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Phytochemicals as Emerging Neuroprotective Agents in Parkinson's Disease: Mechanistic Insights into Oxidative Stress and Autophagy

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Abstract

Parkinson's disease (PD) is a slowly progressive neurodegenerative disorder that mainly affects movement due to the loss of dopamine-producing neurons in the substantia nigra region of the brain. Increasing evidence suggests that oxidative stress, mitochondrial damage, neuroinflammation, and defective autophagy play important roles in the development and progression of the disease. Although current treatments such as levodopa are effective in managing symptoms, they do not stop neuronal degeneration or disease progression.

In recent years, naturally occurring phytochemicals have gained attention for their potential neuroprotective effects. This review discusses the involvement of oxidative stress and autophagy in Parkinson's disease and highlights the protective roles of selected phytochemicals, including vanillin, asiatic acid, ferulic acid, thymoquinone, and chrysin. Findings from experimental studies show that these compounds reduce oxidative damage, protect mitochondrial function, regulate apoptotic pathways, and support neuronal survival. Overall, phytochemicals appear to be promising candidates for future therapeutic strategies aimed at slowing the progression of Parkinson's disease.

1. Introduction

Parkinson's disease (PD) is a chronic, progressive neurodegenerative disorder primarily affecting motor function and is characterized by bradykinesia, resting tremor, rigidity, and postural instability. The global prevalence of PD has increased substantially over recent decades, largely due to aging populations, making it one of the most prevalent movement disorders worldwide. Pathologically, PD is marked by selective degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNpc) and the depletion of dopamine levels in the striatum, resulting in impaired motor control.

A defining neuropathological hallmark of PD is the accumulation of misfolded α-synuclein protein within Lewy bodies. Increasing evidence implicates oxidative stress, mitochondrial dysfunction, neuroinflammation, and impaired autophagy in the progression of PD. Excessive production of reactive oxygen species (ROS), reduced antioxidant defenses, and defective mitochondrial dynamics contribute to neuronal vulnerability and cell death.

Although levodopa remains the gold standard for the symptomatic treatment of PD, it does not prevent disease progression or address non-motor symptoms. Long-term use of levodopa is

also associated with dyskinesia and motor fluctuations. Consequently, there is growing interest in alternative therapeutic strategies aimed at modifying disease pathology rather than providing symptomatic relief alone.

Naturally occurring phytochemicals have emerged as potential neuroprotective agents due to their ability to modulate oxidative stress, inflammation, mitochondrial integrity, and autophagic pathways. This review focuses on the mechanistic role of oxidative stress and autophagy in PD and critically evaluates the neuroprotective potential of selected phytochemicals as promising candidates for adjunctive or preventive therapy.

2. Review of Literature

2.1 DEFINITION

With a variety of origins and clinical symptoms, Parkinson's disease is a recognizable clinical illness. Except for infectious etiology, Parkinson's disease is a neurodegenerative ailment with a rapidly expanding global prevalence that shares many features with pandemics. Monogenic Parkinson's disease, which accounts for 3-5% of the disease in most populations, is caused by genetic factors connected to known Parkinson's disease genes, while non-monogenic Parkinson's disease, which accounts for 16–36% of the heritable risk, is caused by 90 genetic risk variants.

2.2 EPIDEMIOLOGY

The prevalence of Parkinson's disease (PD) is 1-2 per 1000 people at any one time. PD prevalence rises with age and affects 1% of those over the age of 60. Lewy bodies containing

-synuclein and dopaminergic neuron loss in the substantia nigra, which manifests as lessened facilitation of voluntary movements, are the primary neuropathological findings. Lewy body pathology spreads to the neocortex and cortex as Parkinson's disease progresses. Tremor, stiffness, and bradykinesia are considered the three cardinal symptoms of Parkinson's disease (PD).(9) Postural instability is no longer included as a fourth character in the diagnostic criteria, which also describe supporting criteria, absolute exclusion criteria, and red flags. In PD, non-motor symptoms are receiving more attention, and both motor and non-motor symptoms are now considered supportive criteria. In most situations, the cause of PD is unknown. There are known genetic risk factors, such as uncommon monogenetic causes in populations without selection. In 5–10% of patients, a genetic component can be detected. There are several environmental factors linked to an increased risk of PD. Studies on autopsies reveal that a sizable portion of patients do not have their clinical diagnosis of Parkinson's disease confirmed during autopsies. The accuracy of the clinician's diagnosis of PD is anticipated to increase with the revised diagnostic criteria. Soon, it's likely that growing awareness of the genetic and environmental PD risk factors may reveal the disease's underlying cause.

2.3 PATHOPHYSIOLOGY

Dopaminergic neurons in the substantia nigra of the midbrain deteriorate, which leads to Parkinson's disease (PD). Lewy bodies, which are a buildup of the -synuclein protein, are also seen in the peripheral, autonomic, and central nervous systems. (10) The basal ganglia, a collection of control-related brain regions, include the substantia nigra. The motor cortex's connections are traversed by the brain. The striatum, also known as the caudate and putamen combined, receives signals from the pars reticulata, which is a subregion of the substantia nigra,

and relays messages to the thalamus via the neurotransmitter GABA (gamma amino butyric acid). The pars compacta, a substantia nigra damaged region in Parkinson's disease, is the second. Dopamine, a neurotransmitter from the nigrostriatal pathway, is used by the pars compacta to communicate with the striatum, helping to activate the cerebral cortex and start a movement. Therefore, a person must be in a hypokinetic or low movement state to experience the death of the substantia nigra pars compacta neurons.

2.4 ROLE OF OXIDATIVE STRESS IN PD

During metabolic processes, the vital molecule oxygen can produce free radicals. These free radicals are an essential core element in every biochemical or biological reduction reaction [10]. However, due to their extreme instability, these free radicals easily pass-through biomolecules like proteins, lipids, cellular membranes, and nucleic acids [11]. Recent research has also offered novel insights into the biology of free radicals, their influence on brain health, and the formation of numerous clinical disorders [29, 30]. This is owing to the brain's disproportionately high oxygen consumption, which makes it more susceptible to damage from free radicals than other organs. Reactive nitrogen species are the primary causes of oxidative stress and an imbalance in cellular antioxidant capacities (RNS). Radicals are reactive oxygen species (ROS) [31]. Superoxide radicals (O2), which are formed in the brain's mitochondria and slow down mitochondrial action and destroy DNA, interfere with brain function. Hydrogen peroxide (H2O2)(O2)is a significant precursor of superoxide radicals (ROS), which are reactive oxygen species. The NDDs [4] and. Recent in vivo investigations have connected increased ROS production to neuronal cell death and decreased brain function caused by DA metabolism, low glutathione (GSH) levels, high calcium, and iron levels in the substantia nigra (SN), and low glutathione (GSH) levels [31, 32]. The brain also contains significant amounts of membrane polyunsaturated fatty acids. It enhances lipid peroxidation and the formation of neurotoxic byproducts in the presence of oxidative stress. Markers are typical clinical characteristics of PD because of these deficient enzymatic antioxidant mechanisms and elevated oxidative stress [7]. The role ROS plays in the etiology of Parkinson's disease is well-known. Numerous investigations have found that DA autooxidation and mitochondrial complex I dysfunction are typically related to the oxidative status of PD tissues [12].

2.4.1 ROLE OF AUTOPHAGY IN PD

Autophagy, which occurs in reaction to cellular starvation and the destruction of damaged organelles, is the primary physiological catabolic cellular activity [10]. Autophagy is the process of sequestering various cellular components into a double-membrane budding vacuole known as a phagophore, which later matures to seal in a vesicle known as an autophagosome. These components include nucleic acids, entire organelles, lipids, proteins, sugars, and cytoplasmic compartments [13]. Damaged or dysregulated autophagy has been linked to numerous pathological processes, including inflammation, cancer, lipid metabolism, and NDDs [14]. Protein aggregates and lipid droplets are undesirable and frequently dangerous cargo that can lead to cellular dysfunction, and autophagy helps in the removal of damaged organelles. a key pathogenic mechanism, particularly in Parkinson's disease and other NDDs is known to be caused by faulty or dysregulated autophagy [15]. Important elements of autophagy in PD include the modulation of neuronal quality and the preservation of the brain. Recent studies have shown that mice lacking key autophagy genes, such as Autophagy ATG5 and ATG7, display spontaneous neurodegeneration, protein aggregation build-up, and motor

neuron dysfunction [41]. Research on Parkinson's disease frequently uses rotenone, 1-methyl-4-phenylpyridinium (MPP+), 6-OHDA, and phenyl-1,2,3,6-tetrahydropyridine (MPTP), a neurotoxin linked to mitochondrial failure, ATP depletion, and an increase of ROS such H2O2, hydroxyl radicals, and superoxide. In 6-OHDA-induced PD models, changes in the autophagy state have been documented [42]. A recent study found that mucolipin 1, an important calcium-conducting channel situated in the brain, could be activated by a slight rise in ROS levels. to begin the calcineurin-dependent activation of transcription factor EB, known as a master regulator of the autophagy-lysosome pathway, on the lysosome membrane (ALP). In turn, the elimination of too many ROS and the clearance of damaged mitochondria are promoted by the transcription factor EB's stimulation of autophagy. Although excessive ROS levels can result in lysosomal malfunction, autophagic failure, oxidative stress, or cell death, oxidative stress often promotes activation of the autophagic pathway. Additionally, autophagy's activation levels and induction period are crucial for the survival or death of cells [16].

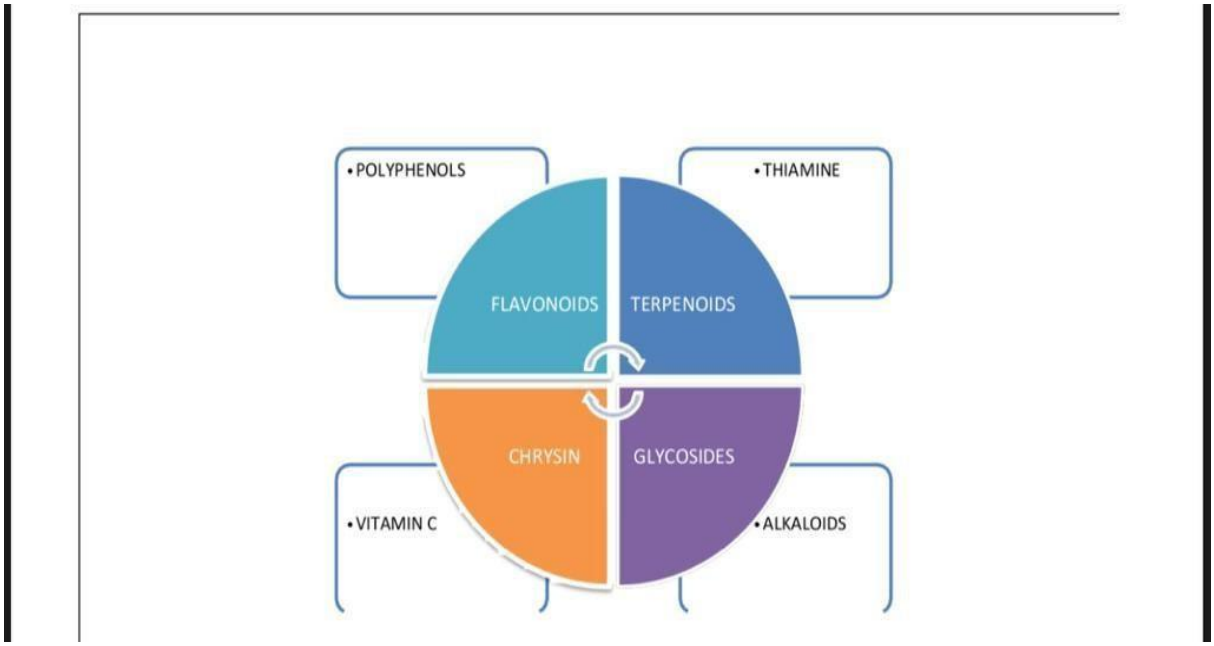

Fig1: Overview of Major Bioactive Phytochemical Classes Contributing to Antioxidant Defense"

2.5 OXIDATIVE STRESS AND ANTIOXIDANT DEFENCE MECHANISMS

They interact with the ubiquitous transcription factor Nrf2 to preserve intracellular homeostasis and protect cells from toxic substances. It accomplishes this by responding to oxidative stress and activating a detoxifying enzyme. Three ubiquitin ligase systems that are known to work properly include E3 ubiquitin ligase Hrd1, glycogen synthase kinase (GSK3), and. Keap1, a protein related to and like kelch, which is essential for the degradation of Nrf2. [17]. Due to their electrophilicity, these three activator genes can oxidize, alkylate, and decrease the thiol group (-SH) groups in Keap1. [17] Freshly made Nrf2 is transported into the nucleus under oxidative stress where it binds to the ARE region of specific target genes, preventing the proper functioning of the Nrf2-ubiquitin ligase system. The proteasomal, autophagic, anti-inflammatory, antioxidant, and detoxifying properties of Nrf2 have been shown to be critical in the regulation of other physiological processes, even though these targets are typically considered antioxidant genes [99, 100]. There are certain physiological systems that are both

directly and indirectly related to the etiology of Parkinson's disease. Numerous PD models have been examined in the past to determine whether Nrf2 signaling provides antioxidant protection for neurons. It was found that Nrf2 directly regulates the activities of catalase (CAT), sulfiredoxin-1 (SRXN1), NAD(P)H: quinone oxidoreductase-1 (NQO1), superoxide dismutase 2 (SOD2), heme oxygenase-1 (HO1), and peroxiredoxin [The cause of Parkinson's disease (PD) may be related to one or more physiological systems directly or indirectly. Numerous PD models have been used to examine whether Nrf2 signaling provides antioxidant protection for neurons. It was found that Nrf2 directly controls the activity of the enzymes catalase (CAT), sulfiredoxin-1 (SRXN1), NAD(P)H: quinone oxidoreductase-1 (NQO1), superoxide dismutase 2 (SOD2), heme oxygenase-1 (HO-1), and peroxiredoxin. The importance of Nrf2- dependent signaling cascades during Parkinson.

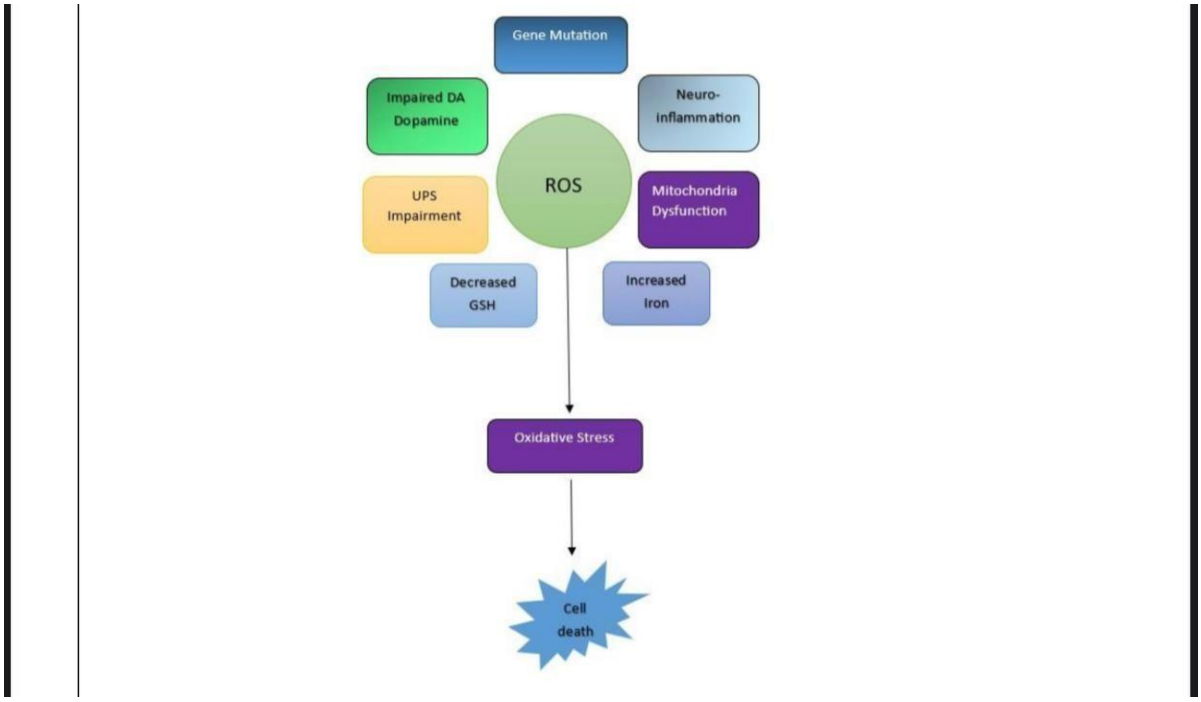

Fig2: Mechanisms of ROS-Mediated Oxidative Stress Leading to Neuronal Cell Death in Parkinsons Diseases.

2.5.1 NEUROPROTECTIVE MECHANISM OF PHENOLIC ACIDS IN PD.

Every plant species on the earth naturally produces phenolic acids as a secondary metabolite. Both hydroxybenzoic and hydroxycinnamic acids are present in them. According to Stalikas (2007), these compounds have important biological and pharmacological effects such as antioxidant, anti-inflammatory, anti-carcinogenic, and antimutagenic properties. Salvia miltiorrhiza is used to make salvianic acid, which has an anti-apoptotic effect by lowering ROS formation and the rate of cell death. Reducing the Bax/Bcl-2 ratio, protecting MMP, altering apoptotic/antiapoptotic agents, lowering caspase-3 activity, and minimizing changes in cell nuclear structure are all recommended (Wang and Xu, 2005). Syringic acid is one of the main benzoic acid derivatives present in edible plants and fruits. Syringic acid has antiparkinsonian characteristics because it reduces lipid peroxidation, boosts GSH levels, and inhibits the development of pro-inflammatory cytokines such TNF-, interleukin (IL)-1, and COX-2 enzymes. It enhanced the expression level of TH and decreased the loss of striatal dopamine

(DA) and its metabolites in chronic 1-methyl-4-phenyl- 1,2,3,6- tetrahydropyridine (MPTP)/probenecid-induced motor impairment.

2.5.2 NEUROPROTECTIVE MECHANISM OF VANILLIN IN PD

Vanillin, a phenolic aldehyde molecule, is a crucial flavoring component used all over the world. There are several plant species that use it, and it is frequently used in the food, beverage, pharmaceutical, perfume, and cosmetic industries [19]. Nearly 50% of synthetic vanillin production is currently used as an intermediate in both food and non-food applications in the pharmaceutical sector, which also produces goods like papaverine, L-dopa, L-methyldopa, and antibacterial medications. [18] Vanillin is used in foods and drinks all over the world in quantities that are regarded as safe for everyday consumption. This implies that nearly all people ingest vanillin-containing items. A daily consumption of 10 mg/kg of vanillin has been authorized by the European Union, the Food and Agriculture Organization of the United Nations (FAO), and the World Health Organization (WHO). For a person weighing 70 kg, the daily recommended intake of vanillin is 700 mg, which is equivalent to at least 700 g of chocolate or 700 g of ice cream [19]. Vanillin has been studied extensively for its pharmacological properties, which are attributable to its structure and main bioactive metabolites, including vanillyl alcohol and vanillic acid; vanillin's bioactive properties include antioxidant, anti-inflammatory, and neuroprotective abilities [193]. By boosting the activities of antioxidant enzymes and lowering levels of lipid peroxidation and NO generation, vanillin exhibits strong brain-neuroprotective potential and can pass through the blood-brain barrier (BBB)with ease [37]. This polyphenolic flavoring ingredient can scavenge the O2 and OH intermediates linked to biological membrane damage [23]. By reducing lipid peroxidation levels, raising levels of enzymatic (SOD, CAT, GPx, and GSH), nonenzymatic (vitamin C, and nonprotein thiol), and preventing DNA damage and histopathological changes, renal oxidative stress is reduced in mice exposed to maneb [63]. In a different study using a rotenone-induced PD model, the neuroprotective abilities of vanillin were shown. Vanillin therapy decreased rotenone-induced ROS generation, mitochondrial dysfunction, caspase activation, and signaling molecule reduction in SH-SY5Y cells.

2.6 NEUROPROTECTIVE MECHANISM OF ASIATIC ACID IN PD

Due to its numerous pharmacological characteristics, the naturally occurring pentacyclic triterpenoid known as Asiatic acid (AA) has promise as a potential neuroprotective therapeutic candidate. It's interesting to note that some bioactive AA components have been shown to offer therapeutic promise for treating a variety of ailments. Several enzymes, growth factors, receptors, transcription factors, apoptotic proteins, and cell signaling components appeared to be impacted by AA. the experimentation the biological benefits of AA include antioxidant, hepatoprotective, anti-diabetic, anti-cancer, anti-inflammatory, and neuroprotective ones, according to the study. [20]. Solid lipid nanoparticles containing AA tromethamine have recently been demonstrated to inhibit proteolytic degradation and promote sustained drug release, hence increasing bioavailability [21]. In a different investigation, rats were given intravenously 75 mg/kg of formulations incorporating glutathione conjugated BSA nanoparticles of AA; five hours later, the nano formulation showed ten times better

bioavailability. than AA alone, in the brain [2 By preserving the BBB's stability and safeguarding mitochondrial processes, AA offers neuroprotection. According to a recent in vitro investigation, AA diagnosis decreased the formation of intracellular ROS in the mitochondria and changed MMPs to control mitochondrial function, which in turn decreased the expression of the Microglia cells containing the NLRP3 inflammasome [19]. Additionally, AA treatment directly enhanced in an MPP+- induced PD paradigm, SY5Y cell and SH survival, and conserved mitochondrial activity was observed [22]. The treatment with AA reduced excessive ROS generation, mitochondrial dysfunction, and the expression of proapoptotic and antiapoptotic markers during apoptosis, based on the SH- SY5Y PD model caused by rotenone.

2.6.1 NEUROPROTECTIVE MECHANISM OF FERULIC ACID IN PD.

Ferulic acid (FA), a phenolic phytochemical that occurs naturally, can be found in a variety of foods, including apples, oranges, peanuts, wheat, rice, barley, and coffee [22]. The advantages of meals and beverages high in FA have been proven in studies. According to recent studies, eating fruits, vegetables, and grains helps reduce diabetes, cancer, and obesity. Heart disease, Parkinson's disease, and AD. FA is used in Japan as a natural antioxidant in foods, drinks, and cosmetics. It has been approved as a food additive. Numerous medical essences and organic extracts of herbs, coffee, vanilla beans, spices, and other botanicals are added to foods as an FDA-approved antioxidant combination in the United States and the majority of European countries [22]. The high FA concentration of these plants is the reason they were chosen. Although there aren't any trustworthy nutritional surveys available on FA intake, it may be estimated that each person gets between 200 and 1000 mg of FA from dietary sources every day. The pharmacological properties of FA, which include immunomodulatory, antioxidant, antiinflammatory, anti-apoptotic, anticancer, antidiabetic, and neuroprotective functions, have lately been found by researchers to have beneficial health impacts. FA also has a low toxicity profile. FA carries out these functions by preventing the synthesis of ROS and lipid peroxidation through the action of its phenolic hydroxyl group. Additionally, FA has been demonstrated to reduce the production of inflammatory enzymes [21,]. The ability of FA to be absorbed and interact with target tissues will determine its health benefits. Recent preclinical investigations found that participants who frequently consumed phenolic acid- containing foods and beverages, as well as fruits and vegetables, consumed about 1 g of polyphenols daily [20]. Animal studies have shown that FA has a higher bioavailability than other phenolic substances.FA may be able to lessen neuroinflammation and neuronal death in NDDs, according to several studies. One of the main mechanisms behind FA-induced neuroprotection in PD is anti-inflammation. Histological findings further demonstrated that FA therapy decreased the Bax/Bcl-2 ratio and the activation of microglial cells, which, respectively, suggested a reduction in inflammation and apoptosis. Additionally, it was discovered that FA effectively restored motor coordination, function, and behavioral deficits brought on by MPTP-induced neuronal death [23].

2.6.2 NEUROPROTECTIVE MECHANISMS OF THYMOQUINONE IN PD

Black cumin seeds and plants from the Lamiaceae family contain thymoquinone (TQ), a substance that has pharmacological activity [38]. Since the beginning of time, black cumin has been utilized in medicine; however, interest in this substance has grown dramatically more recently [24]. The majority of the main effects of the active ingredient in black cumin seeds,

TQ, have been shown to be advantageous, which suggests that clinical trials with TQ may be appropriate. There is a range of recommended daily intake for any black cumin seed between 250 and 1000 mg [25]. TQ and its derivatives exhibit a number of pharmacological activities, including antioxidant, anti-inflammatory, antihypertensive, anti-asthmatic, anti-diabetic, and anticancer effects, according to earlier experimental research [21]. TQ's effects on -synuclein-induced synaptic toxicity were interestingly investigated in cultures of rat hippocampal neurons and neurons generated from human-induced programmable stem cells (IPSCs). TQ raised levels of synaptophysin (a measure of synaptic density), protected neurons in both types of cultures from -synuclein-induced synaptic damage and inhibited the mutant -synuclein from inhibiting synaptic vesicle recycling (P123H). Additionally, the scientists showed that TQ preserved typical bioelectrical activity in the neural network that was harmed by the effects of

-synuclein by employing cells cultivated on multielectrode arrays [24]. It is a normal cellular defense mechanism that is brought on by oxidative or toxic stress and is used to get rid of unneeded or damaged organelles and components. Neurodegenerative illnesses may emerge because of the autophagy system being disturbed. By lowering the production of lactate dehydrogenase and keeping MMP, TQ at a concentration of 0.0110 M prevented the MPP+-induced death of mesencephalic dopaminergic neurons in vitro. The stimulation of autophagy that came along with TQ's impact reduced the mortality of apoptotic neurons [25].

2.7 NEUROPROTECTIVE MECHANISM OF CHRYSIN IN PD

A flavonoid, chrysin is a naturally occurring polyphenolic compound. A wide range of foods, such as fruits, vegetables, mushrooms, blue passionflowers, plants, and notably honey, contain flavonoids [13]. The possibility that flavonoids may be beneficial for health has been supported by several epidemiological, cellular, and animal studies. In Westernized nations, such as Australia, the United States, and many European nations, tea, fruit or vegetable juices, blue passionflowers, and wine are the main sources of flavonoids. Estimates indicate that these foods provide a daily total flavonoid intake of 200 mg in Australia [144] and 500 mg in regions of Europe where tea consumption is significant [15], such as Spain. In Poland, Mexico, and Greece, all of which have diets rich in citrus fruits and wine, dietary flavanones can range from 30 mg to 170 mg daily.

Like this, the daily intake of dietary flavanones varied from 36 mg in Korea to 5 mg in China across Asia (China, Japan, and Korea). Due to its antioxidant, anti-inflammatory, and other pharmacological qualities, chrysin has been studied for its neuroprotective effects. The bioavailability of chrysin and the concentrations that can be obtained in rat cells and target tissues dictate the range of therapeutic effects. Chrysin was given to human volunteers in doses of 400 mg, but it was shown that the bioavailability was very poor [56] due to quick metabolism, insufficient intestinal absorption, and rapid excretion. Conjugated chrysin accounts for nearly 99% of the plasma protein binding, according to research.

Examples of phytochemicals within vitro and their mechanism of action.

Table No:1

phytochemical class	Name of the phytochemical	within-vitro model	Mechanism	References

Protein Acid	L-theanine	exposure of rotenone and dieldrin to SHSY5Yneuroblastoma cells	increase cell viability, minimize nuclear damage and caspase 3	27
Diarylheptanoid	Curcumin E	Exposure of MES23.5 cells to 6-OHDAmesencephalic cells from rats	Boost levels of dopamine, cell survival, LRRK2 mRNA, and LRRK2 protein	28
Fatty acid amides (indoles) Flavone Flavonoid	The moracenin acacetineicosanoyl- 5-hydroxytryptamide	Rotenone, salsolinol, and MPTP were all applied to SHSY5Y neuroblastoma cells. MPTP was also applied to these cells.	Boost: cell viability, nurr1 mRNA and decrease: α- syn mRNA, NO, PGE2, and TNF- alpha.	29
	Hesperidin	SK-N-SH neuroblastoma caused by rotenone exposure	Boost the performance of antioxidants, GSH, and cell viability. antiapoptotic activity and a reduction in ROS and LPD	30
Stilbene	Amurensin G Oxyresveratrol Resveratrol	GFP-LC3-expressing HEK293 cells and rotenone exposed SHSY5Y neuroblastoma cells. 6-OHDAexposed SHSY5Y neuroblastoma cells. Neuroblastoma SH-SY5Y cells treated to 6- OHDA	Increase:LC3 - III: HEK293 cell autophagy induction, Cell survival and decrease in : G2 M cell cycle arrest, alpha synuclein protein. Increase SIRT1, decrease ROS, LDH and caspase-3- activity	31

Phenol	6-Shogaol	Through 6-OHDA- treated PC12 cells, MPTP was made available to rat mesencephalic cells.	Boost cell survival, Nrf2, and reduce NO and TNF-alpha	32
Terpene	Carnosic acid	6-OHDAtreated neuroblastoma SH-SY5Y cells	Nuclear damage, nuclear caspase 3, and PARP are decreased, whereas Nrf2, cell viability, and GSH are increased.	33

Table No:2 Phytochemical Interventions Targeting α-Synuclein Aggregation and Autophagy Pathways"

	Ginsenoside Rg1	Human neuroblastoma BE (2)-M17	Increase alphasynuclein oligomerization	34
	Paeoniflorin	PC12 cells exposed to MPTP	Boost cell viability, lower the LC3-II/LC3-1 ratio, and raise alpha	35
	Paeoniflorin	PC12 cells exposed to MPTP	Cell viability and the LC3 - I/LC3 - I ratio was increased, while - syn accumulation and levels were decreased. ASIC activity and protein expression were also modulated.	36

Cinnamate	Rosmarinic acid e	exposed MES23.5 cells to MPTP	Increase cell viability by reducing ROS and apoptosis.	37
Isothiocyanate	Sulforaphane	Mesencephalic dopaminergic neuronsin CATH.a, SK-N-BE (2)C, and subjected to 6-OHDA, BH4, and MPTP	antioxidant and anti- inflammatory effects, modulation of autophagy, inhibition of inflammatory pathway	38
Phenol glucoside	Amburoside A	exposed rat mesencephalic cells	Boost cell viability while lowering nitrite and LPO	40
Phenolic acid	Salvianic acid A	Neuroblastoma cells SH-SY5Y exposed to MPT	Nuclear damage, ROS, Bax/Bcl-2, MMP protection, cell viability, apoptosis, cytochrome c 41 caspase 3; release	41

Table No:3 Examples of phytochemicals in animal models and their mechanism:

Phytochemical	Phytochemical name	Animal model	Mechanism	References
Terpene	10-O-trans-p coumaroylcatalopolyol	Degeneration of dopaminergic neurons are caused by paraquat in C. elegans strains N2 Bristol and NL5901.	Terpenes may have neuroprotective effects in Parkinson's disease animal models by lowering oxidative stress, inflammation, and apoptosis (cell death), which are thought to be factors in Parkinson's disease-related neurodegeneration	42

Carbohydrate	Trehalose	C57BL/6 mouse MPTP/probene ci d-induced PD	decreased glial activation, astrocyte hypertrophy, and DA, HVA, and HIAA depletion	44
Alkaloid	Acetylcorynoline	Degeneration of dopaminergic neurons caused by 6-OHDA in Bristol N2 wild- type, BZ555 transgenic, and OW13 transgenic C. elegans	Caspase-3, TH, Bax/Bcl-2, cleaved PARP/PARP, and astrocytes are all activated.	45
Benzyl alcohol	Gastrodin	PD brought on by MPTP in C57BL/6 mice.	Astrocytes, TH, Bax/Bcl-2, caspase- 3, and cleaved PARP/PARP are all activated	46
Catechol	Zingerone	Induced by 6- OHDA, PD ICR mice	OH, radical scavenging and superoxide radical scavenging activity; LPO in fresh mouse brain homogenization	46
Diarylheptanoid	Curcumin	PD brought on by 6-OHDA in Wistar rats	DA and DOPAC depletion; loss of dopaminergic neurons;	48

Funding Declaration

There was no funding.

Conclusion

Increased studies on naturally occurring phytochemicals have been focused on numerous age-related NDD pathogenic diseases, and none of these substances have been demonstrated to have any negative clinical effects (49). PD therapies that utilize naturally occurring phytochemicals with antioxidant capabilities as a trustworthy source of therapy have also proven successful.

(50) The degree of phytochemicals' health advantages is still being debated in terms of medical evidence. Although the physical blood-brain barrier (BBB) stops drugs from entering the brain, naturally occurring lipophilic phytochemicals have a strong affinity for receptors and improved bioavailability. (51)A key tactic to increase disease resistance and the capacity to stop the decline in neuron function is the routine injection of these naturally occurring phytochemicals.

(52) According to the findings of the investigation's histopathology and immunohistochemistry, a significant amount of the in vivo experimental data covered in the current study of the potential neuroprotective effects of antioxidant phytochemicals was supported by the preservation of dopaminergic neurons and a decrease in the loss of TH- positive cells. These changes were also accompanied by an improvement in a number of motor balance and cognitive deficits caused by neurotoxins in study animals, as demonstrated by rotational behavior, the open field test, beam walking, the horizontal and vertical grid tests, passive avoidance, the Barnes maze, and other nonmotor behavioral patterns (53). The GDNF and BDNF genes, which are essential for the survival of DA neurons, were expressed at higher levels thanks to the antioxidant phytochemicals mentioned. Recent research indicates that the JNK signaling pathway, a subfamily of MAPKs involved in apoptotic effects, responds to produced ROS and is essential for the start of apoptosis.

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