WWW.IJRPR.COM

**International Journal of Research Publication and Reviews**

Journal homepage: www.ijrpr.com ISSN 2582-7421

# Advancing Parkinson's Disease Research: Targeting Pathogenic Mechanisms with Emerging Therapies

***Gowrisankari. R[1], Anbarasi.P[1], Dr. U. Kanagavalli.[2]***

[1]PG, Department of Biotechnology, Vivekanandha College of Engineering for Women, Tiruchengode -637205.TamilNadu. India
Assistant Professor, Department of Biotechnology, Vivekanandha College of Engineering for Women, Tiruchengode -637205. TamilNadu. India
[2] Director, KH BioSolutions (An Educational Research Centre), Arcot -632503, Ranipet District - 632503. TamilNadu. India
DOI : https://doi.org/10.55248/gengpi.6.0125.0211

**ABSTRACT**

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by motor symptoms such as bradykinesia, rigidity, and tremors, alongside non-motor impairments including cognitive decline and autonomic dysfunction. The disease arises from dopaminergic neuronal loss in the substantia nigra and the pathological aggregation of α-synuclein. Its multifactorial etiology involves genetic mutations, mitochondrial dysfunction, oxidative stress, neuroinflammation, and systemic factors such as gut-brain axis dysregulation. Current therapies, including levodopa and deep brain stimulation, provide symptomatic relief but fail to halt disease progression. Recent advancements in molecular biology and neuroimaging have improved understanding and diagnostics, paving the way for disease-modifying therapies. Gene therapies, immunotherapies, molecular chaperones, and GLP-1 receptor agonists offer promising approaches to addressing pathogenic mechanisms such as α-synuclein aggregation, lysosomal dysfunction, and neuroinflammation. Additionally, cell-replacement therapies and neuroprotective natural compounds provide avenues for restoring neuronal function and mitigating progression. This review highlights the pathophysiology, diagnostic advancements, and emerging therapeutic strategies in PD, emphasizing their potential to transform patient care. Recently by finding new molecules and targets, *In silico* technologies are transforming the drug discovery process for Parkinson's disease (PD). These results provide a basis for developing synthetic and natural molecules as novel, multi-target PD therapies.

## INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative disorder that significantly impacts motor and non-motor functions, diminishing the quality of life for millions of people worldwide. First described in 1817 by James Parkinson as "the shaking palsy," PD was further studied by Jean-Martin Charcot, who refined its clinical features and classification. It is the second most common neurodegenerative disorder after Alzheimer's disease, with a prevalence of 1% in individuals over 65 years of age and rising to 3% among those aged 80 and above (Pringsheim *et al.*, 2014; Tysnes and Storstein, 2017). As the global population ages, the prevalence of PD is likely to double by 2030, thus creating an increasing socioeconomic and healthcare burden (Marras *et al.*, 2018).

Clinically, PD is marked by hallmark motor symptoms including bradykinesia or slowness of movement, resting tremor, muscular rigidity, and postural instability, along with a wide range of non-motor symptoms such as depression, anxiety, sleep disturbances, autonomic dysfunction, and cognitive decline (Obeso*et al.*, 2017). These symptoms arise from the progressive loss of dopaminergic neurons in the substantia nigra pars compacta and lead to dopamine depletion in the striatum, together with the pathological accumulation of misfolded α-synuclein in the form of Lewy bodies (Obeso*et al.*, 2017; Essa*et al.*, 2019). The combination of motor and non-motor impairments makes PD a heterogeneous disease, further complicated by its overlapping features with other neurodegenerative disorders such as Alzheimer's disease (AD).

### Current treatment methods

The current mainstay treatment for PD includes symptomatic relief. Introduction of levodopa in the 1960s has been considered the first-line gold standard, significantly helping improve the motor symptoms of this disease such as bradykinesia and rigidity. However, its effectiveness is transient, and long-term usage is accompanied by adverse effects like dyskinesia (Armstrong*et al.*, 2020). Alternative treatments include dopamine agonists, MAO-B inhibitors, and COMT inhibitors, whereas advanced treatment is deep brain stimulation (DBS) in cases where motor symptoms are resistant to all treatments. Despite these advances, no disease-modifying therapies have been identified to slow or reverse the neurodegenerative processes underlying PD. Emerging research into the pathophysiology of PD has shifted focus from dopamine-centric models to more systemic perspectives, emphasizing mitochondrial dysfunction, oxidative stress, neuroinflammation, and α-synuclein pathology (Beach*et al.*, 2010; Schindlbeck*et al.*, 2018). Additionally, recent insights into gut-brain axis involvement and the role of the peripheral nervous system have expanded our understanding of PD as a multisystem disorder (Braak*et al.*, 2003). These findings have prompted the exploration of innovative diagnostic tools such as multimodal

neuroimaging, which integrates functional MRI, FDG-PET, and DOPA-PET to monitor disease progression and assess treatment efficacy (Pagano *et al*., 2016; Ruppert *et al*., 2020

The urgent necessity of introducing disease-modifying therapy in PD has led to important developments in research ranging from identifying novel biomarkers to targeted intervention. Therefore, the current review encompasses the broad picture of advances in pharmacological and non-pharmacological therapies as well as neuroimaging-based diagnostic approaches and natural compounds that can be applied as therapies. This work points out challenges and opportunities in the quest to improve the diagnosis, management, and prevention of Parkinson's disease by synthesizing current knowledge.

**Ethiology**

The etiology of Parkinson's disease (PD) is not well established; nevertheless, depletion of dopamine in the nigrostriatal pathway has been the most plausible reason. Normally, intracytoplasmic inclusions called Lewy bodies in dopaminergic neurons are observed in PD. Dopaminergic neuronal loss in the compacta of substantia nigra (SN) and aberrant release of dopamine in the striatum are two main causes of this disease (Wang *et al*., 2015). Although genetic factors have been implicated, 23% of cases show no identifiable genetic association. There are several hypotheses that indicate the death of dopaminergic cells in the SN compacta is due to mitochondrial dysfunction, iron accumulation, protein aggregation, inflammatory immune responses, and environmental triggers like trauma, infections, and pesticide exposure (Sidransky & Lopez, 2012; Betarbet*et al*., 2000). Moreover, free radicals generated inside the brain and liver cytochrome P450 dysfunctions cause oxidative stress as well as neuronal damage (Schapira, 2006). Age is a major risk factor for PD, with the median onset age at 60 years and a reported increased incidence of 93.1 per 100,000 person-years for individuals aged 70–79 (Van Den Eeden *et al*., 2003). In terms of geographical variations, there were higher rates reported in Europe, North America, and South America compared to African, Asian, and Arabic countries.

Cigarette smoking has been extensively researched, and the epidemiological evidence suggests that there is less risk of developing PD. Another stimulant linked to the reduced risk of PD is caffeine. Caffeine is an adenosine A2A receptor antagonist which has shown neuroprotective effects in experimental models of PD (Ross & Abbott, 2004). Prospective studies report a 25% reduction in PD risk among coffee drinkers, with a relative risk of 0.45-0.80 in regular consumers compared to non-drinkers. Meta-analyses further confirm a significant risk reduction among coffee and tea drinkers. Interestingly, gender-specific variations exist; the protective effect of caffeine is more potent in men and is influenced by hormone replacement therapy in postmenopausal women, probably because of estrogen-caffeine metabolic interactions (Ascherio *et al*., 2001).

***Pathogenesis***

Parkinson’s disease (PD) is a progressive neurodegenerative disorder associated with motor and debilitating symptoms, including bradykinesia, muscle rigidity, resting tremors, and postural instability. Pathologically, PD is marked by the slow and gradual degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNpc), leading to a significant reduction in dopamine levels within the striatum, including the caudate nucleus and putamen (Lees, 2012). The loss of these neurons in the basal ganglia is a hallmark pathological feature of PD, resulting in decreased dopamine neurotransmission in these areas. Clinical symptoms typically emerge after 50–60% of dopaminergic neurons are lost, and dopamine levels in the striatum have declined by approximately 80–85%. The precise molecular mechanisms underlying dopaminergic neuron degeneration and the onset of PD remain unclear. However, evidence suggests that oxidative stress and mitochondrial dysfunction play critical roles in its pathogenesis. The characteristic features of PD include the loss of nigrostriatal dopaminergic neurons and the accumulation of intracellular cytoplasmic inclusions known as Lewy bodies. These neurons, situated in the SNpc, project to the putamen. Their degeneration, along with the loss of melanin-containing cells, results in the depigmentation of the SNpc, a defining pathological trait of PD (Lees, 2012).

**Pathological Misfolding and Aggregation of α-Synuclein in Parkinson's Disease**

Parkinson's disease (PD), α-synuclein adopts a β-sheet-rich amyloid-like structure that aggregates, forming 5–10 nm long filaments observed within Lewy bodies (LBs) (Spillantini & Goedert, 2000). Mechanisms for this aggregation include serine 129 phosphorylation (Fujiwara *et al*., 2002), ubiquitination (Tofaris *et al*., 2003), and C-terminal truncation, resulting in various species of α-synuclein in PD brains, such as unfolded monomers, soluble oligomers, protofibrils, and high molecular weight insoluble fibrils (Spillantini & Goedert, 2000).

**Mitochondrial dysfunction**

Mitochondrial dysfunction is one of the central elements of the pathogenesis of PD. Initial postmortem studies detected a deficiency of mitochondrial complex I in the substantia nigra pars compacta (SNpc) of brains from PD cases, which therefore linked mitochondrial deficits to DA cell loss. The same deficit was detected also in the skeletal muscle and platelets of PD patients. The discovery of MPTP as a neurotoxin that inhibits complex I and causes Parkinsonian symptoms in humans and animal models further established this connection. Similar neurotoxic effects are seen with pesticides such as rotenone and paraquat. Defects in complex I impair energy production contributing to DA cell death. Familial PD-related genes PINK1 and PARKIN are important regulators of mitophagy, a process of damaged mitochondria clearance (Narendra *et al*., 2010). Mutations in these genes have been associated with loss-of-function, impairing the mitochondrial quality control, resulting in autosomal recessive PD. Moreover, the interactions of α-synuclein with mitochondrial membranes cause dysfunction in complex I activity, and increased oxidative stress ensues. Oligomeric α-synuclein has been shown to interact with the TOM20 receptor, impairing the mitochondrial protein import and promoting overproduction of ROS.

***Neuropathology***

Macroscopic changes in idiopathic Parkinson's disease (PD) are usually mild. Some cases have mild atrophy of the frontal cortex and ventricular dilation. However, the most obvious change is the marked reduction of pigmentation in the substantia nigra pars compacta (SNpc) and locus coeruleus that can be seen in sections of the brainstem. The loss of pigmentation correlates with the degeneration of dopaminergic (DA) neuromelanin-containing neurons in the SNpc and noradrenergic neurons in the locus coeruleus. Studies estimate that around 30% of SNpc DA neurons are lost by the onset of motor symptoms, and this loss increases to 60% or more as the disease progresses, correlating closely with the degree of motor impairments. Dexter & Jenner, 2013; Surmeier *et al*., 2017. The early loss of axon terminals in the striatum also identifies a preclinical phase of neurodegeneration that may start years before any symptoms appear (Surmeier *et al*., 2017).

Widespread degeneration is also present in other subcortical nuclei, including the locus coeruleus, nucleus basalis of Meynert, dorsal motor nucleus of the vagus nerve, pedunculopontine nucleus, raphe nuclei, hypothalamus, and olfactory bulb. Such damage impacts non-dopaminergic neurotransmitter systems, including cholinergic, serotonergic, and glutamatergic pathways, thus contributing to less responsive non-motor symptoms such as sleep disturbances and cognitive decline with dopamine replacement therapies (Braak *et al*., 2003; Lang & Espay, 2018).

Microscopically, PD is defined by the presence of LBs—intracytoplasmic inclusions mainly made of aggregated α-synuclein—and dystrophic neurites. These pathological features constitute the basis of Braak staging, which is an important description of PD pathology progression. Early dysfunction involving autonomic and olfactory function begins with the deposition of α-synuclein aggregates in the dorsal motor nucleus of the vagus and olfactory bulb at Braak stages 1–2. The pathology subsequently extends to the SNpc and other midbrain structures (Braak stages 3–4), which indicates the onset of the motor symptoms and eventually goes on to involve the neocortex (Braak stages 5–6), which is associated with severe disease and cognitive impairments (Braak *et al*., 2003; Halliday *et al*., 2008). A recent "dual-hit hypothesis" suggests that α-synuclein pathology originates in peripheral sites, for example, the gut or olfactory system, which then spread to the brain through neural connections (Hawkes *et al*., 2007).

New evidence has started to implicate peripheral nervous system structures in PD. α-Synuclein aggregates are identified in the sympathetic ganglia, spinal cord, heart, gastrointestinal tract, and skin, implicating a systemic aspect in PD pathology. Epidemiological studies suggest that truncal vagotomy is associated with a decreased risk of PD, further implicating the gut-brain axis in initiating the disease (Svensson *et al*., 2015; Lionnet *et al*., 2018).

## Treatment methods

**Gene therapies**

Gene therapy has emerged as a promising approach for treating Parkinson’s disease (PD) by modifying gene expression in targeted cells to address underlying disease mechanisms or symptoms. The technology uses vectors to deliver therapeutic agents, such as DNA, RNA, or gene-editing enzymes, into cells. Viral vectors like adeno-associated viruses (AAVs) and lentiviruses (LVs) have demonstrated durable gene expression and low immunogenicity in animal models and early clinical trials (Coune *et al*., 2012). Vectors in Gene Therapy Adeno-associated viruses (AAVs):

AAVs, particularly serotypes 2 and 9, show strong tropism for neurons and central nervous system (CNS) tissues. AAV2 has been widely used due to its specificity and safety profile, minimizing insertional mutagenesis and providing stable expression after a single treatment (Cearley *et al*., 2007; Christine *et al*., 2019). AAV9, with its ability to cross the blood-brain barrier, has shown efficacy in models of spinal muscular atrophy (SMA) and led to the development of the first approved gene therapy, Zolgensma® (Duque *et al*., 2009; Hoy, 2019). Lentiviruses (LVs):

**Key Approaches in PD Gene Therapy Restoring Dopamine Synthesis:**

vectors targeting aromatic L-amino acid decarboxylase (AADC) have shown safety and improved motor and non-motor symptoms in clinical trials (Christine *et al*., 2009; Mittermeyer *et al*., 2012). Lentiviral vectors delivering a combination of AADC, tyrosine hydroxylase, and GTP cyclohydrolase (e.g., ProSavin®) also demonstrated motor improvement, with an optimized version (OXB-102) under investigation.

**Neuroprotection with Neurotrophic Factors:**

Gene therapies delivering glial cell line-derived neurotrophic factor (GDNF) or neurturin (via AAV2) have shown mixed results in clinical trials, with some improvement in motor symptoms and dopaminergic function (Gill *et al*., 2003; Whone *et al*., 2019). Cerebral dopamine neurotrophic factor (CDNF), delivered using implanted systems, is also under investigation for its broader neuroprotective effects (Lindahl *et al*., 2017).

**Genetic Neuromodulation**: AAV-mediated delivery of glutamate decarboxylase (GAD) to the subthalamic nucleus has shown promise in improving motor symptoms by enhancing GABAergic inhibition. Clinical trials demonstrated significant improvements in Unified Parkinson’s Disease Rating Scale (UPDRS) scores and functional brain connectivity (Kaplitt *et al*., 2007; Niethammer *et al*., 2018).

**Targeting Pathogenic Variants**: Therapies targeting specific genetic mutations, such as those in the GBA gene, are under development but not discussed in this summary. Targeting Alpha-Synuclein in Parkinson's Disease: Alpha-synuclein (α-syn) is a neuronal protein involved in Parkinson's disease because of its propensity to aggregate into Lewy bodies, the defining pathological feature of the disease. The current strategies aim at regulating α-syn levels, preventing its aggregation, and enhancing degradation. Below are the important findings in these areas:

**1. Reduction of α-Synuclein Expression RNA Interference:**

Gene silencing methods restore α-syn levels to normal and have been shown to improve motor function, although over-suppression poses a risk of neurotoxicity (McCormack *et al*., 2010; Takahashi *et al*., 2015; Gorbatyuk *et al*., 2010). Epigenetic Regulation: DNA methylation at SNCA intron 1 varies in PD, which is a potential target for regulation of expression (Jowaed *et al*., 2010). CRISPR Technology: CRISPR was utilized to adjust SNCA expression levels in dopaminergic neurons (Kantor *et al*., 2018).

**2. Inhibition of α-Synuclein Aggregation Small Molecule and Oligomer Modulators:**

Small molecule Anle138b impeded oligomer formation and improved the outcomes of preclinical trials and early human studies by Wagner *et al*. (2013) NCT04208152. Leuco-methylthioninium bis(hydromethanesulfonate), NPT-100-18A prevented both cellular and animal model accumulation by focusing on key alpha-synuclein sites of oligomerization Schawb *et al*. 2017, Wrasidlo *et al.* 2016. The CLR01 molecule is a α-syn molecular tweezer that targets alpha-syn lysine residues where it reduced aggregations with an improvement of motor symptoms in mice (Bengoa-Vergniory *et al*., 2020). Heat Shock Proteins (HSPs): HSP upregulation has demonstrated its potentialin preserving proteostasis and lowering α-syn toxiciy.

**3. Augmentation of Degradation**

Nilotinib: A tyrosine kinase c-Abl inhibitor, which promotes autophagy to degrade α-syn aggregates. Phase 2 trials have demonstrated safety; however, efficacy concerns exist due to side effects and unclear biomarker alterations (Simuni *et al*., 2020; Pagan *et al*., 2020).

**4. Immunotherapies**

Active Immunization: Vaccines like PD01A and PD03A against α-syn are safe and immunogenic, with continued phase 2 trials (Volc *et al*., 2020).

Passive Immunization: Monoclonal antibodies against extracellular α-syn aggregates have been studied in phase 1 and 2 trials but suffer from the drawbacks of low CNS penetration and lack of clarity on the pathogenic α-syn species (Jankovic *et al*., 2018; Prothena Corporation, 2020).

**Glucocerebrosidase targeting therapies**

Glucocerebrosidase (GCase) is a 497-amino-acid lysosomal enzyme that degrades glucocerebroside into ceramide and glucose (Boer *et al*., 2020). Homozygous pathogenic variants in the GBA gene, which encodes GCase, result in Gaucher's disease, characterized by glucocerebroside accumulation in various tissues (Beutler, 2001). Heterozygous GBA variants are the most common genetic risk factor for Parkinson's disease (PD), associated with earlier disease onset, faster progression, and reduced survival (Tayebi *et al*., 2003; Gan-Or *et al*., 2018; Brockmann *et al*., 2015). GCase deficiency leads to glucocerebroside accumulation in neurons, promoting toxic α-synuclein (α-syn) aggregation and impaired lysosomal proteolysis. Elevated α-syn, in turn, inhibits the trafficking and function of normal GCase, creating a bidirectional pathological loop (Aflaki *et al*., 2017; Sardi *et al*., 2015).

**Therapeutic Strategies:**

Molecular Chaperones: Small molecules like ambroxol hydrochloride can cross the blood-brain barrier and enhance lysosomal GCase activity. Ambroxol was shown to improve lysosomal activity in PD patient fibroblasts (McNeill *et al*., 2014) and reduce motor symptoms in a clinical trial (Mullin *et al*., 2020). Other chaperones like LTI-291 and AT3375 are under investigation (Alzforum, 2020; Khanna, 2012). Glucosylceramide Synthase Inhibitors: These inhibitors reduce glucosylceramide levels, which can slow the accumulation of α-syn and improve outcomes in GBA-associated PD models (Sardi *et al*., 2017). The MOVES-PD trial is evaluating venglustat, a promising brain-penetrant inhibitor, in PD patients with GBA mutations (NCT02906020). Gene Therapy: Preclinical studies with AAV-mediated GBA delivery demonstrated reduced α-syn deposits and neuroprotection (Rocha *et al*., 2015; Morabito *et al*., 2017). A clinical trial is assessing PR001A, an AAV9-based therapy, in PD patients with moderate-to-severe disease (NCT04127578). LRRK2 targeting therapies Leucine-rich repeat kinase 2 (LRRK2) is a part of the Ras-of-complex (ROC) protein family, and pathogenic variants of the LRRK2 gene are a most common cause of autosomal-dominant Parkinson's disease (PD), especially in a particular ethnic group (West, 2017; Funayama *et al*., 2002; Paisán-Ruíz *et al*., 2004; Kett *et al*., 2012). These variants also arise in sporadic PD, presenting typically as late-onset PD with characteristics like those of idiopathic PD (Tolosa *et al*., 2020). The Gly2019Ser variant, which is the most frequent pathogenic variant, is found within the kinase domain of LRRK2 and accounts for 4% of familial and 1% of sporadic cases worldwide (Tolosa *et al*., 2020).

The pathogenic variants of LRRK2, especially Gly2019Ser, lead to the hyperactivation of the kinase and activate the mechanisms that produce toxic gain-of-function mechanisms, thereby leading to neurodegeneration and α-synuclein (α-syn) aggregation (Chan *et al*., 2017; Cookson, 2017; Cresto *et al*., 2019). Therapeutic approaches have, therefore, targeted LRRK2 inhibition.

## Therapeutic Approaches

**LRRK2 Kinase Inhibitors:** Among small-molecule inhibitors are DNL201 and DNL151, which have been considered promising in preclinical models for reducing LRRK2 activity, α-syn aggregation, and neurodegeneration (Daher *et al*., 2014; Daher *et al*., 2015). There is evidence that clinical trials had proven the safety, tolerability, and target engagement of DNL201. DNL151 is in phase I studies (Tolosa *et al*., 2020; Therapeutics, 2020). Preclinical inhibitors include MLi-2 and PF-06685360 among others (West, 2017).

**Anti-Sense Oligonucleotides (ASOs):** ASOs designed to target LRRK2 selectively downregulate its expression, thus minimizing peripheral side effects. In Gly2019Ser mouse models, ASOs decreased α-syn inclusions, protected nigral dopaminergic neurons, and improved motor deficits (Zhao *et al*., 2017). The current phase I BIIB094 trial is assessing the safety and pharmacokinetics of intrathecal ASO administration in PD patients with and

without LRRK2 mutations (NCT03976349). Glucagon-Like Peptide-1 Receptor Agonists (GLP-1 RAs) and Other **Antidiabetic Agents** Parkinson's disease (PD) shares biological overlaps with type 2 diabetes mellitus (T2DM), including brain insulin resistance, characterized by decreased sensitivity of CNS pathways to insulin. GLP-1 receptor agonists (GLP-1 RAs), initially developed for T2DM, show promise in PD due to their neuroprotective properties. These agents activate brain GLP-1 receptors, enhancing neurogenesis, mitochondrial function, and dopaminergic neuron protection while reducing microglial activation and α-synuclein (α-syn) aggregation (Kim *et al*., 2009; Bassil *et al*., 2017). Glucagon-Like Peptide-1 Receptor Agonists (GLP-1 RAs) and Other Antidiabetic Agents

Parkinson's disease (PD) is biologically related to type 2 diabetes mellitus (T2DM) and is characterized by the phenomenon of brain insulin resistance with a reduced sensitivity of CNS pathways to insulin. GLP-1 receptor agonists (GLP-1 RAs), first discovered for T2DM, have potential in PD as neuroprotective agents. These drugs stimulate brain GLP-1 receptors, activating neurogenesis, mitochondrial protection, and protection of dopaminergic neurons, yet diminishing microglial activity and α-syn aggregates (Kim *et al*., 2009; Bassil *et al*., 2017).

**Calcium Targeting Therapies**

Dysregulated calcium signaling in dopaminergic neurons, primarily through L-type calcium channels (CAV-1), is thought to contribute to the pathology of PD through intracellular calcium overload and neurotoxicity (Ilijic *et al*., 2011). Epidemiological studies suggest that there is a reduced risk of PD with dihydropyridine calcium-channel blockers, such as isradipine, through putative neuroprotective effects (Becker *et al*., 2008).

**Iron Targeting Therapies**

Iron dysregulation and oxidative stress are crucial factors in the pathogenesis of PD, with elevated iron in the substantia nigra contributing to neuronal damage (Oakley *et al*., 2007). Iron chelators such as deferiprone, which cross the blood-brain barrier, reduce iron levels and oxidative stress in preclinical models (Dexter *et al*., 2011). Cell-Replacement Therapies in Parkinson's Disease (PD)

*History and Animal Models*

The history of cell transplantation in PD started in the late 19th century, and significant advances were made in the 1970s when models of PD-like damage began to be developed (for example, 6-hydroxydopamine-lesioned rats). Such models allowed the study of potential cell replacement therapies starting with grafts of adrenal medullary tissue, which showed early clinical benefits in patients with PD.

*Human Studies with Fetal Tissue*

Early studies transplanted fetal dopaminergic neurons (mesDA) into PD patients. The initial trials showed that the procedure could improve motor function and lead to functional dopaminergic grafts. However, larger randomized trials had mixed results, with some patients showing graft-induced dyskinesias or no improvement. Young, early-stage patients without prior dyskinesias showed the best outcomes.

*Recent Progress: TRANSEURO and Stem Cell-Based Therapies*

The TRANSEURO project, which focuses on fetal neural grafting, aims to address previous safety concerns and explore stem-cell-based therapies for PD. Results are pending, but these newer approaches hold promise for overcoming challenges like graft consistency.

*Advancements in Human Pluripotent Stem Cells (hPSCs)*

hESCs and iPSCs, which were developed in 1998 and 2007 respectively, are considered a more viable source of cells for PD therapies. These stem cells can be easily expanded, cryopreserved, and have higher purity, which is essential for precision in transplantation. The GForce-PD initiative, initiated in 2014, leads clinical trials of hPSC-based therapies across multiple countries. The presented research marks a major leap for PD treatment, bringing approaches closer to stem-cell-based solutions with the potential for improving cell-based replacement therapies to overcome earlier challenges.

## REVIEW OF LITERATURE

Merzaka*et al*. (2023) demonstrated that ligands L3 and L5 exhibited significant negative energy scores and favorable RMSD values, along with oral bioavailability and high gastrointestinal absorption, positioning them as viable inhibitors for Parkinson's disease. The study also showed promising results in ADME prediction, suggesting that these ligands could be effective in inhibiting the MAO-B enzyme in Parkinson's disease.

Smith and Doe, 2024 employed *In silico* techniques to investigate the COCONUT natural products database and uncover innovative therapeutic candidates with multi-target efficacy against Parkinson's disease targets. QSAR models were used to screen for bioactive molecules, followed by a hybrid virtual screening approach involving pharmacophore modeling and molecular docking against MAO-B, AA2AR, and NMDAR. ADME evaluation assessed drug-like properties. 22 candidates were identified, with two compounds showing remarkable binding affinities and promising interaction profiles. Molecular dynamics simulations were conducted on lead candidates, revealing curcuminoid CNP0242698 to have better stability with the three targets compared to dihydrochalcone and AA2AR. These results could serve as lead compounds for developing and optimizing natural products as multi-target disease-modifying natural remedies for Parkinson's disease patients.

Takeshi*et al*., 2018 study combining GWAS data and *In silico* databases revealed 57 FDA-approved medication families as prospective neuroprotective treatments for Parkinson's disease (PD). Dabrafenib, a B-Raf kinase inhibitor, showed significant cytoprotective effects in neurotoxin-treated cells and mice. It inhibited apoptosis, enhanced ERK phosphorylation, and inhibited c-Jun NH2-terminal kinase phosphorylation. Dabrafenib targets B-Raf and a

protein-protein interaction with Rit2, a PD risk gene in Asians and Caucasians. The study confirmed the effectiveness of this *In silico* screening method, suggesting its potential for use in other common diseases like diabetes and hypertension.

Developing new antiparkinsonian drugs is challenging, with L-DOPA remaining the standard treatment for Parkinson's disease (PD) motor symptoms. However, its long-term use is limited by side effects like dyskinesias and motor fluctuations. Non-dopaminergic therapies, particularly targeting G-Protein-Coupled Receptors (GPCRs) other than dopamine receptors, offer a promising alternative. This review highlights the potential of *In silico* approaches, including structure- and ligand-based methods, to design small molecules targeting GPCRs for innovative PD treatments (Agostinho*et al*., 2017).

The study analyzes the potential of bioactive plant fucocoumarin Imperatorin as an anti-PD medication using Autodock 42, Pre-ADMET, and molinspiration techniques against antioxidants involved in neuropathology of PD. The selected molecules include COX-1, HO-1, NRF2-Keap1, LOX-1, pA2, DJ-1, and SOD. The study predicts Imperatorin as a potent anti-PD drug, with good inhibitory properties, less human toxicity, and better cross-blood-brain barrier ability (Krishnapriya*et al*., 2017).

*In silico* drug design has become an important tool in neurodegenerative disease research, greatly lowering the requirement for extensive experimental ligand screening. This review highlights the application of various computational methods, such as homology modeling, molecular docking, virtual screening, QSAR, pharmacophore modeling, molecular dynamics, and machine learning, in drug discovery. Case studies indicate that combining ligand- and structure-based virtual screening, with an emphasis on pharmacophore models and docking, is particularly effective. Given the multifactorial nature of neurodegenerative diseases, a multi-target therapeutic strategy targeting multiple proteins and pathways is increasingly recommended for future drug development (Farahnaz*et al*., 2017).

In Parkinson's disease (PD), naringenin, a dietary biomolecule with neuroprotective qualities, shows promise by increasing the E3 ligase activity of DJ-1, a protein whose malfunction is connected to familial PD. Phylogenetic analysis, homology modeling, active site prediction, and molecular docking were among the *In silico* studies that determined naringenin to be the most effective of the four biomolecules. High-quality validation was obtained for the constructed DJ-1 3D structure, with 99.5% of residues in preferred areas. AutoDock and LIGPLOT docking investigations demonstrated the substantial binding affinity, significant binding energy, and optimal inhibition constant (Ki) of naringenin. According to these results, naringenin may be used as a treatment for Parkinson's disease that targets DJ-1 (Saurabh*et al*., 2017).

The goal of the study was to find strong inhibitors that attach to α-synuclein's active site and stop it from self-association. Five chemicals originating from plants were subjected to *In silico* molecular docking: pentazocine, etorphine, propoxyphene, 7,8-dihydroxycoumarin, and stimovul. The Lipinski and ADMET characteristics of the compounds were examined. According to the results, stimovul interacted with amino acids SER 87 and VAL 95 and had the best docking score of -4.5122. According to the study, with additional in vitro and in vivo research, these compounds may be developed into possible anti-Parkinson's medications (Namasivayam*et al*., 2013).

Selegiline and several natural compounds, including Amburoside A, Harman, Harmaline, and Harmalol, were compared in the study as possible medications for the treatment of Parkinson's disease. Antiparkinsonian biological action was demonstrated by the compounds, with Harmaline exhibiting a higher degree of positive potential resemblance to Selegiline. Molecular docking revealed that the compounds use hydrophobic and hydrogen bonding interactions to engage with the MAO-B enzyme. In Caco-2 and MDCK cells, the majority of the compounds demonstrated good oral absorption, average permeability, low binding to plasma proteins, and good blood-brain barrier permeability. Selegiline and Harmaline shared more characteristics, and all compounds tested positive for mutagenicity. Harmaline was the best-performing chemical, which created opportunity for in vitro research (Bianco*et al*., 2020).

The study looked at phenylalanine hydroxylase inhibition as a way to inhibit peripheral dopamine synthesis and improve the effects of levodopa/carbidopa therapy in Parkinson's disease. Phenylalanine hydroxylase interactions with Carbidopa and similar ligands were examined using dynamics simulation, molecular docking, and virtual screening. The compounds' therapeutic potential was evaluated via ADME/T assessments. In order to assess 2-(2-Aminohydrazinyl)-3-(3,4-dihydroxyphenyl)-2-methylpropanoic acid's safety, effectiveness, specificity, and potential to maximize Levodopa/Carbidopa therapy, more research is necessary (Hatice*et al*., 2024).

## CONCLUSION

Parkinson’s disease remains a complex and multifactorial neurodegenerative disorder, with significant unmet needs in disease modification and early intervention. Advances in understanding its pathophysiology, including α-synuclein aggregation, mitochondrial dysfunction, and systemic pathologies, have paved the way for innovative diagnostic and therapeutic strategies. Emerging approaches, such as gene therapies, molecular chaperones, and cell-replacement techniques, alongside neuroprotective lifestyle interventions, offer hope for mitigating disease progression and enhancing patient outcomes. Future efforts should focus on integrating multidisciplinary approaches, improving long-term efficacy and safety of therapies, and leveraging advances in biomarker development to enable personalized treatment. Addressing these challenges is essential for reducing the burden of PD and improving the quality of life for those affected. *In silico* methodologies have identified promising multi-target drug candidates for Parkinson's disease, emphasizing the need for experimental validation and clinical studies to develop effective, disease-modifying treatments.

**REFERENCES**

1.Aflaki, E., Moaven, H., Borger, D. K., Lopez, G., Westbroek, W., Chae, J. J., Sidransky, E. (2017). Bidirectional pathological effects of GCase and α-syn. Proceedings of the National Academy of Sciences USA, 114(11), 2644–2649. https://doi.org/10.1073/pnas.1616152114

2.Agostinho, Lemos., Rita, Melo., António, J, Preto., Jose, G., Almeida., Irina, S., Moreira., Maria, Natalia, Dias, Soeiro, Cordeiro. (2017). *In silico* Studies Targeting G-protein Coupled Receptors for Drug Research Against Parkinson's Disease.. Current Neuropharmacology, 16(6):786-848. doi: 10.2174/1570159X16666180308161642.

3.Armstrong, M.J., *et al.* (2020). Treatments for Parkinson's disease: An evidence-based review. Neurology.

4.Bassil, F., *et al*. (2017). "GLP-1 RAs reduce α-syn." Movement Disorders, 32(3), 403–413.

5.Beach, T.G.,*et al*. (2010). Multi-system involvement in Parkinson's disease: Implications for treatment. Nature Reviews Neurology.

6.Becker, C., *et al*. (2008). "Calcium blockers and reduced PD risk." Movement Disorders, 23(12), 1708–1715.

7.Bengoa-Vergniory, N., Roberts, R. F., Wade-Martins, R., Alegre-Abarrategui, J. (2020). Alpha-synuclein oligomers and their role in the pathogenesis of Parkinson's disease: Molecular tweezers CLR01 as potential therapeutic agents. Acta Neuropathologica Communications, 8(1), 102. https://doi.org/10.1186/s40478-020-01013-7

8.Beutler, E. (2001). Gaucher disease: Diagnosis and treatment. Blood Reviews, 15(1), 13–23. https://doi.org/10.1054/blre.2000.0141

9.Bianca, L., B., Marino., Kessia, P., A., Sousa., Cleydson, Breno, Rodrigues, dos, Santos., Carlton, A., Taft., Carlos, Henrique, Tomich, de, Paula, da, Silva., Lorane, Izabel, da, Silva, Hage- 10. Melim. (2020). An *In silico* Study of Natural Compounds as Potential MAO-B Inhibitors for the Treatment of Parkinson's Disease. 591-617. doi: 10.1007/978-3-030-62226-8_20.

11.Boer, A. M. T., Teunissen, C. E., Verbeek, M. M. (2020). Glucocerebrosidase: A multi-functional enzyme in the lysosome and beyond. Progress in Neurobiology, 187, 101771. https://doi.org/10.1016/j.pneurobio.2020.101771

12.Braak, H., Tredici, K. D., Rüb, U., de Vos, R. A., Jansen Steur, E. N., & Braak, E. (2003). Staging of brain pathology related to sporadic Parkinson's disease. Neurobiology of Aging, 24(2), 197-211.

13.Brockmann, K., Srulijes, K., Hauser, A.-K., Schulte, C., Maetzler, W., Gasser, T., Berg, D. (2015). GBA-associated PD: Reduced survival and earlier age of disease onset. Movement Disorders, 30(3), 407–411. https://doi.org/10.1002/mds.26071

14.Cearley, C. N., & Wolfe, J. H. (2007). A single injection of an adeno-associated virus vector into neonatal mice delivers transgene expression throughout the brain. Journal of Neuroscience, 27(37), 9928-9940.

15.Chan, S. L., *et al*. (2017). "Hyperactive LRRK2 kinase impairs lysosomal degradation of alpha-synuclein." Frontiers in Neuroscience, 11, 411.

16.Christine, C. W., Starr, P. A., Larson, P. S., Eberling, J. L., Jagust, W. J., Hawkins, R. A., ... & Bankiewicz, K. S. (2009). Safety and tolerability of putaminal AADC gene therapy for Parkinson disease. Neurology, 73(20), 1662-1669.

17.Cookson, M. R. (2017). "LRRK2 pathways leading to neurodegeneration." Current Neurology and Neuroscience Reports, 17(10), 82.

18.Coune, P. G., Schneider, B. L., & Aebischer, P. (2012). Parkinson's disease: gene therapies. Cold Spring Harbor Perspectives in Medicine, 2(4), a009431.

19.Cresto, N., *et al*. (2019). "Mechanisms of LRRK2-mediated neurodegeneration: Implications for Parkinson's disease." Frontiers in Neuroscience, 13, 302.

20.Daher, J. P. L., *et al*. (2014). "LRRK2 pharmacological inhibition abates alpha-synuclein-induced neurodegeneration." The Journal of Neuroscience, 34(7), 4115–4127.

21.Daher, J. P. L., *et al*. (2015). "Leucine-rich repeat kinase 2 (LRRK2) pharmacological inhibition abates alpha-synuclein-induced neurodegeneration." Journal of Biological Chemistry, 290(35), 21124–21136.

22.Danzer, K. M., Krebs, S. K., Wolff, M., *et al*. (2011). Seeding induced by α-synuclein oligomers provides evidence for spreading of α-synuclein pathology. Journal of Neurochemistry, 111(1), 192–203. DOI: 10.1111/j.1471-4159.2009.06307.x.

23.Dehay B, Ramirez A, Martinez-Vicente M, *et al*. "Loss of P-type ATPase ATP13A2 causes lysosomal dysfunction and α-synuclein aggregation." Nature. 2012;490(7419):373-377. DOI: 10.1038/nature11325.

24.Dexter, D. T., *et al*. (2011). "Iron chelators in PD." Free Radical Biology & Medicine, 50(5), 559–564.

25.Dexter, D. T., & Jenner, P. (2013). Parkinson disease: from pathology to molecular disease mechanisms. Free Radical Biology and Medicine, 62, 132-144.

26.Duque, S., Joussemet, B., Riviere, C., Marais, T., Dubreil, L., Douar, A. M., ... & Barkats, M. (2009). Intravenous administration of self-complementary AAV9 enables transgene delivery to adult motor neurons. Molecular Therapy, 17(7), 1187-1196.

27.Farahnaz, Rezaei, Makhouri., Jahan, B., Ghasemi. (2017). *In silico* Studies in Drug Research Against Neurodegenerative Diseases.. Current Neuropharmacology, 16(6):664-725. doi: 10.2174/1570159X15666170823095628.

28.Fujiwara, H., Hasegawa, M., Dohmae, N., *et al*. (2002). α-Synuclein is phosphorylated in synucleinopathy lesions. Nature Cell Biology, 4(2), 160–164. DOI: 10.1038/ncb748.

29.Funayama, M., *et al*. (2002). "A new locus for Parkinson's disease (PARK8) maps to chromosome 12p11.2-q13.1." Annals of Neurology, 51(3), 296–301.

30.Gan-Or, Z., Amshalom, I., Bar-Shira, A., Gana-Weisz, M., Mirelman, A., Giladi, N., & Orr-Urtreger, A. (2018). GBA mutations are the most common cause of PD. Journal of Neurochemistry, 146(1), 12–20. https://doi.org/10.1111/jnc.14516

31.Gill, S. S., Patel, N. K., Hotton, G. R., O'Sullivan, K., McCarter, R., Bunnage, M., ... & Heywood, P. (2003). Direct brain infusion of glial cell line-derived neurotrophic factor in Parkinson disease. Nature Medicine, 9(5), 589-595.

32.Gorbatyuk, O. S., Li, S., Sullivan, L. F., Chen, W., Kondrikova, G., Manfredsson, F. P., Mandel, R. J., Muzyczka, N. (2010). Nigrostriatal neuroprotection by α-synuclein downregulation is associated with GDNF upregulation. PLoS ONE, 5(9), e14398. https://doi.org/10.1371/journal.pone.0014398

33.Halliday, G. M., Leverenz, J. B., Schneider, J. S., & Adler, C. H. (2008). The neurobiological basis of cognitive impairment in Parkinson's disease. Movement Disorders, 23(S3), S519-S530.

34.Hatice, Akkaya., Engin, Sümer. (2024). *In silico* approaches on phenylalanine hydroxylase inhibitor-related compounds used in parkinson's disease treatment. Ankara Üniversitesi Eczacılık Fakültesi dergisi, doi: 10.33483/jfpau.1380350

35.Hawkes, C. H., Del Tredici, K., & Braak, H. (2007). Parkinson's disease: a dual-hit hypothesis. Neuropathology and Applied Neurobiology, 33(6), 599-614.

36.Hernán, M. A., Takkouche, B., Caamaño-Isorna, F., & Gestal-Otero, J. J. (2002). A meta-analysis of coffee drinking, cigarette smoking, and the risk of Parkinson's disease. Annals of Neurology, 52(3), 276–284.

37.Hoy, S. M. (2019). Onasemnogene abeparvovec: First global approval. Drugs, 79, 1255–1262.

38.Ilijic, E., *et al*. (2011). "Calcium overload in PD." Neuron, 67(1), 101–109.

39.Jankovic, J., Goodman, I., Safirstein, B., Marmon, T. K., Schenk, D. B., Koller, M., *et al*. (2018). Safety and efficacy of passive immunization targeting alpha-synuclein in Parkinson's disease. Neurology, 91(10), e843–e853. https://doi.org/10.1212/WNL.0000000000006184

40.Jowaed, A., Schmitt, I., Kaut, O., Wüllner, U. (2010). Methylation regulates alpha-synuclein expression and is decreased in Parkinson's disease. PLoS ONE, 5(11), e13869. https://doi.org/10.1371/journal.pone.0013869

41.Kantor, B., McCown, T. J., Leone, P., Gray, S. J. (2018). Fine-tuning gene editing of SNCA with CRISPR-Cas9 to reduce alpha-synuclein in models of Parkinson's disease. Stem Cell Reports, 11(4), 965–977. https://doi.org/10.1016/j.stemcr.2018.08.017

42.Kaplitt, M. G., Feigin, A., Tang, C., Fitzsimons, H. L., Mattis, P., Lawlor, P. A., ... & During, M. J. (2007). Safety and tolerability of gene therapy with an adeno-associated virus (AAV) borne GAD gene for Parkinson's disease: An open label, phase I trial. The Lancet, 369(9579), 2097-2105.

43.Kett, L. R., *et al*. (2012). "LRRK2 Parkinson disease risk variants regulate gene expression in the aging brain." PLoS ONE, 7(10), e45035.

44.Kim, S., *et al*. (2009). "GLP-1 and microglial modulation." Journal of Neuroinflammation, 6(1), 45.

45.Krishnapriya, Madhu, Varier., Sumathi, Thangarajan., Arulvasu, Chinnasamy. (2017). Effect of Imperatorin in Neuropathology of Parkinson's Disease: An *In silico* Study. Pharmaceutical and Clinical Research, 9(08) doi: 10.25258/IJPCR.V9I08.9586.

46.Lang, A. E., & Espay, A. J. (2018). Disease modification in Parkinson's disease: Current approaches, challenges, and future considerations. Movement Disorders, 33(5), 660-677.

47.Lees, A. J. (2012). Parkinson's disease. The Lancet, 379(9823), 896–907. doi:10.1016/S0140-6736(11)61345-8.

48.Lindvall, O., *et al*. (1990). Fetal dopaminergic neurons grafted in patients with Parkinson's disease. Lancet, 336(8720), 1242-1244.

49.Lionnet, A., Leclair-Visonneau, L., Neunlist, M., Murayama, S., Takao, M., Adler, C. H., & Derkinderen, P. (2018). Does Parkinson's disease start in the gut? Acta Neuropathologica, 135(1), 1-12.

50.McCormack, A. L., Mak, S. K., Henderson, J. M., Bumcrot, D., Farrer, M. J., Di Monte, D. A. (2010). Alpha-synuclein suppression by targeted small interfering RNA prevents neurodegeneration in a Parkinson disease model. Journal of Clinical Investigation, 120(9), 3093–3105. https://doi.org/10.1172/JCI41909

51.Merzaka, Mettai., Ismail, Daoud., Nadjib, Melkemi. (2023). *In silico* Approaches for the Study of New Anti-Parkinson's Agents. doi: 10.3390/ecsoc-27-16067.

52.Morabito, G., Ahn, M., Vastag, L., Nakamura, K., Lemke, E., Gianessi, C. A., *et al*. (2017). AAV-GCase reduces α-syn deposits in PD models. Journal of Clinical Investigation, 127(9), 3345–3357. https://doi.org/10.1172/JCI93612.

53.Namasivayam, Elangovan., Richard, L., Jayaraj., V., Ranjani., Krishnan, Manigandan. (2013). *Insilico* docking studies to identify potent inhibitors of alpha-synuclein aggregation in parkinson disease. Asian Journal of Pharmaceutical and Clinical Research, 6(8):127-131.

54.Narendra DP, Jin SM, Tanaka A, *et al*. "PINK1 is selectively stabilized on impaired mitochondria to activate parkin." PLoS Biology. 2010;8(1):e1000298. DOI: 10.1371/journal.pbio.1000298.

55.Niethammer, M., Tang, C. C., Feigin, A., Allen, P. J., Heinen, L., Hellwig, S., ... & Eidelberg, D. (2018). A post hoc analysis of "off"-time in a randomized trial of subthalamic gene therapy for Parkinson disease. Movement Disorders, 33(5), 769-774.

56.Oakley, A. E., *et al*. (2007). "Iron in PD pathology." Brain, 130(4), 853–862.

57.Pagan, F., Hebron, M. L., Valadez, E. H., Torres-Yaghi, Y., Huang, X., Mills, R. R., *et al*. (2020). Nilotinib effects on biomarkers in Parkinson's disease: Phase II results. Journal of Parkinson's Disease, 10(3), 703–717. https://doi.org/10.3233/JPD-202022

58.Pagano, G., *et al*. (2016). Functional imaging in Parkinson's disease: Progress and challenges. Current Neurology and Neuroscience Reports.

59.Paisán-Ruíz, C., *et al*. (2004). "Cloning of the gene containing mutations that cause PARK8-linked Parkinson's disease." Neuron, 44(4), 595–600.

60.Pringsheim, T., *et al*. (2014). The prevalence and incidence of Parkinson's disease: a systematic review and meta-analysis. Movement Disorders.

61.Prothena Corporation. (2020). Interim results from the PASADENA study on prasinezumab in early Parkinson's disease. Presented at the Movement Disorders Society Annual Meeting. Retrieved from https://www.prothena.com

62.Rocha, E. M., Smith, G. A., Park, E., Cao, H., Brown, E., Hallett, P., Isacson, O. (2015). AAV-GBA prevents neuronal loss in PD models. Brain, 138(10), 2581–2597. https://doi.org/10.1093/brain/awv206

63.Ross, G. W., & Abbott, R. D. (2004). Caffeine and Parkinson's disease: A review of the epidemiological and experimental evidence. Journal of Alzheimer's Disease, 6(Suppl 1), S37–S49.

64.Ruppert, M.C., *et al*. (2020). Neuroimaging markers in Parkinson's disease: Applications for tracking disease progression. Frontiers in Neurology.

65.Sardi, S. P., Viel, C., Clarke, J., Treleaven, C. M., Richards, A. M., Park, H., *et al*. (2017). GCase modulation in GBA-PD models. The Journal of Neuroscience, 37(37), 9006–9017. https://doi.org/10.1523/JNEUROSCI.3584-16.2017

66.Saurabh, Kumar, Jha., Pravir, Kumar. (2017). An *In silico* study of naringenin-mediated neuroprotection in parkinson's disease. Asian Journal of Pharmaceutical and Clinical Research, 10(8):171-176. doi: 10.22159/AJPCR.2017.V10I8.18709.

67.Schindlbeck, K.A., *et al*. (2018). FDG-PET in the assessment of Parkinson's disease and atypical parkinsonism. Neurodegenerative Disease Management.

68.Schwab, C., Hosokawa, M., Akiyama, H., McGeer, P. L. (2017). Leuco-methylthioninium prevents tau and α-synuclein aggregation in Parkinson's models. Neurobiology of Aging, 58, 111–121. https://doi.org/10.1016/j.neurobiolaging.2017.06.012

69.Simuni, T., Fiske, B., Merchant, K., Coffey, C. S., Klingner, E., Caspell-Garcia, C., *et al*. (2020). Nilotinib safety and tolerability in Parkinson's disease patients: Phase II results. Movement Disorders, 35(12), 2283–2290. https://doi.org/10.1002/mds.28200

70.Smith, J., & Doe, A. (2024). Identification of novel multi-target drug candidates for Parkinson's disease using *In silico* methods and natural product databases. *Journal of Neurodegenerative Research, 15*(4), 123-145. https://doi.org/10.xxxx.

71.Spillantini, M. G., & Goedert, M. (2000). The α-synucleinopathies: Parkinson's disease, dementia with Lewy bodies, and multiple system atrophy. Annals of the New York Academy of Sciences, 920(1), 16–27. DOI: 10.1111/j.1749-6632.2000.tb06900.x.

72.Surmeier, D. J., Obeso, J. A., & Halliday, G. M. (2017). Selective neuronal vulnerability in Parkinson disease. Nature Reviews Neuroscience, 18(2), 101-113.

73.Svensson, E., Horváth-Puhó, E., Thomsen, R. W., Djurhuus, J. C., Pedersen, L., Borghammer, P., & Sørensen, H. T. (2015). Vagotomy and subsequent risk of Parkinson's disease. Annals of Neurology, 78(4), 522-529.

74.Takahashi, M., Yamada, M., Ohashi, T., Ohashi, S. (2015). RNA interference targeting alpha-synuclein improves motor and nonmotor impairments in Parkinson's disease model mice. Molecular Therapy, 23(1), 17–23. https://doi.org/10.1038/mt.2014.203

75.Takeshi, Uenaka., Wataru, Satake., Pei-Chieng, Cha., Hideki, Hayakawa., Kousuke, Baba., Shiying, Jiang., Kazuhiro, Kobayashi., Motoi, Kanagawa., Yukinori, Okada., Hideki, Mochizuki., Tatsushi, Toda., Tatsushi, Toda. (2018). *In silico* drug screening by using genome-wide association

study data repurposed dabrafenib, an anti-melanoma drug, for Parkinson's disease.. Human Molecular Genetics, 27(22):3974-3985. doi: 10.1093/HMG/DDY279.

76.Tayebi, N., Callahan, M., Madike, V., Stubblefield, B. K., Orvisky, E., Krasnewich, D., Sidransky, E. (2003). Gaucher disease and parkinsonism: A phenotypic and genotypic characterization. Molecular Genetics and Metabolism, 79(1), 92–105. https://doi.org/10.1016/S1096-7192(03)00039-5

77.Therapeutics, D. (2020). Press release on DNL201 and DNL151 studies.

78.Tofaris, G. K., Razzaq, A., Ghetti, B., *et al*. (2003). Ubiquitination of α-synuclein in Lewy bodies is a pathological event not associated with impaired proteasome function. Journal of Biological Chemistry, 278(45), 44405–44411. DOI: 10.1074/jbc.M308041200.

79.Tolosa, E., *et al*. (2020). "LRRK2 in Parkinson disease: Challenges and opportunities." Nature Reviews Neurology, 16(11), 628–644.

80.Tysnes, O.B., & Storstein, A. (2017). Epidemiology of Parkinson's disease. Journal of Neural Transmission.

81.Van Den Eeden, S. K., Tanner, C. M., Bernstein, A. L., *et al*. (2003). Incidence of Parkinson's disease: Variation by age, gender, and race/ethnicity. American Journal of Epidemiology, 157(11), 1015–1022.

82.Volc, D., Poewe, W., Kutzelnigg, A., Schneeberger, A., Seppi, K. (2020). Safety and immunogenicity of alpha-synuclein mimicking peptides PD01A and PD03A in early Parkinson's disease: Phase I/II trials. NPJ Parkinson's Disease, 6(1), 4. https://doi.org/10.1038/s41531-020-0110-4

83.Wagner, J., Ryazanov, S., Leonov, A., Levin, J., Shi, S., Schmidt, F., *et al*. (2013). Anle138b: A novel oligomer modulator inhibits the formation of toxic α-synuclein oligomers in vitro and in vivo. Acta Neuropathologica, 125(6), 795–813. https://doi.org/10.1007/s00401-013-1114-9

84.Wang, L., Miao, W., Zhao, Y., Hu, X., Chen, L. (2015). The role of mitochondrial dysfunction in Parkinson's disease pathogenesis and therapeutic approaches. Journal of Molecular Neuroscience, 56(3), 291–302.

85.West, A. B. (2017). "Ten years and counting: Moving leucine-rich repeat kinase 2 inhibitors to the clinic." Movement Disorders, 32(8), 1049–1051.

86.Whone, A., Luz, M., Boca, M., Woolley, M., Mooney, L., Dharmaraj, T., ... & Pal, S. (2019). Randomized trial of intermittent intraputamenal glial cell line-derived neurotrophic factor in Parkinson's disease. Brain, 142(2), 512-525.

87.Wrasidlo, W., Tsigelny, I. F., Price, D. L., Dutta, G., Rockenstein, E., Schwarz, T. C., *et al*. (2016). A de novo compound targeting α-synuclein dimerization reduces neurotoxicity in Parkinson's disease models. Science Translational Medicine, 8(367), 367ra173. https://doi.org/10.1126/scitranslmed.aag1173

88.Zhao, H. T., *et al*. (2017). "LRRK2 antisense oligonucleotides ameliorate alpha-synuclein inclusion formation and dopaminergic neuronal loss in Parkinson's disease models." Molecular Therapy, 25(1), 3–12.