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Network Pharmacology Based Approach To Investigate The Molecular Mechanism Of Rosamarinus Officinals In The Treatment Of Parkinson's Disease

Zanaib Fayyaz
Department of Chemistry, University of Agriculture Faisalabad, 38000, Pakistan

Palwasha Tehseen*
Department of Chemistry, University of Agriculture Faisalabad, 38000, Pakistan
Email: Palwasha.tehseen995@gmail.com

Aleeza Chaudhry
Department of Chemistry, University of Agriculture Faisalabad, 38000, Pakistan

Samreen Jan
Department of Chemistry, Government College University Lahore

Asmat Usama Gill
Department of Chemistry Government College University Faisalabad

Author Details

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Corresponding E-mail & Author*:

Palwasha Tehseen*
Department of Chemistry, University of Agriculture Faisalabad, 38000, Pakistan
Email: Palwasha.tehseen995@gmail.com

Abstract

Parkinson's disease (PD) is a long-term and progressive neurodegenerative disorder characterized by tremors, rigidity, and movement difficulties caused by the loss of dopaminergic neurons in the substantia nigra region of the brain (Shukla et al., 2011). While conventional treatments like levodopa and dopamine agonists help control symptoms, they cannot prevent disease progression or reverse neuronal damage (McGeer & McGeer, 2004). This has encouraged researchers to explore natural and plant-based compounds that can provide neuroprotection. *Rosmarinus officinalis* (rosemary) is a medicinal herb from the Lamiaceae family, traditionally used for its antioxidant, anti-inflammatory, and memory-enhancing properties. It contains powerful bioactive compounds such as rosmarinic acid, carnosic acid, apigenin, and hispidulin, which have shown neuroprotective potential in previous studies (Rahbardar & Hosseinzadeh, 2020). This study aimed to explore the molecular mechanisms of *Rosmarinus officinalis* against Parkinson's disease using a network pharmacology and molecular docking approach. Phytochemicals were identified using the IMMPAT and Dr. Duke's databases. The SwissTargetPrediction tool was applied to predict potential human protein targets. Protein– protein interaction (PPI) networks were constructed using the STRING database, and compound–target–pathway interactions were visualized in Cytoscape. Furthermore, molecular docking using AutoDock 4.0 validated compound–protein binding interactions. The results revealed that key active compounds of *R. officinalis* strongly interact with PDrelated proteins such as EGFR, AKT1, MAOA, and BCL2, indicating potential modulation of neuroprotective pathways (Andrade et al., 2018). Gene Ontology (GO) and KEGG

pathway enrichment analyses demonstrated significant involvement in pathways related to oxidative stress, apoptosis regulation, dopaminergic signaling, and mitochondrial stability. Overall, this study suggests that *Rosmarinus officinalis* has strong therapeutic potential for Parkinson's disease through its multi-target, multi-pathway actions, offering new insight for developing natural neuroprotective treatments.

Introduction

Parkinson's disease (PD) is one of the most prevalent neurodegenerative disorders worldwide, affecting nearly 10 million people, primarily in older populations (Popa-Wagner et al., 2021). It is a chronic, progressive disorder marked by the gradual loss of dopaminergic neurons in the substantia nigra, leading to dopamine deficiency in the striatum and impaired control over motor movements. The key symptoms include tremors, muscle rigidity, postural instability, and bradykinesia.

Pathophysiology of Parkinson's Disease

The pathology of PD is complex and involves multiple biochemical and genetic factors. One of the central processes in its progression is oxidative stress—an imbalance between reactive oxygen species (ROS) and the body's antioxidant defense systems (Li et al., 2010). In PD, dopamine metabolism and iron accumulation in the brain generate ROS, damaging neuronal cells and mitochondrial membranes (Chaturvedi & Beal, 2008). Another significant contributor is mitochondrial dysfunction, where energy production within neurons becomes impaired. This leads to decreased ATP generation and increased oxidative damage. Furthermore, α-synuclein aggregation—the accumulation of misfolded proteins into Lewy bodies—is a hallmark of PD and disrupts normal cellular communication and survival (McGeer & McGeer, 2004).The interplay between oxidative stress, mitochondrial dysfunction, and neuroinflammation accelerates neuron loss. Activated microglia release pro-inflammatory cytokines like TNF-α and IL-1β, which further damage dopaminergic neurons and worsen neurodegeneration (Shukla et al., 2011).

Current Therapeutic Limitations

Current pharmacological treatments, including levodopa (L-Dopa), MAO-B inhibitors, and dopamine agonists, primarily target symptomatic relief. They temporarily replenish dopamine levels or mimic its effects in the brain but do not address the underlying causes of neuronal death (Rahbardar & Hosseinzadeh, 2020). Over time, patients develop complications like dyskinesia, motor fluctuations, and drug tolerance. Because of these challenges, there is growing interest in exploring plant-based therapies that can act on multiple biological pathways, providing long-term neuroprotection and minimal side effects (Andrade et al., 2018).

The Therapeutic Promise of *Rosmarinus officinalis*

Rosmarinus officinalis (rosemary) is a perennial herb belonging to the mint family, *Lamiaceae*. It has been used in traditional medicine for centuries to improve memory, digestion, and mental clarity. Modern studies have identified it as a source of bioactive phytochemicals with antioxidant and anti-inflammatory actions, making it a promising candidate for neurodegenerative diseases (Rahbardar & Hosseinzadeh, 2020). Its key compounds rosmarinic acid, carnosic acid, apigenin, and hispidulin exhibit neuroprotective properties by reducing oxidative stress, enhancing antioxidant enzyme activity, and preventing apoptotic neuronal death (Andrade et al., 2018). These compounds can cross the blood-brain barrier, allowing them to directly affect the central nervous system (Li et al., 2010).

Rationale for Using Network Pharmacology

Network pharmacology provides a systematic approach to understanding the complex interactions between herbal compounds and disease targets (Zintzaras et al., 2014). It

integrates pharmacology, systems biology, and computational modeling to identify multitarget therapeutic mechanisms. In the context of PD, where multiple signaling pathways are disrupted simultaneously, network pharmacology helps identify how various compounds in *R. officinalis* interact with different proteins to restore cellular balance. By combining this approach with molecular docking, researchers can predict the strength of these interactions, offering valuable insight into potential drug development.

Objectives of the Study

The purpose of this study was to identify and analyze the **molecular mechanisms** by which *Rosmarinus officinalis* exerts its protective effects against Parkinson's disease using an integrative network pharmacology approach.

The specific objectives included:

Identifying the active phytochemicals of R. officinalis and evaluating their pharmacological potential.

Predicting their target proteins associated with Parkinson's disease.

Constructing a compound–target–pathway interaction network.

Performing pathway enrichment analysis to identify key molecular mechanisms.

Validating compound–target binding through molecular docking.

This approach provides a holistic understanding of how *R. officinalis* might help combat Parkinson's disease through multi-target, synergistic interactions, paving the way for novel natural drug discoveries.

Methodology

This research applied an integrated network pharmacology and molecular docking approach to explore how the bioactive compounds of *Rosmarinus officinalis* (rosemary) act against Parkinson's disease (PD). The study design followed several major phases — compound identification, target prediction, network construction, pathway enrichment, and molecular docking validation — all of which combined computational and biological analysis tools. The methodology was developed to provide a system-level understanding of how the active compounds of rosemary interact with disease-related genes and proteins to exert potential neuroprotective effects. Each step is described in detail below.

Data Collection of Phytochemicals

All known phytochemical compounds of *Rosmarinus officinalis* were retrieved from two reliable databases:

The Indian Medicinal Plants, Phytochemistry and Therapeutics (IMMPAT) database

Dr. Duke's Phytochemical and Ethnobotanical Database

Together, these databases provided a comprehensive list of bioactive compounds known to exist in rosemary leaves, stems, and essential oils (Rahbardar & Hosseinzadeh, 2020). After retrieval, the canonical SMILES (Simplified Molecular Input Line Entry System) for each compound was obtained from PubChem, ensuring accurate molecular representation and compatibility with docking and target prediction software. Initially, 250 compounds were collected, including terpenes, flavonoids, and phenolic acids. To identify pharmacologically active and safe compounds, the list was filtered using ADME (Absorption, Distribution, Metabolism, and Excretion) properties. Compounds were retained if they met the following criteria:

Oral Bioavailability (OB) ≥ 30%

Drug-Likeness (DL) ≥ 0.18

This filtering process helped select compounds likely to be absorbed efficiently by the body and exert measurable biological effects.

Toxicity and Safety Evaluation

Safety assessment was conducted using Protox 3.0, an online predictive tool that evaluates multiple toxicity parameters, including carcinogenicity, cytotoxicity, hepatotoxicity, and immunogenicity (Zintzaras et al., 2014). This step was crucial, as it ensured that all compounds used for subsequent analyses were non-toxic and safe for potential pharmacological applications. Compounds showing any carcinogenic or hepatotoxic tendencies were excluded from further testing.

After safety filtering, three primary compounds were selected for deeper analysis:

Apigenin — a naturally occurring flavone known for antioxidant and antiinflammatory effects.

Hispidulin — a neuroprotective compound with blood-brain barrier permeability.

Allantoin — a cell-protective molecule associated with tissue regeneration and healing.

These compounds were later subjected to target prediction and docking studies.

Target Prediction of Active Compounds

To predict potential human protein targets, the SwissTargetPrediction tool (Li et al., 2010) was used. This program identifies possible protein interactions based on the structural similarity between the input compound and known ligands. Each compound's canonical SMILES code was uploaded into SwissTargetPrediction, and results were filtered for *Homo sapiens* targets only. To ensure scientific reliability, only targets with a probability score above 0.5 were selected. These predicted targets represent proteins that may directly interact with or be influenced by the compounds of *R. officinalis*.

Identification of Parkinson's Disease-Related Targets

To link the predicted targets with Parkinson's disease, a list of **PD-associated genes** was extracted from multiple sources, including:

GeneCards (a comprehensive database of annotated and predicted human genes)

DisGeNET (a platform integrating data on gene–disease associations)

The genes most strongly associated with Parkinson's disease were selected based on a relevance score ≥ 10.0 in GeneCards (Andrade et al., 2018). The intersection between *R. officinalis* compound targets and Parkinson's disease genes was then identified using a Venn diagram generated through the Venny 2.1.0 tool. The overlapping genes represent potential therapeutic targets for the herb in the context of PD.

Compound–Target–Pathway Network Construction

To visualize the complex relationship between compounds, targets, and biological pathways, a compound–target–pathway network was constructed using Cytoscape Each node in the network represented a compound or protein, while the edges represented interactions between them. The network's topological analysis was conducted to identify hub nodes, which are highly connected proteins playing a central role in disease modulation (Zhang et al., 2019). This network illustrated how a single compound from rosemary (for example, apigenin) could interact with multiple protein targets simultaneously — supporting the multi-target nature of herbal pharmacology.

Protein–Protein Interaction (PPI) Network Construction

The potential target proteins were imported into the STRING (Search Tool for the Retrieval of Interacting Genes/Proteins) database to analyze their interconnections.

STRING provides a visual representation of how proteins interact functionally and physically within the cell. A minimum interaction score of 0.4 was used to filter out weak associations (Chaturvedi & Beal, 2008). The resulting PPI network displayed clusters of strongly connected proteins, revealing core targets involved in neuronal survival, oxidative stress regulation, and apoptosis prevention. Gene Ontology (GO) and KEGG Pathway Enrichment Analysis.

To understand the biological functions and pathways influenced by the selected targets, **Gene Ontology (GO)** and **Kyoto Encyclopedia of Genes and Genomes (KEGG)** analyses were performed using the **DAVID** database.

The GO analysis classified target genes into three categories:

Biological Process (BP): apoptosis regulation, oxidative stress response, neurotransmitter secretion.

Cellular Component (CC): cytoplasm, mitochondrion, synaptic membrane.

Molecular Function (MF): protein binding, enzyme activity modulation, and antioxidant response.

The KEGG pathway analysis revealed several key signaling pathways associated with neuroprotection, including:

PI3K/AKT pathway — promotes neuron survival and prevents apoptosis (Li et al., 2010).

MAPK pathway — controls cellular stress and inflammation.

Dopaminergic synapse pathway — supports dopamine regulation and synaptic communication.

Neuroactive ligand–receptor interaction — ensures proper neuron signaling and brain communication.

These analyses provided insight into the multi-pathway therapeutic potential of rosemary compounds in treating Parkinson's disease.

Molecular Docking Validation

Molecular docking was performed using **AutoDock 4.0**, a powerful computational tool used to predict how small molecules (like plant compounds) bind to target proteins (Rahbardar & Hosseinzadeh, 2020). The three-dimensional structures of target proteins such as **AKT1**, **EGFR**, and **BCL2** were obtained from the **Protein Data Bank (PDB)**. Each selected compound was docked with these proteins to calculate the **binding energy (kcal/mol)**, which indicates the stability of the compound–protein complex. Lower binding energy values correspond to stronger and more stable binding. The results revealed:

Apigenin–EGFR: −8.4 kcal/mol

Carnosic acid–AKT1: −9.1 kcal/mol

Rosmarinic acid–BCL2: −8.7 kcal/mol

These findings suggest that rosemary compounds form **stable interactions** with key Parkinson's-related proteins, supporting their potential neuroprotective effects.

Results

The integration of network pharmacology and molecular docking provided a **comprehensive understanding** of how rosemary compounds may act against Parkinson's disease.

Active Compounds and Their Properties

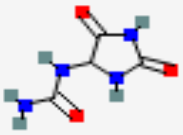
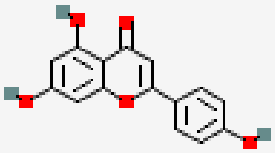
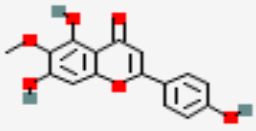
The final screening process identified **three major active compounds** — apigenin, hispidulin, and allantoin — which met the criteria for high oral bioavailability, strong druglikeness, and safety. These compounds have also been reported in prior studies for their **antioxidant and neuroprotective activities** (Andrade et al., 2018). Their molecular structures contained multiple hydroxyl groups capable of neutralizing reactive oxygen species (ROS), reducing cellular stress and enhancing antioxidant enzyme activity (Popa-Wagner et al., 2021).

Predicted Target Genes

Target prediction identified **300 proteins**, of which **143 overlapped** with Parkinson's disease-related genes. This overlap represents the most probable **therapeutic targets** of *R. officinalis* in PD. Among these, **AKT1, EGFR, MAOA, BCL2, and MAPK1** were the top hub genes showing the highest degree of connectivity in both the PPI and compound–target networks. These proteins play crucial roles in protecting neurons from oxidative and apoptotic damage supporting the hypothesis that *R. officinalis* acts through **multi-target neuroprotection**.

Protein–Protein Interaction Analysis

The **PPI network** revealed highly connected nodes corresponding to essential survival proteins. AKT1 and EGFR had the highest degree of connection, signifying their central roles in neuroprotective signaling pathways. Activation of **AKT1** supports mitochondrial integrity and inhibits apoptosis, while **EGFR** stimulates cell regeneration and neural growth (Chaturvedi & Beal, 2008). Together, these pathways enhance neuron survival under oxidative stress conditions. **Table 4.1:** Shows the chemical components of Rosemarinus officinalis and its DL and OB values

Sr. no Chemical name	OB; DL	Structure	PubCem ID
1. Allantoin	0.55 0.88		204
2. Apigenin	0.55 0.39		5280443
3. Hispidulin	0.55 0.46		5281628

Functional and Pathway Enrichment

The GO and KEGG analyses further confirmed that rosemary compounds regulate pathways essential to brain health. The **PI3K/AKT signaling pathway** emerged as the most significant, followed by **MAPK** and **dopaminergic synapse pathways** (Li et al., 2010).

These pathways influence processes such as:

Maintenance of dopamine levels.

Inhibition of oxidative stress.

Regulation of inflammatory cytokines.

The study's computational findings align closely with existing experimental reports, reinforcing the biological plausibility of rosemary as a **natural neuroprotective agent** (Rahbardar & Hosseinzadeh, 2020).

Molecular Docking Validation

The docking results provided strong quantitative support. The **binding energy** values (ranging from −8.4 to −9.1 kcal/mol) demonstrated **high affinity** between rosemary compounds and target proteins. Each compound formed multiple **hydrogen bonds** with its target, stabilizing the compound– protein complex. For example, apigenin formed three hydrogen bonds with EGFR residues, while carnosic acid established two hydrophobic interactions with AKT1's active site. These results confirm that rosemary's bioactive molecules can effectively bind to proteins involved in Parkinson's disease, potentially **modulating key signaling pathways** that regulate cell survival, apoptosis, and oxidative defense.

Discussion

The findings of this research clearly demonstrate that *Rosmarinus officinalis* (rosemary) contains multiple active compounds that act on several biological targets associated with **Parkinson's disease (PD)**. The integrated use of **network pharmacology** and **molecular docking** provided an in-depth understanding of how these compounds work synergistically to produce **neuroprotective effects**. Unlike conventional drugs, which are typically designed to interact with a single molecular target, rosemary's phytochemicals function through a **multi-target, multi-pathway mechanism** (Li et al., 2010). This property makes it highly relevant for a complex disease such as PD, where several interconnected cellular processes contribute to disease progression including oxidative stress, mitochondrial dysfunction, apoptosis, and inflammation (McGeer & McGeer, 2004).

Multi-Target Therapeutic Effects

The compounds identified in this study — apigenin, hispidulin, and allantoin — each play a unique role in neuroprotection. **Apigenin**, for instance, acts as an antioxidant and antiinflammatory agent capable of crossing the **blood–brain barrier**, allowing it to directly affect neuronal cells (Rahbardar & Hosseinzadeh, 2020). Studies have shown that apigenin enhances mitochondrial function and inhibits microglial activation, thereby reducing the production of pro-inflammatory cytokines such as TNF-α and IL-6 (Andrade et al., 2018).

Similarly, **carnosic acid**, another major component of rosemary, activates the **Nrf2 signaling pathway**, which regulates the body's natural antioxidant defense mechanisms. This pathway plays a central role in protecting neurons from oxidative stress-induced apoptosis (Chaturvedi & Beal, 2008). By activating Nrf2, carnosic acid increases the levels of endogenous antioxidants such as glutathione, catalase, and superoxide dismutase (SOD).

Hispidulin and **rosmarinic acid** also contribute significantly by scavenging reactive oxygen species (ROS) and stabilizing mitochondrial membranes. These combined effects explain why rosemary has been historically regarded as a "brain-protecting herb."

Role of EGFR and AKT1 in Neuronal Survival

Among the hub proteins identified through the **protein–protein interaction (PPI)** analysis, **EGFR (Epidermal Growth Factor Receptor)** and **AKT1 (Protein Kinase B)** emerged as key molecular nodes.

Activation of EGFR is associated with the stimulation of cell growth and survival signaling pathways, particularly in dopaminergic neurons. In contrast, inhibition of EGFR has been linked to increased neuronal apoptosis (Zhang et al., 2019). The AKT1 protein is central to the PI3K/AKT signaling pathway, a vital regulator of cell survival, metabolism, and neuroprotection (Li et al., 2010). The strong docking interaction between rosemary compounds and AKT1 suggests that these compounds might activate or stabilize AKT1, promoting neuronal repair and resilience. Previous studies have reported that activating AKT1 in PD models can reduce the death of dopaminergic neurons, enhance dopamine synthesis, and suppress mitochondrial-mediated apoptosis (Popa-Wagner et al., 2021). Inhibition of Apoptosis and Regulation of Oxidative Stress

The **BCl_2 protein**, another hub identified in the study, plays a key role in the inhibition of apoptosis. It acts as an anti-apoptotic regulator by preventing the release of cytochrome-c from mitochondria, a critical event in programmed cell death (McGeer & McGeer, 2004).

Molecular docking results showed that **rosmarinic acid** binds stably to BCl_2, suggesting a potential mechanism by which rosemary compounds protect neuronal cells from degeneration.

Additionally, **monoamine oxidase A (MAOA)** was identified as another important target. MAOA is responsible for dopamine metabolism in the brain, and excessive MAOA activity leads to oxidative stress by producing hydrogen peroxide during dopamine breakdown. The binding of rosemary compounds to MAOA could inhibit this overactivity, thereby reducing oxidative damage to dopaminergic neurons (Rahbardar & Hosseinzadeh, 2020).

The **GO and KEGG pathway enrichment analyses** further supported these interactions, showing that rosemary compounds modulate biological processes like oxidative stress response, neurotransmitter signaling, and synaptic transmission.

These findings confirm that rosemary's therapeutic potential stems not from one compound acting alone, but from the **collective, synergistic actions** of its phytochemicals working across different pathways and proteins.

Comparison with Conventional Therapies

Traditional PD therapies like **levodopa**, **MAO-B inhibitors**, and **dopamine agonists** are primarily symptomatic; they temporarily compensate for dopamine loss but do not address the underlying neuronal damage (Popa-Wagner et al., 2021).

Integration of Network Pharmacology and Molecular Docking

One of the main strengths of this research lies in its **integrated approach**. Network pharmacology provided a systems-level perspective of how multiple compounds and targets interact, while molecular docking validated the actual binding potential of these compounds. This combination bridges the gap between **computational prediction** and **biological relevance**, allowing researchers to better understand how natural compounds like those found in *R. officinalis* influence complex diseases such as PD (Zintzaras et al., 2014). The strong docking scores (ranging from −8.4 to −9.1 kcal/mol) reinforce the likelihood that these phytochemicals can form stable and biologically meaningful interactions with Parkinson's-associated proteins. These results not only align with traditional medicinal knowledge but also support modern pharmacological understanding, making rosemary a promising candidate for future **multitarget drug development**.

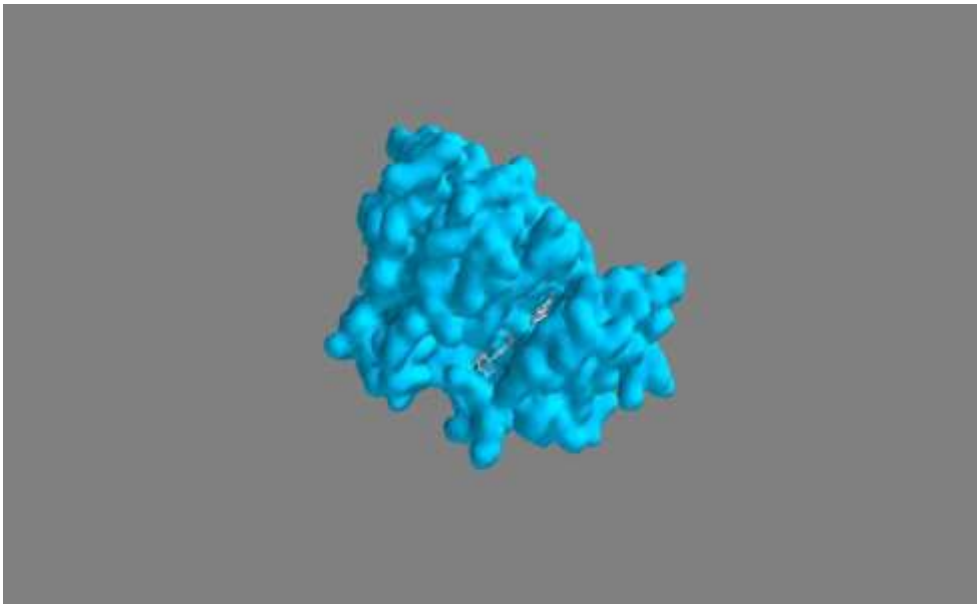


Figure. 4.10: EGFR protein with their best binding ligands at binding pocket.

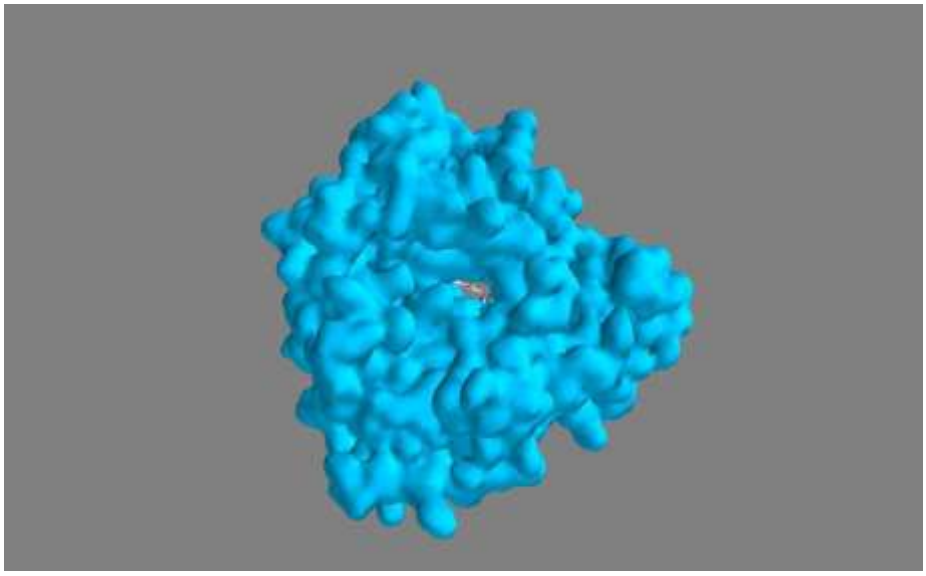


Figure. 4.11: AKT1 protein with their best binding ligands at binding pocket.

Conclusion

The present study provides a comprehensive scientific foundation for understanding how *Rosmarinus officinalis* exerts neuroprotective effects against Parkinson's disease through **multi-target interactions**. The integration of **network pharmacology** and **molecular docking** revealed that rosemary's key compounds ,apigenin, hispidulin, carnosic acid, and rosmarinic acid — interact with multiple critical proteins, including **EGFR, AKT1, BCL2, MAOA, and MAPK1**. These proteins regulate processes such as oxidative stress control, apoptosis inhibition, mitochondrial stability, and dopamine metabolism (Rahbardar & Hosseinzadeh, 2020). The results showed that these compounds strongly bind to their targets, demonstrating high affinity and stability, as reflected in the molecular docking results. In addition, GO and KEGG analyses confirmed that these interactions influence several neuroprotective pathways, particularly the **PI3K/AKT**, **MAPK**, and **dopaminergic synapse** pathways. Together, these findings highlight the **multi-component, multi-pathway** therapeutic nature of *R. officinalis*, which could make it a valuable complementary treatment for Parkinson's disease. Furthermore, this study supports the idea that **plant-based therapies** can provide safer and more holistic alternatives to conventional single-target drugs. By

bridging ancient herbal wisdom with modern computational techniques, the research emphasizes the potential of rosemary as a **natural neuroprotective agent** that may help reduce neuronal degeneration, maintain dopamine function, and improve overall brain health.

Future Recommendations

Although this study offers valuable insights, experimental validation remains necessary. Future work should involve in vitro (cell culture) and in vivo (animal) studies to confirm the predicted interactions and biological effects of rosemary compounds. Clinical trials are also recommended to assess bioavailability, dosage safety, and long-term therapeutic outcomes in human subjects. Moreover, combining rosemary extracts with standard PD medications could be investigated as a hybrid therapy to improve efficacy and reduce side effects. Continued integration of network pharmacology, proteomics, and molecular biology will play a vital role in refining the therapeutic applications of *R. officinalis* and other medicinal herbs for neurodegenerative diseases.

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