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PARKINSON'S DISEASE: IMPAIRED PATHOLOGICAL DYNAMICS AND ITS MANAGEMENT WITH HERBALS

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ABSTRACT

Parkinson's disease is a neurological disorder characterized by progressive loss of dopaminergic neurons in substantia nigra. The death of dopaminergic neurons causes primary motor symptoms and other complications. In this review, we highlight several risk factors that appear to play a role including genes, environmental triggers, mitochondrial damage, oxidative stress, impairment of protein degradation pathways, aggregation of misfolded proteins, some lifestyle factors and we have also focused on how COVID-19 has changed the lifestyle of PD patients during the lockdown. Approved treatments for PD such as dopamine agonist, MAO-B inhibitors, COMT inhibitors, and anticholinergics are focused on preventing worsening of symptoms along with different side effects, to counteract these limitations herein we highlight some alternative measures such as herbals, surgery, and device aided stimulations which may help to provide a better life of PD patients with improved compliance. These herbal alternates can be substitutes due to their structural diversity possing different therapeutic properties such as anti-inflammatory, antioxidant, anti-apoptotic, and others.

Keywords

Parkinson's disease, mitochondrial dysfunction, pathophysiology, herbals, device aided stimulation

INTRODUCTION

Parkinson's disease (PD) is a widespread neurodegenerative disorder associated with motor impairments together with tremors, inflexibility, bradykinesia, akinesia, and postural instability [1]. The dopaminergic pathway in PD is distinguished by depletion of dopaminergic neurons influencing substantia nigra pars compacta (SNpc) [2] Intracellular and extracellular cytoplasmic inclusions of α-synuclein aggregation in the existence of Lewy bodies (LB) are synonymous with PD's pathological hallmark [3]. The epidemiological studies; reveal the worldwide burden of disease that has doubled from 1990 to 2015 to 6 million and this figure is expected to once again double to 12 million in 2040, in addition the modern ways of lifestyle leading to less mortality and more longevity, could raise the burden to over 17 million [4]. Men are 1.5 times more affected by PD than women [5]. Several studies have also reported cases of PD increases between the ages of 60-65 and early inception (<50 years) and juvenile (<21 years) [6].

The early major motor symptoms in PD may include tremors, soft speech, postural instability, abnormal facial expressions, rigidity, and non-motor symptoms include depression, dementia, cognitive impairment, sleep disorders and others [7]. **Fig.1** The precise etiology of PD is still unclear, although it is probably multifactorial,

those could be eco-triggering, mitochondrial damage, gene alterations, oxidative stress, excitotoxicity, impairment of ubiquitin proteasomal system and aggregation of misfolded proteins [8].

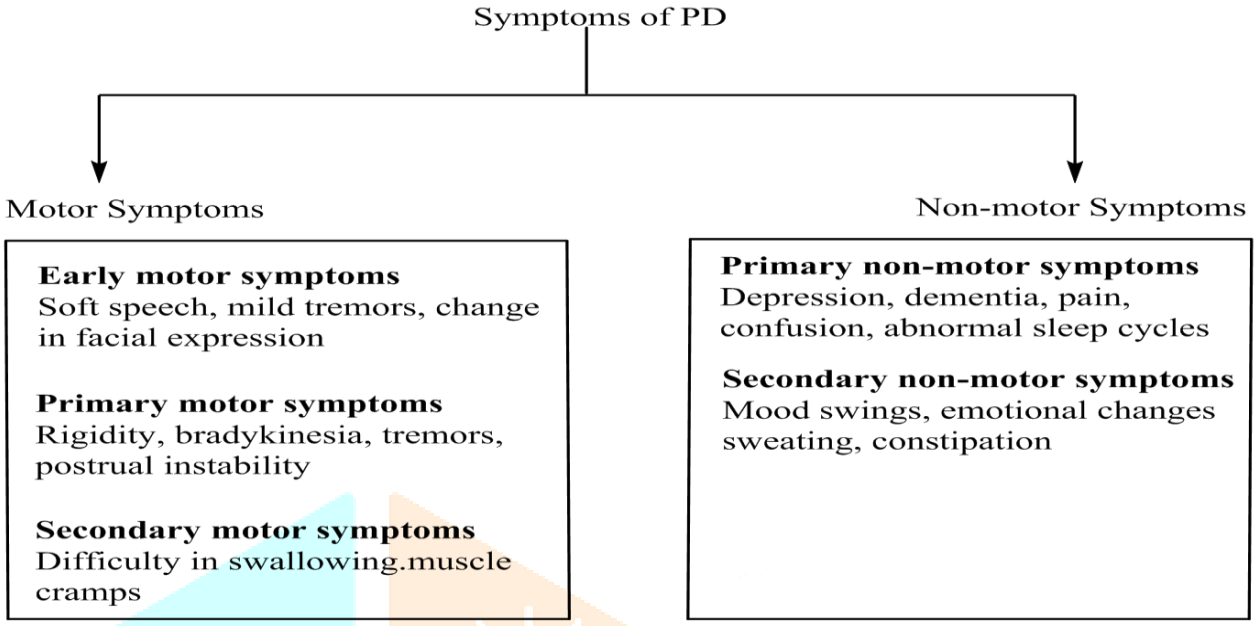

Figure 1 Different symptoms of PD categorized in five subtypes under motor symptoms and non-motor symptoms

1. Historic milestones

In 1899, Brissaud first proposed that damage to substantia nigra may emerge pathologically of PD [9] Significant milestones in PD pathology are recognition of inclusion bodies as a pathological signature by Frederick Lewy and the detection of dopamine insufficiency in 1912 and its participation in the Parkinson's animal models. The connection between dopamine and the PD was established by arvid and his colleagues in 1957 [10]. Polymeropoulos and colleagues discovered in 1996 that, chromosome 4q21-q23 had hereditary markers, which were related to PD phenotype, first confirmed by the mutation in the α-synuclein gene (SNCA) in Italian families and 3 Greek families with autosomal predominant PDs and emphasized the possibility of hereditary etiology for PD [11]. In the year 2001, the First cell-based double-blind controlled trial PD has been executed [12]. In 2014, Nalls et al. discovered that some Genes, for example, SNCA, LRRK2, and VPS13C which were historically identified with familial PD and are located at the risk loci for intermittent sporadic PD [13]. As a typical pathway for the initiation and development of multiple neurodegenerative diseases, recent findings have implicated cell-to-cell delivery of misfolded proteins [14].

2. Etiology and Clinical syndrome

Although the medical condition of PD was initially referred to as the malfunction of basal ganglia and non-dopaminergic neurons have also been identified in other brain areas of human postmortem and animal model studies. Iron content is found to be a significant contributor to the management of dopaminergic neurons of substiantia. Since the mitochondrial electron transport chain is based on iron-sulfur clusters and SNc neurons have especially high bioenergy requirements. High levels of iron content play role in the activity of mitochondria and further generation of ROS and disease progression [15]. Different studies reveal that systems like glutamatergic, GABAergic, cholinergic, noradrenergic, serotonergic, opioidergic, histaminergic, and adenosinergic are involved in the pathogenesis of non-motor symptoms of PD and give a novel idea about modulating these pathways as a therapeutic approach to treat non-motor symptoms [16].

PD is a multifactorial disease, with Age the biggest risk factor with mean age-onset at 60 years [17]. Along with genetic and environmental factors, way of living and pre-existing medical conditions play a major role in the etiology of PD [18]. Other most important mechanisms involved in PD are the accumulation of misfolded protein aggregates, failure of protein clearance pathways like ubiquitin-proteasome and autophagy lysosomal system, mitochondrial abnormalities, antioxidants, excitotoxicity, neuroinflammation [19-21]. Assumptions explain that PD onset occurs in the gut and propagates to the brain via a vagus nerve that helps the alpha-synuclein to reach the target brain. The communication between the gastrointestinal system (GIT) and the central nervous system

(CNS) is bi-directional. Alteration of the intestinal microbial flora contributes to GIT disruption, which induces neuroinflammation via prion α-synuclein expression and produces PD-like symptoms [22]. (**Fig. 2**)

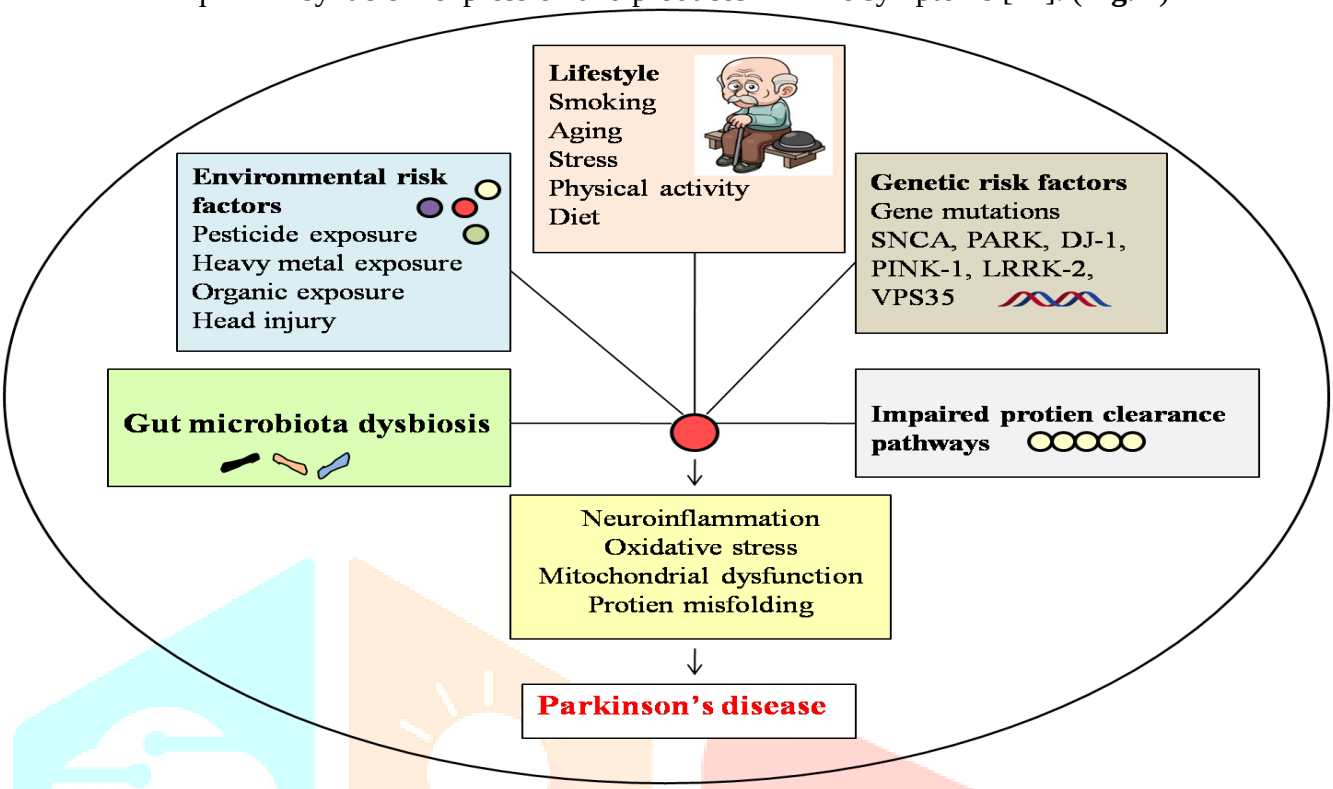

Figure 2 PD etiologies: Biological interactions of different factors such as environmental, genetic and lifestyle leading to activation of different neurodegenerative pathways in PD

3. Pathophysiological mechanisms

Human postmortem trials have revealed that substantia nigra par compacta and locus coeruleus of PD patients have neuronal loss of dark-pigmented region and the onset of motor symptoms is approximately at 30% loss of DA neurons in the SNpc and symptoms becomes severe at 60% [23-25] Death of SNpc containing dopaminergic (DA) neuromelanin and locus coeruleus containing noradrenergic neurons in the locus is related with loss of pigmentation [26]. The exact pathological mechanisms underlying the non-motor symptoms in PD are still unclear, other than dopaminergic system cholinergic, adenosinergic, glutamatergic, GABAergic, noradrenergic, serotonergic, and histaminergic systems are also affected in PD, which may contribute to some of the non-motor symptoms [27]. Stage 1 and 2 of Braak hypothesis suggests that disease starts in the medulla oblongata and olfactory bulb, In stage 3 and 4 diseases is typically diagnosed as the disease progresses to the substantia nigra pars compacta and other midbrain and basal forebrain structures and clinical signs and symptoms arise and at stage 5 and 6 cortical regions are affected [28].

α-synuclein misfolding, aggregation and the other number of mechanisms have been implicated in PD pathogenesis. (**Fig.3**) They include mitochondrial dysfunction, protein clearance deficiency, neuroinflammation and an oxidative stress, related to several events, including transportation damage, microtubules integrity loss, neuronal excitotoxicity, iron metabolism dysregulation, endoplasmic reticular impairment, and other interrelated enzyme activation. Describing the different pathophysiologic mechanisms in depth is beyond the reach of this review. This review will highlight insights that could have potential consequences for counseling.

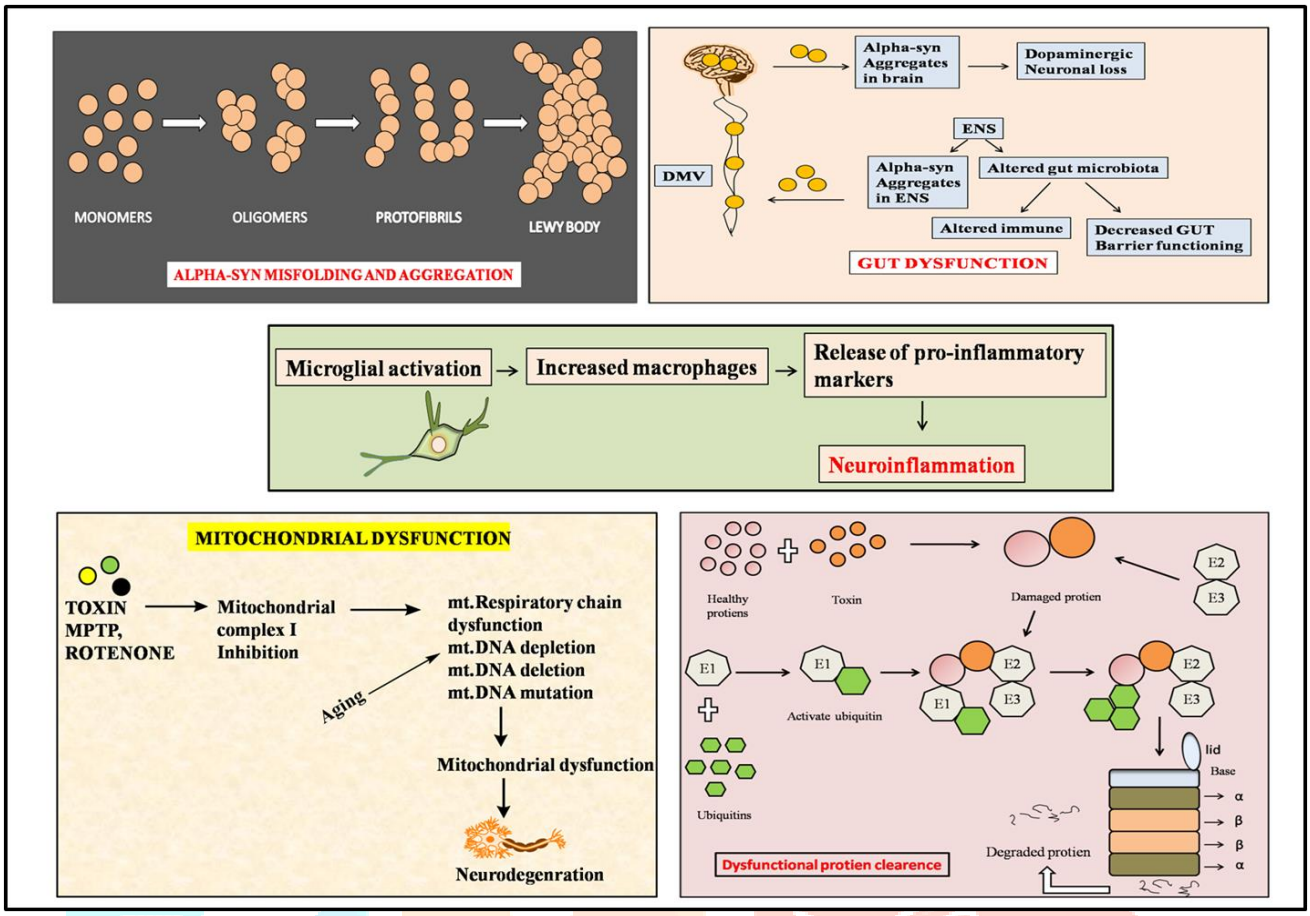

Figure 3 Pathogenesis of PD: Different mechanisms coupled with protien misfolding, gut dysfunction, neuroinflammation And other factors contributing to PD neurogenesis.

3.1. Gut alterations

Different researchers have shown interest in a hypothesis in recent years that PD originates from ENS and slowly spreads to the brain through a variety of pathophysiological pathways explaining a bi-directional connection between GIT and CNS [29]. This hypothesis is backed by several findings, including constipation before motor symptoms, the axonal transport of α-synuclein to the brain through the vagal nerve [22]. Difference in composition of fecal microflora of OPD (old PD patients), healthy control and NPD (new PD patients) which enables us to improve our understanding of PD pathogenesis linked to ENS [30].

Braak and colleagues spent more than 20 years contributing to our understanding of intestinal PD pathogenesis, They went on to observe a six-stage system of PD progression in the brain and surrounding olfactory regions based on observed α-synuclein spreading patterns which could be linked with many clinical features of PD, the disease mechanism is introduced in both the lower brain and the olfactory structure of the dorsal motor nucleus of the vagus nerve (DMV). Then the disorder extends from DMV to susceptible regions of the medulla, pontine tegment, mid-brain and basal forebrain [28]. Further studies illustrate the potential for the neurotrophic agent to be a GIT cause or any external toxins or pathogen entering the olfactory route that contributes to the invasion of the pro-inflammatory mucosal environment increase its permeability to the intestinal epithelium barrier, contributing further to the accumulation of ROS species, and unbalanced homeostasis, which can eventually cause α-synuclein aggregation by different immunological mechanisms. [31].

Under the SPF conditions, it was observed that substiantia nigra and caudate putamen had aggregates of α-synuclein in ASO animals and GF-ASO animals displayed fewer α-synuclein aggregates, thus suggesting microbiota regulates pathways that promote α-synuclein aggregation and prevent the clearance of insoluble protein aggregates. Research done by Sampson, T.R. and colleagues in thy1-αsyn (α-synuclein-overexpressing [ASO]) mouse model showed that 12-13 week-old ASO animals having a complex microbiota and required significantly more time to cross a challenging beam as compared to wild-type and at later age (24-25 weeks old), SPF-ASO (antibiotic-treated specific pathogen-free) animals were found to be exhibiting a progressive decline in motor function, which on other hand was significantly delayed by GF-ASO (Germ-free) animals than healthy

controls [32]. Interestingly, a recent study conducted by Barichella and colleague in PD patients found increased verrucomicrobia, christensenellaceae, Lactobacillaceae, and decreased Lachnospiraceae and ruminococcaceae species [33]. A study conducted by Jin, M and his mates explore the composition of fecal microflora between PD patients with > 1 year (OPD), NPD and healthy controls revealing OPD had high levels of rikenellaceae compared to HCs and higher levels of turicibacteraceae were found in NPD group as compared to HCs [30], thus highlighting that gut microbiota has a major role in the pathogenesis of Parkinson's disease.

3.2. α-synuclein misfolding and aggregation

α-synuclein is mostly found in the brain and has a given tertiary structure regarding biochemical endogenous interactions [34], but in aqueous solutions, α-synuclein aggregation is resisted because of the presence of stable tetramers and is referred to as a natively unfolded protein [35]. Pathological α-synuclein aggregation inside neurons is poisonous to dopamine nerve cells, leading to a decline in synaptic proteins, progressive neuronal disorders, cell death and further associated with the pathogenesis of PD [36]. Relative overproduction of the protein, the presence of mutations such as A53T, E46K, and H50Q [37, 38] and impairments in protein degradation may act as triggers of alpha-synuclein aggregation [39].

α-synuclein have alpha-helical structures shaped by its interaction with its N-terminal with negatively charged lipids [40] some pathological conditions such as mutations in the SNCA gene, oxidative stress and post-translational modifications can influence aggregation and its conformational changes [41]. Danzer, K.M and mates in 2009, suggested that oligomeric species of α-synuclein may increase the abnormal aggregation of protein [42] and evidenced by Winner B and colleagues in 2011 in rats indicating the oligomeric form of α-synuclein are more neurotoxic species instead mature insoluble fibrils [43], thus these observation suggest mechanisms underlying the spread of α-synuclein pathology in the brain.

3.3. The dysfunctional protein clearance system

The ubiquitin-proteasome system (UPS) and autophagy-lysosome system are two major pathways for the clearance of dysfunctional proteins present within the cell. The functioning of UPS is based on breaking of proteins to ubiquitin by tagging them to ubiquitin and degrading it through proteasome as the last step. Macroautophagy, microautophagy, and chaperone-mediated autophagy (CMA) are the main three constituents of the autophagy-lysosome system working with different mechanisms, and damage in either of these leads to the accumulation of dysfunctional proteins, contributing to PD pathogenesis.

3.3.1 Ubiquitin proteasome system (UPS)

Mammalian cells need to balance the production and degradation of their proteins for both cellular homeostasis and neuronal functions, which is done efficiently by the ubiquitin-proteasome system [44]. UPS is an important intercellular pathway which causes the degradation of misfolded/damaged proteins in cells by the use of a ubiquitous, a small protein that is found in all cells. There are many ubiquitins found inside the cells, but they cannot randomly attach to proteins and is regulated control system to avoid any unwanted protein degradation [45]. This process is carried out sequentially by a cascade of enzymatic reactions involving different enzymes E1 activating an enzyme that links itself with carboxyl end of ubiquitin enzyme through thioester bond which is ATP dependent process, E2 conjugating enzyme that transfers activated ubiquitin to cysteine residue and E3 ligating enzyme that transfers the ubiquitin to the target protein [46]. The ubiquitinated protein which is ready to be degraded requires proteosomes composed of two outer alpha rings and two inner beta rings completing 20s proteasome, with these 20s the 19s cap is attached to either one or both alpha subunit rings, thus completing the structure of 26s proteasome fully functional to degrade proteins in peptides [47]. Target ubiquitinated protein is recognized by 19s cap when it binds to ubiquitin chain and pushes the rest of the protein in the proteasome, thus recycling back the ubiquitin-protein into short peptides [48].

Several molecular, genetic, and biochemical studies evidenced that a mixture of multiple protein aggregates, such as α-synuclein are seen in human post-mortem brains of patients who were diagnosed with PD [49],which may be due to dysfunction in ubiquitin, parkin, and UCH-L1 (ubiquitin carboxy-terminal hydrolase-L1) and other proteins [50]. The impairment in the functioning of UPS leads to the accumulation of proteins subsequently resulting in the death of cells. Ubiquitinated α-synuclein is the main component of the Lewy body found in the brain of PD patients having an inhibitory effect on 26s proteasome-mediated protien degradation [51]. Different genetic PD models developed by a mutation in α-synuclein genes such as A53T, A30P, E46K and aggregation in different toxin-induced PD phenotype models have established their pathological role in PD. Kumar, V, and

colleagues demonstrated their work by using zinc as a toxin as a model of Parkinson's, concluding zinc induced UPS impairment and further led to the aggregation of α-synuclein, thus subsequently resulted in the death of dopaminergic neurons [52]. Research done by Lu and colleagues in 2009 in transgenic mice with a mutation in parkin, showed that mice produced progressive hypokinetic motor defects, α-synuclein accumulation and age-dependent dopamine neuron loss in substiantia nigra and striate, which showed that parkin mutation fails to interact with α-synuclein, and further contributes to the accumulation and development of lewy bodies, thus improves the understanding of the interaction between parkin and its substrate is crucial in regulating dopaminergic neurons [53].

A study was done by Lindersson, E, and mates showed that interaction between the α-synuclein aggregate and the 20S complex has shown a highly binding efficiency rather than a 19S regulatory complex and is greatly inhibited by α-synuclein filaments [54]. UCH-L1 gene is regarded as an essential gene for long-term memory storage and its susceptibility, in association with its two mutations I93M and S18Y in the pathogenesis of PD [51]. Experimental studies reveal that UCH-L1 is co-localized within the LB (Lewy body) of PD neurons [50]. Xiong, H in 2009, demonstrated that DJ-1 is essential for PPD complex (Parkin, PINK-1, and DJ-1) that promotes ubiquitination and degradation of parkin and deficit of DJ-1 further cause a reduction in ubiquitination of parkin and increases the accumulation of misfolded parkin substrates [55]. Lu and colleagues in 2009 [53] showed that PINK1 deficiency impairs the proper functioning of UPS and further results in aggregation of α-synuclein, revealing the pathological link between UPS and PINK1 in PD.

3.3.2 Autophagy-lysosome system (ALS)

The lysosomal compartment of ALS is responsible for degrading different cellular components and long-lived proteins [56]. Alteration in enzymes is associated with the pathogenesis of PD since the activity of different lysosomal enzymes was found to be impaired in SN of PD patients. A decrease in structural protein LAMP-1 levels were found in the brain of PD patients [57, 58] another postmortem examination found increased levels of autophagosome marker LC3II [59]. Downregulation of different autophagy genes and elevated protein levels associated with α-synuclein were found in peripheral blood mononuclear cells (PBMCs) in PD patients [60]. Reduction in macroautophagy induction and increased macroautophagy were seen in patients with LRRK2 mutations [61, 62]. Inhibition of CMA and macroautophagy led to α-synuclein accumulation [63] and knockdown of DJ-1 exhibited impairment in α-synuclein uptake and showed lower autophagy-dependent degradation of p62 and LC3 proteins [64], thus these studies support the concept that alterations in the autophagy lysosomal system are involved in PD pathogenesis.

3.4. Neuroinflammation

Neuroinflammation plays a central role in many neurodegenerative disorders like Parkinson's disease (PD), Alzheimer's, Huntington's Disease (HD), and Amyotrophic lateral sclerosis (ALS) [65] Previous analysis has shown that acute neuroinflammatory reaction is good for CNS functioning and persistent chronic neuroinflammation leads to brain damage [66]. The onset of PD has been correlated with a variety of viral infections and these pathogens may infiltrate the basal ganglia through different means such as nasal mucosa and olfactory tracts and eventually contribute to a cascade of neuroinflammatory and neurodegenerative events [67, 68]. α-synuclein pathology is widely believed to be closely related to PD neuroinflammation and evidence for this phenomena stretches over fundamental scientific research of cell culture or animal models [69].The brain is continuously regulated to preserve CNS homeostasis by releasing inflammatory cytokines and chemokines through glial cell activation by Pathogen-Associated Molecular Patterns (PAMPs) and Damage-Associated Molecular Patterns (DAMPs) [70].

3.4.1 Role of microglia

These cells are the main protection of the innate immune system in addition to the homeostatic functions. These cells secrete inflammatory cytokines and chemokines, expel toxic compounds and engage in neuronal repair and remodeling [71]. In standard terms, microglia have a morphology of ramification of several branches used for the identification of injured neurons, abnormally aggregated proteins such as α-synuclein and synapses. In other words, microglia establishes homeostasis in the brain [72]. Two types of microglia phenotypes are activated on brain trauma referred to as M1 type and M2 type. M1 phenotype is promoted by lipopolysaccharide (LPS) and interferon (IFN)-c, and is liable for proinflammatory reactions. M2 phenotype when activated produces anti-inflammatory effects which are classified into three subtypes M2a, M2b, M2c [73]. Resting microglia can be

activated by classical activation (M1 phenotype), alternative activation, and acquired activation (M2 phenotype) [74]. upon activation, microglia produce a broad spectrum of inflammatory mediators like TNFα, IL-6, NOS2, COX2 leading to generation of ROS, and excess accumulation of these results in dopaminergic cell death [75].

3.4.2 Role of astrocytes

Astrocytes characterized by star-shaped morphology are the most abundant glial cells in CNS playing a huge role in providing metabolites for neurons, synaptic repair of tissue plasticity, filling lacunas caused by dead neurons, and secreting trophic factors essential for the survival of neurons and synaptic activity [76]. Like microglia, astrocytes are subdivided into two phenotypes A1 destructive and A2 as defensive. Activation of A1 phenotype is done by classically activated microglia via secretion of the cytokines IL-1α and TNF-α leading to loss of neuronal survival [77]. Astrocytes are activated through a variety of molecules like pro-inflammatory mediators freed from microglia stimulation and these immunosignals are further enhanced by astrocytes. Synergistic neuroinflammation by microglia and astrocytes leads to the death of dopaminergic neurons and eventually, neurodegeneration [78] Involvement of astrocytes in PD is well documented in several in vivo and in-vitro studies. Post mortem studies of the PD brain showed the presence of astrogliopathy and a significant increase in destructive A1 phenotype in SN and striatum [79, 80].

Neuroinflammation is a cascade of activities, including microglia activation, and enhances cytokine secretion. In 1988, a study done by McGeer and colleagues for the first time with evidence suggested that neuroinflammation may be involved in PD pathogenesis via the involvement of reactive microglia in SNpc in the human post-mortem brain [81]. The recent animal model study showed that suppression of M2 microglia polarization marker, in substiantia nigra leads to over activation of microglia and further exacerbated neuronal death [82]. Positron emission tomography (PET) neuroimaging experiments demonstrated that microglia activity is pronounced in different PD brain regions [83]. Activated microglia gets accumulated around the over-expressed/aggregated α-synuclein and further leads to the release of proinflammatory cytokines [84]. In dose-dependent study of primary cultures, α-synuclein mediates activation of microglia [85]. Thus, suggesting the role of α-synuclein and microglia-mediated inflammatory responses. Activated microglia further activates astrocytes by the release of pro-inflammatory markers and other molecules and takes control over further immune processes. Activation of both microglia and astrocytes at a time leads to uncontrolled neuroinflammation and reinforce the death of DA neurons [86].

Genes associated with PD such as α-synuclein (SCNA) might contribute to immune activation by microglia and astrocytes. In vitro study shows that wild type α-synuclein induced activation of microglia and further resulted in increased proinflammatory molecules [87]. Microglial activation is seen in α-synuclein transgenic mice in SNpc [88]. Several other genes associated with PD such as PARKIN, LRRK2, PINK1, DJ-1 are found to controls the expression of pro-inflammatory cytokines, [89-91] suggesting an early role for genes and inflammation in PD pathogenesis. Thus, shreds of evidence clear the engagement of neuroinflammatory responses in exacerbating neuronal dysfunction.

3.5. Mitochondrial dysfunction

Mitochondria are highly complex organelles necessary for maintaining neuronal function and integrity through sustainable energy supply for important cellular functions including synaptic activity [92]. Mitochondria consist of two membranes, the external membrane separating it from the cytosol and the inner membrane surrounding the matrix, the area between these membranes is called intermembrane space. ATP is produced by an oxidative phosphorylation mechanism on the inner membrane. Nutrients have high energy electrons in the NADH form (nicotinamide adenine dinucleotide), which are used in protein compounds to pump proton from matrix to intermembrane, and this continues pumping generate a proton gradient that attracts a more negative matrix to a positively charged proton. The membrane also contain a large protein complex called F1 F0 ATP synthase which uses proton gradient to drive the synthesis of ATP molecules, just as man-made power plants produce electrical energy by using the flow of wind, water, or steam to rotate a turbine, the synthase makes ATP by using proton flow from one side of the inner membrane to other to rotate protein subunit. The pathology of PD concerning mitochondria leading to cell death have many different drivers such as genetic factors, acquired DNA mutations or inherited ones (α-synuclein, parkin, PINK1, DJ-1), environmental factors like toxins (MPTP, Rotenone), aging and some other, causing mitochondrial dysfunction further leading to loss of dopaminergic neurons [93].

A free radical is an unstable molecule that wants to steal an electron from another molecule or give away its own; this makes it highly reactive and destructive for important proteins and cellular structure including DNA.

Free radicals are a normal byproduct of molecular processes in the body and the delicate balance of their presence is beneficial for the normal cellular responses and healthy immune system, but a stressful lifestyle, aging genetic factor, poor diet, and toxicity in the environment leads to an increase in free radical activity and subsequently resulting in oxidative stress [94]. (**Fig.4**) Oxidative stress (OS) is characterized by the overproduction of reactive oxygen (OS) species leading to altering pathways for protection, altered membrane permeability, calcium imbalance, mitochondrial DNA mutations and mitochondrial respiratory damage. ROS are important mediators of signal transduction pathway that act by activating proteins, such as tyrosine kinase, mitogen-activated protein kinase [95]. OS disrupts many important cellular processes and is a key factor in many unhealthy conditions; the body keeps oxidative stress under control by producing antioxidants, [96] such as enzymatic antioxidants (superoxide dismutase (SOD), glutathione peroxidase (GPx), catalase (CAT) and non-enzymatic antioxidants (ascorbic acid (Vitamin C), α-tocopherol (Vitamin E), glutathione (GSH), carotenoids, flavonoids) as a defense against free radicals [97].

In 1983, Langston and colleagues found the link between mitochondrial dysfunction and PD by using MPTP[98]. Lipophilic compound MPTP is transformed by monoamine oxidase (MAO) to 1–methyl 4 phenylpyridinium (MPP+) into its toxic form which penetrates BBB and interferes with respiratory chain (RC) complex I activity (NADH; Ubiquinone oxidoreductase), [99] resulting in disruptions in the respiratory chain complexes and the subsequent generation of reactive oxygen species (ROS) leading to oxidative stress [100]. Arising evidences highlight the role of ROS leading to oxidative stress and its link to dopamine metabolism. The post-mortem of PD patients showed a deficiency of complex I (~60%) and complex II (~65%) in SN [101].

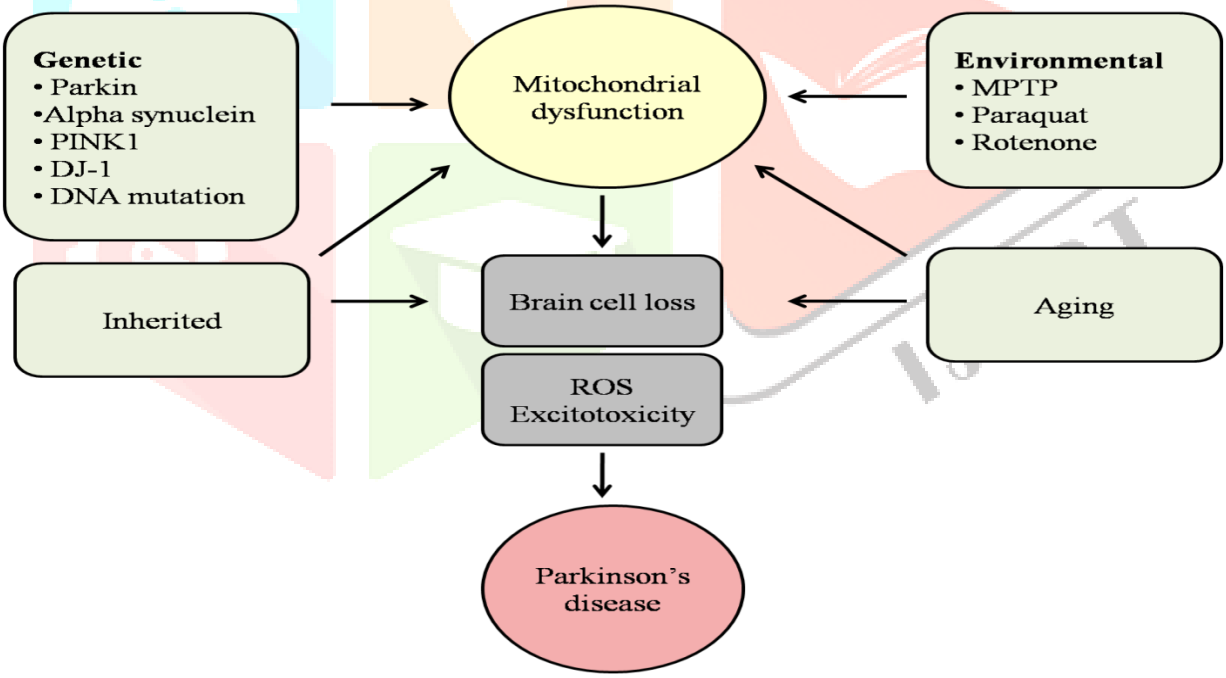

Figure 4 Different factors contributing to mitochondrial dysfunction and subsequently leading to PD

3.5.1 Mitochondrial dysfunction: implications of gene mutation

Genetic research related to PD has described over 20 monogenic forms and 100 loci as risk factors for PD. Modern genetic techniques and population studies have helped in publishing a huge amount of clinical and genetic data related to PD [102, 1]. In this review, we highlight different dominant and recessive PD-related genes in brief.

Autosomal-dominant genes

PARK-SNCA (PARK1)

α-synuclein was the first PD-related gene discovered that provided evidence for the genetic cause of PD [10]. α-synuclein is a pre-synaptic, small protein with a total of 140 amino acids and an N-terminal region with a positively charged, the central hydrophobic region that is strongly acidic C-terminal domain involved in axonal transport, neurotransmitter release, and vesicle docking and priming [103, 104]. The major components of Lewy bodies found in the PD brain are a non-soluble, aggregated, and fibrillar form of α-synuclein as pathological hallmark of PD [49]. Several in vivo studies explain the mitochondrial dysfunction linked to α-synuclein. A recent study done in 2015 in A53T human α-synuclein over expressed mice by using a tissue-specific gene amplification strategy showed early-onset mitochondria abnormalities, characterized by positive cytoplasmic inclusions as a marker of macroautophagy and preceded by dopaminergic neurodegeneration [105]. Subramaniam and colleagues made another analysis in 2014 in the Thy1-aSyn mice model, which showed defects in mitochondrial respiratory complexes I, II, IV, and V due to accumulation of alpha-synuclein in mitochondria of ventral midbrain, striatum, and cortex [106].

Alpha-synuclein decreases the mitochondrial biogenesis ability, by binding to the promoter region of Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1a) which is a key component of mitochondrial biogenesis [107]. It also affects the functioning of mitochondria through indirect mechanisms, such as impaired functioning of autophagy and mitophagy processes. A study done by Winslow and mates in 2010 in overexpressing wild-type alpha-synuclein showed that Rab1 protein, a precursor of autophagosome directly modulated autophagy [108]. These studies indicate that mitochondria may play a central role in spreading alpha-synuclein between neurons.

PARK-LRRK2 (PARK8)

LRRK2 (Leucine-rich repeat kinase 2) is a PD related gene with common G2019S mutation, 4% of family cases and 1% of sporadic cases alone are proposed [109]. LRRK2 has vesicular, autophagic and protein synthesis involving [110]. LRRK2 affects mitochondrial fission, autophagy impairment and increased ROS generation by interacting with Drp1 and fostering mitochondrial fragmentation [111]. The over-expression of G2019S and R1441C mutations have been observed as reducing mitochondrial membranes, decreased complex -IV function, increased uncoupling, changed mitochondrial motility, and impairment of calcium signalling [112]. Accumulation of autophagosomes and increase in p62 levels have been demonstrated in dopaminergic neurons from PD patient-derived induced pluripotent stem cells (iPSCs) expressing LRRK2-G2019S at endogenous levels [113]. A 2012 study found that with G2019S and R1441C mutations in PD Patient iPSCs, a disturbance in mitochondrial motility and increased susceptibility to multiple stressors was treated with Rapamycin [114]. Together these studies suggest that there is a direct link between LRRK2 and mitochondrial dysfunction in the pathogenesis of PD.

Autosomal-Recessive Genes

PARK-Parkin (PARK2)

Parkin is among the most common autosomal recessive PD-related gene, with almost 50% of early onset PD patients [102]. The first case of mutation in the Parkin gene was identified in a Japanese family [115]. Matsuda, N, and mates suggested that parkin is associated with mitochondrial degradation in vitro, [116] which may be due to induction of mutation in parkin, leading to dysfunction of mitophagy, suggesting accumulation of damaged mitochondria contributes to dopamine neurodegeneration [117]. Mitophagy is autophagous removal of damaged/dysfunctional mitochondria, controlled by pathways mediated by PINK1/Parkin and accumulation caused by mutation in PINK1/Parkin lead to dysfunctional mitochondria and subsequently neuronal death [118]. Interestingly, a recent study done by Noda, S, and colleagues in aged parkin knockout mice showed locomotor impairments with hind limb defects and neuronal loss, suggesting that in absence of parkin, impairments in mitochondrial clearance may be one of the emerging pathological hallmarks of PD [119].

PARK- DJ-1 (PARK7)

DJ-1 is a small protein of 189 amino acids, involved in the regulation of mitochondrial activity and protection of neurons against oxidative stress [120]. Bonifati, V and colleagues in 2003 suggested that mutation in DJ-1 is associated with 1-2% of early-onset recessive cases of PD [121]. A study done by Thomas, K.J and his mates in the M17 human dopaminergic neuroblastoma cell line showed that loss of DJ-1 leads to fragmentations of mitochondria, loss of mitochondrial polarization, and accumulation of autophagy markers [122]. Edson and colleagues demonstrated that the DJ-1 knockout (KO) zebrafish line showed a reduction in enzyme tyrosine

hydroxylase, reduction in mitochondrial complex I activity in skeletal muscle, and body mass loss, thus linking DJ-1 with mitochondrial pathology of PD [123]. Another study done by Almikhlafi, M.A, and his mates in DJ-1 knockout rats, revealed that out of 371 mitochondrial proteins 76 were expressed differently which were isolated from the striatum of 3 months old DJ-1 KO rats, 76 proteins expressing differently were involved in mitochondrial functioning pathways [124]. Above few studies improve our understanding about effect of mutation in the DJ-1 and its link with mitochondria-related to the pathology of PD. (**Fig. 5**)

4. Lifestyle

Protective factors

Consumption of greater caffeine, higher levels of vitamin D and cigarette smoking has been shown as a protective factor in multiple studies [125-127]. Caffeine as an adenosine receptor antagonist shows neuroprotective effect by blocking adenosine A2A receptor and is well documented in several experimental models of PD [128, 129]. A cohort study done in Singapore revealed that consumption of black tea is associated with a reduced risk of developing PD [130]. A possible protective effect of smoking is seen in a recent study of dopamine transporter deficit in de novo PD [131]. There are some evidences that physical activity is a protective factor in decreasing the development of PD, and higher physical activities are related to lower risk of PD in the middle or later life [132, 133]. Clinical trials have revealed that physical exercise is feasible and should be prescribed to patients with PD [134]. Consistency of ibuprofen use had shown the 27% reduction in risk of PD in a cohort study but other NSAIDS were not found to be consistent [135].

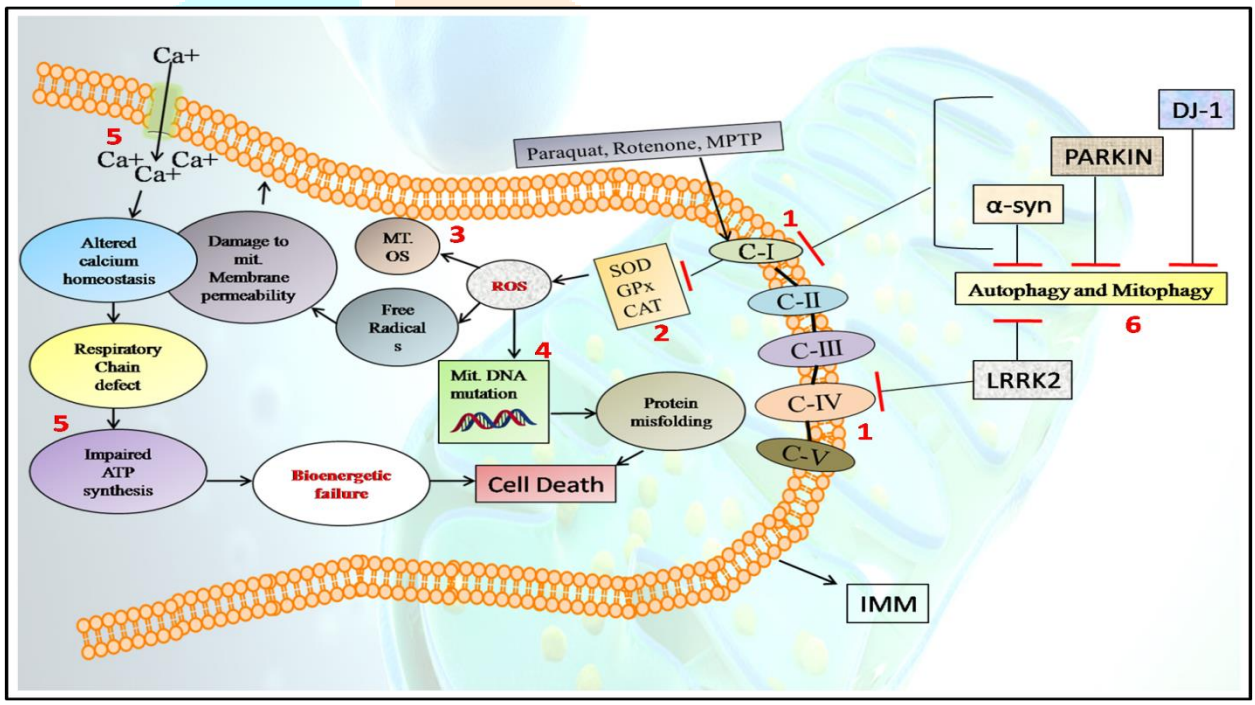

Figure 5 PD with Mitochondrial dysfunction. Pathogenesis of PD have been linked to alterations in different aspects, such as (1) Reduced complex I and IV activity due to interaction with different toxins like PQ,MPTP,RT and alterations in genes such as SNCA,PARKIN,DJ-1,LRRK2. (2) Generation of ROS due to inhibition of antioxidants (SOD, GPx, CAT) (3) Mitochondrial oxidative stress (OS) due to production of ROS. (4) MtDNA damage leading to hyperphosphorylation of protiens, further protien misfolding and cell death (5) Impairment in ATP synthesis due altered calcium homeostasis leading to bioenergetic failure. (6) Inhibition of autophagy and mitophagy. IMM- inner mitochondrial membrane, MT OS- mitochondrial oxidative stress, ROS- reactive oxygen species.

Risk factors

Consumption of high milk and other dairy products has been reported to increase the risk of PD in a meta-analysis involving Health Study and the Health Professionals Follow-up Study (HPFS), Honolulu-Asia Ageing Study (HAAS), and the Cancer Prevention Study II Nutrition (CPS-IIN) [136-138]. Different neurodegenerative disorders have been proposed with a direct link between neuronal damage and life stress. Diagnosis of post-traumatic stress disorder patients showed an increased risk of developing PD and in the presence of severe response to stressful life events adjustment disorder was found to be associated with an increased risk of PD [139,

140]. The risk of PD has increased significantly with the number of stressful activities. Some Case-control study results support the hypothesis that stress may play a role in the development of PD [141].

5. COVID-19 and PD

SARS-CoV and MERS-CoV caused major respiratory and mortality problems in 2002 and 2012 [142, 143]. SARS-CoV-2 (severe ACS 2), which began in China and entered some 200 nations, affected over 664,873,02 individuals 6,724,248 deaths (World Health Organization; 4:57pm CEST, 25 January 2023) and caused the new corona virus disease (COVID-19) among these a total of 13,156,047,747 vaccine doses have been administered till 23 January 2023. Findings indicate that the virus is a form of RNA (genome of 32KB) that has a glycoprotein crown capable of sometimes mutating [144]. Binding of virus glycoprotein to ACE2 (angiotensin-converting enzyme 2) receptors expressed in lungs causes acute alveolar injury, edema, and inflammation through the infection of pulmonary cells that can lead to acute respiratory distress syndrome (ADRs) in adults [145, 146]. Symptoms of COVID-19 develop between 2 and 14 days after infection such as fatigue, fever, non-productive cough, diarrhea, headache, nausea, and loss of smell and taste. [6] Age as the most important risk factor in a severe form of infection along with other factors like hypertension, cerebrovascular disease, diabetes, and immunosuppression increases the severity of COVID-19 [147, 148].

The ongoing COVID-19 had severe consequences on patients with neurological diseases, such as Parkinson's disease (PD) affecting physical and mental status due to compromised healthcare in the lockdown. In 1992 E Fazzini and mate detected antibodies against coronavirus in cerebrospinal fluid of PD patients which suggested a role of infections in neurodegeneration [149]. ACE2 and dopamine are associated with dopamine depletion [150], and penetration of SARS-CoV-2 into the brain can cause synergistic damage and deteriorate PD symptoms with ACE2 receptors [151]. Prasad and colleagues reported during the lockdown, 9% of PD patients showed elevated stress and depression [152]. A survey done in April 2020 showed that patients affected with PD were suffering from higher stress levels and were less active as compared to before the pandemic [153]. A multi-center cohort study of PD patients with COVID-19 showed a higher mortality rate in PD patients to the general population, suggesting the underlying cause may be the advanced age and hypertension in patients with PD [154]. Worsening of PD symptoms such as tremor, stiffness, and fatigue during SARS-CoV-2 infection was also observed [155]. Studies took together clear that COVID-19 had major consequences on patients with PD allowing the researchers to test the risk and protective factors related to PD and COVID-19.

6. Management of Parkinson's disease

Parkinson's disease (PD) has been recognized as one of the complex psychiatric syndromes reflecting a group of neurological disorders. To date, licensed PD therapies have concentrated on countervailing approaches for the management of clinical symptoms, and the biggest barrier in the advancement of medication may be the lack suitable screening system for PD because of the complicated existence of disorders. Measurement of preventive clinical result is done with different clinical scales such as UPDRS [156] which is among the most frequently used and combines objective and subjective data of a patient being used to intervene. For the eventual treatment of this disease researchers have faced a large number of difficulties, the medicines available so far have offered patients with just symptomatic relief and even later in their lives it has caused significant side effects [157]. This review is focused on some alternative interventions other than common therapy such as few herbals and surgical/device-aided treatment as hope with the advancement in the management of PD.

Authorized PD therapy is intended to improve striation Dopamine levels to boost associated motor deficiencies. Regrettably, Treatments like dopamine precursors, dopamine agonists, MAO-B inhibitors, COMT inhibitors, anticholinergics, few miscellaneous therapies are not a long-term solution. [158] and new drugs such as Safinamide, [159] Nourianz (istradefylline) [160] are also being used to modulate dopamine levels in symptomatic PD therapy.

The available medicinal services help prevent patients from feeling worse over a short amount of time and do not target several sites that could prevent disease development. Ayurveda opens up a strong and alternative path with limited side effects in treating this condition. Aromatic plants have been used since ancient times for improving dietary taste and organoleptic properties and several different plants have been defined to have therapeutic benefits for the prevention of neurodegenerative disorders. Ayurvedic plants most commonly used such as Brahmi (Bacopa monnieri), Baicalein and Mucuna pruriens and ashwagandha has withheld positive properties that could act as contributors in treating PD, and (Table 1) explains some other highly recommended drugs that could reflect in treating PD.

Bacopa monnieri

Bacopa monnieri (shared name: brahmi, bacopa or bacopa) (Scrophulariaceae family) water hyssop is a Perennial medicine known to actively sharpen the mind with active constituents Bacosides A and B are considered to be neuroprotective in action by crossing the barrier to blood [161]. Different studies define different pharmacological effects exhibited by Brahmi such as anti-inflammatory, [162] neuroprotective, memory-enhancing, and cognitive functions [163, 164] Drosophila and mouse experimental models of PD indicate that the Bacopa monnieri Extract (BME) induces neuroprotection through the reduction of oxidative stress markers such as malondialdehyde (MDA), hydrogen peroxide and protein carbonyl content against paraquat toxins [165-167]. BME is found to improve mitochondrial membrane potential and restore the activity of mitochondrial electron transport chain complexes and modulate proteasomal functioning [168]. A study in mice model of PD showed the ethanolic extract of Bacopa monnieri has an anti-apoptotic effect on dopaminergic neurons [169]. BME reduced the higher levels of pro-inflammatory markers, oxidative stress, and α-synuclein aggregation in rat experimental model of PD [170]. Thus, adding in our knowledge about the neuroprotective role of Bacopa monnieri in PD.

Baicalein

Baicalein (family Labiatae) a flavonoid obtained from the dried root of Scutellaria baicalensis showed a protective effect in concentration dependent manner by inhibiting ROS accumulation, maintaining mitochondrial membrane potential, and by suppressing apoptosis induced by rotenone in PC12 cells [171]. Baicalein is reported to possess different mechanisms such as modifying enzyme activity, preventing apoptosis, controlling the repression and accumulation of proteins, anti-inflammatory and maintaining the activity of neurotransmitters that are involved in the pathogenesis of PD [172]. The ethanolic extract Scutellaria baicalensis in BV-2 and RAW264.7 cells have attenuated the LPS mediated levels of iNOS, NO, Cyclooxygenase-2 (COX-2), and prostaglandin E2, respectively [173]. Different doses of baicalein show a decrease in muscle tremors and maintain the balance between glutamate and gamma-aminobutyric acid in 6-OHDA rat experimental model [174]. Baicalein was found to increase the levels of DA and 5-hydroxytryptamine [175] and decreased inhibition of proteasome and mitochondrial depolarization along with the reduction in E46K fibrilization rescued toxicity in N2A cells [176].

Mucuna pruriens

Mucuna pruriens (Mp) (velvet bean) have the main phenolic compound L-DOPA isolated from its seeds. A well-reported clinical study suggested that Mp isolated L-dopa shows better tolerability than standard L-dopa [177] and better efficacy is seen with Mp in the long-term management of PD in double-blind clinical trials. [178] Cotyledon powder of Mp is reported to be effective at genomic levels [179]. A study done in 2014 in Drosophila melanogaster (Dm) genetic model with PINK1B9 mutant showed the neuroprotective effect of Mp extract [180]. The effect of oral Mucuna pruriens water extract (MPWE) against Parkinsons was shown in 2012 by Lieu and his mates without triggering drug-induced dyskinesias [181]. Antioxidant properties and the expression for tyrosine hydroxylase in substiantia nigra and striatum were enhanced by Mp's paraquat induced neurotoxicity [182], and the anti-apoptotic effect was seen by increasing expression of bcl2 and decreasing Bax [183]. The effects of Mp on anti-inflammatory conditions have been observed with an inhibition of the expression of MPP-induced neuropathic cytokines and nuclear translocation of NF-κB [184]. The above few studies together can provide an understanding of the therapeutic potential of Mp in the management of Parkinson's disease.

Withania somnifera

Withania somnifera root extract powder (Ashwagandha, Indian ginseng) has an enhanced impact on Parkinson's rotenone-induced model using various mechanisms such as improvement in the respiratory mitochondrial chains and decrease in oxidative stress with its anti-oxidant properties [185]. WS extract is shown to inhibit oxidative stress along with an increase in expression of tyrosine hydroxylase cells in MB–PQ induced PD mice brain [186]. Oral treatment of WS root extract showed an increase in catecholamines [dopamine (DA), 3, 4-dihydroxyphenylacetic acid (DOPAC), and homovanillic acid (HVA)] in corpus striatum in the PD mice model [187]. An increase in anti-apoptotic protein expression Bcl-2 and reduced levels of Bax protein was seen in the MB-PQ model of PD [188]. Further few observations reported in **Tab.1** strengthen our knowledge about pharmacological potential of withania somnifera in treating Parkinson's disease.

The above studies supports the fact that herbal extracts, plays a significant role in attenuating Parkinson's disease by mechanisms such as maintaining NT levels, clearing of protein aggregates, as an antioxidant, regulating apoptotic markers and neuroinflammation that enhance neuroprotection and reflecting a positive hope and opening an alternative way in the treatment of PD and other neurological disorders.

Table 1 Neuroprotective effect of different herbal constituents in models of Parkinson's disease

SNO.	DRUG	EXTRACTED FROM	ACTIVE CONSTITUENTS	TARGETS	MECHANISM	REFERENCES
1.	Tea Catechins	Dried leaves of Camellia sinensis (L.) (Theaceae)	Polyphenols, catechins [epicatechin (EC), epicatechin gallate (ECG), epigallocatechin (EGC) and epigallocatechin gallate (EGCG)]	↓ Apoptosis ↓ Motor impairment ↓Dopaminergic neuronal injury in the substantia nigra	↓ α-synuclein oligomers	199, 200
2.	Ginseng	Root and Rhizomes of Panax ginseng C. A. Mey. (Araliaceae)	Ginsenosides Rb1, Rd, Re and Rg1	↓ Apoptosis ↓ Neuronal death in substantia nigra ↓ Neuroinflammation	↑ Bcl-2 expression ↓ Bax expression ↓Mitochondria-mediated apoptosis. ↓TNF-α, IL-1β, IL-6 mRNA ↓ Microglia activation	201,202
3.	Curcumin	Roots of Curcuma longa L. (Zingiberaceae)	Curcumin	↓ Cell death ↑ Motor Performance	↓ Oxidative damage (↑ glutathione, ↓ reactive oxygen species activity, ↓ malondialdehyde) via activation of the Akt/Nrf2 signaling pathway ↓ Mitochondrial cell death Pathway	203-205
4.	M. Pruriens	Seeds of Mucuna pruriens L.(DC) (Fabaceae)	Levodopa	Restore endogenous level of dopamine	↑ Dopaminergic and mitochondrial complex I activity	182, 206
5.	Coffee	Ground roasted beans (Rubiaceae)	Caffeine (1,3,7-trimethylxanthine) Quercitin, Flavone	↓Loss of striatal Dopamine ↑ Cell viability	↓ NF-κB ↓ Oxidative/ nitrative damage	207
6.	Acanthopanax	Stem bark of A. senticosus Harms (Araliaceae)	Sesamin and Eleutheroside B	Prevent Behavioral dysfunction and modulate transcription factors	Modulates tyrosine hydroxylase (TH), superoxide dismutase, catalase (CAT), inducible nitric oxide synthase (iNOS) and interleukin-6 expression	208
7.	Resveratrol	Grapes, Peanuts, Berries, and Pines	Resveratrol (polyphenolic phytoalexin)	↓ Neuroinflammation ↓ Apoptosis	↓ Microglia activation ↓ COX-2 expression ↓Reduces α-synuclein aggregation	209-211
8.	Baicalein	Dried root of Scutellaria baicalensis (Labiatae)	Baicalein	↓ Neuroinflammation	↓ COX-2 expression ↓ iNOS expression ↓ NO ↓ PGE2 ↓ α-synuclein aggregation	212-214

9.	Ashwagandha	Root powder of withania sominifera (L.) Dunal (Solanaceae)	Withaferin, withanolide	Oxidative stress motor functions ↓ Apoptosis	↑ glutathione (GSH) and glutathione peroxidase (GPx) ↑DA levels in striatum ↓ iNOS expression ↑ Bcl-2 expression ↓ Bax expression	186-188
10.	Brahmi or waterhyssop	Bacopa monnieri a perennial creeping herb (Plantaginaceae)	Bacopaside and bacoside	Oxidative stress motor impairment electron transport chain (ETC) complexes ↓ Apoptosis	↑ glutathione (GSH) and glutathione peroxidase (GPx) ↓a-synuclein aggregation	215

Device aided therapies/Surgical treatment

Deep brain stimulation

Globally 150,000 patients have been operated on with DBS of the subthalamic nucleus (STN) and globus pallidus (GPi) and reported as a successful operating procedure for advanced PD. Other bilateral operating procedure with lesion surgeries such as, thalamotomy, pallidotomy, subthalamotomy have already been conducted but the use of such in present time is restricted due to risk associated with surgical lesions [189]. The success of DBS depends on adequate patient selection and expertise Stereotaxic surgeon [190]. In a randomized controlled trial, DBS treated patients showed again in a mean of 4.6 hours/day without troubling dyskinesia as compared to patients receiving medical therapy with 0 hours/day [191]. In another EARLYSTIM randomized trial patients with a mean age of 52 years showing early motor symptoms were treated with DBS along with medical therapy and comparison with alone medical therapy showed improved quality of life in the DBS group [192]. Adverse effects are seen when surgical procedures and misconduct are negligent of stimulation system [193].

Adaptive deep brain stimulation

Few limitations of cDBS such as, stimulation-induced side effects, the requirement of regular adjustment in stimulation, low battery life have given hope of developing a new possibility with advanced features such as close-loop or adaptive DBS (aDBS). The concept of aDBS is based on recording local field potentials (LFPs) from the implantable DBS lead and getting feedback regarding the clinical status of a patient and automatically adapt to the output and benefits of such a device include increased battery life, efficacious stimulation, and lesser side effects [194]. Several clinical studies have proven DBS as an effective therapeutic strategy in treating disabling motor complications that require expertise for management. Adaptive and other advances such as improving connectivity, directional stimulation can improve other limitations and quality of life by focusing on challenging motor symptoms of the PD patient [190, 195].

Duodenal Infusion of Levodopa-Carbidopa Intestinal Gel (LCIG)

Levodopa and carbidopa are suspended in a carboxymethyl-cellulose forming gel preparation containing Levodopa 20 mg/ml and Carbidopa 4.63 mg/ml and delivered directly into proximal jejunum with infusion pump via percutaneous endoscopic gastrojejunostomy (PEG-J) tube [196]. The use of LCIG has been proven to be beneficial in double-blind, double-dummy, and double-titration trial [197] Double-blind trial with 250 patients in GLORIA showed improvement in non-motor and motor by use of LCIG [198].

Conclusion

PD is a multifactorial neurodegenerative condition with both environmental and genetic factors having compromised cellular mechanisms and thus highly demanding successful treatment. Pathology of PD is related with common set of pathways including gut alterations, mitochondrial dysfunction, oxidative stress, protein

aggregation, impaired autophagy and neuroinflammation. Several ongoing treatments are concerned with providing only symptomatic relief but no strategy for preventing the loss of dopaminergic neurons and restoring dopamine levels in striatum is available. Multiple targets are involved in treatment of PD and available conventional drug treatments act on a single particular with serious side effects making it difficult to control a complex syndrome. Researchers from various experimental studies have found different strategies involving herbal drugs acting on multiple targets and DBS, Adaptive DBS, LCIG which provide hope for better PD therapy in future.

ABBREVATIONS

PD- Parkinson's disease; SNpc- Substantia nigra pars compacta; LB- Lewy bodies; SNCA- Synuclein Alpha; LRRK2- Leucine-rich repeat kinase; ROS- Reactive oxygen species; OPD- Old PD patient; NPD- New PD patient; HCs- Healthy controls; DMV- Dorsal motor nucleus of vagus nerve; ASO- Alpha-synuclein overexpressing ; SPF-ASO- Antibiotic-treated specific pathogen free; GF- Germ free; UPS- Ubiquitin-proteasome system; CMA- Chaperone-mediated autophagy; UCH-L1- Ubiquitin carboxy-terminal hydrolase-L1; ALS- Autophagy-lysosomal system; LAMP-1- Lysosomal-associated membrane protein 1 ; PBMCs- Peripheral blood mononuclear cells; CMA- Chaperone-mediated autophagy; PAMPs- Pathogen-associated molecular patterns; DAMPs- Damage-associated molecular patterns; PET- Positron emission tomography; MPTP- 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MPP+- 1-Methyl-4-phenylpyridine; PGC1a- Peroxisome proliferator-activated receptor gamma coactivator 1-alpha ; iPSCs- Induced pluripotent stem cells; HPFS- The Health Professionals Follow-Up Study ; COVID-19- Coronavirus Disease 2019; SARS- Severe Acute Respiratory Syndrome; MERS- Middle East Respiratory Syndrome; ACE-2- Angiotensin-converting enzyme 2; ADRs- Acute respiratory distress syndrome; UPDRS- Unified Parkinson's Disease Rating Scale; MAO-B- Monoamine oxidase B; COMT- Catechol-O-methyltransferase; Mp- Mucuna pruriens; 6-OHDA- 6-hydroxydopamine; MB-PQ- Maneb–Paraquat; DOPAC- 3,4-Dihydroxyphenylacetic acid; HVA- Homovanillic acid; DBS- Deep brain stimulation; EARLYSTIM- Deep Brain Stimulation in Patients With Early Parkinson's Disease; LCIG- Levodopa-carbidopa intestinal gel; PEG-J- Percutaneous endoscopic transgastric jejunostomy

DECLARATION

Ethical Approval and Consent to Participate (Applicable if animals/human or cell lines are used)

Not applicable.

Human and Animal Rights Participate (Applicable if animals/human are used)

Not applicable.

Format for Availability of Data and Materials

Not applicable.

Format for Consent for Publication

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Conflict of Interest

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