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EXPLORING THE ETIOLOGY OF PARKINSON'S DISEASE AND THE POTENTIAL ROLE OF HERBAL PLANTS IN COMBATING ITS PROGRESSION

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ABSTRACT

Parkinson's disease (PD) is a crippling neurological condition marked by a gradual loss of dopaminergic neurons in the brain's substantia nigra, which causes myotonia, dyskinesia, and tremor. Although the precise cause of Parkinson's disease (PD) is still unknown. Lifestyle, environmental, and genetic variables thought to have a role in the disease's genesis and progression. According to research, several important pathways underlie neuronal degeneration in Parkinson's disease (PD), including protein misfolding, oxidative stress, mitochondrial dysfunction, neuroinflammation, glutathione depletion, and buildup of metal ions. A rising number of people are interested in investigating complementary and alternative methods for treating Parkinson's disease symptoms and maybe slowing the disease's course. Since both are necessary for normal neural functioning, it is clear that redox stabilization and replenishment of mitochondrial function, neuro-protection, and lowering inflammation seem to be a significant therapeutic strategy against Parkinson's disease (PD). Levodopa is a component of the current medication, which slows the course of the disease but has several adverse effects. Numerous studies in this area have demonstrated that a variety of synthetic and natural products have the potential to be neuroprotective and anti-apoptotic without showing adverse effects. Phytochemicals use distinct mechanisms related to their neuroprotective roles to provide symptomatic treatment of PD. This abstract highlights the causes of disease progression and the potential of herbal plants in combating it while promoting neuronal survival and neurite growth. Mucuna pruriens, Ginkgo biloba, Curcuma longa, Withania somnifera, and Bacopa moneiri are a few notable herbal options, these plants work as antioxidants, anti-inflammatory agents that reduce pro-inflammatory cytokines and lipid peroxidation, anti-apoptotic agents, lowering the level of neurotoxins and acting as inhibitors of protein aggregation. Herbal treatments also have the benefit of having few adverse effects, several targets of action, and maybe even a synergistic impact with prescription PD drugs. We have also presented in detail the diagrammatic pathway of representative plants in combatting the progression of PD by acting on various targets such as, NF-κB, MPTP, alpha-synuclein and 6-OHDA, which are linked to oxidative and inflammatory stress in neurons. It is found that thorough clinical trials are necessary to confirm the effectiveness, safety, and long-term advantages of herbal remedies for Parkinson's disease (PD) therapy. To guarantee repeatability and therapeutic efficacy, standardized formulations, ideal doses, and exact mechanisms of action must be clarified. To sum up, using herbal plants to supplement current treatment approaches for Parkinson's disease management is a promising approach.

Keywords: *Parkinson's disease; Phototherapy; Neuroprotection; α-synuclein aggregation; Oxidative stress; Mitochondrial dysfunction; Neuroinflammation; Mucuna pruriens.*

INTRODUCTION

Parkinson's disease (PD) stands as one of the most prevalent neurodegenerative disorders globally, affecting millions of individuals and posing a significant challenge to healthcare systems worldwide. Since its discovery, the disease has been a subject of intense scientific scrutiny. Despite remarkable advancements in our understanding of its clinical manifestations and underlying pathology, PD remains an enigmatic and multifaceted condition that affects not only the individuals diagnosed but also their families and communities. Its prevalence increases with age, with the majority of cases diagnosed in individuals over 60 years old. Incidence rises significantly after the age of 60, and men are generally more susceptible than women (Ascherio & Schwarzschild, 2016; Cerri, Mus, & Blandini, 2019) Geographical differences in PD prevalence exist, with higher rates in North America and Europe compared to Africa and Asia. Ethnic and racial disparities may contribute to variations in PD prevalence among different populations (Ben-Joseph, Marshall, Lees, & Noyce, 2020).According to The Global Burden of Disease about 7 million were suffering from PD in 2015 and is believed that cases will double to about 13 million in 2040 (Jankovic & Tan, 2020).

The clinical condition was first described by James Parkinson a member of the Royal College of Surgeons, in the year 1817 and called Parkinson disease as shaking palsy meaning weakness or paralysis agitans meaning tremors ((Q. Li, Zhao, & Bezard, 2006; Ramachandran & Aronson, 2011), (Goetz, 2011). The cardinal features such as of rest tremor, postural instability, bradykinesia and rigidity including variety of other motor and non-motor symptom characterize parkinson disease (PD). Non-motor conditions (such as, depression, constipation, rapid eye movement sleep disorder and constipation) start appearing at premotor stage and progress, in addition to dysautonomia and cognitive impairment, dominate in the advanced stages of the disease (Poewe, 2008) (Goldman & Postuma, 2014). Also while speech impairments, grip force deficiencies, handwriting impairments, and gait disturbances are among the effects of motor abnormalities (Moustafa et al., 2016).

The foundational pathophysiology of Parkinson's disease (PD) is deeply rooted in key discoveries that have shaped our understanding of the disorder. Frederick Lewy's 1912 identification of intracytoplasmic inclusion bodies, famously termed 'Lewy bodies,' served as a pivotal revelation in recognizing a pathological hallmark associated with PD (Engelhardt & Gomes, 2017).These Lewy bodies formed by aggregation of alpha-synuclein, is implicated in the pathology of PD, contributing to neuronal dysfunction and death (Srivastav, Fatima, & Mondal, 2017; Stefanis, 2012).Mitochondrial dysfunction and increase in level of ER stress that contribute to the production of neurotoxins such as MPP+ and 6-OHDA; affects ubiquitin proteasome system and generates ROS causing neural damage, lipid peroxidation and neuro-inflammation (Srivastav et al., 2017). Recent research highlights that microglial activation lead to further activation of pro-inflammatory cytokines such as tumor necrosis factor, interleukin factors, iNO synthase, nuclear factor κB (NF-κB), appears to play a significant role in the perpetuation of neurodegeneration(Glass, Saijo, Winner, Marchetto, & Gage, 2010; Kostelnik, Cegan, & Pohanka, 2017). Similarly, study shows that glutathione depletion and accumulation of metal ions such as excessive level of iron, lead, mercury, cadmium, have shown to induce injury in dopaminergic neurons (L. Ma et al., 2021),by causing fibrillation, mitochondrial dysfunction, ROS accumulation, and neuroinflammation that contribute to showing the symptoms of PD(Bjørklund, Peana, Maes, Dadar, & Severin, 2021; Pyatha, Kim, Lee, & Kim, 2022). Concurrently, the exploration of parkinsonian animal models uncovered the significance of dopamine deficiency, a critical insight that laid the groundwork for subsequent breakthroughs. The trailblazing work initiated by Arvid Carlsson and Oleh Hornykiewicz, commencing in 1957, played a pivotal role in establishing the link between dopamine deficiency and PD (Fahn, 2018) Their research provided a foundational understanding of the neurotransmitter's central role in the disease's pathophysiology. Unraveling these intricate molecular pathways is a critical step toward developing targeted therapeutic strategies that address the root causes of PD.

Although there is no cure for PD, current treatment strategies primarily focus on symptom management. Levodopa, a precursor of dopamine, remains the gold

standard for alleviating motor symptoms. However, long-term use is often associated with motor fluctuations and dyskinesias (Pasluosta, Gassner, Winkler, Klucken, & Eskofier, 2015).Other pharmacological interventions, such as dopamine agonists and monoamine oxidase inhibitors, aim to modulate dopamine levels or receptor sensitivity (Pasluosta et al., 2015; Pyatha et al., 2022). Ongoing research is exploring innovative herbal approaches, including phytochemicals showing neuroprotective, neurotropic effect, that raises the level of dopamine and decreases inflammation, with the hope of slowing or halting disease progression. Certain plant-derived compounds have shown potential benefits in acting on the targets of PD such as *Mucuna pruriens, Camellia sinensis, Passiflora incarnata, Curcuma longa, Cinnamomum verum*, and *Hericium erinaceus Curcuma longa, Ginkgo Biloba , Mucuna pruriens*, etc., incorporating these compounds as complementary therapies under medical supervision could potentially enhance overall PD management.

In this article, after a detailed study, we have highlighted main natural compounds that not only act directly in increasing the level of dopamine, but also maintain mitochondria functioning and energy production by preventing the generation of neurotoxins and acting as in anti-apoptotic agent. It also act as an anti-inflammatory agent by decreasing the level of free radicals and inflammatory mediators that help in providing neuroprotection, neural regeneration, and maintaining normal functioning, these herbal extract have also shown significant effect as neurotropic factors that help in neural regeneration. In conclusion, Parkinson's disease remains a complex and challenging condition that demands ongoing research efforts. Advances in our understanding of its pathophysiology and the development of targeted therapies hold promise for improving the lives of those affected. As we navigate the intricacies of PD, a comprehensive and multidisciplinary approach is essential to unravel the mysteries surrounding this prevalent neurodegenerative disorder.

2. CAUSES OF PARKINSON DISEASE

The primary cause of Parkinson disease is the transformation of α-synuclein monomer into oligomer that are highly toxic in nature and causes synaptic dysfunction due to oxidative stress and inflammation (Cooper et al., 2006).These small oligomers undergo noncovalent interactions and form protofibrils, which are less structured than mature fibrils(Miraglia, Ricci, Rota, & Colla, 2018). The protofibrils, upon maturation, result in the formation of mature amyloid-like fibrils that is rich in beta sheets, which further undergo the fomation of Lewy bodies (Caughey & Lansbury Jr, 2003).The more than 90 components that make up the LB combination include autophagy, ubiquitin proteasome system, mitochondrial associated protein, PD-linked gene products (DJ-1, LRRK2, Parkin, PINK-1, and alpha synuclein(Wakabayashi, 2013). These fibrillary tangles remain the most important hallmarks of Parkinson disease(Ono & Tsuji, 2020; Wan & Chung, 2012). The generation of Lewy bodies contributes to neuronal degeneration and neurotoxicity, leading to dopaminergic neuron death. These aggregates interfere with key physiological processes, including cytoskeletal organization, protein synthesis, vesicle transport, and lysosomal degradation. Moreover, they disrupt centrosomal and microtubule dynamics, resulting in Golgi apparatus fragmentation, DNA silencing, dysregulation of collagen gene transcription, and ultimately, neuronal apoptosis characteristic of Parkinsonism ((Leverenz et al., 2007; Paiva et al., 2018; Wakabayashi, 2013; Wan & Chung, 2012). This agglomeration formation is stimulated by cellular microenviornment, enviornmental conditions, macromolecular crowding, ligands, toxic specie such as pesticides, herbicides, metal ions, acidic exposure, change in pH, temperature, nitration and oxidation reaction.

The study conducted by Braak et al. explains age dependent aggregation of synuclein, it is found that with increase of age, aggregation increases which proved age-depended cause of PD (Ascherio & Schwarzschild, 2016), similarly, the cellular microenviornment changes undergo Lewy bodies formation by the mutation in gene such as A30P, A53T, E46K, PARK1, PARK7, DJ-1, LRRK2 (G. J. Ho et al., 2011) as shown in figure 1.1. According to Johns Hopkins medicine, PARK2 gene makes the parkin protein, which helps cell break down and recycle protein, while PARK7 makes the protein DJ-1, which protect against mitochondrial stress, on the other hand PINK1 and LRRK2 makes protein kinase that protects mitochondria from stress. It is found that mutation in PARK2 and PARK7 cause rare form of early onset PD, while mutation in LRRK2 is responsible for causing late-onset PD. Other

mutuations of gene such as A30P, A53T, E46K is repsonsible for increasing phospholipid binding affinity hence causing aggregation, and fibrillation of alpha synuclein ((Hauser, Primiani, & Cookson, 2017; Nuytemans, Theuns, Cruts, & Van Broeckhoven, 2010)).

Another pathogenic event in Parkinson's disease (PD) has been identified as the phosphorylation of serine 129 in the C domain that result in agregation, there are other forms of phoshorylation as well such as phsophorylation of ser-87, tyrosine all are related to synucleinpathies and produce harmful effect ((Brahmachari et al., 2016; Fujiwara et al., 2002; Paleologou et al., 2010; Saito et al., 2003; Sugeno et al., 2008). Other post-translational modifications such as the imbalance between SUMOylation and deSUMOylation of protein (Y. Yang et al., 2017)and dopamine oxidation to dopamine-o-quinone aminochrome and 5,6-indolequinone (Segura-Aguilar et al., 2014),acetylation affects aggregation process (Vinueza-Gavilanes et al., 2020). Studies have indicated that DA quinones impact the pathophysiology of Parkinson's disease by changing proteins like α-synuclein, parkin, SOD2, DJ-1, and UCH-L1 (Segura-Aguilar et al., 2014).

Additionally, oxidative stress plays a significant role in the pathophysiology of Parkinson's disease as these proteins undergo lipid peroxidation, glutathione depletion, and dopamine metabolism. Oxidative reactions generate free radicals such as superoxide anion, hydroxyl ions, hydrogen peroxide, and NO. Superoxide anion can cross mitochondrial membrane and can be reduced to hydrogen peroxide by peroxisomes. These anions are produced by mitochondrial complexes I and III of ETC. Hydrogen peroxide if released in cytosol it can cause oxidative stress to that can modify cellular nucleophiles and trigger programmed cell death (Muller, Liu, & Van Remmen, 2004). On the other hand, the nitration process, which produces nitric oxide via nitric oxide synthase (iNOS), acts as an inflammatory mediator and is hence important in exhibiting Parkinson's disease symptoms (Segura-Aguilar et al., 2014).

Metal ions sustain the body's growth and development, which is essential to its appropriate physiological function. These micronutrients, which include Hg, Cu, Mn, Pb, Al, Bi, Zn, Se, Cd, and Fe, are essential for the body's most vital processes, including DNA synthesis, mitochondrial respiration, transportation, and neurotransmitter synthesis. One of the degenerative results of Parkinson's sickness (PD) is accepted to be the development of iron in the substantia nigra region of the mind. Iron is fundamental for supporting cell working in a physiological climate. Then again, in obsessive conditions, the cerebrum has an overabundance of iron due to a breakdown in the blood-brain barrier or an issue with the cycles that store and transport iron. The development of iron can then prompt oxidative pressure as in presence of ferrousiron (Fe^{2+}), H_2O_2 can be converted to highly reactive radical under the presnce of fenton (Valko et al., 2007), it also causes α-synuclein collection, neuroinflammation, and neuronal cell degeneration. Ferric iron (Fe^{3+}) promotes α-synuclein aggregation by binding to its tyrosine and alanine residues, accelerating fibrillization ((Foley, Hare, & Double, 2022; Witkowska, Słowik, & Chilicka, 2021)) Imbalance in iron homeostasis is closely associated with oxidative stress, mitochondrial dysfunction, neuroinflammation, and impaired neurotransmitter transport within both the peripheral and central nervous systems. These disturbances contribute to dopamine and serotonin depletion, ultimately leading to the progressive neurodegenerative symptoms characteristic of Parkinson's disease

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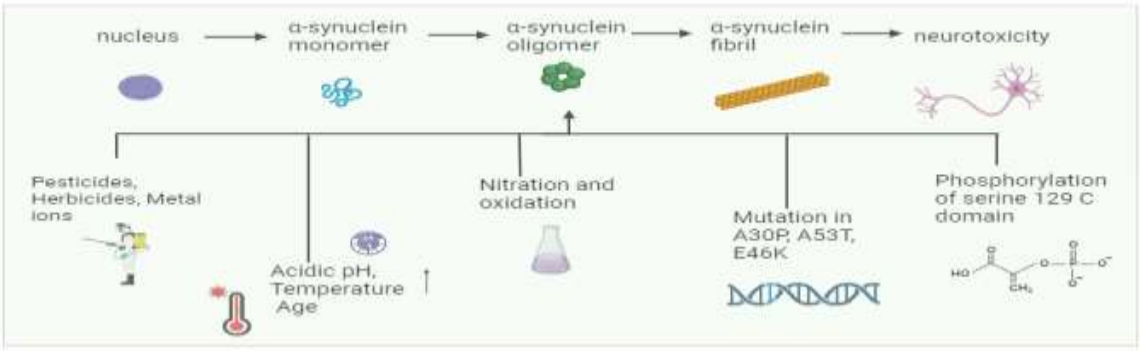

3.

PATHWAY OF PARKINSON DISEASE

Figure 1 Internal and Environmental factors leading to cell death and neurotoxicity

3.1 α-synuclein aggregation

α-synuclein is a α-helical, presynaptic neuronal protein consisting of 140 amino acid that bind to negatively charged lipid, such as phospholipids present on cellular membrane and beta sheets, on incubation, protein have 3 distinct regions; amino N terminus, a carbonyl (C) terminus and non amyloid component (NAC)(Larsen et al., 2006; Lou, Kim, Hawk, & Shin, 2017). Central region; NAC domain that have high hydrophobic sequence for aggregation and leading to protofibril and fibril (Davidson, Jonas, Clayton, & George, 1998; Fusco et al., 2014; Giasson, Murray, Trojanowski, & Lee, 2001). Study states that N-terminal domain binds to negatively charged lipid membrance and form aplha helices while metal ions, protein, small molecules and other domains bind to C-terminal domain and can interact with zwitterionic lipids(Bisaglia, Tessari, Mammi, & Bubacco, 2009; Davidson et al., 1998; T. D. Kim, Paik, & Yang, 2002; Ly & Julian, 2011).

Under physiological conditions α-synuclein is present in soluble, unfolded monomeric or tetrameric, membrane or vesicle bound form (Bartels, Choi, & Selkoe, 2011; Gustafsson et al., 2018; Pirc & Ulrih, 2015; Weinreb, Zhen, Poon, Conway, & Lansbury, 1996)and is involved in neuronal differentiation, regulation of dopamine synthesis and suppression of apoptosis in neuron by laying out a connection point between mitochondria and endoplasmic reticulum. Moreover, oligomeric α-synuclein in the brain is removed by ubiquitin-proteasome and lysosomal autophagic pathways (Benskey, Perez, & Manfredsson, 2016; Calabresi, Di Lazzaro, Marino, Campanelli, & Ghiglieri, 2023; Sharon et al., 2001)However imparied mitochondrial function, genetic dysfunction, disturp normal functioning and increases agregation which lead to oligomer which is involved in various intracellular processes causing neurodegenerative disorders like dementia with Lewy bodies, multiple system atrophy, autonomic failure, inflammation and REM sleep behavior disorder (Bartels et al., 2011). Correspondingly, α- synuclein interact with SNARE complex VAMP2/synaptobrevin-2 and synaptic vesicles resulting in decreasing trafficking by interacting with dopamine transporter (DAT) this effect the proper functioning of transporter reduces dopamine stores, synaptic vesicle endocytosis, dopamine release and uptake of dopmaine hence reducing total dopamine level in neurons and axonal fibers(Abeliovich et al., 2000; Ellis et al., 2005; Mosharov et al., 2006) . It also affect lipid hemeostasis that is essential for vesicle cycling and synaptic localization, this alteration results in slowing down vesicles exocytosis (Fanning, Selkoe, & Dettmer, 2021; Hannestad et al., 2020).

Increased amounts of nitrated tyrosine residues and α-synuclein, the main component of Lewy bodies, have been discovered to be nitrated in postmortem PD brains. Furthermore, it has been discovered that 3-NT alteration prevents α-synuclein from attaching to vesicles, which lowers its rate of breakdown and increases the production of fibrils (Calabresi et al., 2023). It is important conceptually and historically that the first association between α-synuclein and Parkinson's disease (PD) was also the first to provide proof of a genetic abnormality causing PD. Most

people believed that there was at most a little hereditary relation to the condition. According to the research done in 1997, the mutation led to an amino acid change of A53T and matched a G209A substitution in the SNCA gene that codes for α-synuclein. Lewy bodies like fibrils are formed most rapidly by A53T, increasing agregation, while A30P undergo oligomeration more than fibrillation (Conway, Harper, & Lansbury, 1998) Despite initial doubt due to the threonine residue at position 53 in the rodent SNCA homolog, this concern was dismissed after the discovery of two additional SNCA point mutations, A30P and E46K, both linked to autosomal-dominant Parkinson's disease. These mutations disrupt cellular and calcium homeostasis, promote α-synuclein aggregation, and cause lysosomal and mitochondrial dysfunction, ultimately leading to neuronal death (Benskey et al., 2016).However according to research E46K mutuation enhances interaction and contact between N and C terminal domain of synuclein to promote fibrillization (Fredenburg et al., 2007; Rospigliosi et al., 2009))

α-Synuclein aggregates within mitochondria, leading to the formation of neurotoxins such as MPP^+ and 6-OHDA, which induce mitochondrial dysfunction and excessive production of reactive oxygen species (ROS). These ROS damage the endoplasmic reticulum and Golgi apparatus, cause electron leakage, and activate caspases that trigger microglial activation and the release of pro-inflammatory cytokines and interleukins. The resulting inflammation drives neuronal degeneration and impairs the ubiquitin–proteasome system(Al-Hilaly et al., 2016; Klegeris et al., 2008; Mogi et al., 1994). Similarly oligomer proteins binds to membrane of mitochondria and disrupts fusion and fission process hence causing lipid peroxidation, decreasing uptake of calcium, and causing autophagy leading to cellular toxicity (Calì, Ottolini, Negro, & Brini, 2012; Nakamura et al., 2011).

Neurodegeneration is caused by aggregation of α-synuclein, while its oligomers are in charge of mitochondrial malfunction, the production of free radicals, the activation of ER stress, vesicle trafficking, synaptic dysfunction, increase of inflammation and cellular toxicity. Reducing α-synuclein's oligomerization and fibrillation has been identified as a successful PD target, according to research neurodegeneration is caused by increase in stress and inflammation hence reducing inflammation and route cause of it can lead towards neuroregeneration, hence natural plant extract that have a role in reducing oligomer formation that is considered to be route cause of PD can be helpful in combatting the progressive symptoms. Numerous plant extracts have been discovered to be crucial in preventing the development of oligomers and improving fibrils through α-synuclein degradation or autophagy, or by stabilizing oligomers, making them pharmacologically useful targets. *Mucuna pruriens (Radder, Tiel Groenestege, Boers, Muilwijk, & Bloem, 2019), Camellia sinensis (Prasanth, Sivamaruthi, Chaiyasut, & Tencomnao, 2019),Passiflora incarnata, Curcuma longa, Cinnamomum verum*, and *Hericium erinaceus* extracts have been shown in studies to mitigate β-amyloid-induced neurotoxicity by reducing alpha synuclein aggregation and fibrillation linked to the A53T mutation.

Mucuna pruriens has been shown to reduce α-synuclein aggregation and fibrillation by 3.5 times (Zahra et al., 2022) . Similarly, It has been demonstrated that the epigallocatechin-3-gallate-containing extract from (Lampariello, Cortelazzo, Guerranti, Sticozzi, & Valacchi, 2012),*Camellia sinesis* blocks the neurotoxicity caused by β-amyloid by attaching to the areas containing unfolded α-synuclein polypeptide chains and breaking them down into non-toxic amorphous protein structures (Ehrnhoefer et al., 2008; Zhao et al., 2017). It helps to increase dopamine levels, tyrosine hydroxylase and enhances motor function by reducing the interaction between the oligomer and cell membrane(D. Chen, Zhou, Lyons, Pahwa, & Reddy, 2015). The polyphenols indirectly increase the pace at which α-synuclein breaks down through the lowering of 3-NT, which implies a possible role for them in the prevention of Parkinson's disease (Martinez-Perez, Jimenez-Del-Rio, & Velez-Pardo, 2018). Nevertheless, Curcumin extract from *Curcuma longa* binds to amyloid species and prevents in virto aggregation and fibril formation, making them non-toxic (Shrikanth Gadad, K. Subramanya, Pullabhatla, S. Shantharam, & KS, 2012). They reduce its accumulation by restoring macroautophagy by activating the mTOR/p70S6K signaling pathway (Perrone et al., 2019). Chyrin, a flavonoid extract of *Passiflora incarnate*, is involved in reducing α-synuclein aggregation (Angelopoulou, Pyrgelis, & Piperi, 2020). Cinnamon extract stabilizes oligomer in vivo and

invitro and inhibits α-synuclein aggregation produced by mutation of A53T, preventing the development of Lewy bodies (Javed et al., 2019). *Hericium erinaceus (Y.-J. Lin et al., 2023)*, Rosamaric acid extract of Sage, protects brain cells by inhibiting the oxidative process and decreases the cytotoxicity of beta amyloid Aβ(Caputo et al., 2021; Mirza, Amber, Hassan, Ahmed, & Zahid, 2021).

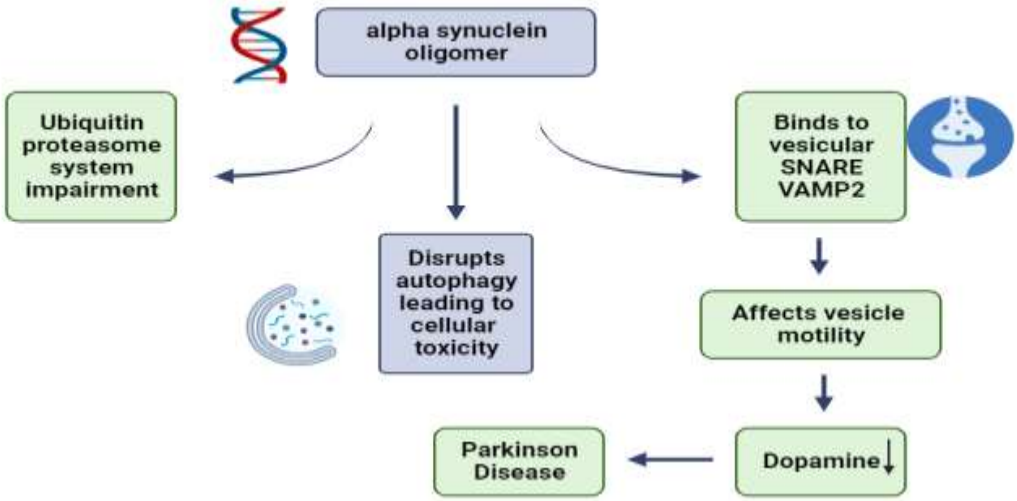

Figure 2 Pathway followed by α-synuclein oligomer to cause Parkinson disease

3.2 SNARE inhibition

The brain is the essential area of the chemical monoamine oxidase-B (MAO-B), which is associated with the enzymatic change of dopamine to homovanillic corrosive and 3,4-dihydroxyphenylacetic acid inorder to maintain homestasis of neurotransmitters in the brain (Di Monte, Wu, Irwin, Delanney, & Langston, 1991) . Age-related expansions in MAO-B levels have been connected to Parkinson's sickness (PD), along with the age the level of MAOB is increased in neuroinflammation and degenerative conditions, while in PD the level of it is increased in astrocytes of SN (substantia nigra) which lowers dopamine level and causes neurodegeneration and inflammation (Chun, Lim, Park, & Lee, 2022). It reports by inhibiting MAO-B enzymatic action keeps dopamine from being separated and improves its accessibility in the synaptic parted, inhibition also results in supressing the inflammation that promote neuroregeneration (Chun et al., 2022; Jo et al., 2014; Park et al., 2019; Youdim, Edmondson, & Tipton, 2006).

Dopamine is released from terminals located inside the caudate and putamen nuclei, it functionally modifies both excitatory and inhibitory synaptic transmission(Nicola & Malenka, 1997). Following its release from presynaptic terminals, dopamine is actively taken up from the synaptic cleft by a variety of monoamine transporters, including dopamine active transporter (DAT), and then vesicular monoamine transporters (VMAT) bundle it into intracellular vesicles (German, Baladi, McFadden, Hanson, & Fleckenstein, 2015). α-synuclein localise presynaptic terminal and associate with synaptic vesicles to undergo fusion and other processes in synaptic vesicle trafficking by interacting with synaptobrevin 2 of SNARE (soluble N-ethylmeleimide sensitive factor activating protein) (B.-K. Choi et al., 2013; Maroteaux, Campanelli, & Scheller, 1988; Yavich, Jäkälä, & Tanila, 2006; Yavich, Tanila, Vepsäläinen, & Jäkälä, 2004). Oligomers formed in response to environmental, cellular, or growth factors bind to synaptobrevin-2 and disrupt the SNARE complex (VAMP2) assembly. This interference impairs synaptic vesicle motility and reduces dopamine release, leading to Parkinson's disease (Lou et al., 2017) as illustrated in figure 1.2.

Parkinson disease symptoms have been reported to be ameliorated by increasing dopamine levels and targeting monoamine oxidase. A study found that moringa balanced neurotransmitter levels and restored monoamine levels in the brain, which

include norepinephrine, dopamine, and serotonin(Pareek et al., 2023) . Conversely, Camellia sinesis reduces the interaction between the oligomer and cell membrane, which enhances motor function and helps to increase dopamine levels (106). In CHO cells expressing DAT, EGCG from Camellia sinesis inhibited the ability of DAT to actively uptake MPP+ and be transported to presynaptic dopaminergic neurons, preventing neurodegeneration (Pan, Fei, Zhou, Jankovic, & Le, 2003). Since inhibiting DAT reduces the availability of dopamine in the nerve terminals, it is one way to stop the progression of the disease (R. Li, Peng, Li, & Le, 2006). Chrysin from Passiflora incarnate has been demonstrated to have anti-inflammatory qualities in addition to increasing dopamine levels in the striatum through monoamino-oxidase B (MAO-B) inhibition (Radder et al., 2019). This process suppresses dopamine metabolism and raises dopamine levels in the striatum, which aids in improving behavioral deficits in animal models of Parkinson's disease. While, dopamine concentrations were markedly raised by M. pruriens (Radder et al., 2019). According to a research, an aqueous extract of C. longa dramatically inhibited monoamine oxidase A (MAOA) in the mice's brain, which stopped dopamine from being metabolized and increased dopamine levels in the striatum (Rajeswari & Sabesan, 2008). The amount of monoaminergic neurotransmitters, such as dopamine and norepinephrine, in hippocampus tissue was increased by curcumin hence proving to be effective to treat symptoms of PD (Kulkarni, Bhutani, & Bishnoi, 2008). Huperzine A is a known acetylcholinesterase (AChE) inhibitor (Hügel & Jackson, 2015). AChE is an enzyme that breaks down acetylcholine, a neurotransmitter involved in various functions, including movement control (McHardy, Wang, McCowen, & Valdez, 2017). In Parkinson's disease, there is a loss of dopamine-producing neurons, but there is also dysfunction in other neurotransmitter systems, including the cholinergic system (McHardy et al., 2017). By inhibiting AChE, huperzine A may increase acetylcholine levels, potentially affecting the balance of neurotransmitters in the brain (Hügel & Jackson, 2015).The cholinergic system, involving acetylcholine, plays a role in regulating movement and cognitive function. Modulation of the cholinergic system could have implications for motor control and cognitive aspects affected in Parkinson's disease(McHardy et al., 2017) .

3.3 Induction of mitochondrial dysfunction

Almost all eukaryotic cells have mitochondria, which are the most significant organelles for generating energy and a component in preserving cellular homeostasis(Farooqui, 2019). Over the past few decades, numerous lines of evidence have demonstrated that the etiology of Parkinson's disease (PD) involves mitochondrial dysfunction, specifically inhibited complex I caused by oxidative stress accumulation in the ER and mitochondria (M. J. Kumar, Nicholls, & Andersen, 2003; Smith et al., 2005). This results in cellular dysfunction, genetic dysfunction, energy failure, mitochondrial chain inhibition, and dopaminergic cell death (Olagunju et al., 2023). The potential for α-synucleins to prompt the making of mitochondrial penetrability transition pores (mPTPs), that causes loss of mitochondrial membrane potential (MMP) resulting in mitochondrial dysfunction and eventually cell death (K.-J. Lin et al., 2019; Mnatsakanyan, Beutner, Porter, Alavian, & Jonas, 2017; Olagunju et al., 2023; Tang, Kang, Berghe, Vandenabeele, & Kroemer, 2019; Zorov, Juhaszova, & Sollott, 2014). MPTP is highly lipohillic compound that can cross the blood brain barrier, once inside the brain the non-toxic substance MPTP is converted into toxic substance MPP+. This MPP+ is an active metabolite of the MPTP, that binds with complex-I and depletes dopamine level. MPP+ is produced by the production of MPPP due the mutation of mtDNA, due to enzymatic action of monoamine oxidase, once its formed it is taken up by DAT where it gets accumulated in dopaminergic neuron and causes neural damage. MPP+ inside mitochrondria fuse with mitochondrial membrane and produces mitochondrial damage that results in e-leakage, it also damage ubiquitin proteasome system and raises permeability and oxidative stress by increasing ROS levels. This, in turn, lowers ATP synthesis and raises Ca levels, damaging neurons in the substantia nigra(Bose & Beal, 2016; Di Monte et al., 1991; Heikkila, Hess, & Duvoisin, 1984; Nicklas, Vyas, & Heikkila, 1985; Risiglione et al., 2020; Watanabe, Himeda, & Araki, 2005)

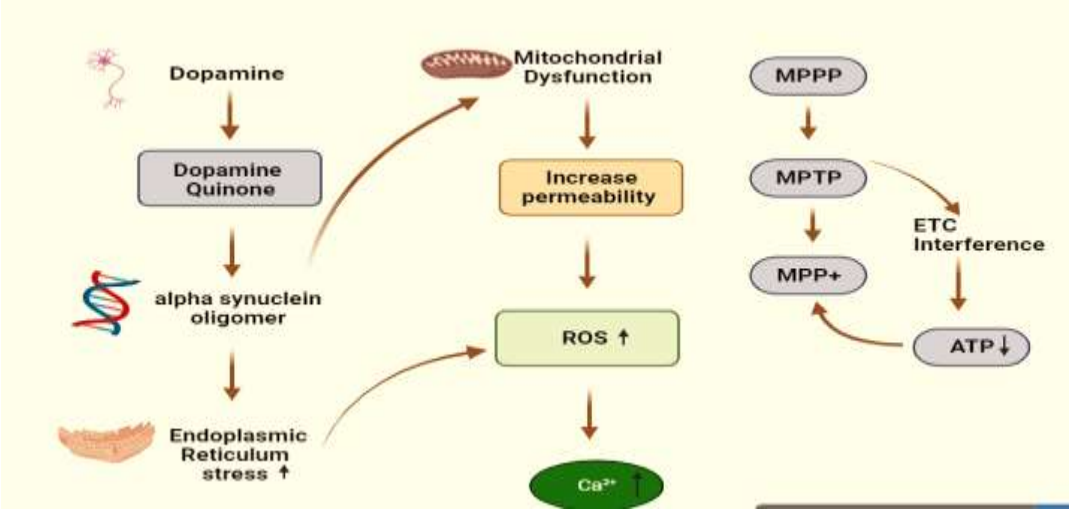

Figure 3 Pathway followed by α-synuclein oligomer to cause PD syndrome

Mitochondrial dysfunction release cytochrome C which activates protein kinases caspases (3, 8, and 9), and altered expression of apoptosis genes like Bcl-2 (Bossy-Wetzel, Newmeyer, & Green, 1998) as shown in figure 1.3. whereas, dopamine under physiological condition, transmits signals needed for coordination of muscle movement. Damage and loss of energy may also lead to loss of energy production can disrupt vesicle that store dopamine, causing dopamine-related oxidative reaction in cytoplasm. Loss of dopamine causes an irregular pattern of nerve firing, loss of movement control and generation of DA quinone that generates ROS which induces mitochondrial respiration failure (Bose & Beal, 2016; Di Monte et al., 1991; Heikkila et al., 1984; Nicklas et al., 1985; Watanabe et al., 2005). The neurotoxins MPTP, 6-OHDA, selectively damages substantia nigra of brain resulting in dopaminergic neuronal loss and is widely involved in progression of PD. 6-OHDA toxin produced by the deterioration of motor function, is structurally similar to the catecholamine's, employed to ascertain dopmainergic function and evaluate progression of neuroactive pharmacological action on dopaminergic system(Michel & Hefti, 1990) . 6-OHDA toxicity selectively destroys substantia nigra neurons through generating reactive oxygen species. 6-OHDA increases lipid peroxidation, generates free radicals, and diminishes enzymatic activity. Hippocampus impairment can lead to cerebral anoxia causing loss of memories. The mesohippocampal pathway's susceptibility to certain toxins like 6-OHDA, exhibits sensitivity to attacks by free radicals(Michel & Hefti, 1990). Since the mesohippocampal pathway plays a crucial role in learning and memory processes, it is evident that numerous cognitive impairments, including memory difficulties, manifest in the early stages of Parkinson's disease (PD) before the disease's typical symptoms appear(Fan et al., 2021) .Overall, the production of different oxidants and free radicals, lipid peroxidation, and deficiencies in the mitochondrial complex are all blamed for this toxin's effects.

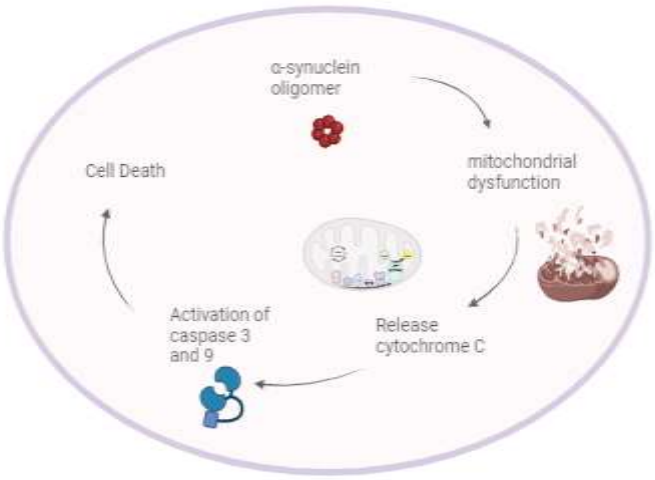

Figure 4 Pathway followed by α-synuclein oligomer to cause PD syndrome

MPTP and 6-OHDA are neurotoxins that are build up in the mitochondria of dopaminergic neurons, inhibiting the activity of the respiratory chain, which causes reversible loss of ATP and stimulating the production of free radicals that cause lipid peroxidation and glutathione depletion (Bossy-Wetzel et al., 1998; Michel & Hefti, 1990). Meanwhile, MPP+ is an active metabolite of MPTP toxins that causes cell death through inhibition of mitochondrial complex-I (Nicklas et al., 1985). Owing to these grave shortcomings, it is imperative that novel therapies be created that include neuroprotective action with fewer adverse effects. A number of therapeutic approaches are being assessed that may be used either as stand-alone therapies. Multiple mechanisms, including oxidative stress, mitochondrial failure, protein aggregation, and neuroinflammation, contribute to neurodegeneration in Parkinson's disease (PD). An effective therapeutic strategy includes the use of herbal plants with fewer side effects. Many plant extracts and phytochemicals are useful in Parkinson's disease (PD) because they directly reduce MPTP and OHDA toxins, which prevent mitochondrial malfunction and the production of radicals.

Mucuna prueins enhance mitochondrial complex-1 activity with the presence of NADH and coenzyme Q10 that prevent mitochrial injury. It also alleviate MPTP intoxication, and normalize the level of iNOS and glial fibrillary acidic protein in MPTP to improve neurotoxicity and dyskinesia, it is reported that MP also restore level of dopmaine and other neurotransmitter without interfering with Monoamine oxiade, however MP restore motor impairement by preventing mitochrondrial induce oxidation and ER stress (Manyam, Dhanasekaran, & Hare, 2004; Zahra et al., 2022). *Bacopa monieri* and *Curcuma longa* act against MPP+ toxicities, and protect PC12 cell by maintaining complex-I activity and membrane potential, while *Curcuma longa* function to balance overexpression of Bcl-2 (J. Chen et al., 2006; B. Singh, Pandey, Rumman, & Mahdi, 2020). *Camellia sinesis* prevent presynaptic transmission of MPP+ by inhibiting dopamine transporters to actively reuptake it, hence preventing neurodegeneration of cell, it increases the expression of Bcl2 and decreasing the expression of Bax to prevent apoptosis of neurons. (Malar et al., 2020). EGCG also supress buildup of ROS, restore MMP and maintain calcium homeostasis, by nhibiting the opening voltage gated Ca channels and mitochondrial Ca uptake, hence provide protection to SH-SY5Y cells from 6-OHDA induced neurotoxicity, it restore MMP, by preventing the opening of mPTP and eventually the release of cytochrome-c (S. Guo, Bezard, & Zhao, 2005). Another plant extract obtained from Moringa prevent mitochondrial dysfunction by preventing the accumulation of MPTP toxicities by targetting the transcription factor, Nrf2 (Ndlovu, Chuturgoon, & Ghazi, 2023). Similarly, Centella asiatica has been shown to restore mitochondrial function by reducing MPTP-induced toxicity (Siddique et al., 2014), Chryin extract from *Passifora incarnata*, reduce 6-

OHDA induced iNOS expression and intracellular NO levels and decrease oxidative stress, its also found to reduce MPTP induce MPP+ toxins, causing up-regulation of pro-apoptotic c-caspase and Bax and downregulation of Bcl-2 hence preventing neuronal cell death (Angelopoulou et al., 2020). *Gingko biloba* and Cinnamaldehyde is found to be effective against 6-OHDA toxins hence imprroving behavioural activity and cell integrity (Mohebbi et al., 2023). It also repairs neuronal cells and inhibit MPP+ toxins hence protecting striatum and preventing dopamine depletion (Mohebbi et al., 2023; Xu et al., 2020).

3.4 ROS generation

Oligomerization and fibrillation caused by the mutation in PARK2, a gene coding, ubiquitin ligase enzyme, responsible for removing excessive agregates of synuclein, impairs ubiquitin proteasome system, hence increasing level of oligomer that gets accumulated in ER hence creating ER stress by interfering with protein folding and increasing permeability (Pyatha et al., 2022; Yavich et al., 2006) as shown in figure 1.2. This increase in ER stress and mitochondrial dysfunction increases reactive oxygen specie level (Muller et al., 2004). It is highly susceptible to oxidative stress (OS) due to elevated levels of pro-oxidant iron and the abundance of unsaturated lipids, which make it prone to lipid peroxidation(Dias, Junn, & Mouradian, 2013; Kavya, Saluja, Singh, & Dikshit, 2006) Reactive oxygen species (ROS) include both free radical and non-radical entities. Increased oligomer formation and endoplasmic reticulum (ER) stress disturb the balance between ROS generation and neutralization, leading to excess free radicals. These oxidants participate in electron transfer and hydrogen abstraction reactions, causing mitochondrial energy failure and oxidative stress. Elevated oxidative stress triggers neurotoxicity by damaging DNA, proteins, and lipids through polyunsaturated fatty acid peroxidation. The resulting cellular disruption contributes to inflammation and the progressive neurodegenerative symptoms of Parkinson's disease.(Bortolanza et al., 2015; Danielson et al., 2009; Valko et al., 2007)

The brain is so sensitive to oxidative stress, that it plays a significant role in neurodegenerative diseases. An increase in free radicals leads to oxidative stress, which can oxidize biological macromolecules and have negative effects on the body, including ligand-induced aging, mitochondrial dysfunction, lipid peroxidation, energy depletion, protein denaturation, DNA strand breakage, and metabolic pathway disruption (Al-Hilaly et al., 2016; M. J. Kumar et al., 2003). By employing ingredients that directly contribute to the quenching of free radicals, significant improvement can be noticed. For this reason, oxidative stress is heavily stressed when managing Parkinson's disease. Most plant extracts used in traditional medicine have been employed for their prospective therapeutic effects as well as their long-standing health advantages. Many scientists are drawn to the phytochemicals because they contain antioxidant enzymes such as catalase, glutathione peroxidase, reductase, and superoxide dismutaseare that play important role in neutralizing free radicals and mediating cytochrome c and caspase activiation.

Numerous anti-oxidants found in *Camellia sinensis* have the ability to directly mitigate the harmful effects of oxidative stress or to interfere with defensive mechanisms. The presence of OH groups in chemical structures, which provide electrons and H+ to neutralize free radicals, is what gives as its antioxidant activity (Danaraddi, Koneru, Hunasgi, Ramalu, & Vanishree, 2014). It increase the level of anti-oxidant enzyme such as catalase and superoxide dimutase and modulates JNK pathway to prevent the oxidation caused due to formation of free radicals such as nitrite free radical that further prevent oxidation of lipids and protein (D. Chen et al., 2015; Good, Hsu, Werner, Perl, & Olanow, 1998). *Mucuna prueins* and Withania somnifera has been shown to demonstrate anti-apoptotic effect and scavenge radicals by displaying enhanced Bcl2 expression in conjunction with a reduction in Bax. Additionally, they scavenge 2,2 diphenyl-1-picrylhydrazyl (DPPH) radicals, which limit lipid oxidation and enhance the redox potential of nigrostriatal pathways. This increases catecholamine levels, boosts antioxidant capacity, and improves redox potential and motor function (Manyam et al., 2004; Prakash, Yadav, Chouhan, Prakash, & Singh, 2013; Sachchida Nand Rai, Chaturvedi, Singh, Singh, & Singh, 2020). *Bacopa monieri* normalizes oxidative indicators by reducing reactive oxygen species through the activation of antioxidant enzymes, BM restore ACh and AChE concentration hence preventing ROS and decreasing superoxide level (B. Singh et al., 2020). By mediating the c-JUN/AP-1 pathway, curcumin from Curcuma longa inhibits inducible Nitric Oxide Synthase (iNOS) and induces antiapoptotic genes like Bcl-2 (J.

Chen et al., 2006). This reduces ROS, abrogates oxidative stress-mediated cytochrome c release or caspase 3 activation and JNK phosphorylation inhibition, thereby preventing neuronal death, restoring mitochondrial membrane potential, and reducing ROS (Pathak-Gandhi & Vaidya, 2017). In 6-OHDA rat PD models, the administration of *Camellia sinensis* polyphenols demonstrated a neuroprotective impact through the prevention of ROS, lipid peroxidation, reduction of iNOS, and decrease in protein-bound 3-nitro-tyrosine level (3-NT). Stress-induced nitrite radicals can combine with protein tyrosine residues to create protein-bound 3-NT, which is observed in a number of neurodegenerative illnesses, including Parkinson's disease (PD). By decreasing H2O2, sage extract's neuroprotective qualities were shown in human dopaminergic cells, SH-SY5Y ((D. Chen et al., 2015; Danaraddi et al., 2014). Moreover, rosmarinic acid dramatically reduces both H2O2-induced apoptotic cell death and changes in the mitochondrial membrane potential(Ghaffari et al., 2014). Additionally, this extract reduced the activation of caspase-9 and 3, upregulated Bcl-2 expression, and downregulated Bax, all of which helped to lessen the consequences of oxidative stress (Hong et al., 2021; Iuvone, De Filippis, Esposito, D'Amico, & Izzo, 2006). Because Moringa enhances blood flow to the brain, which prevents cerebral ischemia and prevent stimulation of the generation of reactive oxygen species (ROS), it is said to be a neuroprotectant (J. Hashim, Vichitphan, Boonsiri, & Vichitphan, 2021). By lowering ROS, the moringa stimulates an antioxidant response that shields the brain. By influencing neuronal cell survival against apoptosis (Guon & Chung, 2017). C. asiatica regulates the caspase-9 pathway in an antioxidant manner. The most reactive ROS, hydroxyls, are rendered inactive by higher concentrations of polyphenols and flavonoids, which contribute to the antioxidant effect (Siddique et al., 2014). It was also verified that the ethanolic extract of C. asiatica exhibited considerable antioxidant activity by means of the DPPH and superoxide radical scavenging activity. Flavonoids scavenge free radicals, while terpene lactones shield mitochondrial membranes from damage caused by free radicals (Siddique et al., 2014). According to descriptions, Gingko containing flavonoids and terpene possesses antioxidant qualities and functions as a powerful free radical scavenger. It has been shown that its ability to scavenge hydroxyl radicals and function as a "radical scavenger" for antioxidants is a result of its superoxide dismutase-like activity (Mohebbi et al., 2023). Similarly treatment with Hericium erinaceus decreased the amount of glutathione, nitrotyrosine, 4-hydroxy-2-nonenal (4-HNE), MPTP-induced dopaminergic cell loss (Kuo et al., 2016). Erinacine A reduces the impairment of MPP-induced neuronal cell cytotoxicity and apoptosis, which were accompanied by the expression of IKB-β and NF-κB, as well as Bax, and sustain ER stress by activation of the JNK1/2 and p38 MAPK pathways (Kuo et al., 2016)

3.5 Induction of cell death by Glutathione Depletion

Glutamic acid, glycine, and cysteine combine to produce a tripeptide known as GSH, which is a ubiquitous tripeptide that acts as an antioxidant (Hasanuzzaman, Nahar, Anee, & Fujita, 2017).The tripeptide takes part in redox activities that lessen the harm that oxygen free radicals bring to nerve cells and hence prevent the accumulation of ROS, free radicals, peroxide and lipid peroxide, mitochondrial dysfunction, impairment of dopaminergic function hence reducing the risk of Parkinson's disease (Dias et al., 2013). It is found that GSH can slightly improve motor function in PD patients and functions to metabolize iron by formation of iron complexes hence act in improving the mitochondrial impairment (Dias et al., 2013).

GSH deficiency is considered as one of the first known events in the development of neurodegenerative disorders such as Parkinson's disease (PD) and other conditions; it is believed that a GSH shortage hinders a cell's defense against reactive oxygen species (ROS), reactive nitrogen species (RNS), and H2O2 as well as its capacity to digest cellular waste (Smeyne & Smeyne, 2013). Figure 1.5 illustrates how glutathione prevents the accumulation of ROS, free radicals, peroxide and lipid peroxide, reducing the risk of Parkinson's disease. On the other hand, in vitro experiments show depletion of glutathione reduces the ETC, leading to selective impairment of mitochondrial complex I activity and ultimately causing cell death (Smeyne & Smeyne, 2013). It also impairs the ubiquitin protease system and increases inflammation by increasing IL1 and JNK signaling. Antioxidant-activated compounds have drawn a lot of

attention for their neuroprotective and cognitive-enhancing properties because of their role in the pathophysiology of Parkinson's disease (PD) caused by oxidative stress (Rahman & MacNee, 2000).Consequently, medications that possess several qualities, such as scavenging free radicals plays an important role in preventing inflammation and neuronal cell death. An important antioxidant present in both neurons and astrocytes is glutathione. It has an important function in protecting cells against ROS toxicity, which is a major factor in the demise of dopaminergic cells in Parkinson's disease.

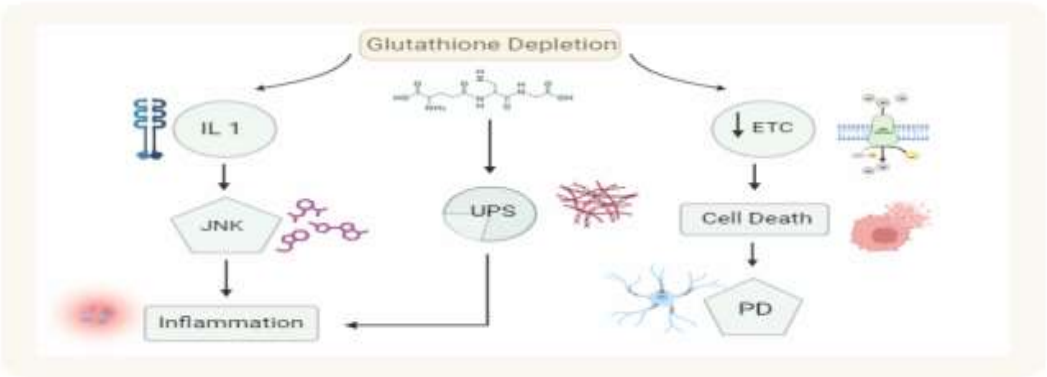

Figure 5 Induction of cell death by Glutathione depletion causing Parkinson sease

Consequently, maintaining its level may be essential to guard against the neurodegeneration associated with Parkinson's disease. Several herbal extract have been discovered that exhibits neuroprotective action by enhancing the level of GSH. According to one-research reports done in natural flies, mutant PINK1B9 Dm exhibits decreased GSH and SOD activities as well as an unexpectedly longer telomerase strand. In the PINK1B9 mutant fly, *Mucuna prueins* decreased the length of telomerase and increased GSH and SOD activities (Fu, Zhuang, Zhou, & Wang, 2015).On the other hand, treatment with *Bacopa monieri* increased endogenous glutathione production via altering the expression of Keap1, which in turn activated the nuclear factor (erythroid-derived) 2 (Nrf2) pathway (B. Singh et al., 2020). It is also found that in both neurons and astrocytes, curcumin administration increases the modifier subunit of the GSH producing enzyme, gamma glutamyl cysteine ligase (GCL), by 3–7 fold. It also raises GSH levels, most likely by improving astrocytic outflow of GSH (Biswas, McClure, Jimenez, Megson, & Rahman, 2005). Another plant extract obtained from C. *asiasta* was observed to lower MDA, a measure of oxidative stress, attenuate

the effects of MPTP, and modify the reduction of DA with increasing concentrations of GSH (Siddique et al., 2014). Research revealed that CA reduces apoptosis resulting from 6-hydroxydopamine by downregulating the inflammatory pathway of p38 and c-Jun-N this induce Nrf2-induced glutathione formation (Faridzadeh et al., 2022). Neurons and astrocytes contain glutathione, an important antioxidant which is essential for protecting cells against ROS toxicity. While, decreasing the levels of malondialdehyde (MDA), cholinesterase, nitric oxide (NO), and amyloid while increasing glutathione, which has a neuroprotective impact, moringa administration restored the dementia-like state in mice (J. Hashim et al., 2021). Chyrin, from Passion flower (Angelopoulou et al., 2020) and gingko biloba (Mohebbi et al., 2023), *Rosamarinus officinalis (Andrade et al., 2018), Zingiber officinale (Morvaridzadeh et al., 2021),* and *Withania somnifera* (Jankovic & Tan, 2020) are found to increase in level of glutathione, preventing inflammation and ubiquitin dysfunction.

3.6 Induction of inflammation

Various explorations have shown that ongoing pathways that happen in the SNpc bring about dopaminergic neuron misfortune in Parkinson's sickness (PD). The natural safe framework is enacted during Parkinson disease (PD) because of the breakdown of the blood-brain barrier (BBB). Oxidative stress, neuronal damage, ER, mitochondrial malfunction, increase in ROS, secretes

inflammatory events, including cytokines causing degeneration of neurons; this generates immune cells that activate microglia cause an increase in cytokines that activate T cells, including IL2, TNF-α, IL1, IL6, IL4, killer cell, and microglial activation that causes inflammation and cytotoxicity. Inflammation is a host-immune response against the pathogens and infection; it plays a major role in removing the foreign particles from the body by activating inflammatory mediators that is an adaptive physiological process of body to provide protection (Glass et al., 2010; Tufekci, Meuwissen, Genc, & Genc, 2012). Overexpression of these mediators resulting from any cellular or genetic neurodegenerative diseases result in progressive neuro-inflammation causing neuronal loss and cytotoxicity. These neuro-inflammation is considered a major factor in showing the symptoms of various neurodegenerative diseases including PD, that is caused due to excessive buildup of free radicals due to increase in oxidative stress within the body, that contributes in showing the symptoms of memory loss, neuron dysfunction, mitochondrial dysfunction, dopaminergic neuron death and cell death Th1/Th2 cytokines (Glass et al., 2010; Tufekci et al., 2012)

Additionally, it triggers TLR4-mediated inflammation, which increases the Major Histocompatibility Complex in Parkinson's disease and induces inflammation in the brain and intestines. Similarly, mutant A53T synuclein overexpression induce pervasive mitochondria macroautophagy defect and promote dopamine neuron degeneration(Yi, Wang, Wang, Ho, & Zhang, 2022). Activated microglia leading to increase in levels of cytokines such CD4 and CD8, Th1/Th2, TNF- α interferon- γ, interleukin-1β (IL-1β) and activation of cascade 3, 9 in substantia nigra. Additionally, it is reported that this lead to inflammation, lipid peroxidation, and apoptosis through their actions on epidermal growth factor, oxides, cyclooxygenase-2, JNK phosphorylation, transcription factor, tumor necrosis factors, and cytokines like interleukin IL-1 β and IL-6 that is responsible for causing memory loss, neuronal dysfunction in people suffering from PD (Tansey et al., 2022).

Numerous inflammatory genes are regulated by NF-κB, which is thought to be the master switch necessary for these genes' expression (Glass et al., 2010). Therefore, one therapeutic strategy for the treatment of Parkinson's disease (PD) is to target and turn off the activity of NF-κB.NF-κB is usually inhibited in the cytoplasm by inhibitor proteins called IκBs (inhibitors of κB) when there are no stimuli present. The NF-κB pathway can be activated by a variety of stimuli, including pro-inflammatory cytokines (e.g., TNF-α, IL-1β), bacterial or viral products (e.g., lipopolysaccharide, LPS), or stress signals. IκB kinase (IKK) is activated when the pathway is activated. IKK marks IκB for ubiquitin system and eventual destruction by phosphorylating it (Tansey et al., 2022; Tufekci et al., 2012; Yi et al., 2022). Degradation of IκB allows the liberated NF-κB to translocate into the nucleus. NF-κB enters the nucleus and binds to specific DNA sequences known as κB sites, leading to the transcription of target genes (Oeckinghaus & Ghosh, 2009). In the nucleus, NF-κB regulates the transcription of genes involved in immune responses, inflammation, cell survival, and other cellular processes. Target genes include those encoding cytokines, chemokines, adhesion molecules, and anti-apoptotic proteins. Negative feedback mechanisms, such as the synthesis of IκB proteins, help terminate the NF-κB response and prevent sustained activation. Various herbs have shown to be effective to show effects in preventing inflammation by regulating the NF-κB response and decreasing the level of cytokines (Oeckinghaus & Ghosh, 2009).

By suppressing the expression of NF-KB, MP reduces inflammation, therefore preventing inflammation brought on by toxins like 6-OHDA and MPTP. Additionally, they reduce inflammation by enhancing the production of DAT and reducing the expression of proinflammatory cytokines such as interleukin-1 beta, TNF-α, and enzymes like iNOS (Manyam et al., 2004; Sachchida N Rai et al., 2017). While BM inhibits iNOS and hence has an anti-inflammatory impact, it also greatly reduces the levels of protein carbonyl and lipid peroxidation caused by colchicine and restores the function of various antioxidant enzymes (B. Singh et al., 2020).Green tea's EGCG extract reduces oxidation via blocking 6-OHDA-induced inflammatory mediators including Cox-2 and iNOS, either directly by blocking MPP+ absorption or indirectly by preventing NFKB from binding to iNOS transcription. By directly suppressing COX-2, which also prevents the synthesis of dopamine quinone, further oxidation is avoided (Bortolanza et al., 2015; J.-Y. Choi et al., 2002; J. S. Kim, Kim, Jeong-Ja, & Jeon, 2010; Mollace, Muscoli,

Masini, Cuzzocrea, & Salvemini, 2005). Additionally, they inhibit the oxidative cell death induced by Aβ, so averting neurodegeneration, they further prevent inflammation by down regulating the expression of pro-inflammatory mediators such as tumor necrosis factor, interleukin-1 and 6, interferon, CD4 and CD8 (Zhou, Zhu, & Liang, 2018). Curcumin inhibits histone acetylase or activates histone deacetylase activity, which in turn inhibits inflammation by preventing AP-1 activation mediated by TNF and IL-1a (Hassan et al., 2019). Curcumin also interacts with DNA binding motif and inhibits the JNK 1/2 and c-Jun phosphorylation as well as the activation of caspase 3 by acting on the c-Jun N terminal Kinase JNK pathway (Zhang et al., 2019). Curcumin from Curcuma longa undergo detoxify ROS by activating anti-apoptotic gene Bcl-2 and inhibiting iNOS expression (Hu et al., 2023). While rosemary functions to reduce oxidation by boosting the activity of GPx and CAT, carnosol, derived from Rosmarinus officinalis, is a powerful antioxidant that prevents Nrf2-induced glutathione production, leading to down regulation of p38 and c-Jun N-terminal kinase signaling pathways. By inhibiting the oxidative process, it reduces the damage caused by Aβ on nerves and acts as an anti-inflammatory agent (Hong et al., 2021). C.asiatica, Salvia miltiorrhiza and moringa have anti-inflammatory properties that stem from their inhibition of Aβ-induced neuroinflammation and oxidative stress, as well as their activation of several anti-inflammatory mediators (J. Hashim et al., 2021; Mundkar, Bijalwan, Soni, & Kumar, 2022). Furthermore, chyrin from passion flowers acts as a cellular antioxidant and radical scavenger by down regulating pro-inflammatory cytokines like TNF-α, IL-1β, and IL-6, which inhibit cognitive defects and lipid peroxidation, as well as the NF-κB pathway and peroxisome proliferator-activated receptor gamma (PPARγ) transcriptional activity (Zeinali, Rezaee, & Hosseinzadeh, 2017). Chyrin inhibits nitric oxide synthase (iNOS) from producing reactive nitrogen species (RNS) and prevents NO levels from rising, which in turn inhibits dopaminergic neuronal death and parkinsonian symptoms(Kavya et al., 2006; Zeinali et al., 2017) . Numerous naturally occurring substances, such as those present in Ginkgo biloba plants, have been investigated for their capacity to alter the NF-κB pathway. By controlling the nuclear translocation or activation of NF-κB, these substances may have anti-inflammatory effects by controlling the expression of genes that promote inflammation. Huperzine A, which has been studied for its possible neuroprotective benefits, notably in the setting of Parkinson's disease (PD), is found in the plant Huperzia serrata. The possible neuroprotective benefits of huperzine A, such as its defense against oxidative stress and programmed cell death (apoptosis), have been investigated (Farooqui, 2019). While Cinnamon and Cinamaldehyde also function to supresses tumor necrosis factor, (IL-1β), IL-6, cytokines, microglial cell and inhibit tau aggregation to provide neuroprotective action against inflammation.(Jana et al., 2013; Khasnavis & Pahan, 2012; Momtaz, Hassani, Khan, Ziaee, & Abdollahi, 2018; Xu et al., 2020)

3.7 Neurotrophic factors

Neuroprotective action refers the substances that protect neurons from damage, they encourage neuron growth and development, such neurotrophic factors include Neurotrophic growth factor (NGF), brain-derived neurotrophic factor (BDNF) and glial cell-derived neurotrophic factor (GDNF) (Turrini, Zaccaria, & Aloe, 2001). BDNF protein is responsible for memory, learning, and mood regulation, it is present in blood and brain region as pro-BDNF that is transformed into mature form by proteases(Miranda, Morici, Zanoni, & Bekinschtein, 2019). While NGF is responsible for growth, differentiation and maturation of central and peripheral neurons, and maintain normal functioning of nervous system and It is present in the cells of medullary layer of thymus. While GDNF play a role in development of intrahippocampal circuitry and in neuronal function and maintenance, it is present in brain and support brain cell in survival especially in PD (Miranda et al., 2019; Turrini et al., 2001). Reduced production of brain-derived neurotrophic factor (BDNF), GDNF, NGF a key neurotrophic factor in the neurogenesis process, has been linked to worse motor function in Parkinson's disease (PD) patients. Tyrosine receptor kinase B (TrkB), a cell surface receptor, is bound by BDNF to initiate its activity. This binding, when phosphorylated and activated, leads to the cell survival mechanism by further activating several intracellular pathways, such as MAPK, Akt, and PLC signaling(Jin, 2020). It has been discovered that α-synuclein interacts with TrkB in the Parkinson's

disease state, inhibiting its activity and ultimately leading to the death of dopaminergic neurons. Moreover, PD patients' brains have a lower amount of BDNF, and GDNF demonstrating the neuroprotective properties of these proteins. In addition to that, the induction of tumor necrosis factor and transcription factor is involved in causing cytotoxicity and neuronal death in PD, which is overexpressed due to oxidative stress created by oligomers buildup (Jin, 2020).

The expression of neurotrophic factors, including Brain-Derived Neurotrophic Factor (BDNF), is crucial for the survival, growth, and maintenance of neurons in the nervous system. BDNF is particularly important for promoting the survival and differentiation of neurons, synaptic plasticity, and overall brain health. The gene encoding BDNF is transcribed into mRNA in the cell nucleus. BDNF mRNA is transported from the cell nucleus to the cytoplasm, where it will be translated into the BDNF protein. BDNF mRNA is translated by ribosomes in the cytoplasm, resulting in the synthesis of the BDNF protein(Lekk et al., 2023). The newly synthesized BDNF is initially in an inactive precursor form called proBDNF. ProBDNF undergoes post-translational processing to produce mature and active BDNF. This processing involves cleavage of proBDNF into mature BDNF, which is released extracellularly (Jin, 2020). Mature BDNF binds to its high-affinity receptor, tropomyosin receptor kinase B (TrkB), on the surface of neurons. This binding activates the TrkB receptor. TrkB receptor activation triggers intracellular signaling pathways, including the mitogen-activated protein kinase (MAPK) pathway and the phosphoinositide 3-kinase (PI3K) pathway. Activation of these pathways leads to various cellular responses, including the promotion of neuronal survival, growth, and differentiation. Additionally, BDNF signaling is

involved in synaptic plasticity, which is crucial for learning and memory. BDNF activation can also lead to changes in gene expression through transcriptional regulation (Bathina & Das, 2015; Lekk et al., 2023). This involves the activation of transcription factors, such as cAMP response element-binding protein (CREB), which binds to the BDNF gene promoter region and enhances BDNF transcription. The BDNF signaling pathway includes feedback mechanisms to regulate its own expression and maintain homeostasis in the nervous system (Bathina & Das, 2015).Enhancing BDNF expression is considered beneficial for promoting neuroprotection and cognitive function. Lifestyle factors such as exercise, a healthy diet, and certain natural compounds, like those found in some herbs (e.g., Ginkgo biloba (Mohebbi et al., 2023), Ashwagandha (Gopukumar et al., 2021), Hericium erinaceus and Cinnamomum verum(Chuang, 2004)), have been studied for their potential to modulate BDNF expression, while Rosmarinic acid and quercetin derived from Salvia officinalis is involved in increasing BDNF level. While flavonoids are involved in secretion of neutrotrophic factors, but more research is needed to understand their mechanisms and therapeutic implications(Lopresti, 2017).

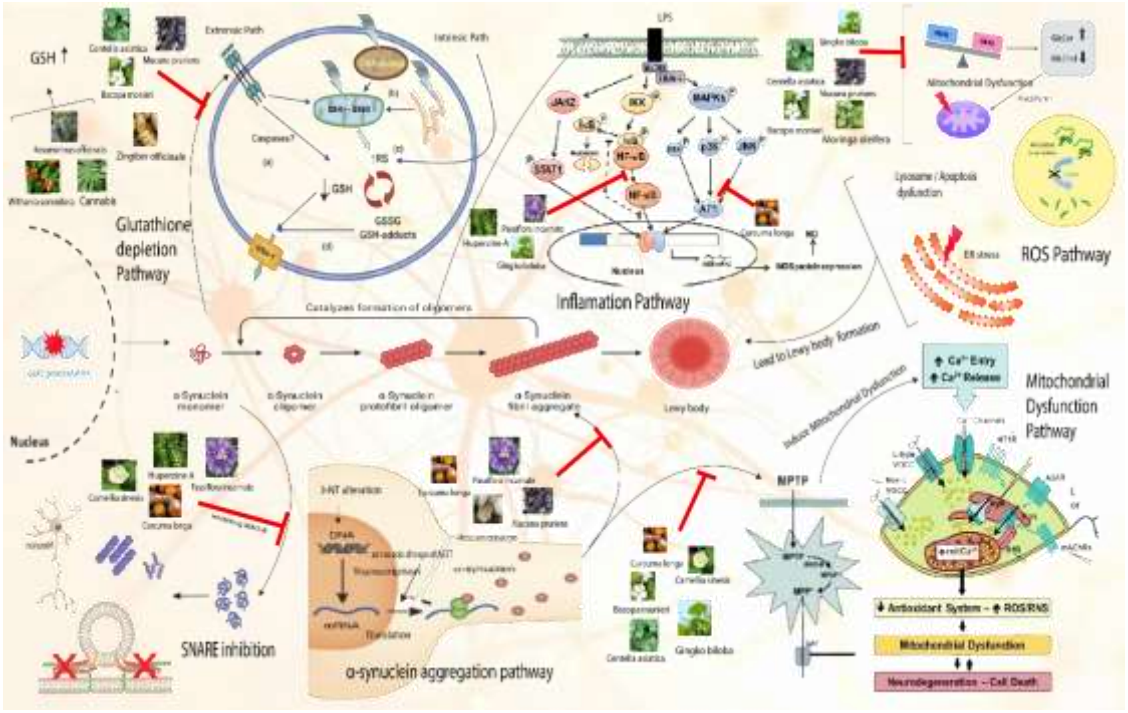

Figure 6 Plants acting on active targets of Parkinson Disease

Methodology:

This review was conducted using a structured narrative approach to summarize and critically evaluate existing evidence on the neuroprotective effects of medicinal plants and their phytochemicals in Parkinson's disease (PD). A comprehensive literature search was performed using PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar databases. The search strategy incorporated combinations of relevant keywords and Boolean operators, including: "Parkinson's disease" OR "Parkinsonism" AND "herb" OR "phytochemical" OR "phytotherapy" OR "neuroprotection" OR "oxidative stress" OR "mitochondrial dysfunction" together with specific plant names such as Mucuna pruriens, Curcuma longa, Withania somnifera, Ginkgo biloba, Centella asiatica, and Passiflora incarnata.

Articles published in English up to the year 2025 were considered. Studies were screened based on title and abstract relevance, followed by full-text evaluation. Experimental studies (both in vitro and in vivo) and clinical investigations addressing molecular mechanisms associated with PD were included, while unrelated or incomplete reports were excluded. Additional references were identified through citation tracking of selected papers.

Key data extracted from eligible studies included plant source, bioactive constituent(s), type of experimental model, dose or concentration used, observed outcomes, and proposed neuroprotective mechanisms. Data were then synthesized descriptively and organized under mechanistic categories such as oxidative stress modulation, mitochondrial protection, inhibition of α-synuclein aggregation, and anti-inflammatory activity.

4. PLANTS INVOLVED IN TREATMENT OF PARKINSON DISEASE

Table 1: Plants involved in treatment of PD

Plant Name	Picture	Active ingredient	Use	MECHANISM OF ACTION

Velvet bean (*Mucuna pruriens)*		Levodopa (L-Dopa)	L-Dopa can cross the blood-brain barrier and replenish dopamine levels.	Attenuate iNOS expression Inhibit NF-KB activity Increase pAKT1 activity Lipid peroxidation. (Lampariello et al., 2012; Poddighe et al., 2014; Radder et al., 2019)
Ginkgo *(Ginkgo biloba)*		Flavonoids Terpenoids Ginkgolic acid Ginkgetin	Antioxidant Anti-inflammatory effect Protect neurons against oxidative stress and inflammation.	Increases autophagosomes Decreases level of SUMO1 level Inhibit MPP+ formation. (Mohebbi et al., 2023)
Brahmi (*Bacopa monnieri*)		Bacosides,	Antioxidant Neuro-protective]] Reduces oxidative damage Promote neuronal health.	Decrease reactive oxygen species hence normalizes oxidative markers and an increase in the activity of antioxidant enzymes, hence decreasing *α*-synuclein aggregates. (Sekhar, Viswanathan, & Baby, 2019; B. Singh et al., 2020)
Turmeric (*Curcuma longa*):		Curcumin	Antioxidant Anti-inflammatory It reduces inflammation and oxidative stress.	Curcumin scavenges inhibited inflammatory cytokine, preventing α-synuclein aggregation, reduces the damage to dopamine neuron, and create a balance to decrease oxidative stress. (Ammon & Wahl, 1991; Khatri & Juvekar, 2016; J. Yang, Song, Li, &

				Liang, 2014; Yi et al., 2022)
Green tea (*Camellia sinensis*):		Epigallocatechin gallate (EGCG) Saponin Theacrine	Antioxidant Neuroprotective Restore mitochondrial function	Saponin increase dopamine and tyrosine hydroxylase +ve cells Theacrine activate SIRT3 to promote SOD2 deacylation (Goetz, 2011; Prasanth et al., 2019)
Ashwagandha (*Withania somnifera*):		Withanolides	Antioxidant Anti-inflammatory Protect neurons Improve motor activity Reduce inflammation.	Enhances Catecholamines Reduces free radical generation Attenuation of activated astrocytes Enhances Bcl2 expression and decreases Bax causing apoptotic activity (Gopukumar et al., 2021)
Chinese club moss *(Huperzia serrate)*		Huperzine A	Improve motor function Ameliorate cognitive abnormalities	The compounds inhibit acetylcholinesterase, an enzyme that breaks down acetylcholine. By inhibiting this enzyme, huperzine A may help increase acetylcholine levels in the brain. (X. Guo et al., 2023)
Lion's mane mushroom (*Hericium erinaceus*)		Hericenones Erinacines	Nerve growth Neuron Maintenance	The compounds may stimulate nerve growth factor (NGF) production. NGF is essential for the growth and maintenance of neurons. (Kuo et al., 2016; Y.-J. Lin et al., 2023)

Sage (*Salvia officinalis*) (*Salvia miltiorrhiza*)		Rosmarinic acid Quercetin Flavonoids	Antioxidant Anti-inflammatory Protect neurons Reduce inflammation.	Rosmarinic acid and quercetin is involved in increasing BDNF level. While flavonoids are involved in secretion of neutrotrophic factors Salvia miltiorrhiza reduces production of ROS and ameliorate mitochondrial stress (Lopresti, 2017)
Drumstick tree (*Moringa oleifera*)		Phenolics Flavonoids Isothiocyanates	Antioxidant Anti-inflammatory action Reduce oxidative stress and inflammation. Neuroprotective action	They are potent NrF2 activators and exhibit antioxidant effect by up-regulation of ARE-driven genes, this up-regulation also decrease inflammatory response through NFxB pathway(Guon & Chung, 2017; J. Hashim et al., 2021; Ndlovu et al., 2023; Pareek et al., 2023)
Gotu kola (*Centella asiatica*)		Triterpenoids Epigallocatechin gallate	Antioxidant effect Neuroprotective effects. Protect neurons Reduce oxidative damage	Triterpenoids undergo potent activation of the Nrf2/ARE pathway hence rendering neuroprotective activity. While epigallocatechin gallate redirects amyloid fibril formation of alpha synuclein into non-pathogenic pathway 13 (Siddique et al., 2014)

Cannabis		Cannabinoids; Tetrahydrocannabinol (THC) Cannabidiol (CBD).	Neuroprotective Anti-inflammatory effects.	Cannabiniods down regulates GSK-3beta, the main inhibitor of WNT/Beta-catenin pathway to control oxidative stress and inflammation, it also reduces apoptosis by reduction of Bax and caspase-3 (Al-Khazaleh et al., 2024; B. Singh et al., 2020)
Rosemary (*Rosmarinus officinalis*)		Rosmarinic acid Carnosic acid Carnosol Abietane-type phenolic diterpenes	Antioxidant Anti-inflammatory properties. Protect neurons Reduce inflammation	Carnosic acid undergoes induction of phase 2 enzymes by activation of NLRP3 activation hence acting as anti-oxidant and anti-inflammatory compound. (Faridzadeh et al., 2022)
Ginger (*Zingiber officinale*)		6-Gingerol 6-Shogaol	Antioxidant Anti-inflammatory effects. Reduce inflammation and oxidative stress.	6-shogaol increase neurotrophic factor hence undergoing proliferation of glial cells. They protect neurons by increasing acetyltransferase and choline transporter 11, they also inhibit production of NO, prostaglandin E, Proinflammatory cytokines(Bode & Dong, 2011; Mao et al., 2019; Morvaridzadeh et al., 2021)

Cinnamon (*Cinnamomum verum*)		Cinnamaldehyde	Antioxidant Anti-inflammatory properties. Protect neurons Reduce inflammation.	They undergo autophagy regulation, antioxidant effects, up regulation of Parkinson, DJ-1, glial cell line-derived neurotrophic factor and modulate NF-κB pathway. It is also involved in preventing synuclein aggregation (Kawatra & Rajagopalan, 2015; Mishra, Bhatti, Singh, & Ishar, 2010; Mollazadeh & Hosseinzadeh, 2016; Peterson et al., 2009; Pasupuleti Visweswara Rao & Siew Hua Gan, 2014)
Passionflower (*Passiflora incarnata*)		Flavonoids Alkaloids	Antioxidant Anti-inflammatory Protect neurons Reduce inflammation	Chrysin is a flavonoid, is involved in reduction of aggregation of synuclein. It also diminish internal cellular reactive oxygen specie. (Britannica, 2020; Janda, Wojtkowska, Jakubczyk, Antoniewicz, & Skonieczna-Żydecka, 2020; Patel et al., 2009)

4.1 Mucuna pruriens

Mucunia pruriens is a hairy, climbing legume from Fabaceae family that grows in tropical and subtropical climates. It is sometimes referred to as an itchy bean, velvet bean, or sea bean. Studies have shown that its main constituents include alkaloids, flavonoids, polyphenols, peroxide or hydro-peroxide derived from roots, leaves, seeds, and stems, are effective against 200 diseases (Katzenschlager et al., 2004; Lampariello et al., 2012). Additionally, a 2018 study found that essential phytochemicals of MP such as Levodopa, some carbohydrates and amino acids are found to be useful in treating the symptoms of Parkinson's disease, as it exhibit antioxidant, anti-inflammatory, neuroprotective, improve locomotor behavior, redox status, helping in neural regeneration and survival (Poddighe et al., 2014; Yadav, Prakash, Chouhan, & Singh, 2013) with enzyme-boosting properties. It is studied that mitochondrial protective action is shown by reducing the level of neurotoxins such as MPP+ and 6-OHDA, according to research by Solari et al., mucuna was responsible for improving mitochondrial defects and recovers serotonergic system that make it a useful treatment for Parkinson's disease(Verma, Balakrishnan, & Dixit, 1993) (Katzenschlager et al., 2004; Manyam et al., 2004). While anti-oxidant property is shown by reducing the level of iNOS and increasing the level of catalase and superoxide dismutase the enzymes which not only reduce oxidation but also have an effect on lipid peroxidation, similarly anti-inflammatory property is shown by undergoing gene expression and reducing level of cytokines (Adepoju & Odubena, 2009; Manyam et al., 2004; Verma et al., 1993) Overall Mucuna have its role in preventing mitochondrial dysfunction, calcium imbalance, aggregation, inflammation, dopamine level. (Sachchida N Rai et al., 2017)

4.2 Ginkgo biloba

The gymnosperm tree species known as *Ginkgo biloba*, which is native to East Asia, is frequently called the maidenhair tree. (Chassagne, Huang, Lyles, & Quave, 2019). Ginkgo nuts, leaves, and seeds have long been utilized as herbal remedies for a variety of ailments. Numerous components, including trilactones and flavonoid glycosides, beta estradiol, and terpenoids like ginkgolides and bilobalide, which exhibit anti-oxidant and neuroprotective properties by reducing or inhibiting monoamine oxidase activity, are linked to the biological activity of ginkgo (Akaberi et al., 2023; Mohebbi et al., 2023). Gingko was found to have a neuroprotective effect against 6 OHDA, and MPP+ toxins in a 2004 study. This means that, with only moderate side effects, gingko is useful against PD, dementia, vasoocclusive disorders, and cochlea-vestibular disorders. Additionally, they possess the ability to undo the harm caused by oxidation. Memory loss and cognitive impairments are improved by gingko extract (EGb761). Ginkgetin was found to inhibit caspase-3, Bc-12/Bax pathway, and reduce intracellular ROS levels. It also plays a significant role in preventing the symptoms of A53T α-synuclein aggregates and improves locomotor activity, maintains dopamine transport, enhances cell viability, and reduces cell apoptosis in SY5Y cells treated in vitro with recombinant monomeric or aggregated α-synuclein (Akaberi et al., 2023; Mohebbi et al., 2023).

4.3 Bacopa monnieri

Bacopa monnieri also known as Brahmi, is an Indian Ayurvedic medicinal plant from Scrophulariaceae family and is found to give anti-oxidant, anti-inflammatory effect. The main constituents' include alkaloids, saponins, triterpenoids that

improves motor outcomes, regulate neuroinflammation and help to provide neuroprotective effect to dopamine neurons (Siddique et al., 2014). It has an effect on cytokinies such as TNF-alpha, IL-6, IL-1 beta and nitric oxide. Bacoside-A enhances the activity of superoxide and catalase glutathione peroxide and reductase, while study conducted in 2017 showed that ethanolic extract has anti-apoptotic effect by acting on nitric oxide (Sekhar et al., 2019). BM reduces NO which contributes to cell death as it lowers the level of NO by inhibiting the activity of enzyme nitric oxide synthases (iNOS) to produce anti-inflammatory effect and provide protection from neuron-inflammation. Bacoside, bacopasides and bacosaponins also provide protection by inhibiting the breakdown of MPTP to MPP+ by inactivating enzyme monoamine oxidase B, hence making it effective remedy in PD, (Sekhar et al., 2019; Siddique et al., 2014)

4.4 Curcuma longa:

Vogel and Pelletier, who were the first to isolate it from Curcuma longa rhizomes in 1815, Curcuma longa is a perennial blooming plant, Curcuma is a native of Southeast Asia and a member of the Zingiberaceae (ginger) family(Ammon & Wahl, 1991; Karłowicz-Bodalska, Han, Freier, Smoleński, & Bodalska, 2017). Due to its many anti-oxidant, anti-inflammatory, anti-cancerous, free radical scavenging, and neuro-protective qualities, it has been utilized in traditional medicine for a number of years (Allegra et al., 2017; Bundy, Walker, Middleton, & Booth, 2004; Chang, Wang, Li, & Wu, 2016; Chaurasia, Chaubey, Patel, Kumar, & Mishra, 2016; Gunes et al., 2016; Motterlini, Foresti, Bassi, & Green, 2000; Srivastava, Saksena, Khattri, Kumar, & Dagur, 2016; Surh et al., 2001). Turmeric, flavonoids, and curcumin are examples of polyphenols that have gained attention due to their lipophilic nature, which enables them to cross the blood-brain barrier and makes them an effective weapon against neurodegenerative diseases and toxins of central and peripheral systems (Bala, Tripathy, & Sharma, 2006; Jiang et al., 2007; Mohebbati, Khazdair, & Hedayati, 2017; Wang et al., 2005). Comparably, elevated ROS levels in Parkinson's disease (PD) cause neuronal injury, mitochondrial malfunction, and decreased ATP levels. On the other hand, curcumin functions as a ROS scavenger by eliminating oxygen by donating H ion from the beta-diketone moiety. In a similar vein, curcumin inhibits protein and alpha synuclein oligomer formation. Polyphenols function by inhibiting the MOA-enzyme, which raises dopamine levels and is a useful tool in Parkinson's disease (PD) development (Khatri & Juvekar, 2016). Additionally, it is reported that they regulate inflammation, lipid peroxidation, and apoptosis through their actions on epidermal growth factor, oxides, caspase, cyclooxygenase-2, JNK phosphorylation, transcription factor, tumor necrosis factors, and cytokines like interleukin IL-1 β and IL-6 (X. W. Ma & Guo, 2017). Curcumin is an effective therapy for Parkinson's disease (PD) because, according to Yang et al., it also affects 6-OHDA by raising levels of BDNF and the Wnt/β-catenin pathway. This improves cell viability and survival and lowers neuronal death(Song, Nie, Li, & Du, 2016; F. Yang et al., 2005; J. Yang et al., 2014)

4.5 Camellia sinensis

Green tea, or Camellia sinensis, is a member of the Theaceae family. This evergreen shrub grows in temperate and tropical regions of Asia, including north Burma and southwest China (Weisburger, 1997). Epicatechin, epicatehin gallate, polyphenol, and epigallocatechin gallate are the main components that have anti-oxidant, anti-inflammatory, free radical scavenger, and neuroprotective properties. Traditionally, it was used as a home treatment to relieve stress in the body, treat headaches, and function as a relaxant. Research has demonstrated that it inhibits synuclein aggregation by attaching to the α-synuclein polypeptide chain and obstructing the

formation of oligomers(Zhao et al., 2017) (Ehrnhoefer et al., 2008). It was also found that it induces the expression of BDNF, phosphorylated PKC- α which helps in combating with PD (121). Additionally, it prevents neuronal death by up regulating and down regulating the expression of Bcl-2 and Bax, respectively (Ehrnhoefer et al., 2008; Prasanth et al., 2019). Moreover, polyphenols and catechins have an antioxidant effect; stimulate the synthesis of L-DOPA from tyrosine, so averting neuronal death, and raise dopamine levels by blocking monoamine oxidase-B. In addition to restoring calcium homeostasis, which protects mitochondrial function, and lowering iNOS levels, which in turn causes the depletion of radicals, peroxide, and superoxide, polyphenols play a significant role in antioxidant defense by inhibiting ROS species and inducing the antioxidant enzyme catalase(M. Chen et al., 2015; J.-Y. Choi et al., 2002). Additionally, by preserving the Akt signaling pathway and caspase activation, they mitigate 6-OHDA-induced toxicity and prevent glutathione depletion, which is involved in neuroprotection and prevents cellular toxicity (S. Guo et al., 2005). It is a useful herb for Parkinson's disease (PD) because it inhibits the overproduction of interleukin, cytokines, and tumor necrosis factor, which all contribute to neuroinflammation protection. By selectively inhibiting COX-2, one might further avoid dopaminergic neurodegeneration by preventing the production of oxidation species, specifically dopamine-quinone (Bortolanza et al., 2015; Ding, Ma, Man, & Lv, 2017; Mollace et al., 2005; Weisburger, 1997).

4.6 Ginger (Zingiber officinale):

Ginger belongs to the Zingiberaceae family. Its botanical name is Zingiber officinale. Native to Southeast Asia, ginger is cultivated in tropical and subtropical regions globally. Commonly known as ginger, it is also referred to as "Jiang" in Chinese (Bode & Dong, 2011). Ginger is often incorporated into herbal formulations to balance and enhance the effects of other herbs. Ginger contains various bioactive compounds, including gingerol, shogaol, zingerone, and paradol. These compounds contribute to ginger's anti-inflammatory, antioxidant, and anti-nausea properties (Mao et al., 2019). Recent studies have explored the potential of 6-shogaol, a bioactive compound in ginger, for Parkinson's disease treatment. 6-shogaol has been investigated for its neuroprotective effects in PD by modulating oxidative stress, neuroinflammation, and mitochondrial dysfunction. Studies suggest that 6-shogaol may enhance the activity of antioxidant enzymes, reduce inflammatory markers, and protect against dopaminergic neuron degeneration (Mao et al., 2019).

4.7 Cinnamon (Cinnamomum verum)

Cinnamon is derived from the bark of Cinnamomum verum, belonging to the Lauraceae family (P. V. Rao & S. H. Gan, 2014). Native to Sri Lanka, Cinnamomum verum is cultivated in various tropical regions, including India, Indonesia, and the Caribbean (162). Commonly known as cinnamon, it is referred to as "Rou GUI" in Traditional Chinese Medicine (TCM) (Mollazadeh & Hosseinzadeh, 2016).In TCM, cinnamon is utilized for its warming properties and is believed to invigorate circulation and dispel cold. Cinnamon contains several bioactive compounds, including cinnamaldehyde, cinnamic acid, and cinnamyl alcohol (Kawatra & Rajagopalan, 2015; Mishra et al., 2010; Pahan, Sheikh, Namboodiri, & Singh, 1997). Cinnamic acid is transformed to sodium benzoate in the liver. Because cinnamic acid may penetrate the blood-brain barrier, it raises the serum level of sodium benzoate that shows neuroprotective effect by modulating mevalonate pathway that reduces mutation of DJ-1 (Jana et al., 2013; Khasnavis & Pahan, 2012). While Cinnamon and cinnamaldehyde prevent oxidation by acting as an anti-oxidant and modulate the process of autophagy, mitochondrial function by decreasing the neurotoxins such as MPP+ and 6-

OHDA(Bae, Choi, & Jeong, 2018; Modi, Jana, Mondal, & Pahan, 2015; Momtaz et al., 2018; Ramazani et al., 2020). It also suppresses cytokines, tumor necrosis factor, iNOS, Interleukin factor, tau and synuclein aggregation along with Aβplaques toxicity that overall provide neuroprotection by reducing inflammation (Frydman-Marom et al., 2011; S.-C. Ho, Chang, & Chang, 2013; Peterson et al., 2009).

4.8 Passion Flower (Passiflora incarnata):

Passionflower also known as Maypop belongs to the family Passifloraceae (Britannica, 2020) .It is native to the southeastern United States. While passionflower is not native to China, it has been used in traditional Chinese medicine for its calming properties(Britannica, 2020; Patel et al., 2009). It is often recommended for treating insomnia, anxiety, and nervousness (Janda et al., 2020). It contains constituents such as Flavonoids (e.g., quercetin, kaempferol), Alkaloids (e.g., harman, harmol), Glycosides, Essential oils and phenolic chemicals. Chrysin is a flavonoid found in passionflower, and it has been studied for its potential neuroprotective effects in Parkinson's disease. The potential neuroprotective effects of chrysin in Parkinson's disease may be attributed to its antioxidant and anti-inflammatory properties. It may also modulate certain signaling pathways associated with neuronal survival and function (Angelopoulou et al., 2020; Biswas et al., 2005; Kavya et al., 2006; Zeinali et al., 2017)

4.9 Cannabis (Cannabis sativa):

Indigenous to Central Asia but now cultivated worldwide, Cannabis belonging to the family Cannabaceae, has been used in traditional Chinese medicine for various purposes, including pain relief and reducing inflammation (Hodgson, 2012). However, its use is controversial and restricted due to legal and cultural considerations. It contains the constituents Cannabinoids: Including THC (tetrahydrocannabinol) and CBD (cannabidiol), terpenes: Aromatic compounds that contribute to the plant's fragrance, flavonoids: Phytonutrients with antioxidant properties Cannabidiol (CBD) has been explored for its potential therapeutic effects in Parkinson's disease (Al-Khazaleh et al., 2024). The potential neuroprotective effects of CBD in Parkinson's disease are believed to involve modulation of the endocannabinoid system and anti-inflammatory properties. CBD may interact with receptors in the brain, reducing neuroinflammation and oxidative stress, which are implicated in Parkinson's disease (Al-Khazaleh et al., 2024; K. Singh et al., 2023).

4.10 Rosemery (Rosmarinus officinalis):

Rosmarinus officinalis (family Lamiaceae) one of the oldest Mediterranean shrubs has a powerful pungent aroma with dark green elongated leaves and white or purple flowers. It belongs to the Lamiaceae family (H. Kumar & Salminen, 2016). It has been used in traditional Chinese medicine for various purposes, including improving circulation, digestion, and memory (H. Kumar & Salminen, 2016). It includes Terpenes: Including camphor, cineole, and pinene, flavonoids: such as diosmin and luteolin, phenolic Acids: Rosmarinic acid. Carnosic acid, found in rosemary, has been studied for its potential neuroprotective effects (Andrade et al., 2018), including in the context of Parkinson's disease. Carnosic acid's potential neuroprotective actions involve antioxidant properties and modulation of cellular signaling pathways associated with inflammation and oxidative stress. These effects may contribute to its potential therapeutic benefits in Parkinson's disease (Mirza, Zahid, & Holsinger, 2023). Similarly rosemaric acid act as neurotropic factor that have effect in reducing aggregation, plague

formation, improving mitochondrial function, along with decreasing inflammation and increasing glutathione level (Caputo et al., 2021; Ghaffari et al., 2014; Hong et al., 2021; Iuvone et al., 2006; Lopresti, 2017; Mirza et al., 2021).

Conclusion:

Numerous herbal plants and their phyto-chemicals have various potential mechanisms useful to PD models such as inhibiting α-synuclein aggregation, antioxidants and mitochondrial protective, modulation of neuro-inflammation and neuro-trophic signaling. Some of the plants such as e.g. Mucuna pruriens, Camellia sinensis, Curcuma longa, Bacopa monnieri and Withania somnifera have robust preclinical evidence on neuroprotection but limited clinical evidence both in quality and quantity. Standardized extracts, high quality RCTs and herb-drug interaction analyses with levodopa and MAO-inhibitors should be priorities for future research and development. Most of the selected phytochemicals may prove beneficial adjuvants to standardized regimens and well-designed clinical trials, for which collaborational research is required. This can lead to better future treatment on plants.

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