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Research article

In Silico Elucidation of Molecular Mechanisms of Luteolin and Gramine against Parkinson's Disease

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Abstract

Parkinson's disease (PD) is a progressive neurodegenerative condition that causes dopaminergic neuronal loss, oxidative stress, mitochondrial dysfunction, neuroinflammation, and α-synuclein aggregation. Natural phytochemicals have received attention because of their multitarget neuroprotective properties. The current study sought to assess the therapeutic mechanisms of Luteolin and Gramine against Parkinson's disease utilizing integrated network pharmacology and molecular docking methods. Potential Luteolin and Gramine targets were identified using SwissTargetPrediction and PubChem, respectively, whereas PD-associated genes were identified using GeneCards. STRING and Cytoscape were used to assess common targets, which were then enriched for Gene Ontology (GO) and KEGG pathways. Major targets found by network pharmacology include PIK3R1, PTK2, AKT1, EGFR, AKR1C3, IGF1R, CDK1, and CYP19A1, which are linked to oxidative stress, neuroinflammation, apoptosis, and neuronal survival. The dopaminergic synapse signaling pathway played a substantial role, according to KEGG analysis. Luteolin binds better to PIK3R1 (PDB: 6D85; -7.4 kcal/mol) and PTK2 (PDB: 4NY0; -7.6 kcal/mol) than Levodopa and Gramine, according to molecular docking analysis. The data imply that luteolin and gramine have neuroprotective effects in Parkinson's disease via modulating many targets and pathways.

1. Introduction

Parkinson's disease (PD) is the world's second most common neurodegenerative ailment, defined by the gradual degradation of dopaminergic neurons in the substantia nigra pars compacta, which causes motor deficits such as tremors, stiffness, bradykinesia, and postural instability. In addition to movement impairment, Parkinson's disease is associated with cognitive decline, depression, and autonomic abnormalities. Parkinson's disease has several causes, including oxidative stress, mitochondrial failure, neuroinflammation, protein aggregation, and apoptosis. Despite the availability of symptomatic medicines, existing treatment options fail to arrest disease progression, emphasizing the critical need for safer and more effective therapeutics [1-4].

Natural phytochemicals are gaining popularity as possible neuroprotective drugs due to their pleiotropic pharmacological effects and low safety profiles. Among these substances, luteolin, a naturally occurring flavonoid found in medicinal plants and foods, has been shown to have strong antioxidant, anti-inflammatory, antiapoptotic, and neuroprotective effects. Previous research indicates that luteolin affects several signaling pathways linked to neurodegeneration, such as NF-κB, MAPK, PI3K/Akt, Nrf2, and JAK/STAT. In experimental models of Parkinson's disease, luteolin has also been shown to reduce oxidative stress, inhibit neuroinflammation, and preserve dopaminergic neurons. Gramine, an indole alkaloid found

mostly in cereal grasses and medicinal plants, has sparked scientific attention due to its several biological activities, which include antioxidant, anti-inflammatory, and neuroprotective properties. Although the pharmacological effect of gramine in Parkinson's disease is little understood, its molecular properties indicate that it has the ability to interact with a variety of protein targets related with neurodegenerative processes. Investigating the synergistic or complimentary treatment processes of luteolin and gramine may bring fresh insights into multi-target methods for Parkinson's disease management [5-14].

Network pharmacology has evolved as a powerful systems-level method to understanding the complicated relationships between bioactive chemicals, target proteins, signaling pathways, and illnesses. This computational technique, when combined with molecular docking, allows for the identification of new therapeutic targets as well as the evaluation of ligand-protein binding affinities, which speeds up drug discovery and mechanistic research. Several recent research have effectively used integrated network pharmacology and molecular docking techniques to uncover new phytochemical candidates for Parkinson's disease. Thus, the current study aims to evaluate the therapeutic potential and underlying molecular processes of luteolin and gramine against Parkinson's disease utilizing an integrated network pharmacology and molecular docking method [15-20].

2. Materials and Methods

2.1 Chemical Candidates and Compound Related Targets

The literature was used to aid the chemical selection process. The selected bioactive compounds were then searched in the PubChem database to obtain their chemical structures and SMILES notations. Potential target proteins linked with these chemicals, with likelihood scores larger than zero, were then predicted using the Swiss Target Prediction Database.

2.2 Identification of Parkinson's Disease-Related Targets

We searched the GeneCards database for possible targets related with Parkinson's Disease. This database combines data from several sources to provide complete information on human genes. The selected targets were collated for additional study and classified as Parkinson's Disease-related targets [21].

2.3 Venn Diagram

We developed a Venn diagram to assess the overlap between Parkinson's Disease-associated targets and possible targets for Luteolin and Gramine.

2.4 Protein-Protein Interaction (PPI) Network

The STRING database (https://string-db.org/) collects known and projected protein-protein interactions, including functional and physical correlations. For this study, we utilized STRING [22] to look at the connections between the chemicals in our analysis and the targets associated with Parkinson's Disease, finding potential therapy targets. To build a reliable protein-protein interaction (PPI) network for these targets, we employed the "Homo sapiens" organism with a confidence level of 0.4. This confidence score is commonly employed because it strikes a good balance between sensitivity and specificity, resulting in a credible criteria for interaction prediction. As a consequence, only proteins with interaction scores of 0.4 or higher were included to the PPI network, increasing the accuracy of our potential target identification.

2.5 Functional Enrichment and Pathway Analysis

To identify key pathways and related Gene Ontology (GO) concepts, all potential therapeutic targets were analyzed using pathway and GO enrichment analyses in the String database [22] (https://string-db.org/). This investigation shed light on the biological processes (BP), molecular functions (MF), and cellular components (CC) connected with the targets. Pathways and GO keywords having a significance level of $p < 0.05$ were chosen for further study.

2.6 Building a Compound-Target Network

The compound-target interaction network was created by linking the targets associated with each chemical. Cytoscape 3.10.2 (Cytoscape Consortium, San Diego, CA, USA) was used to visualize the network [23]. Nodes in the network represent drugs and their targets, while edges show their interactions.

2.7 Molecular Docking

Molecular docking investigations were carried out in accordance with the previously published approach described by Ahmad et al. (2024). The three-dimensional structures of target proteins were obtained from the Protein Data Bank, while ligand structures were obtained from PubChem. AutoDock Vina was used to investigate binding affinity and protein-ligand interactions. The docked complexes with the lowest binding energy were chosen and visualized using PyMOL and Discovery Studio, following the previously defined computational process [23-24].

3. Result and Discussion

3.1 Potential Therapeutic Targets of Compounds Used to Treat Parkinson's Disease

Using Parkinson's Disease as a keyword, data were gathered from the GeneCards database, resulting in 8987 target genes. Among them, 98 targets were identified as shared by the chemicals and Parkinson's Disease-related genes, indicating prospective therapeutic targets for compounds used to treat

Parkinson's disease. A Venn diagram is used to demonstrate these overlapping objectives (Figure 1).

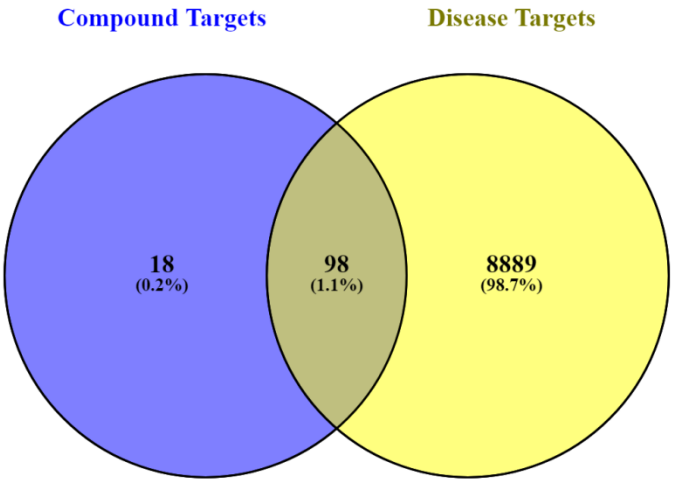


Figure 1. Venn Diagram.

3.2 Construction of the Compound-Target Network

To investigate the signaling pathways and functional functions of the identified target genes, we used Cytoscape data analysis. This strategy made it easier to create a thorough compound-target network, as seen in Fig. 2. The network highlights the pharmacological methods by which the drugs may impact Parkinson's disease treatment, with a focus on interactions with 98 target proteins. Network analysis shows that different components are converging across numerous targets, implying that these bioactive chemicals may have synergistic effects. These interactions may improve the therapeutic efficacy of these drugs not just in the treatment of Parkinson's disease, but also in other associated disorders.

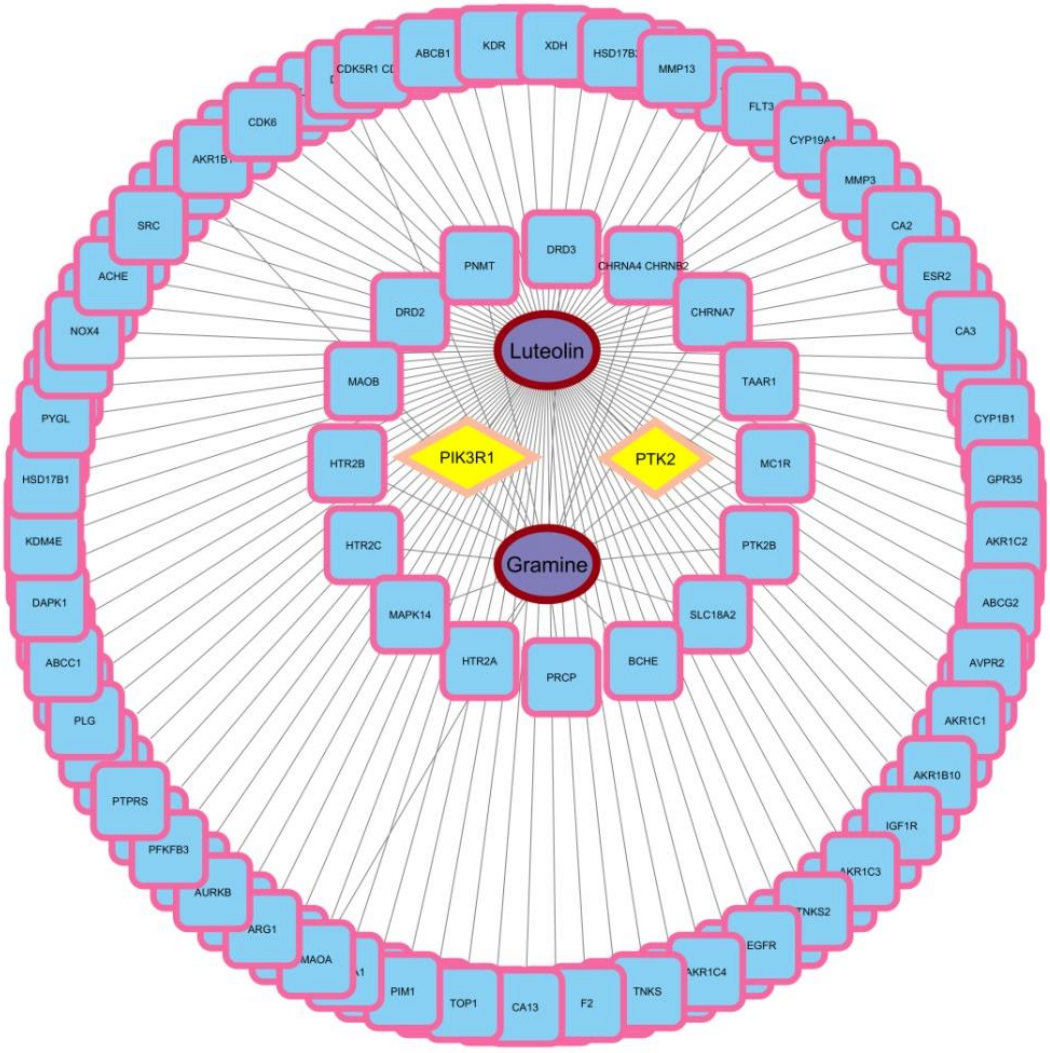


Figure 2. Compound Target Network.

3.3 PPI Network Visualization and Analysis

The STRING database was utilized to examine the interactions among 98 potential therapeutic targets. The resulting protein-protein interaction (PPI) network comprised 98 nodes and 85 edges, with an average node degree of 1.73 and a local clustering coefficient of 0.507 (Figure 3). In this network, nodes correspond to individual proteins, whereas edges indicate the connections between them. A higher degree value signifies a more critical role of the protein within the network. Following a filtering process based on the established criteria, several hub genes were identified, including PIK3R1, PTK2, AKT1, EGFR, AKR1C3, IGF1R, CDK1 and CYP19A1. These proteins, which include biological enzymes and cytokines, are integral to various regulatory processes, including signal transduction and protein phosphorylation. Among these genes, PIK3R1, PTK2, AKT1, EGFR and AKR1C3 emerged as the top five nodal targets. The strong associations of these genes with other potential therapeutic targets underscore their importance in the context of Parkinson's disease management.

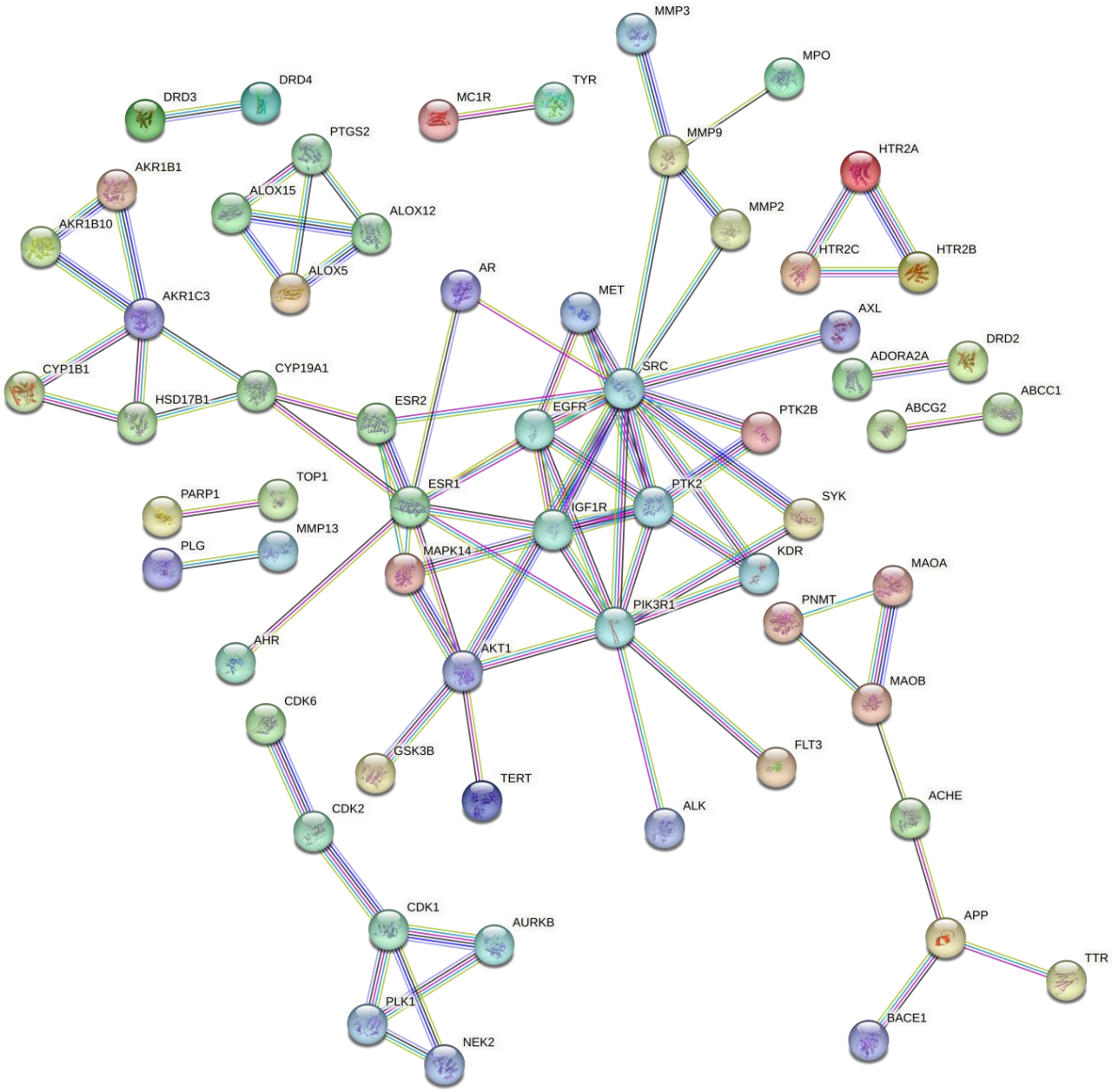


Figure 3. PPI Network.

3.4 GO enrichment analyses

To further understand the molecular processes by which drugs affect Parkinson's disease, we performed Gene Ontology (GO) enrichment analysis on 98 possible therapeutic targets linked with these medications using the string database. This study divided into three categories: biological process (BP), molecular function (MF), and cellular component. The top ten GO keywords found in each category are displayed in a bar plot, with findings described in Tables 1 (BP), 2 (MF), and 3 (CC), as well as (Figure 4A), (Figure 4B), and (Figure 4C). In the visualizations, the size of each bar correlates to the number of enriched genes linked with that GO word, while the color gradient indicates the importance of the p value, with deeper colors representing lower p values. A higher bar indicates a greater number of enriched therapeutic genes inside the associated GO word, implying a stronger link between that phrase and Parkinson's disease therapy than the other terms.

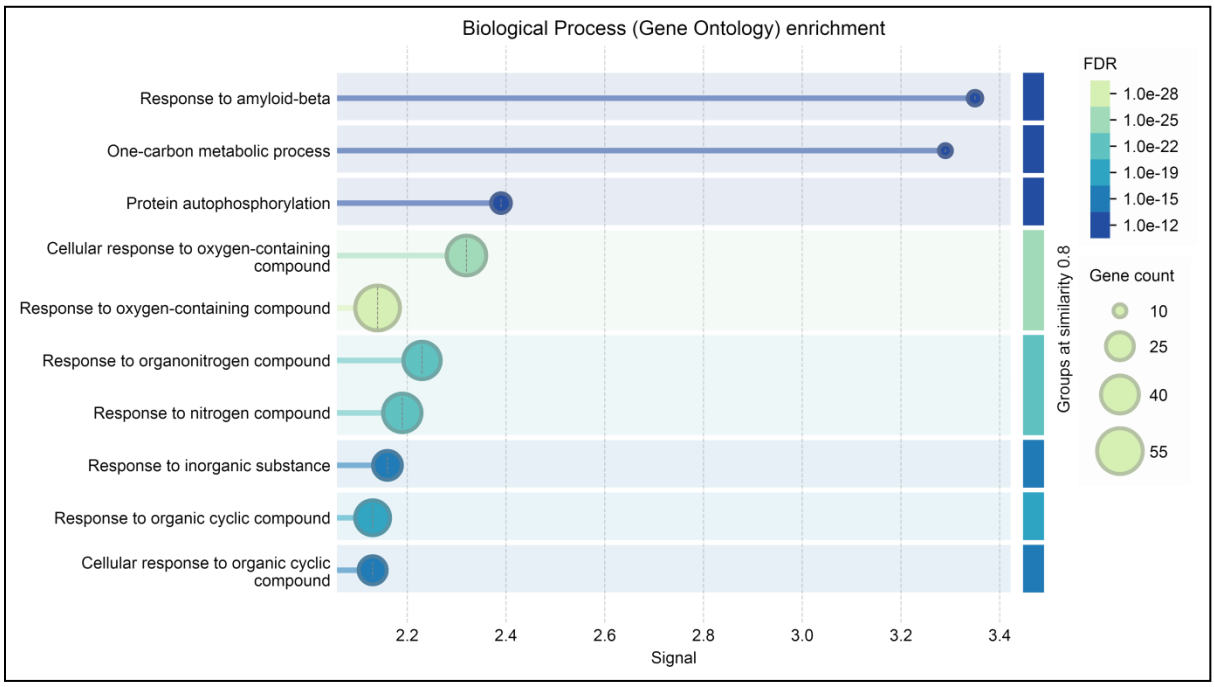


Figure 4A. Biological Process.

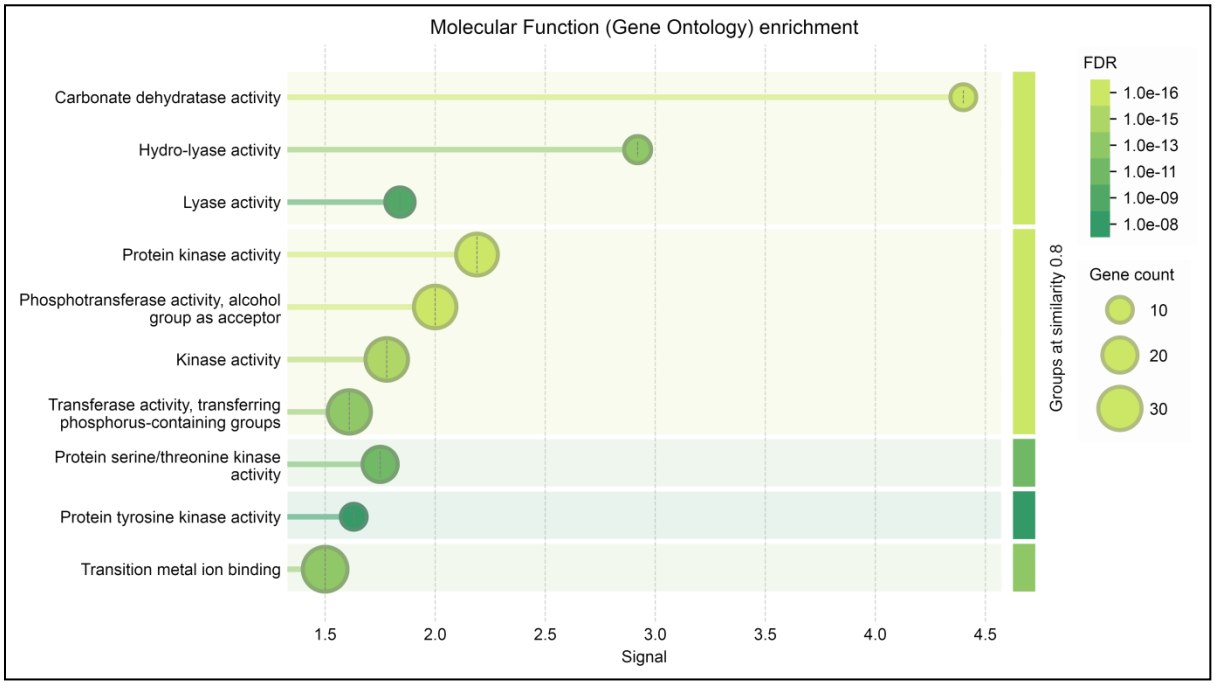


Figure 4B. Molecular Function.

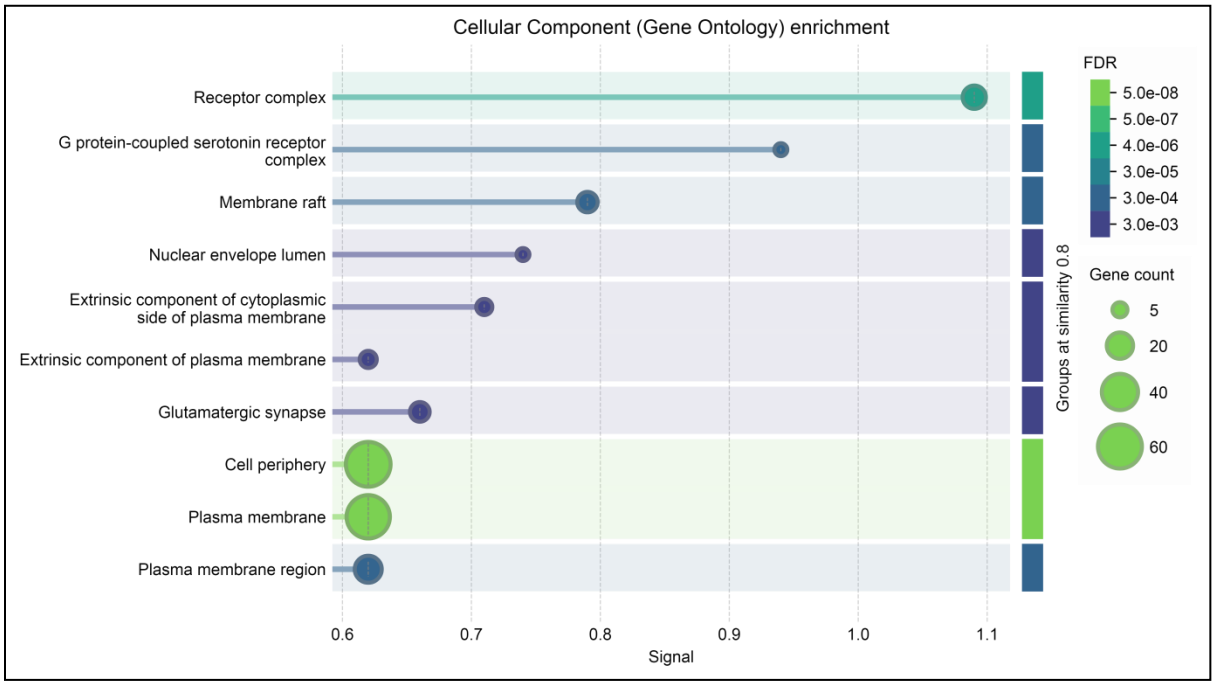


Figure 4C. Cellular Components.

Table 1. Biological Process.

Description	Count in gene set	False discovery rate
Response to oxygen-containing compound	53	4.44E-28
Cellular response to oxygen-containing compound	43	2.43E-24
Response to organic substance	60	1.04E-23
Response to chemical	70	1.16E-23
Response to nitrogen compound	41	1.66E-22
Metabolic process	89	6.84E-22
Response to organonitrogen compound	39	6.84E-22

Table 2. Molecular Function.

Description	Count in gene set	False discovery rate
Ion binding	81	1.60E-22
Catalytic activity	75	1.06E-19
Protein kinase activity	28	1.55E-16
Carbonate dehydratase activity	11	2.20E-16
Phosphotransferase activity, alcohol group as acceptor	29	6.26E-16
Kinase activity	29	1.50E-14
Transferase activity, transferring phosphorus-containing groups	30	1.02E-13

Table 3. Cellular Components.

Description	Count in gene set	False discovery rate
Cell periphery	62	5.71E-08
Plasma membrane	58	1.61E-07
Receptor complex	15	2.34E-06
Cytoplasm	83	0.00019
Intrinsic component of plasma membrane	26	0.0002
Integral component of plasma membrane	25	0.00024
Vesicle	41	0.00024
Membrane raft	11	0.00024
Synapse	22	0.00024
Plasma membrane region	21	0.00024

3.5 KEGG pathway enrichment analyses

The pathways associated with potential therapeutic targets for Parkinson's disease treatment were identified through KEGG pathway enrichment analysis. Signaling pathways were obtained via the string database. The top 10 signaling pathways were then visualized in a bar graph (Table 4 and Figure 5), organized by their P values in ascending order. The analysis indicated that the key targets were notably enriched in the Dopaminergic synapse signaling pathway (Figure 5A).

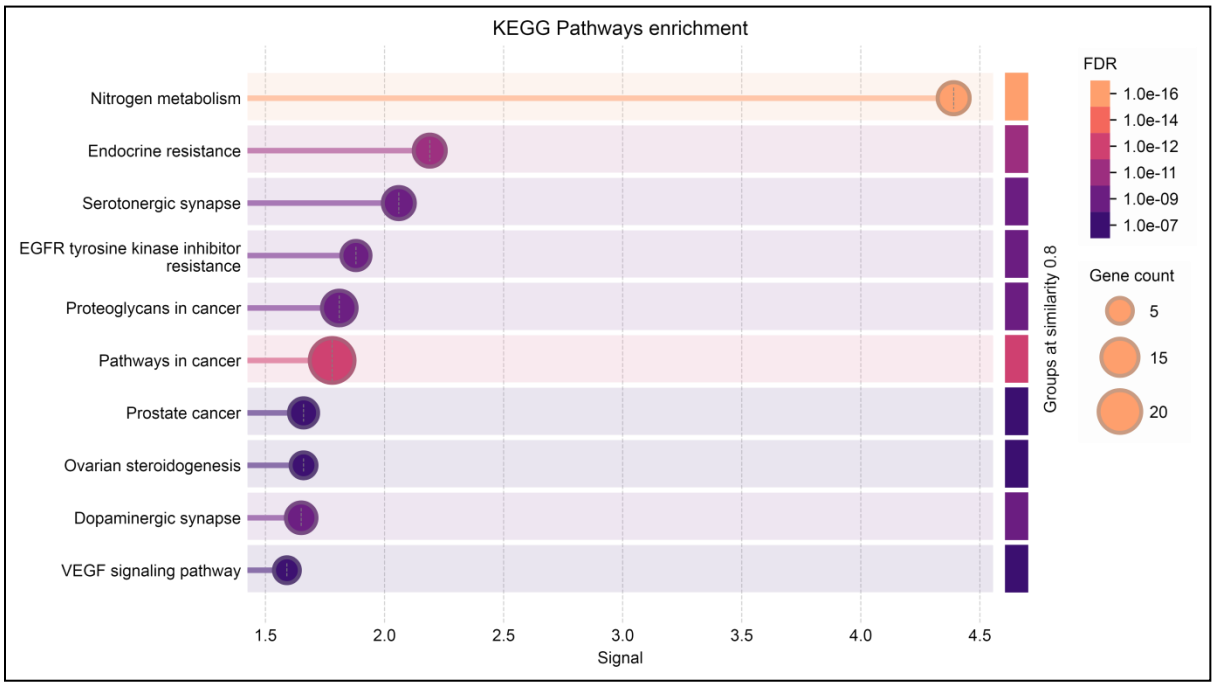


Figure 5. KEGG Pathway.

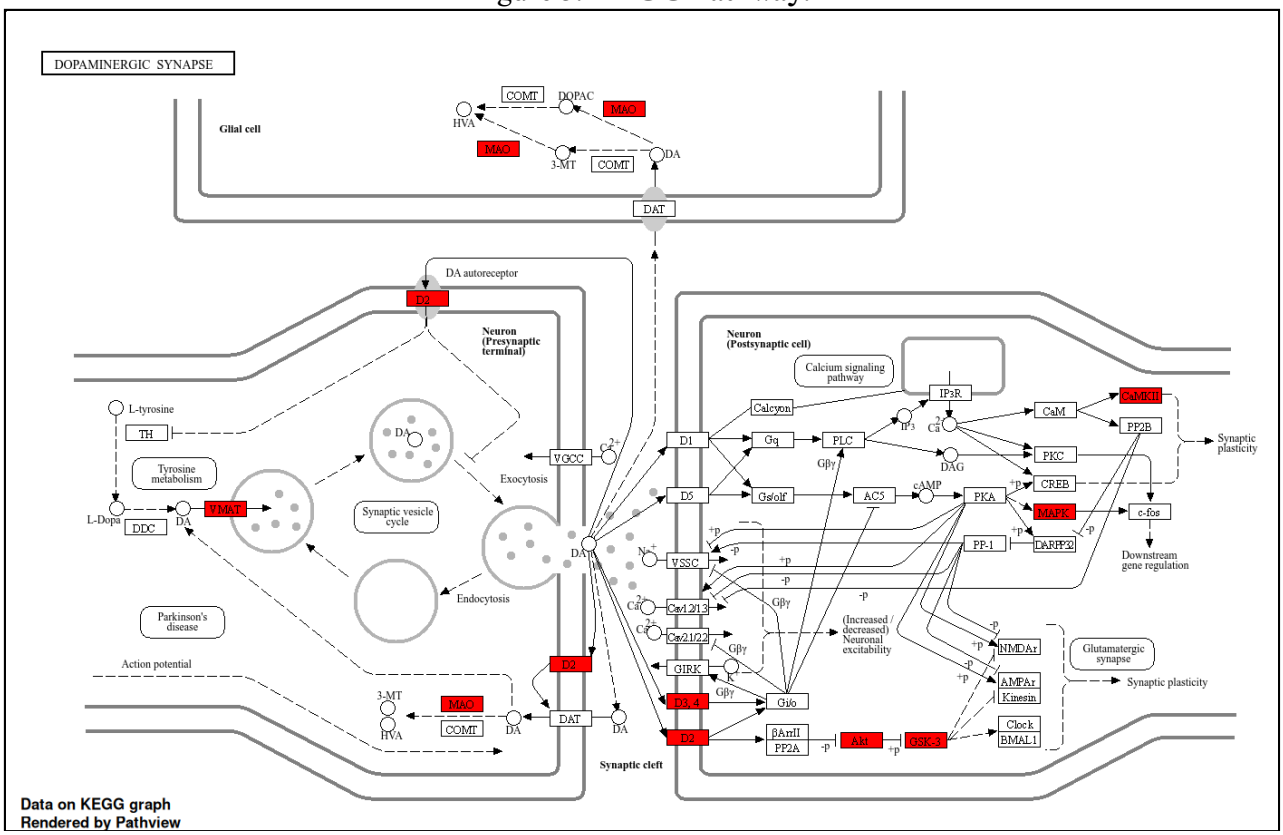


Figure 5A. Dopaminergic synapse Pathway.

Table 4. KEGG Pathway.

Description	Count in gene set	False discovery rate
Nitrogen metabolism	11	1.65E-16
Metabolic pathways	30	7.75E-10
Serotonergic synapse	11	1.12E-09
Dopaminergic synapse	10	5.90E-08
Proteoglycans in cancer	13	1.69E-09

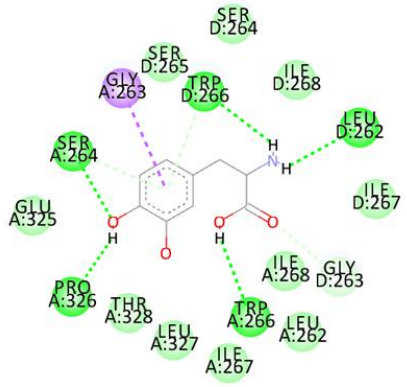
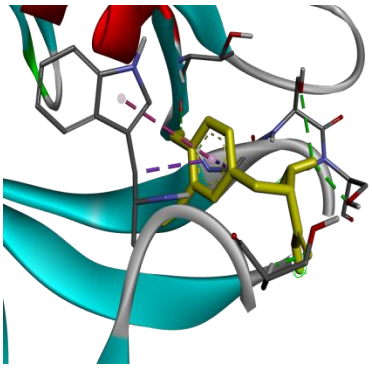
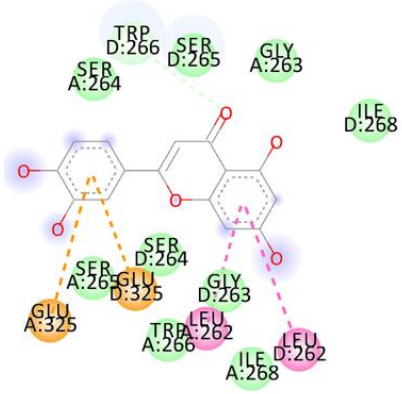
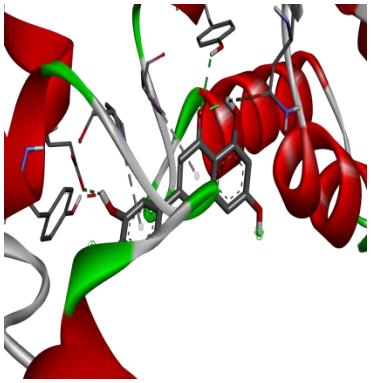
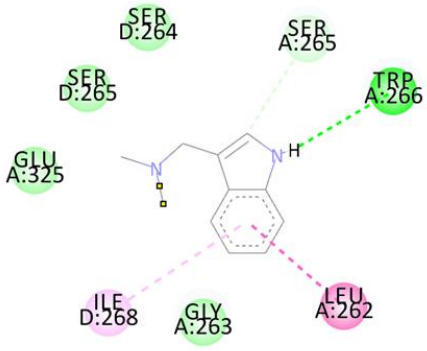
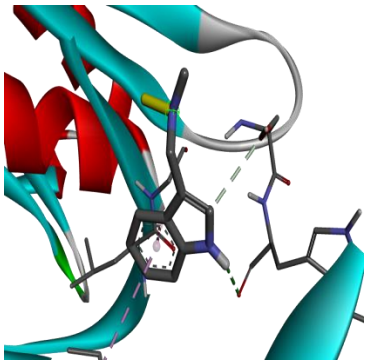
Compound-Targets	2D	3D
Levodopa-(4NY0)		
Luteolin-(4NY0)		
Gramine-(4NY0)		

Figure 6. Illustrates 2D and 3D docking poses of Levodopa, Luteolin and Gramine with protein PTK2 (4NY0).

Table 5. Molecular docking analysis.

Sr. No.	Compound	Target Protein	PDB ID	Binding Energy (kcal/mol)	Observation
1	Levodopa	PIK3R1	6D85	-5.5	Demonstrated moderate binding affinity toward PIK3R1 protein.
2	Luteolin	PIK3R1	6D85	-7.4	Exhibited strong binding affinity against PIK3R1 compared to standard and Gramine.
3	Gramine	PIK3R1	6D85	-5.2	Showed moderate interaction with the target protein.
4	Levodopa	PTK2	4NY0	-6.8	Demonstrated good binding affinity toward PTK2 protein.
5	Luteolin	PTK2	4NY0	-7.6	Showed the strongest binding interaction among all tested compounds against PTK2.
6	Gramine	PTK2	4NY0	-5.8	Exhibited moderate binding affinity with PTK2 protein.

3.6 Molecular docking

Molecular docking studies of Luteolin and Gramine against key hypertension-associated target proteins, including PIK3R1 (degree = 10) and PTK2 (degree = 8), were performed using AutoDock Vina to evaluate their binding affinities and interaction profiles. The docking analysis primarily focused on binding affinity values (kcal/mol) to predict the stability of protein-ligand interactions. The obtained docking scores are presented in Table 5 and graphically illustrated in Figure 6.

The molecular docking study demonstrated favorable interactions of Gramine and Luteolin against the selected Parkinson's disease-associated target proteins PIK3R1 (6D85) and PTK2 (4NY0), using Levodopa as the standard compound. Among all tested compounds, Luteolin exhibited the strongest binding affinity with docking scores of -7.4 kcal/mol against PIK3R1 and -7.6 kcal/mol against PTK2, indicating stable protein-ligand interactions within the active binding pockets of the target proteins. Levodopa showed moderate binding affinity with docking scores of -5.5 kcal/mol and -6.8 kcal/mol against PIK3R1 and PTK2, respectively, whereas Gramine demonstrated comparatively moderate interactions with docking energies of -5.2 kcal/mol against PIK3R1 and -5.8 kcal/mol against PTK2. The enhanced binding affinity of Luteolin may be attributed to its polyphenolic structure, which facilitates hydrogen bonding and hydrophobic interactions with key amino acid residues of the target proteins. Previous reports have suggested that Luteolin possesses significant antioxidant, anti-inflammatory, and neuroprotective activities associated with modulation of neuronal signaling pathways. Gramine also exhibited appreciable binding interactions, suggesting its potential involvement in neuroprotective mechanisms related to Parkinson's disease. The docking findings indicate that the selected phytochemicals possess multitarget therapeutic potential and may contribute to modulation of molecular pathways associated with neurodegeneration and neuronal survival.

4. Conclusion

The current study used integrated network pharmacology and molecular docking analysis to show that Luteolin and Gramine have multitarget therapeutic potential against Parkinson's disease. Luteolin showed higher binding affinity for important targets PIK3R1 and PTK2, indicating potential neuroprotective action. The discovered targets and signaling pathways provide scientific evidence to support the possible use of these phytochemicals in the development of new treatment techniques for Parkinson's disease management.

Author Contribution

Shaikh Sahil Asif contributed to data collection and network pharmacology analysis. Syed Izhan carried out molecular docking studies, visualization, and result interpretation. Dr. Shaikh Mehmood Dawood conceptualized and supervised the study and revised the manuscript critically.

Funding Statement

The authors declare that no financial support or funding was received for this study.

Conflict of Interest

The authors declare that there are no conflicts of interest regarding the publication of this manuscript.

Ethics Approval and Consent to Participate

This study was entirely based on computational and *in silico* methodologies including network pharmacology and molecular docking approaches. Therefore, ethical approval and informed consent were not required as no human participants or experimental animals were involved in the study.

Consent for Publication

All authors have read and approved the final version of the manuscript for publication.

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Declaration of Generative AI

During the preparation of this manuscript, generative artificial intelligence (AI)-assisted tools were utilized only for language refinement, grammatical correction, and improvement of scientific readability.

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