

Explores the network pharmacology and molecular docking-based prediction of the molecular target and signaling pathways of Piperine in the treatment of Parkinson's disease

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Abstract

Parkinson's disease (PD) is the second most prevalent neurodegenerative disease. *Piper nigrum*, a traditional Chinese medicine, has been commercially successful in treating PD. However, the underlying processes and therapeutic efficacy of *Piper nigrum* in PD remain unknown. A network pharmacology approach was used to determine the active components, possible targets, and signaling pathways in *Piper nigrum* for PD treatment. In order to determine the active components, possible targets, and signaling pathways in *Piper nigrum* for the treatment of PD, a network pharmacology approach was used in the present study. We investigated the active ingredient–target–pathway network in the present research and determined that Piperine, Quercetin, Carvacrol, Limonene, Myrcene, Piperidine, Nerolidol and Eugenol greatly contributed to the management of PD by influencing the genes AKT1, GAPDH, EGFR, and ALB. Molecular docking was then used to confirm that the active molecules were effective against possible targets. At last, we conclude found four highly active constituents—namely, Piperine, Quercetin, Carvacrol, and Nerolidol help to regulate the expression of GAPDH, EGFR, AKT1, and ALB, which could potentially act as potential therapeutic targets for PD. By influencing PD-related mitogen-activated protein kinase (MAPK), they also have potential exerting effects on the peripheral system and inhibiting neuronal apoptosis through regulating the PI3K-Akt pathway Piperine shown a potential preventative impact on PD, according to integrated network pharmacology and docking analysis. This offers a foundation for comprehending how Piperine works to prevent Parkinson disease.

1. Introduction

The *Piper nigrum* is one of the most widely used herbs which belong to Piperaceae family. It is referred to as the king of species among other species [1]. *Piper nigrum* is popularly referred to as peppercorn, white pepper, green pepper, black pepper, and pippali in Sanskrit, milagu in Tamil, Madagascar pepper in English, and kali mirch in Urdu and India. Numerous tropical countries, including, Brazil, Indonesia, and India cultivated black pepper [2]. The most popular and most used spice in the world, black pepper, produces peppercorns that are hot and peppery. Black pepper is a preservative, medicinal and fragrance ingredients [3]. Whole *Piper nigrum* peppercorns or their active ingredients are utilized in a variety of cuisines and medications. Around the globe, pepper is use in a variety of source and foods, includes piperine (peppery piperidine) a significant pungent alkaloid with a variety of pharmacological properties [4]. It is extensively used in several traditional medical systems, such as the Ayurveda and Unani systems. Because it contains natural phytoconstituents, piperine exhibits a variety of pharmacological qualities, including antioxidant, anti-hypertensive, anti-platelet, neuroprotective, anti-cancer, anti-depressant and anti-pyritic effects. Alkaloids, Steroids, Tannin, Flavonoids, and Phenolic compounds are among the secondary chemical isolated form *piper nigrum* [5].

Parkinson disease is neurodegeneration disorders that are pretense a serious threat to physical and mental health of middle age and elderly person. The disease successively attacks patient's motor cortex and directed to long lasting impairment in motor function, namely movement and coordination [6]. The chief treatment for Parkinson disease is symptomatic. Chinese herbal medicine was re-counted

impressive in attenuate clinical symptoms, namely tremor and paralysis, hereby improving the quality of life of PD patients. Piperine is one of the most widely used traditional Chinese medicines (TCM) for treating PD. Even though its impact is well documented, the exclusive mechanism underlying its action in PD treatment is stagnant unclear. Advances in computational science, molecular biology, genomics, and network pharmacology have resulted in the development of new models for the prediction of drug interactions related to illness. Today, tremendous strides have been achieved in deciphering the mechanism of TCM via the use of network pharmacology, making it a potent tool for exploring the precise targets and pathways involved in illness therapy. Examining the possible useful element and comprehending the mechanism of action of piperine in the management of Parkinson's disease (PD) by means of network pharmacology and molecular docking was the goal of this research [7].

The potential for treating a variety of disease is promising, as is the utilization of phytoconstituents to transform medications in the future. Investigated the active components of *Piper nigrum* for the treatment of PD using network pharmacology-based methodology. Therefore, network pharmacology offered a potent way to find bioactive components and herbs used in traditional Chinese medicine to cure disease and disorder [8]. In the present study the active compound of *piper nigrum* were investigated using network pharmacology based methodology. To the base of our knowledge, this is the first research to analysis the mechanism of *piper nigrum* for the treatment of PD by combining bioinformatics analysis and NP [9]. This work speeds up the drug development process and provides a fresh knowledge of the molecular mechanism behind *piper nigrum* of anti-Parkinson action. Furthermore, the hunt for potential medications derived from *piper nigrum* had gained renewed attention as a result of this discovery [10]. This research used a network pharmacology technique it conjunction with molecular docking analysis to examine the bioactive components of *piper nigrum* and potential mechanism behind its anti-Parkinson actuation. Furthermore, it is recommended that laboratory test be showed soon to examine the substance pharmacological probable [11].

2. Materials and Methods

2.1. Collection and Screening of Active Compound

Dr. dukes (<https://phytochem.nal.usda.gov/>) is an open and accessible database resource containing information about active compound, potential targets, and related disease of Chinese medicine were utilized to gather knowledge about the active constituents of *Piper nigrum* from literature and a database of biologically active phytochemicals. "Piperine" was used as a database term, and Google Scholar were searched for relevant material. The bioavailability (BO) and drug-likeness (DL) indices, which are essential to the absorption, distribution, metabolism, and excretion (ADME) features of medications, were used to effectively screen all of the components in *Piper nigrum*. In order to meet ADME requirements, components were only kept if $DL > 0.18$ and $(BO) \geq 30\%$. In this context, SwissADME were used to compute the (BO) 30% and DL of each active chemical. In the meanwhile, PubChem were used to gather the chemical data (CID number, structure, and molecular weight) of the screened molecules.

2.2. Screening for potential target Genes for *Piper nigrum* Active Constituents against Parkinson disease

Swiss Target Prediction's online platform employed the SMILES number of each ingredient to produce targets using the opposite pharmacophore matching technique. Gene card database used for disease genes [36] were used to predict the potential targets of the chosen compounds of *Piper nigrum*. In order to meet the both the targets, PD-related targets and the projected target genes of screened *Piper nigrum* compounds were then intersected, (<https://www.bioinformatics.org/gvenn/>) and a Venn diagram was created to identify the common gene. Then screened common compounds were uploaded to the STRING database (<https://string-db.org/>) is an online proteins interaction database. It can use computational prediction to supplement the existing information on protein-protein interactions, where the search was restricted to "Homo sapiens", and the minimum interaction score was 0.4 to build a protein interaction network. The result was exported as a "TSV" format file for further uses. The Exploring the molecular mechanism of medicinal herbs to cure various diseases and conditions begins with the prediction of genes linked to disease. The Parkinson related genes were found from GeneCards (<https://www.genecards.org/>) with "Parkinson" as the keyword. The targets corresponding to *Piper nigrum* active compounds and targets retrieved from the disease database were crossed, and the duplicate genes were deleted to obtain the anti-parkinson targets of *Piper nigrum*. AlphaFold was used to determine the target gene's standard name.

2.3. Pathway and Functional Enrichment Analysis

The Gene Ontology Federation created the Gene Ontology database. The GO database is divided into three levels: biological process (BP), molecular function (MF), and cellular component (CC) which, in turn, explains the biological processes involved, the potential molecular function, and the cellular milieu where the gene product is found. The majority of known metabolic pathways and certain known regulatory pathways are included in the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway knowledge base. An online biological resource for gene functional categorization, function annotation, and enriched pathways is the Shiny GO database. For GO and KEGG enrichment analysis, the species was identified as *Homo sapiens*, and the targets of *Piper nigrum* were imported into the database. For KEGG enrichment analysis, a p-value of less than 0.01 was used, and for GO enrichment analysis, a p-value of less than 0.05. Using Shiny GO, a bubble chart was plotted.

2.4. Network Construction

To gain insight into the mechanism of *Piper nigrum* in Parkinson disease, network analysis was conducted. Cytoscape 3.10.3, a freely available visual user interface for importing, graphically exploring, and analyzing biomolecular interaction networks, was used to build and analyze the network. The network's target genes and active components were represented by nodes, and the interactions between the active constituents and their target genes were shown by edges [39]. Degree, a topological feature that indicates the significance of compounds, target genes, and pathways in network diagrams, was

computed using a network analyzer program. Moreover, "key targets" are characterized as target genes with the greatest level of linkage.

2.5. Protein-Protein Network Construction and Molecular Docking

The great variety, flexibility, and precision of protein–protein interactions (PPI) make them very important [40]. Key targets with a combined score of more than 0.4 were found to have functional interactions using the Search Tool for the Identification of Interacting Genes/Proteins (STRING) [41]. The result was exported as a 'TSV' file format and imported into the Cytohuba module of Cytoscap 3.10.3 version for visual analysis. Set the size and color of the node according to the degree value, and set the thickness of the edge according to the combination score [42]. For molecular docking verification, choose the active components of *Piper nigrum* with the number of gene targets > 3 as the ligand and the target with the highest value in the PPI network as the receptor [43]. The molecular docking technique was used to confirm key targets. Potential targets X-ray crystal structures were acquired using AlphFold, which also saved the target molecule in PDB format [44]. Initially, the PubChem database (<https://pubchem.ncbi.nlm.nih.gov>) provided the two-dimensional (2D) structure diagrams of these compounds, which were then imported into Chem3D software to create three-dimensional (3D) structure diagrams and save the structure in PDB format. Second, open the protein structure (PDB) format in Arguslab [45]. Next, add hydrogen. Finally, right-click on the amino acid residue. Choose the binding site and create a group from the chosen residue. Arguslab displays the ligand structure (PDB) format. Choose ligand, then use the right-click mouse to create a ligand group from this residue and properly clean the geometry [46]. Choose to initiate their active pockets and put up a dock calculation. For every docking run, the dock and flexible ligand docking mode was used as the docking calculation type. The search and redocking conditions resulted in a co-crystal that was attached to the protein with the root mean square derivation (RMSD) value choose. GA and Argusdock are the two docking algorithm choices available in the ArgusLab 4.0 application [47]. The results were analyzed and interpreted using the Discovery Studio Visualizer program 2024.

2.6. ADMET Profiling

The biochemical properties of drugs, such as absorption, distribution, metabolism, excretion, and toxicity, were examined using the Swiss ADME web server [48]. Each of those characteristics affects the drug's levels or the kinetics of its release into the tissues, which in turn affects the compound's pharmacological activity and therapeutic efficacy [49]. At a therapeutic dosage, high-quality drug molecules should have suitable ADMET characteristics and sufficient activity against the therapeutic targets [50]. By clearing 175 criteria, such as solubility, logp, and pKa sites of CYP metabolism, the machine learning program ADMET prediction can accurately identify the best drug candidates [51, 52]. Protox database was utilized for the toxicity prediction of different types of toxicity such as carcinogens, cytotoxicity and mutagenicity.

3. Result

3.1 Screening of Active Compound and Targets

Eight potential component of *piper nigrum* is isolated, quercetin, piperine, piperidine, eugenol, limonene, myrcene, narolidol and carvacrol with F > 30% and DL ≥ 0.18 were chosen after the search, filtering, and elimination of duplicates (table 1) F 30 indicates a bioavailability. The step and degree to which a medicines active constituents or active moiety is absorbed from a drug product and enters the bloodstream is known as bioavailability [12]. since they enable the body to absorb more of the right nutrient without requiring bigger dosages, compounds designed to have a higher bioavailability will work better. In terms of bioavailability, drug likeness devices a chemicals probability of becoming an oral medication [13]. In the early stages of the enlargements, drug likeness generated from the structures and specific of both current and potential medications has been routinely employed to weed out unwandered molecules. Additionally, the Swiss target prediction data base yielded 252 potential target genes from 8 active compound. Following the identification of compounds potential targets 551 genes linked to PD were obtained from the OMIM and gene card database [14]. Latera Venn diagram and <https://bioinformatics.psb.ugent.be/webtools/Venn/> was used to anticipate the shared targets of the compound related genes and PD. 136 of *Piper nigrum* potential PD genes were chosen and identified as key targets.

3.2. Compound and Target network construction

There were 8 active compounds that were found to be satisfactory from *piper nigrum*. In addition, 136 key targets and their associated pathways with a maximum number of genes were selected for the creation of a network diagram called “active compound-targeted genes-connected pathways”. Each of this active substance correlated to multiple targets, which is a strong indication that many targets may have a combined effect when *piper nigrum* is used as an anti-Parkinson agent. These 8 compounds degree in the network of compound-targeted genes-connected pathways was then assessed (Table 2). the degree of connection was greatest for alkaloid, flavonoid and monoterpene as shown in table 2, whereas it was relatively low for monoterpene and terpene additionally, 8 was chosen for docking analysis. One alkaloid, piperine one flavonoid quercetin and one monoterpene carvacrol and one sesquiterpene, narolidol with high degree of connectivity specifically, eugenol, volatile-myrcene monoterpene.

3.3. PPI Network Construction

The 136 overlapped genes were submitted into the STRING database for the construction of the PPI network. In the PPI, node and their related interaction indicate the interrelationship between multiple targets during disease development (figure A) and (Figure B) show relationship between target gene and compound gene or pathway. The PPI network of overlapping genes was then examined using network analyzer program (Figure C). The largest levels of overlap were seen in GAPDH (120), AKT1(118), EGFR (102), ALB (98), SRC (95), HSP90AA1(91), ESR1(89), HIF1A (88), MTOR (80). And PPARG (79) (Figure D). the highest degree indicates a strong correlation between the targets genes may be important targets. Four genes, namely GAPDH, AKT1, EGFR and ABL, were determined to be the piperine anti-Parkinson

targets of *Piper nigrum* and were selected for molecular docking studies after these result were compare with those provided by enrichment analysis (Table no 4)

3.4. KEGG Gene Pathway and GO Enrichment Analysis

Gene ontology (GO) operational and Kyoto Encyclopedia of genes and genomes(KEGG) enrichment analyses of the possible targets were conducted using Shiny GO 0.80 software. The following three indicators of GO function were calculated: Molecular Function (MF), Cellular Component (CC), and Biological Process (BP) 20 pathways ($P < .05$) exhibiting the greatest enrichment from the findings of GO and KEGG analyses were chosen. The potential biological roles of *Piper nigrum* targets were identified by the functional annotation and enrichment analysis. GO functional analysis revealed that *Piper nigrum* targets were associated with PI3K-Akt signaling pathways, inflammatory mediator regulation of TRP channels and other related processes (Fig. 2). To determine the important signaling pathways connected to *Piper nigrum* anti-parkinsons action, a KEGG pathway analysis was conducted. Notably, the majority of the genes were implicated in the following pathways, PI3L-Akt signaling pathways, Inflammatory medicated regulation of TRP channels and other related processes. Finally, GAPDH, AKT1, EGFR and ALB were identified as highly enriched genes by KEGG pathway analysis (Fig. 4). The pathways were displayed as dot plot.

3.5. Molecular Docking

The top 4 compounds GAPDH, AKT1, EGFR, and ALB were chosen for molecular docking after a thorough examination of the PPI network. Target proteins GAPDH(AF-P04406-F1-v4). AKT1(AF-P31749-F1-v4), EGFR(AF-P00533-F1-v4), and ALB(AF-P02768-F1-v4) all have their crystal structures obtained from alpha fold. The Argus tool was used to finish the structural refinement. In order to prevent conflicts and improper configurations, nonstandard residues were also eliminated from the proteins receptors, and energy minimization was finished at 1000 reasonable steps. To identify potential targets for components that might reduce the incidence of Parkinson disease, molecular docking was used.

The significant binding affinity between the components and the binding pockets of four target proteins was accurately predicted by docking analysis. Two important parameters for chemical screening were docking score and binding energy (Table 4 and Fig. 6). Cluster with the highest conformation and largest absolute binding energy value were chosen. AF-P04406-F1-v4 had the greatest binding energy and RMSD; with piperine and quercetin, AF-P31749-F1-v4 has the highest RMSD and binding energy; with piperine and narolidol, AF-P00533-F1-v4 has the highest binding energy and RMSD; and with piperine and carvacrol, AF-P02768-F1-v4 has the highest binding energy and RMSD with piperine and narolidol. These finding thus suggest that *Piper nigrum* active ingredients work as a Parkinson repressor by forming stable bond with target proteins. GAPDH, AKT1, EGFR, and ALB were also shown to be positively controlled by Amantadine [15, 16], Pramipexole [17]. Piperine, Quercetin, Carvacrol and narolidol all exhibited great binding energies with the target protein than positive control medications, according to molecular docking analysis (Table 4). This fact demonstrated the current works validity. Furthermore,

understanding how these four targets interact is essential to fully comprehending how active ingredients work to prevent Parkinson disease.

3.6. ADMET Profiling

In drug development, ADMET analysis is a difficult procedure. This was accomplished using the Swiss ADME database, which demonstrated the favorable pharmacokinetic characteristics of the chosen drugs. All of the to-selected medication candidates ADMET profiles reveal that none of the possible compounds pharmacokinetics characteristics have any negative effects (Table 6). Positive findings from the probable compounds related ADMET qualities for many models, including gastrointestinal absorption, BBB penetration, and P-glycoprotein substrates, clearly indicate the compounds potential as a therapeutic candidate. Notwithstanding the fact that each molecule has several forms of toxicity assessed, piperine and quercetin compound shows toxicity behavior, although different types of toxicity were measured for all compound.

4. Discussion

Parkinson disease is a kind of chronic neurodegenerative illness or motor ailment that manifests as a deficiency of dopamine in the basal ganglia. Bradykinesia, stiffness and disorder, excessive limb movements, and constipation are some of the symptoms it exhibits [6]. About 1% of those over 60 have Parkinson disease. In 1912, Frederick Lewy identified Lewy bodies as pathological markers, or hallmarks. He also found that dopamine deprivation and its effects in an animal model of Parkinson's disease. Research by Oleh Hornykiewicz and Arvid Carlsson began in 1957 [8]. Ergot and non-ergot medications are the two kinds of dopamine agonists that are currently on the market. Cabergoline, bromocriptine, lisuride, and pergolide are ergot medications, whereas ropinirole and pramipexole are mostly non-ergot pharmaceuticals. Drugs like rasagiline, selegiline, and safinamide are examples of MAO-B inhibitors; they are also used to treat Parkinson's disease symptoms [9]. These medications may be used in conjunction with other therapies or treatments, although they are not given in combination in the early stages.

Although they contain naturally occurring chemicals, medicinal plants are regarded as a natural pool and an endless supply of therapeutic agents [18, 19]. The structural diversity, multi-target action, and minimal toxic side effects of natural chemicals and their derivatives, which account for about half of all clinically used medicines, have made them a popular study subject and potential source for targeted medications in recent years. In the last 12 years, high-throughput methods have emerged as a powerful tool for evaluating the pharmacological effectiveness of herbal remedies in drug development [20, 21]. Finding possibly bioactive substances that stop the pathophysiology of illnesses and diseases will be seen as a shock of the modern era.

The therapeutic plant *Piper nigrum* is widely distributed across the world's Afro-Asian areas. Many diseases may be treated using this plant's medicinal qualities. There are several medicinal uses for the plant's seeds, roots, and leaves, among other components. The primary constituents of *Piper nigrum* include alkaloids, triterpenoids, volatile, flavonoids, and monoterpene [22, 23]. Numerous publications

have highlighted the traditional use of *Piper nigrum* in the management and treatment of Parkinson disease [24, 25]. Notably, *Piper nigrum* chemicals have shown promise in the treatment of PD [26] and breast cancer [27]. This work serves as a benchmark for the preliminary screening of *Piper nigrum* bioactive chemicals and as a novel therapeutic idea for more research into the processes behind *Piper nigrum*' ability to management of Parkinson Disease. According to screening findings in our field, the primary bioactive compounds of *Piper nigrum* were triterpenoids, flavonoids, monoterpene, and alkaloids. These compounds significantly influenced the AKT1, GAPDH, EGFR, and ALB genes, which in turn contributed to the Management of PD. Additionally, molecular docking supported our results that core chemicals and important targets have stable binding forces. We found that piperine, quercetin, carvacrol, nerolidol, eugenol, and myrcene showed a significant relationship in the network after building a model of "herb-active compounds–targets–pathways," suggesting that it has anti-Parkinson qualities. Furthermore, our results were further evidenced by molecular docking, which effectively confirmed the connection between highly active elements and their potential targets. Lastly, the related ADMET characteristics of possible compounds for several models, including gastrointestinal absorption, BBB penetration, and P-glycoprotein substrates, demonstrated favorable outcomes that strongly confirm the compounds' appropriateness as therapeutic candidates [28].

The PD targets of *Piper nigrum* were mostly implicated in cellular response to oxygen-containing compound, regulation of programmed cell death, apoptotic control, and protein phosphorylation binding, according to GO functional analysis. Targets were focused in Parkinson disease pathways, according to KEGG pathway studies. Apart from their involvement in PD-related processes, anti-Parkinson targets were also implicated in additional pathways that are closely linked Parkinson disease including the ErbB signaling system, the PI3K-Akt signaling circuit, relaxing signaling pathway, MAPK, and EGFR tyrosine kinase inhibitor.

We found several target genes involved in different metabolic pathways in the present investigation. Disease pathophysiology may be stopped by focusing on the genes that disrupt metabolic pathways. A few investigations supported our conclusions, including one that demonstrated that regulation of DA secretion and the related metabolic processes are closely associated with mechanisms of PD. Notably, AKT1 and GAPDH, EGFR, and ALB, 4 our primary targets, are mostly implicated in endocrine resistance pathways. Akt is highly expressed in TH dopaminergic neurons of substantia nigra or AKT1 [29]. This provides strong support for the idea that disruption of AKT1 signaling pathways might be linked to the Parkinson disease. Developing a deeper understanding of the signaling pathways influencing Parkinson is the main focus of research in the following years of the global rise in the illness. According to our findings, the cholinergic synapses, TH17 cell differential, dopaminergic synapses, PI3K-Akt signaling pathways, MAPK, are directly impacted by AKT1, GAPDH, EGFR, and ALB. Variations in these genes may thereby disrupt the related processes, resulting in a disease state. Furthermore, the active ingredients' targeted genes are also more abundant in inflammatory diseases like rheumatoid arthritis, suggesting that they may influence Parkinson disease by acting on different anti-inflammatory cytokines [30].

During a docking experiment, we screened four genes and 8 chemicals based on the "compounds–targets network." Additionally, docking results confirmed our findings and demonstrated that piperine, quercetin, carvacrol, and nerolidol bind stably with the active pockets of target genes. This suggests that these compounds may be used to treat Parkinson disease by blocking the AKT1, GAPDH, EGFR, and ALB genes. The present study provides a theoretical foundation for further experimental research by focusing on the active chemicals, their possible targets [31], and related pathways to treat Parkinson disease in the field of network pharmacology. Given network pharmacology's limitations, data mining is the only way to determine the fundamental pharmacological pathways for treating Parkinson disease. Currently, network pharmacology uses many datasets for bioactive mining. Despite being well filtered, databases may have inefficiencies because of the wide variety of information sources and experimental data [32]. Using current, high quantities chemical identification methods like electrospray mass spectroscopy and ultra-performance liquid chromatography is one approach to get around this issue [33]. Even though we have provided some curious findings, further research and clinical trials are required to fully examine *Piper nigrum* potential and confirm its therapeutic uses.

5. Conclusions

This study provides the most recent scientific framework for evaluating the effectiveness of multi-component, multi-target chemical formulations and investigating additional therapy targets for Parkinson disease. In this research, we used molecular docking in conjunction with a network pharmacology method to identify the molecular processes of *Piper nigrum* for the management of Parkinson disease. Furthermore, our research suggests that the genes AKT1, GAPDH, EGFR, and ALB are genuine and prospective therapeutic targets to lower the incidence of Parkinson disease as well as treat the condition. This study does, however, have some limitations since our results still need validation via pharmacological and clinical research. The therapeutic mechanisms of *Piper nigrum* for Parkinson disease and the use of network pharmacology in drug development are both explored further using this method.

Declarations

- The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.
- All data generated or analysed during this study are included in this published article.

Consent of Publication declaration

Not applicable

Funding Declaration

There is no funding for this study.

Clinical trial registration number

Not applicable

Consent to participate declaration

Not applicable

Conflict of interest

The author declares no conflict of interest, financial or otherwise

Ethical statements (or Informed Consent in case of human study)

Not applicable

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Tables

Tables 1 to 6 are available in the Supplementary Files section.

Figures

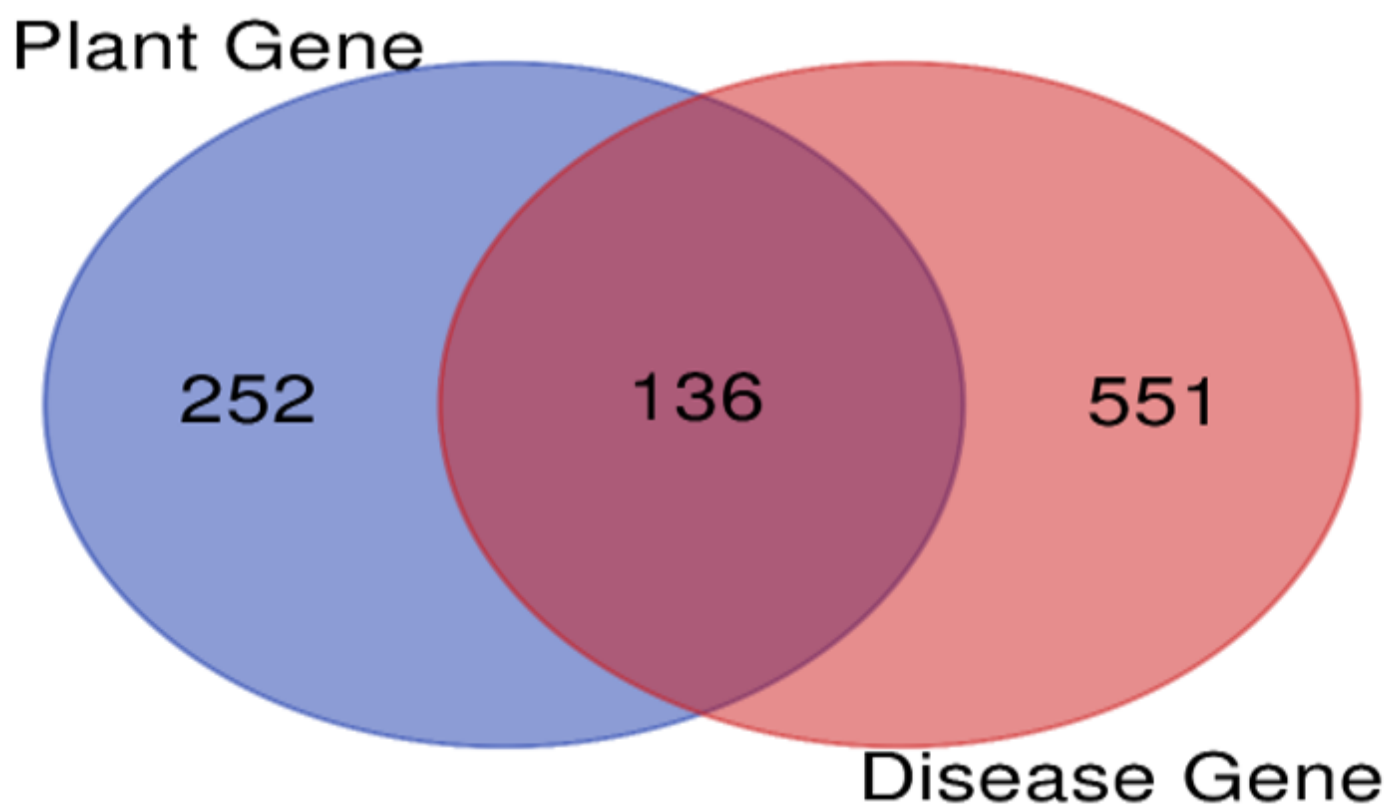


Figure 1

Venn diagram of Parkinson disease(PD) target and Piperine therapeutic target.

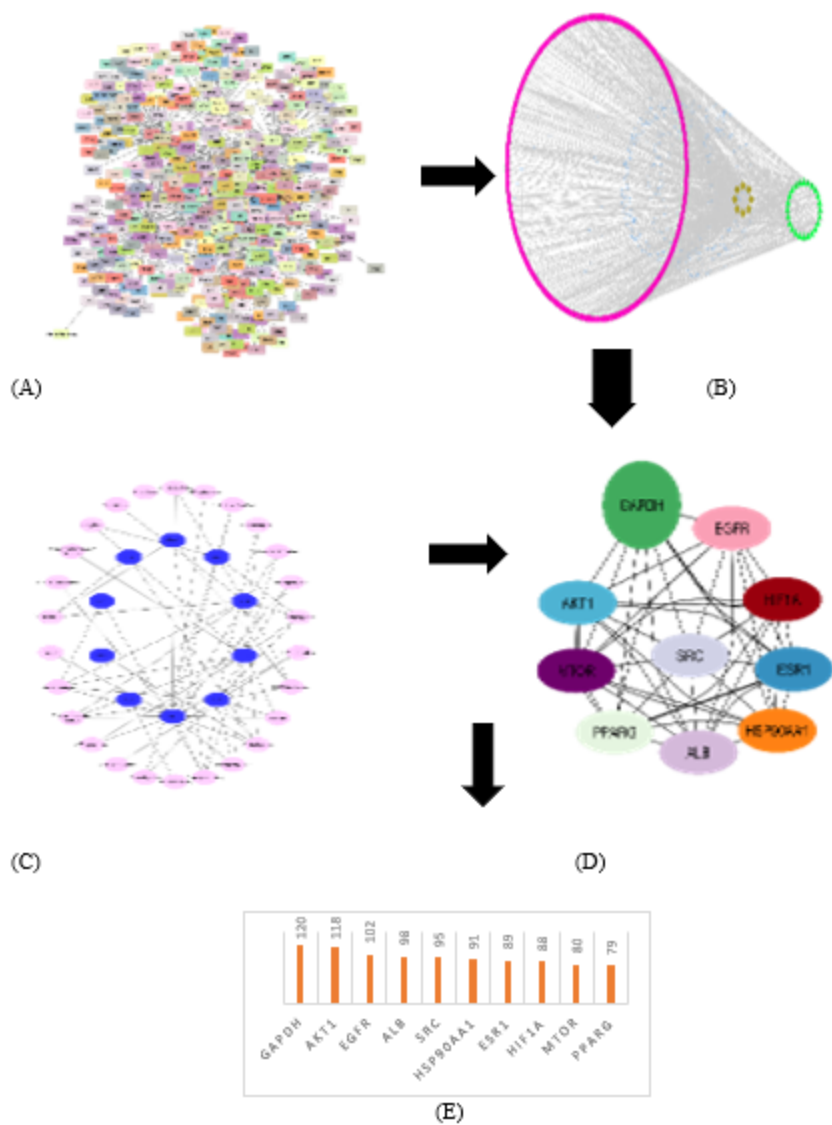
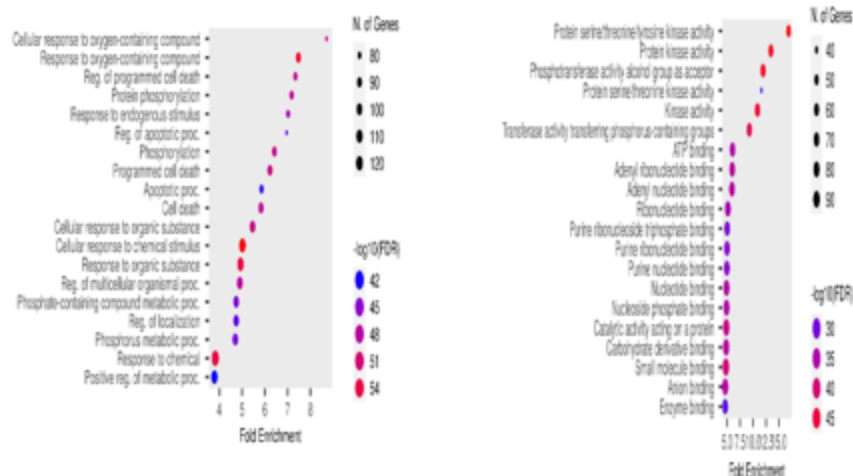


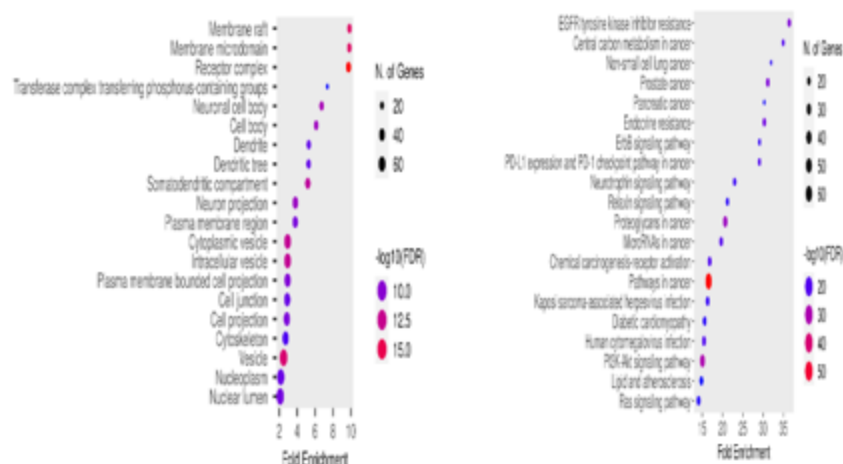
Figure 2

Network pharmacology based analysis of multi-targeted, and multi-pathway treatment for Parkinson disease. (A) network diagram of compound and their targets. (B) Network diagram of bioactive-pathway and their targets. (C) Network diagram of target genes-enrichment pathways. (D) Top 10 genes ranked by degree. (E) The bar plot of the PPI Network.



(A)

(B)



(C)

(D)

Figure 3

Indication of functional annotation and enrichment pathways in form of bubble plot. (A) GO in terms of Biological Processes. (B) GO in terms of Molecular Function. (C) GO in terms of Cellular Component. (D) KEGG pathway Analysis

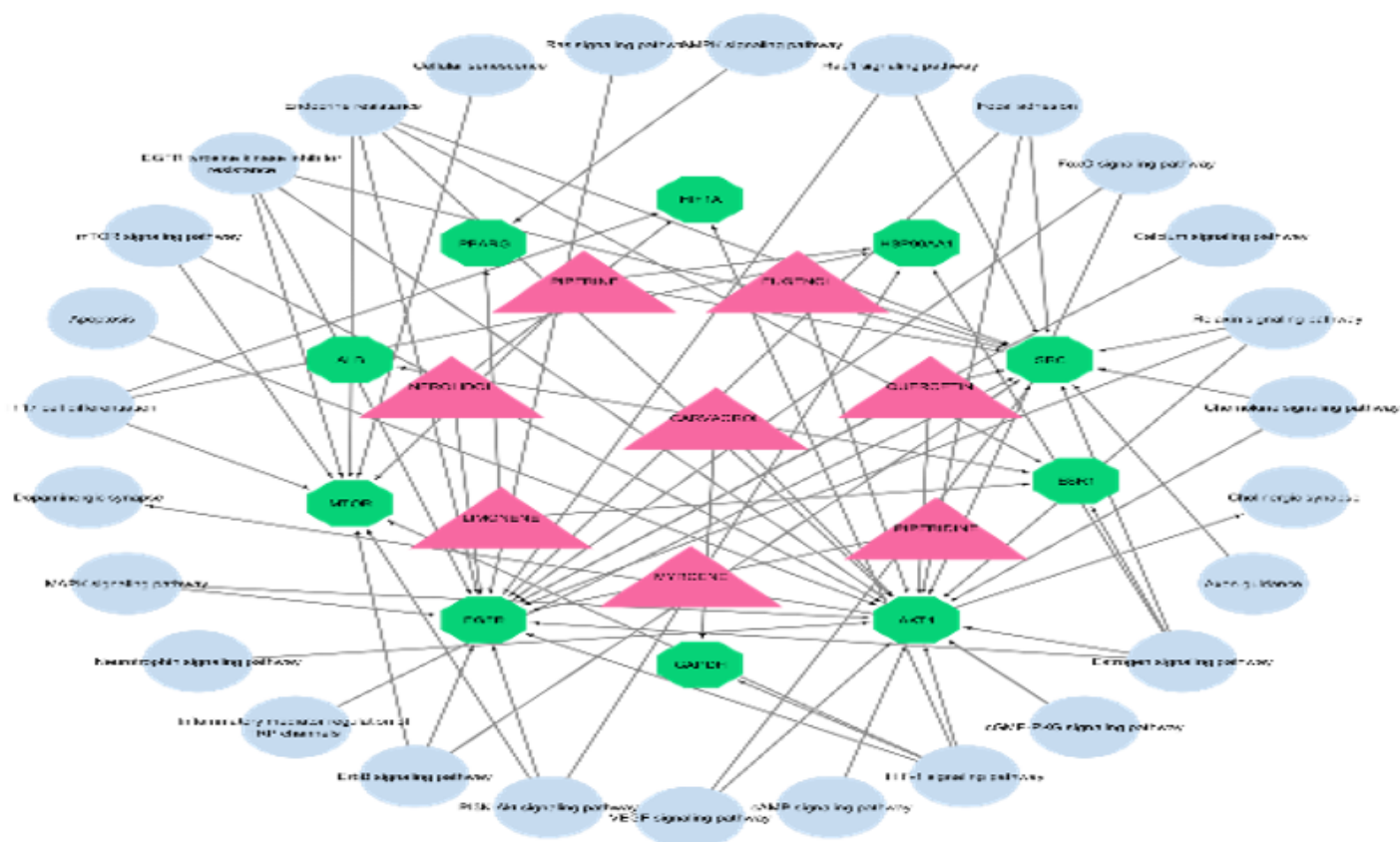


Figure 4

Pathways influenced by *Piper nigrum*, the green nodes represent the hub genes, the pink nodes represent the active compound, and light blue nodes are the pathways associated with the core targets.

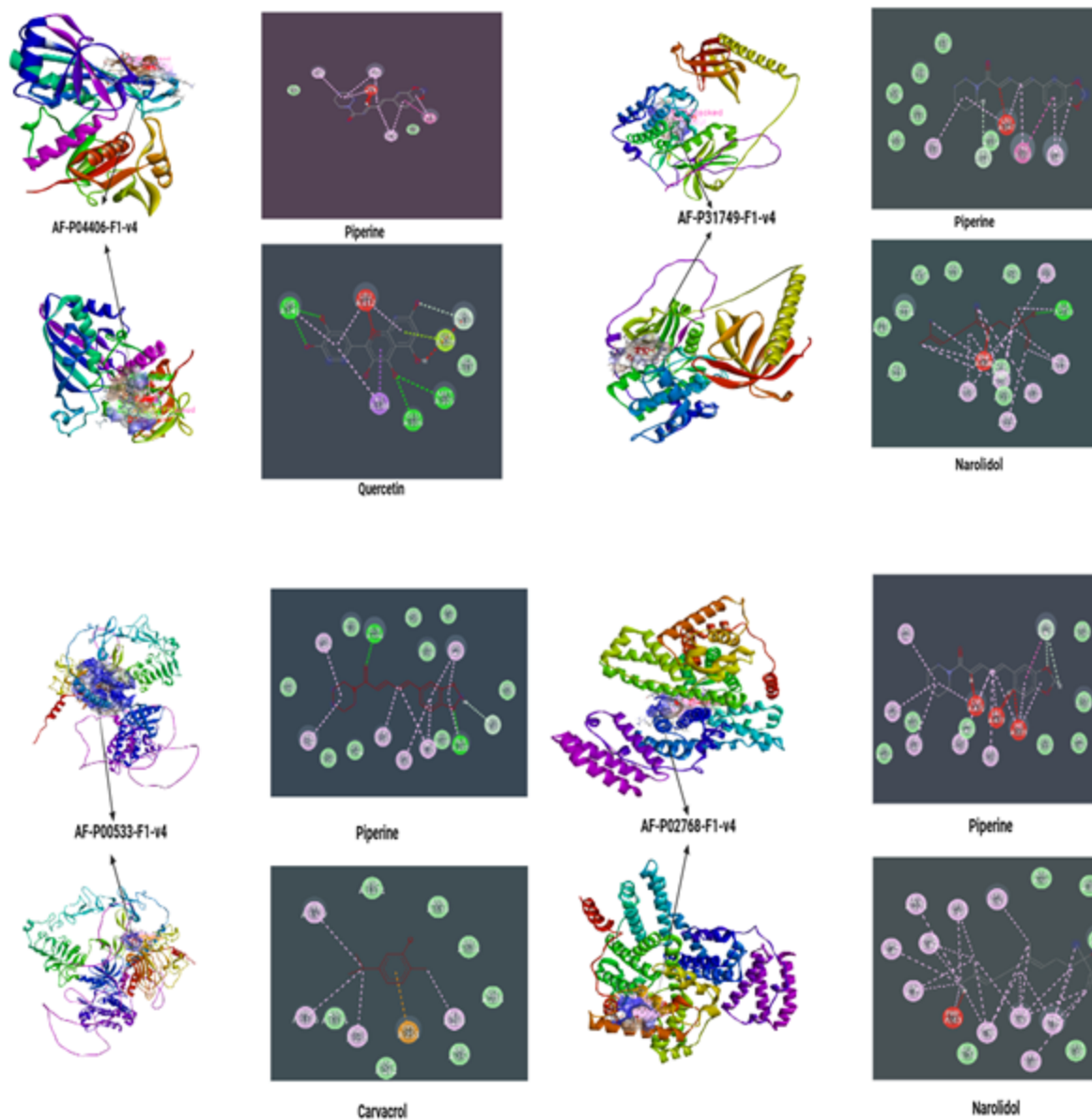


Figure 6

Binding energy and interactions of potential active compounds and their four target proteins.

Supplementary Files

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