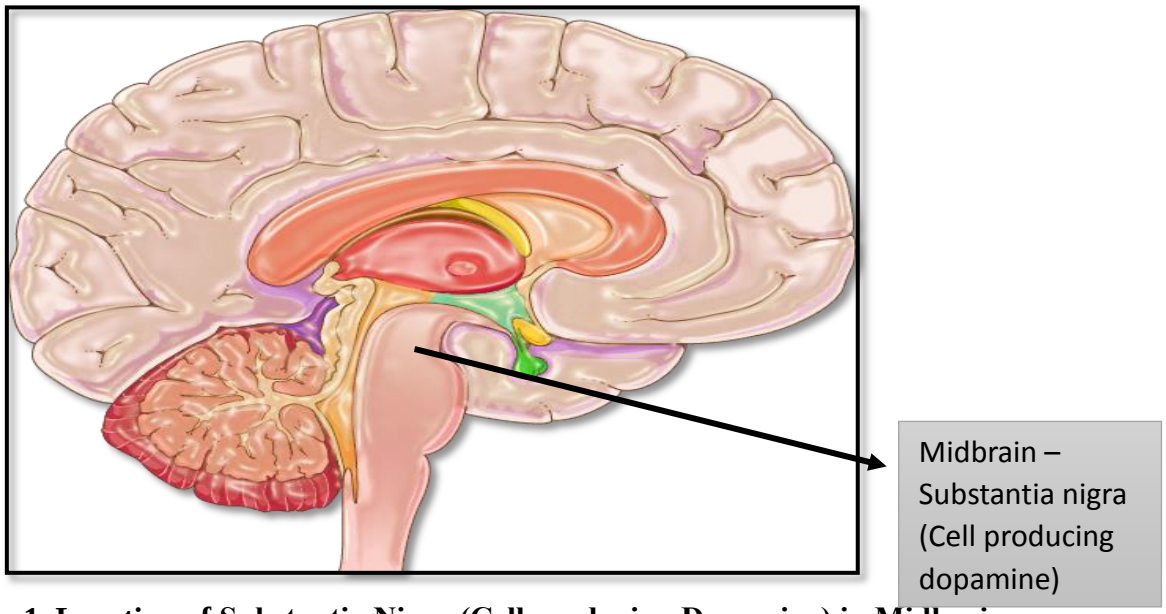

Figure 1, Location of Substantia Nigra (Cell producing Dopamine) in Midbrain

Parkinson's disease (PD) is the second most common aging-related neurodegenerative disease after Alzheimer's disease (AD).(4) In 1817, James Parkinson published "An Essay on the Shaking Palsy," which was the first one to describe it. (5) According to historical sources, Parkinson's disease originated in ancient India and was known as kampavata. (6) In Parkinson's disease, the major pathophysiological alteration is the decline of dopamine - producing neurons in the substantia nigra of the centre of the brain(7) In 1912, Fritz Heinrich Lewy revealed the first main pathological hallmark of Parkinson's disease, nerve cell inclusions, in the human brain of Parkinson's patients. These neurological inclusions, known as Lewy bodies, were later found to be mainly composed of -alpha -synuclein misfolded proteins (8).

Even though the cellular mechanism affecting DA neuronal cell death remains unknown, recent studies have demonstrated (9) that free radicals, oxidative stress, inflammation, mitochondrial dysfunction, and -synuclein aggregation are involved. Furthermore, increased concentrations of redox-active metals like iron as well as copper, decreased glutathione levels, and elevated lipid peroxidation have also been mentioned in Parkinson's disease. (10) The occurrence of classic motor symptoms like rigidity, bradykinesia, and tremors, as well as non-motor symptoms like hyposmia, insomnia, and depression, is generally triggered by DA reduction from synaptic terminals in various sections of a basal ganglia. A few initial non-motor signs, such as depressive episodes or hyposmia, could be related to the preclinical phases of the disease, which take place before motor symptoms appear. (11) Environmental

carcinogens, pesticide exposure, and genetic predisposition such as genetic variations in the -synuclein or Parkin genes have been associated to PD morbidity. Environmental factors include 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), toluene, carbon disulphide, and cyanide2, whereas pesticides involve paraquat, organophosphates, and rotenone. Dopaminergic neuron declines and clinical parkinsonism both have been linked to MPTP exposure. Likewise, rotenone and paraquat have been shown in preclinical studies to cause neuronal cell loss and typical parkinsonism.(4,10) Therapeutic approaches available today can only provide limited temporary symptomatic relief for patients with Parkinson's disease and have very little effectiveness in restoring the disease's underlying neurodegenerative changes. AS a result, there seems to be a clinical need for us to identify bioactive molecules that can alleviate or slow the harmful events associated with Parkinson's disease. (10)

Parkinson's disorders are the most common progressive neurological disorder, affecting over 10 million people globally, and its prevalence rises with age. It is predicted that 4% of Parkinson's disease case scenarios are diagnosed before the age of 50 (12) Men are twice as likely as women to develop Parkinson's, but women have a greater mortality rate and disease growth(13) Furthermore, the average drug therapy expenditure per person suffering from Parkinson's disease is somewhere around $2500 per year, and therapeutic surgical procedure for patients may expenses around $100,000. Furthermore, the total number of Parkinson's disease patients around the world is rising enormously, having a great impact on a patient's personal and social life. (12)

As a result, herbal remedies have gotten a lot of attention in recent decades for treating and preventing Parkinson's disease. (14) Naturally occurring substances, in addition to conventional drugs, have been identified as potential effective drugs targeting multiple pathways. (15) Herbal remedies, phytochemicals, and polyphenolic compounds derived from food supplements, fruits, vegetables, and spices can help to avoid, lag, or relieve the symptoms of prolonged neurological disorders, as well as enhance cognitive abilities, learning, and overall brain health and welfare (16) Scientific studies during the last couple of Years has recognized numerous plants and polyphenolic compounds that have shown healing properties against neurological disease such as Parkinson's disease and Alzheimer's disease. As a result, the purpose of this review is to explain some of the most medicinally important herbal remedies and polyphenols in terms of their neuroprotective potency, as well as in the discovery of potential therapeutic interventions against Parkinson's disease. (12)

PARKINSON'S DISEASE PATHOPSHYIOLOGY (19-24):

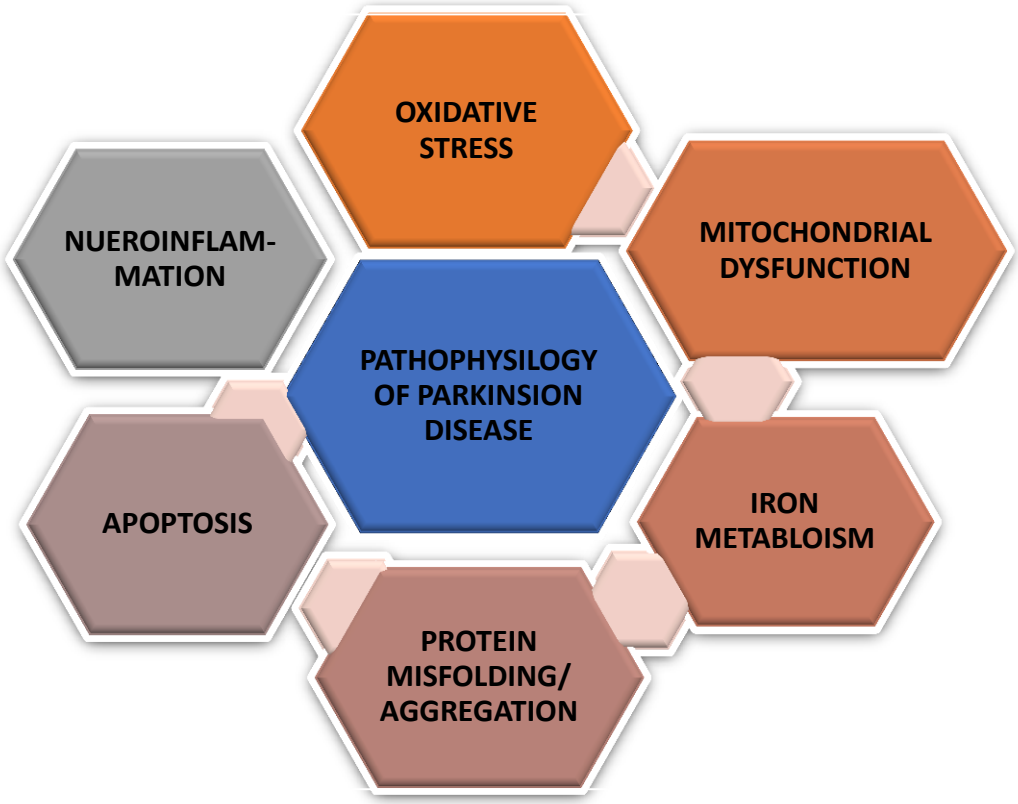

Figure 2, Pathophysiology of Parkinson's disease

The principal cause of dopaminergic neurodegeneration is oxidative stress. oxidative stress has an impact on homeostatic mechanisms including mitophagy and the ubiquitin proteasome system. As a result, oxidative stress plays a pivotal role in the development of Parkinson's disease. According to hypothesis, the neurotransmitter dopamine (DA) could be a source of OS. Iron is essential to the survival of nearly all types of cells, which include brain cells. It is a necessary cofactor for proteins that are involved in neuronal tissue function. Many neurotransmitters, including dopamine, require elemental iron for synthesis. Finding suggest that increases in midbrain iron levels may play a significant role in the neurodegeneration connected with Parkinson's disease. Mitochondria is not only the major source of reactive oxygen species (ROS) but also the primary target of oxidative stress. There is strong evidence that mitochondrial dysregulation is responsible for the onset of Parkinson's disease. The most widely accepted theories for the death of nigrostriatal neurons in Parkinson's disease is abnormal alpha-synuclein protein misfolding.

PARKINSON'S DISEASE CURRENT THERAPEUTIC THERAPIES:

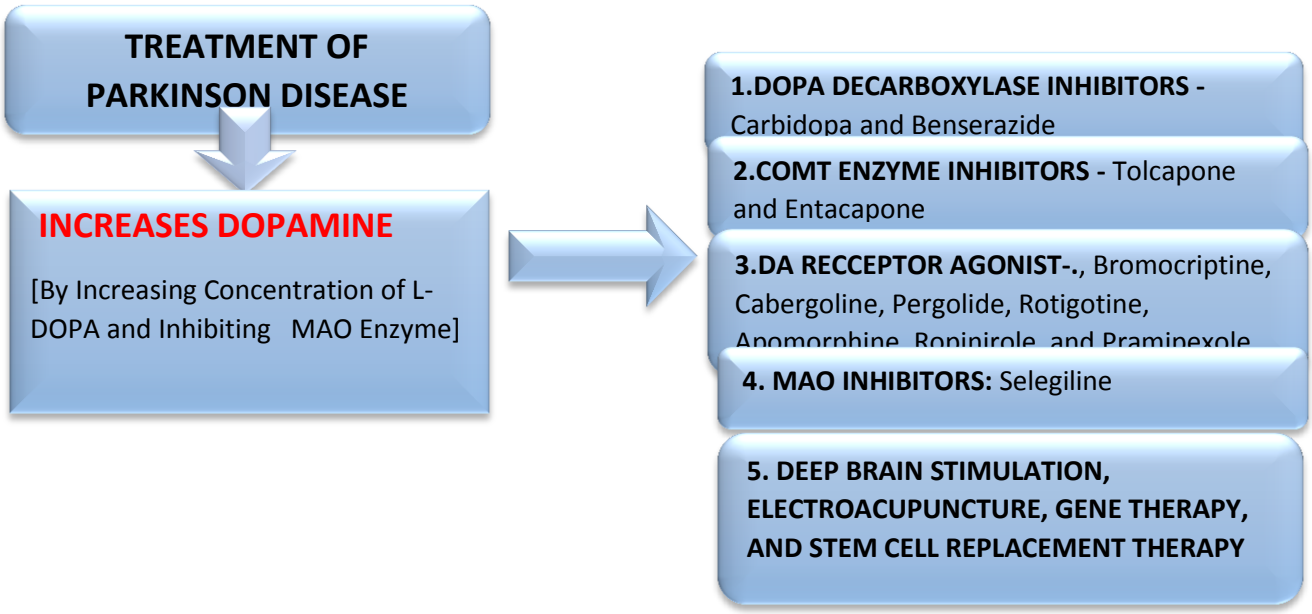

Figure 4, Current Therapeutic Treatment for Parkinson's disease

Till date, there is no curative therapy for Parkinson's disease, prevention is more important than ever. (4) Increasing the amount of DA by impairing monoamine oxidase (MAO), which is liable for metabolising DA to less active compounds, or increasing the concentration of the DA precursor Levodopa far (L-DOPA) have been the only therapies for Parkinson's disease so far. (25) DA is unstable in nature and cannot passes the blood-brain barrier (BBB). It is synthesised in the brain through the conversion of its precursor L-DOPA.(10) Since the 1960s, L-Dopa (L-3, 4-dihydroxyphenylalanine) has been the drug of choice for Parkinson's disease treatment. However, it has adverse effects such as gastrointestinal toxicities such as emesis, nausea, giddiness, and orthostatic hypotension movement disorders, behavioural adverse effect, end of dose deterioration, or the on-off phenomenon with motor dysfunction strongly associated with the disease itself (6,12,26). These numerous adverse effects have been reported because 95–99% of it is metabolised to dopamine inside the body in areas other than the dopamine neurons in the SN. As a result, by blocking the peripheral degradation of L-DOPA to DA, dopa decarboxylase inhibitors and COMT enzyme inhibitors (4)significantly raise the plasma levels of L-DOPA and thus improve its effect. The primary class of drugs used to cure Parkinson's symptoms are DA receptor agonists (e.g., bromocriptine, cabergoline, pergolide, rotigotine, apomorphine, ropinirole, and pramipexole). By suppressing subthalamic nucleus overstimulation and exerting anti-apoptotic effects, DA agonists act as endogenous free-radical scavengers, controlling DA synthesis and alleviating excitotoxicity. DA agonists focus on providing moderate symptomatic relief but are linked to higher occurrence of adverse side effects such as hallucinations, swelling, sudden sleep attacks, and impulse control disorders when compared to levodopa (ICD). Surprisingly, motor fluctuations such as dyskinesias have become less common after DA agonist administration (10) Monoamine oxidase B (MAO-B) inhibitors are another potential treatment for Parkinson's disease. Monoamine oxidases (MAO-A & MAO B) are flavonoid-

containing enzymes that catalyse the conversion of neurotransmitters to hydrogen peroxide (H2O2), aldehydes, and ammonia in the central and peripheral nervous systems. The MAO-B enzyme's activity is increased as a result of DA metabolism, which leads to increased oxidative stress and mitochondrial dysfunction. MAOI controls the breakdown of dopamine (DA) into its metabolites in the brains of people with Parkinson's disease. MAOIs can thus be used therapeutically to keep DA levels in check(10,12) In addition, recent advancements in neuroimaging and neurosurgical techniques have emphasised surgical intervention for this disease. Deep brain stimulation of the subthalamic nucleus helps to improve motor control while decreasing dyskinesia and motor fluctuations.(3) Electroacupuncture, gene therapy, and stem cell replacement therapy are some other anti- Parkinson's disease therapies. (15)Natural remedies are recommended to conquer the negative side effects associated with allopathic medicine (6)

HERBAL APPROACH IN TREATING PARKINSON DISEASE

Medicinal herbs and other natural compounds have wide and varied stereochemistry and pharmacophore accessibility, resulting in better hits for drug screening against complex targets that has several protein interactions. Herbal medicines also have metabolite-like characteristics like high bioavailability, which are advantageous in target site delivery and functional assay-based drug screening. Herbal medicines are also less expensive, safer, and have fewer side effects. Traditional medicines' use has decreased significantly in the last two decades as a result of concerns about incompatibility with high throughput screening perspectives to synthetic drug discovery, doubtful reproducibility, and limited numbers of single compounds isolation caused by seasonal and geographical variabilities. Although, technological advances that have been made such as enhanced screening and isolation using chromatography-based separation and spectroscopic (Mass Spectroscopy, Nuclear Magnetic Resonance) methodologies, along with collaborative effort with medicinal chemistry, are resurrecting the phototherapeutics field. (27)

Following are the list of plant used to treat Parkinson's disease:

SR. NO	PLANT NAME
1	*Mucuna Prunies*
2	*Bacopa monnieri:*
3	*Withania somnifera (Indian ginseng or Ashwagandha)*
4	*Centella Asiatica*
5	*Ginseng*
6	*Tinospora Cordifolia*
7	*Luteolin*
8	*Puerarin*
9	*Rutin*
10	*Naringenin*
11	*Baicalein*
12	*Resveratrol*
13	*Epigallocatechin gallate (ECGG):*
14	*Quercetin*

15	*Curcumin*
16	*Ginkgo biloba*

Table 1, List of Plants used to treat Parkinson's disease

1]*MUCUNA PRUNIES:*

L-dopa, which is considered the gold standard for PD treatment, is one of the main components of this plant. (12,28) The antioxidant and metal chelating activity of *M. pruriens* has been shown to protect neurons from oxidative damage caused by levodopa (29). In addition to being a naturally occurring substance of levodopa, the seeds of *M. pruriens* have cognitive benefits, a decline in dyskinesia, mood improvement, and an enhance in libido (29) The prickly trichomes of *Mucuna Pruriens*, also known as velvet beans (6) cow hedge, kept stray cows out of farms. (29)Africa and tropical Asia, including southern China and eastern India (30), as well as the tropics, including Central and South America (10), are its native habitats. *Mucuna pruriens (MP)* is a tropical leguminous plant with a long history of medicinal use. (12). MP seeds are often used in Indian traditional medicine to treat ageing, rheumatoid arthritis, diabetes, and neurodegenerative disorders, as well as a tonic and aphrodisiac for male virility (30) It has anti-inflammatory characteristics which is used in the treatment of ulcers and helminthiasis. (12) MP's neuroprotective result was obtained through its anti-inflammatory and antioxidative activities (30), in which it helps to improve redox status by reducing oxidative stress via its antioxidant properties and metal chelating attributes. MP seed extract also strengthens mitochondrial and synaptic activities, both of which are important for neuronal survival, as well as TH expression (12). In MPTP-affected brain tissues, it also reported to inhibit NF-B signalling, reduced lipid peroxidation and nitrite levels, and encouraged pAKT1 activity, reversing the animals' behavioural deformities [H16]. In comparison with synthetic L-Dopa, MP extract had twice the Antiparkinson's. As a result, in the treatment of Parkinson's disease, MP seed extract provides better results than synthetic levodopa. (12) Its safety in humans has been established, even at very high doses of 15- 30g administered over a period of 12-20 weeks (29). It is an adjuvant that improves the effectiveness of L-Dopa[H7]. When compared to the standard combination of levodopa (200 mg) and carbidopa (50 mg) treatment options, 30 grammes of Mucuna seed powder has been shown to have antiparkinsonian effects in PD patients, with a faster onset of action, shorter latency, and improved improvement(10) without any rise in deleterious effects(12).

2] *BACOPA MONNIERI:*

Bacopa monnieri, also known as Brahmi (Bm), is a perennial, creeping herb with numerous medicinal properties. (12) It is well recognised as a powerful "tonic for the human brain" that behaves as a memory enhancer(31). It's been shown to have antioxidative, anti-inflammatory, anti-microbial, neuroprotective, and memory-improving attributes. Bm extract (BME) has also been shown to improve cognitive abilities.(12) Bacosides A and B are the active ingredients in Bacopa that give it its cognitive effects. [H6] Bacoside A is a blend of four saponins: bacopaside II, bacoside A3, bacopasaponin C, and the jujubogenin isomer of bacopasaponin C. Because of their lesser intracellular reactive oxygen species (ROS) and greater cell viability, bacopaside II and bacoside A3 were found to have relatively better neuroprotective functionalities among these four components. (31)BME's antioxidant, free radical scavenging, and DA-enhancing properties are thought to be the mechanism of action

(10)Treatment with *B. monnieri* decreased alpha-synuclein accumulation (15) and slowing down DA-nergic neuron degradation. (12) It adjusted the levels of oxidative markers (ROS, MDA, and hydroperoxides) as well as protein carbonyl content herbs(12,32) Taking supplements of BME enhances mitochondrial function by restoring normalised electron transport chain (ETC) complex activity. In the SN region of the brain, BME improves tyrosine hydroxylase (TH) activity as well as neurogenic gene expression(12) It has been proven that *Bacopa monnieri* extract (BME) has a protective effect by improving behavioural activity and restoring GSH levels, dopamine levels, cytosolic antioxidant enzyme activity (12) as well as Na^{+}/K^{+} ATPase, Mg^{+2}, and Ca^{+2} ATPases(31) and neurotransmitter function(32) It also lowers lipid peroxidation.(10)As a result, BME appears to have a lot of potential as a herbal anti-parkinsonism treatment. More research is needed, however, to fully understand the mechanism of action before it can be used as a promising therapeutic target against Parkinson's disease. (12)

3] *WITHANIA SOMNIFERA* (INDIAN GINSENG OR ASHWAGANDHA)

Withania somnifera (Ws) is a popular Indian medicinal plant that has been used for centuries. (12)The medicinal plant *Withania somnifera* (WS), also known as Ashwagandha or Indian ginseng (32), is a member of the *Solanaceae* family. It contains a high concentration of triterpene lactones, alkaloids, tropine, steroidal lactones, and Withanolides. Because Withanolides have a chemical structure like ginsenosides derived from *Panax ginseng*, and hence WS is usually referred to as "Indian ginseng." (30) Antioxidant, antiperoxidative, and free-radical quenching properties have been reported for *W. somnifera* extract which is potential for neuroprotective activity(25).Ws decrease oxidative stress by normalising antioxidant potential, the lipid peroxidation marker (29) raising glutathione (GSH) and glutathione peroxidase (GPx), and enhancing TH expression, catecholamines, and physiological irregularities.(12,25) It was also discovered that the levels of DA metabolites 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) increased dramatically (10) In the brain tissues of PD patients, it substantially resulted in significant reduction of iNOS (oxidative stress) and GFAP protein (a proinflammatory marker of astrocyte activation.(30) Ws's potential to ameliorate gait ailments, inflammation, and brain ageing, as well as its ability to upregulate p13 kinase and improve neuronal growth (10) As a result, Ws appears to be a promising platform for drug development against Parkinson's disease; however, more research is needed to confirm its potential (12).

4] *CENTELLA ASIATICA* –

Centella Asiatica (CA), a psychoactive medicinal herb belonged to the *Apiaceae (Umbelliferae)* family, it has been used as a medhya rasayna in the Ayurvedic system of medicine from ancient times. It has been demonstrated that it reduces oxidative stress level. Asiaticoside, oxyasiaticoside, centelloside, brahmoside, brahminoside, thankunoside, isothankunoside, and related sapogenins are among the plant's most important bioactive components. Asiatic acid, madecassic acid, Brahmic acid, isobrahmic acid, betulic acid, and other triterpenoid acids can also be found in it. Nevertheless, the precise mechanism of action in the management and treatment of neuro impairments is unknown. (33) However, supplementing with *Centella Asiatica* extract lowered lipid hydroperoxides and protein

carbonyl levels in the striatum significantly. (15) Asiaticoside, a saponin isolated from *C. Asiatica*, reduced MPTP-mediated neurotoxic effects in rats by raising the Bcl-2/Bax ratio and boosting antioxidant effects. Madecassoside, an antioxidative triterpenoid isolated from C. Asiatica, guarded model rats from MPTP-induced early symptoms of parkinsonism by raising the Bcl-2/Bax ratio and brain-derived neurotrophic factor (BDNF) expression. (25)MPTP-induced Parkinsonism can be treated with *Centella Asiatica*. It works by acting as an antioxidant in the brain's hippocampus and corpus striatum. The extract boosts superoxide dismutase, xanthine oxidase, glutathione peroxidase, catalase, and overall antioxidants while decreasing protein carbonyls and lipid peroxidation. (32,34)

5] *GINSENG* –

Ginseng is the genus roots of *Panax ginseng* Meyer (from the Greek pan = all and akèia = cure) (*Araliaceae*) In Chinese medicine, it is one of the most used herbs for uplifting energy levels. Ginseng encourages vitality, extends life, and has therapeutic properties for a variety of ailments, including immune regulation, antitumor, antifatigue, antiaging, antioxidation, depression, diabetes, inflammation, dyspepsia, nervous system diseases, and many others. (33,35) Ginsenosides have been shown to improve brain function, mitigate neuroinflammation and oxidative stress, and decrease or weaken the symptoms of a number of neurodegenerative diseases like Parkinson's disease, Alzheimer's disease, traumatic brain injury, and Huntington's disease (HD). Ginseng's active ingredients are responsible for its various pharmacological properties. (36)It contains ginsenosides, polysaccharides, peptides, polyacetylenic alcohols, and fatty acids. Ginsenosides are classified into two groups: protopanaxadiols (PPD, e.g., Ra, Rb1, Rc, Rd, Rg3, Rh2) and protopanaxatriols (PPT, e.g., Re, Rf, Rg1, Rg2, Rh1) [H10] The major ginsenosides in ginseng are Rb1 and Rg1. (25)

Ginsenoside Rg1 is a key chemical constituent of ginseng that has low toxicity, anti-inflammatory, and neuroprotective properties. The research indicate that Rg1 has neuroprotective effects not only in vivo but also in vitro PD models. (35) Caspase-3 activation was clearly inhibited by pre-treatment with ginsenoside Rg1. Rg1 also diminished iNOS protein levels and NO production. Through activation of the PI3K/Akt pathway, Rg1 enhanced the inhibitory effects of phosphorylation of the pro-apoptotic protein. The production of DA-induced ROS and the release of mitochondrial cytochrome c into the cytosol were both lowered after pre-treatment with ginsenoside Rg1. It also inhibits 6-OHDA-induced upregulation of an iron importer protein (divalent metal transporter 1 (DMT1) + iron responsive element (IRE), and also the influence of Rg1 on DMT1 + IRE expression was owing to its antioxidant potential on iron regulatory proteins (IRPs) (7) Because of its antioxidant nature and ability to inhibit JNK signalling, ginsenoside Rg1 (5, 10, and 20 mg/ kg/day) hindered MPTP-induced substantia nigra neuron loss in C57BL mice. Only Rb1 was found to be a powerful inhibitor of alpha-synuclein fibrillation and toxicity, functioning as a defibrillator, among all the ginsenosides tested (i.e., Rb1, Rg3, and Rg1). As a result, Rb1 has the potential to be used as a drug in the treatment of Parkinson's disease and other neurological diseases.(35) Ginsenoside Re prevented apoptotic cell death in an MPTP-induced Parkinson's disease mouse model by increasing Bcl-2 expression, decreasing Bax and iNOS expression, and preventing caspase-3 activation. (25) Ginsenoside Rd, one of the important bioactive monomer compounds found in *Panax ginseng*, reverses the loss of tyrosine hydroxylase positive cells in the substantia nigra of MPTP-treated mice by altering

the PI3K/AKT survival-signalling pathway. Ginsenosides also increase the activity of SOD and aconitase enzymes, reduce MMP depolarization, and re-establish calcium levels in rotenone-induced SH-SY5Y cells. *Panax ginseng* extract inhibits the development of locomotor deficits by lowering dopaminergic cell loss, microgliosis, and the accumulation of alpha-synuclein aggregate particles. (33)A ginseng water extract protected MPP^+-treated SH-SY5Y cells, most likely by suppressing Production of ROS and inhibiting mitochondria-dependent apoptosis. (25)

6] *TINOSPORA CORDIFOLIA*:

T. cordifolia is a *Menispermaceae* herbaceous climber that goes by many names in India, including Giloya, Amrita, Guduchi, Gulancha, Ambervel, and Gulvel. *T. cordifolia* has traditionally been used by Ayurvedic practitioners to treat a variety of conditions such as fever, asthma, dysentery, leprosy, diarrhoea, jaundice, skin infections, and diabetes. When compared to negative control (6-OHDA alone treated) animals, experimental Parkinsonian animals treated with *T. cordifolia* had higher levels of dopamine, enhanced mitochondrial complex-I activity, and stronger neuromuscular coordination. *T. cordifolia* extract also inhibited 6-OHDA-induced iron deposition in the rat brain, which produces dopaminergic neurodegeneration in Parkinson's disease. (27)*T. cordifolia* extract is highly attractive against Parkinsonism, according to Birla et al. In a 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)- Parkinsonian mouse model, they found that aqueous extract had anti-inflammatory action The extract reverted the behaviour of MPTP-intoxicated mice, implying that *T. cordifolia* secured dopaminergic neurons by suppressing neuroinflammation in a Parkinson's disease mouse model stimulated by MPTP. (37)More research is needed in this area to see if *T. cordifolia* has the potential to prevent and treat diseases.

ROLE OF DIEATERY POLYPHENOL IN PARKINSON DISEASE:

Dietary phenolics, also known as polyphenols, are among the most abundant and widely spread natural compounds groups in the kingdom plantae. Over 8000 phenolic structures have been identified, with over 4000 flavonoids among them. However, the word "polyphenols" is often used to refer to the several sub-groups of phenolic compounds.(38) Fruits, vegetables, tea, cereals, medicinal plants, microalgae, edible, and wildflowers are all natural sources of polyphenolic compounds. Vegetables are an important part of most people's diets and are plentiful in polyphenols. (39) They help in providing plant pigmentation and serve as signaling molecules in growth and ripening processes, in addition to protecting plants from UV radiation and aggressive pathogens. A fruitful period of scientific study revealed the therapeutic potential of polyphenol-rich diet and lifestyle in the prevention of diseases such as heart disease, diabetes, osteoporosis, cancers, as well as neurological diseases, elevating them to the forefront of clinical research. (40) Polyphenols are extremely powerful antioxidants, owing to their ability to scavenge or rummage free radicals and their iron chelating action. Antitumor, anti-inflammatory, and antimicrobial effectiveness are just a few of the therapeutic potential it possesses. As a result, polyphenolic substances have been recognized as Natural plant sources for the treatment of a wide range of ailments, including neurodegenerative diseases. Polyphenolic compounds derived from a variety of sources have been shown to be effective mechanisms**.** Flavonoids, phenol acids, stilbenoids, tannins, phenolic alcohols, and lignans are among the polyphenolic compounds

that are classified into several classes.(41,42) Polyphenols were classified into several subclasses depending on the number of phenol rings they contain and the structural components that attach to these rings, that were distributed into several subclasses, such as phenolic acids, flavonoids, and stilbenes (39)At least one phenolic ring is attached to hydroxyl groups in either ortho or para positions in all polyphenols, allowing for redox reactions to occur. Antioxidant properties are provided by hydroxyl groups and phenolic rings(43) . Polyphenolic compounds are gaining more attention from researchers in the area of Parkinson disease due to their antioxidative properties, which contribute to minimize oxidative stress, that plays a key role in the disorder.

FLAVANOIDS:

Flavonoids are plant-derived polyphenolic compounds with low molecular weight. (44) It is one of the most abundant classes of naturally occurring polyphenols, and it is plentiful in nutritional fruits and vegetables (45). Flavonoids have a wide range of pharmacological effects. They have a wide range of biological effects, including anti-inflammatory, anti - oxidative, antiviral, and antitumor properties. Flavonoids in the diet have been shown to be potentially neuroprotective (26,44). Besides this, little is understood about the interactions of flavonoids or their circulatory metabolic products with the brain endothelial cells that form the blood–brain barrier (BBB), making it difficult to identify flavonoid compounds that enter the CNS. (46) Flavonoids have been revealed in roughly 4000 different fruits, vegetables, and herbs. Plants contain many different types of flavonoids, including flavones, flavanones, flavanols, isoflavones, anthocyanidins, and flavanols. These flavonoids are excellent free radical scavengers and try to protect oxidative stress in the body.(47) In vitro, flavonoids can chelate metal ions, affect the activities of cellular antioxidants and antioxidant enzymes like catalase and GSH, regulate NO generation, tumor necrosis factor a secretion, and nuclear factor kB (NFkB) based gene expression, and have anti-inflammatory characteristics by suppressing lipoxygenase and cyclooxygenase activities. (48)The aforesaid neuroprotective action of flavonoids aids in the prevention of Parkinson's disease signs and symptoms. The flavonoids listed below are mostly utilized in Parkinson's disease.

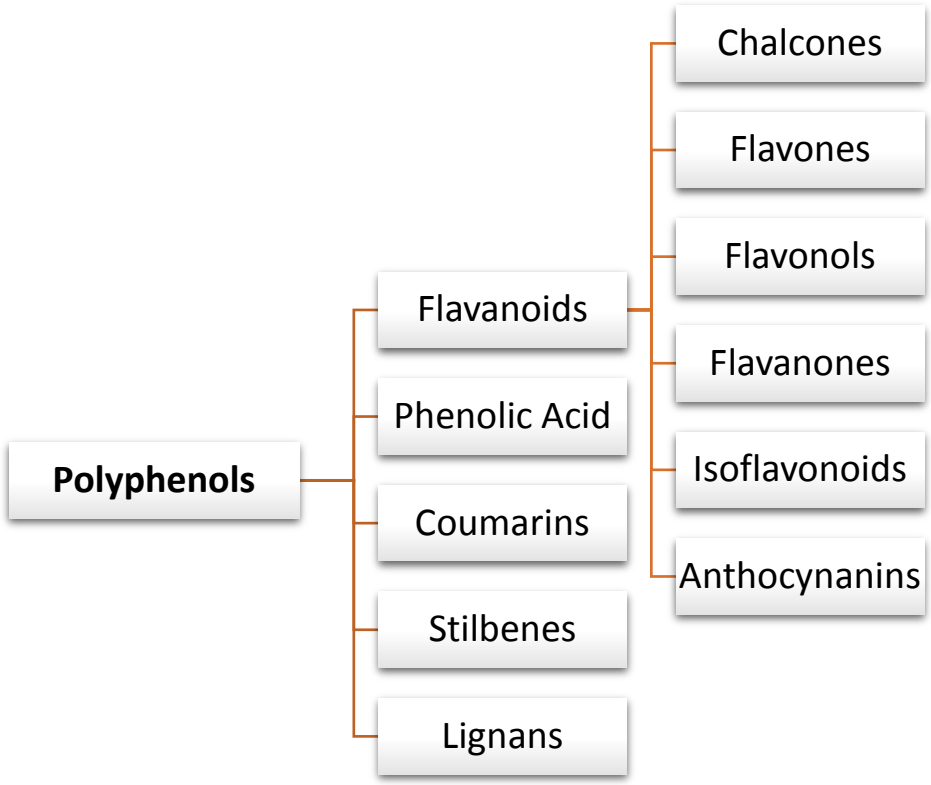

Figure 5, Classification of Polyphenols

1.*LUTEOLIN* -

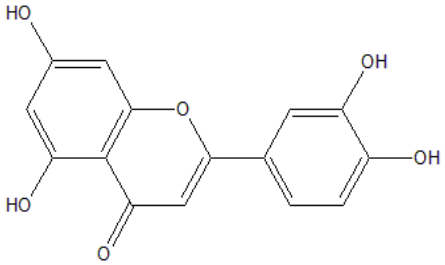

Figure 6, Chemical Structure of Luteolin

Luteolin, a polyphenolic component found in plant-based foods, belongs to the flavone subclass of flavonoids, and is commonly found as glycosylated versions in celery, green pepper, perilla leaf, and camomile tea. (49) In addition to antioxidant activity, it exhibits anti-inflammatory, antimutagenic, antitumorigenic, immunomodulating, and anxiolytic-like properties, as well as an inhibitory effect on the Beta -site amyloid precursor protein-cleaving enzyme-1. (49,50) Luteolin inhibited the oxidative damage caused by H2O2 by increasing the production of microRNA21, stimulating the P13k/AkT pathway, and inhibiting the PDCD4/P21 pathway. (5) Luteolin inhibited astrocyte-induced neuroinflammation by modulating the levels of extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK), and p38 MAPK, (51)as well as STAT3 activation. It also blocked activated STAT3

and NF-kB from being translocated to the nucleus of activated astrocytes, lowering their DNA binding potential. In a dose-dependent way, luteolin stimulated neurite outgrowth as well as enhanced expression of the differentiation marker growth-associated protein-43 (GAP-43) (5). Many experimental research has found that using luteolin at different concentrations can help with neuroprotective effects. Lutein provided neuroprotection against H2O2-induced apoptosis in SH-SY5Y cells(52)Luteolin has also been reported to aid memory improvement by influencing numerous neurotransmitters in the brain, such as the cholinergic and glutamatergic systems (53) Despite all the evidence of Luteolin's preventive benefits, more research and exploration into the clinical significance of this antioxidative molecule in the setting of PD pathogenesis is needed.

2. PUERARIN -

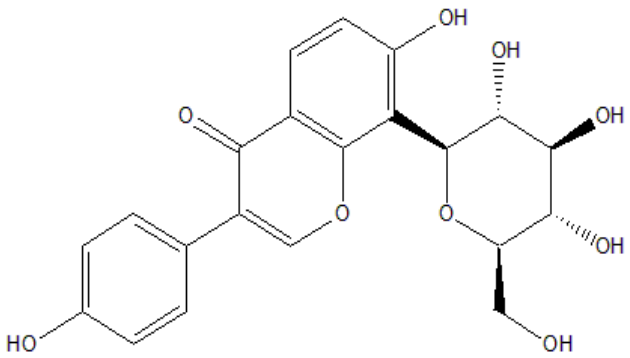

Figure 7, Chemical Structure of Puerarin

Puerarin is the major active ingredient isolated from the root of *Pueraria lobata* (Wild.) Ohwi, also known as Gegen in traditional Chinese medicine (54). It has a variety of pharmacological effects and can be used to treat cardiovascular events, gynecological disease, osteoporosis, and cognitive deficits(55) . We show that Puerarin can activate the PI3K/Akt pathway in an MPP+-induced human neuroblastoma SH-SY5Y cellular model, lowering MPP+-induced p53 nuclear accumulation and preventing subsequent Puma, Bax-caspase 3-dependent PCD. (55,56) Puerarin administration can affect the neuroprotective effect on MPP+-induced apoptosis in PC-12 cells, as well as whether the effects are triggered by inhibiting the c-Jun N-terminal kinase (JNK) signaling pathway(57) The diminished expression of TH in the rotenone-induced rodent model was also shown to be significantly rehabilitated after Puerarin treatment (58) The findings suggest that Puerarin has neuroprotective properties and could be used to treat Parkinson's disease in humans, but further research and clinical relevance are needed.(52)

3. RUTIN-

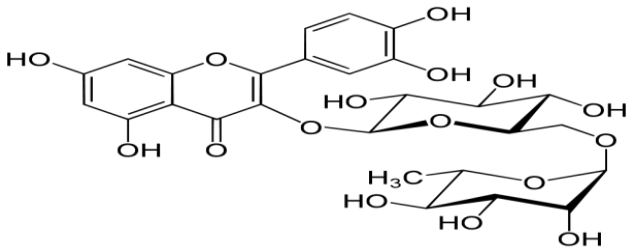

Figure 8, Chemical Structure of Rutin

Rutin is abundant in citrus fruits, grape and lime rinds, and berries such as cranberries and mulberries (59). Rutin, also known as vitamin P, is a bioflavonoid that has been shown to have anti - oxidative, anti-inflammatory, antiallergenic, antiviral, and anticarcinogenic attributes, as well as the ability to scavenge superoxide anion (60). Rutin is a flavanol-based aglycone of quercetin. Due to the ability of rutin or its metabolic products to cross the blood-brain barrier, this substance modulates the cognitive and behavioral clinical signs of neurodegenerative disorders; this results effects on various cellular activities under pathological processes (61) Rutin's antioxidant activity was demonstrated by inhibiting Ros generation by suppressing free radical mechanisms at 3 phases: superoxide ion formation, hydroxyl radical production in the Fenton reaction, and lipid peroxide radical formation. (62) Rutin scavenges superoxide radicals, retains biological antioxidant capacity, enhances antioxidant enzymatic activity in vitro, decrease lipid peroxidation and cytokine production, and inhibits cognitive deficits, according to several research.(63) Rutin has anti-inflammatory properties, as evidenced by its suppression of microglia cell activation, iNOS expression, and cytokine production (60)Rutin suppressed p38 MAPK and JNK phosphorylation, reversed changes in Bcl-2 and Bax levels, and prevented apoptosis and caspase-9/3 activation in SH-SY5Y cells, protecting them from rotenone-induced toxicity (3) In 6-OHDA-induced PC-12 cells, rutin significantly increased catalase enzyme levels while decreasing SOD.(62) Rutin increased the expression of the TH gene, which is required for dopamine biosynthesis, as well as the expression of ion transport and antiapoptotic genes (NSF and Opa1) (3) The impacts and molecular basis of this flavonoid need to be investigated further (61)

4. NARINGENIN –

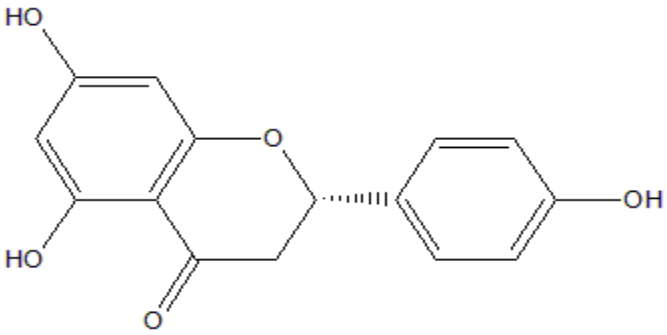

Figure 9, Chemical Structure of Naringenin

In 1907, Power and Tutin found a compound known as chalcone, which they decided to name Naringenin. Dean then continued to improve on its formulation in 1963 (64) Grapes, tomatoes, and citrus fruits all contain naringin, a flavanone glycoside [43]. Naringenin has been used as nutraceutical compound to treat a variety of neurodegenerative diseases, including Alzheimer's disease and Parkinson's disease.(47) Naringin is a glycosylated form of naringenin with two glucose units bonded to its flavanone structure, giving it a higher water solubility than naringenin. As a consequence, these distinctions have a direct impact on their metabolic activities and bioavailability, both of which are absolutely essential to their pharmacokinetics and pharmacodynamics (65). NGN has been shown to have anti-tumorigenic, anti-atherogenic, hepatoprotective, anti-oxidative, antihypertensive, antihyperlipidemic, and anti-obesity characteristics (47,64) Naringenin's benefits have been contributed to its antioxidant, radical scavenging, and metal chelation properties, as well as its ability to regulate enzyme activity and gene expression (64) NGN has also been shown to cross the blood-brain barrier.(46) NGN has the capacity to protect against MPTP-induced dopaminergic degenerative changes by lowering SYN pathology and neuroinflammation while enhancing DAT, TH, and dopamine and its metabolite levels. In mice intoxicated with MPTP, NGN diminishes NO levels, raises GSH content and SOD activity, and recovers motor function (66) Furthermore, naringenin has been shown to reduce oxidative injury, as illustrated by declining lipid peroxidation and protein damage.(65). Naringenin may also inhibit the phosphorylation of mitogen-activated protein kinases (MAPKs) (67), thereby triggering the glucose-regulated protein 78 (GRP78), an endoplasmic reticulum (ER) chaperone that controls a variety of cellular responses such as apoptotic cell death and response to stress. They exert their potential benefits by stimulating key signal transduction pathways that encourage the migration of transcription factors involved in the cellular oxidative response, like Nrf2, NFB, and PPAR, which in turn induces the antioxidant response element (64,65). As a result, Naringenin might be the next promising compound to be tested in humans in the hopes of one day being able to treat Parkinson's disease. (64)

5. BAICALEIN-

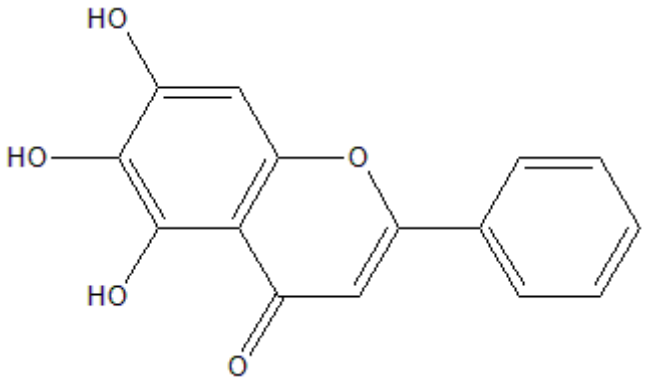

Figure 10, Chemical Structure of Baicalein

Baicalein (5,6,7-trihydroxyflavone; C15H10O5) is a key flavonoid. primarily isolated from the roots of *Scutellaria baicalensis* Georgi (*Labiatae*). The aglycone derivative of baicalin is baicalein.(2) *Scutellaria baicalensis* roots (Scutellaria radix) are extensively used in Chinese

traditional medicine to treat a wide variety of chronic conditions including hepatitis, hyperlipidemia, atherosclerosis, hypertension, dysentery, common cold, and other respiratory disorders. antioxidant, anti-viral, anti-thrombotic, anti-inflammatory, and anti-cardiovascular disease (45,68) In a rat ischemic model, a few of them also show neuron-protection in vitro and in vivo (45). Baicalein in its oxidized form prevents the formation of – alpha-synuclein fibrils(26) By preferentially blocking NO-producing NF-B activity in LPS-induced BV2 cells, baicalein reduced microglial activation-induced stilbene cell death (AICD). Flavonoid Baicalein Attenuates Activation-Induced Cell Death of Brain Microgli (44) Baicalein inhibited rotenone-Induced apoptosis and prevented the deposition of ROS, ATP insufficiency, mitochondrial membrane potential dissipation, and caspase-3/7 activation in PC12 cells by alleviating mitochondrial dysfunction associated with oxidative stress (69). Baicalein has the capability to minimize the production of TNFα and free radicals like NO and superoxide in LPS-induced neuron-glia cultures, which is in conjunction with the downregulation of LPS-induced iNOS gene expression.(70) Suppression of ROS excessive production, preservation of mitochondrial function, modification of anti- and pro-apoptotic proteins, and inactivation of the ERK1/2 pathway are among the neuroprotective effects of baicalein against rotenone-induced autophagy in dopaminergic SH-SY5Y cells.(71) Baicalein has been shown to have a neuroprotective role in 6-OHDA-induced cytotoxic activity and neurotoxic effects by increasing the amount of dopamine neurons, which may be due to an anti-apoptotic, pro-differentiation, and anti-inflammatory pathway .(72) Iron-induced lipid peroxidation and DA depletion in the substantia nigra have been shown to be reduced by these compounds. They can also increase GSH levels, inhibit alpha -synuclein agglomeration, and alleviate iron-induced mitochondrial stress (10). As a result, compounds such as baicalein may provide protection, but the mechanism is still unknown, and much research into PD pathology remains to be done.

6. RESVERATROL-

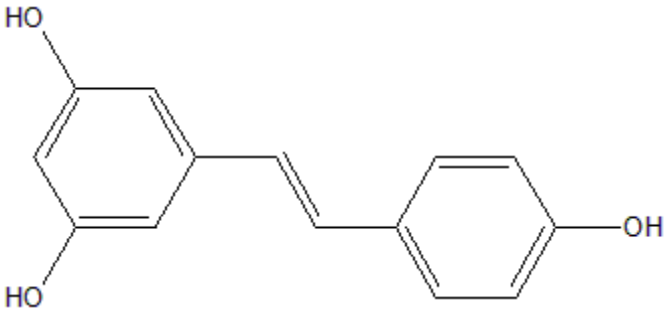

Figure 11, Chemical Structure of Resveratrol

Resveratrol (3,5,49-trihydroxy-trans-, a stilbene) is a stilbene that occurs naturally (25). Resveratrol is a non-flavonoid polyphenol found in the skins of grapes, blueberries, peanuts, raspberries, mulberries, and red wine. (52,73) Anticarcinogenesis, cardiovascular protection, and anti-inflammatory effects, anti-apoptosis, antioxidation, antifungal, regulation of enzyme and protein activities and expression levels, and regulation of ion channels have all been proved by resveratrol (7,73) Resveratrol's antioxidative or sirtuin-activating potential can protect dopaminergic neurons. (74) It is water-soluble substance and can cross the blood-brain barrier, allowing it to reach the brain and acting as a neuroprotective agent against

neurodegenerative disorders(17,75) The anti-inflammatory impacts of Rsevasterol are associated with altered neutrophil function, decreased COX-2 and TNF-a overexpression, and reduced nuclear NF-kB p65 expression .(76) The overexpression of miR-214 in the PD midbrain decreases alpha -synuclein expression and agglomeration, demonstrating the neuroprotective role of resveratrol (75) Rsevastreol reduces the Bax/Bcl-2 protein ratio and prevents the release of cytochrome c with Apaf-1 protein (77)Resveratrol may provide neuroprotection against Parkinson's disease. First, oxidative stress, which has been identified as a major contributor to the development of Parkinson's disease, must be reduced. Not only by scavenging ROS and neutralizing these free radicals, but also by activating the expression and activity of enzymatic antioxidants and suppressing other ROS-producing enzymes, including nitric oxide synthase, that can damage DNA (particularly mtDNA) and induce LDL peroxidation as well as being capable of preventing Ros generation by altering gene expression and protein activity. Second, Resveratrol enhances the removal of harmful protein aggregation and dysfunctional organelles by boosting autophagy, most prominently through the AMPK pathway. Furthermore, while clinical trials have shown that resveratrol supplements are safe, there is currently insufficient clinical proof to substantiate its efficacy against neurological disorder. (8)

7] EPIGALLOCATECHIN GALLATE (ECGG):

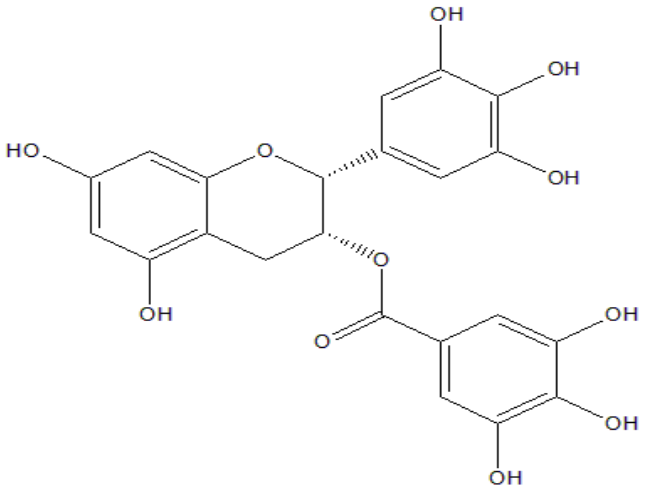

Figure 12, Chemical Structure of Epigallocatechin gallate (ECGG)

EGCG Green tea is the primary source of(2R,3R) -5,7, -dihydroxy-2(3,4,5-trihydroxyphenyl) chroman-3-yl 3,4,5-trihydroxybenzoate.(52) Green tea is a type of tea made from *Camellia sinensis* leaves that have not been treated. It has Chinese origins, as do all commercialised teas, and has been utilised for centuries throughout Asia, from Japan to the Middle East. Green tea has gained popularity throughout the world in recent years, owing to its therapeutic properties, which include the prevention of cancer, heart disease, diabetes, and neurological disorders. (16)Green tea's rich in polyphenol content, particularly the flavans known as catechins, is responsible for many of its health benefits. Green tea contains many catechins, the most important of which are (-)-epicatechin (EC), (-)-epicatechin-3-gallate (ECG), (-)-epigallocatechin (EGC), and (-)-epigallocatechin-3-gallate (EGG) (EGCG)

[Poly5] The catechin with the highest concentration is EGCG. They can function as ROS scavengers as well as iron chelators. Because of its iron chelation property, it can easily remove redox active ferrous iron from the substantia nigra by passing through the blood-brain barrier, trying to protect dopaminergic neurons and minimising iron-induced oxidative stress, which can lead to neuronal death. (4,52) It has been revealed that ECGG binds directly to unfolded/misfolded proteins such as α-syn and inhibits harmful agglomeration.(52) The phenolic compound EGCG increases the level of mRNA and enzymatic expression of enzymes such as superoxide dismutase (SOD) 1, enzymes catalyse (CAT), striate antioxidative, and glutathione peroxidase 1 (GPx1), and the sharp decline of reactive oxygen species (ROS). EGCG aims at promoting the expression of TH proteins along with TH action, playing an important role in catecholamine and dopamine synthesis, as well as blocking dopaminergic neuronal loss. Protein kinase C (PKC), which plays an important role in the function of neural cell membranes and tight junctions, reported a rise in proteomic expression. Thus, among the other mechanisms of EGCG in the significant management of PD are improving the proteinic expression of the antiapoptotic protein Bcl-2 as well as reduced in the cell up regulation of the apoptosis - inducing agent Bax. (42) In light of the preceding reports, it is clear that more research is needed to scientifically prove that ECGG has therapeutic relevance in Parkinson's disease therapeutic applications (52)

8] QUERCETIN –

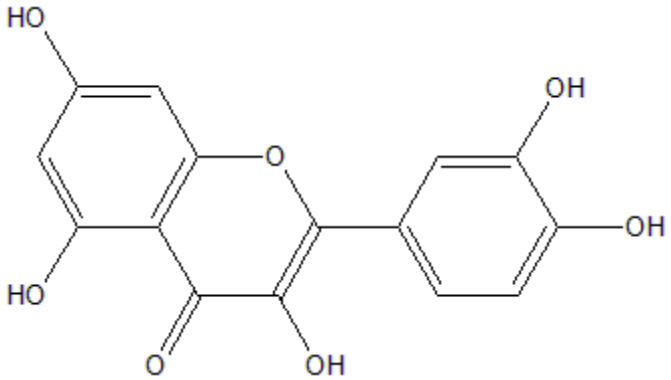

Figure 13, Chemical Structure of Quercetin

Quercetin (3,3′,4′,5,7-pentahydroxyflavone) is a flavonoid found in onions, apples, broccoli, and red wine, among other foods. (61) Quercetin's main feature is its multiple OH groups in its structure, that can attach to reactive oxygen species (ROS) and preserve cell survival, and quercetin has a greater antioxidant capacity than many flavonoid compounds. (78) Pollen is the primary source, with quercetin in the glycosylated form seems to be the most abundant flavonoid. Quercetin has anti-inflammatory, antitumor, immunomodulating, antioxidant, cardioprotective, antiapoptotic, and neuroprotective characteristics, according to scientific evidence (16,61) Its antioxidant and anti-inflammatory properties could be used as a neuroprotective agent because of its ability to cross the blood-brain barrier. By forming a covalent bond with synuclein, quercetin is able to form adducts. This can attach with some transition metals like iron and copper due to its ion chelation capacity, and thus protects the brain from oxidative stress-induced injury problems.(52) Oxidases and nitric oxide synthase

(NOS) enzymes are blocked by quercetin(78) . A plethora of experimental proofs support quercetin's neuroprotective effect on the CNS via a variety of processes such as lowering lipid peroxidation, blocking GSH decline, rising the activity of superoxide dismutase and catalase, and so on. Quercetin also communicates with and regulates signalling pathways like PI3K/Akt, tyrosine kinase, PKC, and MAPK, all of which have been linked to cognition, neurogenesis, and neuronal survival. (40) An in vivo testing of the efficiency of quercetin in combatting oxidative stress and memory impairment in 6-OHDA-lesioned rats confirmed the previous findings. When animals were given quercetin before and after the founding of a lesion, they demonstrated a significant improvement in cognitive abilities and a decrease in damage caused by induced oxidative stress when compared with the control group. (16) Quercetin also inhibits enzymes such as catechol-O-methyltransferase (COMT) and monoamine oxidase (MAO), increasing the absorption rate of L-dopa (levodopa) in the brain (42)

9] CURCUMIN:

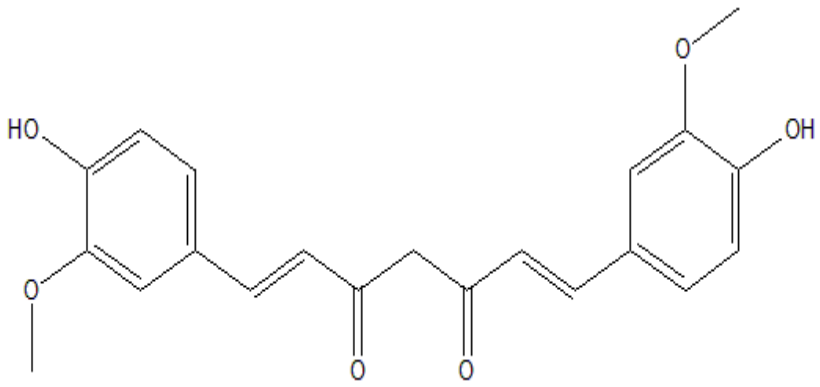

Figure 14, Chemical Structure of Curcumin

Curcumin is a polyphenol derived from the rhizome of *Curcuma longa*, a plant native to Asia. The rhizome powder is used as a spice and as a natural alternative in traditional oriental medicine. Curcumin has antioxidant, anti-inflammatory, and neuroprotective properties, which can help to Parkinson's disease treatment.(16) Extensive research has revealed that it has tremendous medical benefit, as evidenced by its anti-oxidative, anti-inflammatory, anti-microbial, anticarcinogenic, and antidepressant properties. Furthermore, it is neuroprotective against the ageing of brain neuronal death, behavioural deficits, and injury to the blood-brain barrier (BBB) Its efficacy has also been evaluated in neurological conditions such as Alzheimer's and Parkinson's. (12) Polyphenolic curcuminoids, including curcumin, dimethoxy curcumin (DMC), and bis-dimethoxy curcumin (BDMC), provide its diverse cytoprotective activity. Curcumin has been shown in in vitro and in vivo studies of Parkinson's disease to have a disease-modifying consequence by preserving dopaminergic neurons from LPS and alpha -synuclein-induced neurotoxicity, minimising DA loss, reducing oxidative stress, and restricting mitochondrial dysfunction. (10)Curcumin-glucoside, a synthetic derivative of curcumin, has also been found to be very effective of binding alpha-

synuclein oligomeric form and thus blocking further fibrillization of alpha-synuclein. Curcumin raises the levels of SOD and GPx while lowering MDA. DA and ACh levels were also found to be upregulated. Additionally, it was discovered that memory ability had significantly improved. In vitro, it also retains mitochondrial complex I activity and protects against nitrosative stress and brain mitochondrial damage. (12) Curcumin treatment may be linked to MAO-A enzyme inhibition, whereas MAO-B inhibition results in an increase in central dopamine levels. Both of these activities are mainly accountable for its antidepressant qualities, as they improve the amount of serotonin and dopamine in the brain. Because the systemic absorption of curcumin is increased when combined with piperine, it may be a useful natural adjuvant in antidepressant therapy (79). A water-soluble extract of curcumin has been shown to significantly raise serotonin and dopamine levels in brain. In hippocampal tissue, curcumin enhanced the content of monoaminergic neurotransmitters such as norepinephrine and dopamine(28) Curcumin prevented apoptosis by decreasing intracellular reactive oxygen species and impairing the mitochondrial apoptotic cell death pathway.(80) In the striatum of MPTP-intoxicated mice, curcuminoids suppressed iNOS overexpression, diminished pro-inflammatory cytokines, and lower total nitrite generation. (10)Curcumin's anti-inflammatory and antioxidant qualities, as well as its suppression of JNK pathways, prevented MPTP and MPP+-induced neurotoxic effects in C57BL/6N mice and SH-SY5Y cells. (25)Curcumin inhibits cell death by increasing Bcl-2 expression, preventing the loss of mitochondrial membrane potential, overproduction of ROS, and enhances in nitric oxide synthase activity. Curcumin pre-treatment protects brain mitochondria from peroxynitrite-induced loss of mitochondrial functions in vitro through direct detoxification and the prevention of 3-nitrotyrosine formation, and in vivo through an increase in total cellular GSH concentration.(15) Furthermore, curcumin has no toxicity. As a result, its use in PD gains even more benefits. As a consequence of the aforementioned findings, it appears that Cl has enormous potential as a potential candidate drug for clinical studies in the context of PD. (12)

10] GINKGO BILOBA (GB)-

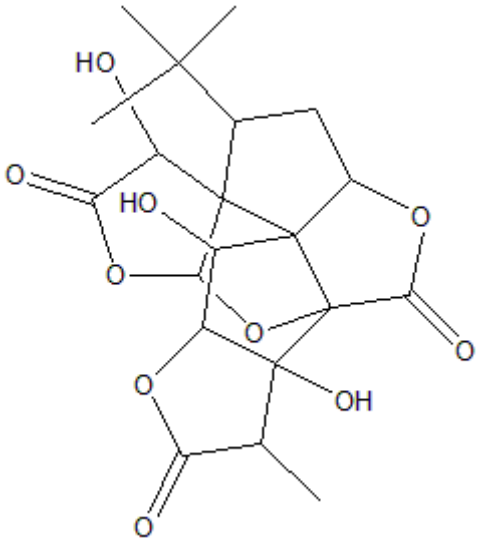

Figure 15, Chemical Structure of *Ginkgo biloba*

Ginkgo biloba (Gb) is really the only species found in the division Ginkgophyte, and it has been used in traditional Chinese medicine for ancient times. Its extracts contain a high concentration of flavonoids and terpenoids.(16) Gb seeds have been documented in ancient Chinese herbals as having medical benefit. Antioxidant, anti-inflammatory, anti-aging, and neuroprotective properties of Gb are well known.(12) The herb improves memory by increasing the supply of oxygen to the body and assisting in the elimination of free radicals.(33) The antioxidant activities of flavonoids and ginkgolides against the formation of free radicals were suggested as a possible mechanism of neuroprotection. EGb761 is a patented and very well combination of active ingredients extracted from the leaves of *Ginkgo biloba*, a Chinese medicinal tree. The free radical scavenging activity, inhibition of lipid peroxidation, and decrease of superoxide radical production, as well as the ability to stimulate several antioxidant enzymes, are all linked to EGb761's neuroprotective effect against MPTP neuronal damage. whereas the activity of SOD, glutathione peroxidase (GPx), and glutathione reductase was increased. It also slows the degeneration or apoptosis of dopaminergic neurons in the nigrostriatal area. (10,15,16) Because EGb761 has a strong MAO inhibitory effect, it has been shown to block both MAO isoforms (MAO-A and MAO-B) when taken in supplement form (15). As a result, these supplements were found to be effective in reducing MAO activity, increasing DA metabolism, and preventing MPP+-neurotoxicity(25). EGb761's protective effect against MPP + -neurotoxicity has been attributed to the regulation of copper ion homeostasis in the brain (15) Gb supplementation helps to improve locomotor activity, muscle coordination, and behavioural rotation in a 6-OHDA induce rat model of Parkinson's disease. Taking supplements EGb 761 to a rat model of PD with reserpine regulates redox status, enhances mitochondrial function and ATP production, and reduces apoptosis.(12) As a result, a dose-optimized combination of levodopa and Gb may provide greater therapeutic efficacy than either drug alone. As a result, it appears that Gb extract, EGb 761, not only helps to normalise redox status in Parkinson's disease, but also helps to rejuvenate mitochondrial function and locomotor activity. EGb 761 also has a low molecular weight and can cross the BBB. As a result, Gb appears to be a promising candidate for use in PD therapies; however, preliminary clinical trials are required to confirm its efficacy. (12)

CONCLUSION:

The exact cause of Parkinson's disease is unknown, but a lot of evidence suggests that redox destabilisation and mitochondrial dysfunction are key players. Moreover, the current PD treatment strategy is based mainly on Levodopa, which can only increase dopamine level in the brain, slow progression of the disease to a limited extent and has associated side effects. As a result, new approaches that are beneficial in combating Parkinson's disease with minimal side effects and at a lower cost are urgently needed. Various natural products with anti-PD properties have been the subject of numerous experimental investigations, and their pharmacokinetic effects have been well described. As a result, in this article attempt has done to include herbals and polyphenolic compounds that have been primarily discovered to be effective in Parkinson's disease pathogenesis and could be studied further and developed as potent anti-PD molecules. The mechanisms responsible of the polyphenols must be

investigated thoroughly before they can be used clinically as a combination treatment for Parkinson's disease patients.

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