

Study on Syzygium Cumini's Potential Therapeutic Effects on Alzheimer's Disease from A Mechanistic Perspective

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Research Article

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Abstract

Syzygium Cumini (SC), known for its efficacy in diabetes management, has shown promise in the treatment of Alzheimer's disease (AD). Nevertheless, the precise pharmacological mechanisms responsible for its therapeutic potential in AD have remained elusive. This study employed network pharmacology and molecular docking analysis to delve into the SC-related mechanisms for treating AD. Initially, 165 bioactive compounds from *Syzygium Cumini* were retrieved from the IMPPAT 2.0 and KNApSACk databases. These compounds subjected to rigorous screening based on drug likeness, bioavailability scores, and toxicity parameters, resulting in the identification of eight promising candidates. Subsequently, 500 targets predicted for 8 compounds through Swiss target prediction and the STITCH database. To establish the connection with AD, 14,655 genes associated with the disease were extracted from Gene Cards and OMIM databases, ultimately identifying 261 common gene targets through Venn diagram analysis. To shed light on the underlying mechanisms, GO and KEGG pathway enrichment analyses were conducted. A protein-protein interaction (PPI) network was constructed and hub genes were identified based on degree centrality using Cytoscape and the CytoHubba plugin. The study revealed that SC treatment for AD primarily targets two key proteins, ESR1 and HSP90AA1, utilizing eight active ingredients: (-)-Globulol, BETA-OCIMENE, Epi-Beta-Bisabolol, Ascorbic Acid, Citric Acid, Nicotinic Acid, Riboflavin, and Thiamine. Further Docking studies highlighted the high binding affinity of (-)-Globulol and Riboflavin to ESR1 and HSP90AA1, with binding scores of -7.6 and -7.8, respectively.

1. Introduction

With the growing global burden of Alzheimer's disease (AD), the search for effective treatments has intensified in recent decades. Alzheimer's disease affects individuals' quality of life and healthcare systems significantly as it wreaks havoc on cognitive function, memory, and neural pathways (Breijyeh and Karaman 2020). Alzheimer's disease accounts for 60–70% of dementia cases, with 10 million cases reported annually. It is estimated that by 2050, around 152 million people will have dementia around the world, with two-thirds of those living in low- and middle-income countries (LMIC). (Kravitz et al. 2012; Livingston et al. 2020) People over the age of 65 are the most likely to suffer from the disease. In Alzheimer's disease, the degeneration of neurons occurs along with the accumulation of abnormal proteins such as beta-amyloid (A) and tau (T). As traditional therapeutic approaches often fall short of providing a definitive solution, the exploration of alternative sources, such as medicinal plants, has gained significant traction. Nowadays Natural products play an important role in the effective treatment of disease because of their less adverse effects and easy availability and affordability. Active compounds obtained from herbal plants like berberine, curcumin, triterpenoids, flavanol, glycosides, genistein etc have been reported to reduce the progression and symptoms of Alzheimer's disease (Da Rosa et al. 2022).

Syzygium cumini L. (SC)(black plum or jamun) is a traditional medicinal plant that is native to the Indian and Asian subcontinents. This evergreen tree, native to the Indian subcontinent, has a rich history in traditional medicine, where its various parts have been used to treat an array of ailments. Various parts of

plants have a variety of pharmacological uses like anti-diabetic, antioxidant, anti-allergic, anti-ulcer, anti-hyperlipidemic, hepatoprotective, neuro-psychopharmacological, antipyretic, anti-inflammatory, anti-arthritic, anti-fertility, anti-microbial, nephroprotective and anti-diarrhoeal etc. Its potential role in combating Alzheimer's disease is gaining interest, which has prompted a multidisciplinary approach to unravel the therapeutic mechanisms underlying this natural remedy (Ayyanar and Subash-Babu 2012; Chhikara et al. 2018).

Network pharmacology (NP) is an emerging approach that integrates huge biological data utilizing bioinformatics and computational biology techniques. NP can be used for the mechanism elucidation of active components. It establishes the molecule-target-gene-biological pathway network to illustrate the mechanism behind the therapeutic action of drugs. In the context of *Syzygium cumini*, network pharmacology offers a unique opportunity to elucidate the intricate relationships between the plant's bioactive compounds and the molecular players implicated in Alzheimer's disease (Kibble et al. 2015; Noor et al. 2022). By constructing comprehensive interaction networks, we can identify key target proteins and pathways that may be modulated by the plant's constituents. Within the realm of network pharmacology, docking studies emerge as a pivotal technique to predict the binding affinity between bioactive molecules and their putative protein targets (Pinzi and Rastelli 2019; Dnyandev et al. 2021). By leveraging computational algorithms, we can virtually screen the active constituents of *Syzygium cumini* against a panel of proteins associated with Alzheimer's disease. These proteins encompass a spectrum of vital functions, including neuroinflammation, amyloid beta aggregation, and synaptic plasticity. Through docking simulations, potential interactions can be quantified, offering insights into the plausibility of therapeutic effects. While identifying potential drug candidates is a crucial step, the journey towards clinical translation demands a comprehensive evaluation of their pharmacokinetic properties and safety profiles. Here, absorption, distribution, metabolism, and excretion (ADME) analysis assume significance, as it gauges the drug-likeness and bioavailability of the plant's bioactive molecules. Furthermore, toxicity analysis is essential to ascertain the compounds' potential adverse effects on human cells and organs, ensuring that their therapeutic promise outweighs any associated risks (Daoud et al. 2021).

In this article, we delve into the convergence of network pharmacology, docking studies, ADME analysis, and toxicity assessment to illuminate the therapeutic potential of *Syzygium cumini* in Alzheimer's disease. By amalgamating traditional wisdom with contemporary scientific tools, we aim to provide a comprehensive framework for harnessing the power of natural remedies in the quest for effective Alzheimer's treatments. As the global population continues to age, innovative approaches rooted in interdisciplinary collaboration offer newfound hope for managing and mitigating the impact of neurodegenerative disorders. Workflow of the study is illustrated (Fig. 1)

2. Material and methods

2.1 Collection and screening of bioactive compounds

The bioactive compounds present in *Syzygium cumini* were retrieved from Indian Medicinal Plants, Phytochemistry and Therapeutics 2.0 database (IMPPAT 2.0, <https://cb.imsc.res.in/imppat/home>) (Vivek-Ananth et al. 2023) and a Comprehensive Species-Metabolite Relationship Database (KNAPSAcK, <http://www.knapsackfamily.com/KNAPSAcK/>) (Takahashi et al. 2009). Collection of compounds ID and canonical smiles have been done from the PubChem database (<https://pubchem.ncbi.nlm.nih.gov/>). Then the screening of bioactive compounds was done on the basis of drug-likeness score analysis by the Molsoft software tool (<https://www.molsoft.com/mprop/>) and bioavailability score analysis using Swiss ADME tool (<http://www.swissadme.ch/>) (Daina et al. 2017). Further toxicity prediction of filtered compounds was done using Protox-II (https://tox-new.charite.de/protox_II/) (Banerjee et al. 2018) which is a virtual tool for the prediction of toxicity of small molecules.

2.2 Finding targets and disease-related genes

Filtered compounds after toxicity prediction used for prediction of targets using Swiss target prediction (<http://swisstargetprediction.ch/>) (Gfeller et al., 2014) and stitch database (<http://stitch.embl.de/>) (Kuhn et al. 2014). Further the genes associated with Alzheimer's disease were retrieved from GeneCards (<https://www.genecards.org/>) (Stelzer et al. 2016) and OMIM databases (<https://www.omim.org/>) (Amberger et al. 2015). Then we determined the common potential target genes of *Syzygium cumini* L. in treatment of Alzheimer disease with the help of Venn diagram (<http://www.bioinformatics.com.cn/srplot>) for further analysis.

2.3 Functional Annotation of SC-AD common genes

To explore the SC related mechanism to treat AD, Gene Ontology (GO) (Tomczak et al. 2018) and Kyoto Encyclopedia of genes and Genomes (KEGG) enrichment analysis was done on common target genes with the help of DAVID database (<https://david.ncifcrf.gov/>) (Sherman et al. 2022), which is a Database for Annotation, Visualization and Integrated Discovery. GO functional analysis includes determination of biological functions of gene products and divides the possible targets into diverse functional modules like cellular component (CC), molecular function (MF) and biological pathway (BP). Further, KEGG analysis helps to find out the functions of gene at molecular level.

2.4 PPI interaction and Hub gene identification

Protein-protein interaction network for target genes was visualized by string database and further hub gene identified by cytohubba module of Cytoscape (<https://cytoscape.org/>) (Shannon et al. 2003) and all factors were set as default except species type which was set as 'Homo sapiens'. Top 10 genes ranked by degree are selected for further network construction with the help of Cytoscape-v3.10.0.

2.5 Molecular Docking

The proteins associated with ESR1 (PDB ID: 6VJD) and HSP1 (PDB ID: 1BYQ) genes were obtained from RCSB protein data bank (<https://www.rcsb.org/>) based on the resolution. The 3D conformers of the chemical structures of the screened phyto-constituents were downloaded in .sdf format from PubChem database. Protein preparation by removing water and ligand molecules was done using Biovia Discovery

Studio 2021 Client(Pawar and Rohane 2021). Energy minimization and ligand preparation to .pdbqt format was performed in PyRx version 0.8 software(Dallakyan and Olson 2015). Docking of all 8 phyto-constituents was done against ESR1 and HSP90AA1 proteins and the docking scores were compiled. The dock poses and amino acid interactions were visualized using Biovia Discovery Studio software.

3. Results

3.1 Bioactive compound collection and screening

A total of 165 bioactive compounds present in different parts of plant *SyzygiumCumini* were retrieved from IMPPAT 2.0 and KNApSAcKdatabase.Active compound ID and canonical smiles were retrieved from PubChem database. ADME analysis of compounds was done on basis of drug likeness and bioavailability score by MOLSOFT and Swiss ADME tool respectively. Compounds were screened on the basis of a drug-likenessthreshold of greater than or equal to 0.18 and a bioavailability threshold of greater than or equal to 0.3.The screening process has led to the retention of 21 active compounds. Further, in-silico toxicity prediction of filtered compounds was done through PROTOX-II. Compounds that are inactive for hepatotoxicity, carcinogenicity, immunotoxicity, and mutagenicity together were processed for further analysis. Finally, 8 compounds were obtained after screening through different filters [(-)-Globulol, (Z)-BETA-OCIMENE, Epi-Beta-Bisabolol, Ascorbic Acid, Citric Acid, Nicotinic Acid, Riboflavin, Thiamine].

3.2 Target prediction and detection of disease-related genes

The target prediction through Swiss target prediction webtool and the Stitch database resulted in the prediction of 500 targets for 8 compounds. After the removal of duplicate targets and applying the thresholds of $P < 0.05$, final obtained targets were 61. The 14,472 genes of Alzheimer disease was found from Gene cards and 183 from OMIM database. After removal of duplicate genes from the combined genes, we got 14155 genes finally. Further the Venn diagram was plotted based on targets of AD and SC (to map and intersect) and finally 261 intersected targets were obtained, which may be potential target of SC for treatment of AD(Fig. 2)

3.3 GO and KEGG functional annotations

On 261 potential targets, GO and KEGG pathway enrichment analysis was performed using DAVID database. The top 10 most notable Gene Ontology terms were selected within the Biological Process (BP), Cellular Component (CC), and Molecular Function (MF) categories (Fig. 3). In terms of BP terms, the co-target genes exhibited noteworthy associations with response to xenobiotic stimulus, inflammation and chemical synaptic transmission. Furthermore these genes are related to positive regulation of cytosolic calcium ion concentration, response to lipo-polysaccharide, protein phosphorylation and adenylate cyclase-inhibiting G-protein coupled glutamate receptor signalling pathway. Cellular

component analysis showed that the plasma membrane, cytoplasm and cytosol accounted for most significant components. The target proteins in molecular function category were involved in protein binding, ATP binding and metal ion binding.

A total of 236 potential co-target gene signaling pathways obtained through KEGG analysis which includes top 20 pathways with $P < 0.01$. Top 20 pathways were displayed through bubble chart. The bubble's size reflects the count of enriched pathways, while its colour represents the magnitude of the P-value. The findings revealed the top enriched pathways as follows: Neuroactive ligand receptor interaction, CAMP signalling pathways, Chemical carcinogenesis receptor activation, calcium signalling pathway and metabolic pathway etc. Among them neuroactive ligand receptor interaction found to be most enriched pathway (Fig. 4).

3.4 PPI network construction and Hub gene analysis

261 common potential targets used for creating protein protein interaction network using string database(Fig. 5).Plant-Active Constitutents –target Network construction done by Cytoscape(Fig. 6). Cytohubba plugin was installed on cytoscape software. Nodes are ranked on basis of degree method. Ten hub gene with highest degree are ESR1, HSP90AA1, JUN, HIF1A, STAT3, MTOR, PPARG,PTGS2, PPARG and PRKCA.The network of Hub genes selected by degree method was constructed by cytoscape (Fig. 7). Based on degree, the top 2 gene targets were chosen for subsequent docking analysis:ESR1 and HSP90AA1.

3.5 Docking Analysis

All ligands had a binding score of -5 and below, hence they show decent binding affinity towards the targets.(-)-Globulol and riboflavin showed strongest binding affinity towards ESR-1 and HSP-1 gene associated proteins. The binding affinity of (-)-Globulol towards ESR-1 and HSP-1 gene associated proteins was - 7.6 and - 6.2kcal/mol respectively, while that of riboflavin was - 7 and - 7.8kcal/mol. The docking scores of 8 compounds against two top rankedtargets by cyto-hubba are summarised in Table 1.

Table 1
Binding affinities of ligands against ESR1& HSP1 associated target proteins

Target	PDB ID	Compound	Binding affinity
ESR-1	6VJD	(-)-Globulol	-7.6
		Riboflavin	-7.0
		Epi-Beta-Bisabolol	-6.9
		Thiamine	-6.0
		(Z)-Beta ocimene	-5.4
		Ascorbic acid	-5.3
		Nicotinic acid	-5.2
		Citric acid	-5.0
HSP1	1BYQ	Riboflavin	-7.8
		(-)-Globulol	-6.2
		Thiamine	-6.2
		Epi-Beta bisabolol	-5.7
		Ascorbic acid	-5.2
		Citric acid	-5.1
		Nicotinic acid	-5.0
		(Z)-Beta ocimene	-4.8

The 2D amino acid interaction for 4 compounds having best docking scores against ESR1 and HSP1 related protein depicted in Figs. 8 and 10 respectively. The 3D binding poses of (-)-Globulol and Riboflavin against ESR1 and HSP1 associated target proteins are represented in Figs. 9 and 11 respectively.

(PDB ID: 6VJD)

Fig 10. 2D amino acid interaction diagram of Riboflavin(a), (-)-Globulol(b), Thiamine(c) and Epi-beta-bisabolol (d) and against HSP1 associated target protein (PDB ID: ID: 1BYQ)

Protein (PDB ID: ID: 1BYQ)

Table 2
Amino acid interactions of ligands with ESR1 associated target protein

Molecule	Target	PDB ID	Interaction type	Amino acid residues
(-)-Globulol	ESR1	6VJD	Conventional H bond	Gly:521
			Hydrophobic	Ala:350, Leu: 384, Met:388,Ile: 424
Riboflavin	ESR1	6VJD	Conventional H bond	Met:343
			Hydrophobic	Leu:346, Ala:350, Val:533, Leu:525
			Miscellaneous (Sulfur bond)	Met:421
Epi-beta bisabolol	ESR1	6VJD	Hydrophobic	Leu:346, Leu:349, Ala:350, Leu:384, Leu:387, Leu:525
Thiamine	ESR1	6VJD	Hydrophobic	Ala:350, Leu:387, Met:388, Leu:391
			Miscellaneous (Sulfur bond)	Phe:404,Phe: 425

Table 2
Amino acid interactions of ligands with HSP1 associated target protein

Molecule	Target	PDB ID	Interaction type	Amino acid residues
(-)-Globulol	HSP1	1BYQ	Hydrophobic	Ala:55, Met: 98
Riboflavin	HSP1	1BYQ	Conventional H bond	Asn: 106, Gly:135
			Hydrophobic	Ala:55, Val:186
Epi-beta bisabolol	HSP1	1BYQ	Hydrophobic	Leu:48, Ala:55, Met:98, Phe:138, Val:186
Thiamine	HSP1	1BYQ	Conventional H bond	Ser:52, Asp:93
			C-H bond	Asn:51
			Hydrophobic	Leu:48, Ile:91: Val:186

4. Discussion

The results obtained from our research represent a comprehensive and systematic approach to exploring the potential therapeutic benefits of bioactive compounds from *Syzygium cumini*(SC) for the treatment of Alzheimer's disease (AD). In this discussion, we will delve into the key findings and their implications: Our initial step involved the identification and screening of bioactive compounds from different parts of the *Syzygium cumini* plant. A total of 165 compounds were retrieved and subjected to ADME (Absorption, Distribution, Metabolism, and Excretion) analysis. This rigorous screening process resulted in the

selection of 21 active compounds, which demonstrated favorable drug-likeness and bioavailability properties. Furthermore, in-silico toxicity prediction through PROTOX-II ensured that the chosen compounds were safe for further investigation, ultimately leading to the retention of 8 promising compounds. Subsequently, we conducted target prediction for these 8 selected compounds. The prediction, based on Swiss target prediction and the Stitch database, yielded a substantial list of potential target proteins, which was further refined to 61 unique targets. To establish relevance to Alzheimer's disease, we collected a comprehensive list of 14,472 AD-related genes. By comparing these AD-associated genes with the predicted targets of SC compounds, we identified 261 common intersected targets. These 261 targets represent a potential molecular basis for the therapeutic effects of SC against AD.

To gain insights into the biological processes and pathways involved, we performed GO and KEGG pathway enrichment analysis. Our findings revealed that these co-target genes are significantly associated with various biological processes, such as response to xenobiotic stimulus, inflammation, and chemical synaptic transmission. Importantly, these genes are implicated in processes relevant to AD, such as response to lipopolysaccharide, protein phosphorylation, and adenylate cyclase-inhibiting G-protein coupled glutamate receptor signaling pathway. Cellular component analysis highlighted the involvement of the plasma membrane, cytoplasm, and cytosol, while molecular function analysis emphasized protein binding, ATP binding, and metal ion binding.

Through KEGG pathway analysis, we identified 236 potential co-target gene signaling pathways, with the most enriched pathways encompassing neuroactive ligand receptor interaction, cAMP signaling pathways, chemical carcinogenesis receptor activation, calcium signaling pathways, and metabolic pathways. Notably, neuroactive ligand receptor interaction emerged as the most enriched pathway, suggesting a key role in the potential therapeutic mechanism of SC in AD.

To elucidate the interactions among the identified targets, we constructed a Protein-Protein Interaction (PPI) network. Ten hub targets with the highest degrees of connectivity were identified, including ESR1, HSP90AA1, JUN, HIF1A, STAT3, MTOR, PPARG, PTGS2, PPARA, and PRKCA. These hub genes play crucial roles in the network, indicating their significance in the potential therapeutic mechanism of SC against AD. Based on their high degree of connectivity, we selected ESR1 and HSP90AA1 as the top two gene targets for further molecular docking analysis.

The ligands bound to proteins associated with the target genes ESR1 & HSP1 showed different interactions with the amino acid residues (table 3 and table 4). The most favourable interactions were conventional H-bonds and C-H bond in hydrophilic interactions, alkyl and pi-alkyl interactions in hydrophobic interactions, and pi-sulfur bonds in miscellaneous interactions. Since there is the occurrence of interaction between common amino acid residues of protein with different groups of compounds, it can be concluded that there is a common ligand binding site in the target protein in order to show activity towards AD which validate the current docking study.

5. Conclusion

In conclusion, our research paper has provided valuable insights into the potential therapeutic efficacy of *Syzygium cumini*, a medicinal plant, against Alzheimer's disease through network pharmacology and docking studies. Alzheimer's disease is a complex neurodegenerative disorder with limited treatment options, and the search for novel therapeutic agents is of utmost importance. Our study utilized a comprehensive approach to identify potential bioactive compounds in *Syzygium cumini* and understand their interactions with key Alzheimer's disease-related targets.

We employed the network pharmacology approach to unveil the chemical foundation and explore the mechanism of action of *Syzygium cumini* (SC) in Alzheimer's disease (AD). 165 compounds, After filtration through drug likeness score, bioavailability score and toxicity analysis threshold resulted in final 8 compounds [(-)-Globulol, (Z)-BETA-OCIMENE, Epi-Beta-Bisabolol, Ascorbic Acid, Citric Acid, Nicotinic Acid, Riboflavin and Thiamine] and two SC core target genes (ESR1 and HSP90AA1) against AD were identified. Further by Gene ontology and KEGG studies suggested that Neuroactive ligand receptor interaction, CAMP signalling pathways, Chemical carcinogenesis receptor activation, calcium signalling pathway and metabolic pathway shows close correlation with the protective influence of SC on AD. In addition to this our docking studies provided molecular insights into the binding interactions between the identified compounds and their respective protein targets. The strong binding affinities observed in these studies support the potential therapeutic relevance of *Syzygium cumini* in Alzheimer's disease treatment. In this way, As the understanding of Alzheimer's disease continues to evolve, *Syzygium cumini* presents itself as a potentially valuable resource in this ongoing quest for a cure. These findings lay a solid foundation for further experimental studies, such as in vitro and in vivo investigation to validate and elucidate the therapeutic potential of SC in AD treatment.

Declarations

The authors state that there is no conflict of interest.

Ethical Approval- Not applicable.

Author Contribution

Dr. Priyanka Kamaria has done network pharmacology study and Ms. Aisvarya S has done docking analysis. both authors have contributed in writing part and reviewed manuscript together.

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References

1. Amberger JS, Bocchini CA, Schiettecatte F et al (2015) OMIM.org: Online Mendelian Inheritance in Man (OMIM®), an online catalog of human genes and genetic disorders. *Nucleic Acids Res* 43:D789–D798. <https://doi.org/10.1093/nar/gku1205>
2. Ayyanar M, Subash-Babu P (2012) *Syzygium cumini* (L.) Skeels: A review of its phytochemical constituents and traditional uses. *Asian Pac J Trop Biomed* 2:240–246. [https://doi.org/10.1016/S2221-1691\(12\)60050-1](https://doi.org/10.1016/S2221-1691(12)60050-1)
3. Banerjee P, Eckert AO, Schrey AK, Preissner R (2018) ProTox-II: a webserver for the prediction of toxicity of chemicals. *Nucleic Acids Res* 46:W257–W263. <https://doi.org/10.1093/nar/gky318>
4. Breijyeh Z, Karaman R (2020) Comprehensive Review on Alzheimer's Disease: Causes and Treatment. *Molecules* 25:5789. <https://doi.org/10.3390/molecules25245789>
5. Chhikara N, Kaur R, Jaglan S et al (2018) Bioactive compounds and pharmacological and food applications of *Syzygium cumini* – a review. *Food Funct* 9:6096–6115. <https://doi.org/10.1039/C8FO00654G>
6. Da Rosa MM, De Amorim LC, Alves JVDO et al (2022) The promising role of natural products in Alzheimer's disease. *Brain Disorders* 7:100049. <https://doi.org/10.1016/j.dscb.2022.100049>
7. Daina A, Michielin O, Zoete V (2017) SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. *Sci Rep* 7:42717. <https://doi.org/10.1038/srep42717>
8. Dallakyan S, Olson AJ (2015) Small-molecule library screening by docking with PyRx. *Methods Mol Biol* 1263:243–250. https://doi.org/10.1007/978-1-4939-2269-7_19
9. Daoud NE-H, Borah P, Deb PK et al (2021) ADMET Profiling in Drug Discovery and Development: Perspectives of In Silico. In Vitro and Integrated Approaches *CDM* 22:503–522. <https://doi.org/10.2174/1389200222666210705122913>
10. Dnyandev KM, Babasaheb GV, Chandrashekhar KV et al (2021) A Review on Molecular Docking. *IRJPAC* 60–68. <https://doi.org/10.9734/irjpac/2021/v22i330396>
11. Gfeller D, Grosdidier A, Wirth M et al (2014) SwissTargetPrediction: a web server for target prediction of bioactive small molecules. *Nucleic Acids Res* 42:W32–W38. <https://doi.org/10.1093/nar/gku293>
12. Kibble M, Saarinen N, Tang J et al (2015) Network pharmacology applications to map the unexplored target space and therapeutic potential of natural products. *Nat Prod Rep* 32:1249–1266. <https://doi.org/10.1039/C5NP00005J>
13. Kravitz E, Schmeidler J, Schnaider Beerli M (2012) Cognitive Decline and Dementia in the Oldest-Old. *RMMJ* 3:e0026. <https://doi.org/10.5041/RMMJ.10092>
14. Kuhn M, Szklarczyk D, Pletscher-Frankild S et al (2014) STITCH 4: integration of protein–chemical interactions with user data. *Nucl Acids Res* 42:D401–D407. <https://doi.org/10.1093/nar/gkt1207>
15. Livingston G, Huntley J, Sommerlad A et al (2020) Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *The Lancet* 396:413–446. <https://doi.org/10.1016/S0140->

16. Noor F, Tahir Ul Qamar M, Ashfaq UA et al (2022) Network Pharmacology Approach for Medicinal Plants: Review and Assessment. *Pharmaceuticals* 15:572. <https://doi.org/10.3390/ph15050572>
17. Pawar SS, Rohane SH (2021) Review on Discovery Studio: An important Tool for Molecular Docking. *Asian J Res Chem* 14:86–88. <https://doi.org/10.5958/0974-4150.2021.00014.6>
18. Pinzi L, Rastelli G (2019) Molecular Docking: Shifting Paradigms in Drug Discovery. *IJMS* 20:4331. <https://doi.org/10.3390/ijms20184331>
19. Shannon P, Markiel A, Ozier O et al (2003) Cytoscape: A Software Environment for Integrated Models of Biomolecular Interaction Networks. *Genome Res* 13:2498–2504. <https://doi.org/10.1101/gr.1239303>
20. Sherman BT, Hao M, Qiu J et al (2022) DAVID: a web server for functional enrichment analysis and functional annotation of gene lists (2021 update). *Nucleic Acids Res* 50:W216–W221. <https://doi.org/10.1093/nar/gkac194>
21. Stelzer G, Rosen N, Plaschkes I et al (2016) CP in Bioinformatics 54. <https://doi.org/10.1002/cpbi.5>. The GeneCards Suite: From Gene Data Mining to Disease Genome Sequence Analyses
22. Takahashi H, Hirai A, Shojo M et al (2009) Species-Metabolite Relation Database KNAp SAc K and Its Multifaceted Retrieval System, KNAp SAc K Family. In: Ballantyne B, Marrs TC, Syversen T et al (eds) *General, Applied and Systems Toxicology*, 1st edn. Wiley
23. Tomczak A, Mortensen JM, Winnenburg R et al (2018) Interpretation of biological experiments changes with evolution of the Gene Ontology and its annotations. *Sci Rep* 8:5115. <https://doi.org/10.1038/s41598-018-23395-2>
24. Vivek-Ananth RP, Mohanraj K, Sahoo AK, Samal A (2023) IMPPAT 2.0: An Enhanced and Expanded Phytochemical Atlas of Indian Medicinal Plants. *ACS Omega* 8:8827–8845. <https://doi.org/10.1021/acsomega.3c00156>

Figures

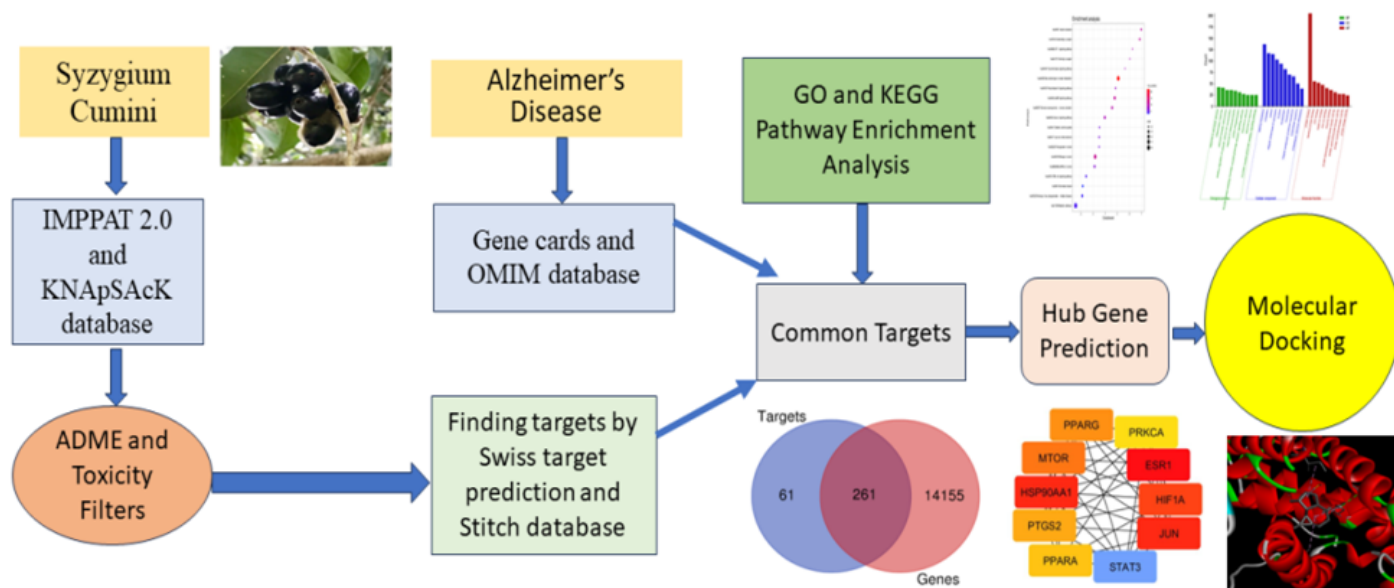


Figure 1

A flow chart exploring SC against AD based on network pharmacology

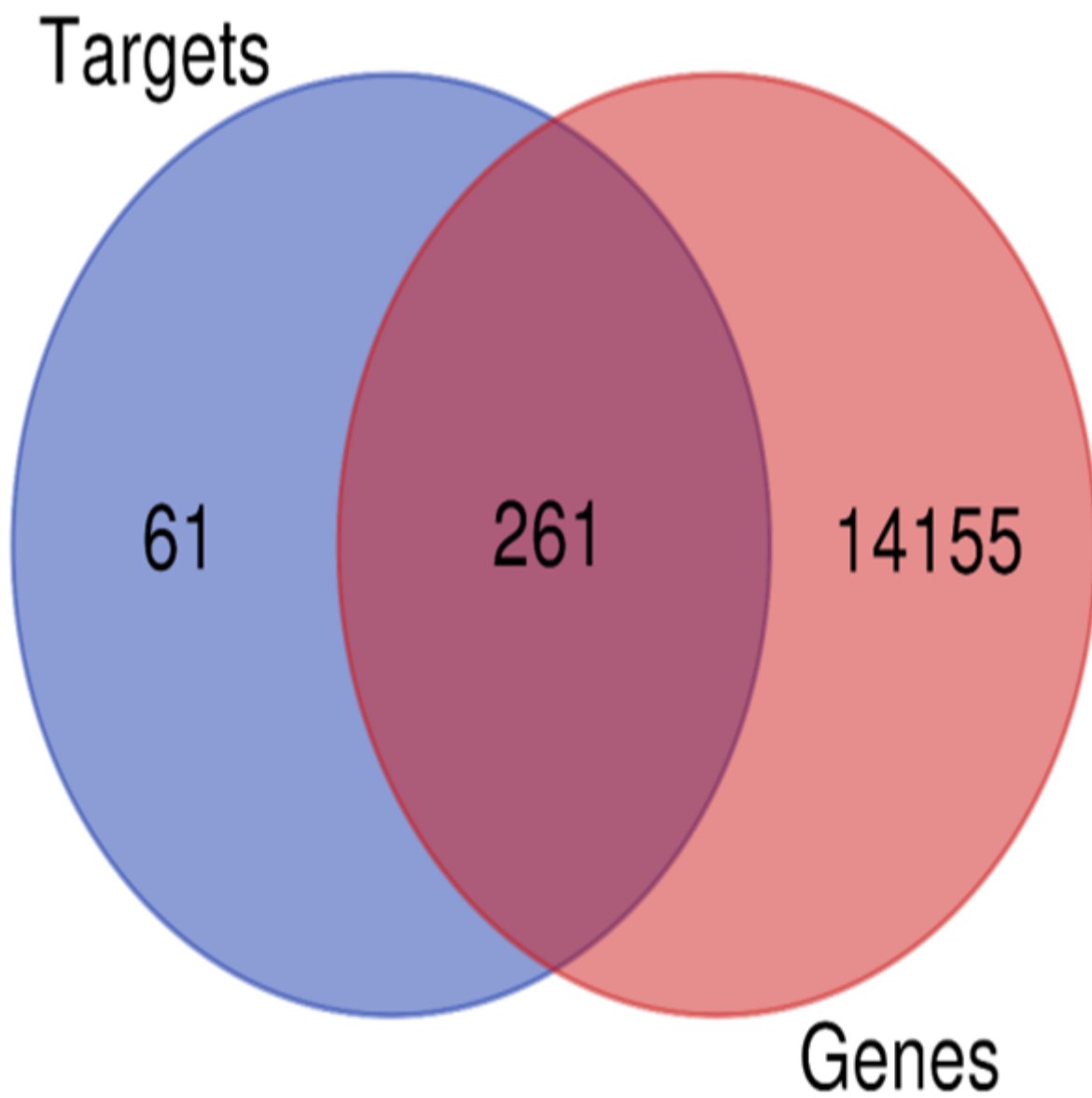


Figure 2

VENN diagram of common targets between SC and AD

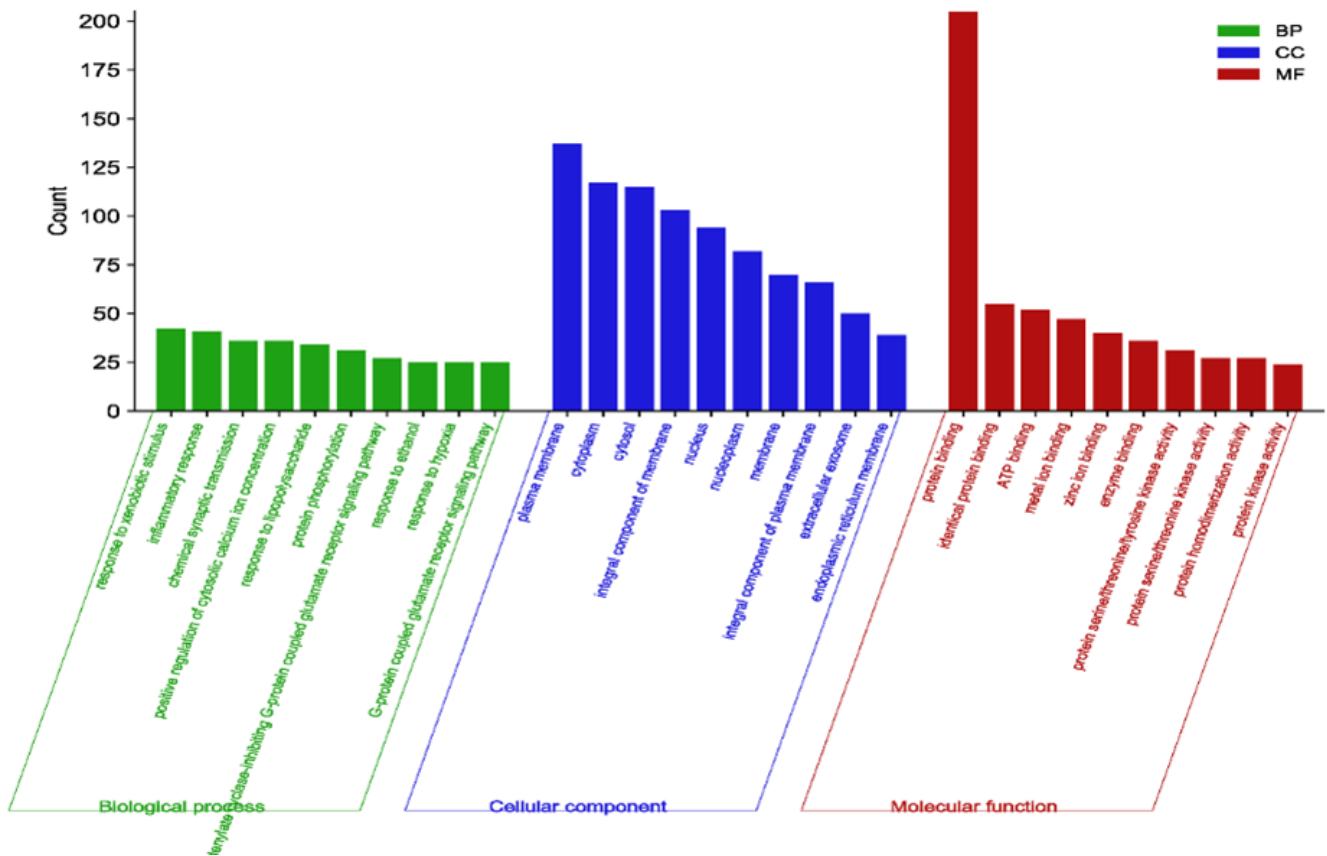


Figure 3

GO Functional Enrichment Analysis of AD-SC common targets. Greencolumns represent biological process (BP); blue columns represent cellular component (CC); Red columns represent molecular function (MF). The top 10 terms of BP, CC, and MF are shown in the figure

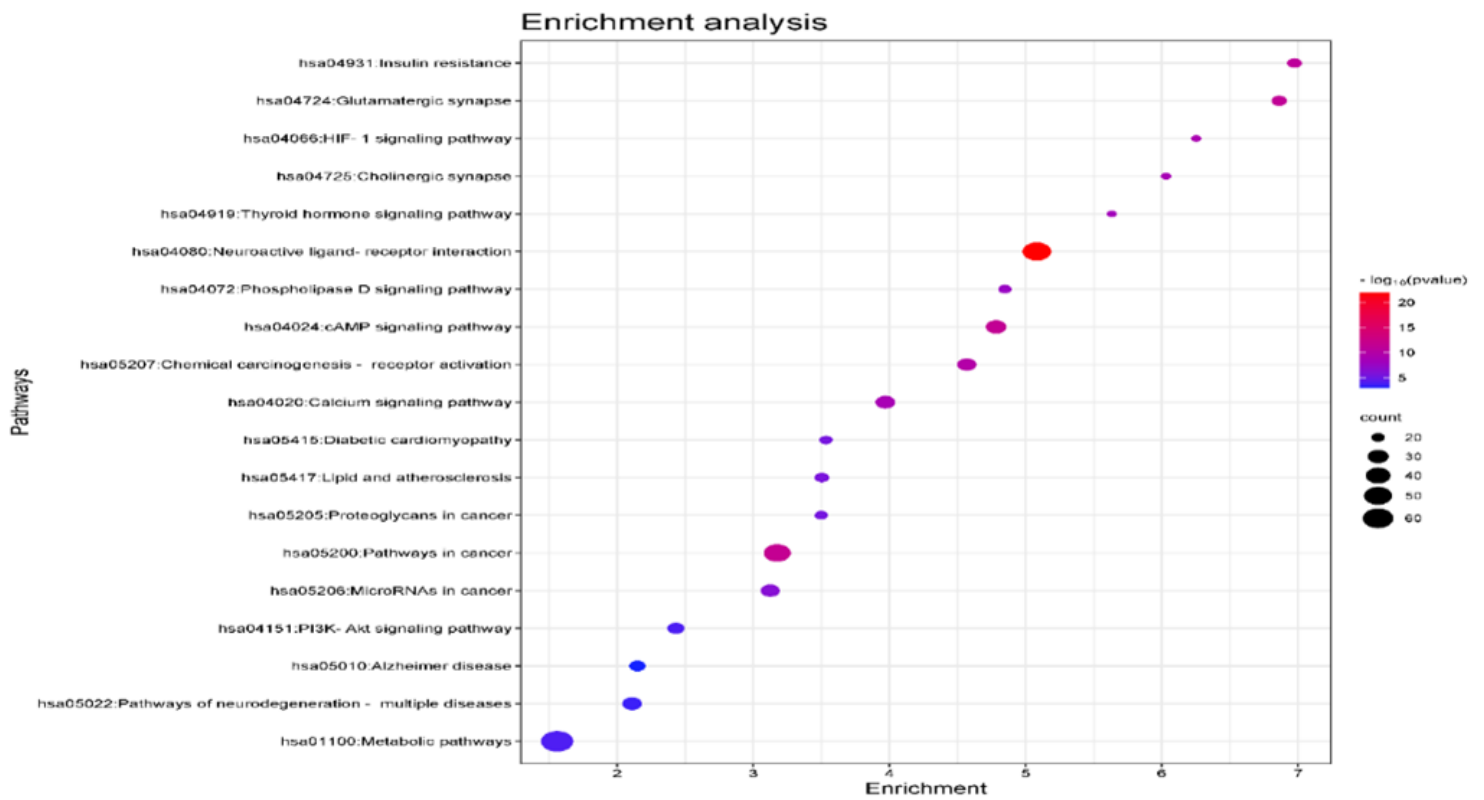


Figure 4

KEGG Pathway Enrichment Analysis of AD-SC common targets. The color scale shows the adjusted P value and dot size indicate the gene count in each term.

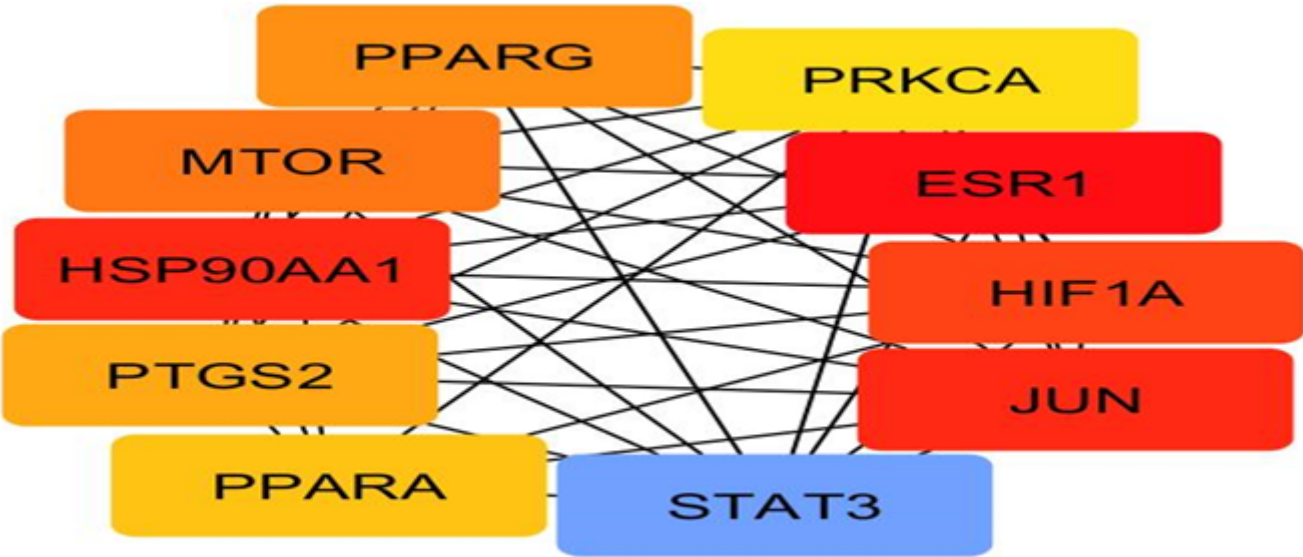


Figure 7

Hub gene network construction through Cytoscape

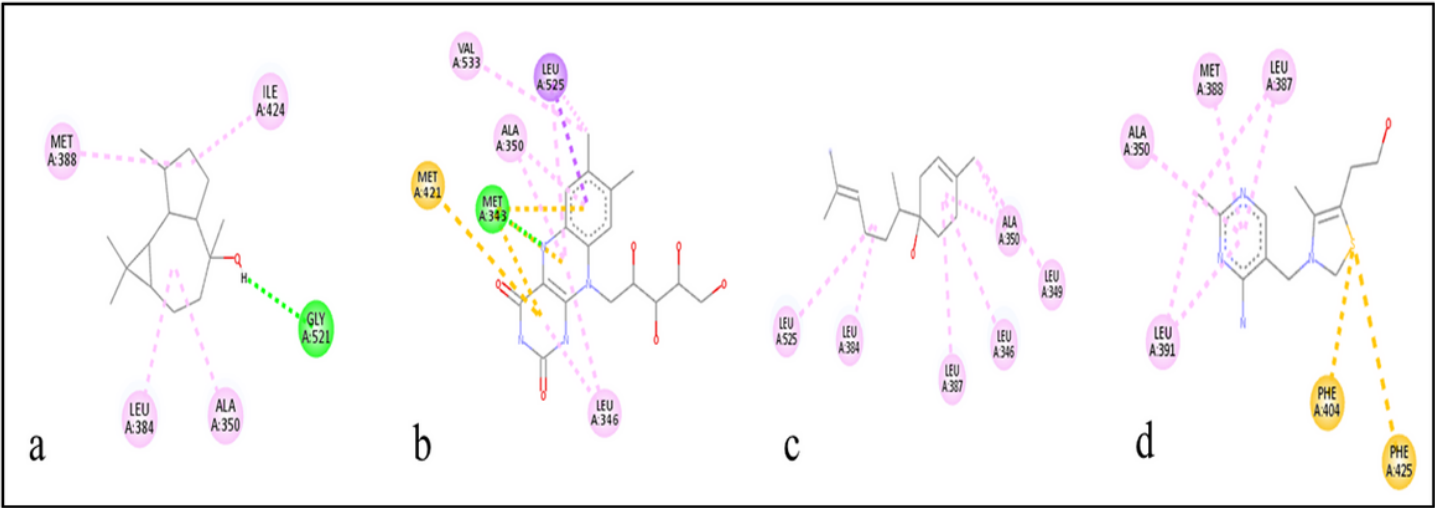


Figure 8

2D amino acid interaction diagram of (-)-Globulol (a), Riboflavin, Epi-beta-bisabolol (c) and Thiamine(D) against ESR1 associated target protein (PDB ID: 6VJD)

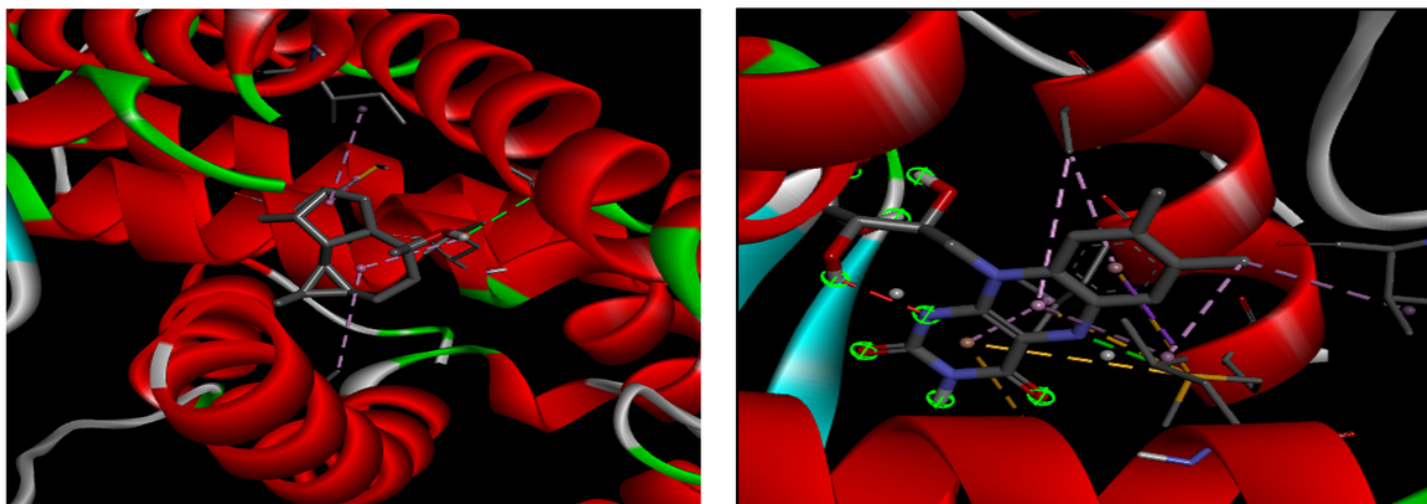


Figure 9

3D binding pose of (-)-Globulol (left) and Riboflavin (right) with ESR1 associated target protein (PDB ID: 6VJD)

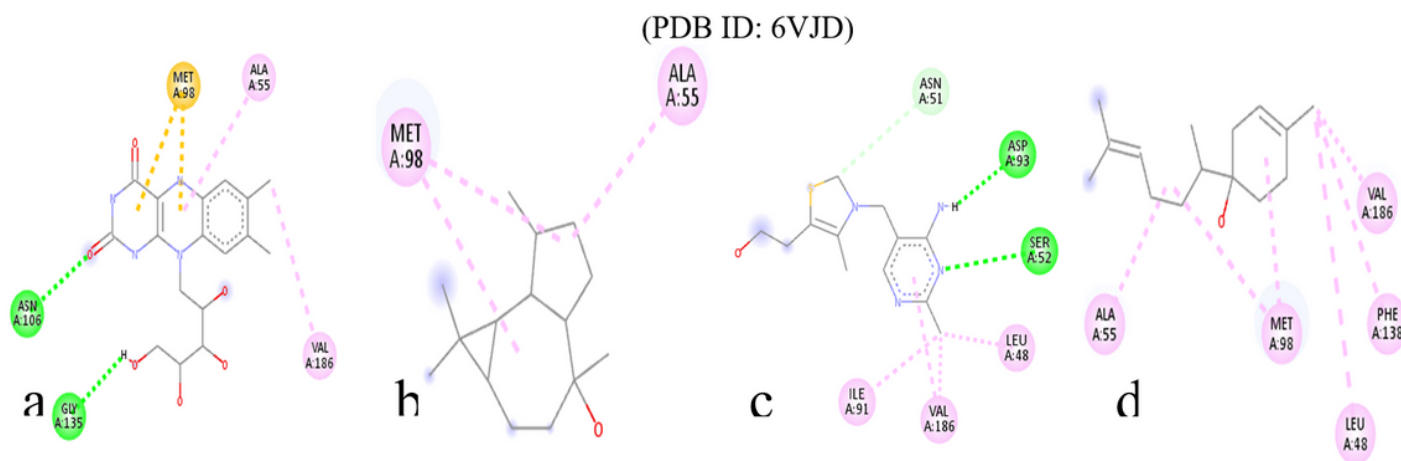


Figure 10

2D amino acid interaction diagram of Riboflavin(a), (-)-Globulol(b), Thiamine(c) and Epi-beta-bisabolol (d) and against HSP1 associated target protein (PDB ID: ID: 1BYQ)

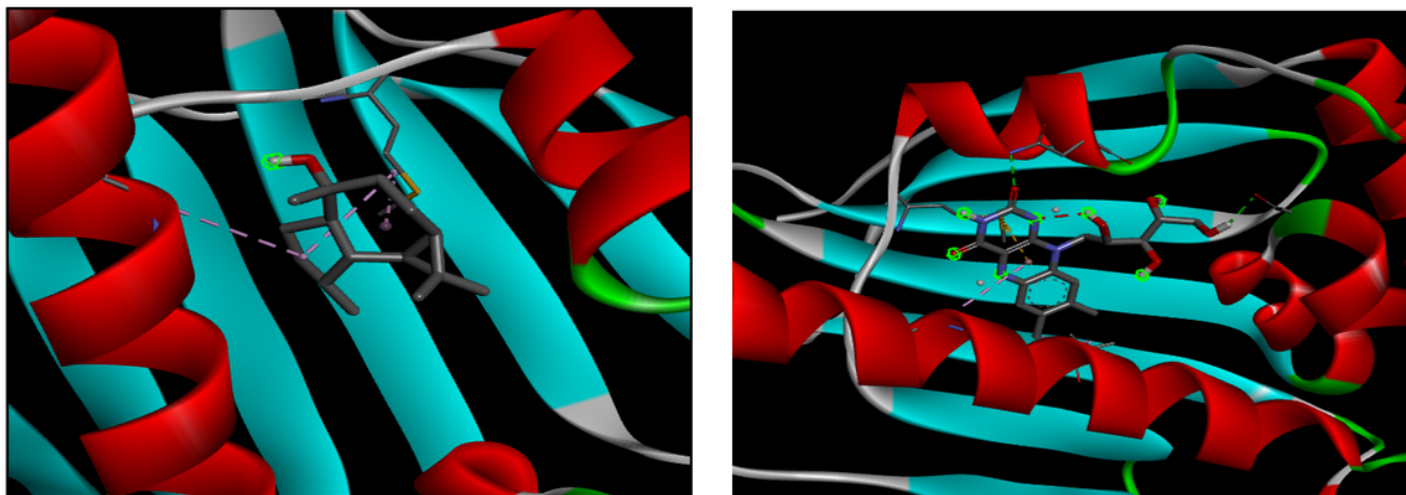


Figure 11

3D binding pose of (-)-Globulol (left) and Riboflavin (right) against HSP1 associated target

Protein (PDB ID: ID: 1BYQ)