Unravelling the role of nutraceutical supplements in treatment of Parkinson's Disease

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Abstract: Parkinson's Disease (PD) causes motor dysfunction that usually begins in the elderly population. The prevalence rate of PD is increasing significantly. Currently available therapies are able to manage the disease, however, they have certain side effects associated with long term usage. Hence, there is a dire need to bring therapies that can offer good treatment to PD with less side effects. Recent research has revealed that food supplements which are specifically rich in antioxidants and vitamins have shown better efficacy against PD with a better safety profile. Hence, the present study focuses on the role of nutraceuticals in treatment of PD. Nutritional supplements targeting PD pathology were explored between 2016 and 2022 through Scopus, google scholar and PubMed. The review deciphered the neuroprotective benefits of vitamins, minerals, natural compounds, and phytochemicals that might procrastinate or help in the prevention of PD's progression by targeting some of the major pathological mechanisms such as oxidative stress, neuroinflammation, misfolding of alpha-synuclein, and mitochondrial dysfunction. Various studies indicating the potential of nutraceutical supplements are discussed in detail.

1 Introduction

Parkinson's Disease (PD) is a progressive and an age-dependent neurodegenerative disorder that predominantly affects the dopaminergic neuronal system in the Substantia nigra (SN) region of the brain gradually causing its deterioration. This deterioration gives rise to motor abnormalities in a PD affected patient causing tremor, bradykinesia, akinesia, postural instability, slurred speech etc. Recent research has also enlightened the occurrence of non-motor dysfunctions in an individual that got initiated in the advanced stage of PD. It comprises mainly of cognitive dysfunction, constipation, sleep disorder, depression, anxiety etc. PD is known to affect at least 0.3% of the worldwide population and over 3% of those over 80 years of age. PD ranges from 5 to >35 new cases per 100,000 individuals yearly as per a worldwide incidence[1], [2], probably reflecting to the clear discrepancies in the demographics of participants in the research, or methodology. Before 50 years of age, PD is rare[3], but a 5–10 fold increase in the incidences are observed from the sixth to the ninth decade of life[4]. Overall, the estimated 0.3% global prevalence was seen to rise rapidly to more than 3% in people over the age of 80[5].

1.1 Cardinal symptoms

The symptoms of PD gradually start showing up with worsening over time and with worsening comes inevitable consequences, for instance, difficulty in walking and talking to begin with, accompanied by memory difficulties, depression, mental and behavioural changes, sleep problems, and fatigue[6], [7]. PD has the ability to affect both men and women with 50 percent more cases observed in men than women.Age isone of the major risk factors for PD with its first symptomatic appearance starting at the age of 60, but 5-10% of PD people have "early-onset" typically beginning before the age of 50, with the latter being more often and is specifically linked to specific gene mutations[8]. Neuronal or nerve cell impairment producing dopamine (DA) in thearea of the brain controlling movement is responsible for causing PD. Some of the earlier indications of PD includes the difficulty of getting out of a chair, alteration in the rate of speech which is either too fast of too sluggish[9]. Parkinsonian gait generally develops in people with PD that includes a tendency to lean forward, reduced swinging of the arms, and small quick steps as if hurrying forward, trouble in continuing/initiating movement. One side of the body/limb is often affected in PD with both sides getting affected as the disease progresses. The nerve endings that produce norepinephrine, the main chemical messenger of the sympathetic nervous system, controlling functions such as heart rate and blood pressure are lost in people suffering from PD[10], which quite effectively explains the non-motor symptoms of PD like fatigue, reduction in food digestion, and a sharp drop of blood pressure after a person rises from a seated or lying-down position[10], [11].

1.2 PD risk factors

An advancing age, nearly 60 is the biggest risk factor for developing PD. PD is evidenced to be more prevalent in men than in the in women[12], [13]. PD risk is high in individuals with a parent or sibling who is affected. Medical experts believe that PD risk may also be triggered by environmental causes. For instance, exposure to farming chemicals, like pesticides and herbicides[14]; Vietnam-era exposure to Agent Orange[15]; and working with heavy metals, detergents and solvents etc[16]. Moreover, repeated head blows is likely to increase one's risk of developing PD, although evidences supporting this fact is still ambiguous[17].

1.3 PD pathogenesis

The most prevalent contributing factors for PD pathogenesis includes the following:

1.3.1 Oxidative stress

The dopaminergic neurons substantia nigra are particularly vulnerable to oxidative stress because of the toxins produced in the metabolism of DA[18]. DA can spontaneously oxidise into harmful hydrogen peroxide and superoxide radicals (dopamine-quinone species) at neutral pH levels[18].. Monoamine oxidase enzyme can deaminate dopamine into harmless metabolite (3,4-dihydroxyphenylacetic acid)[19]. Superoxide dismutase enzyme in the presence of nitric oxide can convert superoxide which is particularly not a reactive molecule into labile per radicals or hydrogen peroxide[20]. Iron can catalyse a reaction process, which can convert hydrogen peroxide to hydroxyl radicals which are cytotoxic in nature. In the substantia nigra the quantity of hydrogen peroxide was found to be in a higher levels[21]. Functional alterations in proteins, DNA and lipids are caused by reactive oxygen species. In turn, lipid damage, leads to membrane integrity loss and increased permeability to calcium, promoting excitotoxicity[22]. NADPH oxidase (NOX) is an enzyme that is responsible for dopamine neurotoxicity and is the key source of cellular reactive oxygen species (ROS)[23]. In PD patients, an increase of NOX can be observed in the substantia nigra part[24]. The crosstalk that takes place between NOX1 and microglial NOX2 intensifies the neuroinflammatory response[25]. The structure of various nutraceuticals that are used to treat oxidative stress/PD are shown in Fig.1.

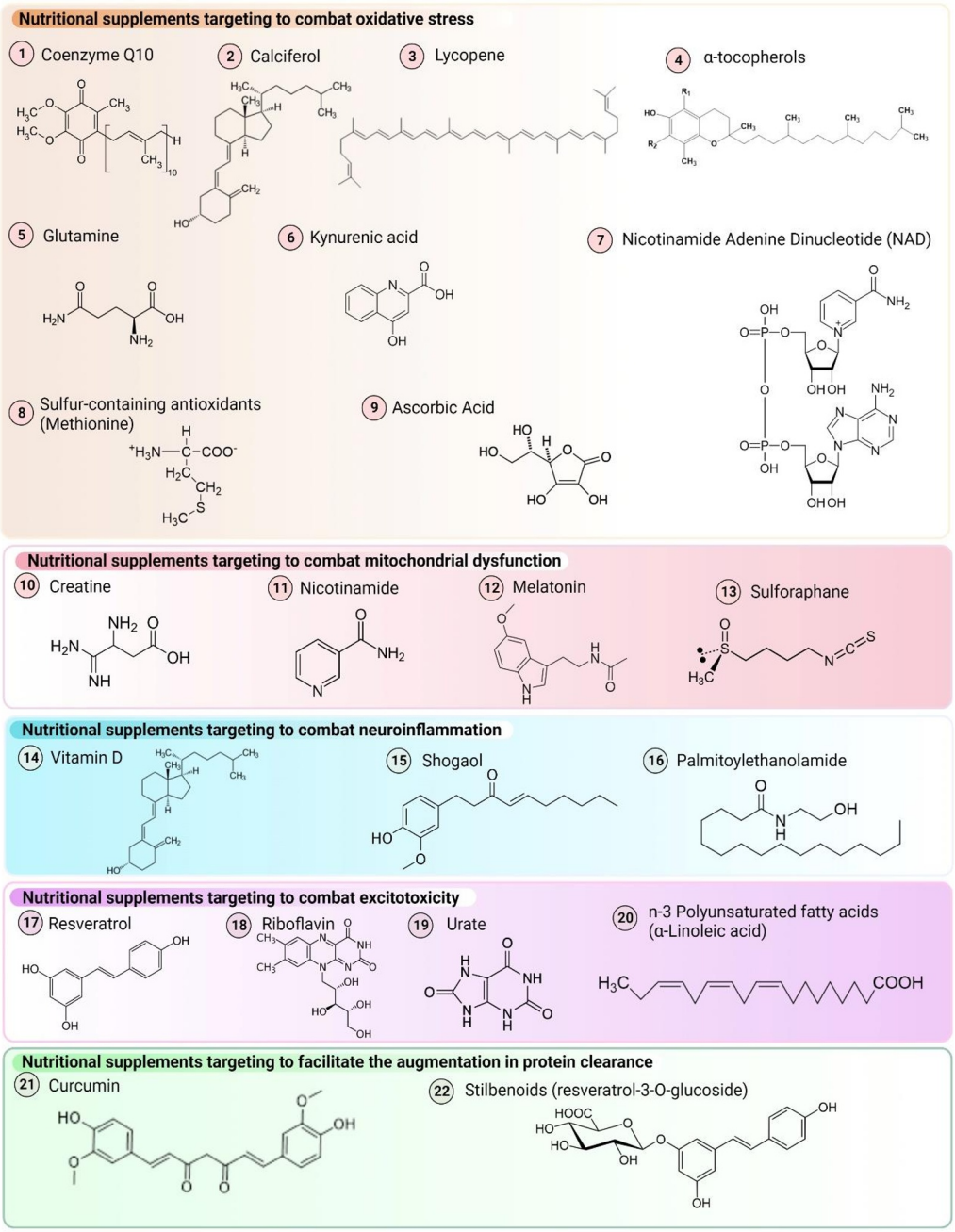

Fig.1 Structure of various nutraceuticals that are used to treat oxidative stress/PD

1.3.2 Alpha-synuclein misfolding and Lewy bodies formation

Sporadic PD is commonly marked by the presence of a rounded eosinophilic inclusion, known as Lewy body, majorly found in the cell soma and neurites of certain neuronal populations, most prominently in the SN[26]. In addition, Lewy bodies can also be found in normal patients ,other than Alzheimer's and dementia affected patient[27].A presynaptic protein of unknown function, i.e., filamentous α-synuclein (α-syn) is an elemental component of Lewy bodies[28].

Mutations in three genes i.e., PARK1, PARK2 and PARK5 encoding α-syn, parkin and Ubiquitin carboxy-terminal hydrolase L1 (UCHL1), respectively1,2 is seen during the formation of Lewy bodies[28]. On an onset age of around 45 years, PARK1 mutations can lead to autosomal dominant PD. Parkin, an E3 ubiquitin ligase is encoded by PARK2 which is involved in the damage protein degradation led by ubiquitinated proteins[29], [30].Finally, the enzyme UCHL1 is encoded by PARK5,which is also involved in the ubiquitin pathway, in which the ubiquitin molecules are recycled by cleaving the carboxy-terminal tails of ubiquitinated proteins[29]. Recent findings suggests that UCHL1 might play two distinct role in ubiquitin pathway's breakdown of α-syn and polymorphisms in PARK5 may even lessen the incidence of Parkinson's disease[31].

1.3.2.1 Failure of protein clearance pathway

One of the most common causes for aggregation of neurodegenerative disease is protein misfolding, aggregation, and deposition, which further deteriorated due to failure in the protein clearance pathway. This failure can be attributed to various reasons like aging, environmental, and also genetic factors. The first line of a defence system for the clearance or removal of these misfolded proteins is the molecular chaperons[32]. To maintain intracellular homeostasis, neurons rely on these two major proteolytic pathways, the ubiquitin-proteasome system (UPS) and autophagy lysosomal pathways (ALP), for the removal and refolding of abnormal proteins[32]. The USP breakdown the short-lived proteins, while the ALP degrades the intracellular components, proteins, and organelles in the lysosomes. Endoplasmic reticulum-associated degradation (ERDA), which is typically for the folding of the protein in the endoplasmic reticulum, which occur through proteosomes, can also occur when aggregate-prone proteins levels are too high[32]. Studies to evaluate proteasome activity in brain tissue found evidence of UPS malfunction in PD. In vivo studies for the relationship between UPS and sporadic PD in rotenone or 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced toxins, demonstrated a significant decrease in proteasome activity[33]–[36]. In a pathological study for the involvement of ALP in PD, accumulation of autophagic vacuoles was found in the SN of PD patients[37].

1.3.2.2 Linkage between protein clearance and α-syn aggregation

The protein clearance pathway is associated with progression of neurodegeneration and can be witnessed within neurons. The pathway connects the neurons with the microglial cells. In the brain, microglial cells are one of the crucial phagocytes, Microglia's phagocytosis of misfolded proteins can accelerate the degeneration of the neurons, via releasing of chemokines and cytokines[38]–[40].

The α-syn can be degraded by both autophagy- lysosomal pathways (as shown in Fig. 2) [41], [42]. Normal α-syn gets degraded by Chaperone-mediated-Autophagy (CMA) by binding to the CMA-specific receptor lysosome-associated membrane protein 2A (LAMP-2A) which leads to the dysfunction of neurons. Both wild and mutant α-syn can increase vulnerability to neurodegeneration. Lamp2a and heat shock cognate 71 kDa protein (Hsc70) are the two proteins that are implicated in CMA. A higher concentration of α-syn can prevent the removal or clearance of proteins, which could result in the development of Lewy bodies[43], [44]. The extraneuronal mechanism is responsible for the extraneuronal clearance of α-syn. Extraneuronal forms of α-syn are responsible for the activation of glial cells that can lead to the formation of proinflammatory molecules[45], [46].

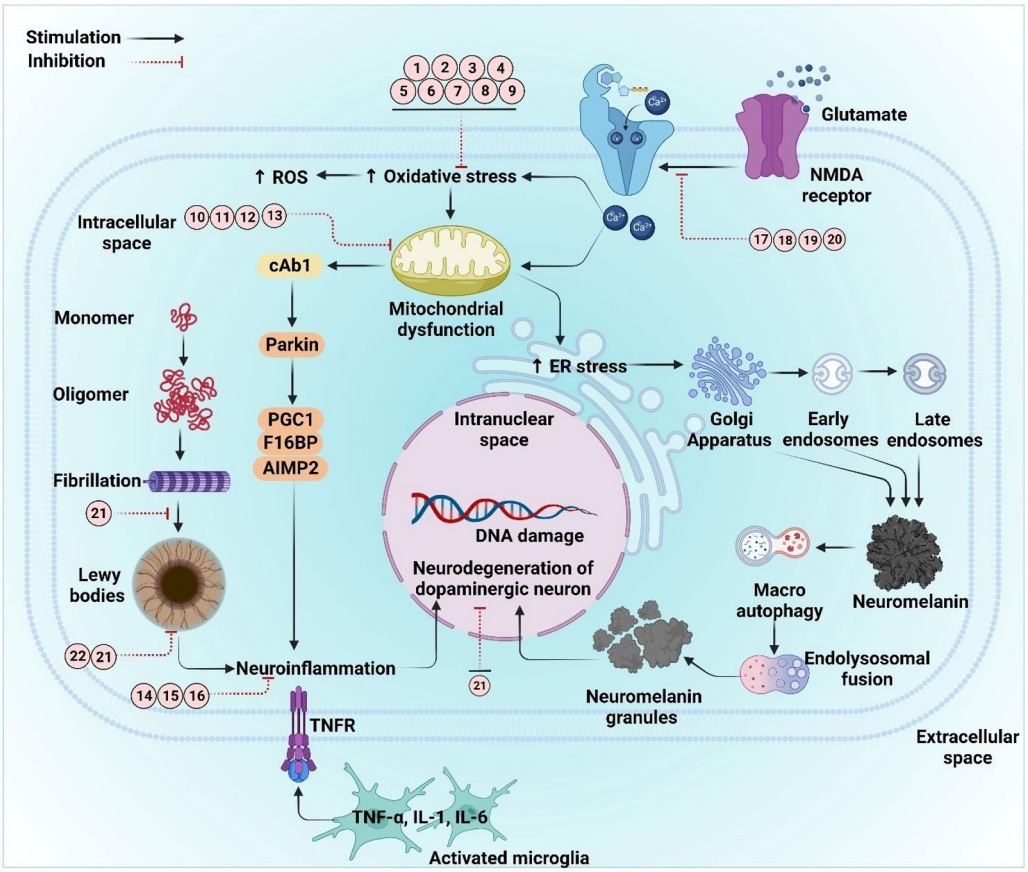

Fig2 Potential target sites of nutritional supplements for combating neurodegenerative pathology in PD. Numbers signifying the nutritional supplements have been shown in the figure 1.

1.3.3 Mitochondrial dysfunction

The presence of complex 1 inhibitor in the mitochondrial respiratory chain (MRC) can results in the degeneration of SN and can cause Parkinson's disease[47]. Complex 1 and to a lower extent complex III are considered to be the main site of ROS production[48]. Mitochondrial ROS are produced when electron leaks from electron transport chain (ETC) and react with dioxygen to produce superoxide anion[49].

Complex 1 is the first enzyme that contributes to adenosine triphosphate (ATP) synthesis, the defects in complex 1 can cause a decreased rate of ATP and can also lead to mitochondrial depolarization and excessive generation of ROS. Studies have discovered a decline of about 30% in complex 1 activity in the frontal cortex of PD patients[50]. Parkin and PTEN-induced kinase 1 (PINK1) genes of PD patients were seen to have lower complex 1 activity. Changes in mitochondrial complex II, III, IV, and V were also seen in Parkinson's but not consistently[51], [52]. The mutation in some of the genes linked with mitochondrial proteins such as leucin-rich kinase (lrrk2), PINK1 and parkin that can causes respiratory complex insufficiency, provided additional evidence of mitochondrial failure[49].

In a neuronal culture, it has been shown that α-syn, mostly a systolic protein interacts with the mitochondrial membrane and inhibits complex 1[53]. The level of Mitochondrial DNA (mtDNA) deletions above the age of 65 appears to be increased[54]. Two studies used genetic transplantation for the determination of complex 1 defect. In the first study, unselected PD platelets were grown together in a mixed culture, and in the second study, in a mixed culture, the PD patient's cells fused with rho-zero cells and grown. Results in both studies show that mtDNA induced Complex 1 defects[54].

Elevated levels of mtDNA mutation in the initial stages of PD were found for the first time in the SN[55]. However, there is still no evidence linking the involvement of mtDNA to the aetiology of Parkinson's disease[56]. α-syn after treatment with MPTP, shows mitochondrial abnormalities, reduced complex IV activity, and mtDNA damage in mouse models. Decreased complex 1 activity and α-syn accumulation were seen in higher amounts as compared to control subjects in SN and striatum of PD patients[56].

In lymphocytes of Parkin (PARK2) mutation-positive patients, a decrease in complex 1 was observed[54]. PINK1 (PARK6) genes are essential in preserving homeostasis and also serve as a cytoprotective role. In SH-SY5Y cells, overexpression of PINK1 causes the suppression of autophagy and maintains mitochondrial membrane potential[57] and loss of PINK1 can alter mitochondrial homeostasis[58]. PARK7, also known as DJ-1 which is a protein found in the cytosol and in lesser amounts in mitochondria, was found to be directly bound to complex 1, and the decrease in its function will suppress the activity of mitochondrial complex 1, but DJ-1 overexpression in MPTP-induced was seen to protect the complex-1[59].

The breakdown of misfolded proteins present in the cytosol is carried out by the UPS. PINK1, DJ-1 and parkin are normally responsible for the functioning of mitochondria whereas UCHL1, α-syn, and parkin are responsible for maintaining UPS[60]. The mutation of parkin was seen to reduce the activity of ubiquitin-ligase enzymatic activity in SN of PD[32]. Inhibition of complex 1 was found to decrease the aggregation of α-syn, increased oxidative stress (OS), and lower the ATP synthesis, which can in turn affect the functioning of UPS[61].

1.3.4 Neuroinflammation

Neuroinflammation mainly caused neuronal damage and cell death due to OS and activation of glial cells like astrocytes and microglial[61].Microglia are cells that mediate the immune defence system in the brain and act as scavengers during inflammation, infection, or degeneration. Activated glial cells promote neuronal damage by generating ROS/RNS, tumor necrosis factor α (TNF-α), and can also release glutamate which can cause neurotoxicity[62]. Inflammation can also be caused by brain infection, and traumatic brain injury. Studies showed that there is enriched microglial in the substantia nigra compacta of patients with PD, and their activation can cause neuronal degeneration. The presence of proteins such as parkin, DJ-1 LRRK2, and α-synuclein can cause microglial activation[63].

Hirsh et al. reported the presence of CD8-positive T lymphocytes in the SN of PD patients[64]. Following this observation, interferon- (IFN-) γ-positive cells were found in high density in the SN of PD patients[64]. This suggests that immunogenic mediators are being released due to the presence of injured dopaminergic neurons and can thereby cause neurodegeneration. Cyclooxygenase-2 (COX-2) enzyme expression along with prostaglandin E2 (PGE2) was seen to be increased in glial cells of the SN and thus can cause toxicity[65].

PD patients was also observed to show T-cell infiltration in the SN[66]. Studies in mice, to check the influence of T cell on death of dopaminergic neuron indicates that there is a decrease in the death of dopaminergic neurons[67]. In study on helper T-cells (CD4) and cytotoxic T-cells (CD8)- deficient mice, CD4+ was observed to mediate cytotoxic effects but not CD8+. But in a recent study, both CD4+ and CD8+ were seen within the SN of PD patients[67].
The majority of the findings regarding neuroinflammation points to the microglial as a mediator, but the reaction of the astrocytes is also one of the pathological characteristics in SN of PD patients[68] which also supports the neuronal functions and homeostasis. In a post-mortem PD investigation, the SN was showed to contain huge astrocytes levels and glial fibrillary acidic protein (GFPA) immunoreactivity[69].

1.3.5 Excitotoxicity

Excitotoxicity is a process by which neurons are destroyed by overstimulation of glutamatergic receptors by glutamate, the main excitatory neurotransmitter in the central nervous system (CNS), and by calcium overload, triggering apoptosis. Glutamate is usually stored in the vesicles as well as glial cells and can activate receptors like N-methyl-D-aspartate receptors (NMDARs), alpha-amino-3-hydroxy-5methyl-isoxazole-4-propionate (AMPA) receptors, and kainate receptors (KA)[70].

Excessive glutamate levels can cause neurotoxicity mostly through overstimulation of N-methyl-D-aspartic acid (NMDA). NMDARs sub-types includes: NR1, NR2, and NR3, and positive ions, notably calcium ions, can pass through these three subtypes[71]. The presence of NR2B which is a subunit of NMDARs is thought to be responsible for excitotoxicity and NR2A was seen to activate neurotrophic pathways[72]. It has been reported that mitochondrial fission/fusion imbalance can lead to up-regulation of NMDARs and oxidative stress which can also contribute to excitotoxicity[73]. Ca^{2+} overload can trigger the mitochondrial permeability transition (MPT) pore and release of cytochrome c and can cause activation of apoptogenic pathways. Calcium overload can also induce the working of nitric oxide synthases and enhance ROS and reactive nitrogen species (RNS) production[74]. Neuroinflammation and activated microglia which are also some of the main pathogenesis for PD progression potentiate glutamate receptor-mediated response and contribute to excitotoxicity phenomena[75], [76].

Recent studies show the microglial activation and neuroinflammation of kainate receptors and promote excitotoxicity[74]. Nuclear factor erythroid 2-related factor 2 (Nrf2) is a transcription factor and plays a role in protection against oxidative damage by binding through antioxidant response elements (ARE), Nrf2 is usually present in the promoter region of genes encoding antioxidant enzymes[77].

2 Molecular targets for debilitating PD

2.1 Chaperons

The proteins which guide the folding of polypeptide, refolding & degradation of proteins to sustain proteostasis are called chaperons. These proteins are labelled as “HSPs” as they are upregulated in response to temperature. Their classification depends on their molecular weight comprising of HSP40, HSP60, HSP70, HSP90, HSP100, and small HSPs. The “cochaperones” modulates action of the HSP family which are further subdivided based on the presence of the tetratricopeptide domain, B-cell lymphoma-2 associated Athanogene (BAG) domain or J domain[78].
In eukaryotes, HSP70 and HSP90 carry out majority of the chaperone’s duties. And interestingly, HSP70 family members have attracted the attention of PD researchers due to their ability to show neuroprotective effects in preclinical trials. Stress and transcriptional activator control the expression patterns of HSP70 chaperones subsets, including HSPA1B, HSPA1A, and HSPA6, i.e., the heat shock factor 1 (HSF-1)[79], [80]. HSF-1 is normally in an unactive form due to their ability to bind to HSP90. However, following misfolding of proteins, HSF-1 segregates from HSP90 and move to the nucleus which then causes increase in the transcription of targeted genes. HSP90 attaches to HSF-1 which results in its inactivation, to decrease the expression induced by HSP70 after proteostasis has been stabilized. Due to this negative feedback pattern, cells were enabled to carry out proteostasis-related functions and were also able to respond to proteostasis-related stress[81].

2.2 Molecular chaperons

According to the report by Auluck et al. in 2002, in a Drosophila model, the overexpression of HSP70 slow down the dopaminergic neurodegeneration caused by α-syn[82]. Another study demonstrated the prevention of α-syn aggregation by overexpression of HSP70 & HSP40 members[83]. Patients are more likely to develop PD if there is a mutation in either HSP90 or HSP70 molecular chaperone[82], [84]. PD development is further exacerbated by mutation of mitochondrial HSP70. Following the overexpression of mitochondrial HSP70, α-syn decreased the toxicity in rat model of PD and promote cell death in yeast[85], [86]. HSP70 prevents cell death brought by MPTP, by hindering the mitochondrial complex 1 (Fig. 2).
HSPA5 (FR78/Bip) were observed to be present in Dementia with Lewy bodies patients, and its levels are elevated in cingulate gyrus of patients in relation to α-syn. Several studies suggested that increased HSPA5 levels may reduce the toxicity associated with α-syn. Studies also shown that through the ubiquitin proteasomal system (UPS), α-syn

aggregation can be prevented with an overexpression of HSPA5, which involve refolding and breakdown of proteins[87], [88].

2.3 The protein Abelson

Protein Abelson (c-Abl) is a member of tyrosine kinase family which comprises of SH3, SH2 and a catalytic domain, is activated by oxidative and cellular stress[89]. The position of c-Abl within the cell affects how it functions. The presence of c-Abl within the cytoplasm support in survival mechanism and it also aid in cellular adhesion, whereas the presence of c-Abl within the nucleus and the mitochondria results in cell apoptosis[90]. Numerous studies suggested that the activation of c-Abl by MPTP plays a significant role in the progression of PD and elevated number of phosphorylated c-Abl have been seen in the brains of patients with PD[91].

2.3.1 c-Abl interaction with Parkin

The presence of neurotoxins and stress in the dopaminergic area can lead to the activation of c-Abl engendering tyrosine-143 parkin to be phosphorylated. The phosphorylation of Tyrosine-143 parkin causes the E3 ubiquitin ligase to be inhibited, and the complex interaction between aminoacyl-tRNA synthetase-interacting multifunctional protein 2 (AIMP2) and fructose-1,6-bisphosphatase 1 protein (FBP1) causes aminoacyl tRNA synthetase to accumulate[92]. The accumulation of these proteins results in the reduction of the peroxisome proliferator activated receptor-gamma (PPARγ) coactivator-1 (PGC-1), which leads to the mitochondrial dysfunction and death of dopamine cells[93]. Moreover, Poly [ADP-ribose] polymerase-1 (PARP1) is activated by AIMP2 overexpression which results in age-related degradation of DA neurons[94]. Other variables which cause the neuronal death and parkin inactivation includes S-nitrosylation. Conjugation of DA and OS also play a vital role in it. PD patients frequently experiencing OS, can also trigger the activation of c-Abl[95].

3 Nutritional supplements for PD targeting specific pathological mechanisms

3.1 Nutritional supplements targeting to combat oxidative stress

3.1.1 Coenzyme Q10

Coenzyme Q10 (CoQ10) or 1,4-benzoquinone is ubiquitously expressed in most animals and bacteria and is also known as ubiquinone. The known sources of CoQ10 are based on a natural origin such as tuna or salmon, whole grains, and organ meats, but recently CoQ10 rich food supplements are also gaining popularity. Physiologically, CoQ10 participates in the aerobic cellular respiration and is a component of the ETC, contributing to energy formation in the form of ATP. CoQ10 also act as an antioxidant affinity for free radical, apart from acting as a crucial electron carrier in the ETC[96].

3.1.2 Calciferol

Calciferol is generated internally by skin cells exposed to UV -B light (vitD). Since just a small number of foods contain a significant amount of vitamin D3, dietary supplements are the most efficient way to obtain vitamin D exogenously (e.g., tuns, carp, salmon, fatty cheese, and some forest mushrooms). Vitamin D3, which is involved in numerous intracellular signalling and metabolic pathways, including calcium metabolism and bone development. It is the most important form of vitamin D.As per neurochemical analysis, vitD supplementation in PD mouse model helps in protection against the oxidative stress and dopaminergic neuron loss[97].

3.1.3 Lycopene

Lycopene is a carotenoid compound that occurs naturally in fruits like papaya, pink guava, watermelon, pink grapefruit, and tomato, and has the greater ability to scavenge free radicals when compared to other carotenoids[98]. Lycopene's ability to scavenge reactive oxygen species/ reactive nitrogen species was also seen on exposure to 3-morpholinosydnonimine. Moreover, it has been noted that lycopene effectively detoxify additional ROS such as OH^- and peroxynitrite, which are formed in substantial quantities in the brain[99], [100].

3.1.4 Tocopherols and tocotrienols

Fat-soluble compounds with antioxidant activity comprise of tocopherols (vitE), and the main form is α-tocopherol (α-tocph). Some of the function of tocopherols and tocotrienols are inhibition of lipid peroxidation and free radicals scavenging[101]. Based on nutritional questionnaires, a higher intake of Vit E reduces the risk of PD[102]. Unfortunately, vitE hasn't shown any effect on clinical symptoms of PD as reported in a clinical study led by Sceider et al[103]. The findings by Sceider et al. and the largest clinical trial on the impact of vitE on PD, known as the Deprenyl and Tocopherol Antioxidative of Parkinsonism (DATATOP), were likewise in agreement[104].

3.1.5 Glutamine

Glutamine is the most prevalent free amino acid in the human body and has a very rapid rate of cell turnover and a wide range of physiological functions[105]. It is also responsible as a source of energy (ATP) for mitochondria. Additionally, the oxidation of glutamine can remove some potent oxidizers from cells and shield other vital cell components from oxidative damage[106]. Glutamine reduces oxidative stress damage and in cultured PC12 cells suppresses MPTP-induced cytotoxicity[105].

3.1.6 Nicotinamide Adenine Dinucleotide (NAD)

NAD is a dinucleotide that consists of two forms, the oxidized form NAD+ and the NADH which is the reduced form. It has been discovered that NAD deficiency may result in mitochondrial malfunction and neuronal death[107], [108].

3.1.7 Kynurenic Acid (KA)

The metabolites of tryptophan degradation, i.e., KA and quinolinic acid (QA) have important neurological activities. The occurrence of PD is crucially associated with KA/QA ratio changes[109], [110].

3.1.8 Sulphur-containing antioxidants

Some of the endogenous antioxidant compounds can easily induce a reducing environment within the cytoplasm due to the specific characteristics of the interaction between the intracellular environment and sulphur-hydrogen bonds[111]. Because of their unique antioxidant properties, these compounds are discussed with N- acetylcysteine as a separate group. This exogenous molecule serves as a crucial precursor to the production of endogenous GSH[112].

3.1.9 Carotenoids and Retinoids

The antioxidant, β-carotene, which is mostly present in a variety of vegetables and fruits, enters the body through the food as a precursor to retinol (vitamin A) (mostly in carrots, mangoes, spinach and corn)[113].

Lycopene, which is mostly present in tomatoes and other red fruits and vegetables, is a precursor to carotene, a vivid red pigment. Surprisingly, lycopene is the carotenoid found in the human diet the most frequently[114]. According to several investigations, lycopene may benefit those with pancreatitis because of its antioxidative qualities, which lessened the severity of the condition by avoiding excessive ROS from including autophagy[115].

TANK- binding kinase 1 (TBK1) gene mutations have been associated with amyotrophic lateral sclerosis (ALS)[116]. A crucial stage in macro-autophagy is the phosphorylation of SQSTM1 (sequestosome 1; p62), which is regulated by TBK1. According to Catanese et al., immature phagophores build up in TBK1-mutant motoneurons because of a failure in the elongation phase. 4-hydroxy(phenyl) retinamide has been identified as a potent autophagy modifier, worsening the autophagy status of cells by upregulating p62 and concurrently lowering the level of Atg10[117].

A high intake of carotene in the diet was associated with a lower risk of developing PD in a prospective cohort analysis. However, the Lancet reported in 2005 that carotene did not appear to have any preventive characteristics against PD. The same outcomes were achieved 16 years later in a published study, which demonstrated that there is no correlation between levels of carotene and the risk of PD[102], [118]. A carotenoid called crocin, which is present in Gardenia jasminoides Ellis has been used for generations in traditional Chinese medicine, possesses anti-proliferative, anti-inflammatory, and anti-oxidant properties[119]. According to several investigations, lycopene which is a carotenoid may benefit those with pancreatitis because of its antioxidative qualities, which lessened the severity of the condition by avoiding excessive ROS including autophagy[115].

3.1.10 Ascorbic Acid

The most popular vitamin C is ascorbic acid, which has the strongest antioxidant activity and can prevent damage to the mitochondria, among other things (nearly 70,000 records in PubMed). The main sources of vitamin C are fruits,

particularly citrus fruits, strawberries, and vegetables. Vitamin C- containing dietary supplements are also quite popular throughout the flu season.
A march 2021 paper found a significant association between low vitamin C levels and a higher frequency of Parkinson's disease (p0.001)[120]. A Mendelian randomization study revealed no link between plasma vitC levels and the likelihood of developing PD when it looked at the impact of genetically higher plasma vitC levels in relation to the age of first PD symptoms[121]. However, it has been demonstrated that the genes: SLC23A3, CHPT1, BCAS3, SNRPF, RER1, MAF, GSTA5, RGS14, AKT1, FADS1 have been linked to greater plasma levels of vitamin C[121], [122]

3.2 Nutritional supplements targeting to combat mitochondrial dysfunction

3.2.1 Creatine

α –methyl–guanidine acetic acid (Creatine) is an organic acid that is synthesized from three amino groups arginine, glycine, and methionine in the pancreas and liver. It undergoes phosphorylation to become phosphocreatine which donates a phosphate group to adenosine diphosphate (ADP) to create ATP[123]. It has been discovered that creatine functions directly as an antioxidant against ROS /RNS, peroxynitrite, and superoxide[124]. In a 6-week, double-blind, placebo-controlled, crossover research, supplementation of creatine (5g/d) significantly improved cognition in healthy vegans/vegetarians[125].

3.2.2 Nicotinamide

Nicotinamide is a form of vitamin B3 or niacin found in foods like yeast, milk, eggs, meat, beans, etc, and has been shown to be neuroprotective in PD. It is a precursor of NADH, which is a cofactor of mitochondrial enzymes like complex-1 and possibly an actively functioning endogenous antioxidant[126].

3.2.3 Melatonin

Melatonin (N-acetyl-5-methoxytrytamine) is a naturally occurring hormone that is largely secreted by the pineal gland, and it is known to have antioxidant and free radical scavenging qualities, and can generate a mitochondrial protective action that is receptor independent[127]. Melatonin has low toxicity and high efficacy from a pharmacological perspective, and it can easily penetrate the blood brain barrier (BBB). In PD patients, low levels of melatonin was observed[128].

3.2.4 Sulforaphane

Sulforaphane (SFP) is an isothiocyanate compound found commonly in cruciferous vegetables such as brussels sprouts, and broccoli[77]. It has also been shown to be neuroprotective in cortical culture, which has been exposed to hydrogen peroxide and glutamate[129], and it is thought that the protection is due to the activation of Nrf2-pathways. SFP was also seen to have a protective effect against GM-induced neurotoxicity, which was thought that it could possibly prevent mitochondrial dysfunction[130].

3.3 Nutritional supplements targeting to combat neuroinflammation

3.3.1 Vitamin D

Vitamin D is a hormone needed for the regulation of plasma concentrations, it is produced when 7-dehydrocholesterol present in the skin is exposed to ultraviolet, the enzyme 25-hydroxylase present in the liver then converts vitamin D into 1,25 (OH)2D which is the biologically active form of Vitamin D[131]. According to clinical studies, a vitamin D deficiency raises the likelihood of developing brain disorders like Alzheimer's disease[132].

3.3.2 6-Shogaol

6-Shogaol [1-(4-hydroxy-methoxy)-4-decen-one], is a pungent substance derived from ginger, has been seen to have anti-inflammatory and neuroprotective properties. In rats with spinal cord damage, the natural substance 6-shogaol decreases cell death and restores motor functions[133]. In lipopolysaccharide treated astrocytes 6-shagaol was also observed to reduced glial cell proliferation through a rise in brain neurotrophic factor[134].

3.3.3 Palmitoylethanolamide

Palmitoylethanolamide (PEA), is a lipid signalling molecule that exerts a neuroprotective effect in neurodegenerative disease in animal models[135]. The hypothesis that PEA was a cannabinoid receptor agonist was

formerly put forth; however, it has also been published that PEA had no impact on PPAR-knockout mice[136], [137]. The pharmacological actions of PEA are currently understood to be mediated through PPAR activation[138].

3.4 Nutritional supplements targeting to combat Excitotoxicity

3.4.1 Resveratrol

Resveratrol (Re) belongs to the polyphenolic stilbenes group and is mostly found in grapes skin and seeds and in red wine. The neuroprotective properties of Re in animals and neural cell cultures have been proven in a variety of experimental paradigms[148]. In some, out of the multiple studies, which include dietary intake of Re in rats and mice, it has been seen to prevent acute brain injury, and guards against neurotoxicity caused by 6-OHDA and MPTP[139]–[141].

3.4.2 Riboflavin

Riboflavin is basically a vitamin B complex which is a vitamin known to be water-soluble. It is bright yellow in color. It serves as a coenzyme in metabolic pathways and shown wide range of functions. Two active forms of riboflavin are- flavin mononucleotide and flavin dinucleotide[142].

Riboflavin can manipulate the neurotoxic cycle of glutamate excitotoxicity. Riboflavin inhibits the exocytosis of glutamate vesicles by suppressing the cortical neuronal endogenous release of glutamate. By decreasing the concentration of glutamate in the synapses, riboflavin protects against glutamate excitotoxicity[143], [144].

3.4.3 Urate

The anionic form of uric acid (Urate), is the end product of purine metabolism in humans and other higher primates, whereas in other mammals, in the presence of enzyme uricase, allantoin is produced after further urate metabolism[145]. A lower risk for PD is associated with high levels of urate[146] and in animal models of the disease, changes in urate levels can predict PD development[147].

3.4.5 n-3 Polyunsaturated fatty Acids

Omega 3 polyunsaturated fatty acids (n-3 PUFA) was seen to be strongly linked to positive benefits in neurodegenerative illness such as Parkinson's disease. In order for the brain and visual system to develop and function properly, n-3 PUFA are crucial nutrients. Additionally, there is mounting proof that they are still crucial to human health[148]. Docosahexaenoic acid (DHA) has continuously been demonstrated to play distinct and crucial roles in the neuronal membrane, making it the most significant n -3 PUFA[149].

3.5 Nutritional supplements targeting to facilitate the augmentation in protein clearance

3.5.1 Polyphenols

3.5.1.1 Curcumin and Stilbenoids

Curcumin is obtained from Curcuma longa. It is basically bright yellow in colour and belongs to the family of ginger. Curcumin can be used as an antioxidant, antiseptic, anti-inflammatory, and antitumor agent[150]. Curcumin inhibits the aggregation of α-syn in a dose-dependent manner[151]. Resveratrol which is a polyphenolic stilbene shows neuroprotective effects in PD[152]. In a study, it is reported that stilbenoids inhibit the formation of amyloid aggregates. Resveratrol is also a polyphenol that can be found in grapes and blueberries[153].

Apart from the aforementioned nutritional supplements, some of the in vitro. In vivo and clinical studies have been included in table 1.

Table 1 List of *in vitro/in vivo* and clinical studies conducted with certain nutritional supplements for therapeutic management of PD

Disease	Causes	Supplements	*In vitro/In vivo*/Clinical studies	Reference

PD	Oxidative Stres	CoQ10	• In an animal study it has been highlighted that oral CoQ10 supplementation reduced the loss of dopamine and its axons in 1-year-old mice striatum in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) induced mouse model of PD. • A prospective, randomized, double-blind study with 20 subjects in each group conducted by Shults and collaborators in 2002, compared three dosages of CoQ10 (300, 600, and 1200 mg/day) with placebo, and found that CoQ10 at high dosages were safe and well tolerated, and with comparison to placebo coenzyme treated patient has shown a reduction in their disability, indicating a progressive therapeutic approach for PD. • Moreover, during the 4 weeks of treatment, for the determination of symptomatic response for the daily oral application of 360 mg CoQ10, Muller et al. in 2003 performed a trial on monocentric, parallel-group, placebo-controlled and double-blind, that exerted moderate beneficial effect in PD patients by supplementation of oral CoQ10. • On the contrary, in a clinical study performed by Storch et al. in 2007 there was no beneficial result in mid-stage PD even after applying the same protocol and maximum dosage of the Shults' study i.e. 1200mg/day.	[154], [155] [156] [157] [158]
		Calciferol	• Jang et al. presented results in which it is shown that supplementation of vitD3 reduces the ROS level in a cellular model of PD (SH-SY5Y cells with rotenone-mediated neurotoxicity). • The same team also observed a rise in the levels of the autophagy markers LC3, beclin- 1, and AMPK following vitamin D3 treatment. These findings indicated that rotenone treatment reduced beclin-1 protein levels while increasing mTOR levels, an effect that was reversed by incubating with vitamin D3.	[159] [159]
		Lycopene	• A study to evaluate the neuroprotective effect of Lycopene on oxidative stress in Rotenone-induced PD showed that malondialdehyde (MDA) levels were notably decreased (24.33%) after lycopene administration when compared to control groups[105]. It was also seen to inhibit the complex-1 activity of mitochondrial ETC in rotenone-induced toxicity. • Glutathione (GSH) levels and Superoxide dismutase (SOD) activity were significantly reduced after rotenone treatment, but the GSH levels were restored by 42.69% in rats, and the	[98] [98]

			SOD activity increases by 12% on lycopene administration.	
		Tocopherols and tocotrienols	• PD development is delayed by 2.5 years compared to the placebo group when VitE and VitC are given together in the early stages. • In another study, α-tocph has not shown any effect on the disease, while the PD symptoms delay was shown by selegiline. However, a 2021 meta-analysis showed a reduction in PD development in people taking vitE. Vit E mainly possesses antioxidative properties.	[160][161] [162]
		Glutamine	• Glutamine inhibits the PI3K/Akt signalling pathway, bringing back baseline levels of SOD, GSH-Px, and lipid peroxidation indicators in those cells.	[105]
		NAD	• In a study conducted, Shan et al. administered NAD into the striatum. They discovered that this reduced the animals motor impairments and dopaminergic neuronal damage.	[108]
		KA	• In an ex vivo rat model of PD, KA administration prevented Quinolinic-Acid-induced brain damage by preventing changes in Nrf2 levels, oxidative damage and mitochondrial dysfunction.	[109], [110]
		Carotenoids and Retinoids	• It has been demonstrated in several papers that lycopene reduces gentamicin-mediated cell death, apoptosis, and autophagy. According to the research, lycopene may be used as a strong antioxidant to reverse an excessive autophagy flux. • Compounds that are a part of the carotenoid family are called xanthophylls. There are numerous plants that contain these yellow pigments. This family member, astaxanthin, has been shown to influence the autophagy process in a variety of experimental scenarios. However, astaxanthin deactivated autophagy in the vast majority of the studies compiled in a study by Kim and Kim, primarily through the PI3K/Akt (phosphatidylinositol 3- kinase/ protein kinase B) and p38 (mitogen-activated protein kinase p38) pathways. • Astaxanthin has been demonstrated to mitigate the neurotoxicity brought on by amyloid and 6-OHDA (6-hydroxydopamine, pointing to its potential utility in the treatment of neurodegenerative illness. • Furthermore, it has been demonstrated that astaxanthin inhibits H. Pylori-induced apoptosis by triggering autophagy through an AMPK-dependent mechanism. In a human	[163] [164], [165] [165] [164], [165]

			nasopharyngeal cancer C666-1 cell line, fucoxanthin, a carotenoid produced from marine algae, has been shown to upregulate the Atg7, p62 and LC3-II protein levels while downregulating the Atg4B protein level.	
		Ascorbic Acid	• Ascorbic acid has been shown to be able to inhibit autophagy as seen by the decrease in de novo beclin-1 synthesis in the pilocarpine-induced seizure rat model. Pre-treatment with L-ascorbate prevented methamphetamine-induced neurotoxicity in primary rat cortical neuron-glia cells by lowering the autophagy markers, reducing ROS generation, and suppressing the expression of cleaved caspase-3. • VitC has been found to prevent ROS from inducing autophagy in bone marrow stromal cells.	[139], [140] [166]
	Mitochondrial dysfunction	Creatine	• In a laboratory model of PD, creatine protected against cell death, when administered in doses 1-2% diet by weight, where it protected the cell that is damaged by MPTP which destroys about 30% of dopaminergic cells in rodents. Creatine has antioxidant properties and can be an effective inhibitor of mitochondrial permeability transition pore opening and mitochondrial iron accumulation • In recent investigations, creatine was shown to protect tyrosine hydroxylase immunoreactive dopaminergic neurons in MPP+ and 6-OHDA-treated dopaminergic cell culture.	[167] [123]
		Nicotinamide	• Studies on complex I activity in MPP^+-treated cells show that nicotinamide treatment increases complex I activity by up to 20% compared to the MPP^+ treated. Additionally, the Ketoglutarate Dehydrogenase (KGDF) activity in cells pre-treated with nicotinamide increased to about 70% compared to the cells treated with MPP. • Using Dichlorofluorescein (DCF) staining to check the oxidative damage and mitochondrial dysfunction induced by MPP^+, nicotinamide was also seen to decrease the MPP^+induced ROS generation. Nicotinamide at 15 and 30mg/100g significantly improved the climbing activity of PD Drosophila. In a comet assay, nicotinamide treatment protected the DNA oxidative damage induced by MPP^+.	[126] [126]
		Melatonin	• In a study conducted by Zampol and Barros, the treatment of melatonin to cultured cells was observed to alter damage caused by alpha-synuclein in the mitochondria.	[168]

			• Additionally, it has been shown by Patki and Lao, that melatonin protected neurons as well as mitochondria in a chronic PD animal model. This ability makes melatonin potentially beneficial in lowering oxidative stress and inhibition of the respiratory chain in different disorders of the mitochondria, as well as decreasing the progression of idiopathic PD. • Similarly, in another study performed by Paul et al., administration of melatonin was observed to improve behaviour impairments, lessen nigral dopamine loss, and minimize oxidative stress, by keeping out free radicals and increasing antioxidant enzyme activity. • Melatonin supplements administered to animals failed to enhance locomotor activity, despite helping to reverse some 6-OHDA and rotenone-induced damage in rats. • Additionally, a reduction in COX-2 activity, lipid peroxidase, nitrites and nitrates which usually help in clinical improvement in PD, was seen after administering melatonin. • However, in mice, the L-DOPA adverse effects were reduced when combined with melatonin. • In an animal study, the treatment with melatonin was seen to improve sleeping disorders in PD, even though its clinical study results were debatable.	[127] [169] [170], [171] [172] [173] 74], [175][176], [177]
		SFP	• In SH-SY5Y cells, Deng et al. found out that cytotoxicity induced by 6-OHDA was inhibited in the presence of SFP, by enhancing Nrf2 translocation and HO-1 expression. • In Cysteinyldopamine (CysDA) induced injury, it has also been shown that via the activation of extracellular signal-regulated protein kinase (ERK1/2) the cortical neurons were being protected by SFP[138]. • In an *in vivo* MPTP-induced mouse model, basal ganglia affected by Nrf2-independent phase-II response, SFP prevented the death of the cells and microgliosis. Furthermore, in 6-OHDA-lesioned mice, SFP shows neuroprotective effects, this may be due to the ability of SFP to increase GSH levels and modulate pathways like ERK1/2.	[77] [129] [178]
	Neuroinflammatio	Vitamin D	• In an MPTP-induced mouse model, the impact of 25(OH)D3 was investigated *in vivo*. The findings demonstrated that vitamin D shields dopaminergic neurons against cell death.	[131]
		6-shagaol	• Studies using 6-Shogaol on inflammatory response induced by MPP^+ using cell supernatant, shows that the MPP+ treated group increased TNF-alpha levels and NO and	[179]

			the group treated with 6-Shogaol suppressed these increased levels, compared to the control group. In a pole test against MPTP-induced neurotoxicity, T-turn and T-LA were found to be shortened in the MPTP+6-Shagoal treated group.	
		PEA	• In a 6-OHDA-induced neurotoxicity, PEA was seen to improve behavioural impairments in mice, reduction in inflammation, ER stress, and apoptosis • In mice treated with MPTP-induced neurotoxicity, PEA was seen to protect tyrosine hydroxylase-positive neurons in SNpc. In a western blot analysis, glial fibrillary acidic protein (GFAP) expression which is a marker for the activation of astrocytes is significantly decreased after PEA administration in the SN on day 8 post-MPTP injection.	[180] [135]
	Excitotoxicity	Re	• It has been shown that Re was able to pass the blood-brain barrier, and therefore can be used for the treatment of neurodegenerative disease. • In rat cerebrocortical nerve, Re was seen to directly suppress the glutamate release by suppressing the Ca^{2+} channel activity and by decreasing the activation of protein kinase by mitogen. Studies using rat hippocampal show that Re decreases neuronal impairment by reducing AMPA/NMDA mediated excitotoxicity in oxygen-glucose deprivation-induced. • In studies with rat cortical neurons, Re inhibit ROS generation, increased intracellular calcium, and suppress NMDA-induced apoptosis. Re- administration attenuates KA-induced neuronal damage in rat hippocampus. Activation of microglial cells or astrocytes and KA-induced neuronal damage were seen to reduce in Re treated.	[139] [140] 5], [181], [182]
		Riboflavin	• In a clinical trial conducted for 19 patients with PD riboflavin 30 mg was administered every 8 hours. The result after one month shows that the patients improved their motor capacity. • Pyridoxine, which requires riboflavin for its activation also has intrinsic neuroprotective properties against glutamate excitotoxicity.	[183] [143], [144]
		Urate	• In a study by Coolen et al, uric acid levels were seen to be elevated in a trial with daily 5000mg ATP supplements administration through the oral route. Parallelly, in a study by Andreadou et al, a decreased level in serum level of urate was seen in patients with PD, pointing out the possible utility of this molecule in the treatment of this disease.	[171] [172]

			• Furthermore, in an experiment where animals were given a diet containing 1% uric acid, a reversal of PD symptoms were observed. The antioxidant response pathways (Nrf2-ARE)-linking with NF-E2- related factor 2 (Nrf2) could be responsible for these effects. • Additionally, treatment with the urate precursor inosine was observed to promote the amelioration of PD symptoms in people and was seen to be safe.	[173] [174] [184]
		n-3 Polyunsaturated Fatty Acids	• In a study conducted on docosahexaenoic acid (DHA) and DHAH, by Hernando et al., a favourable effect was seen on the Nrf2 pathways which were investigated on an animal model of PD induced by 6-OHDA. This beneficiary effect was observed because of the putative antioxidant action observed in these chemicals in treated groups.	[148]
	Protein clearance	Polyphenols (Curcumin)	• The mechanisms by which curcumin inhibits aggregation are- ROS, and mitochondrial depolarization. • Curcumin inhibits the A53T mutant in SH-SY5Y cells. It also exhibits by disintegrating the preformed α-syn fibrils. Interestingly, it also inhibits the synphilin-1 which is a component of Lewy bodies in SH-SY5Y dopaminergic cells. • Regulation of protein in iron metabolism can be done by curcumin. It has also been reported that curcumin can induce iron regulatory protein activation and reduction in levels of hepcidin. • It is reported that curcumin inhibits the formation of higher oligomers or soluble oligomers. Curcumin-induced inhibition of α-syn works by the mechanism of intramolecular diffusion.	[185,189] [186,191] [187,192] [180,193] [188]
		Stilbenoids	• In MPTP-treated mice, Re increases the autophagic degradation of α-syn and improves motor functions. It was also found to decrease the apoptosis induced by rotenone in SH-SY5Y cell models of PD. • In rodent model studies, it was found that the administration of Re both orally and intravenously can protect against neurodegeneration in Snpc. The toxic effect of the amyloid beta peptide can be blocked by Re.	[153] [153]

4 Conclusion

PD is a rapidly growing neurodegenerative disorder that demands immediate attention regarding its therapeutic strategy. Significant efforts have been made towards the development of drug/formulations those can treat PD. Majority of drugs belong to synthetic category including their nanoformulations. These drugs have certain adverse effects. Hence, the need for an alternative therapy to treat PD is a prime requirement. In recent years' nutraceuticals have gained importance worldwide due to their better safety profiles as well as they have shown excellent therapeutic efficacy in treating various diseases including PD. In last two decades, a number of studies have been reported deciphering the role of nutraceutical based formulations for treating various diseases. In fact, a number of pharmaceutical companies have started manufacturing as well as marketing nutraceutical formulations globally. The current annual growth rate (CAGR) of nutraceutical market is about 7.2 % and it is expected that the global market of nutraceuticals by the end of 2025 would be USD 404.8 billion. Looking at the role of nutraceutical supplements in the area of PD, the current manuscript has highlighted the molecular targets and various mechanisms through which the nutraceutical supplements can treat PD. In addition, the regulatory requirement for product approval or, clinical trial is less stringent as that of synthetic products.

Despite these advantages, there are only limited nutraceuticals that have reached to clinical trial/market due to some inherent limitations. These limitations include poor characterization/quantification of active component in the formulation due to the presence of multiple components, stability of bioactives, lack of consistency in the quantity of bioactives obtained from various geographical regions as well as difficulty in their standardization. Hence, the researchers as well as industries have to focus to control these factors when they want to produce nutraceuticals at larger scale. Such challenges, indeed have opened a new avenues of research in the field of nutraceuticals. Understanding as well as addressing these challenges through tailored research would bring excellent nutraceutical supplements in market to treat neurodegenerative as well as other diseases including PD. In fact, resolving these challenges would make the regulatory approvals easy for nutraceutical supplements.

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