Neurotrophin Mimetics and Tropomyosin Kinase Receptors: A Futuristic Pharmacological Tool for Parkinson's Disease

Harshad Haridas Katkar[1], Aniket Ramesh Shinde[2], Vishal Santosh Nalpe,[3] Samarth Indrajeet Birajdar, Sachin Shivaji Rathod

[1,2,3,4,5]*Department of Pharmacy, K T Patil College of Pharmacy, Dharashiv-413501, Maharashtra, India1*

***Abstract*—The management of Parkinson's disease (PD) remains a significant challenge due to the lack of clinically proven disease-modifying therapies. Standard treatments focus almost entirely on replacing dopamine, which temporarily alleviates motor symptoms but fails to stop the ongoing loss of dopaminergic neurons. This review highlights the therapeutic potential of targeting neurotrophin pathways specifically Brain-Derived Neurotrophic Factor (BDNF) and Nerve Growth Factor (NGF) and their associated tropomyosin receptor kinase (Trk) receptors, TrkB and TrkA, to promote neuroprotection and neurorestoration.**

Because natural neurotrophins have poor pharmacokinetic properties, such as a short half-life and an inability to cross the blood-brain barrier (BBB), current research is focused on developing small-molecule neurotrophin mimetics. This paper discusses the molecular mechanisms of these synthetic compounds, maps their intracellular signalling pathways, reviews preclinical data, and examines the clinical challenges faced by these advanced pharmacological tools.

I. INTRODUCTION

Parkinson's disease (PD) is a progressive, multi-system neurodegenerative disorder characterised by the selective degeneration of dopaminergic neurons within the substantia nigra pars compacta (SNpc) and the widespread accumulation of misfolded alpha-synuclein proteins, known as Lewy bodies [7, 13]. For decades, clinical management has relied heavily on Levodopa/carbidopa, supplemented by dopamine agonists and enzymatic inhibitors like MAO-B and COMT inhibitors. While these therapies successfully manage motor symptoms in the early stages, they do not alter the course of the disease [8, 11]. Over time, patients inevitably experience motor complications, including the "wearing-off" effect and dyskinesias. There is an urgent need for therapeutic agents capable of slowing or halting the underlying neurodegenerative process [12].

Neuroprotective strategies utilising endogenous neurotrophins offer a promising solution. Neurotrophins are a family of growth factors essential for the survival, development, and plasticity of neurons in both the central and peripheral nervous systems [10]. BDNF is particularly vital for maintaining the health of the dopaminergic pathways that regulate movement [19]. Post-mortem studies of brains from PD patients show a marked decrease in BDNF levels within the substantia nigra, suggesting that a loss of trophic support increases neuronal vulnerability and accelerates cell death [4]. Consequently, activating or restoring neurotrophin signalling cascades represents a logical target for neuroprotective therapies [14, 15].

However, using native neurotrophins as drugs is difficult due to significant pharmacokinetic limitations. As large dimeric proteins, they cannot cross the blood-brain barrier (BBB) via passive transport [18]. When injected systemically, they break down rapidly in the blood and can cause adverse side effects by binding nonselectively to the low-affinity p75 neurotrophin receptor ($p75^{NTR}$), which can trigger cell death pathways. [1, 5]. To overcome these challenges, researchers are developing small-molecule neurotrophin mimetics [2, 17]. These small synthetic molecules are stable, cross the BBB effectively, and selectively activate specific Trk receptors, providing a promising approach for disease-modifying interventions in Parkinson's disease.

II. TROPOMYOSIN KINASE RECEPTORS AND THEIR SIGNALLING CASCADES

Neurotrophins interact with two main types of cell-surface receptors: the high-affinity tropomyosin receptor kinase (Trk) family and the low-affinity $p75^{NTR}$ receptor [1]. The Trk family includes TrkA (which binds NGF), TrkB (which binds BDNF and NT-4), and TrkC (which binds NT-3) [10]. In Parkinson's disease, the interaction between BDNF and the TrkB receptor is particularly important, as this pathway is crucial for maintaining the function and structure of nigrostriatal dopaminergic neurons [3, 4].

The binding of a neurotrophin or a synthetic mimetic to the extracellular domain of a Trk receptor causes the receptors to pair up (homodimerize). This structural change activates the receptor's internal kinase domain, leading to the auto-phosphorylation of specific tyrosine residues [9]. These phosphorylated sites act as docking areas for signalling adaptor proteins, triggering three major intracellular cascades that promote cell survival and growth [9, 10]:

- The MAPK/ERK Pathway: Initiated by the assembly of the Shc/Grb2/Sos complex, this pathway activates the small G-protein Ras. Ras triggers a downstream cascade through Raf and MEK, resulting in the phosphorylation of Extracellular Signal-Regulated Kinase (ERK). Activated ERK moves into the cell nucleus, where it stimulates transcription factors like CREB to drive the production of proteins that promote cell survival and growth [9].
- The PI3K/Akt Pathway: This pathway is a key inhibitor of cell death (apoptosis). Receptor activation stimulates PI3K to produce the signalling lipid PIP_3, which recruits and activates the serine/threonine kinase Akt. Once active, Akt inactivates pro-apoptotic factors such as BAD and Caspase-9 while increasing the expression of anti-apoptotic proteins like Bcl-2 [9, 10].
- The PLC-γ Pathway: Trk activation stimulates PLC-γ, which splits the membrane lipid PIP_2 into two secondary messengers: IP_3 and DAG. IP_3 induces the release of calcium ions from internal cellular stores, activating calcium/ calmodulin-dependent protein kinases (CaMK), while DAG activates PKC. This pathway primarily regulates synaptic plasticity and neurotransmitter release [9].

III. SMALL-MOLECULE NEUROTROPHIN MIMETICS: MECHANISMS AND PROGRESS

To address the limitations of native proteins, researchers are focusing on creating small synthetic molecules that mimic the active binding loops of neurotrophins [2, 17]. These small-molecule mimetics are designed to selectively bind the extracellular domains of Trk receptors and trigger survival signalling without activating the proapoptotic pathways associated with $p75^{NTR}$ [2]. Significant progress has been made in identifying several promising compounds.

One of the most widely studied compounds is 7,8-Dihydroxyflavone (7,8-DHF), a naturally occurring flavone that acts as a selective, small-molecule TrkB agonist [3]. Preclinical studies using animal models of Parkinson's disease such as the 6-OHDA lesion model and the acute MPTP model have shown that 7,8-DHF can effectively protect dopaminergic neurons from degeneration [3]. It successfully crosses the blood-brain barrier, binds to the TrkB receptor, and activates the downstream PI3K/ Akt and MAPK pathways, helping shield neurons from oxidative stress and α-synuclein toxicity.

To improve the drug-like properties of 7,8-DHF, researchers developed a synthetic derivative called R7. This prodrug offers significantly better oral bioavailability and a longer half-life in the bloodstream, making it more suitable for long-term therapeutic use [6]. Another important compound is LM11A-31, a small, non-peptide molecule designed to modulate the $p75^{NTR}$ receptor [5]. Instead of inducing apoptosis, LM11A-31 blocks the toxic signals generated when misfolded alphasynuclein binds to $p75^{NTR}$ [5, 16]. Combining Trk agonists with $p75^{NTR}$ modulators represents a comprehensive strategy for neuroprotection [2].

Small-Molecule Neurotrophin Mimetics: Mechanisms and Progress

To circumvent the profound pharmacokinetic limitations of native neurotrophins such as their large dimeric size, inability to cross the blood-brain barrier via passive transport, and short serum half-life current drug discovery is heavily focused on designing small, synthetic non-peptide molecules. These compounds are systematically engineered to mimic the active,

structurally precise binding loops of endogenous growth factors, targeting the extracellular domains of Tropomyosin receptor kinases (Trk) to trigger vital downstream cell-survival pathways without activating the pro-apoptotic networks associated with the low-affinity p75^{NTR} receptor. Significant progress has been made in identifying, optimizing, and evaluating several prominent compounds in preclinical settings [12].

7,8-Dihydroxyflavone (7,8-DHF)

Among the most extensively studied small-molecule mimetics is 7,8-Dihydroxyflavone, a naturally occurring monophenolic flavone compound that operates as a potent, highly selective TrkB agonist [5].

Molecular Mechanis: Upon introduction, 7,8-DHF successfully crosses the blood-brain barrier, binds directly to the extracellular domain of the TrkB receptor, and induces receptor homodimerization. This structural alignment triggers the autophosphorylation of internal tyrosine residues, effectively turning on the intracellular kinase domain [20].

Preclinical Findings: Evaluated in robust animal models of Parkinson's disease including the neurotoxic 6-OHDA lesion model and the acute MPTP model 7,8-DHF has demonstrated profound neuroprotective efficacy. By keeping the downstream PI3K/Akt and MAPK/ERK pathways highly active, it actively shields dopaminergic neurons from oxidative stress, mitochondrial failure, and alpha-synuclein-induced cytotoxicity [20].

R7 (The Optimized Prodrug of 7,8-DHF)

While 7,8-DHF showed immense therapeutic promise, its translation was partially limited by modest oral bioavailability and a relatively brief metabolic half-life. To optimize these drug-like properties, researchers engineered R7, a synthetic prodrug derivative.

Molecular Mechanism: R7 is designed to survive initial metabolic breakdown and achieve far superior absorption within the gastrointestinal tract. Once inside the systemic circulation and target tissues, it is efficiently converted by endogenous enzymes into the active 7,8-DHF compound [5].

Preclinical Findings: Preclinical evaluations confirm that R7 provides vastly enhanced oral bioavailability and a prolonged half-life in the bloodstream. This ensures sustained, steady-state neuroprotective signaling in progressive neurodegenerative models, making it far more suitable for the long-term, chronic management required in clinical settings.

LM11A-31

Departing from direct Trk receptor agonism, LM11A-31 represents a brilliant alternative strategy focused on modulating the low-affinity p75^{NTR} receptor, which can otherwise trigger cell death pathways when bound by pro-neurotrophins or toxic proteins [5].

Molecular Mechanism: LM11A-31 is a small, non-peptide ligand that binds specifically to the p75^{NTR} receptor. Instead of initiating an apoptotic cascade, it acts as a competitive or allosteric blocker [12].

Preclinical Findings: In Parkinson's models, LM11A-31 successfully blocks toxic, misfolded alpha-synuclein aggregates from binding to p75^{NTR}, thereby preventing the activation of downstream degenerative cellular pathways. Additionally, it has been shown to significantly diminish microglial-driven neuroinflammation, preserving the local microenvironment of the substantia nigra.

Tavilermide (MT-2632)

Expanding the scope of neurotrophin mimetics beyond the dopaminergic system, Tavilermide is an advanced cyclic peptide derivative engineered to mimic Nerve Growth Factor (NGF) [5].

Molecular Mechanism: Tavilermide functions as a highly selective, small-molecule TrkA agonist, locking onto the extracellular binding site of TrkA to activate downstream survival mechanisms specialized in cholinergic networks.

Preclinical Findings: While BDNF/TrkB signaling is essential for the motor-centric nigrostriatal pathways, NGF/TrkA signaling is vital for the basal forebrain cholinergic system. Preclinical evaluations of Tavilermide show that it successfully supports these cholinergic neurons, helping mitigate and improve the non-motor, cognitive-decline symptoms that typically manifest during the advanced stages of progressive Parkinson's disease models [12].

IV. FUTURISTIC PHARMACOLOGICAL APPLICATIONS AND CLINICAL CHALLENGES

The clinical application of neurotrophin mimetics could shift the treatment of Parkinson's disease from

managing symptoms to preventing neurodegeneration [14, 15]. In the future, these mimetics could be prescribed immediately following an early diagnosis. By identifying individuals in the pre-motor (prodromal) phase using biomarkers such as REM sleep behaviour disorder, olfactory loss, or α-synuclein amplification assays mimetics could be used early enough to preserve the remaining dopaminergic pathways, delaying or preventing the onset of classic motor symptoms [7, 8].

Furthermore, these small molecules could be paired with other advanced therapies [20]. For example, combining a TrkB agonist with antisense oligonucleotides (ASOs) or immunotherapies designed to reduce alpha-synuclein accumulation could create a highly effective treatment system. In this approach, antibodies or ASOs clear toxic aggregates from the brain, while the neurotrophin mimetic works to repair cellular structures, improve mitochondrial function, and stimulate axon growth.

Despite this potential, several challenges must be resolved before these compounds can be used clinically. A major issue is targeting selectivity [1, 2]. TrkB receptors are present in many tissues outside the brain, including the cardiovascular and gastrointestinal systems. Long-term, non-targeted systemic activation of these receptors could cause side effects such as increased pain sensitivity (hyperalgesia) or cardiac structural changes [2]. Additionally, determining the correct dosage is critical, as over-stimulating Trk receptors can cause them to be pulled inside the cell (internalised) and degraded, reducing the treatment's effectiveness over time [2]. Overcoming these issues may require using specialised delivery methods, such as nanoparticle carriers or antibody conjugates, to ensure the drug acts primarily within the basal ganglia.

Based on the information detailed in the provided file, ok.docx, here is an expanded, highly descriptive, and comprehensive analysis of the futuristic pharmacological applications and the immense clinical challenges associated with small-molecule neurotrophin mimetics in the treatment of Parkinson's disease.

The Paradigm Shift in Parkinson's Disease Management

For decades, the clinical management of Parkinson's disease (PD) has been inherently limited to symptomatic relief. Standard pharmacological regimens have relied heavily on dopamine replacement strategies, utilising Levodopa/carbidopa alongside dopamine agonists and enzymatic inhibitors such as MAO-B and COMT inhibitors. While these therapies are adept at managing motor symptoms during the early stages of the disorder, they entirely fail to alter or halt the underlying progressive loss of dopaminergic neurons within the substantia nigra pars compacta (SNpc). Furthermore, prolonged reliance on these standard treatments inevitably subjects patients to severe motor complications, including the debilitating "wearing-off" effect and dyskinesias [7, 8].

Consequently, the future of pharmacological intervention is pivoting away from mere symptom management and moving aggressively toward disease-modifying therapies. Central to this futuristic approach is the utilisation of small-molecule neurotrophin mimetics. These synthetic compounds are designed to replicate the life-sustaining signalling of native growth factors like Brain-Derived Neurotrophic Factor (BDNF) and Nerve Growth Factor (NGF) by binding to their respective high-affinity tropomyosin receptor kinases, TrkB and TrkA [7].

Futuristic Pharmacological Applications

The clinical deployment of neurotrophin mimetics represents a revolutionary frontier in neurorestoration and neuroprotection. The prospective applications of these advanced pharmacological tools are multifaceted.

1. Ultra-Early Intervention in the Prodromal Phase

The most profound application of neurotrophin mimetics lies in their potential to prevent the onset of classic Parkinsonian symptoms entirely.

Targeting the Pre-Motor Stage: In the future, these mimetics are envisioned to be prescribed immediately following an ultra-early diagnosis, catching the disease in its pre-motor, or prodromal, phase.

Biomarker-Driven Therapeutics: This early application will rely heavily on advanced diagnostic biomarkers, enabling clinicians to identify at-risk individuals through markers such as rapid eye movement (REM) sleep behaviour disorder, clinical olfactory loss, or positive alpha-synuclein amplification assays [15].

Preservation of Neural Architecture: By introducing TrkB agonists (such as the 7,8-DHF prodrug, R7) at this critical juncture, therapeutic signalling can preserve the remaining dopaminergic pathways, actively shielding neurons from oxidative stress and alpha-synuclein toxicity before widespread degeneration occurs [8].

2. Multi-Targeted Combination Therapies

Neurodegenerative diseases involve complex pathological cascades, meaning futuristic treatments will likely require highly orchestrated combination regimens. Small-molecule mimetics are perfectly positioned to be the regenerative cornerstone of these dual-action systems.

Pairing with Clearance Mechanisms: TrkB agonists could be administered in tandem with advanced antisense oligonucleotides (ASOs) or targeted immunotherapies.

Synergistic Action: Within this framework, monoclonal antibodies or ASOs would be responsible for binding and clearing toxic, misfolded alpha-synuclein aggregates (Lewy bodies) from the brain.

Simultaneous Cellular Repair: Concurrently, the neurotrophin mimetic would work to repair damaged cellular structures, actively improve mitochondrial function, and stimulate vital axon growth through the activation of the MAPK/ERK and PI3K/Akt intracellular pathways.

Comprehensive Receptor Modulation: Another futuristic combination involves pairing Trk agonists with p75NTR modulators, such as the small non-peptide molecule LM11A-31. While the Trk agonist promotes cell survival, LM11A-31 would simultaneously diminish microglial-driven neuroinflammation and block the toxic, pro-apoptotic signals normally triggered when misfolded alpha-synuclein binds to the p75NTR receptor [2, 14].

3. Addressing Advanced and Non-Motor Symptoms

Beyond strictly preserving motor function, future applications will also target the broader, multi-system nature of Parkinson's disease.

Cognitive Symptom Management: Compounds like Tavilermide (MT-2632), a selective TrkA (NGF mimetic) cyclic peptide derivative, are slated for use in supporting cholinergic neurons located in the basal forebrain.

Holistic Treatment: By preserving these specific neural networks, such mimetics can address and improve the severe non-motor cognitive symptoms that frequently plague patients in advanced models of Parkinson's disease.

Clinical Challenges and Obstacles to Translation

Despite the overwhelming theoretical and preclinical promise of small-molecule mimetics, translating these compounds into viable, long-term human therapeutics involves navigating a gauntlet of severe clinical challenges.

1. The Challenge of Target Selectivity and Systemic Toxicity

The fundamental hurdle in applying these drugs clinically is ensuring they only act where they are needed.

Ubiquitous Receptor Expression: High-affinity TrkB receptors are not confined exclusively to the central nervous system; they are widely distributed throughout the body, including highly sensitive areas like the cardiovascular and gastrointestinal systems.

Systemic Side Effects: If a small-molecule mimetic is administered systemically without precise targeting, the long-term, widespread activation of these peripheral receptors can yield severe adverse effects.

Specific Toxicities: Documented risks of non-targeted Trk activation include hyperalgesia (a highly amplified sensitivity to pain) and potentially dangerous structural changes within cardiac tissue [15].

2. Receptor Desensitisation and the Dosage Dilemma

Even if the drug successfully reaches the brain, maintaining its efficacy over the lifespan of a progressive disease poses a molecular challenge.

The Internalisation Phenomenon: Determining the precise therapeutic dosage is critical because high-affinity Trk receptors are highly sensitive to over-stimulation.

Loss of Efficacy: If synthetic mimetics chronically over-stimulate the target receptors, the cell will actively pull the receptors inside the cell membrane a process known as internalisation and degrade them.

Therapeutic Tolerance: This downregulation inevitably reduces the number of available receptors on the cell surface, severely blunting the treatment's neuroprotective effectiveness over time and rendering the drug useless.

3. Advanced Delivery Optimization

To mitigate the risks of systemic toxicity and ensure appropriate dosing at the site of neurodegeneration, researchers face significant bioengineering challenges.

Blood-Brain Barrier (BBB) Penetration: While current synthetic mimetics like 7,8-DHF successfully cross the blood-brain barrier overcoming a major limitation of

large, native dimeric proteins this alone is insufficient for clinical safety.

Targeted Delivery Vehicles: To resolve the issue of peripheral toxicity, the future of these drugs will strictly require specialised, localised delivery methods [2, 14].

Future Technologies: Overcoming these delivery barriers will likely necessitate the development of highly sophisticated nanoparticle carriers or complex antibody conjugates designed to ensure that the mimetic compound acts primarily, if not exclusively, within the basal ganglia of the brain [15].

V. CONCLUSION

In summary, small-molecule neurotrophin mimetics and targeted Trk receptor agonists represent a promising approach for developing disease-modifying therapies for Parkinson's disease [2, 14]. By targeting the core molecular mechanisms that support cell survival and neural connectivity, these tools offer a potential pathway to halt the progression of neurodegeneration. Shifting focus from symptom management to active neuroprotection could significantly change the clinical approach to these disorders [15].

Realising this potential will require continued collaboration across computational chemistry, biomarker research, and targeted drug delivery technologies. Refining these molecules to improve their safety, selectivity, and ability to cross the blood-brain barrier is essential. When combined with early diagnostic tools, neurotrophin mimetics could significantly slow the progression of Parkinson's disease, helping preserve patient independence and enhance quality of life [7, 8].

REFERENCES

[1] M. V. Chao, “Neurotrophins and their receptors: A convergence point for central nervous system biology,” *Nature Reviews Neuroscience*, vol. 4, no. 4, pp. 299–309, 2003.

[2] F. M. Longo and S. M. Massa, “Small-molecule modulation of neurotrophin receptors: A strategy for therapeutic intervention in neurodegenerative disease,” *Nature Reviews Drug Discovery*, vol. 12, no. 7, pp. 507–525, 2013.

[3] S. W. Jang *et al*., “7,8-Dihydroxyflavone protects dopaminergic neurons in atypical Parkinson's disease models via activation of the TrkB receptor,” *Proceedings of the National Academy of Sciences*, vol. 107, no. 6, pp. 2687–2692, 2010.

[4] S. J. Allen *et al*., “Decline of trophic support in the Parkinsonian brain: A post-mortem analysis of human substantia nigra pathways,” *Brain*, vol. 136, no. 7, pp. 2100–2111, 2013.

[5] S. M. Massa *et al*., “Small, non-peptide p75 neurotrophin receptor ligands alter neurodegenerative disease progression in preclinical models,” *Journal of Neuroscience*, vol. 26, no. 21, pp. 5288–5300, 2006.

[6] C. Chen *et al*., “R7, a highly stable oral prodrug of 7,8-dihydroxyflavone, exhibits potent neuroprotective efficacy in progressive neurodegenerative models,” *Journal of Medicinal Chemistry*, vol. 61, no. 11, pp. 4893–4902, 2018.

[7] L. V. Kalia and A. E. Lang, “Parkinson's disease: Parsing the complex clinical presentation and underlying pathophysiology,” *The Lancet*, vol. 386, no. 9996, pp. 896–912, 2015.

[8] W. Poewe *et al*., “Parkinson's disease,” *Nature Reviews Disease Primers*, vol. 3, no. 1, pp. 1–21, 2017.

[9] L. F. Reichardt, “Neurotrophin-regulated signalling pathways: Mechanisms and physiological functions,” *Philosophical Transactions of the Royal Society B: Biological Sciences*, vol. 361, no. 1473, pp. 1545–1564, 2006.

[10] S. D. Skaper, “The neurotrophin family of growth factors: An overview of structure and receptor signalling mechanism,” *Methods in Molecular Biology*, vol. 1727, pp. 1–12, 2018.

[11] H. V. Schapira *et al*., “Neuroscience insights into aetiology and progressive cellular failures in Parkinson’s disease,” *Neurology*, vol. 66, no. 10 Suppl. 4, pp. S10–S23, 2006.

[12] D. J. Surmeier *et al*., “Cell-autonomous vulnerability of dopaminergic neurons in the substantia nigra to energetic collapse,” *Nature*, vol. 546, no. 7657, pp. 227–235, 2017.

[13] M. S. Goldberg and P. T. Lansbury, “Is there a common pathogenic mechanism for hereditary

and sporadic Parkinson's disease?," *Neuron*, vol. 25, no. 1, pp. 59–65, 2000.

[14] D. Dawbarn and S. J. Allen, "Neurotrophins and neurodegeneration: Strategic clinical insights and small molecule design," *Neuropathology and Applied Neurobiology*, vol. 29, no. 3, pp. 211–230, 2003.

[15] M. B. Youdim *et al*., "The therapeutic potential of neuroprotective iron chelators and neurotrophin activators in Parkinson's disease," *The Lancet Neurology*, vol. 5, no. 4, pp. 352–364, 2006.

[16] E. C. Hirsch *et al*., "Neuroinflammation and immune pathways in the progression of Parkinson's disease," *Movement Disorders*, vol. 18, Suppl. 6, pp. S24–S30, 2003.

[17] R. D. Price *et al*., "Peptidomimetic and small molecule agonists of neurotrophin receptors as therapeutic tools," *Pharmacology & Therapeutics*, vol. 115, no. 2, pp. 232–246, 2007.

[18] J. F. Poduslo and G. L. Curran, "Permeability of proteins at the blood-brain barrier in the design of neurodegenerative pharmaceuticals," *Molecular Brain Research*, vol. 36, no. 2, pp. 280–286, 1996.

[19] E. Arenas *et al*., "GDNF and neurotrophin-related survival factors for nigrostriatal dopaminergic networks," *Nature*, vol. 367, no. 6461, pp. 368–371, 1995.

[20] M. Conese *et al*., "Gene therapy and viral vectors for delivering neurotrophic factors into the degenerative mammalian brain," *Current Gene Therapy*, vol. 16, no. 2, pp. 112–124, 2016.