RESEARCH PAPER

Multi-Target Therapeutic Potential of Wrightia Tinctoria Against Alzheimer's Disease Revealed Through Integrated Network Pharmacology and Molecular Docking

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ABSTRACT
Alzheimer's disease (AD) is a progressive neurodegenerative disorder mainly associated with cognitive impairment, memory loss, and neuronal degeneration. Since AD involves multiple genes, proteins, and signalling pathways, multi-target approaches are being explored for its treatment. In this study, the therapeutic potential of Wrightia tinctoria against AD was investigated using network pharmacology and molecular docking. A total of 27 unique phytochemicals were obtained from the IMPPAT database, and 25 compounds passed the Lipinski's Rule of Five criteria in SwissADME. Swiss Target Prediction identified 373 protein targets, among which 334 targets overlapped with AD-related genes obtained from OMIM and GeneCards. A protein-protein interaction network was then developed using STRING and examined using the CytoHubba plugin in Cytoscape. AKT1, TNF, CTNNB1, SRC, BCL2, HSP90AA1, EGFR, HIF1A, PPARG, and ESR1 were identified as the top 10 hub genes. Gene Ontology and KEGG enrichment analysis showed their involvement in neuroinflammation, apoptosis, estrogen signalling, and HIF-1 signalling pathways. Molecular docking through CB-Dock2 produced binding affinities between 6.1 and 10.1 kcal/mol. Cycloartenone showed the highest affinity for HSP90AA1, with a binding score of -10.1 kcal/mol. Overall, the results indicate the multi-target potential of Wrightia tinctoria against AD and support further experimental studies.

Keywords: Therapeutic Potential, Wrightia Tinctoria, Alzheimer's Disease, Integrated Network Pharmacology, Molecular Docking.

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INTRODUCTION:

The most common cause of cognitive decline and dementia among older adults is Alzheimer's disease, which primarily affects people aged and above. It is a slowly progressing neurodegenerative disease in which changes begin to develop in the brain many years before any obvious symptoms appear. As the condition progresses, a person may gradually experience problems with memory, thinking, behaviour, and other cognitive abilities. Worldwide, currently 24 million people were affected by Dementia, and this prevalence is expected to double every 20 years until 2040, placing a substantial burden on healthcare systems globally. The interconnected biological processes that destroy neural cells drives the pathophysiology of AD. Formation of amyloid plaques, resulting from the accumulation of amyloid-beta (AB) peptides which stemmed from the breakdown of the amyloid precursor protein (APP) is the hallmark feature of this. By activating immune cells these plaques trigger neuroinflammation which releases harmful reactive oxygen species and inflammatory molecules that further damage nerve cells. The abnormal hyperphosphorylation of tau proteins simultaneously forms neurofibrillary tangles inside neurons which disrupt the cell function and precipitating neuronal death. Acetylcholinesterase inhibitors (e.g., Donepezil, Galantamine, Rivastigmine), which is the current treatment for AD primarily offers temporary

symptomatic relief by enhancing cholinergic activity however they fail to halt underlying disease progression because of ongoing oxidative stress and inflammation. Anti-amyloid monoclonal antibodies (e.g., lecanemab, aducanumab) which was newly approved by FDA have shown modest slowing of cognitive decline yet they are often associated with side effects such as brain swelling and fail to address the highly multifactorial mechanisms of the disease.

Wrightia tinctoria, a small deciduous tree of the Apocynaceae family, has been substantially used in traditional medicine. Flavonoids, alkaloids, steroids and terpenoids are its phytochemical composition which lends significant antioxidant, anti-inflammatory and neuroprotective properties. Despite of all these properties, the specific molecular mechanisms underlying the therapeutic effects of Wrightia tinctoria against Alzheimer's disease remain largely unexplored.

Network pharmacology offers a systems-based way to understand how a drug can act on multiple biological targets and influence different disease-related pathways. Unlike the traditional 'one drug, one target' approach, it helps provide a more comprehensive picture of how drugs work within the complex biological network of the body. This study aims to make use of integrated network pharmacology, functional enrichment analysis and molecular docking which identifies systematically, the bioactive compounds in Wrightia tinctoria predicts their targets and elucidate their potential multi-target neuroprotective mechanisms against Alzheimer's disease.

MATERIALS AND METHODS:

2.1 Collection of phytochemical constituents:

Through an extensive literature survey and the Indian Medicinal Plants, Phytochemistry and Therapeutics (IMPPAT) database (version 2.0) the phytochemical constituents of Wrightia tinctoria were collected. To compile a comprehensive, non-redundant dataset, duplicate compounds were removed. The canonical SMILES for all unique compounds were retrieved from the PubChem database for computational analysis.

2.2 Drug-Likeness and ADME Screening:

By using the SwissADME web server, the selected phytochemicals underwent pharmacokinetic evaluation. Based on Lipinski's Rule of Five, drug-likeness was primarily assessed. The additional parameters, including gastrointestinal absorption, blood-brain barrier (BBB) permeability, oral bioavailability and synthetic accessibility, were analysed to filter out compounds that lacked acceptable drug-like characteristics.

2.3 Prediction of Phytochemical Targets:

The potential molecular targets of the screened drug-like phytochemicals were predicted using the SwissTarget Prediction database. Based on chemical similarities, the canonical SMILES were used as input to predict human protein targets. The predicted targets were standardized to official human gene symbols utilizing the UniProt Knowledgebase (UniProtKB), and duplicate entries were removed to create a unique target dataset.

2.4 Identification of Alzheimer's Disease-Associated Genes:

From the Online Mendelian Inheritance in Man (OMIM) and GeneCards databases Alzheimer's disease-associated genes were retrieved to define the disease landscape. To establish a comprehensive AD gene dataset, duplicate genes across databases were eliminated.

2.5 PPI Network Construction and Hub Gene Identification

Using VENNY, the overlapping targets between the predicted phytochemical genes and the AD-associated genes were identified and by using STRING database (Version 12.0), these common genes were mapped targeting Homo sapiens with a confidence score threshold of ≥ 0.40 to construct a protein-protein interaction (PPI) network. For visualizing, Cytoscape (Version3.10) was used. The CytoHubba plugin was employed to identify core hub genes using topological algorithms including Degree Centrality, Maximum Clique Centrality (MCC), Maximum Neighbourhood Component (MNC), Closeness Centrality, and Betweenness Centrality.

2.6 Functional Enrichment Analysis

The execution of analysis of Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment were undergone while using the ShinyGO database. Categorization of genes into Biological Process (BP), Cellular Component (CC), and Molecular Function (MF) with a significance threshold set at $p < 0.05$ were done in GO analysis.

2.7 Molecular Docking and Survival Analysis

The 3D crystal structures of hub proteins were retrieved from the Protein Data Bank (PDB) and prepared by removing water molecules and adding Kollman charges and by using MMFF94 force field Ligand structures were energy-minimized. Through the CB-Dock2 server (integrating AutoDock Vina), Molecular docking was performed to calculate binding energies (kcal/mol) and interaction profiles. The clinical significance of the hub genes was cross-validated finally through Kaplan-Meier survival analysis using the UALCAN database.

RESULTS:

3.1 Identification and ADME Screening of Phytoconstituents

27unique phytochemicals followed by duplicates were advanced form IMPPAT database by an initial retrieval of 38 phytochemicals. 25 out of these 27 compounds successfully satisfied Lipinski's Rule of Five which was revealed through subsequent ADME screening, exhibiting excellent physicochemical parameters required for oral drug-likeness. Key retained compounds included Cycloartenone, Oleanolic acid, Quercetin, Fucosterol, Desmosterol, and Ursolic acid. To ensure the

reliability of downstream in silico screening, [Table 3.1], the two compounds were excluded which presented multiple Lipinski violations.

3.2 Prediction of Targets and Target Intersection

The 25 compliant phytochemicals were submitted to SwissTargetPrediction, initially generating 2,500 predicted protein targets. 373 unique target genes were modulated by Wrightia tinctoria and was established after duplication. Concurrently, disease target collection yielded 546 unique AD-genes from OMIM and 17,324 targets from GeneCards. Integration resulted in a comprehensive dataset of 17,741 AD-associated genes. An overlap of 334 common therapeutic targets between the plant's predicted genes and AD disease genes were identified by Venny diagram analysis. [Figure3.2]

3.3 PPI Network Construction and Hub Gene Identification

The 334 intersecting target genes were imported into the STRING database, generating a highly interconnected PPI network consisting of 329 nodes and 4,376 edges and this dense interconnectivity implies extensive functional interactions among the therapeutic targets. [Figure 3.3a] Through the CytoHubba plugin, topological analysis isolated the top 10 most influential hub genes regulating the network: AKT1, TNF, CTNNB1, SRC, BCL2, HSP90AA1, EGFR, HIF1A, PPARG, and ESR. These hub genes show the strongest interactions within the network and play key roles in regulating important cellular processes, including cell survival, neuroinflammation, apoptosis, and oxidative stress. [Figure3.3b]

3.4 Gene Ontology and KEGG Pathway Enrichment

The GO Biological Process (BP) analysis demonstrated significant enrichment in the regulation of apoptotic signalling pathways, response to oxidative stress, regulation of smooth muscle cell proliferation, and positive regulation of protein localization. Cellular Component (CC) enrichment located these targets heavily in neuronal structures, specifically the dendritic growth cone, dendrite terminus, postsynaptic specialization, and myelin sheath. Molecular Function (MF) analysis highlighted nitric oxide synthase regulator activity, protein kinase binding, and nuclear estrogen receptor binding [Figure3.4a]. The common target genes significantly modulate multiple critical signalling cascades, which was revealed through KEGG pathway enrichment. The most enriched pathways strongly correlated with neurodegeneration included the Estrogen signalling pathway, HIF-1 signalling pathway, Thyroid hormone signalling pathway, Focal adhesion, and Lipid and atherosclerosis pathways. [Figure3.4b]

3.5 Molecular Docking Analysis

Molecular docking was conducted between key phytochemicals and the top 10 hub proteins using the CB-Dock2 server to validate the interactions structurally. All evaluated complexes demonstrated robust binding affinities, with AutoDock Vina scores ranging from −6.1 to −10.1 kcal/mol.

- ❖ HSP90AA1 & Cycloartenone exhibited the strongest binding stability with a remarkable score of −10.1 kcal/mol.
- ❖ BCL2 & Oleanolic acid recorded high affinity at −9.4 kcal/mol.
- ❖ SRC & Quercetin demonstrated an excellent docking score of 9.4 kcal/mol.
- ❖ TNF & Fucosterol/Desmosterol both achieved robust binding scores of −9.3 kcal/mol.
- ❖ AKT1 & Quercetin interacted strongly with a score of −9.1 kcal/mol.

PPARG & β-Sitosterol showed a favourable interaction at −9.0 kcal/mol.

These results provide firm structural confirmation of the network pharmacology findings. [Figure3.5]

3.6 UALCAN Survival Analysis

Through the UALCAN database, the 10 hub genes were subjected to Kaplan-Meier survival analysis so that the further validation of clinical significance takes place. Differential survival patterns were distinctly observed between high-expression and low/medium-expression groups for all hub genes (AKT1, TNF, CTNNB1, SRC, BCL2, HSP90AA1, EGFR, HIF1A, PPARG, and ESR1). These findings highlight their important biological roles and suggest that they could serve not only as prognostic biomarkers but also as potential therapeutic targets for managing disease progression.

ADME properties and Lipinski's Rule of Five evaluation of the phytochemical constituents of *Wrightia tinctoria*.

Table No: 3.1: (SwissADME result of phytochemical constituents)

S.No	Phyto chemical Constituents	Formula	MW	GI absorption	BBB permeant	Lipinski #violations	Bioavailability Score	Synthetic Accessibility
1	Benzoate	C7H5O2	121.11 g/mol	High	No	0	0.85	1
2	Lupeol benzoate	C37H54O2	530.82 g/mol	Low	No	2	0.17	5.88
3	alpha-Amyrin	C30H50O	426.72 g/mol	Low	No	1	0.55	6.17
4	beta-Amyrin	C30H50O	426.72 g/mol	Low	No	1	0.55	6.04
5	Lupeol	C30H50O	426.72 g/mol	Low	No	1	0.55	5.49
6	beta-Sitosterol	C29H50O	414.71 g/mol	Low	No	1	0.55	6.3
7	Quercetin	C15H10O7	302.24 g/mol	High	No	0	0.55	3.23
8	Rutin	C27H30O16	610.52 g/mol	Low	No	3	0.17	6.52
9	Wrightial	C27H44O2	400.64 g/mol	High	No	1	0.55	5.71
10	Cycloartenone	C30H48O	424.70 g/mol	Low	No	1	0.55	6.38

11	Cycloeucalenol	C30H50O	426.72 g/mol	Low	No	1	0.55	6.3
12	Oleanolic acid	C30H48O3	456.70 g/mol	Low	No	1	0.85	6.08
13	Ursolic acid	C30H48O3	456.70 g/mol	Low	No	1	0.85	6.21
14	Indigo	C16H8N2Na2O8S2	466.35 g/mol	Low	No	0	0.55	3.28
15	Desmosterol	C27H44O	384.64 g/mol	Low	No	1	0.55	5.9
16	24-Methylenecholesterol	C28H46O	398.66 g/mol	Low	No	1	0.55	6.02
17	Stearic acid	C18H36O2	284.48 g/mol	High	No	1	0.85	2.54
18	24-Methylene,25-methylcholesta-5-en-3beta-ol	C29H48O	412.69 g/mol	Low	No	1	0.55	6.15
19	Fucosterol	C29H48O	412.69 g/mol	Low	No	1	0.55	6.15
20	Clerosterol	C29H48O	412.69 g/mol	Low	No	1	0.55	6.21
21	Myristic acid	C14H28O2	228.37 g/mol	High	Yes	0	0.85	2.09
22	9-Hydroxyoctadecanoic acid	C18H36O3	300.48 g/mol	High	Yes	0	0.85	3.03
23	Isoricinoleic Acid	C18H34O3	298.46 g/mol	High	Yes	0	0.85	3.66
24	Palmitic acid	C16H32O2	256.42 g/mol	High	Yes	1	0.85	2.31
25	Arachidic acid	C20H40O2	312.53 g/mol	Low	No	1	0.85	2.77
26	Oleic acid	C18H34O2	282.46 g/mol	High	No	1	0.85	3.07
27	Linoleic acid	C18H32O2	280.45 g/mol	High	Yes	1	0.85	3.1

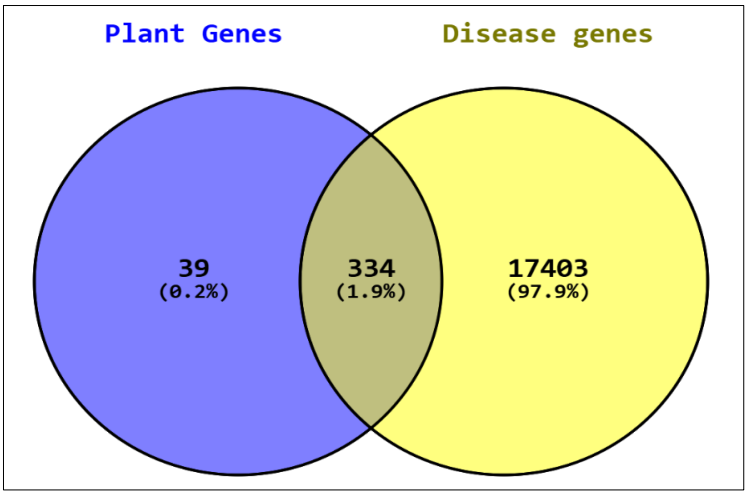


Figure 3.2: Venn diagram illustrating the overlap between the predicted target genes of *Wrightia tinctoria* phytochemicals and Alzheimer's disease-associated genes.

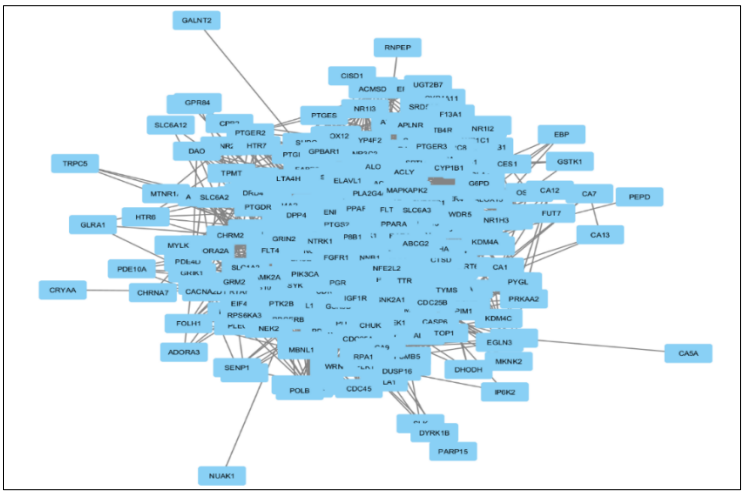


Figure3.3a: Protein–protein interaction (PPI) network of the common target genes constructed using the STRING database and visualized in Cytoscape

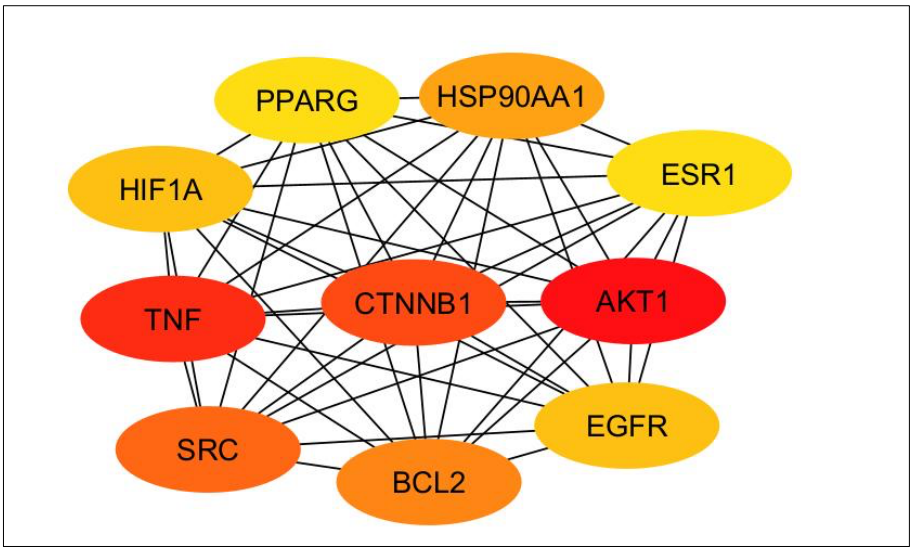


Figure3.3b: Identification of the top 10 hub genes using the CytoHubba plugin in Cytoscape

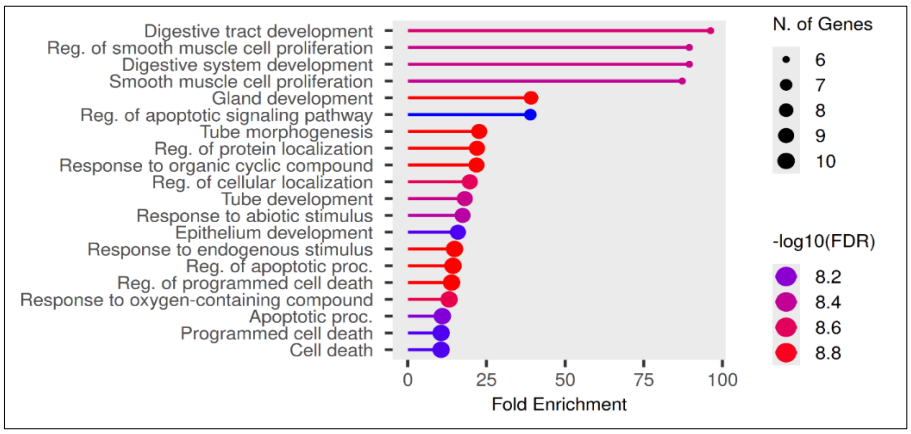


Figure3.4a: Gene Ontology Biological Process enrichment analysis of the common target genes

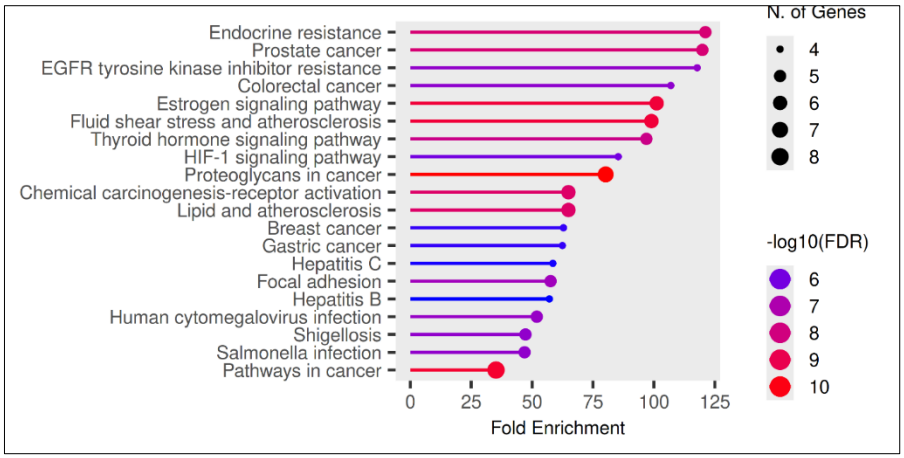
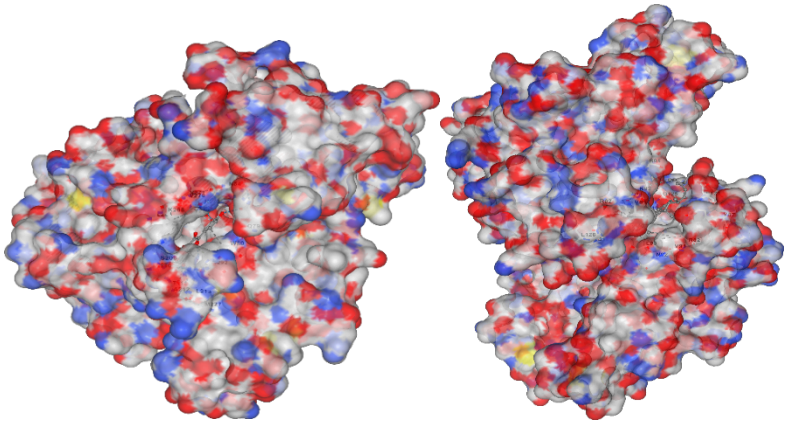
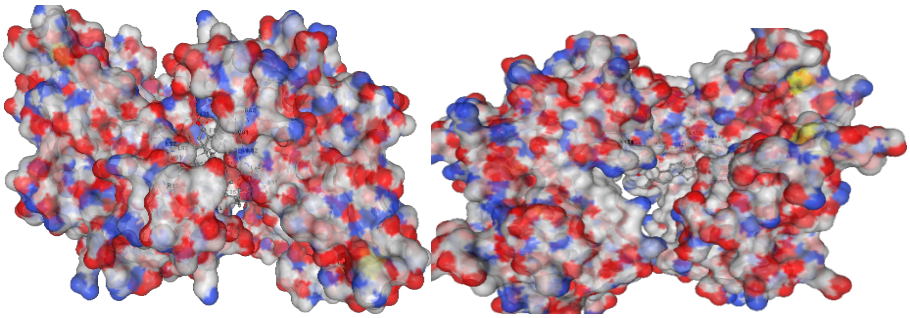


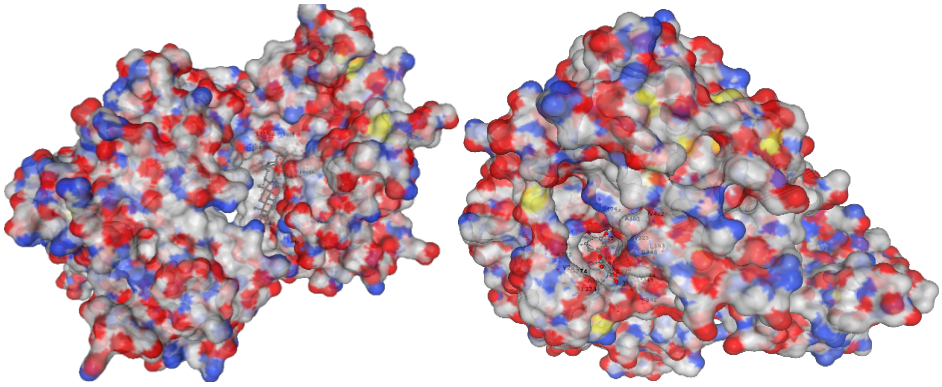
Figure3.4b: KEGG pathway enrichment analysis of the common target genes



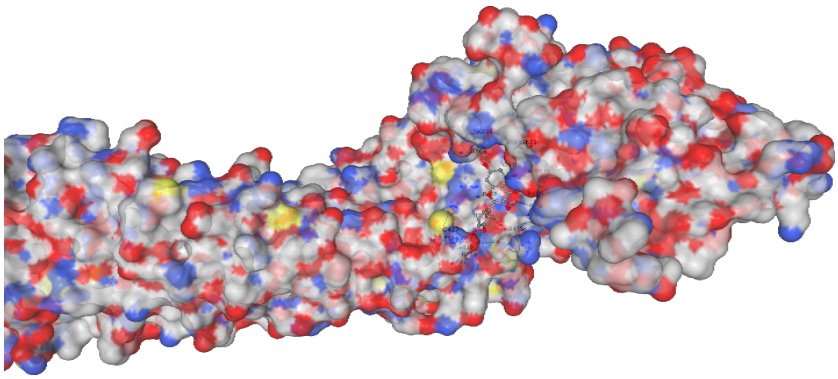
AKT1 Quercetin **TNF Fucosterol**



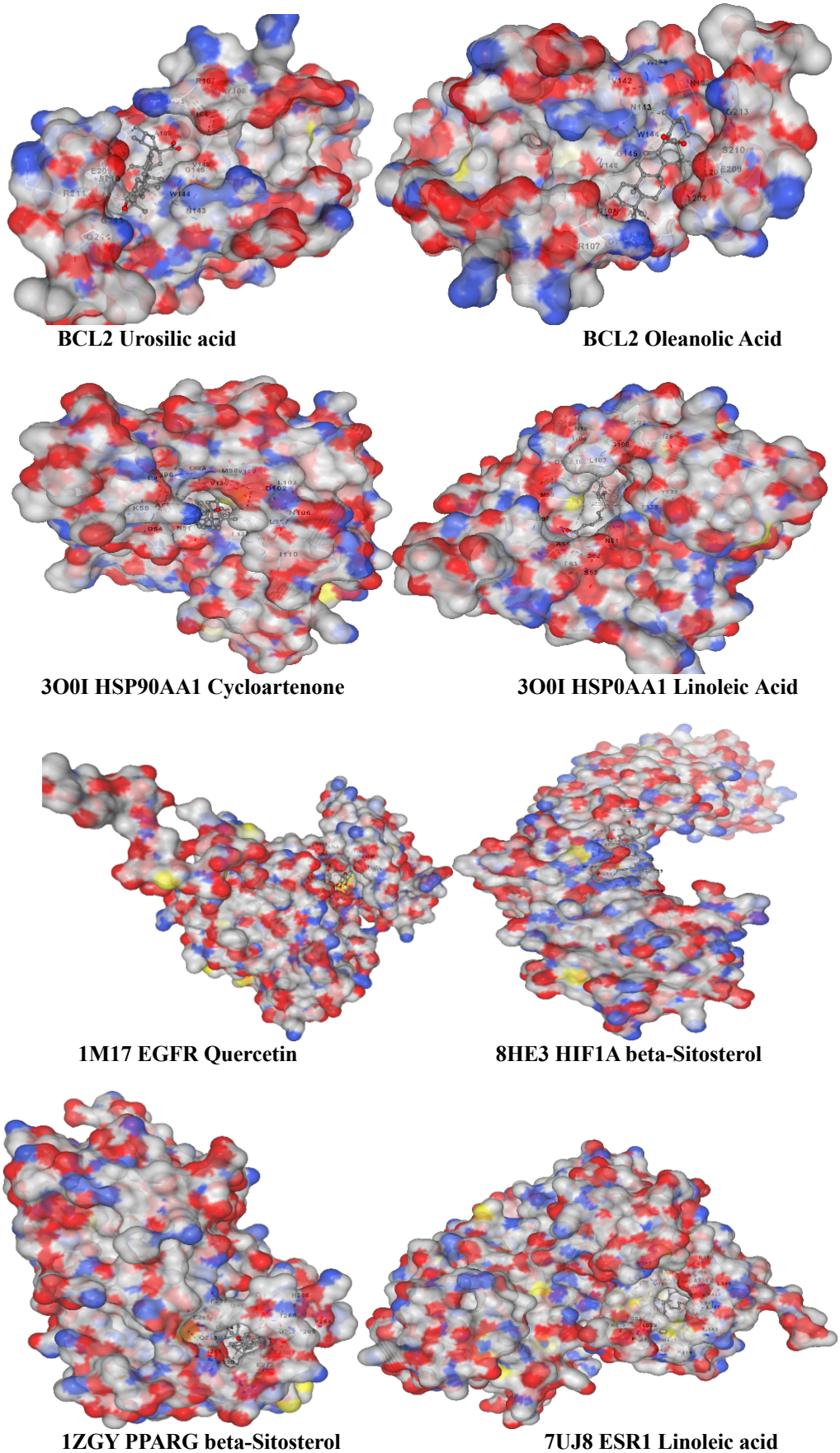
TNF Desmosterol **TNF Cycloartenone**



TNF Clerosterol **SRC Quercetin**



CTNNB1 Quercetin



BCL2 Urosilic acid **BCL2 Oleanolic Acid**

3O0I HSP90AA1 Cycloartenone **3O0I HSP0AA1 Linoleic Acid**

1M17 EGFR Quercetin **8HE3 HIF1A beta-Sitosterol**

1ZGY PPARG beta-Sitosterol **7UJ8 ESR1 Linoleic acid**

Figure3.5: Three-dimensional binding interactions of the selected phytochemicals with Alzheimer's disease-associated hub proteins obtained from the CB-Dock2 molecular docking analysis

DISCUSSION:

Alzheimer's disease develops through a combination of complex factors, including impaired communication between brain cells, chronic inflammation, oxidative stress, and the gradual loss of neurons. It has been proved that the traditional single-target therapeutic paradigms are insufficient to halt disease progression, underscoring the urgent need for multi-target therapies derived from medicinal plants. This study represents a comprehensive network pharmacology and molecular docking exploration of Wrightia tinctoria against AD.

In silico screening has been done carefully so that 25 highly bioavailable phytochemicals were isolated that targets 334 AD-associated genes. The densely connected PPI network (4,376 edges) revealed a highly integrated mechanism of action, pinpointing AKT1, TNF, CTNNB1, SRC, BCL2, HSP90AA1, EGFR, HIF1A, PPARG, and ESR1 as central hub genes. These proteins are fundamental regulators of neuroinflammation (TNF, SRC), apoptosis (BCL2, AKT1), and cellular stress survival (HIF1A).

Gene Ontology functional analysis provided deep mechanistic insights. The localization of targets to the dendritic growth cone, postsynaptic specializations, and myelin sheath suggests that Wrightia tinctoria phytochemicals directly participate in repairing or protecting synaptic structural integrity and neuronal communication. Simultaneously, KEGG pathway analysis highlighted the modulation of the Estrogen and HIF-1 signalling pathways. Targeting these pathways suggests the plant's constituents collectively combat mitochondrial dysfunction, oxidative stress, and inflammatory cascades.

The strong binding interactions observed in the molecular docking study further support the findings from the network pharmacology analysis. Among the compounds studied, cycloartenone showed particularly strong and stable binding with the chaperone protein HSP90AA1, with a binding energy of −10.1 kcal/mol. Since HSP90AA1 plays an important role in protein folding and tau protein degradation, this interaction suggests that cycloartenone may have potential in influencing these processes. Quercetin showed strong interactions with the kinases SRC and AKT1, with binding energies of −9.4 and −9.1 kcal/mol, respectively. Oleanolic acid also displayed a strong affinity for the anti-apoptotic protein BCL2, with a binding energy of −9.4 kcal/mol. Similarly, the phytosterols Fucosterol and Desmosterol showed notable binding to the pro-inflammatory cytokine TNF, with an affinity of −9.3 kcal/mol. These findings suggest that these compounds may help regulate inflammatory and cell-survival pathways, supporting their potential anti-inflammatory properties.

Finally, UALCAN survival analysis highlighted the potential clinical significance of these hub genes by demonstrating their strong association with patient prognosis. Overall, these findings provide a clearer picture of how *Wrightia tinctoria* may exert its neuroprotective effects through multiple targets and interconnected biological pathways.

CONCLUSION:

The present study used an integrated network pharmacology and molecular docking approach to better understand the complex, multi-target mechanisms through which *Wrightia tinctoria* may exert therapeutic effects against Alzheimer's disease. In silico screening identified 25 drug-like phytochemicals that could potentially interact with 334 Alzheimer's disease–associated targets. Among these, several important hub genes, including AKT1, TNF, CTNNB1, SRC, BCL2, HSP90AA1, EGFR, HIF1A, PPARG, and ESR1, were identified as key targets involved in processes such as neuronal apoptosis and neuroinflammation.

Molecular docking analysis further supported the potential interactions between these phytochemicals and the identified hub proteins. Compounds such as Cycloartenone, Oleanolic acid, Quercetin, Fucosterol, Desmosterol, Ursolic acid, and β-Sitosterol showed strong binding affinities toward several important target proteins. Taken together, these findings suggest that *Wrightia tinctoria* may protect against neurodegeneration through the combined action of multiple compounds acting on different biological pathways. Although these computational findings are promising, further in vitro, in vivo, and clinical studies are needed to confirm their biological effects and determine the therapeutic potential of *Wrightia tinctoria* in Alzheimer's disease.

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