RESEARCH PAPER

Computational Analysis of Pathogenic Pathways in Alzheimer's Disease and Prediction of Potential Therapeutic Drugs

Girish M S[1], Shakeel Ahmed Adhoni[2], Meghana. M[3], Kumaraswamy K L[4], Arya V M[5], Anshu kumar yadav[6], Navitha K R[7], Poornima D[8], Vinod R B[9], Anil Kumar K M[*9], Sunitha C Mesta [*10]

[1]Reader, Dept of Paediatric and Preventive Dentistry, JSS Dental College and Hospital, affiliate to JSS Academy of Higher Education and Research, Mysuru, Karnataka.
[2]Division of Biological Science, School of Science and technology, The University of Goroka, Eastern highland province, Papua New Guinea.
[3]Department of Biochemistry, MMK and SDM Mahila Mahavidhyalaya, Mysore-570004, India
[4]Professor and Head, Department of Oral Pathology and Microbiology, Farooqia Dental College and Hospital Mysore, India
[5]Assistant Professor, Department of Kriya Sharira, JSS Ayurveda Medical College-570028, Mysuru, Karnataka, India.
[6]Department of Biochemistry, JSS Medical College, JSS Academy of Higher Education and Research, Mysuru – 570015, Mysuru, Karnataka.
[7]Department of Environmental Science, Bangalore University – 560056, Karnataka, India.
[8]Associate Professor of Biotechnology, Tumkur University, Tumakuru – 572103
ORCID ID- 0000-0001-7665-3890
[9]Department of Environmental Science, School of Life Sciences, JSS Academy of Higher Education & Research, Mysuru, Karnataka, India.*
[10]Department of Microbiology, School of Life Sciences, JSS Academy of Higher Education & Research, Mysuru, Karnataka, India.*
Corresponding author(s).

Sunitha C Mesta, Anil Kumar K M*,*

E-mail(s)- sunitamesta@jssuni.edu.in, Anilkumarenvi@jssuni.edu.in,

ABSTRACT
Dementia, which is characterized by a decline in thinking and independence daily tasks, is mostly brought on by Alzheimer's disease (AD), a sickness that results in the degradation of brain cells. The cholinergic and amyloid hypotheses were put up as two key causes of AD, and AD is thought to be a complex illness. The condition is also influenced by a number of risk factors, including as advancing age, hereditary factors, head injuries, vascular diseases, infections, and environmental variables. Only two kinds of medications are now approved to treat AD, cholinesterase enzyme inhibitors and N-methyl d-aspartate (NMDA) antagonists. These medications only work to treat the symptoms of AD; they do not treat the underlying cause of the disease. The goal of current research is to understand the pathology of AD by focusing on a number of mechanisms, including abnormal tau protein metabolism, -amyloid, inflammatory response, cholinergic and free radical damage, in order to create effective therapies that can slow or alter the progression of AD. This overview addresses the medications that are currently on the market as well as potential possibilities for new AD therapies, such as disease-modifying therapeutics (DMT), chaperones, and natural substances.
Key words: Alzheimer's disease (AD), dementia, Molecular docking (MD)..
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INTRODUCTION

The Alzheimer Association attributes 60–80% of dementia cases to AD, a degenerative brain illness. Depending on the disease's stage, it the progression of symptoms that make it difficult to do daily tasks, including apathy, despair, decreased communication, confusion, poor judgement, difficulties swallowing and walking, and behavioral changes [1]. Age, genetics, and sex are only a few of the

**Author for Correspondence: Sunitha C Mesta, Anil Kumar K M*

variables that affect how long it takes for a continuum of these symptoms to emerge. According to data, over six million Americans aged 65 and older currently have AD, and that number is expected to rise to nearly 13.8 million by the year 2060 [2]. The progressive cognitive decline observed in Alzheimer's disease (AD) is linked to the accumulation of amyloid-beta (Aβ) and tau proteins. Aβ is generated through a series of cleavage processes of amyloid precursor protein (APP) involving beta-secretase and gamma-secretase. The aggregation of Aβ leads to the formation of toxic oligomers that harm neurons [3, 4]. Conversely, tau proteins are created through alternative splicing of the microtubule-associated protein tau (MAPT) gene, resulting in various soluble protein isoforms. Numerous functional connections have been uncovered between Aβ and tau, contributing to neural circuit damage and cognitive decline in AD. This insight emphasizes the importance of adopting a comprehensive approach when designing potential therapies for AD. [5].

An enzyme called secretase recognises the remaining membrane-bound APP and produces fragments of the A monomer that are (A40/A42) 40–42 amino acids long out of which, A40 is primarily formed, with only 10% being A42. A peptide's many monomers can aggregate as senile plaques or thick, soluble oligomers. According to the amyloid hypothesis, APP is broken down by BACE-1 to produce A-peptides [10, 11]. The misfolded peptides that are created have variable conformations, and they are discharged from donor neurons into the extracellular environment either as naked proteins or as vesicles called exosomes that recipient neurons take up via receptor-mediated endocytosis [12, 13]. By inhibiting ion channels and neurotransmitters through calcium, the produced A40/A42 accumulates on glucose transporter receptors, NMDARs, AMPARs, nAChRs, and mAChRs, impairing synaptic transmission. Astrocytes and microglia are stimulated by A plaques produced in the neurons to create chemokines and cytokines involved in the production of reactive oxygen species (ROS) [14]. By producing p53, Bad, and Bax, this induces oxidative stress and actnce of apoptotic caspases, which causes lipid peroxidation, membrane damage, and neuronal death. Protein kinases A, C, and ERK2 are all activated by ROS produced by A, which also causes tau to be hyperphosphorylated and destabilises microtubules, resulting in NFTs [15, 16]. The activation of protein kinase B (PKB) or Akt to activate glycogen synthase kinase 3 (GSK3) or tau hyperphosphorylation is another mechanism. Cyclin-Dependent Kinase 5 (CDK5) and P25 are also activated by P35-Calpain, which causes tau to be hyperphosphorylated to generate NFTs [17].

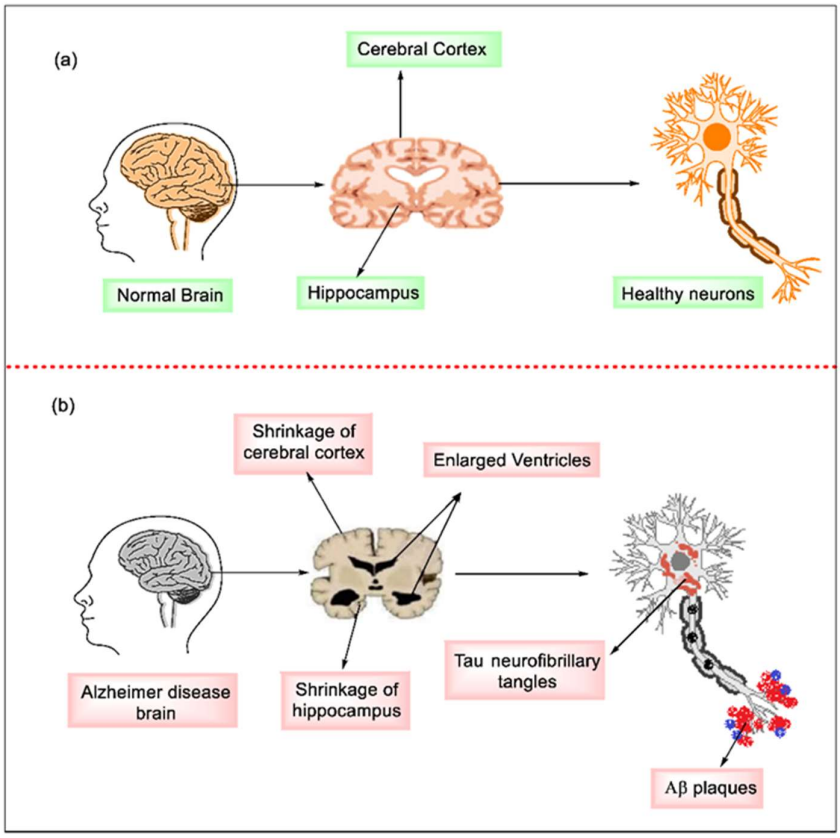


Figure 1: Physiology of the human brain a) during normal state b) during AD state [15]

Currently, there is no cure for Alzheimer's disease (AD), and the available treatments are focused on managing its symptoms. The approved medications for AD fall into two categories: cholinesterase inhibitors and partial N-methyl D-aspartate (NMDA) antagonists. [15, 16].

Eclipta alba (L.) Hassk., a member of the Asteraceae family, is known as "false daisy" in Bangladesh and India and goes by the names "bhringoraj" or "bhringraj" in traditional Indian systems of medicine, including Ayurveda, Unani, and Siddha. This herb is recognized for its significant ethnomedical uses and is considered hepatoprotective in Ayurvedic Pharmacopoeia [38]. *Eclipta alba* is a plant that grows wild in fallow fields in Bangladesh and is often considered a weed by farmers. It is frequently utilized in traditional medicine to address various health issues, including gastrointestinal disorders, respiratory ailments like asthma, fever, hair loss, liver conditions such as jaundice, skin problems, spleen enlargement, as well as cuts and wounds. This usage is prevalent not only in the Indian subcontinent but also among tribal practitioners [39].

Figure 2. *Eclipta alba* plant

Our approach involved in silico investigations to assess whether endogenous brain molecules, specifically L-phosphoserine (L-PS) and 3-hydroxyanthranilic acid (3-HAA), could bind to the specific region of β-amyloid responsible for protein misfolding. In vitro experiments were conducted to measure the effectiveness of these molecules in preventing β-amyloid aggregation at various concentrations. The results of our in-silico studies revealed that both L-PS and 3-HAA, which naturally occur in the brain, exhibited the ability to bind to the histidine13–histidine–glutamine–lysine16 (HHQK) region of β-amyloid involved in misfolding, and these interactions were thermodynamically favored. In the in vitro assays, it was demonstrated that both L-PS and 3-HAA effectively inhibited β-amyloid aggregation in a concentration-dependent manner.

Materials and Methods

2.1. Protein preparation

The complex structure proteins were targeted for insilico analysis as protein is a molecule which should constitute of efficiency with the ligand structure, chain and resolution the target protein Brain derived Neurotrophic Factor, Neurotrophin4 (1B8M), Human Gamasecretase (5A63),Apolipoprotein E4(1GS9) of X-ray crystallographic Protein Data Bank(PDB) structure with resolution of 2.75Å,3.40Å,1.70Å was extracted from the structural bioinformatics tool Research Collaboratory for Structural Bioinformatics(RCSB) protein data bank.

Then through PyMol 2.0 software is one of the user-friendly open access visualization software, where the protein is cleaned with only chain A for binding the ligands which is without constituting undesirable bonds and other water molecules are cleared and cleaned protein were retrived and saved using the access of the software link.

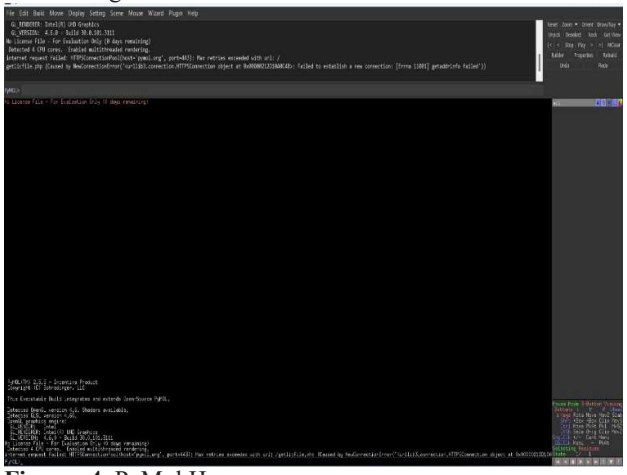


Figure :4. PyMol Home page.

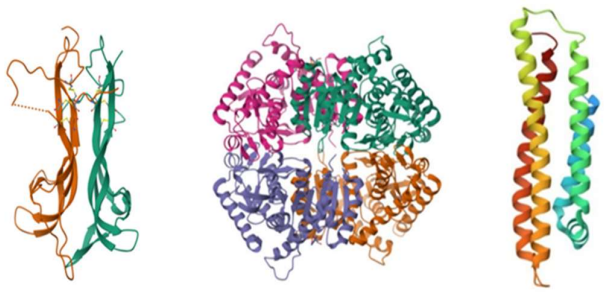


Figure:5 3D structure of Protein a)1B8M, b)5A63, c)1GS.

2.2. Protein validation

Protein purification is a method used to obtain large amounts of important proteins for research, both in labs and commercially. To isolate a specific protein from a mix for studying its function, precise techniques are required. Nowadays, there are various biochemical methods available

that can produce proteins that are over 95% pure. The authors have discussed some common chromatographic methods used in labs to obtain pure proteins. They also confirmed the quality of predicted protein models using the PROCHECK module of the PDBSum server, which considers factors like the arrangement of residues and the presence of glycine and proline residues.

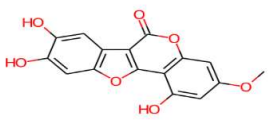
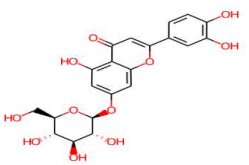
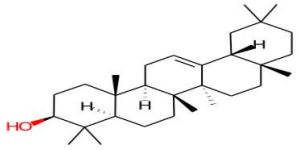
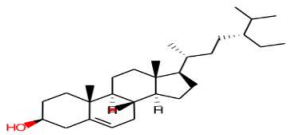
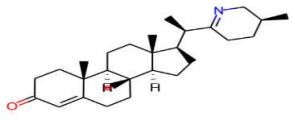
2.3. Active Site Prediction

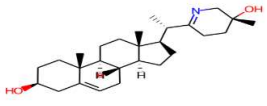
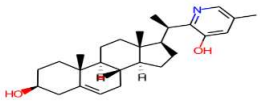
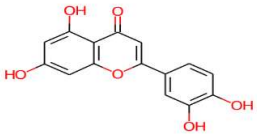
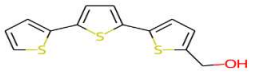
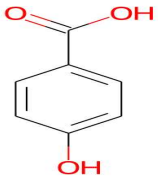
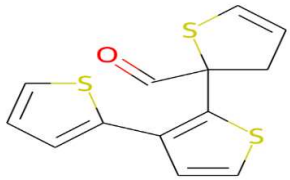
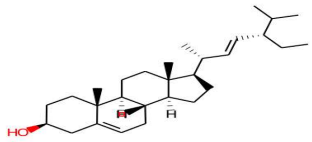
After preparing the protein, the next step is to predict its active site. While a receptor may have several active sites, we select the specific one of interest. If present, water molecules and heteroatoms are typically removed. The binding site of a protein is characterized by the specific residues within the protein that interact with the ligand. To predict this binding site, we utilized the CASTp 3.0 server, which stands for Computed Atlas of Surface Topography of Proteins. CASTp, as described by Jain et al. in 2021, is a tool that identifies and quantifies surface pockets and internal cavities. The server identifies the amino acids crucial for binding interactions based on the protein model under consideration

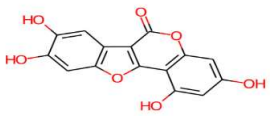
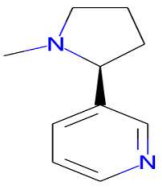
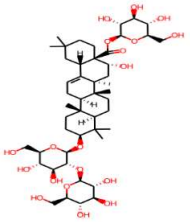
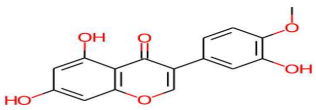
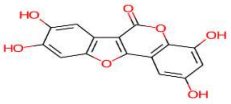
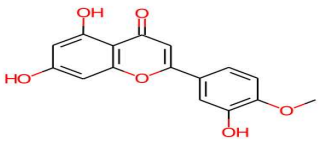
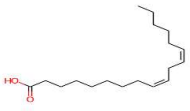
2.4. Ligand preparation

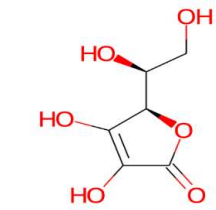
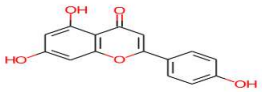
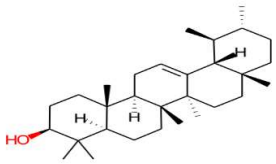
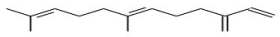
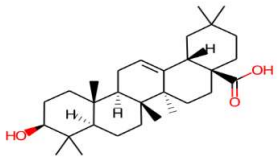
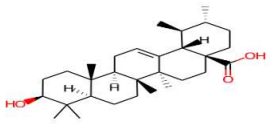
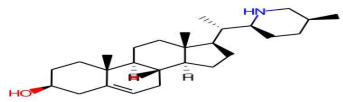
Among different phytocompounds of *Eclipta alba* ,thirty phytochemical compounds were downloaded from the format of the ligands in IMPPAT database that constitute substance ,compound 2D and 3D structure, physiochemical properties ,drugs linkages and ADMET properties based on the molecular scaffolds .In nutshell IMPPAT is largest database of the phytocompounds and provide chemoinformatic approach to overcome natural product in drug discovery .IMPPAT is the initial database used (Indian Medicinal plants ,Photochemistry ,and Therapeutics) using the access link. Through which the upgradation of phytochemical structures is done.

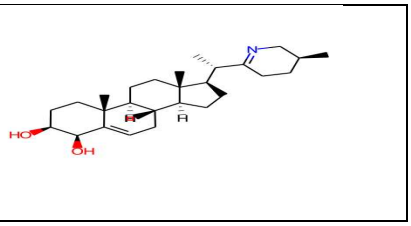
Table:1. List of phytochemicals present in *Eclipta alba*

SL.NO	PHYTOCHEMICAL IDENTEFIER	PHYTOCHEMICAL NAME	PLANT PART	STRUCTURE
1	IMPHY004585	Wedelolactone	Aerial part	
2	IMPHY011646	Cynaroside	Aerial part	
3	IMPHY012223	beta-Amyrin	Aerial part	
4	IMPHY014836	beta-Sitosterol	Aerial part	
5	IMPHY000107	phenanthren-3-one	leaf	

6	IMPHY000172	25beta-Hydroxyverazine	leaf	
7	IMPHY000543	Ecliptalbine	leaf	
8	IMPHY004660	Luteolin	leaf	
9	IMPHY009791	Alpha-Terthienylmethanol	leaf	
10	IMPHY010083	4-Hydroxybenzoic acid	leaf	
11	IMPHY014646	2-Formyl-terthienyl	leaf	
12	IMPHY014842	Stigmasterol	root	

13	IMPHY006131	Demethylwedelolactone	Whole plant	
14	IMPHY007301	Nicotine	Whole plant	
15	IMPHY002935	1-Nonacosanol		
16	IMPHY007886	Eclalbasaponin III	Whole plant	
17	IMPHY004610	Pratensein		
18	IMPHY005008	Isodemethylwedelolactone		
19	IMPHY005431	Diosmetin		
20	IMPHY014990	Linoleic acid		

21	IMPHY006362	Ascorbic acid		
22	IMPHY004661	Apigenin		
23	IMPHY011619	alpha-Amyrin		
24	IMPHY0061651	1-Heptacosanol		
25	IMPHY011658	beta-Farnesene		
26	IMPHY011826	Oleanolic acid		
27	IMPHY011880	Ursolic acid		
28	IMPHY007132	1-Hentriacontanol		
29	IMPHY001522	Veramiline	leaf	

30	IMPHY000102	4beta-Hydroxyverazine	leaf	

Once all of the ligand has been downloaded, they are cleaned and converted to PDB format, the Argus lab program must be downloaded. Followed by PyRx software link. A computational drug discovery of virtual screening used to autodoc the libraries of phytocompounds which is targeted on the disease protein by creating the macromolecule and ligand saved in docking format.

Protein validation under Ramachandran plot: Ramachandran plot is a two-dimensional (2D) plot of the torsional angles of amino acids (phi) and (psi) in a protein sequence. The phi represents the dihedral angle and psi is the backbone dihedral angle of the molecule. The physicist G N Ramachandran developed the plot in 1963. The Ramachandran plot gives the protein efficient validation that should be above 90% and above for molecular docking, if not then using galaxy web.

2.5. Binding site prediction

The protein and ligand binding structure were prepared by identifying using CASTp server that gives multiple active sites as result along with the values of the area and volume covered by the structure. The binding molecular structure was determined by choosing the specific residue in PyRx with the grid pink color analysis before to dock the protein structure. Then the protein surface binding pockets and protein void detection are displayed as the results. The database link is at URL http://sts.bioe.uic.edu/ leads to the action of molecule binding examination.

2.6. Molecular docking

The basic step before docking both the target structures were prepared by stabilizing charges, filling missing residues, followed by removing water molecules in the crystallographic structure. then this creates the target protein stable and biologically active. then the grid based molecular docking was followed using PyRx software and only the exceptional scoring fit with binding score was noted for each small molecule. the binding residues of the target protein were held rigid while the ligands are copied that gives the flexible poses of each ligand. The docking scores were saved as PDBQT format and then all the thirty docked binding pose with [kcal/mol] of each ligand were considered to analyze next for non-covalent interactions using Chimera and PyMol for visualization software.

Result and Discussion

3.1. Protein Preparation

For in-silico inhibition studies, specific enzymes were selected to dock the identified phytocompounds. These enzymes are pivotal for memory and cognition activities. The three-dimensional structures of BNDF proteins, identified through Protein Data Bank (PDB) with IDs such as 1B8M, 5A63, and 1GS9, were essential for conducting the in-silico investigations.

3.2. Protein Validation

To verify the stereochemical stability of the predicted models, we conducted additional assessments using the PROCHECK module of the PDB Sum server, which can be accessed at [https://servicesn.mbi.ucla.edu/PROCHECK/]. This evaluation involved various protein quality-based parameters, such as the percentage of residues situated within favored and allowed regions, as well as an examination of glycine and proline residues.

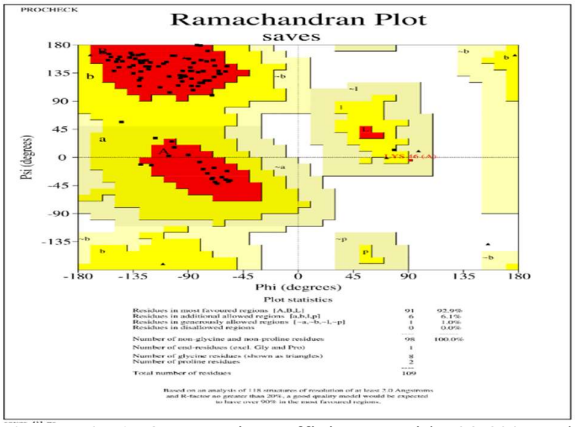


Figure 6: 1B8M protien efficiency with 92.9% under insilico analysis of Ramachandran plot predicted by PROCHECK rampage validation server.

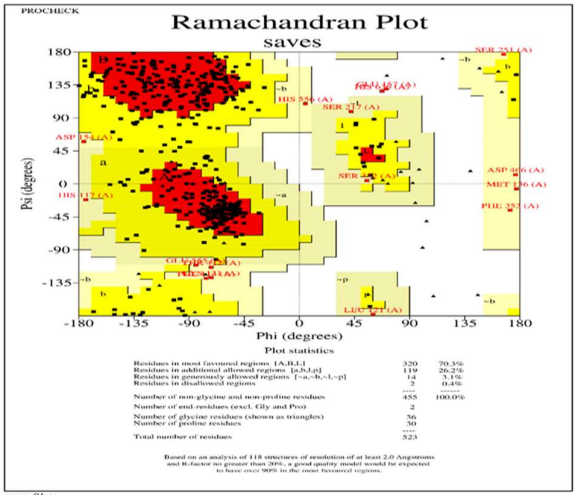


Figure:7. 5A63protein efficiency with 70.3% under insilico analysis of Ramachandran plot predicted by PROCHECK rampage validation server.

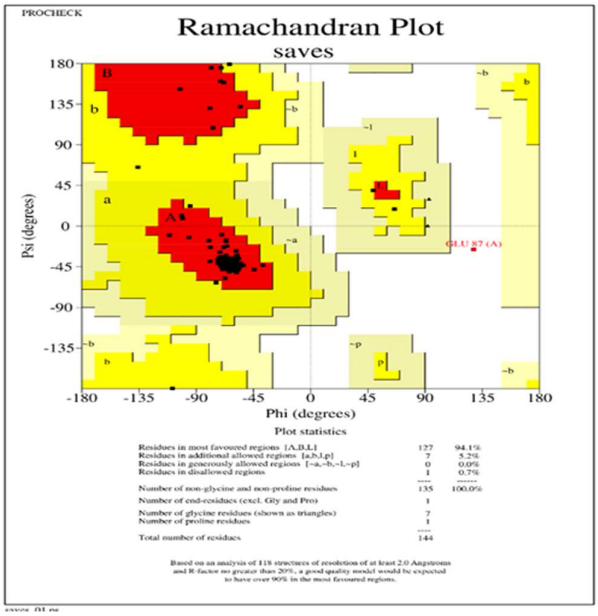


Figure:8. 1GS9 protein efficaency with 94.1% under the insilico analysis of Ramchandran plot predicted by PROCHECK rampage validation server.

3.3. Molecular Docking

The ligand is docked with the protein, and we examine their interactions. A scoring function gives a score to the best-docked ligand complex. Molecular Dynamics (MD) is a method for studying how proteins behave when they bind, commonly used in drug development. We used PyRx 0.8 for molecular docking, and a genetic algorithm was effective in exploring the space of docked conformations. Molecular docking is a technique that predicts how a ligand binds to a protein, forming a stable compound. This helps forecast the bond strength or binding affinity using scoring systems. Docking is commonly used to anticipate how potential drug candidates will bind to protein targets, a critical step in drug development. Molecular docking aims to simulate the molecular matching process and optimize the system's energy. Developing new drugs is challenging, and modern drug discovery relies on computational, chemical, and biological approaches. Computer-aided techniques in drug research and development are becoming increasingly popular. Discovery Studio 3.1 software was used to examine molecular dynamics results for interactions, both bonded and non-bonded.

Table 2: Docking results of 1B8M protein with phytochemicals of *Eclipta alba.*

Ligand	Binding affinity	Hydrogen bonds
Ascorbic acid	-6.6	3
Demethylwedelolactone	-10.8	3
Eclabasaponin III	-8.6	3
Pratensein	-10.0	3
Wedelolactone	-9.9	3

Table 3: Docking results of 5A63 protein with phytochemicals of *Eclipta alba.*

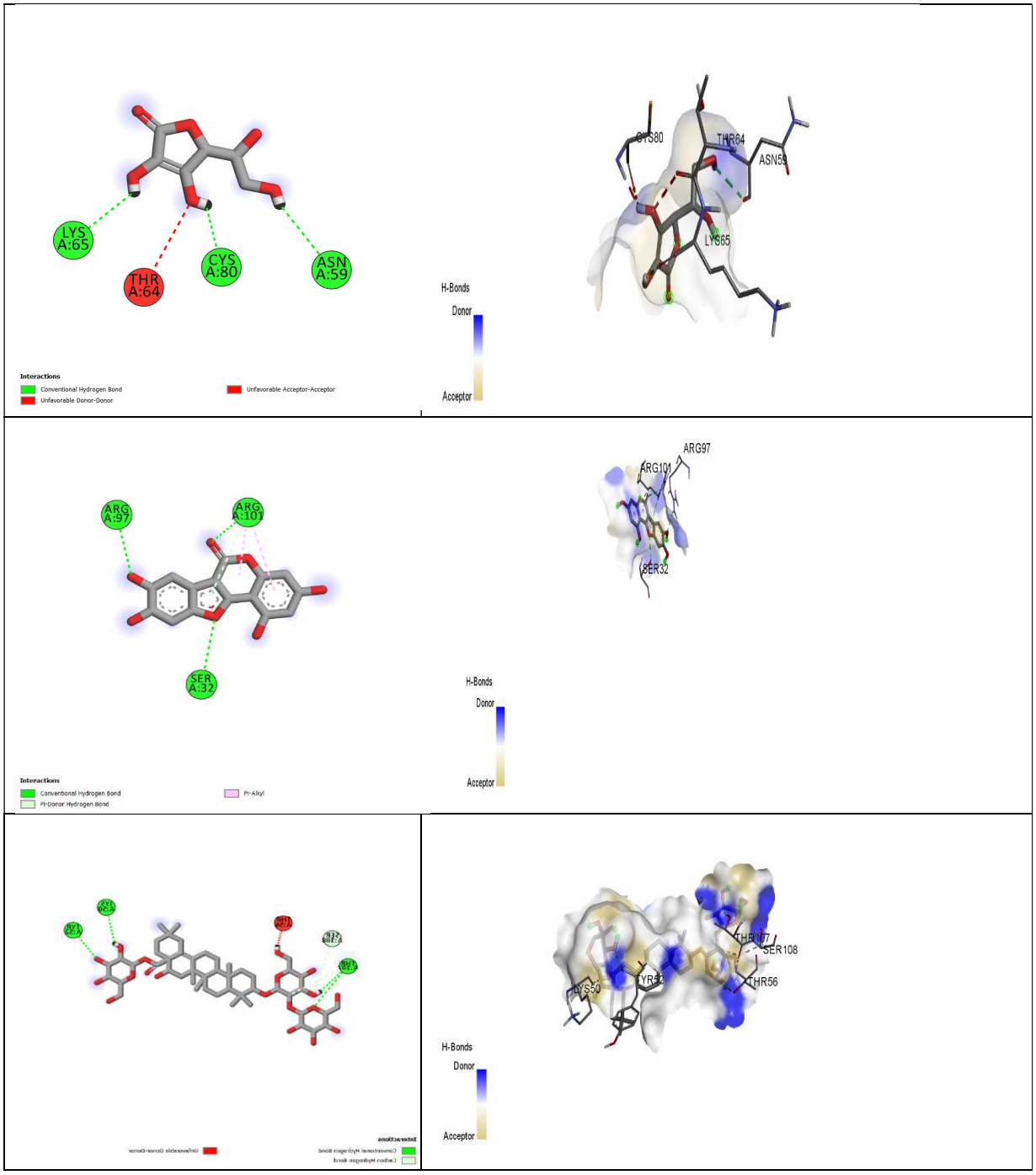
Ligand	Binding affinity	Hydrogen bonds
Apigenin	-7.8	4
Ascorbic acid	-5.1	4
Cynaroside	-5.2	5
Eclalbasponin III	-8.4	3

Table 4: Docking result of 1GS9 protein with phytochemicals of *Eclipta alba.*

Ligand	Binding affinity	Hydrogen bonds
Cynaroside	-6.4	5
Diosmetin	-8.3	3
Linoleic acid	-7.1	3
Pratensein	-8.2	3

3.4. Molecular Docking Interaction

The strength of the bond formed between a protein and its ligand is determined by their interaction affinity, which is influenced by a range of forces, including hydrogen bonds, van der Waals interactions, and hydrophobic effects. To identify the optimal orientation of the ligand-protein complex, a docking process is conducted and validated through docking scores. Binding energy scores, which take into account these various forces, are used to gauge the binding affinity in complexes with established 3D structures. For a comprehensive understanding of these interactions, advanced visualization software such as Discovery Studio 3.1 is employed to analyze both 3D and 2D interactions. In summary, the analysis and visualization of the most favorable docking poses are essential for comprehending the strength of the connection between a protein and a ligand. Prior to screening ligands, the docking process is rigorously validated by exploring diverse ligand-protein complex orientations to determine the most suitable one. The assessment of binding quality is facilitated through docking scores, and the binding affinity of a specific protein-ligand complex with a known 3D structure is quantified by calculating the binding energy score, accounting for factors like hydrogen bonds, van der Waals interactions, and hydrophobic effects. Advanced visualization tools, including Discovery Studio 3.1, are pivotal in scrutinizing both 3D and 2D interactions within these complexes, enabling the identification of vital molecular interactions like hydrogen bonding and hydrophobic contacts. By examining and visualizing the molecular docking poses and the interactions occurring within protein-ligand complexes, researchers gain valuable insights into the binding affinity and the precise molecular mechanisms contributing to the strength of the protein-ligand interaction. This knowledge is fundamental in evaluating the potential effectiveness and suitability of a particular ligand as a therapeutic agent or drug candidate.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THR A:64
CYS A:80
ASN A:59
Interactions
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Unfavorable Donor-Donor
Unfavorable Acceptor-Acceptor
H-Bonds
Donor
Acceptor
CYS80
THR64
ASN59
LYS65
ARG A:97
ARG A:101
SER A:32
Interactions
Conventional Hydrogen Bond
Pi-Donor Hydrogen Bond
Pi-Alkyl
H-Bonds
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Acceptor
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Acceptor
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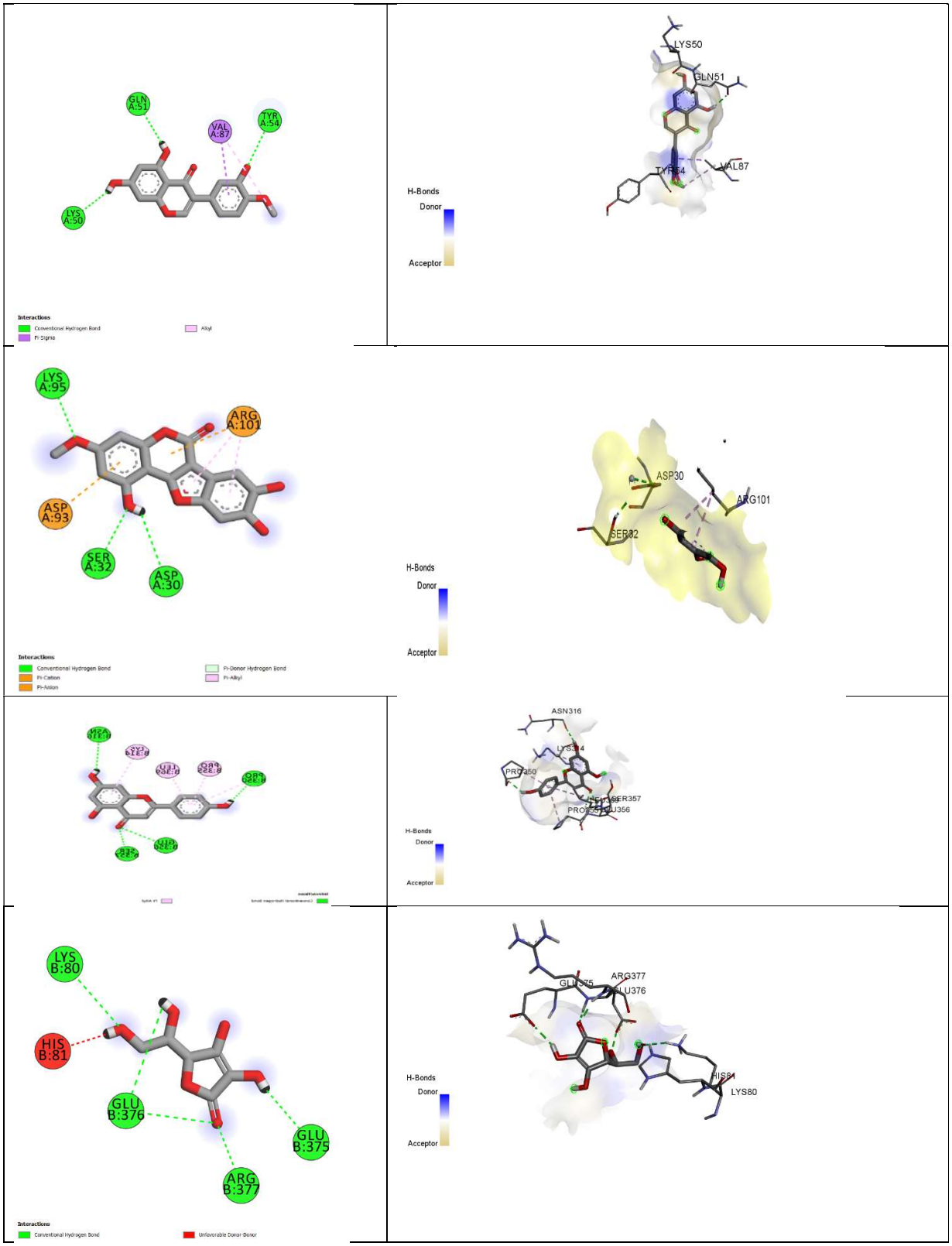
THR56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VAL A:87
TYR A:54
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Pi-Sigma
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TYR54
VAL87
H-Bonds
Donor
Acceptor
LYS A:95
ARG A:101
ASP A:93
SER A:32
ASP A:30
Interactions
Conventional Hydrogen Bond
Pi-Donor Hydrogen Bond
Pi-Cation
Pi-Alkyl
Pi-Anion
ASP30
ARG101
SER32
H-Bonds
Donor
Acceptor
ASN316
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SER357
GLU356
H-Bonds
Donor
Acceptor
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HIS B:81
GLU B:376
GLU B:375
ARG B:377
Interactions
Conventional Hydrogen Bond
Unfavorable Donor-Donor
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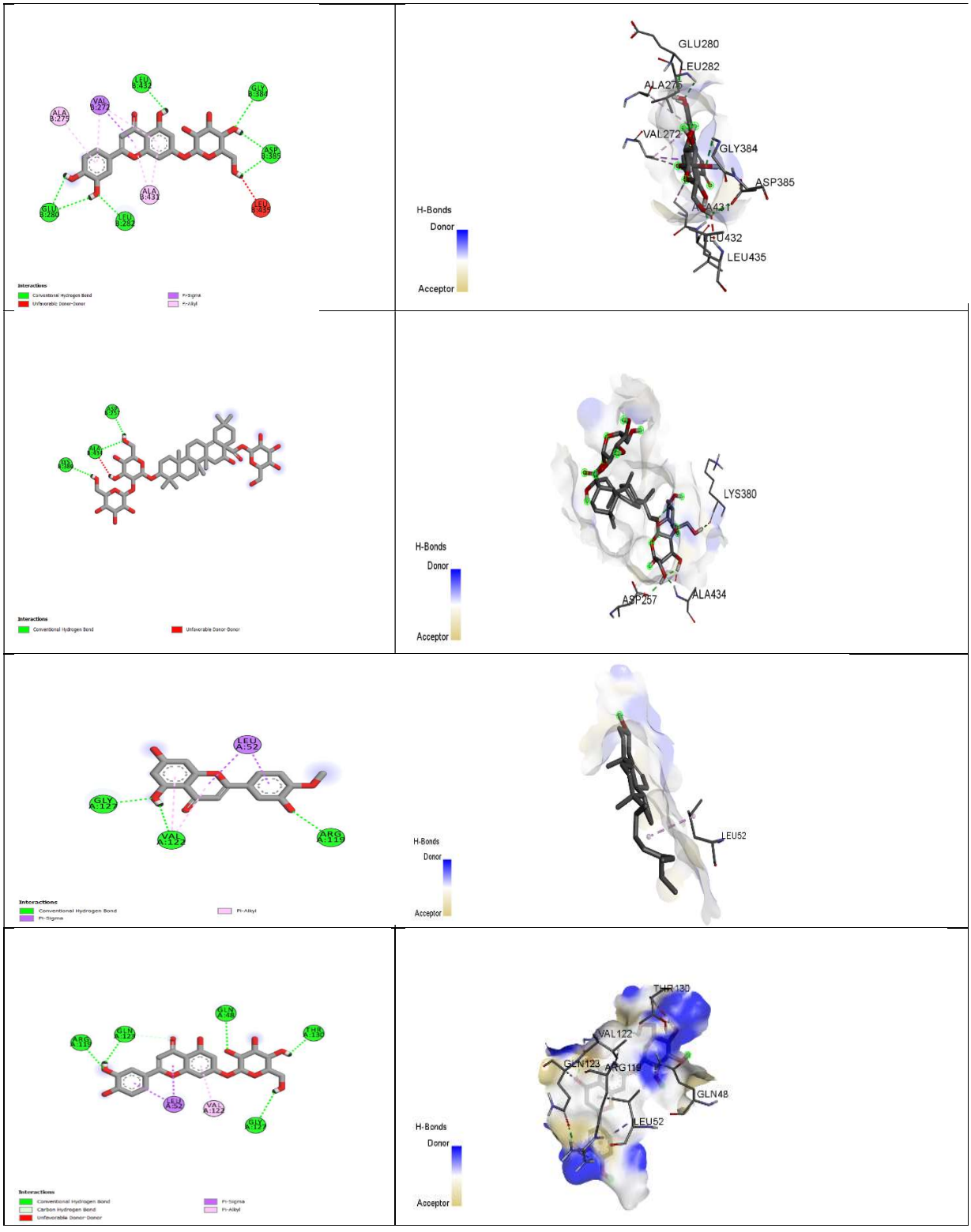
HIS84
LYS80
H-Bonds
Donor
Acceptor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H-Bonds
Donor
Acceptor
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ASP257
ALA434
LEU52
THR130
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ARG119
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Interactions
Conventional Hydrogen Bond
Unfavorable Donor-Donor
Pi-Sigma
Pi-Alkyl
Carbon Hydrogen Bond

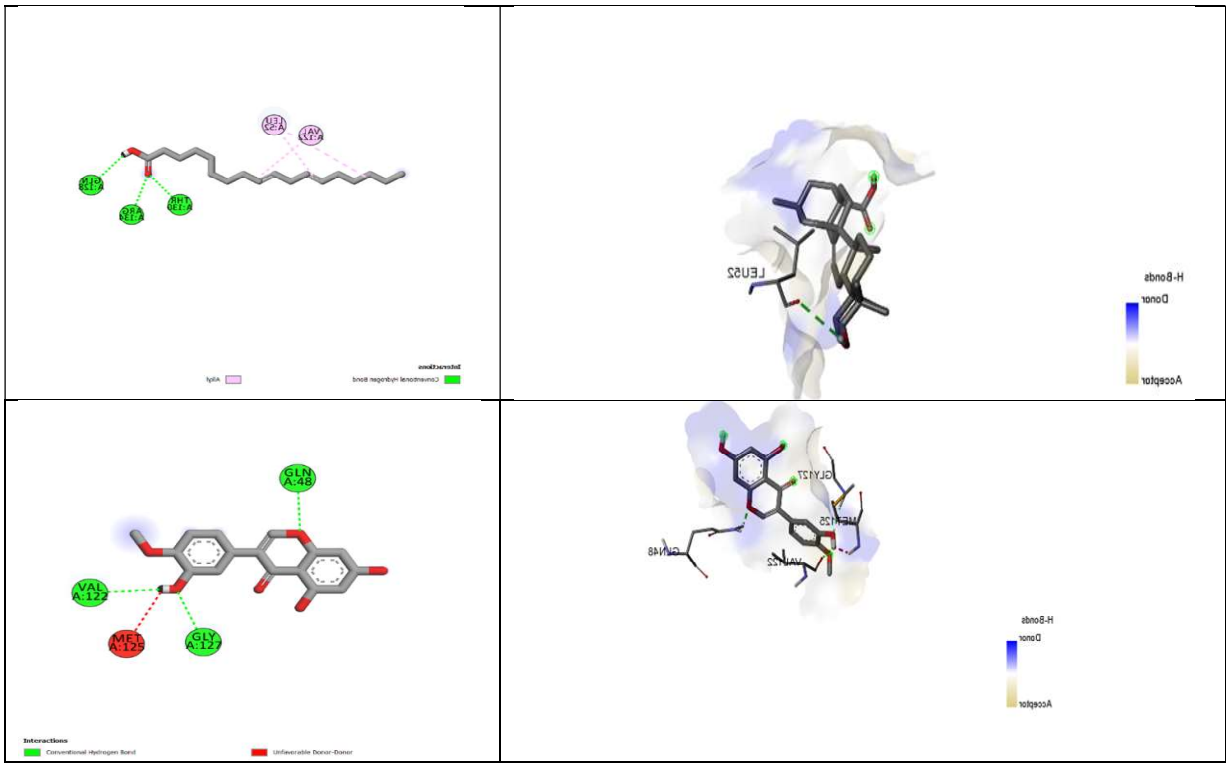

Figure 6:

Discussion

The Insilco approach of study determines the analysis of this thirty phytocompounds retrieved from *Eclipta alba* and targeted against the AD 1B8M,5A63,1GS9 protein in association with a covalent interaction constituting with respect to the molecular structure predictions using the different database and tools were used to the computational analysis. Where each protein and ligand were cleaned with the pocket atoms and took for docking level. So that, the interaction model of protein and ligand carried via molecular docking analysis using PyRx Auto dock. By this study they were visualised under the discovery studio visualizer for three-dimensional modelling of analyzed protein and small molecule were obtained. Hence, The *In-silico* studies through docking analysis showed the selected phytocompounds results with the 'five' molecules with 1B8M, four molecules with 5A63, four molecules with 1GS9 having high affinity binding level and good hydrogen interaction with ligand- target protein.

Conclusion

A collection of phytochemical compounds from *Eclipta alba* was created by employing a network-based characterization approach, drawing information from the IMPPAT database. These compounds were then analyzed through molecular docking studies, involving the use of protein structures 1B8M, 5A63, and 1GS9 as part of the investigation. During this analysis, the standardization process was conducted to evaluate and compare their binding affinity to specific proteins. Notably, the results revealed a significant degree of binding affinity among these compounds, which was particularly evident through the formation of hydrogen bonds. These interactions were targeted at a crucial protein known as Brain Derived Neurotrophic Factor (BDNF). In summary, this research involved the creation of various phytochemical compounds from *Eclipta alba* by utilizing data sourced from the IMPPAT database. Through molecular docking studies with specific protein structures, it was evident that these compounds exhibited a high degree of binding affinity, with a notable focus on forming hydrogen bonds with Brain Derived Neurotrophic Factor (BDNF). These findings hold promise for potential therapeutic applications and warrant further exploration and experimentation.

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