Int. J. Pharm. Investigation, 2026; 16(3):880-884.
https://www.jpionline.org

Review Article

Exploring Novel Emerging Therapeutic Strategies for Parkinson's Disease: A Narrative Review

Vishal Kulkarni[1], Sai Kumari R T[2], Sanjunath Satteppa Muchandi[3], Sanatkumar Bharamu Nyamagoud[4,*], Nanjappaiah H M[5], Vishwanath Jagadevappa Hooli[6], Sangamesh Sharanbasappa Tadkal[7], Prasad Nijaguni Bali[8]

[1]Department of Medical Oncology, Karnataka Medical College and Research Institute, Hubballi, Karnataka, INDIA.
[2]Consultant Radiation Oncologist, Karnataka Cancer Therapy and Research Centre, Navanagar, Hubballi, Karnataka, INDIA.
[3]Formulation Development (Pharma), Himalaya Wellness Company, Makali, Bengaluru, Karnataka, INDIA.
[4]Department of Pharmacy Practice, SDM Trust's Danigond College of Pharmacy, Terdal, Karnataka, INDIA.
[5]Department of Pharmacology, BLDEA's SSM College of Pharmacy and Research Centre, BLDE University Campus, Vijayapura, Karnataka, INDIA.
[6]Department of Pharmacognosy, HKE's Institute of Pharmacy, Kalaburagi, Karnataka, INDIA.
[7]Department of Pharmacy Practice, Shetty Institute of Pharmaceutical Sciences, Kalaburagi, Karnataka, INDIA.
[8]Department of Pharmacy Practice, HKE's Matoshree Taradevi Rampure Institute of Pharmaceutical Sciences, Kalaburagi, Karnataka, INDIA.

ABSTRACT

Parkinson's Disease (PD) is a common neurodegenerative disorder. It is defined by a progressive loss of dopamine neurons in the substantia nigra pars compacta and neurodegeneration, which eventually results in a decrease in dopamine levels. This review provides an overview of PD. Parkinson's disease patients exhibit both non-motor symptoms like depression and anxiety as well as motor symptoms including bradykinesia, tremor and rigidity. PD involves Lewy body formation, dopamine neuron death and molecular pathways with α-synuclein clumping. Current PD management focuses on relieving motor symptoms through dopamine medications, glutamateblocking and surgery. However, non-motor symptoms require additional medications. This literature review also explores innovative treatment approaches like Aiming for α-Syn Aggregation, enhancing autophagy and promoting neuroprotection. It stops bad proteins from forming, blocks harmful genes and boosts the body's cleaning systems. There's also a focus on creating treatments that protect nerve cells. Some are channel blockers; others encourage cell response. Iron binders are used too. Inflammation in the brain is another focus. This is done through enzyme control and tweaking certain cell responses.

Keywords: Autophagy, Neurodegeneration, Neuroinflammation, Neuroprotection, Parkinson's disease, α-synuclein aggregation.

Correspondence:
Dr. Sanatkumar Bharamu Nyamagoud
Associate Professor and Head, Department of Pharmacy Practice, SDM Trust's Danigond College of Pharmacy, Terdal-587315, Karnataka, INDIA.
Email: dr.sanathnyamagoud@gmail.com

Received: 28-01-2026;
Revised: 02-03-2026;
Accepted: 11-05-2026.

INTRODUCTION

Approximately 1% of those over 60 suffer with Parkinson's Disease (PD) and it is the second most prevalent neurological condition worldwide. Men are more likely than women to have Parkinson's Disease (PD) at a prevalence rate of 1.6:1. Bradykinesia, stiffness, postural instability and resting tremor are the main clinical indicators of PD. Dopamine (DA) insufficiency in the striatum, resulting from the progressive death of dopaminergic neurons in the substantia nigra pars compacta is the primary source of these symptoms (Dong *et al.*, 2016). Other symptoms include difficulty sleeping, mental health issues and issues with the bladder and digestive system. Parkinson's disease can have various causes, including heredity, environment, malnourishment, age of growth, gender and brain injury. Many proteins and molecular pathways are connected to the genesis of Parkinson's disease. Alpha-Synuclein (α-Syn) and other misfolded or abnormal proteins accumulate and deposit, signaling or actually causing dying DA neurons (Gouda *et al.*, 2022). Some Parkinson's Disease (PD) instances have been connected to genes like Daisuke-Junko-1, phosphatase, Ubiquitin C-terminal Hydrolase L1 (UCHL1), Glucocerebrosidase (GBA1) and Tensin homolog (PTEN)-Induced Kinase 1 (PINK1) among others (Cacabelos, 2017).

DOI: 10.5530/ijpi.20261067

Innovative Treatment Approaches for Parkinson's Disease

Aiming for α-Syn Aggregation

Misfolding Inhibitors of α-Syn

Finding efficient methods to inhibit the α-Syn aggregation process has been difficult because it is an intricate procedure that is dependent on external factors (Pfeiffer, 2016). However, in

order to preserve cellular proteostasis under stressful situations, a number of Heat Shock Proteins (HSPs), in particular HSP70 and HSP104, helped to ATP-independently partially stabilize the transitory folding intermediates. This enabled them to stop α-Syn aggregation in both *in vivo* and *in vitro* settings (Gorenberg and Chandra, 2017). Moreover, curcumin, a spice and other naturally occurring α-Syn aggregation inhibitors have a strong neuroprotective effect (Nebrisi, 2021). Nowadays, a lot of focus is placed on the study of small-molecule α-Syn inhibitors. NPT088 and NPT200-11 are two exceptional candidates that are presently undergoing clinical studies. In the cortex of a transgenic mouse model for Parkinson's disease, NPT200-11 therapy reduced α-Syn aggregation and neuroinflammation (astrogliosis). Additionally, NPT200-11 improved striatal Dopamine Transporter (DAT) levels and motor performance (Levenson *et al*., 2016). NPT088 decreased protein aggregation in an animal model of Parkinson's disease. It was assessed in a phase I clinical trial with individuals with mild-to-moderate AD (Michelson *et al*., 2019). In spite of NPT200-11's encouraging clinical results, the discovery of SMSIs for PD is imperative in the next upcoming years.

ASOs or antisense oligonucleotides

By upregulating the degradation of α-Syn messenger RNA levels (mRNA), which can delay the onset of PD, ASOs can also is utilized to slow down the disease's progression. Here's an additional technique to lower the expression of the SCNA (α-Syn gene). Uehara *et al.* created an ASO with improved stability and cellular absorption *in vivo* that targets the α-Syn gene using amido-bridged Nucleic Acid (AmNA). AmNA-ASO effectively reduced the amounts of α-Syn mRNA and protein (Uehara *et al*., 2019). Subsequent investigation revealed that mouse brainstem monoamine nuclei's native α-Syn mRNA and protein levels were decreased by triomonoamine reuptake inhibitor indatraline conjugated with ASO and small interfering RNA sequences that specifically target norepinephrine or serotonin (5-HT) neurons (Alarcón-Arís *et al*., 2018).

Beta2-Adrenoreceptor (β2AR) Agonists

Early in the 1990s, open-label trials were conducted to evaluate the brain-penetrant asthma medicine salbutamol, a β2AR agonist, in an effort to make the first clinical attempts to utilize β-adrenergic agonists in Parkinson's disease (Patterson *et al*., 2022). In 2003, additional studies validated the synergistic effects of β2AR agonists with L-DOPA. By objectively evaluating endogenous gene expression, a novel mechanism has been postulated for how β2AR agonists regulate the α-Syn gene and reduce its production, accumulation and deposition. A lower chance of acquiring Parkinson's Disease (PD) was linked to salbutamol during the 11-year follow-up. Alternatively, a β-adrenergic antagonist called propranolol was linked to a higher risk (Thenganatt and Jankovic, 2016). Evidence from Israeli and Norwegian populations also contributed to these conclusions, indicating that β2AR antagonist-treated patients had an elevated chance of Parkinson's illness and β2AR agonist-treated patients had a decreased risk (Gronich *et al*., 2018). β2AR agonists have been suggested to have a neuroprotective impact through immunomodulatory effects because their stimulation of astrocytes through adrenergic stimulation causes the synthesis of additional proteins or trophic factors connected to glutamate-induced excitotoxicity (Laureys *et al*., 2010).

The receptor for Lymphocyte-Activation Gene 3 (LAG3)

An intracytoplasmic portion and four domains that resemble extracellular Immunoglobulin (Ig) (D1-D4) are features of the transmembrane protein LAG3, also known as CD223 (Andrews *et al*., 2017). Largely expressed on microglia and neuronal cells, LAG3 has recently been connected to the etiology of Parkinson's disease, specifically in relation to α-Syn transmission, even if its exact function is yet unknown. Out of the three transmembrane protein candidates that were discovered, about binding to α-Syn PFFs that are exogenous rather than α-Syn monomers, LAG3 demonstrated the highest level of selectivity. By attaching to LAG3, α-Syn-biotin PFF caused neurotoxicity to be distributed through endocytosis and neuronal transmission followed (Angelopoulou *et al*., 2020). The neuroinflammatory mechanisms that contribute to the pathogenesis of Parkinson's illness may involve LAG3. In a newest Chinese population study, serum levels of LAG3 were considerably greater in patients with Parkinson's disease than in sex- and age-matched control groups as well as those with essential tremor. This finding raises the possibility that LAG3 is a promising molecular biomarker of Parkinson's disease (Cui *et al*., 2019).

Enhancing Autophagy

Mammalian Target of Rapamycin (mTOR) Signaling

Autophagy is regulated at multiple stages by the mTOR signaling pathway (Zhu, 2019). The different stages of Parkinson's disease are associated with both activation and inactivation of mTOR signaling. As mentioned before, autophagy is necessary for the breakdown of α-Syn. Overexpression of α-Syn increases mTOR activity, which in turn limits autophagy. Patients with α-Syn accumulation was found to have higher levels of mTOR protein expression in the temporal cortex. On the other hand, the elevated mTOR activity brought on the overexpression of α-Syn was diminished by the mTOR inhibitor rapamycin (Gao *et al*., 2015). However; a stress-related protein called RTP801/REDD1 dramatically lowers mTOR activity, which results in neuronal death. It was discovered that PD patients' substantia nigra pars compacta neurons have higher levels of RTP801 (Malagelada *et al*., 2006). Early studies on the combination of rapamycin and L-DOPA were carried out in an animal model with Parkinson's disease. Thankfully, it did not result in increased mTOR activity or decreased L-DOPA-induced dyskinesia (Calabrese *et al*., 2020).

Therefore, Treatment with L-DOPA for Parkinson's disease is supported by science when paired with autophagy activation to improve α-Syn breakdown and rapamycin-induced reduction of mTOR signaling. Rapamycin protected neurons in Parkinson's disease-stricken mice by suppressing mTOR and increasing autophagy flux, which blocked RTP801 translation (Bové *et al.*, 2011).

Inhibition of Cellular Homolog of ABL1 (c-Abl)

Tyrosine kinases from the ABL (Abelson murine leukemia virus oncogene) family are found in the cytoplasm and nucleus, which includes the c-Abl. It performs a variety of physiological functions, including autophagy, DNA repair, cytoskeleton dynamics, cell growth and receptor endocytosis (González-Martín *et al.*, 2021). The importance of c-Abl biology in the central nervous system extends beyond cerebellar development to include neurite growth, synapse creation and neuronal proliferation. DA stress and DA neurotoxins cause phosphorylation of E3 ubiquitin ligase PRKN by activating c-Abl tyrosine kinase. Consequently, PRKN ubiquitination is inhibited and its protective effect is compromised (Abushouk *et al.*, 2018). Microglial cells are rendered inactive and their production of pro-inflammatory mediators is reduced by c-Abl suppression. Furthermore, it increases autophagy to improve α-Syn clearance, suggesting a role for c-Ab1 inhibition in Parkinson's disease therapy (Hebron *et al.*, 2013). Additionally, brain samples taken from people with Parkinson's illness showed activation of c-Abl, suggesting a pathophysiological role for the disease. Three c-Abl inhibitors have been investigated thus far as potential therapies for Parkinson's disease modification: imatinib, nilotinib and bafetinib (Breedveld *et al.*, 2005).

RhoA-ROCK Signaling

The signaling protein RhoA is involved in the synthesis of actin, membrane trafficking and inflammation, among other physiological activities. The main RhoA downstream effectors are ROCK I and II (Villar-Cheda *et al.*, 2012). RhoA/ROCK signaling may activate microglial cells, which could lead to DA depletion. When Rho kinase is activated, microglia's ROCK activity is increased, raising ROS levels and, in turn, inflammatory cytokines are released (Roser *et al.*, 2017). RhoA-ROCK can block cofilin, which results in DA depletion (Tilve *et al.*, 2015). The actin-binding protein cofilin is necessary for the depolymerization of actin filaments and, as a result, the prevention of actin filament elongation. Rho increases the polymerization of actin filaments by removing cofilin's ability to bind actin. Actin has been found in cytoplasmic α-Syn aggregates, leading to an increasing body of evidence suggesting a connection between PD and actin dynamics (Moussaud *et al.*, 2014). Therefore, it is believed that ubiquitous RhoA/ROCK contributes to Parkinson's disease.

Promoting Neuroprotection

L-type Voltage-dependent Ca2+ Channel (L-VDCC)

By lowering mitochondrial stress, L-VDCC antagonists prevent MPTP-induced degeneration in SN neurons (Ilijic *et al.*, 2011). As SN neurons age, they become dependent on L-VDCCs and Ca2+, which makes them vulnerable to neurotoxicity that L-VDCC antagonists can prevent. Additionally, α-Syn causes dysregulation of Ca2+, which in turn causes α-Syn aggregation (Lautenschläger *et al.*, 2018). Research revealed that PD risk was decreased in patients receiving L-VDCC antagonist treatment. Moreover, microglia' transitioning the immune effector state from "rest" to "active" is regulated by intracellular $Ca2^{+}$ (Hopp, 2021).

Agonists of Glucagon-Like Peptide-1 (GLP-1)

The GLP-1 receptor, also known as GLP-1R, is present in every other tissue except the pancreas. Seven transmembranes make up the GLP-1R class B G protein-coupled receptor. It initiates the process of activating protein kinase A (PKA) by increasing intracellular cAMP levels on neuronal cells. Moreover, it starts the PI3K/AKT signaling pathway's activity. Several downstream targets, such as the forkhead box protein O1 and glycogen synthase kinase-3 beta, are influenced by these pathways, which are essential to Parkinson's disease's degenerative processes and maintain an antiapoptotic cell survival pathway (Athauda and Foltynie, 2016).

Peroxisome Proliferator-Activated Receptors (PPARs) Agonists

PPARG, PPARG and PPARG/δ are the three ligand-activated transcription factors (PPARs) in the nuclear hormone receptor superfamily (Tyagi *et al.*, 2011). Several research conducted both *in vivo* and *in vitro* have indicated that PPAR agonists may have neuroprotective advantages (Vega *et al.*, 2000). It has been found that via reducing MAO-B activity, the PPARγ agonist pioglitazone protects DA neurons against MPTP and prevents MPTP from being converted to 1-Methyl-4-Phenylpyridinium (MPP+) (Chaturvedi and Beal, 2008). Pioglitazone helps the brain's mitochondrial potential and DA neuronal activity by reducing oxidative damage (Ulusoy *et al.*, 2011).

Iron Chelators

PD patients' SN neurons have been found to accumulate iron, which is thought to be a disease-causing process related to the severity of the condition (Hayflick *et al.*, 2018). Transferring iron from the cytoplasm to inclusions rich in α-Syn, overexpression of α-Syn results in an increase in intracellular iron levels. This causes α-Syn to combine and form fibrils more quickly, most likely as a result of increased α-Syn protein synthesis (Lingor *et al.*, 2017). Moreover, ROS can be produced by iron. Therefore, iron elimination from the SN could halt the illness's progression. Preclinical studies indicate that iron chelators that

are BBB-permeable, which remove excess iron, could be used as disease-modifying medications to treat Parkinson's disease (Dexter *et al.*, 2011). A study that employed a Parkinson's disease model in mice with MPTP induction found that dexteroamine treatment significantly improved behavioral deficits and increased DA neuron survival.

Targeting Neuroinflammation

Phosphodiesterase 10A (PDE10A)

The medium spiny neurons in PDE10A are the target of striatal enzyme hydrolyzing cAMP and cGMP (Fujishige *et al.*, 1999). PDE10A controls DA signaling in addition to a variety of other brain functions, such as synaptic plasticity, ion conductance. PDE10A deficit was linked to PDE10A and dopaminergic activity may be related, according to DAT deficiency in Parkinson disease patients' striatum who were treated with L-DOPA early on and de novo (Giorgi *et al.*, 2008). Conversely, papaverine, a PDE10A inhibitor decreased the mortality of DA neurons by enhancing the production of neurotrophic factors, including B cell lymphoma 2, PKA signaling regulates both Brain-Derived Neurotrophic Factor (BDNF) and Glial cell line-Derived Neurotrophic Factor (GDNF) (Lee *et al.*, 2019).

TLRs

There is growing evidence connecting PD and TLR2 and TLR4. In PD patients' postmortem brain tissue, TLR2 levels were elevated. Moreover, the TLR2 agonist PAM3CSK4 stimulates neuronal TLR2 and raises endogenous α-Syn levels in conjunction with elevated *p*62, a hallmark of the autophagy/lysosomal pathway (Kim *et al.*, 2015).

CONCLUSION

Parkinson's disease has a wide spectrum of symptoms and complicated underlying biological causes, making it an ongoing challenge to treat. Although the current management options focus on symptom alleviation, novel approaches that target autophagy enhancement, neuroprotection, α-synuclein aggregation and neuroinflammation regulation provide intriguing paths for future therapeutic development. With more study to be done to fully understand the pathophysiology of Parkinson's disease, these novel medicines may be able to alter the course of the disease and enhance the quality of life for those who are afflicted.

ACKNOWLEDGEMENT

The authors are thankful to the management of SDM Trust's Chairman Dr. Mahaveer S Danigond, Managing Director Dr. Pushpadant Mahaveer Danigond and Managing Trustee Pratibha Mahaveer Danigond for providing necessary support.

ABBREVIATIONS

PD: Parkinson's Disease; **DA:** Dopamine; **α-Syn:** Alpha-synuclein; **mTOR:** Mammalian Target of Rapamycin; **L-DOPA:** Levodopa; **ASOs:** Antisense Oligonucleotides; **DAT:** Dopamine Transporte**:** Heat Shock Proteins; **LAG3:** Lymphocyte-Activation Gene 3; **c-Abl:** Abelson Tyrosine Kinase; **ROCK:** Rho-associated Protein Kinase; **L-VDCC:** L-type Voltage-Dependent Calcium Channel; **GLP-1:** Glucagon-Like Peptide-1; **PPARs:** Peroxisome Proliferator-Activated Receptors; **ROS:** Reactive Oxygen Species; **PDE10A:** Phosphodiesterase 10A; **TLRs:** Toll-Like Receptors.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

REFERENCES

Abushouk, A. I., Negida, A., Elshenawy, R. A., Zein, H., Hammad, A. M., Menshawy, A., & Mohamed, W. M. Y. (2018). C-Abl inhibition; A novel therapeutic target for Parkinson's disease. *CNS & Neurological Disorders Drug Targets*, *17*(1), 14–21. https://doi.org/10.2174/1871527316666170602101538

Alarcón-Arís D, Alarcón-Arís, D., Recasens, A., Galofré, M., Carballo-Carbajal, I., Zacchi, N., Ruiz-Bronchal, E., Pavia-Collado, R., Chica, R., Ferrés-Coy, A., Santos, M., Revilla, R., Montefeltro, A., Fariñas, I., Artigas, F., Vila, M., & Bortolozzi, A. (2018). Selective α-synuclein knockdown in monoamine neurons by intranasal oligonucleotide delivery: Potential therapy for Parkinson's disease. *Molecular Therapy*, *26*(2), 550–567. https://doi.org/10.1016/j.ymthe.2017.11.015

Andrews, L. P., Marciscano, A. E., Drake, C. G., & Vignali, D. A. A. (2017). LAG3 (CD223) as a cancer immunotherapy target. *Immunological Reviews*, *276*(1), 80–96. https://doi.org/10.1111/imr.12519

Angelopoulou, E., Paudel, Y. N., Villa, C., Shaikh, M. F., & Piperi, C. (2020). Lymphocyte-activation gene 3 (LAG3) protein as a possible therapeutic target for Parkinson's disease: Molecular mechanisms connecting neuroinflammation to α-synuclein spreading pathology. *Biology*, *9*(4), Article 86. https://doi.org/10.3390/biology9040086

Athauda, D., & Foltynie, T. (2016). The glucagon-like peptide 1 (GLP) receptor as a therapeutic target in Parkinson's disease: Mechanisms of action. *Drug Discovery Today*, *21*(5), 802–818. https://doi.org/10.1016/j.drudis.2016.01.013

Bové, J., Martínez-Vicente, M., & Vila, M. (2011). Fighting neurodegeneration with rapamycin: Mechanistic insights. *Nature Reviews. Neuroscience*, *12*(8), 437–452. https://doi.org/10.1038/nrn3068

Breedveld, P., Pluim, D., Cipriani, G., Wielinga, P., van Tellingen, O., Schinkel, A. H., & Schellens, J. H. M. (2005). The effect of Bcrp1 (Abcg2) on the *in vivo* pharmacokinetics and brain penetration of imatinib mesylate (Gleevec): Implications for the use of breast cancer resistance protein and P-glycoprotein inhibitors to enable the brain penetration of imatinib in patients. *Cancer Research*, *65*(7), 2577–2582. https://doi.org/10.1158/0008-5472.CAN-04-2416

Cacabelos, R. (2017). Parkinson's disease: From pathogenesis to Pharmacogenomics. *International Journal of Molecular Sciences*, *18*(3), Article 551. https://doi.org/10.3390/ijms18030551

Calabrese, V., Di Maio, A., Marino, G., Cardinale, A., Natale, G., De Rosa, A., Campanelli, F., Mancini, M., Napolitano, F., Avallone, L., Calabresi, P., Usiello, A., Ghiglieri, V., & Picconi, B. (2020). Rapamycin, by inhibiting mTORC1 signaling, prevents the loss of striatal bidirectional synaptic plasticity in a rat model of L-dopa-induced dyskinesia. *Frontiers in Aging Neuroscience*, *12*, Article 230. https://doi.org/10.3389/fnagi.2020.00230

Chaturvedi, R. K., & Beal, M. F. (2008). PPAR: A therapeutic target in Parkinson's disease. *Journal of Neurochemistry*, *106*(2), 506–518. https://doi.org/10.1111/j.1471-4159.2008.05388.x

Cui, S.-S., Du, J.-J., Liu, S.-H., Meng, J., Lin, Y.-Q., Li, G., He, Y.-X., Zhang, P.-C., Chen, S., & Wang, G. (2019). Serum soluble lymphocyte activation gene-3 as a diagnostic biomarker in Parkinson's disease: A pilot multicenter study. *Movement Disorders*, *34*(1), 138–141. https://doi.org/10.1002/mds.27569

Dexter, D. T., Statton, S. A., Whitmore, C., Freinbichler, W., Weinberger, P., Tipton, K. F., Della Corte, L., Ward, R. J., & Crichton, R. R. (2011). Clinically available iron chelators induce neuroprotection in the 6-OHDA model of Parkinson's disease after peripheral administration. *Journal of Neural Transmission*, *118*(2), 223–231. https://doi.org/10.1007/s00702-010-0531-3

Dong, J., Cui, Y., Li, S., & Le, W. (2016). Current pharmaceutical treatments and alternative therapies of Parkinson's disease. *Current Neuropharmacology*, *14*(4), 339–355. https://doi.org/10.2174/1570159x14666151120123025

Fujishige, K., Kotera, J., & Omori, K. (1999). Striatum- and testis-specific phosphodiesterase PDE10A isolation and characterization of a rat PDE10A. *European Journal of Biochemistry*, *266*(3), 1118–1127. https://doi.org/10.1046/j.1432-1327.1999.00963.x

Gao, S., Duan, C., Gao, G., Wang, X., & Yang, H. (2015). Alpha-synuclein overexpression negatively regulates insulin receptor substrate 1 by activating mTORC1/S6K1 signaling. *The International Journal of Biochemistry and Cell Biology*, *64*, 25–33. https://doi.org/10.1016/j.biocel.2015.03.006

Giorgi, M., D'Angelo, V., Esposito, Z., Nuccetelli, V., Sorge, R., Martorana, A., Stefani, A., Bernardi, G., & Sancesario, G. (2008). Lowered cAMP and cGMP signalling in the brain during levodopa-induced dyskinesias in hemiparkinsonian rats: New aspects in the pathogenetic mechanisms. *The European Journal of Neuroscience*, *28*(5), 941–950. https://doi.org/10.1111/j.1460-9568.2008.06387.x

González-Martín, A., Moyano, T., Gutiérrez, D. A., Carvajal, F. J., Cerpa, W., Hanley, J. G., Gutiérrez, R. A., & Álvarez, A. R. (2021). c-Abl regulates a synaptic plasticity-related transcriptional program involved in memory and learning. *Progress in Neurobiology*, *205*, (Article 102122). https://doi.org/10.1016/j.pneurobio.2021.102122

Gorenberg, E. L., & Chandra, S. S. (2017). The role of co-chaperones in synaptic proteostasis and neurodegenerative disease. *Frontiers in Neuroscience*, *11*, Article 248. https://doi.org/10.3389/fnins.2017.00248

Gouda, N. A., Elkamhawy, A., & Cho, J. (2022). Emerging therapeutic strategies for Parkinson's disease and future prospects: A 2021 update. *Biomedicines*, *10*(2), Article 371. https://doi.org/10.3390/biomedicines10020371

Gronich, N., Abernethy, D. R., Auriel, E., Lavi, I., Rennert, G., & Saliba, W. (2018). β2-adrenoceptor agonists and antagonists and risk of Parkinson's disease. *Movement Disorders*, *33*(9), 1465–1471. https://doi.org/10.1002/mds.108

Hayflick, S. J., Kurian, M. A., & Hogarth, P. (2018). Neurodegeneration with brain iron accumulation. *Handbook of Clinical Neurology*, *147*, 293–305. https://doi.org/10.1016/B978-0-444-63233-3.00019-1

Hebron, M. L., Lonskaya, I., & Moussa, C. E.-H. (2013). Nilotinib reverses loss of dopamine neurons and improves motor behavior via autophagic degradation of -synuclein in Parkinson's disease models. *Human Molecular Genetics*, *22*(16), 3315–3328. https://doi.org/10.1093/hmg/ddt192

Hopp, S. C. (2021). Targeting microglia L-type voltage-dependent calcium channels for the treatment of central nervous system disorders. *Journal of Neuroscience Research*, *99*(1), 141–162. https://doi.org/10.1002/jnr.24585

Ilijic, E., Guzman, J. N., & Surmeier, D. J. (2011). The L-type channel antagonist isradipine is neuroprotective in a mouse model of Parkinson's disease. *Neurobiology of Disease*, *43*(2), 364–371. https://doi.org/10.1016/j.nbd.2011.04.007

Kim, C., Rockenstein, E., Spencer, B., Kim, H.-K., Adame, A., Trejo, M., Stafa, K., Lee, H.-J., Lee, S.-J., & Masliah, E. (2015). Antagonizing neuronal toll-like receptor 2 prevents synucleinopathy by activating autophagy. *Cell Reports*, *13*(4), 771–782. https://doi.org/10.1016/j.celrep.2015.09.044

Laureys, G., Clinckers, R., Gerlo, S., Spooren, A., Wilczak, N., Kooijman, R., Smolders, I., Michotte, Y., & De Keyser, J. (2010). Astrocytic β2-adrenergic receptors: From physiology to pathology. *Progress in Neurobiology*, *91*(3), 189–199. https://doi.org/10.1016/j.pneurobio.2010.01.011

Lautenschläger, J., Stephens, A. D., Fusco, G., Ströhl, F., Curry, N., Zacharopoulou, M., Michel, C. H., Laine, R., Nespovitaya, N., Fantham, M., Pinotsi, D., Zago, W., Fraser, P., Tandon, A., St George-Hyslop, P., Rees, E., Phillips, J. J., De Simone, A., Kaminski, C. F., & Schierle, G. S. K. (2018). C-terminal calcium binding of α-synuclein modulates synaptic vesicle interaction. *Nature Communications*, *9*(1), Article 712. https://doi.org/10.1038/s41467-018-03111-4

Lee, Y.-Y., Park, J.-S., Leem, Y.-H., Park, J.-E., Kim, D.-Y., Choi, Y.-H., Park, E.-M., Kang, J. L., & Kim, H.-S. (2019). The phosphodiesterase 10 inhibitor papaverine exerts anti-inflammatory and neuroprotective effects via the PKA signaling pathway in neuroinflammation and Parkinson's disease mouse models. *Journal of Neuroinflammation*, *16*(1), Article 246. https://doi.org/10.1186/s12974-019-1649-3

Levenson, J. M., Schroeter, S., Carroll, J. C., Cullen, V., Asp, E., Proschitsky, M., Chung, C. H.-Y., Gilead, S., Nadeem, M., Dodiya, H. B., Shoaga, S., Mufson, E. J., Tsubery, H., Krishnan, R., Wright, J., Solomon, B., Fisher, R., & Gannon, K. S. (2016). NPT088 reduces both amyloid-β and tau pathologies in transgenic mice. *Alzheimer's and Dementia*, *2*(3), 141–155. https://doi.org/10.1016/j.trci.2016.06.004

Lingor, P., Carboni, E., & Koch, J. C. (2017). Alpha-synuclein and iron: Two keys unlocking Parkinson's disease. *Journal of Neural Transmission*, *124*(8), 973–981. https://doi.org/10.1007/s00702-017-1695-x

Malagelada, C., Ryu, E. J., Biswas, S. C., Jackson-Lewis, V., & Greene, L. A. (2006). RTP801 is elevated in Parkinson brain substantia nigral neurons and mediates death in cellular models of Parkinson's disease by a mechanism involving mammalian target of rapamycin inactivation. *The Journal of Neuroscience*, *26*(39), 9996–10005. https://doi.org/10.1523/JNEUROSCI.3292-06.2006

Michelson, D., Grundman, M., Magnuson, K., Fisher, R., Levenson, J. M., Aisen, P., Marek, K., Gray, M., & Hefti, F. (2019). Randomized, placebo controlled trial of npt088, a phage-derived, amyloid-targeted treatment for Alzheimer's disease. *The Journal of Prevention of Alzheimer's Disease*, *6*(4), 228–231. https://doi.org/10.14283/jpad.2019.37

Moussaud, S., Jones, D. R., Moussaud-Lamodière, E. L., Delenclos, M., Ross, O. A., & McLean, P. J. (2014). Alpha-synuclein and tau: Teammates in neurodegeneration? *Molecular Neurodegeneration*, *9*(1), Article 43. https://doi.org/10.1186/1750-1326-9-43

Nebrisi, E. E. (2021). Neuroprotective activities of curcumin in Parkinson's disease: A review of the literature. *International Journal of Molecular Sciences*, *22*(20), Article 11248. https://doi.org/10.3390/ijms222011248

Patterson, J. R., Hirst, W. D., Howe, J. W., Russell, C. P., Cole-Strauss, A., Kemp, C. J., Duffy, M. F., Lamp, J., Umstead, A., Kubik, M., Stoll, A. C., Vega, I. E., Steece-Collier, K., Chen, Y., Campbell, A. C., Nezich, C. L., Glajch, K. E., & Sortwell, C. E. (2022). Beta2-adrenoreceptor agonist clenbuterol produces transient decreases in alpha-synuclein mRNA but no long-term reduction in protein. *npj Parkinson's Disease*, *8*(1), Article 61. https://doi.org/10.1038/s41531-022-00322-x

Pfeiffer, R. F. (2016). Non-motor symptoms in Parkinson's disease. *Parkinsonism and Related Disorders*, *22*(1) (Suppl. 1), S119–S122. https://doi.org/10.1016/j.parkreldis.2015.09.004

Roser, A.-E., Tönges, L., & Lingor, P. (2017). Modulation of microglial activity by Rho-kinase (ROCK) inhibition as therapeutic strategy in Parkinson's disease and amyotrophic lateral sclerosis. *Frontiers in Aging Neuroscience*, *9*, Article 94. https://doi.org/10.3389/fnagi.2017.00094

Thenganatt, M. A., & Jankovic, J. (2016). The relationship between essential tremor and Parkinson's disease. *Parkinsonism and Related Disorders*, *22*(1) (Suppl. 1), S162–S165. https://doi.org/10.1016/j.parkreldis.2015.09.032

Tilve, S., Difato, F., & Chieregatti, E. (2015). Cofilin 1 activation prevents the defects in axon elongation and guidance induced by extracellular alpha-synuclein. *Scientific Reports*, *5*(1), Article 16524. https://doi.org/10.1038/srep16524

Tyagi, S., Gupta, P., Saini, A. S., Kaushal, C., & Sharma, S. (2011). The peroxisome proliferator-activated receptor: A family of nuclear receptors role in various diseases. *Journal of Advanced Pharmaceutical Technology and Research*, *2*(4), 236–240. https://doi.org/10.4103/2231-4040.90879

Uehara, T., Choong, C.-J., Nakamori, M., Hayakawa, H., Nishiyama, K., Kasahara, Y., Baba, K., Nagata, T., Yokota, T., Tsuda, H., Obika, S., & Mochizuki, H. (2019). Amido-bridged nucleic acid (AmNA)-modified antisense oligonucleotides targeting α-synuclein as a novel therapy for Parkinson's disease. *Scientific Reports*, *9*(1), Article 7567. https://doi.org/10.1038/s41598-019-43772-9

Ulusoy, G. K., Celik, T., Kayir, H., Gürsoy, M., Isik, A. T., & Uzbay, T. I. (2011). Effects of pioglitazone and retinoic acid in a rotenone model of Parkinson's disease. *Brain Research Bulletin*, *85*(6), 380–384. https://doi.org/10.1016/j.brainresbull.2011.05.001

Vega, R. B., Huss, J. M., & Kelly, D. P. (2000). The coactivator PGC-1 cooperates with peroxisome proliferator-activated receptor α in transcriptional control of nuclear genes encoding mitochondrial fatty acid oxidation enzymes. *Molecular and Cellular Biology*, *20*(5), 1868–1876. https://doi.org/10.1128/mcb.20.5.1868-1876.2000

Villar-Cheda, B., Dominguez-Meijide, A., Joglar, B., Rodriguez-Perez, A. I., Guerra, M. J., & Labandeira-Garcia, J. L. (2012). Involvement of microglial RhoA/Rho-kinase pathway activation in the dopaminergic neuron death. Role of angiotensin via angiotensin type 1 receptors. *Neurobiology of Disease*, *47*(2), 268–279. https://doi.org/10.1016/j.nbd.2012.04.010

Zhu, Z., Yang, C., Iyaswamy, A., Krishnamoorthi, S., Sreenivasmurthy, S. G., Liu, J., Wang, Z., Tong, B. C.-K., Song, J., Lu, J., Cheung, K.-H., & Li, M. (2019). Balancing mTOR signaling and autophagy in the treatment of Parkinson's disease. *International Journal of Molecular Sciences*, *20*(3), Article 728. https://doi.org/10.3390/ijms20030728

Cite this article: Kulkarni V, Kumari RTS, Muchandi SS, Nyamagoud SB, Nanjappaiah HM, Hooli VJ, *et al*. Exploring Novel Emerging Therapeutic Strategies for Parkinson's Disease: A Narrative Review. Int. J. Pharm. Investigation. 2026;16(3):880-4.