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In Silico Analysis and Docking Study of the Active Phytocompounds of *Bacopa monnieri* Against Alzheimer Disease

Anushka Sahu*

Abstract

Objective: *Alzheimer's is a neurodegenerative disease and is the cause of 60–70% of cases of dementia. It infected a million people worldwide. An effort was undertaken to explore the potential of natural compounds found in Bacopa monnieri, a plant renowned for its extensive medicinal properties in Indian Ayurveda, to combat the disease. This was achieved through molecular docking studies, evaluation of drug-likeness, and comprehensive ADME (absorption, distribution, metabolism, and excretion) analysis, along with toxicity predictions.* ***Methods:*** *The primary β-secretase protein was obtained from the PDB database. Ligands with weak binding affinity and molecules that could interfere with the docking process were excluded. Docking was then performed using the PyRx tool. The pharmacokinetic properties, including absorption, distribution, metabolism, and excretion (ADME), as well as the drug-likeness of the compounds, were assessed utilizing the Swiss-ADME and ChemAGG platforms.* ***Results:*** *Ramachandran plot analysis illustrates the statistical distribution of the backbone dihedral angles ϕ (phi) and ψ (psi), providing insights into the conformational preferences of the protein structure. Molecular docking studies identified that only one compound from Bacopa monnieri exhibits significant binding affinity, potentially inhibiting the β-secretase enzyme by preventing plaque formation. The ADMET analysis, along with drug-likeness and toxicity predictions, confirmed that ascorbic acid is both safe and possesses favorable drug-like characteristics.* ***Conclusion:*** *This study indicates that ascorbic acid demonstrates a specific binding affinity with the potential to inhibit the β-secretase enzyme. This suggests its potential role in therapeutic strategies for managing Alzheimer's disease.*

Keywords: Alzheimer's disease (AD), β-secretase (BACE), *Bacopa monnieri* (BM), docking, 4ACU, amyloid

INTRODUCTION

German psychiatrist Alois Alzheimer was the first to study and identify Alzheimer's disease (AD) as the primary cause of senile dementia in 1906. It cannot be diagnosed with certainty while an individual is alive and has, up to now, been associated with an unclear or complex etiology. AD is a neurodegenerative disorder that advances progressively and has no known cure. It is characterized by cognitive and functional deficiencies, loss of functional independence, and behavioral changes. Deficits in short-term memory, praxis, visuospatial impairment, and executive dysfunction are the primary cognitive signs of AD. The impact of AD on patients, caregivers, and healthcare systems is enormous. The precise cause of AD is still unknown despite decades of research; it is thought to involve several genetic, environmental, and molecular variables. In 2020, the global number of dementia patients was

***Author for Correspondence**
Anushka Sahu
E-mail: anushkasahu.1403@gmail.com

Student, School of Biotechnology, Devi Ahilya Vishwavidyalaya, University in Indore, Madhya Pradesh, India

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approximately 55 million. This figure is projected to reach 78 million by 2030 and is expected to nearly double by 2050, rising to 139 million.

A key protein involved in the development of AD is beta-secretase, also known as beta-site amyloid precursor protein (APP) cleaving enzyme 1 (BACE1). The production of the amyloid-beta peptide (Aβ), a crucial factor in the advancement of the illness, is facilitated by its multifarious involvement in AD . The Golgi apparatus and endoplasmic reticulum of neurons are the primary locations for the aspartyl protease enzyme BACE1. It cleaves the APP at the beta-secretase site, which is the main way it helps AD by starting the peptide formation of Aβ. Neurotoxic oligomers and amyloid plaques are the result of the accumulation of Aβ peptides, especially the more hydrophobic and longer Aβ42 form . These plaques cause neuroinflammations that impair neuronal function and are linked to cell death and malfunction in synapses. BACE1's connection to the initial phases of Aβ synthesis highlights its function in AD. While overexpression or overactivity of BACE1 is often detected in sporadic AD, which accounts for most cases, overproduction of Aβ is caused by mutations in either the presenilin or APP genes in familial AD cases. Consequently, a primary objective in the development of AD treatments has been to inhibit the activity of BACE1. It is believed that decreasing Aβ generation will slow or perhaps stop the disease from progressing . It is crucial to remember that BACE1 has substrates besides APP, and therefore totally inhibiting BACE1 could have unexpected effects. Furthermore, the link between Aβ and AD is complicated, and the disease is also greatly influenced by other variables such as inflammation and tau pathology.

The medical system known as Ayurveda originated in India and has persisted as a separate entity from distant antiquity to the present. The Ayurvedic tradition emerged and evolved in India between 2500 and 500 BC. Often referred to as the "science of longevity," Ayurveda provides a comprehensive framework for promoting a long and healthy life. . Ayurveda provides programs designed to rejuvenate the body through proper diet and nutrition. It also offers therapeutic approaches to address various common ailments, including food allergies, for which there are limited modern treatment options.

Bacopa monnieri (BM) has been utilized by Ayurvedic practitioners in India for nearly 3000 years and is categorized as a *medhyarasayana*, a type of herbal remedy that enhances memory and cognitive function (*medhya*). The earliest documented reference to BM can be found in various ancient Ayurvedic texts, such as the *Caraka Samhita* (6th century A.D.), where it is recommended in formulations for addressing a variety of mental health issues, including anxiety, impaired cognition, and lack of concentration. Additionally, it is mentioned in the *Bravprakash Var-Prakarana* (16th century A.D.). *Bravprakash Var-Prakarana* (16th century A.D.) Brahmi, or BM (Linn.) Pennell (Scrophulariaceae), is a well-known Ayurvedic herb that is said to enhance memory and cognition. BM may be able to enhance cognition, according to a meta-analysis of randomized controlled trials on the extract's effects on cognition.

It also has demonstrated significant pharmacological properties such as gastrointestinal discomfort, rejuvenation, promoting memory and intellect, skin disorders, epilepsy, pyrexia, and analgesia as well as antiepileptic, anxiolytic, depressive, sedative, antioxidant, and anti-inflammatory properties. It was discovered that the standardized extract of Bacopa enhanced with bacosides functionally activated the synaptic proteins. Neurological conditions such as AD, anterograde/retrograde amnesia, memory loss brought on by okadaic acid, aluminum chloride, a specific protein phosphatase inhibitor, oxidant damage, and signs of autism brought on by sodium valproate, a feeble sodium ion. Bacopa therapy has been demonstrated to enhance channels and Gamma-Aminobutyric Acid (GABA) transaminase inhibitors. The decrease of cholinergic neuronal activity in the hippocampus is the main characteristic of AD. It has been discovered that BM reduces the acetylcholinesterase (AChE) activity throughout the brain, which may possibly indicate that BM is a useful memory-restoring medication in the treatment of Alzheimer's and other related dementias. In this study, an attempt was made to identify new active

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and stable inhibitors of beta-secretase protein (4ACU) from a total of 34 different active phytocompounds of the BM plant.

MATERIAL AND METHODS

Protein Preparation

The three-dimensional (3D) crystal structure of the β-secretase [BACE-1] protein (Protein Data Bank (PDB) ID: 4ACU) was retrieved from the Research Collaboratory for Structural Bioinformatics PDB (*https://www.rcsb.org/*) (Figure 2). It has a single chain A consisting of 411 amino acids. It has a crystal resolution of 1.75Å. Prior to docking, protein crystal structures are prepared to optimize hydrogen bonding and eliminate atomic collisions. Using the Discovery Studio Visualizer 21.1 standard protocol, protein preparation was carried out. After removing the water molecules and heteroatoms from the proteins, polar hydrogen was introduced. Moreover, the prepared protein's active site was predicted.

Ramachandran Plot

A plot of a peptide's torsional angles, phi, and psi, is called a Ramachandran plot. Utilizing the web-based PDB sum service of EMBL-EBI (*https://www.ebi.ac.uk/thornton-srv/databases/cgi-bin/pdbsum/GetPage.pl?pdbcode=4acu&template=procheck_summary.html*), a Ramachandran plot analysis was conducted. After submitting the PDB ID for Protein (4ACU), a Ramachandran plot analysis was performed, labeling outliers according to the type, number, and chain of residues and showing all the labels.

Ligand Selection

A total of 36 active phytocompounds from BM were extracted to document possible BACE-1 inhibitors. The 3D SDF (Three-Dimensional Structure Data File) format was used to retrieve phytocompound structures from the PubChem chemical database (*https://pubchem.ncbi.nlm.nih.gov/*). The PyRx tool was used to optimize the ligand, minimize its energy, and convert it to a 3D PDB format to prepare it for use.

Molecular Docking

The molecular docking method simulates the atomic-level interaction between a tiny molecule and a protein, allowing us to better understand fundamental biochemical processes and define the behavior of small molecules in the binding sites of target proteins.

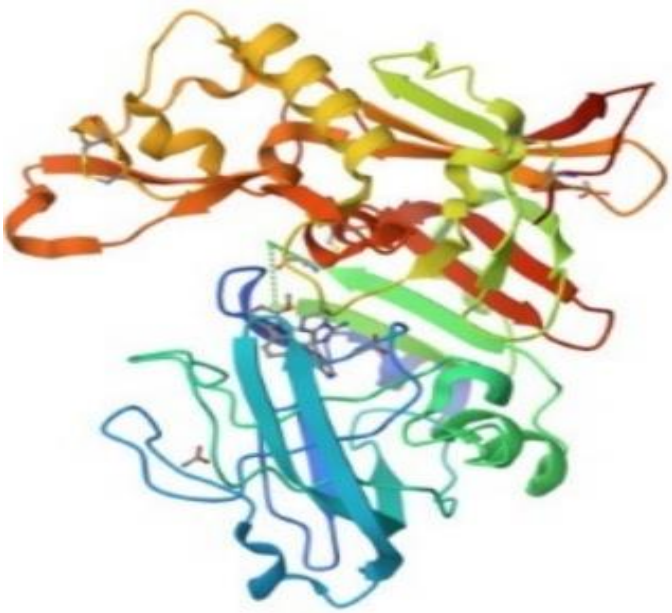

Figure 2. 3D structure of beta-secretase (4ACU) protein.

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The molecular docking investigation employed PyRx, a virtual screening tool software. All 36 active phytocompounds of BM were docked with BACE-1 using the PyRx program (PDB ID: 4ACU). Targets for the docking investigation were specified using prepared receptors and ligand files. Using the tool's open-babel tab, ligands were imported and produced once the protein was loaded and transformed into a macromolecule for docking . The grid box was defined by maximizing to examine all possibilities for ligands to bind with proteins after the protein and ligand molecules were identified. Docking was initiated by clicking the forward button after everything had been adjusted. Following docking, we were given a table with each ligand's binding affinity. The top five ligands were selected for further study based on the highest binding affinity of the ligand, but they did not pass ADME analysis. The next top five compounds are selected and saved in PDB file format. Discovery Studio Visualizer 21.1 was used to conduct an interactive two-dimensional (2D) 3D visualization investigation.

Analysis of Absorption, Distribution, Metabolism, and Excretion (ADME)

SwissADME (*http://www.swissadme.ch/*) was employed to evaluate the pharmacokinetic parameters of the ligands, focusing on absorption, distribution, metabolism, and excretion (ADME). The primary aim of this analysis is to provide insights that support drug development. These four criteria influence the compound's performance and pharmacological activity, as they play a crucial role in determining drug levels and the kinetics of drug exposure within tissues. In this research study, the top five compounds having the highest binding affinity were taken for the drug-likeness test and ADMET analysis, but they did not pass the test. The next five compounds were taken for drug-likeness, and ADMET analysis was done using SWISS-ADME (*http://www.swissadme.ch/*) [26] and ProTox 2 (*https://tox-new.charite.de/protox_II/*). Boiled-Egg analysis was also carried out with the SWISS-ADME tool (Figure 3). The ADME analysis took Lipinski's rule of five into account. When a molecule conforms to two or more of the five criteria listed by Lipinski, it can be predicted whether a drug-likeness will be successful. Conditions,

1. Molecular mass.
2. Log P < 4.15.
3. H-bond donor < 5.
4. H-bond acceptor < 10.
5. 40<molar refractivity < 130.

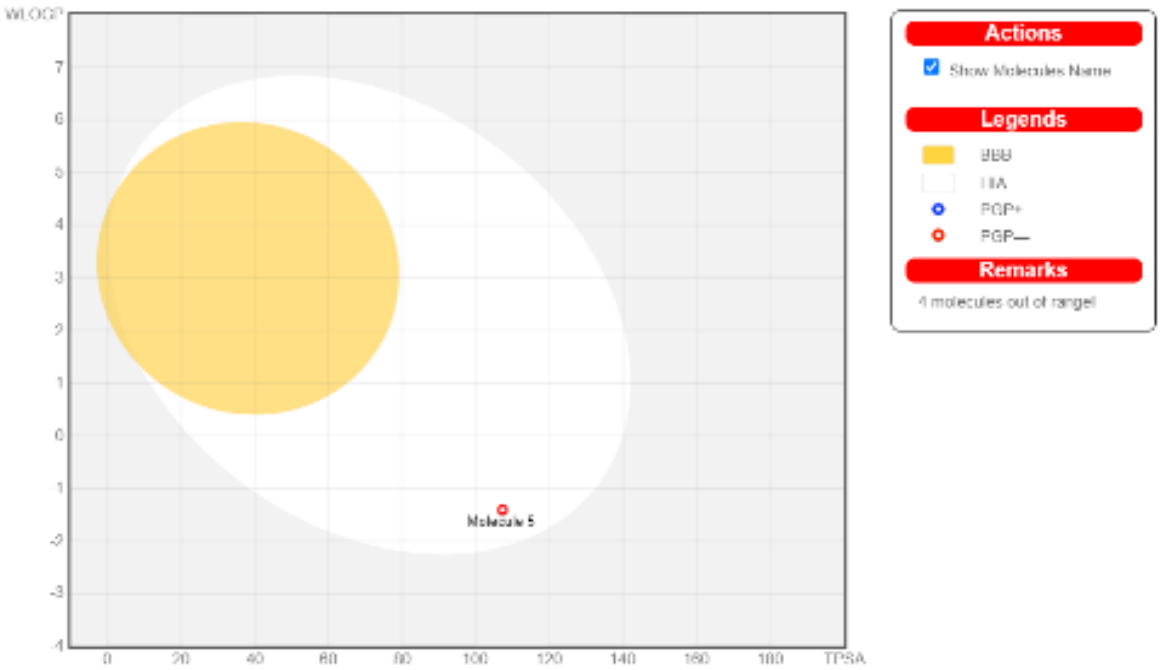

Figure 3. Boiled-egg analysis: Ascorbic acid.

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RESULTS

Ramachandran Plot

In the Ramachandran plot (Figure 1), considering protein geometry as below,

Residues in most favored regions [A, B, L]	286	89.9%
Residues in additional allowed regions [a, b, l, p]	31	9.7%
Residues in generously allowed regions [~a, ~b, ~l, ~p]	1	0.3%
Residues in disallowed regions	0	0.0%
Number of non-glycine and non-proline residues	318	00.0%
Number of end-residues (excl. Gly and Pro)		3
Number of glycine residues (shown as triangles)		33
Number of proline residues		18
Total number of residues		**372**

Molecular Docking

According to molecular docking research, one of BM's active phytocompounds has a strong binding affinity for 4ACU. The top five phytocompounds from BM that have the most affinity for binding 4ACU (Table 1). We discovered that 10 of the 36 compounds from BM exhibit a considerable binding affinity (more than 9 Kcal/mol) with 4ACU based on the findings of molecular docking studies conducted using PyRx. The top five compounds (Table 2) were chosen based on docking results for ADME analysis and drug-likeness prediction.

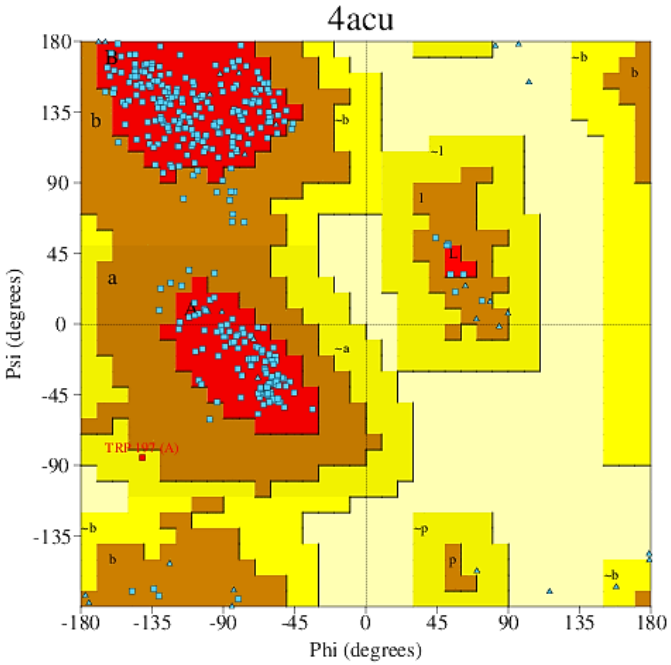

Figure 1. Ramachandran plot analysis of 4GH9.

Table 1. The top 5 phytocompounds from *B. monnieri* have the highest binding affinity with beta-secretase.

S.N.	PubChem Compound ID	Name of Phytocompound	Binding energy (kcal/mol)
1	CID_11636	Heptacosane	–9.8
2	CID_92043183	Bacoside-A	–9.6
3	CID_129636603	Stigmastenol	–9.5
4	CID_21599442	Bacopaside l	–9.4
5	CID_54670067	Ascorbic acid	–9.5

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Table 2. ADME analysis of best-docked compounds based on Lipinski's rule.

S.N.	Ligand name	Molecular weight (g/mol)	H-bond donor	H-bond acceptor	Log-P	Molar refractivity
1.	Heptacosane	380.73	0	0	7.32	131.9
2.	Bacoside A	768.97	8	13	4.96	198.88
3.	Stigmastenol	414.71	1	1	5.13	133.64
4.	Bacopaside l	979.13	9	20	3.62	232.37
5.	Ascorbic acid	176.12	4	6	0.39	35.12

Molecular Visualization

Discovery Studio Visualizer 21.1 was used to visualize the interactions between the receptor and ligand of the top five phytocompounds with the highest binding affinity. PyRx was used to save docked ligands in PDB file format, which was subsequently opened by pure protein 4ACU. Various 2D and 3D interactions between phytocompounds and 4ACU were noted. We saw a variety of interactions on a 2D interaction diagram, including Van der Waals forces, conventional and carbon-hydrogen bonds, Pi-sulfur interactions, alkyl and Pi-alkyl interactions, Pi-Pi T-shaped interactions, and unfavorable interactions [28, 29].

Heptacosane

Heptacosane forms different 2D-3D interactions with 4ACU. It includes a pi-sigma bond with residue LYS 107 only, carbon-hydrogen bond with TYR 71 formed as shown in Figure 4.

Bacoside-A

Bacoside-A forms different 2D-3D interactions with 4ACU. It includes conventional hydrogen bonds with GLY 11, THR 232, and TYR 298; forms alkyl bonding with ILE 126; forms carbon-hydrogen bond with SER 35; and forms unfavorable donor-donor with ASN 233 formed, as shown in Figure 5.

Stigmastenol

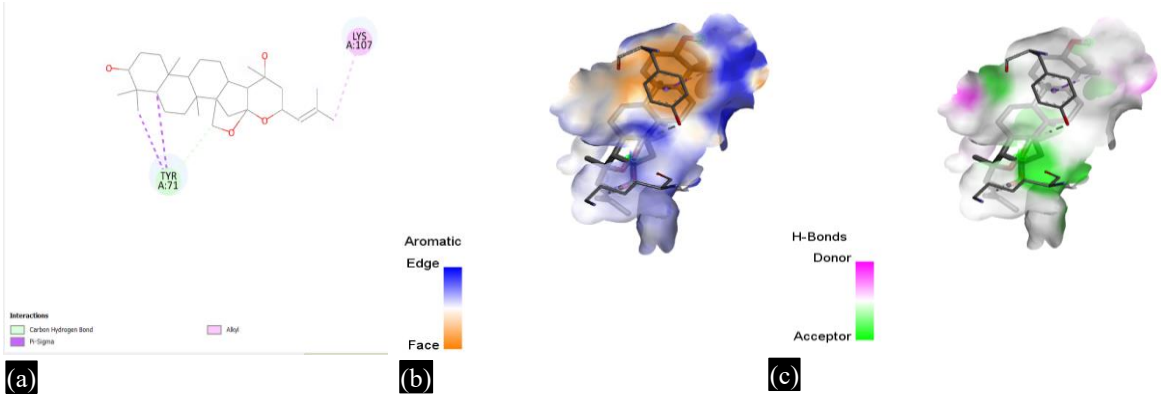
Stigmastenol forms different 2D-3D interactions with 4ACU. It includes a conventional hydrogen bond with ARG 128 residues only; and forms Pi-alkyl bond with TYR 71, as shown in Figure 6.

Bacopaside-1

Bacopaside-1 forms different 2D-3D interactions with 4ACU. It includes a conventional hydrogen bond with ASN 233, ARG 307, GLY 11, THR 232, GLY 230, TYR 198, and ARG 128 and forms an alkyl and PI-alkyl bond with residues TRP 76 and VAL 69, as shown in Figure 7.

Ascorbic Acid

Ascorbic acid forms different 2D-3D interactions with 4ACU. It forms a conventional hydrogen bond with residues ARG 128, TYR 198, ASP 228, ARG 235, ASP 32, and SER 325. It also forms a carbon-hydrogen bond with SER 35 residue. It also forms an alkyl bond with LYS 321, as shown in Figure 8.



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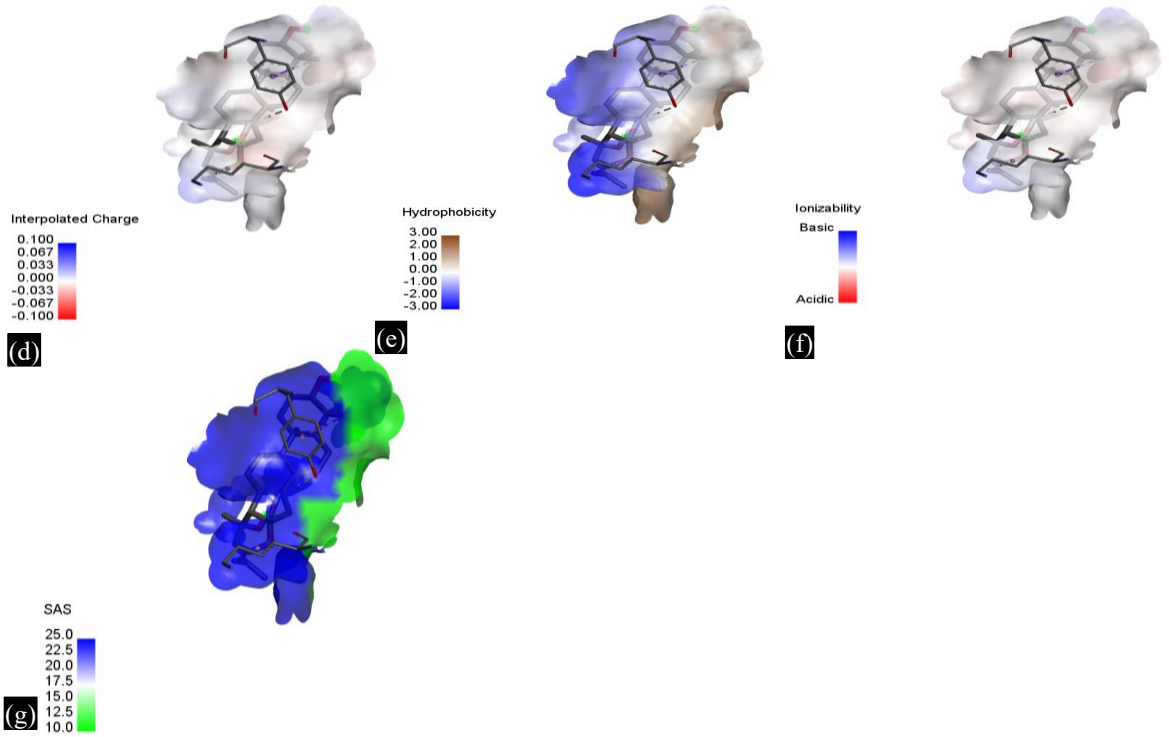
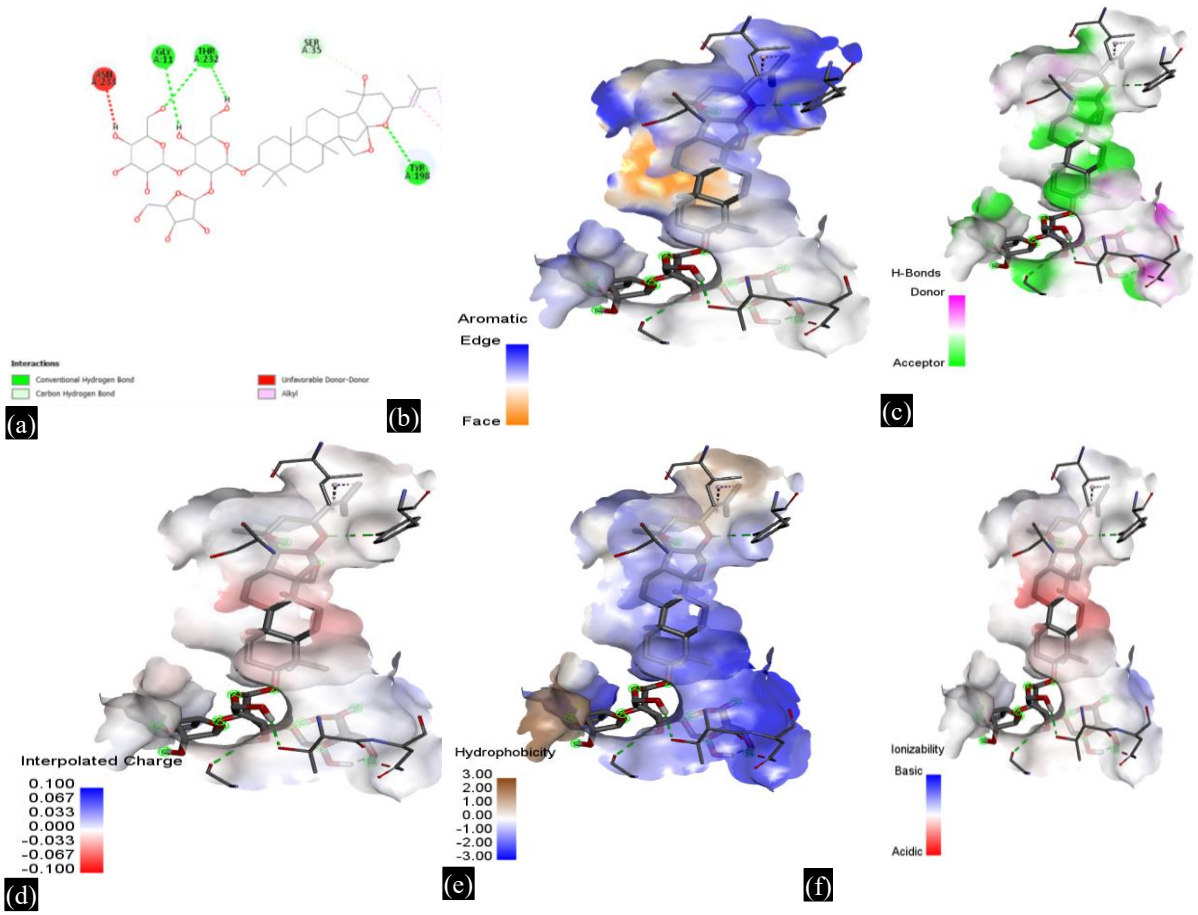


Figure 4. 2D and 3D diagram of interactions of heptacosane with beta-secretase (4ACU) (a) 2D structure (b) aromatic (c) H-bonds (d) interpolated charges (e) hydrophobicity (f) ionizability (g) SAS.



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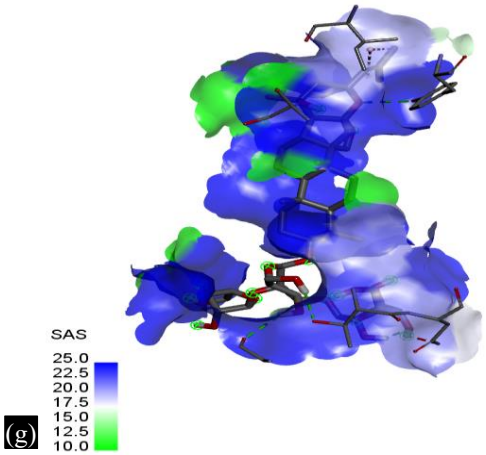

Figure 5. 2D and 3D diagram of interactions of Bacoside-A with beta-secretase (4ACU)(a) 2D structure (b) aromatic (c) H-bonds (d) interpolated charges (e) hydrophobicity (f) ionizability (g) SAS.

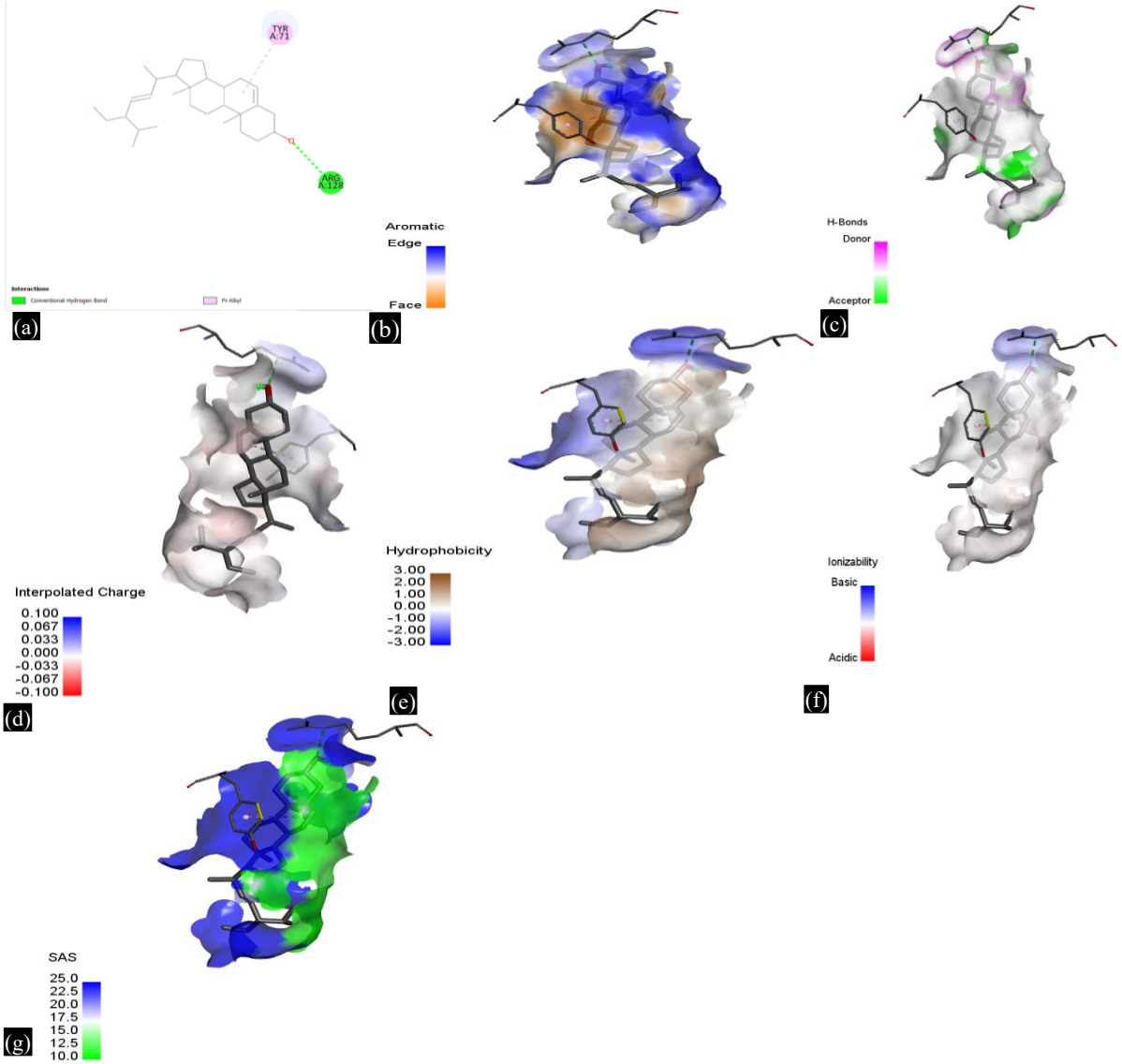

Figure. 6. 2D and 3D diagram of interactions of Bacopaside-l with beta-secretase (4ACU) (a) 2D structure (b) aromatic (c) H-bonds (d) interpolated charges (e) hydrophobicity (f) ionizability (g) SAS.

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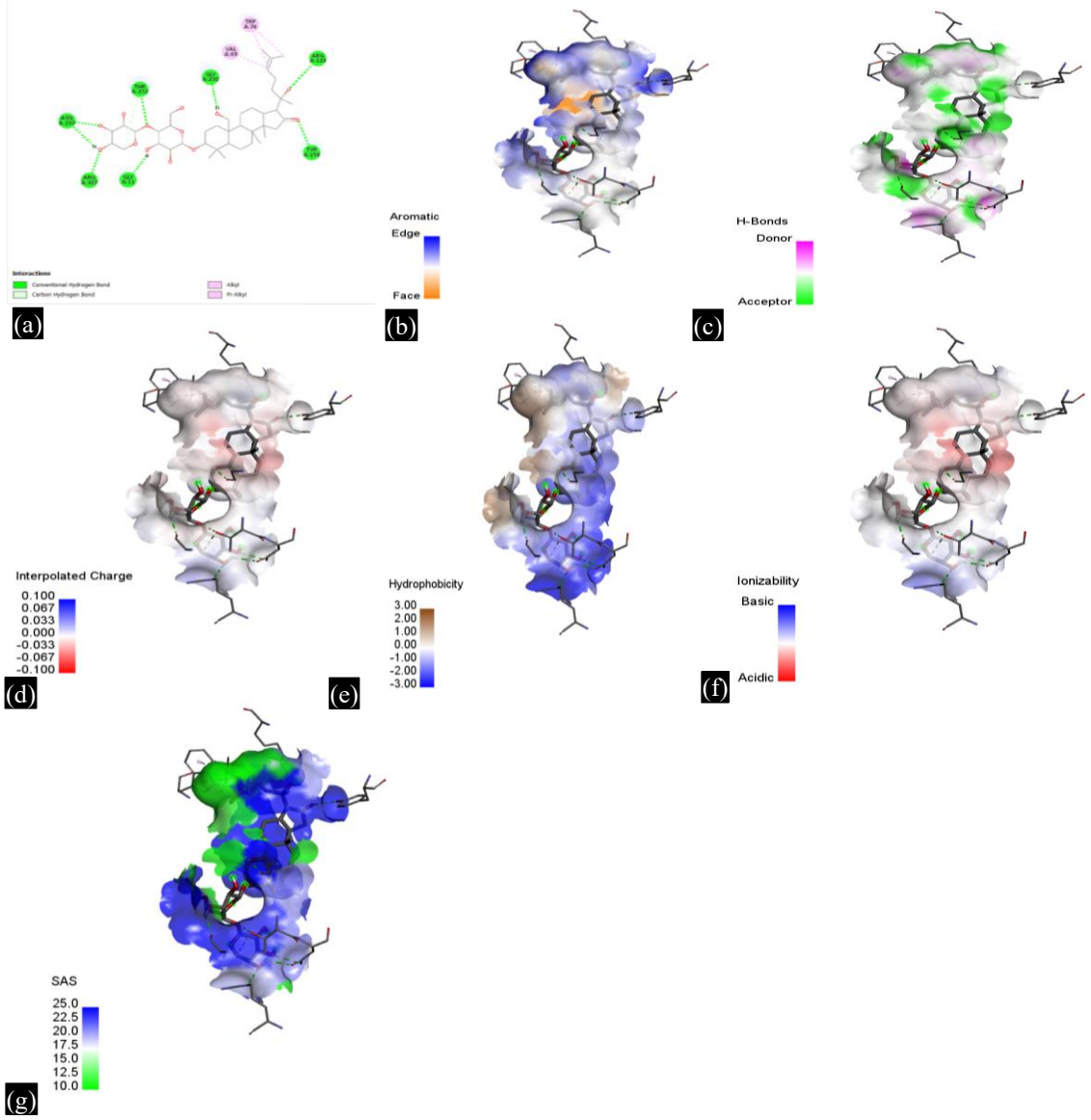
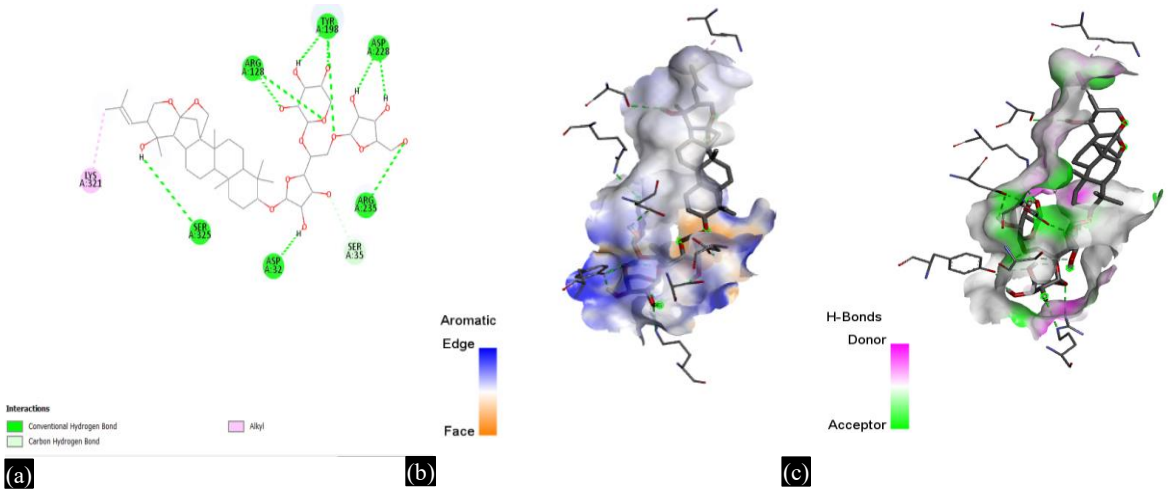


Figure 7. 2D and 3D diagram of interactions of Bacopaside-l with beta-secretase (4ACU) (a) 2D structure (b) aromatic (c) H-bonds (d) interpolated charges (e) hydrophobicity (f) ionizability (g) SAS.



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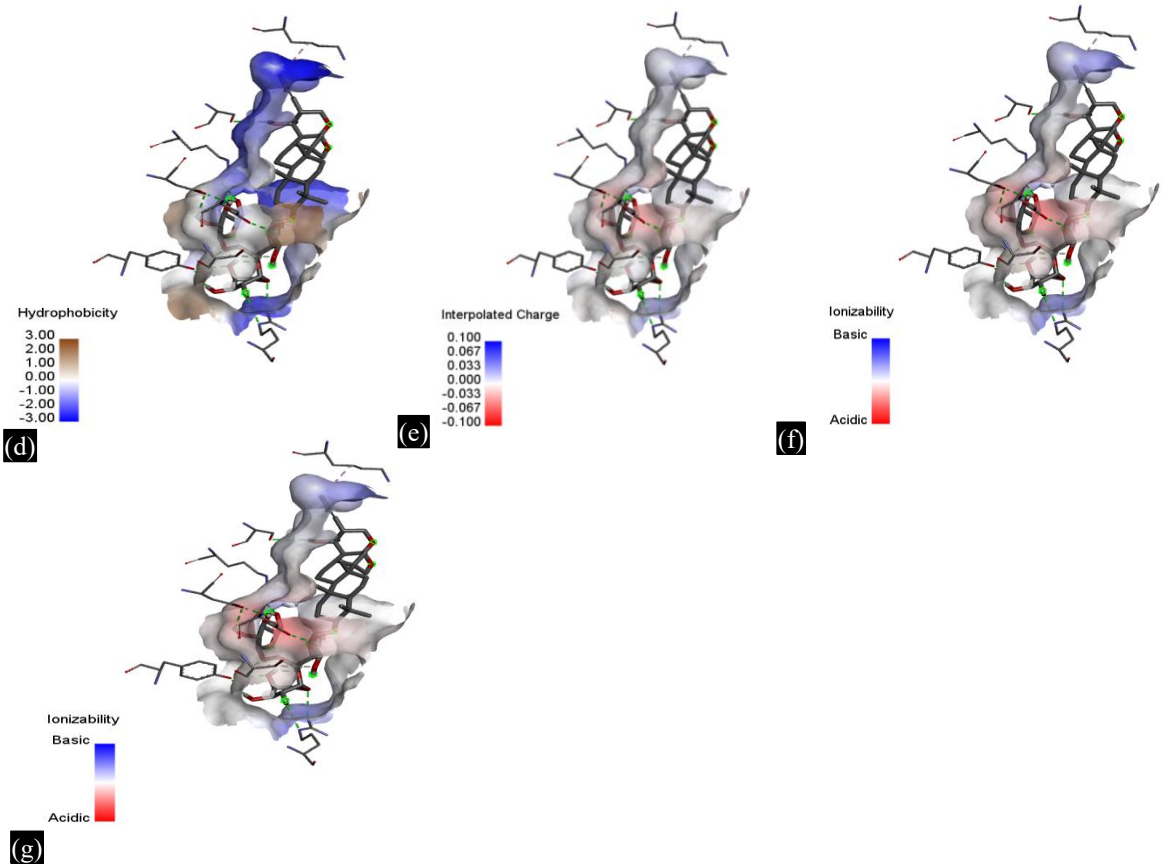

Figure 8. 2D and 3D diagram of interactions of ascorbic acid with beta-secretase (4ACU). (a) 2D structure (b) aromatic (c) H-bonds (d) interpolated charges (e) hydrophobicity (f) ionizability (g) SAS.

Drug-Likeness Prediction, ADMET Analysis, and Toxicity Prediction

Lipinski's rule of five helps distinguish between molecules that are drug-like and those that are not by considering five different factors. For the best-docked compounds, drug-likeness prediction was carried out. Utilizing Lipinski's rule of five, ADME analysis was carried out with the ProTox 2 server and the Swiss.

ADME web server. Analysis of boiled eggs was additionally conducted utilizing ProTox and the Swiss-ADME tool (Table 2). The toxicity was calculated using two prediction servers (Table 3). Furthermore, BOILED EGG analysis was performed using the Swiss-ADME technique. Watch for the blood-brain barrier's passive brain access forecast (BBB) as well as intestinal absorption (HIA) and gastrointestinal absorption of some phytocompounds (Figure 3).

Furthermore, the human intestinal absorption (HIA), permeability, and water solubility (logS) of the best-docked compounds were assessed using the standard scale, along with evaluations based on Lipinski's rule of five, potential carcinogenic consequences, blood-brain barrier (BBB) penetration, and glycoprotein substrate verification (Table 4).

DISCUSSION

In modern medicine, AD is treated with anti-viral and cognitive stimulation therapies. Natural phytocompounds from medicinal plants such as BM can be utilized due to their lower toxicity compared to synthetic compounds. Molecular docking, ADME analysis, and molecular dynamic simulation are examples of in silico techniques that have been demonstrated to be useful for more research to examine the ligand's stability, interactions, and binding affinity with the target.

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Table 3. Toxicity prediction using ProTox-2 server.

S.N.	Ligand name	Predicted LD50 (mg/kg)	Predicted toxicity	Avg. similarity class	Prediction accuracy
1.	Heptacosane	750	3	100%	100%
2.	Bacoside-A	1500	4	86.43%	70.97%
3.	Stigmastenol	5000	5	77.45%	69.26%
4.	Bacopaside l	225	3	60.29%	68.07%
5.	Ascorbic acid	3367	5	100%	100%

Table 4. ADME analysis using Swiss-ADME.

S.N.	Ligand name	LogS	HIA	PGP-sub	BBB	Lipinski's rule
1.	Heptacosane	–9.59	Low	Yes	No	1
2.	Bacoside-A	–5.69	Low	Yes	No	3
3.	Stigmastenol	–8.78	Low	No	No	1
4.	Bacopaside l	–5.88	Low	Yes	No	3
5.	Ascorbic acid	0.1	High	No	No	0

In addition to affecting the host's immunity, BACE1 is an enzyme that cleaves the APP to generate Aβ peptides, particularly the longer and more aggregation-prone forms of Aβ. In AD, the accumulation of Aβ peptides can lead to the formation of toxic Aβ aggregates and the subsequent neuronal damage and cognitive decline associated with the disease. Hence, beta secretase can be considered as a significant target. The Ramachandran plot illustrates the statistical distribution of backbone dihedral angles ϕ and ψ, representing the allowed conformations of proteins.

A current study revealed the role of phytocompounds from BM, which have multiple medicinal properties according to Ayurveda. The research study indicates that one of the phytocompounds from the source shows promising potential for further investigation. BM has been found effective against AD. For the research study, 4ACU was analyzed for Ramachandran plot to validate the purity of the protein, and there were no outliers and poor rotamers observed. Z-score of protein observed was –1.31 for whole residues. To conduct an in-silico study, the molecular docking technique was utilized to verify the binding affinity of all 34 phytocompounds against the beta secretase protein (PDB ID: 4ACU). Heptacosane, bacoside A, ascorbic acid, stigmastenol, and bacopaside-1 were the five phytocompounds from BM that had the highest binding affinity after the compounds that do not follow ADME analysis. After molecular docking study, all the five compounds were further studied for ADME analysis to validate the drug likeness and toxicity. The binding of these phytochemicals with beta secretase inhibits the production of toxic amyloid β (Aβ). Among these identified phytocompounds, ascorbic acid can be predicted as potential inhibitors based on their significant binding affinity, drug-likeness properties, ADMET prediction, and toxicity prediction (based on predicted LD 50). These phytocompounds help reduce the accumulation of amyloid plaques and counteract amyloid β toxicity and were found safe and effective against AD without toxicity.

CONCLUSION

The purpose of this study is to find BM natural plant components that may be used as Alzheimer disease treatment agents. Herpes Simplex Virus 1 (HSV-1) is a known cause, and according to reports, there were 43.8 million people worldwide suffering from dementia in 2016, marking a 117% increase from 20.3 million cases in 1990. A key target in AD prevention is β-secretase, which triggers the production of amyloid-β (Aβ). Inhibiting BACE is a promising approach to combating Alzheimer's. Natural phytocompounds that target BACE can help inhibit the formation of senile plaques, thus potentially slowing the progression of the disease. This study shows one phytocompound from BM predicted to suppress the action of β-secretase β-secretase by preventing the formation of plaques. These phytocompounds have high potential inhibition and best binding affinity with β-secretase. The well-

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studied phytocompounds with drug-like qualities, a safe ADMET profile, and efficaciousness may contribute to the development of optimal Alzheimer inhibitors and the use of Ayurvedic medicine to treat AD.

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