

## CURRENT STATUS AND NOVEL STRATEGIES FOR PREVENTION AND TREATMENT OF PARKINSON'S DISEASE

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### ABSTRACT

Parkinson's Disease is a chronic, second most common neurodegenerative disorder characterized by the degeneration of dopaminergic neurons. The pathological role of several factors namely, oxidative stress, neuroinflammation, protein misfolding, mitochondrial dysfunction and genetic predispositions has been highlighted however, its etiology remains unknown. Clinical pathology shows that parkinson's disease involves progressive premature death of dopaminergic neurons in the Substantia Nigra pars compacta (SNpc) and abnormal protein aggregates termed Lewy bodies (LW), which contain  $\alpha$ -synuclein. Current treatments for parkinson's disease give symptomatic relief in patients and improve their motor function. Thus, parkinson's disease remains an incurable disease and quality of life of parkinson's disease patients get affected. Therefore, it is very

important to understand the pathophysiologies of Parkinson's disease and focus on the new therapeutic strategies for the treatment and develop new therapies for the betterment of patients. Under new treatment options gene and cell/ stem cell-based therapies, neurosurgeries, insulin resistance therapies, natural products are currently being studied in animal models of parkinson's disease or recently been tested in clinical trials. Thus, these new therapeutic targets would be the best options for prevention and treatment of parkinson's disease patients.

**KEYWORDS:** Parkinson's Disease, Stem Cell Therapy, A-Synuclein, Gene Therapy.

## INTRODUCTION

Parkinson's disease (PD) is one of the most common neurodegenerative disorder which is characterized by tremors, muscle rigidity, bradykinesia, gait etc. Parkinson's disease is incurable disorder of central nervous system (CNS) which affect millions of people worldwide. Parkinson's disease is also the second most common age-related neurodegenerative disorder.<sup>[1]</sup>

Parkinson's disease is a slowly progressive disorder which causes depletion of dopaminergic neurons in several dopaminergic networks (mesocortical, mesolimbic and nigro-striatal pathways). However, substantia nigra pars compacta (SNpc) region get mostly affected. Loss of dopaminergic neurons at substantia nigra pars compacta and their axonal projections to the caudate putamen region leads to striatal dopamine (DA) deficiency which is mainly responsible for the sensory-motor symptoms of PD. Noradrenergic, cholinergic, serotonergic projections as well as neurons in cerebral cortex, olfactory bulb and autonomic nervous system are also involved in the PD which makes PD a multisystem neurodegenerative disorder in which non-motor symptoms (autonomic, psychiatric, cognitive) play an important role and significantly affect patients quality of life.<sup>[2]</sup>

PD is incurable disorder and currently symptomatic therapies are available. Current treatments improve PD motor symptoms and patient's life expectancy. However, it has long been known that these DA pharmacotherapies cause motor complications, such as L-DOPA induced dyskinesia (LID) and motor fluctuations.<sup>[3]</sup>

More recently, it has been observed and noted that motor complications are often accompanied by disturbances in the psychiatric-cognitive domain, such as mood swings, impulsive compulsive behaviors and psychotic features.<sup>[2]</sup>

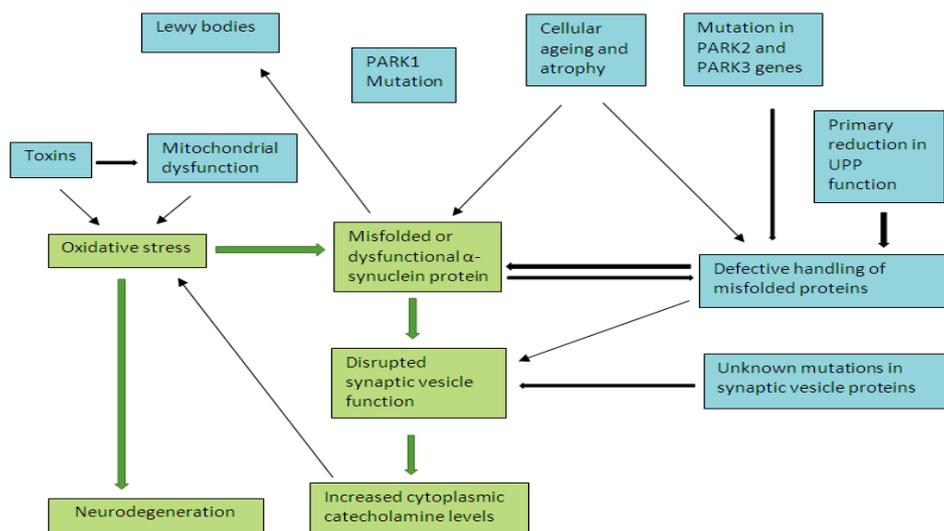
Around 80% populations with PD are considered as idiopathic because of their unknown source of etiology whereas the remaining 20% cases are presumed to be genetic. Some genes such as GBA (glucocerebrosidase) mutation affect enzymatic functions along with cognitive decline, and reduction in GBA activity increases  $\alpha$ -synuclein levels is the primary neuropathological hallmark of PD.<sup>[4]</sup>

Other causative factors that contribute to development of PD include environmental factors, aging, head trauma, oxidative stress, neuroinflammation. Due to the limitations of current

clinical therapies it is very essential to study and find better therapies and to gain deep knowledge of disease mechanism. Thus, this review will focus on the limitations of the current clinical therapies and new therapeutic targets in the treatment of PD.

### **Pathology and Pathogenesis**

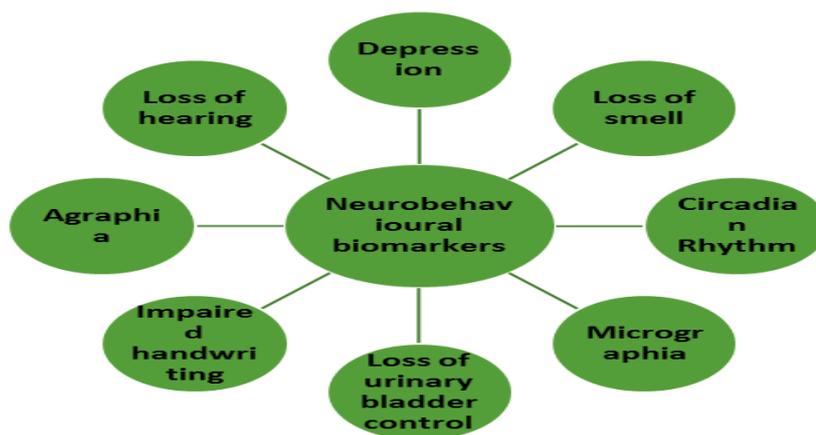
Abnormal aggregation of proteins  $\alpha$ -synuclein is observed in the pathological examination of the brains of PD patients which is also termed as Lewy bodies (LB). In addition, there is marked loss of dopaminergic neurons in the substantia nigra region of brainstem which ultimately leads to degeneration of projections to other regions of the brain. Most of these projections terminate in the putamen and globus pallidus, although there are also projections to the cerebral cortex, thalamus and other areas of the brainstem. Other neurotransmitters, acetylcholine, serotonin and non-adrenaline are also affected in this condition however, dopamine deficiency is the hallmark of PD. This neurotransmitters degeneration ultimately leads to dysfunction of a complex network of excitatory and inhibitory feedback loops, resulting in the symptoms seen in PD. Other neurotransmitters degeneration is likely to be involved in the pathophysiology of non-motor symptoms that is autonomic dysfunction, sleep abnormalities and neuropsychiatric features.<sup>[4,5]</sup> The unfolded protein response (UPR), an ER-stress related pathway which can induce proapoptotic mechanisms during chronic stress can be triggered by the overexpression of  $\alpha$ -synuclein pathological forms. In LB-containing neurons in the brain of PD patients it has been shown that the pancreatic (PKR)-like ER kinase (PERK) related pathway of the UPR get activated. Therefore, chronic ER-stress and activation of the UPR has been found to be important for the manifestation of  $\alpha$ -synucleinopathy “in vivo”.  $\alpha$ -synuclein accumulation within the ER can directly activate the PERK-related pathway of the UPR by binding to the ER-stress sensor/UPR activator GRP78/BiP, a phenomenon which coincides with the occurrence of a central proapoptotic event: cytochrome c release from the mitochondria. It is known that GRP78/BiP binds to misfolded protein aggregates within the ER and activates UPR by dissociating from three ER stress sensors, consisting of the pancreatic (PKR)-like ER kinase (PERK), activating transcription factor 6 (ATF6) and inositol-requiring enzyme 1 (IRE1) to bind the misfolded protein aggregates. Dissociation of GRP78/BiP from PERK, ATF6 and IRE1 allows the activation of these factors resulting in the induction of three UPR-related pathways.<sup>[6]</sup> These pathways ultimately develop stress into the neurons and result into degeneration of neurons. Fig. 1 shows the relationship of different pathways to the oxidative stress and how it leads to neurodegeneration.



**Fig. 1. Different pathways involved in neurodegeneration.**

### Indicators of PD

1) **Biological Markers:** Markers such as cerebrospinal fluid tests, non-motor clinical symptoms of PD, and several imaging modalities are used as early diagnostic measures of PD. Non-motor clinical symptoms include the neuro-psychiatric disorders, REM behavior sleep disorder, olfactory abnormalities and depression.<sup>[4]</sup>



**Fig. 2. A flow diagram illustrating various neurobehavioral biomarkers of PD.**

2) **Neuroimaging modalities:** Positron emission tomography, functional magnetic resonance imaging, transcranial sonography, magnetoencephalography or single-photon emission computed tomography are the new neuroimaging techniques to develop novel diagnostic methods of PD can be used to examine the dopaminergic system of the brain to understand its pathology. These new diagnostic techniques can help us to understand molecular, structural and functional neuroimaging of the PD brain.<sup>[4]</sup>

**Current Therapies**

Current clinical therapies for PD management: Parkinson's disease is incurable and chronic disorder. In the management of PD only symptomatic clinical therapies are available. Though these therapies are not enough for the management of PD thus, new therapeutic perspective are important with the aim of slowing or stopping progression of disease.

**Pharmacotherapy:** Dopaminergic- L-DOPA, DA Agonist, MAO Inhibitors, COMT Inhibitors, Extended release or duodenal infusion of carbidopa/levodopa.

**Dopamine precursors:** Levodopa (L-DOPA) is commonly given to increase the dopamine level in PD patients. Levodopa has considered as the gold standard for the treatment of PD symptoms and is an integral component of combination therapies.

**Limitation:** Levodopa starts to lose efficacy over time with greater than 80% of patients on therapy for longer than 10 years experiencing dyskinesia and on-off periods.

Carbidopa is also given in combination to reduce systemic metabolism of L-DOPA and increase central exposure. It allows lower doses of L-DOPA to maintain efficacy and helps in reducing the side effects such as nausea.

**Dopamine agonists:** D1-D5 are five types of dopamine receptors functional in the brain. D1 and D5 are D1 like receptors which acts through GPCRs coupled to G $\alpha$  resulting into activation of adenylyl cyclase and increases cyclic adenosine monophosphate (cAMP). D2, D3, and D4 (D2-like) are coupled to G $\alpha$  inhibiting adenylyl cyclase with a commensurate reduction in formation of cAMP. Approved dopamine agonists which acts on dopamine receptors and are prescribed for treatment of PD are apomorphine, bromocriptine, ropinorole, pramipexole, rotigotine. Each of these drugs act potently as agonists of D2 like receptors. Also, several of them exert some balance of D1 like agonism and 5-HT,  $\alpha$ -adrenergic and beta-adrenergic antagonism.

**MAO-B inhibitors:** Monoamine oxidase B is an enzyme which is involved in the metabolism of dopamine thus leading into the decrease's concentration of dopamine in brain. MAO-B inhibitors have been added to the therapeutic regimen for PD treatment with the aim to decrease dopamine metabolism and increase dopamine concentrations in the brain which ultimately results into reduction of motor symptoms. Approved MAO-B inhibitors (irreversible inhibitors) include selegiline, and rasagiline.

**COMT inhibitors:** Catechol-O-methyl transferase (COMT) which functions same as that of MAO-B that is transforming dopamine into 3-methoxytyramine which is oxidized by MAO-B to produce homovanillic acid. Inhibition of COMT leads to increase in dopamine levels of brain which ultimately reduces motor symptoms. From past two decades COMT inhibitors has been added to the PD treatment as a combination therapy. Approved COMT inhibitors now used as components of standard of care are entacapone and tolcapone.

**Non-Dopaminergic:** Adenosine receptor agonists,  $\alpha$ -2 adrenergic antagonists, Noradrenergic reuptake inhibitors, Amantadine, Metabotropic glutamate receptor antagonists, Metabotropic glutamate receptor agonists, Serotonin receptor agonists, Histamine receptor antagonists, Cholinesterase inhibitors, Calcium-channel blockers, Endogenous neurotrophic factor inducers.

**Anticholinergic:** Acetylcholine is involved in the regulation of movement and can have beneficial effects on tremor and dystonia in PD patient. Two approved drugs Benztropine and trihexyphenidyl act as antiparkinsonian agent that decreases the activity of acetylcholine. Miscellaneous approved therapies: Several non-dopaminergic treatments are also employed in the management of symptomatic PD manifestations.

**e.g Amantadine:** NMDA type glutamate receptor antagonist that was used as an antiviral therapy and now has been prescribed to reduce dyskinesia in PD, however its efficacy has been questioned. Droxidopa was recently approved in the US for the management of neurogenic orthostatic hypotension in disorders such as PD, MSA and pure autonomic failure. It is a prodrug of norepinephrine. Pimavanerin, a 5-HT inverse agonist has been prescribed for the treatment of hallucination, delusions and psychosis associated with PD. Rivastigmine an acetylcholinesterase inhibitor is also used for the treatment of dementia due to PD.<sup>[7]</sup>

Table. 1. Drawbacks and side effects of Current pharmacological therapies.<sup>[5]</sup>

Drug Class	Examples	Drawbacks	Side effects
<b>Oral dopamine agonists</b>	Ropinirole Pramipexole Cabergoline Pergolide	Ergot-derived agonists (cabergoline and pergolide) can cause cardiac valvulopathy Troublesome adverse effects Less well tolerated in the elderly	Typical dopaminergic side effects: Nausea and vomiting, postural hypotension, somnolence, vivid dreams, confusion, visual hallucinations
<b>Levodopa</b>	Co-careldopa (Sinemet) Co-beneldopa (Madopar)	Short half-life ( $t_{1/2}$ 60 min) metabolized, therefore combined with dopa decarboxylase inhibitor Motor complications End-dose effect Dyskinesias	Typical dopaminergic side effects
<b>Monoamine oxidase type B inhibitors</b>	Selegiline Rasagiline	No convincing evidence of neuroprotection Effective only for mild symptoms	Dry mouth Headache Urinary symptoms Depression Agitation Postural hypotension
<b>COMT inhibitors</b>	Entacapone Tolcapone Stalevo (combination of Sinemet and entacapone)	More tablets for patients Modest effect Tolcapone can cause liver damage therefore, needs regular monitoring of liver function tests	Typical dopaminergic side effects Diarrhoea Orange discolouration of urine Dyskinesias
<b>Transdermal dopamine agonists</b> <b>Subcutaneous dopamine agonists</b>	Rotigotine Apomorphine	Less familiar to patients Specialist administration required, costly, very short half-life, therefore prolonged infusion required	Typical dopaminergic side effects Potently emetogenic Severe skin site reactions
<b>Amantadine</b>		Limited role in PD management	Confusion Hallucinations Ankle oedema Livedo reticularis
<b>Anticholinergics</b>	Trihexyphenidyl (benzhexol) Orphenadrine	Significant cognitive side effects, even in young patients Generally, to be avoided	Confusion Hallucinations Cholinergic features

## New Therapies

### Neurosurgery

Patients who do not respond to clinical medical therapy or who suffer from adverse effects of medical therapy, surgical treatment of PD has also emerged as a significant promising option. It includes.

### Functional Neurosurgery

Pallidotomy, stereotactic thalamotomy and DBS.

Pallidotomy/Stereotactic thalamotomy: in this treatment method, the head of the patient is immobilized in a stereotactic frame and an electrode probe is inserted into the target location to thermally ablate the target as the patient is observed closely for symptom abatement. Response observed in 80-90% of patients because stereotactic surgery results in positive rigidity and/or tremor control.<sup>[8,9]</sup>

However, this is invasive surgical operations thus risk factor for complications including internal bleeding, permanent tissue damage along the electrode insertion path, and possible neural fiber damage which may result in paresis, gait disorder, dystonia and dysarthria.

**DBS:** DBS is deep brain stimulation in which preferred targets are STN (Subthalamic nucleus) and GPi (globus pallidus internus). Choice between these two targets depends on patient factors and the experience of the surgeon. STN stimulation has consistently across studies been shown to allow for greater reduction in dopaminergic medication postoperatively. GPi stimulation is often more effective at reducing dyskinesia directly, unaccounted for by a reduction in dopaminergic medications.<sup>[10]</sup>

**Procedure:** Preoperatively neurosurgeon based on magnetic resonance imaging (MRI) and visual landmarks choose the location of the surgical target. Coregistration with a standardized brain atlas can also be employed. Brain mapping software determines the 3-dimensional coordinates of the target, which can then be entered a frame secured to the patient's skull. If a frameless system is used, the angle and depth of the target is calculated with respect to skull fiducial markers. After burr hole placement, a microelectrode is slowly passed along the trajectory, and the depth of the target is identified based on microelectrode recording. The stimulating macroelectrode is then placed and tested intraoperatively to verify the threshold for side effects (depending on the target, these can include paresthesia's, muscle contraction, conjugate eye deviation, visual phosphenes). The macroelectrode is secured into position and the contralateral target is approached in a similar manner if a bilateral procedure is being performed. The electrodes are then connected to an implantable pulse generator (IPG), often in a separate procedure.<sup>[11]</sup>

**Gene therapy:** Gene therapy can provide long-term expression of a therapeutic protein with limited distribution through a single surgical pathway, potentially providing long-term histological and behavioral improvement for PD patients. Adeno-associated virus (AAV) is the most commonly used viral vector for expressing and secreting the encoded human genes

via genetically engineered modification. The AAV vector does not produce inflammatory response and has been used safely in gene delivery clinical trials.<sup>[12]</sup> Currently, potential targets of gene delivery for PD therapy such as glutamic acid-decarboxylase (GAD), aromatic L-amino acid decarboxylase (AADC) and glial derived neurotrophic factor (GDNF) are in clinical trials.

In the biosynthetic route of dopamine, to decarboxylase L-Dopa and generate dopamine, requires tyrosine hydroxylase (TH), which translates tyrosine into L-3,4-hydroxyphenylalanine as well as AADC. AADC transforms L-Dopa into dopamine thus AADC is critical enzyme in the biosynthetic pathway of dopamine. It has been demonstrated that transfer of cDNA encoded human AADC can effectively reduce the required L-Dopa doses in animal PD models to restore dopamine to normal levels and this approach is currently in clinical trials.

On the other hand, neurotrophic factors, like Neurturin (NTN, an analogue of GDNF isoform) and GDNF might protect against neurodegeneration and can improve neuronal function.<sup>[10]</sup>

**Gene transfer:** NAT, GAD and DA enzyme.

**Cell-based therapy:** PD is characterized by the loss of DAergic neurons thus replacement of DAergic neurons in SN could be the effective therapeutic approach. As per the evidence it was observed that stem cells can differentiate into DAergic neurons *in vitro* and can also protect or promote regeneration of damaged DAergic neurons. Stem cells have ability of self-renewal and to differentiate into different specialized cell types. Introduction of cells into tissues to treat neurodegenerative diseases is an increasing interest in cell therapy. Stem cells are categorized in different types based on their origin: embryonic stem cells, neuronal stem cells, induced pluripotent stem cells and mesenchymal stem cells (MSCs).

MSCs are multipotent cells, non-hematopoietic and advantageous compared with other stem cells thus, have gain more attention in the last decade. Indeed, MSCs present low immunogenicity, no teratoma risk, and presented no ethical problems.

MSCs were first isolated from the bone marrow (BM), but they can be isolated from various sources like adult and neonatal tissues. E.g. Adipose tissue, Umbilical cord.

### Application of Bone marrow derived MSCs in PD animal models

Researchers showed that 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) lesioned mice were transplanted with BM-MSCs a week after lesion induction. Improvements were evaluated on the rotarod test 35 days after MPTP injection. MSCs survived at least 4 weeks in the transplanted area after administration and expressed TH. MSCs can differentiate into neuronal-like cells, some experimental studies tried to evaluate if differentiated BM-MSCs possessed better neuroprotective potential. Undifferentiated BM-MSCs transplanted in a PD model survived and differentiated into DAergic neurons, leading to behavioral improvements.<sup>[13]</sup>



Some open-labeled clinical trial showed that dopaminergic neuron transplantation can be beneficial and promising to PD patients. However, transplanted patients showed clear adverse effects like graft-induced dyskinesia. Thus, a new clinical trial was established giving major impact on neural transplantation with fetal dopaminergic tissues, and with human embryonic stem cell (hESC)- and human induced pluripotent stem cell (hiPSC)-derived dopaminergic neurons in future.

**Pluripotent stem cells:** Two different methods has been achieved for reprogramming of somatic cells to pluripotency. Firstly, nuclear transfer in which nuclei transplanting from differentiated somatic cells to oocytes and secondly, cell fusion- involving fusion of two or more cells into one, which reveals the fact that silent genes in differentiated cells can be activated by certain regulators.

In 2006, Yamanaka and co-workers showed that somatic cells can be reprogrammed into an embryonic-like state by introducing 4 transcriptional factors. Octamer-binding transcription factor 4 (Oct4), SRY (sex determining region Y)-box 2 (Sox2), C-myc and Kruppel-like factor 4 (Klf4), into embryonic fibroblasts. These reprogrammed cells were designated as induced pluripotent stem cells (iPSCs), which possess characteristic of typical embryonic stem cells.<sup>[14]</sup>



**Natural Anti-PD products:** With respect to recent discoveries it is observed that natural products provide potential therapeutic agents. Natural products exert antioxidant, anti-inflammatory actions as well as inhibitory roles regarding iron accumulation, protein misfolding, maintenance of proteasomal degradation and mitochondrial homeostasis. Natural products can also act as anti-PD agents by affecting different pathogenic pathways of Parkinson's disease.

**Flavonoid and polyphenol compounds:** Baicalein is a flavonoid monomer compound which is extracted from plant *Scutellaria baicalensis* has *Lamiaceae* family. The study by Mu et al. showed that baicalein could exert protective effects on dopaminergic neurons in C57BL/6 mice with neuronal injury induced by 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) and could significantly increase the number of dopaminergic neurons due to its excellent anti-oxidative stress properties.<sup>[15]</sup>

In addition, Li et al. also found that baicalein could also effectively attenuate progressive degeneration of dopaminergic neurons regulated by inflammation.<sup>[16]</sup>

The study by Yu et al. also indicated that baicalein could exert antiparalysis agitans effects in PD through the regulation of the balance between the neurotransmitter's GABA and Glu in the basal ganglia.<sup>[17]</sup>

Quercetin found in the flowers, leaves and fruits of many plants. Haleagrahara et al. tested the effect of quercetin in 6-OHDA treated rats and observed that this flavonoid exerted anti-PD functions through a significant increase in the levels of antioxidant enzymes in the rats.<sup>[18]</sup>

Zhang et al. showed that quercetin inhibited the inducible nitric oxide synthase/nitric oxide (iNOS/NO) system and the expression of pro-inflammatory factors in PD animal models, which induced neuroprotective effects.<sup>[19]</sup>

Puerarin is a glycoside flavonoid component extracted from the plant *Pueraria mirifica* of family Fabaceae. Zhu et al. treated PD mice with puerarin and showed that puerarin produced excellent anti-PD effects through the inhibition of the degeneration of dopaminergic neurons,

an increase in the number of tyrosine hydroxylase (TH)-positive neurons, and an increase in the expression of glial cell-derived neurotrophic factor (GDNF).<sup>[20]</sup>

Other natural components Hyperoside, Naringin, Curcumin, Epigallocatechin gallate, Resveratrol, Danshensu, salvianolic acid, Magnolol these are some natural agents which exerts protective effect in PD animal model. Scientist has observed effect of these natural products in different animal models.<sup>[21]</sup>

### **Insulin resistance as a potential therapeutic strategy**

Defective insulin signaling is increasingly recognized in its association with PD. Although it remains to be shown whether dysregulated insulin signaling is a primary contribution to PD or a secondary consequence of the neurodegenerative process. Due to the growing links between PD and type 2 diabetes mellitus (T2DM) drugs used in the treatment of T2DM are amongst the most promising treatments currently being prioritized for repositioning as possible novel treatments for PD.<sup>[22]</sup>

**Insulin:** Experimental studies of PD on animals demonstrate overexpression of IGF-1 protects dopaminergic neurons from 6-OHDA and MPTP-induced cell death and also by alpha-synuclein induced toxicity. Neuroprotection was accompanied by elevation of phospho-Akt (Ser 473) and inhibition of GSK-3B and improvements in both motor and behavioral functional deficits.<sup>[23]</sup>

**Thiazolidinediones:** The thiazolidinediones are a class of drugs that increases insulin sensitivity. These drugs act as selective ligands of the peroxisome proliferator-activated receptor gamma (PPAR  $\gamma$ ) receptor. These receptors are expressed in insulin sensitive tissues such as liver and pancreas, but are also expressed in nigral and putaminal nuclei. Two drugs of this class Pioglitazone and Rosiglitazone have demonstrated neuroprotective effects across a range of animal toxin model of PD, including the 6-OHDA and rotenone models resulting in improvements in behavioral and motor responses.<sup>[24,25]</sup>

**Glucagon-like peptide-1 (GLP-1) analogs:** GLP-1 is one of two hormones responsible for mediating the “incretin” effect secreted from L-cells from small intestine in response to food ingestion. GLP-1 also produced in the brain in small amounts released from hypothalamic nuclei from nerve endings with cell bodies in the nucleus of the solitary tract and caudal brainstem which project to cortical, hypothalamic and hippocampal nuclei. A increasing

number of studies show that GLP-1 receptor stimulation can act as neurotrophic factor, enhance mitochondrial biogenesis, inhibit apoptosis, and inhibit inflammatory cascade and reduce oxidative stress. The first GLP-1 analogue exenatide derived from exendin-4 have shown neuroprotective effects in experimental models of PD such as 6-OHDA and MPTP induced dopaminergic degeneration. It was observed exenatide restored dopaminergic imbalance and led to persistent improvements in motor function.<sup>[26]</sup>

## CONCLUSION

PD is the second most common neurodegenerative disorder characterized by a variety of motor and non-motor features. Currently, symptomatic therapies are available for the treatment of PD however, there is need to focus on new therapeutic potential targets by understanding the pathophysiology and mechanism involved in PD. Therefore, gene therapies and stem cell therapies have been developed and are under clinical trials to meet the clinical challenges of treating and modifying the course of the disease. In addition to these therapies the natural products, neurosurgeries and anti-diabetic agents can also be developed as potential therapies to tackle PD in a multidimensional and more effective ways.

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