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EXPLORING THE NEUROPROTECTIVE POTENTIAL OF TIRZEPATIDE IN PARKINSON'S DISEASE: AN IN SILICO ANALYSIS

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ABSTRACT

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by the loss of dopaminergic neurons in the substantia nigra, leading to both motor and non-motor symptoms. While current therapies such as levodopa and dopamine agonists offer symptomatic relief, they do not halt disease progression, emphasizing the urgent need for disease-modifying therapies (DMTs). Emerging evidence suggests that incretin-based agents, especially GLP-1 and GIP receptor agonists, possess significant neuroprotective properties, including anti-inflammatory, antioxidant, and mitochondrial-supporting effects. This review focuses on tirzepatide, a novel dual GLP-1/GIP receptor agonist, and evaluates its therapeutic potential in PD. Comprehensive insights into the molecular mechanisms of PD pathogenesis—including α-synuclein aggregation, mitochondrial dysfunction, oxidative stress, and neuroinflammation—are presented. Additionally, we explore the ability of tirzepatide to modulate these pathological pathways based on in silico target prediction, protein-protein interaction network analysis, GO/KEGG pathway enrichment, and molecular docking studies. Tirzepatide demonstrated significant binding affinity to key targets involved in neuroinflammation and dopaminergic signaling, supporting its potential as a multitarget therapeutic agent. Overall, the evidence suggests that tirzepatide may serve as a promising DMT candidate for PD by targeting key neurodegenerative mechanisms. Further preclinical

and clinical studies are warranted to validate its efficacy and safety profile in human PD populations.

KEYWORDS: Disease-modifying therapy, GLP-1/GIP receptor agonist, Neuroprotection, Parkinson's disease, Tirzepatide.

1. INTRODUCTION

Research shows that Parkinson's disease (PD) develops as a progressive neurological disease which destroys dopaminergic neurons within the substantia nigra pars compacta thus causing striatum dopamine depletion [1,2]. The disease manifestation causes characteristic motor deficits such as bradykinesia and rigidity along with resting tremors and impaired postural control [3]. Development of PD involves genetic and environmental, as well normal aging processes, the above factors synergize to form aging cells through alpha-synuclein aggregation and other disease inducing factors which are oxidative stress and mitochondrial dysfunction, together with Neuroinflammation and protein degradation [4,5].

Existing disease approaches aim to control the symptoms without any power to halt PD progression [6,7]. Patients achieve the greatest relief of motor symptoms from the therapeutic combination of Levodopa and carbidopa [8,9]. The continuation of levodopa medication treatment leads to the appearance of motor fluctuations as well as levodopa-induced dyskinesia (LID) resulting in the deterioration of its therapeutic effectiveness [9,10]. Dopamine agonists and monoamine Oxidase-B inhibitors and Catechol-O-methyl transferase inhibitors serve as alternative pharmacological treatments for PD but might cause impulse control disorders and orthostatic hypotension in addition to other side effects [11,12]. Surgeons use deep brain stimulation (DBS) directed to the subthalamic nucleus (STN) or globus pallidus interna (GPi) as an operation that works well to treat advanced PD patients with motor complications but entails operating risks and leaves the disease to continue progressing [13,14].

The existing therapy has limitations thus disease-modifying strategies is needed greatly [15]. Scientists are conducting clinical research which is aimed at the development of treatments for alpha-synuclein aggregation and oxidation stresses reduction and mitochondrial therapy and neuroinflammatory response management [16]. Research has focused on the use of adeno-associated viruses (AAVs) in the delivery process of the gene therapy, but clinically their performance is unpredictable [17]. Experimental human research in terms of glial cell

line-derived neurotrophic factor (GDNF) and neurturin (NRTN) did show promise but their application is sporadic [18]. Scientists are researching on non-invasive vagus nerve stimulation (nVNS) as a new strategy of boosting PD symptoms (both movement and non-movement) [19].

The quality of life of the PD patients is largely defined by its non-motor aspect, which consists of cognitive decline, psychiatric disturbances, overlap combination with sleep disorders, and autonomic dysfunction and sensory abnormalities [20]. The gut-brain relationship gains increasing attention as scientific evidence is known to establish that pathology of alpha-synuclein starts in enteric nervous system (ENS) before migrating in vagus nerve towards central nervous system [21]. Current scholars explore the gut microbiota-based treatments as potentially applicable therapeutic procedures aimed to change PD course [22]. Exercise and dietary alterations as life style intervention measure promises to safeguard the nervous system in Parkinson's disease because they can limit oxidative harm and enhance brain plasticity [23]. The main goal is the development of neuroprotective and regenerative treatments, which change the course of PD, and improve the patients' recovery, although PD pathogenesis's study and symptomatic therapy improvement remain the main research focus [24].

Incretin hormones GLP-1 and GIP have seemingly promising neuroprotective properties for treating both PD and AD, by the research [25]. Both of the two hormones which both arose from research into cure for diabetes demonstrate neuroprotective activity thanks to their ability to modulate processes of neuronal survival and inflammation processes and oxidative stress and mechanisms of mitochondrial functions [26]. Experimental research evidences reveal these agents have ability to cross BBB [27]. These agents therefore present as potential therapeutic candidate for neurodegenerative disorders.

GLP-1 and GIP activities' obtaining of synthetic neurotrophic factors along with the protection against synapse and improved cognitive functions and motor functions. The peptides reduce neuroinflammation after their ability to decrease pro-inflammatory chemicals, prevent the activations of microglial cells and astrocytes as reported in the studies [28,29]. GLP-1 and GIP, the peptides, protect against oxidative stress as they prevent the production of reactive oxygen species (ROS). Additionally, they enhance the antioxidants inside the cells. The drugs can maintain mitochondria due to prolonging the dynamics and reducing the death markers of cells [30,31].

Being a front-running neuroprotective candidate among the receptor agonists, tirzepatide provides better efficiency than monoplex GLP-1 receptor agonists. The brain entrance abilities of dual agonists such as Tirzepatide increase to give enhanced protective effects that might alter both the AD and PD development. Researches show that such compounds as GLP-1 and GIP activators simultaneously decrease brain inflammations well and promote better mitochondria health and regulation of cell self-digestion process than individual treatments with GLP-1 hormone. It has been revealed that Tirzepatide needs GIPR to promote the release of the hormones in human islets due to the fact that, dual agonism plays a key role in ensuring therapeutic outcomes [32].

2. Pathophysiology of Parkinson's Disease

2.1 Central Mechanism: Degeneration of Dopaminergic Neurons in the Substantia Nigra

a) **Key Event:** The primary pathological feature in PD is the progressive degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNpc).
b) **Consequence:** This neuronal loss results in a substantial reduction of dopamine levels in the striatum, a brain region critical for regulating movement.
c) **Clinical Manifestations:** The dopamine deficit impairs the function of basal ganglia circuits, leading to the classical motor symptoms (tremor, rigidity, bradykinesia) and numerous non-motor symptoms (e.g., cognitive decline, mood disorders, autonomic dysfunction)[33].

2.2 α-Synuclein Aggregation and Lewy Body Formation

a) **α-Synuclein Role:** Abnormal accumulation and misfolding of the α-synuclein protein leads to the formation of Lewy bodies—intracellular aggregates that are pathological hallmarks of PD.
b) **Cellular Disruption:**

1. **Synaptic Dysfunction:** Aggregates impair synaptic vesicle trafficking, neurotransmitter release, and synaptic integrity, severely disrupting neuronal communication.
2. **Axonal Transport Blockade:** Lewy bodies physically and functionally block axonal transport, hindering delivery of essential materials along neurons.
3. **Mitochondrial Damage:** α-Synuclein aggregates damage mitochondria, leading to energy deficits and overproduction of reactive oxygen species (ROS).

4. **Impaired Protein Clearance:** Lewy bodies overwhelm and impair the ubiquitin-proteasome and autophagy-lysosomal pathways, causing toxic protein accumulation.
5. **Neuroinflammation:** These aggregates activate microglial cells, triggering chronic inflammation that further injures neurons.

c) **Net Effect:** The convergence of these disruptions causes selective death of dopaminergic neurons, manifesting clinically as both motor and non-motor symptoms.[34,35]

2.3 Oxidative Stress, Mitochondrial Dysfunction, and Chronic Neuroinflammation

a) **Mitochondrial Dysfunction:**

1. Defective mitochondrial function leads to bioenergetic failure (reduced ATP), disrupted calcium homeostasis, and increased ROS production.
2. Genes like PINK1 and PARKIN are directly involved in mitochondrial quality control; their mutations exacerbate mitochondrial impairment.

b) **Oxidative Stress:**

1. Chronic overproduction of ROS damages cellular proteins, lipids, and DNA, promoting apoptosis in vulnerable neurons.
2. Mitochondrial dysfunction and α-synuclein aggregation both intensify oxidative stress.

c) **Neuroinflammation:**

1. Persistent activation of microglia and astrocytes in response to neuronal injury maintains a proinflammatory environment, contributing to ongoing neurodegeneration.

d) **Feedback Loop:** These processes are mutually reinforcing—mitochondrial dysfunction increases oxidative stress, which worsens mitochondrial injury and promotes further α-synuclein aggregation [36–38]

2.4 Genetic and Environmental Risk Factors

Table 1 summarizes key genes implicated in Parkinson's disease, their protein products, and their roles in disease pathophysiology.

Table 1- Genetic Factors.

Gene	Protein Product	Effect on PD Pathophysiology
SNCA	α-Synuclein	Mutation increases α-synuclein aggregation (Lewy bodies)
LRRK2	LRRK2 kinase	Common in certain groups; alters neuronal signaling
PARK2	Parkin (E3 ligase)	Impairs mitochondrial quality control

PINK1	PINK1 kinase	Disrupts mitophagy; increases mitochondrial stress
PARK7	DJ-1	Reduces protection against oxidative stress
GBA	Glucocerebrosidase	Influences lysosomal function and protein clearance

- **Epidemiology:** About 5-15% of PD cases are familial with a strong genetic link. The remaining cases are sporadic but may carry polygenic risk [39].

(a) Environmental Factors

1. **Pesticides and Herbicides:** Chronic exposure is linked to increased PD risk (e.g., organochlorines, paraquat, rotenone).
2. **Heavy Metals:** Lead, manganese, and others may exacerbate oxidative stress and dopaminergic toxicity.
3. **Industrial Chemicals:** Solvents like trichloroethylene (TCE) are associated with higher PD risk.
4. **Air Pollution/Head Trauma:** Additional factors that may contribute to PD onset and progression.

2.5 Clinical Manifestations: Motor and Non-Motor Symptoms

a) **Motor Symptoms:** Result directly from dopamine depletion in the striatum—tremor, rigidity, bradykinesia, postural instability.

b) **Non-Motor Symptoms:** Emerge from widespread Lewy body pathology and neurotransmitter imbalances affecting cognitive (dementia), psychiatric (depression, anxiety), and autonomic (constipation, orthostatic hypotension) systems. [33,40]

Table 2 summarizes the principal pathological events contributing to Parkinson's disease by outlining the associated molecular or cellular mechanisms and their clinical consequences.

Table 2- Key Pathophysiological Events in Parkinson's Disease.

Pathological Event	Molecular/Cellular Mechanism	Clinical Outcome
Dopaminergic neuron loss in SNpc	Apoptosis, α-synuclein toxicity, mitochondrial dysfunction	Motor & non-motor symptoms
Lewy body (α-synuclein) accumulation	Synaptic/axonal disruption, protein degradation failure, mitochondrial damage	Neuronal death, symptom spread
Oxidative stress and mitochondrial failure	ROS-induced damage, energy deficit, impaired mitophagy	Accelerated neurodegeneration
Chronic neuroinflammation	Microglial activation, cytokine release	Persistent neuronal injury
Genetic/environmental risk	Mutations (SNCA, PARKIN, PINK1,	Increased disease

factors	LRRK2, etc.)/Toxins (pesticides, metals, TCE)	susceptibility

3. Current Pharmacological and Surgical Approaches

3.1 Levodopa/Carbidopa

3.1.1 Mechanism of Action

a) Levodopa is a precursor of dopamine that crosses the blood-brain barrier and is converted to dopamine in the brain, replenishing depleted levels and improving motor symptoms.

b) Carbidopa inhibits peripheral metabolism of levodopa (by dopa decarboxylase), increasing the amount of levodopa available to the central nervous system and reducing peripheral side effects like nausea and vomiting [41].

3.1.2 Clinical Efficacy

a) Levodopa/carbidopa remains the gold standard for PD motor symptom management, with robust evidence for efficacy in both early and advanced disease.

b) Newer formulations in 2024, such as extended-release and continuous subcutaneous infusions (e.g., foslevodopa-foscarbidopa, VYALEV™), offer more stable plasma levels, reducing motor fluctuations and "off" periods (AbbVie News: FDA Approves VYALEV™).

c) Significant improvements in cognitive scores have been observed with levodopa/carbidopa/entacapone in moderate to advanced PD (MMSE and MoCA, P=0.004 and 0.001, respectively).[42]

3.2 Monoamine Oxidase-B (MAO-B) Inhibitors

3.2.1 Mechanism of Action

a) MAO-B inhibitors (e.g., rasagiline**,** selegiline**,** safinamide**,** zonisamide) block the MAO-B enzyme responsible for dopamine breakdown in the brain, thereby increasing synaptic dopamine availability [43].

3.2.2 Clinical Efficacy and Outcomes

a) MAO-B inhibitors provide modest improvement in motor symptoms and may delay the need for levodopa therapy in early PD.

b) Rasagiline has been noted as the most effective among MAO-B inhibitors for motor symptom improvement.

c) Studies in 2024 indicate enhanced quality of life (mobility, daily activities, emotional well-being) and possible neuroprotective effects with long-term use.

d) Common side effects: nausea, headache, insomnia, dizziness; rare but severe—serotonin syndrome [44].

3.3 Catechol-O-methyltransferase (COMT) Inhibitors

3.3.1 Mechanism of Action

a) COMT inhibitors (entacapone**,** opicapone) block the COMT enzyme in the periphery, reducing levodopa breakdown and extending its efficacy, thereby reducing "wearing-off" periods [45].

3.3.2 Clinical Efficacy

a) Used as adjuncts to levodopa/carbidopa, COMT inhibitors prolong the therapeutic effect of each levodopa dose, improving motor symptom control and reducing fluctuations.

b) Cost-effectiveness studies in 2024 support adding COMT inhibitors, showing both clinical and economic benefits.

4. Common Side Effects of Pharmacological Therapy

4.1 Levodopa-Induced Dyskinesia (LID)

a) LID refers to involuntary, often choreic movements that develop after chronic levodopa use.

b) Risk increases with longer disease duration and higher cumulative levodopa exposure[9].

4.2 Impulse Control Disorders (ICDs)

a) Impulse control disorders such as compulsive gambling, hypersexuality, shopping, and eating are most commonly associated with dopamine agonists rather than levodopa.

b) Management centers on reducing or discontinuing dopamine agonists (tapering used by ~92% of experts), with careful balancing to maintain motor control.[46]

c) Multidisciplinary care, patient/caregiver education, and sometimes cognitive behavioral therapy or emerging neuromodulation (e.g., TMS) are used as adjuncts [47].

5. Surgical Intervention: Deep Brain Stimulation (DBS)

5.1 Indications

a) DBS is indicated for advanced PD with motor fluctuations or dyskinesia not adequately controlled by medication [48].

5.2 Mechanism

a) DBS involves implanting electrodes in target brain regions (primarily the subthalamic nucleus [STN] or globus pallidus interna [GPi]).

b) Electrical stimulation modulates abnormal neuronal activity, improving motor circuit function.

5.3 Outcomes

1. Short- and long-term studies (up to 7 years) show DBS provides:
2. Significant and sustained improvements in motor function.
3. Reduction in "off" time and medication-induced dyskinesia.
4. Improved activities of daily living (ADLs) and quality of life.
5. Reduction in dopaminergic medication requirements.[49]

5.4 Limitations and Risks

1. Cognitive status and age are key eligibility criteria; significant cognitive impairment or dementia are contraindications due to potential cognitive worsening .[50]
2. Surgical risks include infection, hemorrhage, and device-related complications.
3. DBS does not halt disease progression or address all non-motor symptoms; some cognitive and neuropsychiatric symptoms may still progress [14].

5.5 Decision-Making Framework in Parkinson's Therapy

Table 3 provides a comparative overview of conventional pharmacological treatments and surgical deep brain stimulation (DBS), highlighting differences in approach, effectiveness, and clinical considerations.

Table 3- Comparative Overview of Pharmacological and Surgical (DBS) Approaches in Parkinson's Disease.

Factor	Pharmacological Approach	Surgical (DBS) Approach
Motor Symptom Control	High (levodopa/carbidopa most effective)	High (especially for fluctuations/dyskinesia)
Non-Motor Symptom Control	Modest (some benefit with MAO-B inhibitors)	Limited
Cognitive Impact	Stable or improved with some regimens	Potential decline in vulnerable patients
Main Risks	LID, ICDs, other drug side effects	Surgical, cognitive, device-related
Quality of Life Improvement	Marked (esp. early to mid-stage)	Marked (advanced disease, refractory symptoms)
Eligibility Considerations	Broad; adjust per comorbidities	Age, cognitive status, comorbidities
Disease Progression Modifying	Unclear; MAO-B may offer neuroprotection	No disease-modifying effect

5.6 Key 2024 Updates

- FDA approvals of new continuous infusion and extended-release formulations (e.g., VYALEV™, Produodopa) provide more stable symptom control for advanced PD.
- National and international guidelines increasingly emphasize shared decision-making and individualized therapy .[51]
- Real-time, adjustable therapies and multidisciplinary care models are improving patient engagement and care outcomes.

6. Need for Disease-Modifying Therapies

Despite substantial advancements in symptomatic treatment, no current therapeutic approach has been proven to halt or reverse the neurodegenerative progression of Parkinson's Disease (PD). Conventional pharmacological strategies, including levodopa and dopamine agonists, primarily aim to manage motor symptoms but fail to address the underlying pathology, allowing the disease to advance over time [6]. This therapeutic gap underscores an urgent need for disease-modifying therapies (DMTs) that can slow, stop, or ideally reverse the neurodegenerative process.[52]

Experimental approaches are being investigated, including gene therapies using adeno-associated viruses (AAVs) to deliver neuroprotective genes such as glial cell line-derived neurotrophic factor (GDNF) and neurturin (NRTN). While early trials have shown promise in enhancing dopaminergic survival, clinical efficacy has been inconsistent and limited by delivery challenges and variable patient responses [17,18].

Other novel non-invasive strategies such as non-invasive vagus nerve stimulation (nVNS) are gaining attention for their potential to modulate neuroinflammation and neuroplasticity, thus improving both motor and non-motor symptoms. Additionally, the gut-brain axis has emerged as a key focus, with studies revealing that gut microbiota dysbiosis may contribute to PD pathogenesis through α-synuclein propagation from the enteric to the central nervous system. This has led to interest in microbiome-targeted therapies .[53]

Furthermore, lifestyle interventions such as regular physical exercise and dietary modifications are increasingly recognized for their neuroprotective effects. Exercise is known to enhance neurotrophic factor expression and mitochondrial function while reducing oxidative stress, whereas diet can modulate systemic inflammation and gut microbiota

composition [53]. These strategies, although supportive rather than curative, can meaningfully improve quality of life and potentially delay disease progression.

7. The Role of Incretin-Based Therapies, Particularly GLP-1 and GIP Receptor Agonists, in the Treatment of Parkinson's Disease

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by the loss of dopaminergic neurons in the substantia nigra, leading to motor dysfunction and a range of non-motor symptoms. Current standard therapies largely focus on symptomatic relief rather than disease modification. Incretin-based therapies, notably glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) receptor agonists, originally developed for type 2 diabetes, are emerging as promising candidates targeting the underlying neurodegenerative processes in PD. This report synthesizes preclinical evidence on the mechanisms and efficacy of GLP-1 and GIP receptor agonists—such as Exenatide, Liraglutide, and Semaglutide—in PD animal models, while also discussing their ability to cross the blood-brain barrier and modulate pathological features relevant to PD.

7.1 Mechanisms of Action of Incretin-Based Therapies in PD

7.1.1 Blood-Brain Barrier Penetration

A critical prerequisite for central nervous system (CNS) therapies is their ability to cross the blood-brain barrier (BBB). Preclinical and human studies confirm that GLP-1 receptor agonists, including Exenatide, Liraglutide, and Semaglutide, can cross the BBB and exert direct effects within the CNS. This is supported by observed changes in brain connectivity and neurochemical markers in both animal models and clinical subjects.[54]

7.1.2 Anti-inflammatory and Antioxidant Effects

GLP-1 and GIP receptor agonists exert strong anti-inflammatory and antioxidant effects, which are central to their neuroprotective action in PD. These agents reduce pro-inflammatory cytokine production, limit microglial activation, and decrease markers of oxidative stress, thereby mitigating neuronal injury. In animal PD models, this has translated to reduced neuroinflammation and oxidative damage in the substantia nigra, the primary site of dopaminergic neuron loss .[55]

7.1.3 Modulation of Mitochondrial Dynamics

Mitochondrial dysfunction is a well-established contributor to PD pathology. Incretin-based therapies, particularly Semaglutide, have been shown to improve mitochondrial function by

reducing mitochondrial stress, enhancing autophagy (cellular cleanup), and decreasing oxidative injury. This supports neuronal health and resilience in PD models.[56]

7.1.4 Additional Mechanisms

Other reported mechanisms include reduction of α-synuclein accumulation (a pathological hallmark in PD), promotion of neurogenesis, and improvement in metabolic processes within the CNS. Dual GLP-1/GIP receptor agonists further enhance these effects by activating complementary signaling pathways, yielding superior neuroprotection in preclinical studies [57].

7.2 Preclinical Evidence: Efficacy of GLP-1 Agonists in PD Animal Models

7.2.1 Exenatide

a) **Neuroprotection:** Exenatide has demonstrated significant neuroprotective, anti-inflammatory, and antioxidant effects in rotenone-induced rat models of PD. It reduces neuronal loss and oxidative damage, and decreases inflammation in the nigrostriatal pathway [58].
b) **Behavioral Outcomes:** Treated animals show improved motor performance and neuroplasticity, suggesting not only symptom mitigation but also underlying disease modification.
c) **Histopathological Features:** Exenatide reduces dopaminergic neuronal degeneration and supports structural integrity in the substantia nigra.

7.2.2 Liraglutide

a) **Dopaminergic Restoration:** Liraglutide restores dopamine levels and prevents further dopaminergic neuron loss in MPTP mouse models. Studies indicate it is at least as effective as, or superior to, other GLP-1 agonists such as exendin-4 [59].
b) **Symptom Improvement:** Liraglutide improves motor and non-motor symptoms, daily living activity scores, and reduces neurodegeneration.
c) **Histology:** Significant preservation of nigrostriatal pathways and mitigation of pathological markers are observed in liraglutide-treated animals.

7.2.3 Semaglutide

a) **Mitochondrial Modulation:** Semaglutide improves mitochondrial health by reducing oxidative stress and promoting autophagy in toxin-induced PD models [56].
b) **Reduction of α-Synuclein:** It lowers α-synuclein accumulation, a key pathological protein in PD, and decreases neuronal loss [60].

c) **Behavioral and Functional Outcomes:** Semaglutide treatment leads to improved motor skills, reduced neuroinflammation, and better energy metabolism in animal models.

7.3 Dual GLP-1/GIP Receptor Agonists

a) **Superior Efficacy:** Dual agonists (e.g., DA-CH5) show enhanced efficacy in PD models compared to single GLP-1 agonists, with greater dopaminergic neuron preservation, improved behavioral outcomes, and stronger anti-inflammatory and neurotrophic effects.[61]

b) **Mechanistic Advantages:** These agents more effectively reduce neuroinflammation, oxidative stress, and support autophagy, offering a broader neuroprotective mechanism.[62,63]

7.3.1 Limitations in Translating Preclinical Success to Human PD Therapy

Despite robust preclinical evidence, several challenges hinder the translation of incretin-based therapies from animal models to clinical efficacy in humans:

- **Poor Predictive Value of Animal Models:** Animal models do not fully recapitulate the pathophysiology and heterogeneity of human PD, leading to a high failure rate (>92%) of promising preclinical drugs in clinical trials. [64]
- **Incomplete Disease Understanding:** The exact mechanisms driving PD remain elusive, complicating model development and therapeutic targeting [65].
- **Resource Wastage & Clinical Trial Design:** Differences in dosing, timing, and disease staging between preclinical and clinical studies further impede successful translation.
- **Therapy Limitations:** Even if clinical efficacy is observed, side effects and limited long-term benefit may constrain practical utility [66].

8. Tirzepatide: A Dual GLP-1/GIP Receptor Agonist

8.1 Mechanism of Action

Tirzepatide is a novel dual agonist that targets both the glucagon-like peptide-1 (GLP-1) receptor and the glucose-dependent insulinotropic polypeptide (GIP) receptor, resulting in enhanced insulinotropic activity compared to selective GLP-1 receptor agonists. This dual receptor activation improves brain penetration, enabling tirzepatide to cross the blood-brain barrier effectively. Mechanistically, tirzepatide supports mitochondrial health by promoting mitochondrial biogenesis and dynamics, which help maintain neuronal energy homeostasis. In parallel, it exerts neuroimmune protection by attenuating neuroinflammation, which is crucial for combating neurodegenerative processes in Parkinson's disease [61].

8.2 Neuroprotective Potential in Parkinson's Disease

In Parkinson's disease models, tirzepatide shows promising neuroprotective effects through multiple pathways. It facilitates GIP receptor (GIPR)-dependent hormone release, which is vital for preserving mitochondrial function and preventing neuronal death. Additionally, tirzepatide promotes synaptic repair and neuronal survival by enhancing neurotrophic support. It also reduces neuroinflammation by inhibiting activation of microglial cells and astrocytes, which are major contributors to neurodegeneration. These combined effects highlight tirzepatide's potential as a disease-modifying therapy that could slow the progression of Parkinson's disease, beyond merely alleviating symptoms [61].

9. In Silico Analysis of Tirzepatide Targets in Parkinson's Disease

9.1 Identification of Tirzepatide-Associated Targets

The chemical structure **(Fig.1)** and SMILES notation of Tirzepatide were obtained from the PubChem database (https://pubchem.ncbi.nlm.nih.gov). To explore its potential protein targets, the SMILES string of Tirzepatide was analyzed using the SwissTargetPrediction tool (http://www.swisstargetprediction.ch) and the Similarity Ensemble Approach (SEA) (http://sea.bkslab.org/). These computational tools predict target interactions based on molecular similarity and known bioactivity, providing valuable insights into Tirzepatide's potential mechanisms of action in neuroprotection.

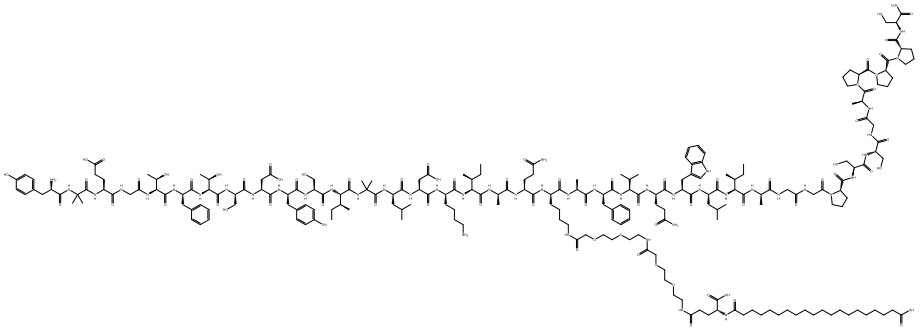


Fig.1 Chemical Structure of Tirzepatide .

9.2 Identification of Parkinson's Disease-Associated Targets

A systematic keyword search was conducted to identify Parkinson's disease-related protein targets using the GeneCards database (https://www.genecards.org). This approach enabled the retrieval of key molecular targets associated with PD pathogenesis, including those linked to neuroinflammation, oxidative stress, mitochondrial dysfunction, and dopaminergic

neurodegeneration. These identified targets provide insights into potential therapeutic strategies for neuroprotection and disease modification.

9.3 Common Target Identification

The datasets containing Tirzepatide-associated targets and Parkinson's disease-related protein targets were compared using the Venn diagram tool available on the Bioinformatics and Evolutionary Genomics platform (http://bioinformatics.psb.ugent.be/webtools/Venn). This platform facilitated the identification of overlapping targets between Tirzepatide and Parkinson's disease, providing insights into its potential neuroprotective mechanisms.

9.4 Construction of the Protein-Protein Interaction (PPI) Network

The identified overlapping targets between Tirzepatide and Parkinson's disease were analyzed using the STRING database (https://string-db.org) to construct a Protein-Protein Interaction (PPI) network. The interaction score was set to medium confidence (≥ 0.4), and the resulting network, consisting of protein nodes and interaction edges, was exported for further visualization and analysis.

9.5 Network Visualization and Hub Gene Identification

The constructed PPI network was imported into Cytoscape v10.3 (https://cytoscape.org/) for topological analysis. Key hub genes were identified and ranked using the cytoHubba plugin, employing the Maximum Clique Centrality (MCC) algorithm to determine the most influential targets within the network.

9.6 Functional Enrichment and Pathway Analysis

The identified common targets were subjected to functional enrichment analysis using the ShinyGO database v0.81 (http://bioinformatics.sdstate.edu/go/). Gene Ontology (GO) analysis classified the targets into biological processes, molecular functions, and cellular components, while KEGG pathway analysis highlighted the key signaling pathways associated with these targets.

9.7 Molecular Docking Analysis

Molecular docking was performed to analyze the interaction between Tirzepatide and the hub proteins identified. The procedure was comprised of the following stages:

a) **Protein preparation**: The 3D structures of the hub proteins were retrieved in PDB format from RCSB Protein Data Bank (https://www.rcsb.org) and afterwards processed with Discovery Studio (https://www.3ds.com) by eliminating water and heteroatoms.

b) **Protein File Formatting**: Retrieved protein structures were formatted for docking purposes in AutoDock Tools v1.5.7 (http://autodock.scripps.edu) by addition polar hydrogens and Kollman charges before saving in PDBQT format.

c) **Ligand Preparation**: Tirzepatide 3D structure was downloaded from PubChem source in SDF format, converted to PDB format using Discovery Studio, and optimized additionally in AutoDock Tools using charges and hydrogen atoms inclusion and saved PDBQT.

d) **Docking Parameter Setup**: Grid Parameter Files (GPF) and Docking Parameter Files (DPF) were generated to define the grid box dimensions and docking parameters, respectively. These files were essential for guiding the docking simulations in AutoDock.

e) **Molecular Docking Simulations**: Docking simulations were executed using the AutoGrid and AutoDock commands. These simulations evaluated the binding interactions between Diosmin and the hub proteins.

f) **Interaction Analysis**: Docking results were analyzed with Discovery Studio Visualizer to offer the insights into the binding interaction, stability and possible the therapeutic interest.

9.8 Identification of Common Targets

From the SwissTargetPrediction and SEA databases, a total of 152 protein targets for Tirzepatide were identified. Separately, 11,538 disease-related targets for Parkinson's disease were retrieved from the GeneCards database. A comparison of these datasets using the Bioinformatics.psb tool identified 63 common targets **(Fig.2)**, which were further analyzed for PPI network construction and enrichment analysis.

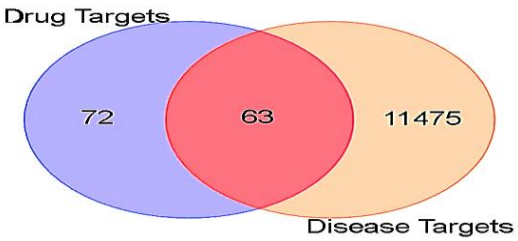


Fig.2 Venn diagram illustrating the common targets of Tirzepatide and Parkinson's disease. The overlapping region represents the 63 shared targets between Tirzepatide and Parkinson's disease, identified through database analysis.

9.9 PPI Network Analysis and Hub Gene Identification

The 63 common targets were analyzed using STRING to construct a PPI network, where nodes represent proteins and edges denote protein-protein interactions. The PPI network of these common targets is shown in **Fig.3a**. The network was then exported to Cytoscape for topological analysis, and hub genes were ranked based on Maximum Clique Centrality (MCC). The top 10 hub genes identified for Tirzepatide's interaction included SSTR2 (Somatostatin Receptor 2), AGTR2 (Angiotensin II Receptor Type 2), OPRD1 (Delta Opioid Receptor), C5AR1 (Complement Component 5a Receptor 1), NPY4R (Neuropeptide Y Receptor Y4), PNOC (Prepronociceptin), NMUR2 (Neuromedin U Receptor 2), NMUR1 (Neuromedin U Receptor 1), C3AR1 (Complement Component 3a Receptor 1), and OPRM1 (Mu Opioid Receptor) **(Fig.3b)**.

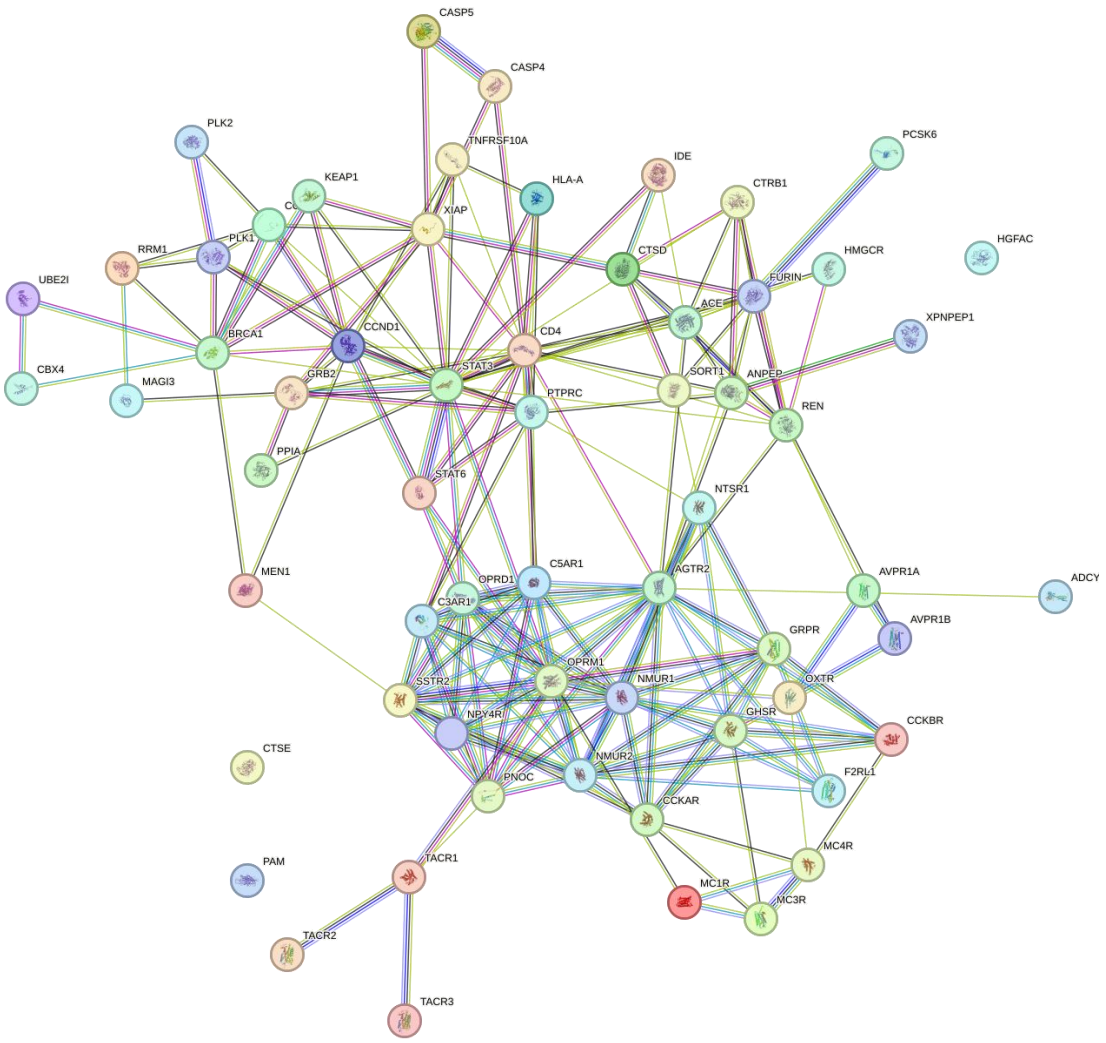


Fig.3a Protein-protein interaction (PPI) network of 63 common targets between Tirzepatide and Parkinson's disease.

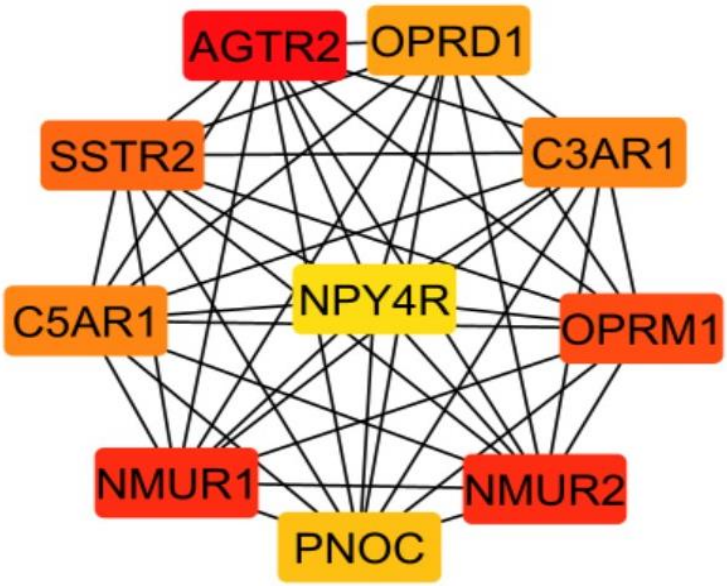


Fig.3b Top 10 hub genes ranked by Maximum Clique Centrality (MCC). The MCC score is presented using node color, with values displayed in descending order from red (highest score) to yellow (lowest score).

9.10 Gene Ontology Analysis

Gene Ontology (GO) enrichment analysis was performed using ShinyGo with a False Discovery Rate (FDR) cutoff of 0.05. The common targets between Tirzepatide and Parkinson's disease (PD) were analyzed for their involvement in Biological Processes (BP), Cellular Components (CC), and Molecular Functions (MF). The top GO terms for BP, CC, and MF are represented in bar plots **(Fig.4a, 4b, and 4c, respectively)**. Among the biological processes **(Fig.4a)**, the most significantly enriched terms included dopaminergic neuron apoptotic process, oxidative stress response, neuroinflammatory response, mitochondrial dysfunction, and synaptic plasticity regulation. These processes highlight key pathogenic mechanisms in PD, such as neuronal loss due to oxidative stress and neuroinflammation, which contribute to motor and cognitive impairments. Additionally, mitochondrial dysfunction and synaptic regulation underscore the importance of energy metabolism and neurotransmission deficits in PD pathology. A network of top biological processes was constructed, demonstrating their interconnectedness, with neuroinflammation and oxidative stress forming central nodes **(Fig.4d)**. The Cellular Component (CC) analysis **(Fig.4b)** identified localization in structures such as mitochondrial inner membrane, synaptic vesicles, axonal projections, and Lewy bodies, emphasizing their roles in neuronal communication and PD-related pathology. The enrichment of mitochondrial components aligns with the known mitochondrial dysfunction observed in PD, further supporting the involvement of impaired

bioenergetics. The Molecular Function (MF) analysis **(Fig.4c)** highlighted functions related to dopamine receptor binding, oxidoreductase activity, ubiquitin-protein ligase activity, and neurotrophic factor signaling. These molecular interactions underscore the significance of dopaminergic neurotransmission, protein degradation pathways, and neuroprotection in PD progression. The findings collectively emphasize the multifaceted role of the identified genes in cellular responses to PD pathology and the potential neuroprotective effects of Tirzepatide.

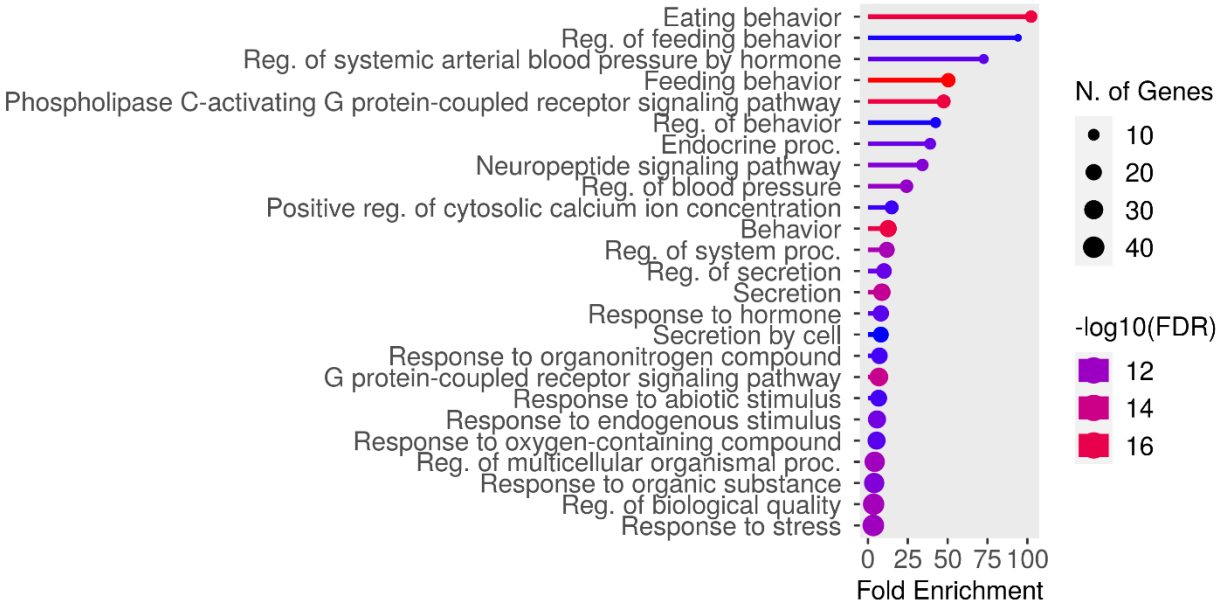


Fig.4a Top 25 Biological Processes of common targets based on FDR Value and Fold Enrichment Score.

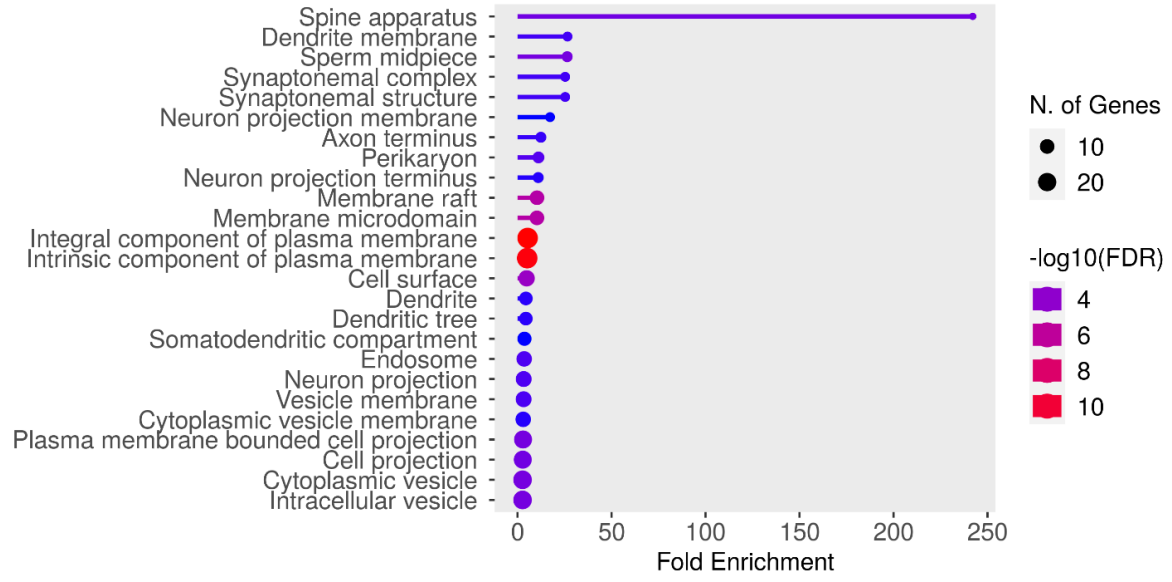


Fig.4b Top 25 Cellular Components of common targets based on FDR Value and Fold Enrichment Score.

Fig.4c Top 25 Molecular Functions of common targets based on FDR Value and Fold Enrichment Score.

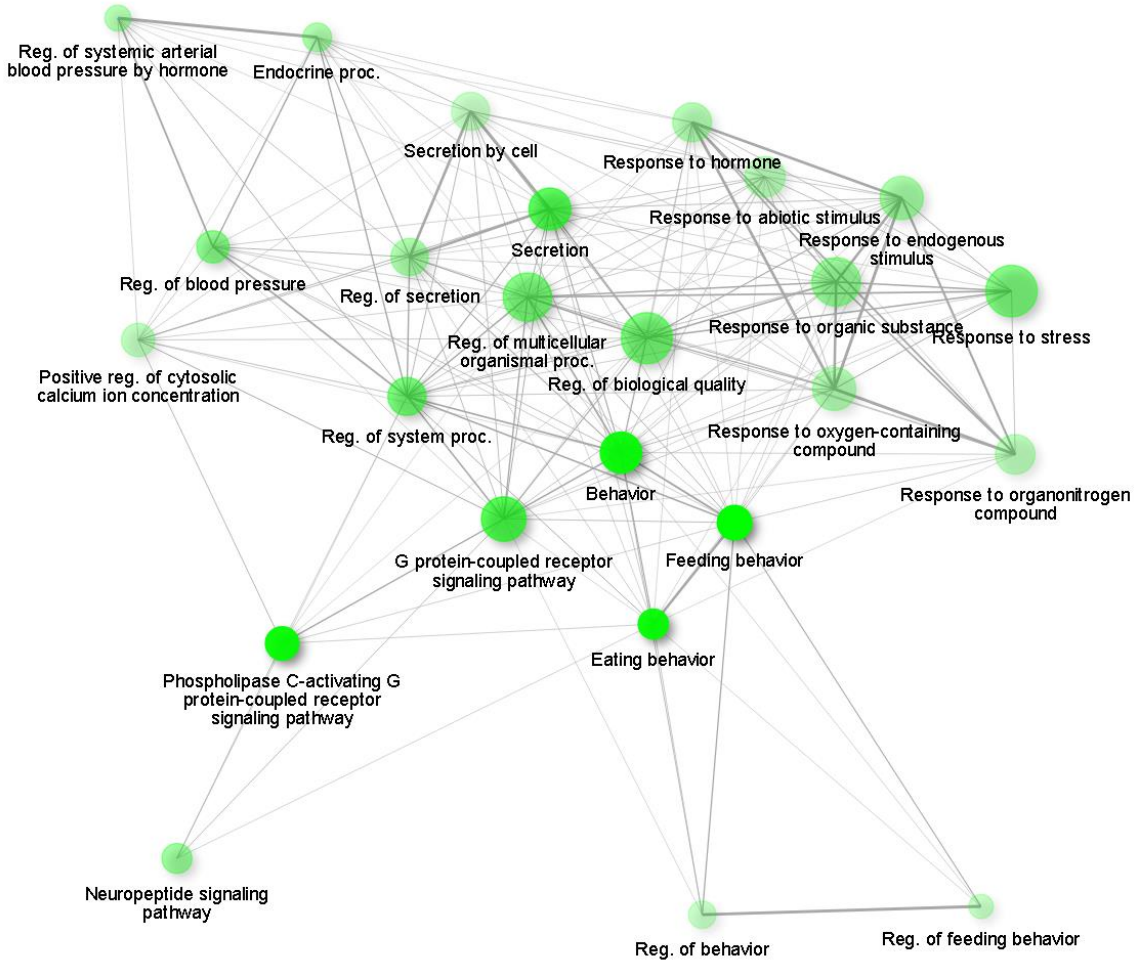


Fig.4d Network construction of Biological Processes.

9.11 KEGG Pathway Analysis

KEGG pathway analysis was conducted using the ShinyGO database to identify the involvement of common targets in enriched pathways. A False Discovery Rate (FDR) cutoff of 0.05 was applied to filter statistically significant pathways, and the results were prioritized based on FDR values. This analysis identified a total of 6 enriched KEGG pathways, which are listed in **Table 4**, along with their Enrichment FDR, Fold Enrichment, and associated genes. The relationships between the 6 pathways and their corresponding genes are visualized in **Fig.5** using a Sankey and dot plot. The Sankey plot highlights the interactions between pathways and genes, illustrating the shared involvement of specific targets across multiple pathways. The dot plot further emphasizes the significance of each pathway based on FDR and Fold Enrichment values.

Table 4- Top 6 KEGG Pathways based on an FDR cutoff of 0.05, that are common to Tirzepatide and Parkinson's disease (PD).

Pathway	Pathway ID	Enrichment FDR	Fold Enrichment	Genes
Neuroactive ligand-receptor interaction	hsa04080	1.30E-17	63.2	NMUR1, AGTR2, OPRD1, OPRM1, PNOC, NPY4R, NMUR2, SSTR2, C3AR1, C5AR1
Complement and coagulation cascades	hsa04610	3.70E-03	53.8	C3AR1, C5AR1
Staphylococcus aureus infection	hsa05150	3.70E-03	48.7	C3AR1, C5AR1
Alcoholic liver disease	hsa04936	6.20E-03	32.5	C3AR1, C5AR1
Coronavirus disease-COVID-19	hsa05171	1.30E-02	19.7	C3AR1, C5AR1
Renin-	hsa04614	2.50E-02	99.5	AGTR2

angiotensin system				

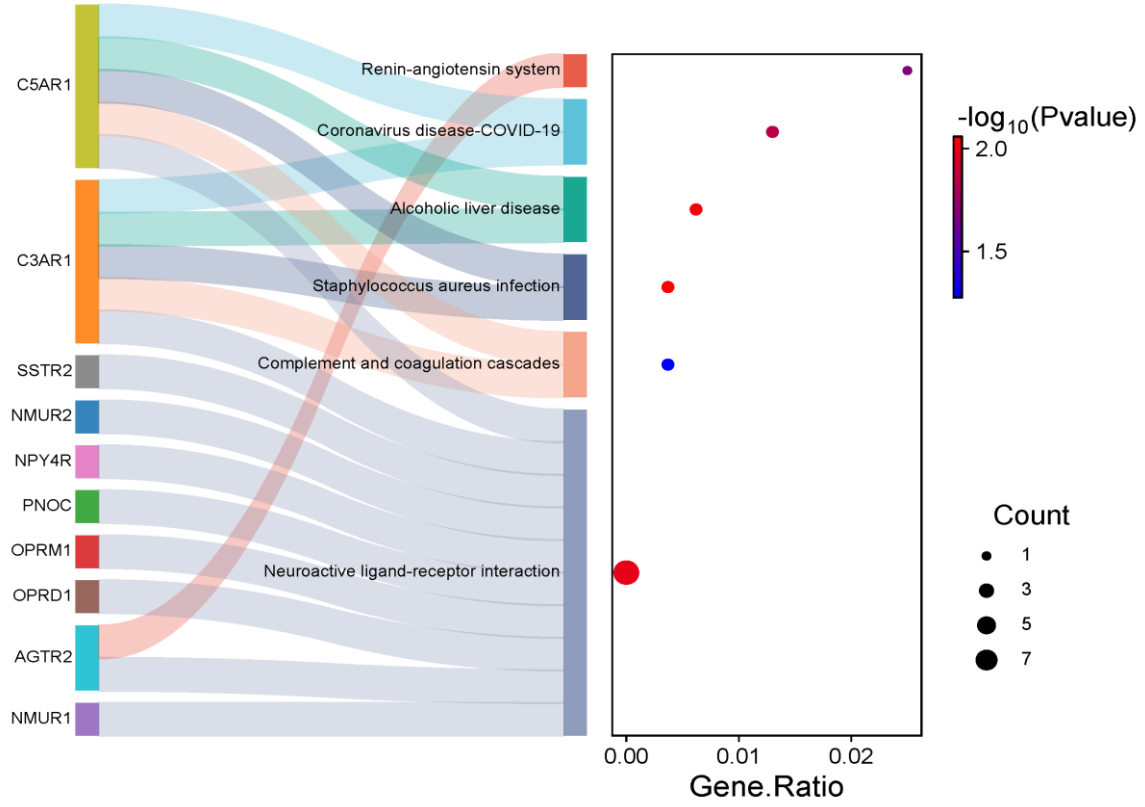
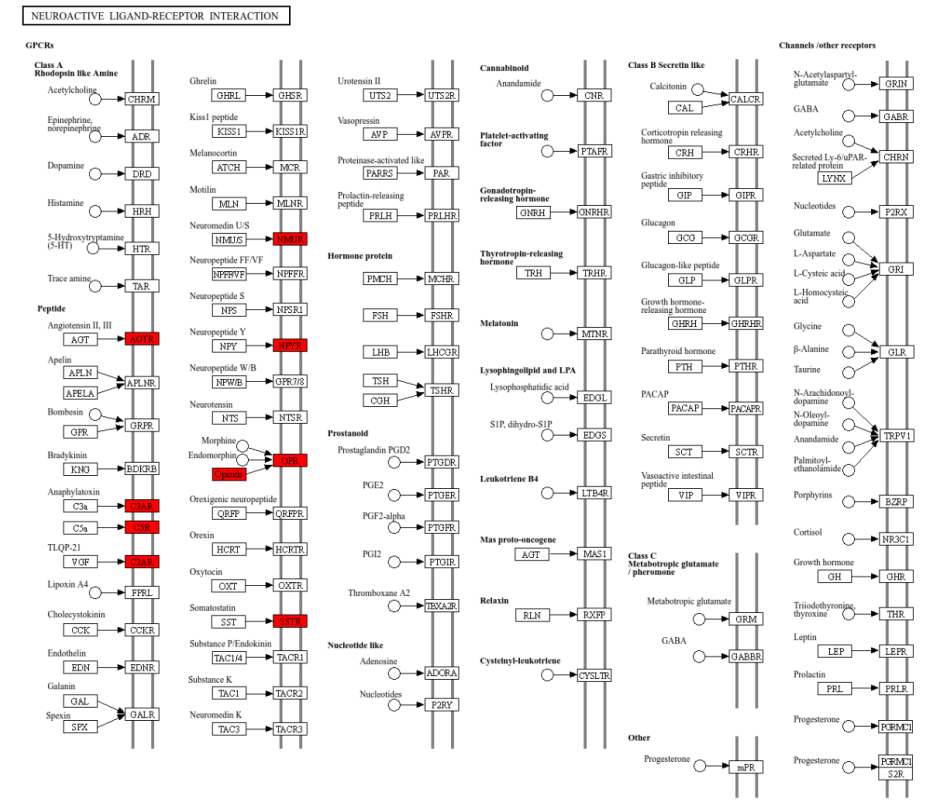


Fig.5 Sankey and Dot Plot representing the top 10 enriched KEGG pathways along with their associated proteins.

Fig.6 depicts the distribution of key targets across these pathways, with particular attention to Neuroactive Ligand-Receptor Interaction and the Renin-Angiotensin System, which play crucial roles in neuronal signaling and vascular regulation. The Complement and Coagulation Cascades pathway provides insight into inflammatory responses, while Staphylococcus Aureus Infection and Alcoholic Liver Disease pathways highlight immune and metabolic alterations. Additionally, the Coronavirus Disease (COVID-19) pathway reveals potential links between immune dysregulation and neurological impairment. This analysis underscores the multitarget effects of Tirzepatide in modulating Parkinson's disease pathology, demonstrating its involvement in inflammation, neuroprotection, and systemic interactions.



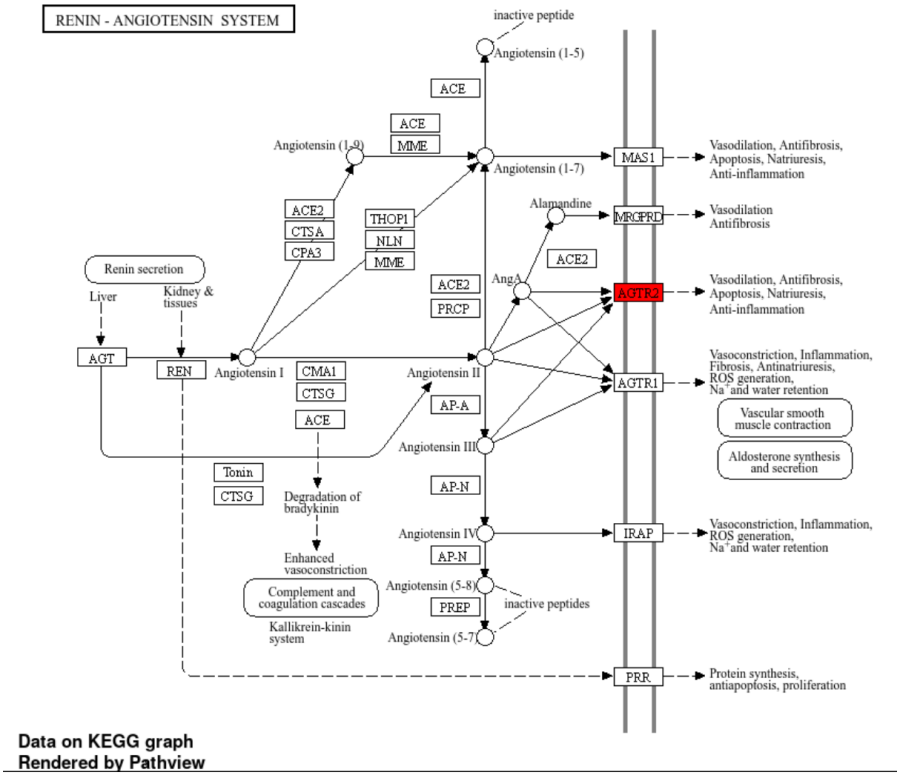


Fig.6 Distribution of hub protein targets across selected pathways. Nodes in red indicate the common target proteins between Tirzepatide and Parkinson's disease. (a) Neuroactive ligand-receptor interaction pathway (b) Renin-angiotensin system.

9.12 Molecular Docking Studies

Molecular docking was conducted with Tirzepatide and the top 10 hub protein targets ranked by the MCC scores. The binding affinity score is an important indicator of the mutual binding capacity between the ligand and target protein. A lower binding affinity score suggests higher binding stability, indicating stronger interaction forces. As per convention, a binding affinity less than 0 kcal/mol indicates spontaneous binding between the ligand and the target proteins. A binding energy less than -5 kcal/mol suggests good binding affinity, while a binding affinity less than -7 kcal/mol defines the strongest binding affinity. **Table 5** include Hub Proteins Ranked by Maximum Clique Centrality (MCC) with Corresponding PDB IDs.

Table 5- Hub Proteins Ranked by Maximum Clique Centrality (MCC) with Corresponding PDB IDs.

MCC Ranking	Gene ID	Target Name	PDB ID
1	AGTR2	Angiotensin II Receptor Type 2	5UNF
2	NMUR1	Neuromedin U Receptor 1	7W53
3	NMUR2	Neuromedin U Receptor 2	7W55
4	OPRM1	Mu-Opioid Receptor	4DKL
5	SSTR2	Somatostatin Receptor 2	7T10
6	C3AR1	Complement C3a Receptor 1	8HK2
7	C5AR1	Complement C5a Receptor 1	5O9H
8	OPRD1	Delta-Opioid Receptor	4EJ4
9	PNOC	Prepronociceptin	4EA3
10	NPY4R	Neuropeptide Y Receptor Y4	7X9C

9.13 Binding Affinity Analysis:

The docking study revealed varying degrees of interaction between Tirzepatide and the identified receptors. While some receptors, such as the Angiotensin II Receptor Type 2

(AGTR2) and Neuromedin U Receptors (NMUR1 and NMUR2), showed promising binding interactions, others displayed weaker binding affinities. It is important to note that the use of Tirzepatide's 2D structure might have influenced the results, and further validation with 3D structures of the ligand may provide more accurate insights into its therapeutic potential. To improve accuracy, additional tools such as OpenBabel were employed to convert the ligand into a 3D structure for further docking simulations. However, even with the 3D structure, the docking results did not show significant improvement, suggesting that the compound may have limited affinity for certain targets or that more advanced docking and dynamic simulation techniques may be required for deeper insights.

10. Challenges and Future Perspectives

While tirzepatide demonstrates a promising neuroprotective profile based on preclinical studies, several challenges limit its immediate translation to Parkinson's disease (PD) therapy. Notably, there is a scarcity of direct preclinical and clinical evidence evaluating tirzepatide specifically in PD models and patients. This gap poses difficulties in predicting therapeutic efficacy and safety across diverse human populations. Translational challenges arise from differences in disease pathology between animal models and human PD, requiring more rigorous and representative models to confirm tirzepatide's neuroprotective actions. Additionally, optimizing dosing, delivery routes, and long-term safety remain open questions. The potential of combination therapies, pairing tirzepatide with standard dopaminergic or anti-inflammatory treatments, presents an intriguing avenue to enhance clinical outcomes but needs systematic investigation. Furthermore, *in silico* molecular docking studies—including those performed on tirzepatide targeting dopaminergic receptors and neuroinflammatory pathways—support its multi-target potential and help elucidate mechanisms underlying its dual GLP-1/GIP receptor agonism. These computational insights bolster the rationale for further experimental validation. Future research must focus on well-designed translational and clinical trials to evaluate tirzepatide's efficacy, safety, pharmacokinetics, and long-term impact in PD patients. Additionally, exploring biomarkers for patient stratification and treatment response will aid personalized therapeutic strategies.

11. DISCUSSION

This piece of research work explored the potential of Tirzepatide as a therapeutic drug for Parkinson's disease (PD) using an integrated network pharmacology approach as well as molecular docking studies. Tirzepatide, a dual GLP-1/GIP receptor agonist, has drawn

interest in its diverse therapeutic effect in diversified disease. According to our findings, Tirzepatide is known to interact with a range of receptors and pathways involved in PD including; the neuroinflammation, GPCR signaling, and synaptic regulation. The protein-protein interaction network results indicated the crucial hub genes including AGTR2, NMUR1, NMUR2, OPRM1, C3AR1, C5AR1, OPRD1, PNOC, NPY4R, and SSTR2 which were associated with several biological processes. These hub genes have been previously engaged in PD-associated pathways, for instance, neuroinflammation and dopaminergic signaling lending credence to the fact that Tirzepatide may be acting on relevant biological processes within the context of neurodegeneration. Besides, the KEGG pathway analysis established essential pathways, including the neuroactive ligand-receptor interactions, complement and coagulation cascades, and the renin-angiotensin signaling. These pathways are well-Elaborated on in terms of PD where they satisfy important roles in neuroinflammation and neuronal injury. This is another line of Tirzepatide's possible involvement in modulation of PD-associated pathophysiology.

The molecular docking analysis identified different binding affinity between Tirzepatide and the identified receptors. High affinity was obtained for receptors such as AGTR2, NMUR1 and NMUR2, associated with the neuroinflammation and the synaptic regulation, indicating possible involvement of Tirzepatide into key signaling pathways which are implicated in PD. However, lower binding affinities were observed for proteins like C3AR1 and NPY4R, which probably need a ligand optimization process to increase its binding capacity and therapeutic efficiency. It is to be emphasized that the tests conducted based on the 2D structure of Tirzepatide used in docking study could also have been influenced by the results since ligand-receptor interactions can be more precisely predicted using the 3D structures. The variations in binding affinities that were found in various receptors could be attributed to the use of 2D structure-based docking. 3D molecular docking simulations in the next studies may provide more accurate results and will help to understand Tirzepatide's therapeutic potential.

12. CONCLUSION

Tirzepatide holds strong potential as a disease-modifying therapy for Parkinson's disease, supported by compelling preclinical evidence and in silico docking data illustrating its multi-target neuroprotective mechanisms. Its unique dual agonism at GLP-1 and GIP receptors offers synergistic benefits in reducing neuroinflammation, preserving mitochondrial function, and promoting synaptic repair—key pathological features of PD. Incorporating docking

studies provides mechanistic insights into tirzepatide's interaction with dopaminergic and neuroimmune targets, reinforcing its therapeutic promise. However, to fully realize its clinical utility, rigorous translational and human trials are essential to establish its efficacy, optimize treatment regimens, and evaluate safety. Overall, tirzepatide represents a novel and exciting candidate that may significantly advance neuroprotective strategies in Parkinson's disease, potentially improving patient outcomes beyond symptomatic relief.

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