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Mitochondrial Dysfunction and *PINK1* Gene Mutation: In Parkinson's Disease (PD)

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ABSTRACT Parkinson's disease (PD) is a progressive neurodegenerative disorder, caused by the loss of dopamine and characterized by the presence of cytoplasmic protein inclusions. In Parkinson's disease, mitochondrial dysfunction has gained attention because number of genes like *LRRK2, SNCA, PARK7, Parkin* and *PINK1* which implicates the pathogenesis of Parkinson's is also found to be essential for the maintenance and proper functioning of the mitochondria. Any mutation in these genes can potentially result in mitochondrial dysfunction. Amidst, *PINK1* gene has a crucial role because it is important for the activation of the mitochondrial quality control mechanism and clearance of damaged mitochondria. Hence, the mutation in the *PINK1* gene may mediate the accumulation of dysfunctional mitochondria and may induce Parkinson's disease. This review elaborates interlink between *PINK1* gene and mitochondrial dysfunction in Parkinson's disease.

INTRODUCTION

Parkinson's disease (PD) is the most common progressive neurodegenerative disorder, which is characterized by the frequent loss of dopamine and by the presence of protein inclusions called Lewy bodies (Hayes 2019; Raza et al. 2019). Alpha-synuclein protein is considered to be a central component of Parkinson's pathogenesis (Rocha et al. 2018). Globally, around 9.3 million people are affected by Parkinson's disease. The clinical symptoms of Parkinson's include both motor (bradykinesia, postural instability, resting tremor and muscular rigidity) and non-motor (cognitive impairment, sleep disturbance, sensory and neuropsychiatric symptoms) (Sveinbjornsdottir 2016). Parkinson's is a multifactorial disorder with risk factors like age, gender, family history of neurological disorders, traumatic brain injury, exposure to pesticides, neurotoxins, caffeine consumption, smoking and non-steroidal anti-inflammatory drugs (NSAIDs) (Ascherio and Schwarzschild 2016; Delamarre and Meissner 2017). At present, there is no cure for Parkinson's disease. Levodopa (L-dopa) is a standard potential dopaminergic therapy for Parkinson's disease (Salat and Tolosa 2013). Stem cell therapy is an emerging potential treatment for Parkinson's. In recent times, several transplantation methods, gene therapies and surgical methods like deep brain stimulation have been targeting dopaminergic neuron in Parkinson's patients for treatment (Dhivya and Balachandar 2017). Dysfunction in the mitochondria has a vital role in Parkinson's pathogenesis (Ryan et al. 2015). The impaired mitochondrial function may be a result of increased damage and decreased ability to repair or clear damaged mitochondria (Zhu and Chu 2010). Mutation in *Leucine-rich repeat kinase 2* (*LRRK2)*, *Synuclein alpha (SNCA)*, *PARK7*, *Parkin* and *PTEN induced kinase 1 (PINK1)* are directly connected with the mitochondrial dysfunction. These five genes are important for the proper maintenance and functioning of mitochondria and are also commonly involved in Parkinson's pathogenesis (Larsen et al. 2018; Park et al. 2018). Among these genes, *PINK1* is pivotal because it has a key involvement inclearances of damaged mitochondria through mitophagy (Truban et al. 2017). Beyond mitophagy, *PINK1*gene is also important for the flawless functioning of mitochondria, integrity maintenance, regulating-complex I activity and cell survival (Koh and

Chung 2012; Voigt et al. 2016). A mutation in the *PINK1* gene implicates Parkinson's disease through insufficient removal of damaged or dysfunctional mitochondria (Miller and Muqit 2019).

Objective

The objective of the paper is to summarize the mitochondrial dysfunction caused by *PINK1* gene mutation in association with Parkinson's.

METHODOLOGY

About, 685 articles regarding Parkinson's disease, interlink between *PINK1* gene and mitochondrial dysfunction were collected from accredited scientific databases including Pubmed, Springer, Wiley, Nature, Elsevier and Science Direct for appropriate content. The research works published inthe past twenty yearswere screened and scrutinized using the keywords like Parkinson's disease, *PINK1* gene, mitochondrial dysfunction and therapeutic approach, the scrutinized content is drafted in the literature review.

OBSERVATIONS AND DISCUSSION

Mitochondria and Parkinson's Disease

Mitochondria are subcellular organelles found in the cytoplasm (Trancikova et al. 2012). Mitochondria are popularly referred as powerhouse of the cell; the major functions of mitochondria are energy biogenesis, apoptosis (Oyewole and Birch-Machin 2015) and which is also involved in various cellular events like regulation of calcium homeostasis, stress response and energy metabolism (Mounsey and Teismann 2010). Mitochondrial dysfunction is considered to be a primary or a secondary contributor to Parkinson's disease (Pickrell et al. 2013). The genetic and environmental factors contribute to the pathogenesis and mitochondrial dysfunction in Parkinson's disease (Hu and Wang 2016). Mitochondrial dysfunction may result from impaired bioenergetics, mutations in mitochondrial DNA (mtDNA) or changes in the dynamics of mitochondria such as imbalances in fusion and fission, impaired calcium buffering and cell death. Complex I mitochondrial respiratory chain impairment is one of the key factor of Parkinson's disease. Reduced level of mitochondrial complexes I, II and IV were reported in Parkinson's patients (Grünewald et al. 2019). Slow Ca^{2+} oscillation is important for the import of Ca^{2+} into mitochondria matrix. Continuous Ca^{2+} influx is essential for physiological release of dopamine, ATP production and oxidative phosphorylation. Imbalance in calcium import may trigger the opening of mitochondrial permeability transition pore and may result in release of cytochrome c, increased ROS production and induce cell death (Ludtmann and Abramov 2018; Rani and Mondal 2020). Several mitochondrial proteins encoded by mtDNA are involved in production of ATP. So alteration in mtDNA may result in mitochondrial dysfunction. In Parkinson's patients, reduced copy number of mtDNA is observed in peripheral blood and substantianigra (Martín-Jiménez et al. 2020). The presence of mutated proteins associated with mitochondria and alterations in the mitochondrial morphology may lead to the neurodegenerative process of Parkinson's disease (Thomas and Beal 2010; Moon and Paek 2015; Bose and Beal 2016). Number of genes linked to the inherited form of Parkinson's disease can implicate the mitochondrial dysfunction, which implies the central participation of the mitochondria in Parkinson's disease (Weng et al. 2018). Recently, 19 Parkinson's disease-causing gene has been revealed some of them are related to the mitochondrial dysfunction (Jiang et al. 2019). Rare genetic variants in Heat Shock Protein A9 (HSPA9), Tumour necrosis factor receptor-associated protein 1 (TRAP1) and Ras homology family member T1 (RHOT1) of Parkinson's linked genes remains as an emerging concept, which could also help in better understanding of the complex genetic structure of Parkinson's disease (Larsen et al. 2018). Some of the Parkinson's related genes associated with mitochondrial impairmentis tabulated in Table 1.

LRRK2

LRRK2 mutation is the strongest genetic risk factors in sporadic Parkinson's disease (Wallings et al. 2015). *LRRK2* is a multi-domain protein, which possesses both GTPase and kinase function (Zhang et al. 2019). *LRRK2* has been associated with the cellular functions and sig-

Table 1: Parkinson's related genes and their functions

Gene	*Chromosome*	*Protein encoded*	*Normal function*
LRRK2 (Autosomal dominant)	12q12	Dardarin	Dardarin is a multidomain protein, which contains Ras of complex domain, kinase enzymatic domains and has been associated with the cellular functions and signaling pathways that includes the retromer complex modulation, mitochondrial function and autophagy (Rosenbusch and Kortholt 2016; Funk et al. 2019).
SNCA (Autosomal dominant)	4q21	α-synuclein	α-synuclein is important for the maintenances of synaptic membrane function, ubiquitin proteasome system and involved in neurotransmitter control (Greten-Harrison et al. 2010; Bellucci et al. 2012).
PARK7 (Autosomal recessive)	1p36	DJ-1	DJ-1 (Deglycase) is a multifunctional, redox sensitive protein with putative roles like controlling protein-RNA interaction, neuroprotection, androgen receptor modulation and protective role against oxidative stress (Bjorjblom et al. 2013; Nieto and Campello 2019).
PINK1 (Autosomal recessive)	1p35–p36	Pink1	PINK1 regulates the mitochondrial quality control and clearances damaged mitochondria through activation of parkin (Leites and Morais 2018; Barodia et al. 2019).
PRKN (Autosomal recessive)	6q25.2–q27	Parkin	Parkin is an ubiquitin ligase helps in degradation of misfolded proteins with ubiquitin proteasome system and it is associated in protein clearance pathways (Dawson and Dawson 2010; Chan et al. 2011).

Source: Authors themselves have tabulated the content from available data. References are given in the table

nalling pathways which includes vesicle trafficking, neurite outgrowth, autophagy and cytoskeletal maintenance. *LRRK2* mutations are associated with late-onset Parkinson's disease (Rideout and Stefanis 2014).

SNCA

Synuclein alpha is a small, highly acidic, 14.5kDa protein which contains 140 amino acids (Bisaglia 2009). *SNCA* is a substantive component of the Lewy bodies, which is the hallmark of Parkinson's disease (Mullin 2013). *SNCA* in oligomeric state can cause the oxidative stress, endoplasmic reticulum stress, mitochondrial dysfunction, disruption of the plasma membrane, proteasome impairment and pore formation which leads to the activation of apoptosis pathway and result in the consequence of cell death (Gallegos et al. 2015). Accumulation and oligomerization of *SNCA* may lead to mitochondrial dysfunction and implicate the Parkinson's disease (Di Maio et al. 2016).

PARK7

PARK7 provides instruction for marking protein DJ-1. It contains 189 amino acids with seven β-strands, nine 5α-helices and present as a dimer (Ariga et al. 2016). The functions of DJ-1 are antioxidative reaction, transcriptional regulation, mitochondrial regulation and protect against the oxidative stress-induced cell death (Maita et al. 2013). Deletion of DJ-1 (cytoprotective protein) is sufficient to cause genetic Parkinson's disease. Impairment in fission/fusion dynamics, respiration, membrane potential maintenance, enhancement of mitochondrial dysfunction and astrocyte mitochondrial motility would be caused by DJ-1 deficiency (Larsen et al. 2011).

PINK1

PINK1 gene has 8 exons and 581 amino acids. The *PINK1*has N terminal with 34 amino acids, mitochondrial targeting sequence (MTS),

transmembrane domain (TMD) with the homology to serine/threonine kinase of Ca^{2+}/calmodulin family exhibiting an autophosphorylation activity (Fig.1) (Gandhi et al. 2006). A functional motif found in the C-terminal region governs kinase activity and substrate selectivity (Mills et al. 2008). Aggregation and clearance of depolarized mitochondria are facilitated by *PINK1* gene (Chu 2010). The cells are protected from mitochondrial dysfunction and cell apoptosis by *PINK1* (Matsuda et al. 2013). *PINK1* gene emphasison mitochondrial quality control and the mitochondria damage response pathway (Minami et al. 2015). The clearance of damaged mitochondria and mitochondrial integrity is maintained by the functional interaction between the PINK1 and Parkin proteins (Pilsl et al. 2012). To prevent cell death and accumulation of damaged mitochondria, they are identified and targeted for degradation by PINK1 (Ando et al. 2017). Presenilin-Associated Rhomboid-Like protein (PARL) mediates the cleavage of PINK1 (Funk et al. 2019). The degradation of PINK1 is inhibited in the absences of PARL (Jin et al. 2010).

The key modulators of the mitochondrial homeostasis are PINK1 and High-Temperature Regulation A2 (HtrA2) (Desideri and Martins 2012). The PINK1 has a potential relationship with HtrA2, TRAP1 and Parkin that implicates network of the pathway on mitochondrial regulation (Chu 2010). TRAP1 is a heat shock protein and it is a cellular substrate for PINK1 protein and it is phosphorylated to prevent the apoptosis induced by oxidative stress (Pridgeon et al. 2007). Omi encoded mitochondrial protease is involved in the *PINK1*/*Parkin* pathway (Whitworth et al. 2008). Accumulation of unfolded proteins in mitochondria, defective mitochondrial respiration and enhanced production of reactive oxygen species (ROS) are the result of HtrA2 loss that could contribute to the neuronal cell death (Moisoi et al. 2009).

PINK1/Parkin pathway is important for mitochondrial biogenesis,which mediates the proteasomal degradation of PARIS and dopamine neuronal survival. PGC-1 family of transcription factors governs larger part of mitochondrial biogenesis but expression of PGC-1α is inhibited by PARIS (transcriptional repressor). PINK1 phosphorylates the PARIS at S613 and S322 to control the ubiquitination and Parkin, which interacts with zinc-finger of PARIS and labels it for destruction (Lee et al. 2017; Jiang et al. 2019; Ge et al. 2020).Upon depolarization, PINK1 is autophosphorylated at different sites which includes Thr-257, Ser-228 and Ser-402. In PINK1 protein, 465th serine residue is identified as one of the autophosphorylation sites (Guo et al. 2017) and Parkin ubiquitin-like domain on protected Ser65 which triggers the mitophagy (Schubert et al. 2017).

Mitochondria and *PINK1* Gene

In the healthy mitochondria, PINK1 is continuously imported and then degraded by mitochondrial membrane potential, which drives the mitochondrial import (PINK1) through translocase of the outer membrane (TOM) and translo-

Fig. 1. Schematic representation of important Domain structures of*PINK1*
***Numbers indicate the positions of amino acid residues; MTS- Mitochondrial targeting sequence; TMD- Transmembrane domain.**
*Source:*Authors have pictured this figure by themselves with the data collected from following sources (Pilsl et al. 2012; Minami et al. 2015; Ando et al. 2017)

case of inner membrane (TIM) complex of the mitochondria where proteases MPP (Mitochondrial processing peptidase) cleaves the full-length PINK1 at the mitochondrial targeting sequence to generate the 60kDa form and the transmembrane domain is cleaved by PARL to form 52kDa within the inner mitochondria (Imai 2012; Pickrell and Youle 2015; Rüb et al. 2017).

In damaged mitochondria, 63kDa full-length of PINK1 protein accumulates in the outer mitochondrial membrane ontranslocase of outer mitochondrial membrane (TOMM7), an accessory subunit of the TOM complex (Pickrell and Youle 2015; Zheng et al. 2018) because the potential to cross the inner membrane cannot be maintained by damaged mitochondria (Jones 2010). The role of PINK1 is to maintain the mitochondrial function through mitophagy (Kawajiri et al. 2011). Mitophagy is a process of selective autophagy of the mitochondria, which eliminates damaged mitochondria (Dernie 2020). Mitophagy of damaged mitochondria is initiated by Parkinson's related *PINK1*and *Parkin* (Rakovic et al. 2013). Two genes *PINK1* and *Parkin* normally work together in the same pathway (Rani and Mondal 2020). Parkin is recruited from the cytosol to mitochondria by PINK1 and initiates the mitophagy (Matsuda et al. 2013). PINK1 phosphorylated ubiquitin that activates *Parkin* for full activation of Parkin E3 activity, phosphorylation of both ubiquitin and Parkin is required. Activated Parkin increases the amount of ubiquitin, which is then phosphorylated by PINK1 to recruit more Parkin (Koyano et al. 2014; Seirafi et al. 2015). In the mitochondrial outer membrane, ubiquitin-binding adaptor such as p62 recognizes the hyper-ubiquitination and forms isolation membrane by interacting with the autophagosomal protein LC3. The formed autophagosome fuses with the lysosome to form autolysosome and degrades the damaged mitochondria (Ashrafi and Schwarz 2013) (Fig. 2a).

Basal mitophagy is independent of *PINK1/Parkin* pathway which is driven by MDVs formation. PINK1 and Parkin regulates adaptive immunity by suppressing the mitochondrial antigen presentation (MitAP) and mitochondrial-derived vesicles (MDVs) formation, but in the absences of these protein inflammation triggers MitAP in immune cells. Parkin inhibits Sorting nexin 9 and Rab9 which is required for the formation of MDVs and MitAP (Matheoud et al. 2016). In *PINK1* knockout mice, intestinal infection engages MitAP and elicits establishment of mitochondria-specific CD8+ T cells (Matheoud et al. 2019). Recently, researchers have found that Human telomerase reverse transcriptase (hTERT) promotes the mitophagy by suppressing the cytosolic processing and cleavage of PINK1 and also enhances its localization by down-regulating mitochondrial processing peptidase β which leads to the full-length PINK1

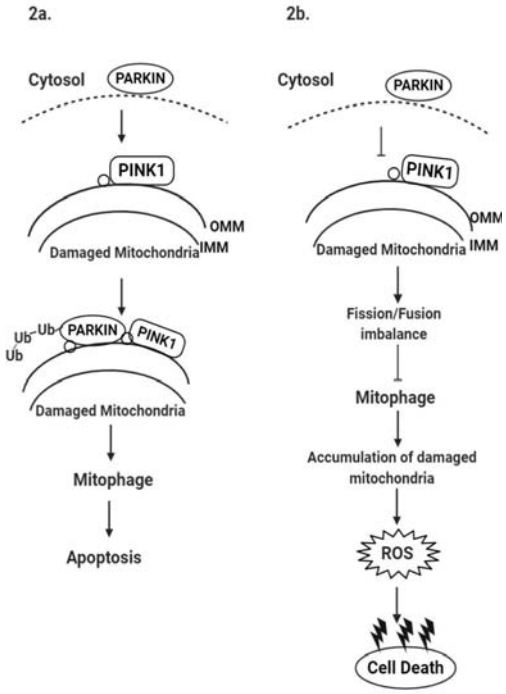

Fig. 2b. Mechanism of *PINK1* linked Parkinson's disease Hypothetical mechanism of *PINK1* mutation induced Parkinson's disease. Loss of function mutation in *PINK1* gene reduces PINK1 kinase activity and decreases the recruitment of Parkin to mitochondria, which results in decreased ubiquitination. Decreased ubiquitination of Parkin causes an imbalance in fission and fusion leading to impaired mitophagy. Impaired mitophagy lacks the potential to clear the accumulation of damaged mitochondria in turn increases the reactive oxygen species production and results in neuronal cell death.

Source: Authors have pictured this figure by themselves with the data collected from following sources (Deng et al. 2008; Keane et al. 2011).

accumulation on the outer mitochondrial membrane. hTERT also increases LC3-II formation (Shin and Chung 2020).

Mechanism of PINK1 Gene in Parkinson's Disease

Different factors and signaling pathways are involved in dopamine neurons degradation causing Parkinson's disease. The PINK1 interacts with other signaling proteins to implicate Parkinson's disease (Mills et al. 2008). *PINK1* gene loss of function is a rare case in autosomal recessive Parkinson's disease (Exner et al. 2007). Truncating nonsense and missense mutation are the two homologous mutations that commonly affect the PINK1 kinase domain (Valente et al. 2004; Taymans et al. 2006). A mutation in the *PINK1* gene causes the reduced activity of the PINK1 protein kinase, which decreases the recruitment of Parkin (Kawajiri et al. 2011). *PINK1/ Parkin* pathway normally promotes mitochondrial fission through optic atrophy 1 (opa1) and Mitofusin (mfn) or drp1 to inhibit fusion (Deng et al. 2008). Outer mitochondrial membrane proteins such as mitofusins, opa1are ubiquitinated by Parkin,which facilitates the isolation of dysfunctional mitochondria for mitophagy (Valente et al. 2004). Hence, decreased ubiquitination of Parkin causes an imbalance in fission/fusion and in addition to this excessive fusion is caused by inhibition of PINK1(Yang et al. 2008) which in turn may lead to defective mitophagy and resulting in the increased mitochondrial dysfunction or accumulation of damaged mitochondria (Maiti et al. 2017). A major source of free radicals within the cell is the mitochondria (Beal 2003). Electron transport chain (ETC) inhibition and mitochondrial dysfunction lead to the generation of ROS (Keane et al. 2011). Excessive ROS causes oxidation of protein, lipids and other macromolecules and induces dopaminergic neuron death (Weng et al. 2018). As the consequences of dopaminergic neuron death, the release of dopamine is decreased and that ultimately results in the neuronal cell death, which is the major pathophysiology of Parkinson's disease (Fig. 2b).

Biomarkers

Biomarkers for Parkinson's disease is divided into 4 criteria: clinical, imaging, biochemical and genetic (Table 2). Metabolomics has become a powerful tool for identifying novel biomarkers and also for profiling the metabolites in biofluids (cerebrospinal fluid, blood and urine), faecesandbrain tissues of neurological disease (Shao and Le 2019). In Parkinson's, metabolite profiling studies revealed that purine metabolism (uric acid) and aromatic amino acids (phenylalanine, tyrosine, tryptophan) are altered. Alteration in fatty acid metabolism, branched-chain amino acids and alanine are also directed to the mito-

Table 2: Various biomarkers used in diagnosis for Parkinson's disease

Biomarkers	*Examinations*	*Reference*
Clinical	Olfactory dysfunction Vision disturbance REM (Rapid eye movement) sleep behaviour disorder Depression	(Cova and Priori 2018; He et al. 2018).
Neuroimaging	Positron emission tomography scan Magnetic resonance imaging Single-photon emission computed tomography scan Transcranial B-mode sonography.	(Pickrell and Youle 2015; Emamzadeh et al. 2018).
Biochemical	Uric acid Apo-lipoprotein A1 α-synuclein Protein DJ-1 Butyrylcholinesterase activity	(Shen and Ji 2013; Saito 2014; Swanson et al. 2015; Dong et al. 2017; Tian et al. 2019).
Genetic	Mutational analysis of *LRRK2,SNCA, PARK7, Parkin, PINK1* and *GBA* (Glucosylceramidase beta) genes.	(Magdalinou et al. 2014; Lotankar et al. 2017).

Source: Authors themselves have tabulated the content from available data. References are given in the table

chondrial dysfunction (Havelund et al. 2017). Methods available for diagnosis of mitochondrial dysfunction are MitoChip, whole-exome sequencing and new chip-based high-throughput platform screening method (Zamzami et al. 2011; Theunissen et al. 2018).

Mitochondrial Dysfunction as a Therapeutic Target for Parkinson's Disease

Environmental factors like exposure to neurotoxins, MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), Rotenone and 6-OHDA (6-hydroxydopamine) also contributes to mitochondrial dysfunction in Parkinson's disease. MPTP can cross the blood-brain barrier because of its high lipophilicity and it is oxidized by monoamine oxidase B in the glial cells, which is further oxidized to toxic compound MPP^+ and can be taken by the dopamine transporter to dopaminergic neurons. Complex I of ETC is inhibited by MPP^+ present within the neurons. As consequences of complex I impairment, generation of ROS and nitrogen species increase, the production of mitochondrial ATP is decreasedcausing neuronal cell death (Winklhofer and Haass 2010). 6-OHDA and rotenone (extremely hydrophobic) can easily cross the cellular membrane of neurons and astrocytes with the help of dopamine transporter and can induce the increased production of ROS, the formation of α-synuclein-aggregates, inhibition of mitochondrial complex I and causing the activation of caspase 9 through release cytochrome C (proapoptotic molecules) which the trigger activation of caspases 3, 6 and 7 and can induce apoptosis (Cabezas et al. 2013). These chemicals are commonly induced in animal models to mimic Parkinson's symptoms which can be useful for therapeutic approach and drug development.

Autophagy and mitochondria shares a strong reciprocal relationship, impairment in one process can result in damage to another one. Correcting the mitophagy could be useful for the development of efficient biomarkers for Parkinson's disease (Liu et al. 2019). Mitochondrial dysfunction has a significant contribution to Parkinson's pathogenesis, which can be used as a drug target.Coenzyme Q (CoQ_{10}) is a cofactor for mitochondrial ETC that accepts electrons from complex I, II and III (Beal 2003) and takes part in ATP production. CoQ_{10} is found in three redox states, they are ubiquinone (fully oxidized), semiquinone and ubiquitol (fully reduced form). Reduced levels of CoQ_{10} were found in mitochondria isolated from Parkinson's patients (Filograna et al. 2016). CoQ_{10} showed neuroprotective effects against mitochondrial toxins such as MPTP (Chaturvedi and Beal 2013). MitoQ is a powerful mitochondrial antioxidant and lipophilic cation. It could be absorbed in the mitochondria and has protection against the oxidative damage (Snow et al. 2010). α-lipoic acid is a natural dithiol compound and which is an essential cofactor for mitochondrial bioenergetic enzymes. It is used in the therapies tochelatesmetals, restores glutathione levels and scavenge free radicals, which declines with advancing age (Smith et al. 2004; Shay et al. 2009).Vitamin antioxidants, apocynin and creatine have also shown neuroprotective potential against MPTP-induced mouse model (Jin et al. 2014). Some compound used in therapeutic approach for Parkinson's disease are tabulated in Table 3.

CONCLUSION

In Parkinson's disease, the reason for the depletion of dopaminergic neurons still remains puzzled. Studies prove that mutation in *PINK1* gene implicates Parkinson's disease through mitochondrial dysfunction. Likewise, many genes and their proteins involved in Parkinson's disease are also found to be connected with mitochondrial dysfunction. On the other hand, potential risk factors for Parkinson's like aging, exposure to neurotoxins, pesticides and oxidative stress is also pointing towards mitochondrial dysfunction. Evidence support's fact that mitochondrial dysfunction has a critical role in Parkinson's pathogenesis. Thus, broadening the knowledge about *PINK1/Parkin* pathway, mitophagy and mitochondrial dysfunction would be optimal for the development of biomarkers and therapeutic approaches to Parkinson's disease.

RECOMMENDATIONS

Further detailed investigations on the functions of *PINK1*, *Parkin* and their proteins in mitochondrial dysfunction and altered mitophagy

Table 3: Compound used in therapeutic approach for Parkinson's disease

Compound	*Animal model/ Cell Line*	*Therapeutic effect*	*Reference*
α-Arbutin	SH-SY5Y (human neuro-blastoma cell) and drosophila	α-arbutindis played neuro protective effect by rescuing the mitochondrial abnormality and motor function and also significantly displayed protective effect against mitochondrial dysfunction and apoptosis	(Ding et al. 2020)
Mangiferin	Rat	Mangiferin is a natural product which can cross the blood brain barrier and exert protective activity against memory decline, mitochondrial dysfunction, oxidative stress, apoptosis and neuroinflammation	(Feng et al. 2019)
Ginseng	Drosophila	On treatment with ginseng total protein, *PINK1*^{B9} mutant flies displayed significant improvement in dopamine content, climbing ability, wing position, mitochondrial function and reduced oxidative stress	(Liu et al. 2020)
Carnosic acid	SH-SY5Y	Carnosic acid counteracted the 6-OHDA toxicity by activating *PINK1/Parkin* mediated mitophagy and also promotedthetransport of parkin into mitochondria	(Lin and Tsai 2019)
Curcumin	SH-SY5Y	siRNA-mediated knock down of *PINK1* in SH-SY5Y cells exhibited decrease in cell viability, mitochondrial respiration, mitochondrial membrane potential and increase in apoptosis. When *PINK1*siRNA cells are pre-treated with Curcumin and followed by paraquat exposure they displayed protective effect against apoptosis and mitochondrial dysfunction	(Van der Merwe et al. 2017)

Source: Authors themselves have tabulated the content from available data. References are given in the table

can be useful for developing therapeutic approaches to Parkinson's disease.

ABBREVIATIONS

PD- Parkinson's disease;
NSAIDs- non-steroidal anti-inflammatory drugs;
L-dopa- Levodopa;
LRRK2- Leucine-rich repeat kinase 2;
SNCA- Synuclein alpha;
PINK1- PTEN induced kinase 1;
mtDNA- mitochondrial DNA;
HSPA9- Heat Shock Protein A9;
TRAP1- Tumour necrosis factor receptor associated protein 1;
RHOT1- Ras Homology family member;
DJ-1- Deglycase;
MTS- Mitochondrial targeting sequence;
TMD- Transmembrane domain;
PARL- Presenilin-Associated Rhomboid-Like protein;
HtrA2- High-Temperature Regulation A2;
ROS- Reactive oxygen species;
Hsp70- Heat Shock Protein 70;
PARIS- Parkin Interacting Substrate;
TOM- translocase of the outer membrane;
TIM- translocase of inner membrane;
MPP- Mitochondrial processing peptidase;
TOMM7- translocase of outer mitochondrial membrane;
MCVs- Mitochondrial-derived vesicles;
MitAP- Mitochondrial antigen presentation;
hTERT-Human telomerase reverse transcriptase;
opa1- Optic atrophy 1;
mfn-Mitofusin; ETC- Electron transport chain;
OMM- Outer mitochondrial membrane;
IMM- Inner mitochondrial membrane;
Ub- ubiquitin; REM- Rapid eye movement;
GBA-Glucosylceramidase beta;
MPTP- 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine;
6-OHDA- 6-hydroxydopamine;
CoQ_{10}- Coenzyme Q.

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