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# *In Silico* Exploration of *Jatropha integerrima* Against Alzheimer's Disease: A Network Pharmacology and Molecular Docking Study

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**ABSTRACT**

**OBJECTIVE:** To identify therapeutic targets and signaling pathways of *J. integerrima* for Alzheimer's disease using network pharmacology and molecular docking.

**METHODOLOGY:** Phytochemicals of *J. integerrima* were collected through a literature review. Targets for the *J. integerrima* compounds were identified using SwissTargetPrediction, while Alzheimer's disease-related genes were obtained from GeneCards and DisGeNET. A Venn diagram was constructed to find common targets. Gene Ontology and KEGG pathway analysis were performed by DAVID. Protein-protein network analysis was performed through Cytoscape. Molecular docking was performed using Schrödinger's GLIDE software.

**RESULTS:** A PPI network was constructed from 141 mutual targets of *J. integerrima* and Alzheimer's disease.10 highly interacting Hub genes were selected, including PPARG, PTGS2, STAT3, EGFR, CASP3, HIF1A, ESR1, MAPK3, MMP9, and MTOR. They were involved in phosphorylation, positive regulation of miRNA, and cellular response to hypoxia. Molecular docking revealed the highest docking scores of –8.01 kcal/mol and –7.22 kcal/mol for PTGS2 with the compounds Cubebol and Silphiperfol-6-ene, respectively.

**CONCLUSION:** In this study, seven anti-Alzheimer's phytochemicals were identified. Five genes, STAT3, PTGS2, CASP3, HIF1A, and EGFR, were found to be therapeutic targets based on their overexpression in Alzheimer's disease. Cubebol showed the highest docking score of –8.01 kcal/mol for PTGS2. However, further research is needed to confirm these findings.

**KEYWORDS:** *Jatropha integerrima*; Alzheimer’s disease; Network pharmacology; Molecular docking; Phytochemicals; Gene Ontology

## INTRODUCTION

Medicinal plants are important because people use them in traditional treatments. They draw attention to new drugs because of their naturally active chemicals. These chemicals, called secondary compounds, include flavonoids, alkaloids, saponins, terpenoids, and rotenoids. They help treat various diseases and are popular because they are often cheaper, easier to find, and safer[1].

*Jatropha integerrima (*peregrina*)* belongs to the Euphorbiaceae family. This plant has medicinal importance due to its anti-inflammatory properties and is used to treat eczema, blisters, and skin warts when administered orally or topically[2]. This plant also shows anti-inflammatory effects in microglia. *J. integerrima* also has antimicrobial, antimalarial, and antitubercular activities[1].

Alzheimer's disease is a neurodegenerative disorder caused by amyloid beta plaques and Tau neurofibrillary tangles[3]. It is characterized by a gradual decline in cognitive abilities, leading to dementia and loss of independence[4]. It is a complex disorder due to the involvement of multiple genetic and environmental factors. Generally, genetic factors include variations in the Amyloid precursor protein (APP), Presenilin 1 (PSEN1), and Presenilin 2 (PSEN2), which result in early-onset Alzheimer's disease. Genetic and environmental factors, such as exposure to chemicals, pesticides, and pollution, may contribute to the late onset of Alzheimer's disease[5]. Other factors also play an important role in Alzheimer's disease progression, including head injury, hypercholesterolemia, Diabetes, and Hypertension[6].

Additionally, research indicates that irregularities in molecular mechanisms contribute to the aggressive progression of Alzheimer's disease. These mechanisms include disrupted signaling pathways, abnormal protein formation, mitochondrial dysfunction, and chronic oxidative damage[7,8].

The prevalence of Alzheimer's disease increases significantly with age. According to the World Health Organization (WHO), approximately 50 million people worldwide are living with dementia, and Alzheimer's disease accounts for 60-70% of these cases[13]. In 2024, an estimated 6.9 million people aged 65 and older are living with Alzheimer's dementia in the United States[14]. In Pakistan, the age-standardized prevalence rate for Alzheimer's disease and other dementias has been estimated at approximately 433.6 per 100,000 population. According to 2021 statistics, 0.43% of the Pakistani population was affected with this disease, which emphasizes the urgent need for a cure or management[15]. Currently, the FDA-approved drugs for Alzheimer's treatment fall into two categories: cholinesterase inhibitors and N-methyl-D-aspartate receptor blockers. The cholinesterase inhibitors include Donepezil, Rivastigmine, physostigmine, metrifonate, and Galantamine[16]. N-methyl-Delta-Aspartate (NMDA) receptor antagonists include Memantine, Ketamine, Dextromethorphan, Phencyclidine, and Nitrous oxide.

However, these anti Alzheimer's drugs can only be used as symptomatic therapy and cause side effects, including gastrointestinal and cardiovascular issues[17]. These limitations of current therapies demand a safe alternative that delivers greater therapeutic benefit with fewer side effects.

Alzheimer’s disease is a complex, multifactorial disease that needs to be addressed through multi-target therapeutic approaches because the conventional drugs that mostly target a single molecular problem have been proven to be ineffective over the course of years. Recent advances in pharmacotherapy emphasized the need for a systematic approach that involves network pharmacology and biological experimental data to explore drug-target-disease interactions[18].

Network pharmacology is an *in-silico approach that helps explore the complex interactions among* drugs, targets, and disease networks to understand multi-target therapeutic mechanisms.

The key principle of network pharmacology is to construct a compound–target–pathway network that reveals the synergistic interactions and mechanisms of drug action[19]. Medicinal plants are being explored for their lower side effects, high efficacy, and cost-effectiveness.
This study aims to investigate the effect of *J. integerrima* on Alzheimer's Disease and to identify potential bioactive ingredients through in *silico* analysis. Molecular docking was also performed through Schrodinger's GLIDE to determine the protein-ligand complexes with the lowest docking scores.

## METHODOLOGY

### Identification of chemical compounds of *Jatropha integerrima*

All the chemical compounds of *J. integerrima* were searched through Google Scholar (https://scholar.google.com.pk) and PubMed (https://pubmed.ncbi.nlm.nih.gov) by using Keywords such as "chemical composition of *Jatropha integerrima"* and "*Jatropha integerrima* GC-MS analysis". After obtaining plant compounds, their canonical SMILES and 3D structures were retrieved from PubChem. Compounds were evaluated using the Lipinski rule of five and ADMET analysis via admetSAR (https://lmmd.ecust.edu.cn/admetsar2) and SwissADME (https://www.swissadme.ch/), with parameters including blood-brain barrier, carcinogenicity, drug-likeness, and oral bioavailability.

### Identification of compounds' targets and Alzheimer's disease genes

Canonical SMILES were used to predict the potential known targets of active compounds using SwissTargetPrediction (http://www.swisstargetprediction.ch/). *Homo sapiens* were selected as the target species. All the compounds' targets were imported into an Excel file. Alzheimer's disease-related genes were retrieved from GeneCards (https://www.genecards.org/) and DisGeNET (https://www.disgenet.com/). A Venn diagram (https://bioinformatics.psb.ugent.be/webtools/Venn) was constructed, and common genes between compound targets and disease genes were identified. These common genes were used for further analysis.

### Functional Annotation of Genes

Retrieved common genes were then imported into the DAVID database (https://david.ncifcrf.gov) for Gene Ontology annotation and functional enrichment analysis. Homo sapiens was selected as the target organism. DAVID analyzed gene lists and provided Functional annotation to predict biological process (BP), cellular component (CC), and Molecular Function (MF), as well as pathway analysis using the KEGG database. GO terms and KEGG pathways were selected based on probability scores ($p < 0.05$). Hiplot (https://hiplot.cn/) was used to visualize GO annotations and KEGG pathways.

### Network pharmacology analysis

### Construction of the PPI network and the Hub genes prediction

The protein-protein Interaction network was constructed through the STRING database (https://string-db.org/). Target genes were imported into the STRING database, and Homo sapiens was selected as the target species. The PPI network was visualized in Cytoscape (version 3.8.2; https://cytoscape.org/), and hub genes were identified using the CytoHubba plugin. The CytoHubba plugin included 12 topological methods; among them, the degree method was used to predict hub genes.

### Compound-Target network

The compound-target network was constructed through Cytoscape. The active compounds of *J. integerrima* and their corresponding disease targets were submitted to Cytoscape. Cytoscape produced results as network nodes, with associations between compounds and targets shown by connecting lines called "edges". The network analyzer was used to analyze the network, and the results were exported for visualization of node interactions.

**Construction of Target-Compound-Pathway Network**

The KEGG pathways were selected based on $p < 0.05$ in DAVID, and the Compound-Target-Pathway network was constructed in Cytoscape.

**Molecular docking**

Molecular docking was performed to evaluate the interaction between ligands and proteins. The technique is essential to calculate the effective interaction between compounds and proteins. The Hub genes were selected based on a high degree of score and their expression in Alzheimer's disease. The protein structures of hub genes were downloaded from AlphaFold (https://alphafold.ebi.ac.uk), and 3D structures of compounds were downloaded in the SDF format from PubChem. Molecular docking was performed with Schrödinger's GLIDE software, where receptor grids were constructed, and docking scores were calculated using the Lamarckian genetic algorithm. The docked protein–ligand complexes were subsequently analyzed through Discovery Studio Client 2024.

## RESULTS

Twenty-six active compounds of *J. integerrima* were identified after removing the duplicate compounds collected from the literature. After applying the Lipinski rule of five and ADMET analysis on these compounds, only 7 active compounds were finalized for further analysis (**Table I**).

**Table I: Lipinski Rule of Five and ADMET Analysis parameters for active compounds of *J. integerrima***

| Compounds names | MW ≤ 500Da | nHA ≤10 | nHD ≤5 | logP ≤5 | nRot ≤10 | BBB permeability ≥0.3 | Ames Toxicity ≤1 | Carcinogenicity ≤1 |
|---|---|---|---|---|---|---|---|---|
| Silphiperfol-6-ene | 204 | 0 | 0 | 4.76 | 0 | 0.99 | 0.38 | 0.62 |
| Cubebol | 222 | 1 | 1 | 4.14 | 1 | 0.45 | 0.20 | 0.62 |
| (E)-Ferulicacid methyl ester | 208 | 4 | 1 | 2.30 | 4 | 0.02 | 0.70 | 0.42 |
| Coumarin | 204 | 0 | 0 | 4.76 | 0 | 0.99 | 0.38 | 0.62 |
| Flavone | 222 | 1 | 1 | 4.14 | 1 | 0.45 | 0.20 | 0.62 |
| Hexadecenoic acid methyl ester | 208 | 4 | 1 | 2.30 | 4 | 0.02 | 0.70 | 0.42 |
| Pentadecanal | 204 | 0 | 0 | 4.76 | 0 | 0.99 | 0.38 | 0.62 |

## Network pharmacology analysis

### Identifying potential targets

SwissTargetPrediction revealed 669 targets of 7 active compounds of *J. integerrima.* The Alzheimer's disease targets identified through GeneCards and DisGeNET were 14317 and 3398, respectively. A Venn diagram was constructed between all the mentioned targets of active compounds and Alzheimer's disease. The Venn Diagram showed 141 potential common targets of *J. integerrima* for Alzheimer's disease (**Figure 1**).

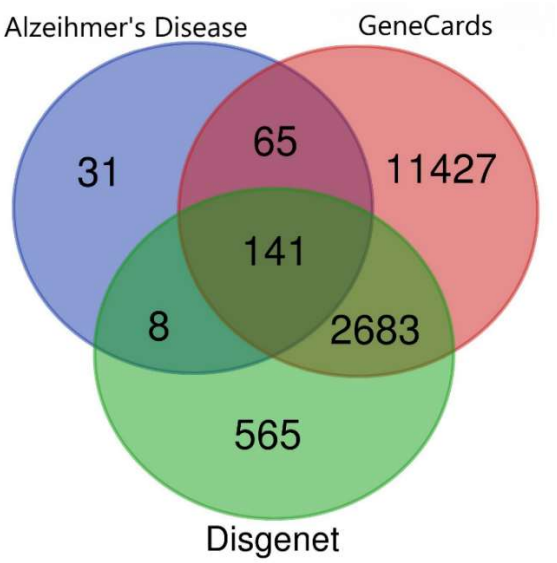


**Figure 1: Venn diagram showing 141 common targets of Alzheimer's disease**

### Analysis of Protein-Protein Interaction Network

Protein-protein interaction analysis was done by Cytoscape. The generated PPI network had 141 nodes and 1256 edges. Using the CytoHubba plugin, the PPI network was further analyzed to identify hub genes. The top 10 hub genes with the highest degree values were: PPARG (65). PTGS2 (64), STAT3 (62), EGFR (61), CASP3(60), HIF1A (58), ESR1(58), MAPK3(54), MMP9(50) and MTOR (49).

### Compound-Target network

A compound-target network of 141 potential targets and 7 active compounds from *J. integerrima* was constructed in Cytoscape. The compound-target network helped analyze interactions between active compounds and potential targets. In Cytoscape, the "network analyzer" provided the interactions as "nodes" and "edges" (**Figure 2**). The degree score in Cytoscape indicates how many interactions each node has with other nodes in the network. A higher degree score indicates higher interactions with other nodes. Benzopyrones and Terpenoids had higher degree values than flavonoids and the other class categories (**Table II**).

**Table II: Degree of seven active compounds analyzed through Cytoscape**

| Compounds | Class categories | Degree |
|---|---|---|
| Coumarin | Benzopyrones | 63 |
| Silphiperfol-6-ene | Terpenoids | 63 |
| Cubebol | Terpenoids | 57 |
| Flavone | Flavonoids | 53 |
| (E)-Ferulic acid methyl ester | Phenol/phenylpropanoids | 50 |
| Hexadecenoic acid methyl ester | Fatty esters | 50 |

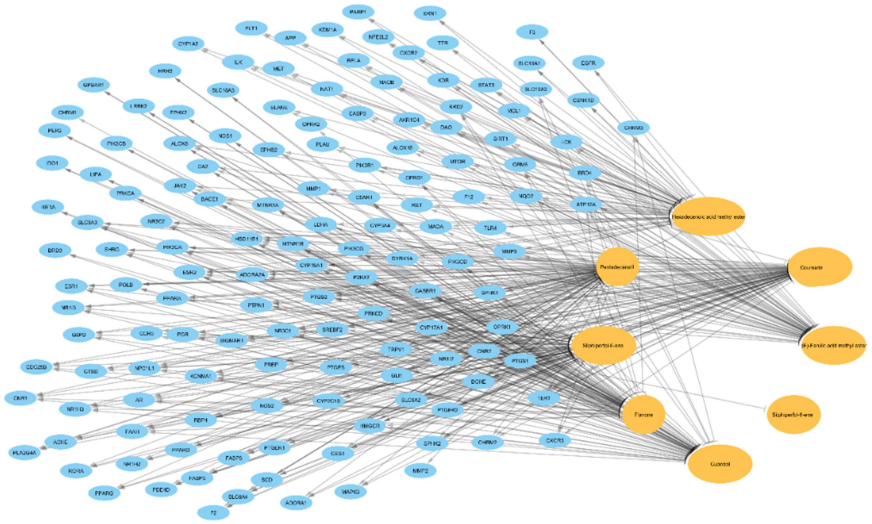

**Figure 2: Compound Target network; Blue color nodes are disease targets, while yellow color nodes are active compounds of *J. integerrima***

**KEGG pathway and GO analysis**

Gene ontology and Enrichment pathway analysis were performed for 141 gene targets. The generated results showed 456 Biological processes, including Inflammatory response, Phosphorylation, Response to lipopolysaccharide, Intracellular receptor signaling pathway, and many more; 70 cellular components (CC), including Plasma membrane, Presynaptic membrane, Dendrite, Cytoplasm, and Receptor complex; 123 Molecular Functions (MF), including nuclear receptor activity, Enzyme binding, Identical protein binding, and Steroid binding. Likewise, KEGG analysis showed 148 pathways. By categorizing Go annotations and KEGG pathways according to $p < 0.05$, the top 20 Gene functional annotations and enrichment pathways were selected (**Figure 3**).

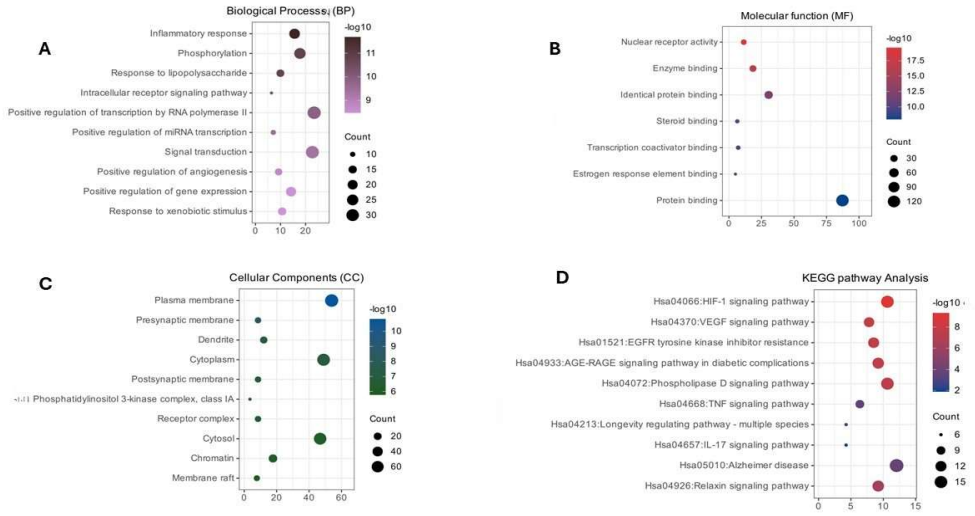


**Figure 3: Bubble Map of GO and KEGG pathway Analysis: (A) Biological processes; (B) Molecular Function (MF); (C) Cellular components (CC); (D) KEGG Pathway**

## Compound-Target-pathway Network Analysis

KEGG pathways were selected based on 141 common targets using the DAVID database. The network was constructed by 141 common targets, 85 KEGG pathways, and seven active compounds of *J. integerrima* through Cytoscape. The compound-target-pathway network displayed gene interactions in enriched pathways. The network was analyzed using the "Network Analyzer," which revealed 233 nodes and 1126 edges (**Figure 4**).

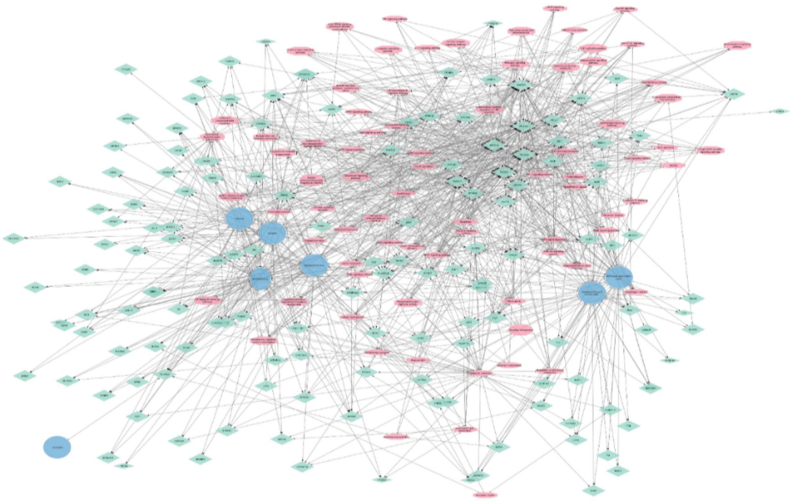

**Figure 4: Compound Target Pathway; Round Blue shapes represent active compounds of *J. integerrima*, Diamond-shaped green color nodes are targets, and pink color nodes represent interacting pathways.**

**Molecular Docking**

Molecular docking is an *in-silico technique that provides docking scores that quantify the strength of molecular interactions*. Molecular docking was performed between seven active compounds of *J. integerrima* with five potential targets overexpressed in Alzheimer's disease (**Table III**). The lowest docking score corresponds to the highest binding affinity to target proteins. The Cubebol and Silphiperfol-6-ene showed the lowest docking scores for PTGS2, -8.006 kcal/mol and -7.22 kcal/mol, respectively (**Figure 5**).

**Table III: Docking scores (kcal/mol) of active compounds against key Alzheimer's targets. The most negative (best binding affinity) score is highlighted in bold text**

| Compounds | Casp-3 (kcal/mol) | EGFR (kcal/mol) | HIF1A (kcal/mol) | PTGS2 (kcal/mol) | STAT3 (kcal/mol) |
|---|---|---|---|---|---|
| (E)-Ferulic acid methyl ester | -3.349 | -3.835 | -3.207 | -4.743 | -5.29 |
| Coumarin | -5.13 | -5.372 | -3.318 | -4.126 | -4.248 |
| Cubebol | | -4.254 | -3.332 | **-8.006** | --5.294 |
| Flavone | -4.592 | -4.505 | -3.326 | | -5.514 |
| Pentadecanal | 1.39 | 1.485 | 2.696 | 0.99 | 0.646 |
| Hexadecenoic acid methyl ester | 1.085 | 1.747 | 2.085 | | 0.717 |
| Silphiperfol-6-ene | -5.411 | -4.368 | -3.375 | **-7.22** | -4.537 |

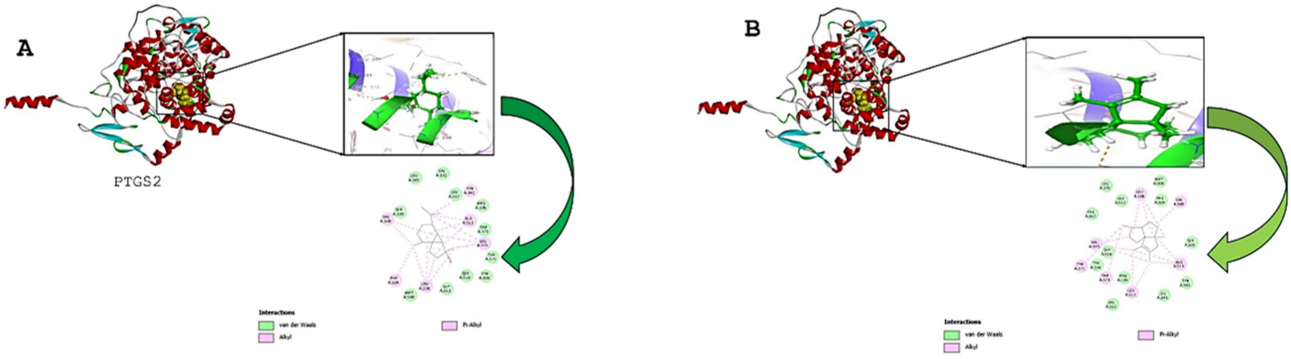


**Figure 5: Docking complex with ligand binding on the active site of protein: (A) PTGS2 with Cubebol; docking score (-8.0 kcal/mol). (B) PTGS2 with Silphiperfol-6-ene; docking score (-7.22 kcal/mol).**

## DISCUSSION

Medicinal plants are widely used for their therapeutic potential. They have been considered as an effective alternative to conventional medicines[20]. Several studies have shown that many countries use medicinal plants as first-line treatment for complex disorders[21]. Network pharmacology provides a practical approach to multi-target Drug discovery by combining experimental analysis with *in-silico* calculations[22]. Nowadays, Network pharmacology is preferred because it screens active compounds through ADMET and their interactions with multiple targets within biological networks, as compared to standard drug development methodologies[1,23]. It particularly involves phytochemical screening, key target predictions, and molecular pathway analysis, making this strategy significant for studying multifactorial diseases, where gene targets, enriched pathways, and processes are closely associated[24].

Alzheimer's disease is a complex disorder, as it involves the dysregulation of multiple genes[25]. Current drug therapies are unable to reverse the progression of Alzheimer's disease and only provide supportive therapy to control symptoms[26]. This promotes the search for effective therapy against Alzheimer's disease to cope with these issues. Because of their lower side effects, cost-effectiveness, and therapeutic potential, medicinal plants can be investigated for anti-Alzheimer's activity[1,23].

Medicinal plants with anti-inflammatory properties are also known to have anti-neurodegenerative effects against Alzheimer's disease[27]. The neuroprotective effects of these medicinal plants disrupt the cycle of oxidative damage, inhibit the overactivation of microglia and astrocytes, and regulate cell signaling which is essential to the normal functioning of neurons[28].

*Jatropha integerrima* is considered a medicinal plant due to its antimicrobial, antimalarial, anti-inflammatory, and antituberculosis activities[2]. It is a rich source of phytochemicals, including benzopyrones, flavonoids, terpenoids, and phenols. This study on the screening of active compounds from Jatropha integerrima will provide preliminary work that may lead to the development of a drug against Alzheimer's disease after further research.

According to GO annotation results, *J. integerrima* targets against Alzheimer's disease were mainly found at the cell surface, in the plasma membrane, the cytoplasm, and the postsynaptic membrane.

They are chiefly involved in phosphorylation, positive regulation of miRNA, and cellular responses to hypoxia. Phosphorylation activity is directly related to maintaining cellular function, and a lack of phosphorylation contributes to many diseases, including neurodegenerative diseases, diabetes, and cancer[29]. Cellular response to hypoxia, as hypoxia is known for its impact on innate and adaptive immunity through hypoxia-inducible factors (HFs)[30]. They enhance immune response by facilitating the migration of CD4+, CD8+, and other immune cells[31]. Around 27 miRNAs are involved in Alzheimer's disease progression; positive regulation of miRNAs could prove an effective way to reduce disease progression[32,33]. Key targets of *J. integerrima* are also involved in cholesterol homeostasis, as studies suggest that poor cholesterol metabolism can be largely responsible for Alzheimer's disease progression[34]. The target genes of *J. integerrima* may play a significant role in the treatment of Alzheimer's disease by negatively regulating inflammatory responses[35].

The abnormal accumulation of amyloid-β, tau hyperphosphorylation, and synaptic dysregulation are revealed to result from underlying disruptive molecular mechanisms, such as hyperactivation of the neuroinflammatory signaling pathways[36]. Multi-target drug development is essential to regulate these pathways[37]. The exploration of multiple inflammatory targets in this study

emphasizes that J.integrrima does not act on a single target but on multiple closely related pathways simultaneously[38].

KEGG pathway analysis showed that multiple genes in *J. integerrima* contributed significantly to Alzheimer's disease-related pathways. In this study, Alzheimer's disease is the primary targeted pathway, and 7 target genes of *J. integerrima*, including APP, RELA, MAPK3, CASP3, MTOR, PIK3CA, and PTGS2, are involved in this pathway. Other enrichment pathways related to Alzheimer's disease included the EGFR tyrosine kinase inhibitor resistance pathway, the HIF-1 signaling pathway, and the Relaxin signaling pathway. Studies show that EGFR upregulation causes neurotoxicity and neuroinflammation, and the use of EGFR tyrosine kinase inhibitors could relieve Alzheimer's disease symptoms[39]. Target genes of *J. integerrima* are also involved in the Relaxin signaling pathway, as Relaxin receptors are known to regulate senescence-related disorders such as dementia, stress, and anxiety[40]. In the HIF-1 signaling pathway, hypoxia inducible factor 1α performs angiogenesis to reverse the effect of a lack of oxygen[41]. It acts as a neuroprotective agent by reducing the formation of Amyloid βeta plaques and suppressing the hyperphosphorylation of tau[42]. The exploration of KEGG pathways revealed target genes involved in various metabolic pathways. Specific genes of these metabolic pathways can be targeted to prevent disease.

Through molecular docking, seven screened active compounds of *J. integerrima* were docked with five key targets based on their expression in Alzheimer's disease. Among the hub genes (categorized by degree), only upregulated genes were selected for analysis. According to research, PTGS2[43], STAT3[44], EGFR[45], CASP3, and HIF1A[46] are overexpressed in Alzheimer's disease. PPARG[47] and ESR1[33] were revealed to be suppressed during Alzheimer's disease progression.

Network analysis was performed for all seven active compounds of the plant against five key targets, yielding the highest binding affinities for Terpenoids. Cubebol and Silphiperfol-6-ene both belong to Terpenoids and could bind with PTGS2 to suppress Alzheimer's disease. Flavonoids, Benzopyrones, and Phenols docking scores also suggested high binding affinity with STAT3, EGFR, and CASP3, respectively (**Table III**). This study explains the active compounds of plants, the mutual targets of plants and disease, and the respective pathways for treating Alzheimer's disease. This study particularly suggests the therapeutic effect of *J. integerrima* against Alzheimer's disease by targeting key disease targets, thereby providing a paradigm for further investigation.

## CONCLUSION

This study provides a scientific basis for identifying multi-target compounds for the treatment of Alzheimer's disease. Potentially active seven compounds of *J. integerrima* were identified, and their targets against Alzheimer's disease were determined. Moreover, network analysis suggested that STAT3, PTGS2, CASP3, HIF1A, and EGFR may be potent therapeutic targets for Alzheimer's disease. However, the present study has some limitations, and further investigation is needed to confirm the findings.

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**Data Sharing Statement:** The corresponding author can provide the data proving the findings of this study on request. Privacy or ethical restrictions bound us from sharing the data publicly.

## AUTHOR CONTRIBUTION

Shahid S: Methodology, formal Analysis, writing original draft
Faisal S: Formal Analysis
Tariq M: Methodology
Khan MA: Supervision, Validation
Bhatti R: Conceptualization, Supervision, Writing original draft, Validation

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