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MOLECULAR DOCKING, DRUG-LIKENESS SCORE PREDICTION, AND ADME EVALUATION OF BACOPA MONNIERI PHYTOCHEMICALS AS POTENTIAL HUMAN PHOSPHOLIPASE D3 MODULATOR AGAINST ALZHEIMER'S DISEASE: IN SILICO APPROACH

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Background: Alzheimer's disease is one of the most prominent issue of memory impairment in the 21st century. It hurts personal and social life, particularly among older people. The herb *Bacopa monnieri* (Local name Brahmi) is renowned for its therapeutic properties for the treatment of neurological disorders. Its phytochemicals can alleviate symptoms of neurological complications. This present study aims to assess the binding affinity of *B. monnieri* phytochemicals with the phospholipase D3 protein of Alzheimer disease. **Materials and Methods:** The IMPPAT database was used to retrieve 39 phytocompounds from *Bacopa monnieri*, and out of which 11 phytochemicals were selected for the molecular docking studies against the target protein phospholipase D3 (PLD3) based on their drug-likeness scores and ADME profile. Molecule docking analysis was performed between phytochemicals i.e. Ascorbic acid, Nicotinic acid, Luteolin, Apigenin, Betulinic acid, β-Sitosterol, Stigmasterol, Stigmastanol, Bacogenin-a1, Pseudojujubogenin, and bacosin as ligands with the receptor proteins phospholipase D3 (PLD3) (PDB ID: 8V5T). Ligand docking scores were compared with those of donepezil (a reference drug). The molecular docking, image visualisation, ADME assessment of phytochemicals were performed using the PyRex docking tool, BIOVIA Discovery Studio visualizer and Swiss ADME software respectively. **Results:** Docking studies showed that bioactive compounds were docked within binding pocket of PLD3 protein. Among the screened phytochemicals, bacosine exhibited the highest binding affinity (−10.2 kcal/mol), followed by pseudojujubogenin (−9.4 kcal/mol) and bacogenin A1 (−9.3 kcal/mol). Stigmasterol (−8.9 kcal/mol), Betulinic acid (−8.8 kcal/mol), beta-Sitosterol (−8.4 kcal/mol), Stigmastanol (−8.4 kcal/mol), Luteolin (−7.9 kcal/mol), Apigenin (−7.7 kcal/mol), Ascorbic acid (−5.6 kcal/mol), Nicotinic acid ((−5.1 kcal/mol) and reference drug, donepezil (−8 kcal/mol) also exhibited favorable binding patterns, indicating complementary modulatory potential against Alzheimer disease. ADME predictions suggested favorable pharmacokinetic properties, including blood–brain barrier permeability and a low risk of toxicity, for the lead compounds **Conclusion:** The findings of this study conclude that *B. monnieri* phytochemicals, Bacosine, pseudojujubogenin, and bacogenin A1 exhibit significant binding affinity with the active site of the phospholipase D3 protein which might be involved in modulation its activity to reduce plaque formation in Alzheimer's disease. These phytochemicals might be promising candidates for future investigation in the treatment of Alzheimer's disease.

KEY WORDS: *Bacopa monnieri*, Phytochemicals, Molecular docking, Binding score.

INTRODUCTION

Neurodegenerative consequences have emerged as life-threatening illnesses worldwide. Due to emerging social and economic implications in the technological era, brain diseases are prevalent among individuals from childhood to old age.[1]We know that all our life activities rely on

the healthy functioning of the brain. The brain is a complicated organ that regulates all bodily functions, including learning, sleep, dreaming, memory, vision, stress, and happiness. Anxiety, depression, brain injury, work pressure, examination marks phobia and family issue etc.are the known causative factors for brain disorders. A broad range of neuropsychiatric and neurodegenerative disorders, including Alzheimer's disease, Parkinsonism, schizophrenia, major depressive disorder, cerebrovascular disorders, seizure-related conditions, and traumatic brain injuries, all contribute to progressive cognitive decline.[2]Brain disorders also impose significant emotional and psychological burdens on affected individuals and their families. The common symptoms of all diseases are memory loss and behaviour changes like stress, anxiety, psychosis, etc.[3] Alzheimer's disease is characterized by progressive memory loss, cognitive decline, and behavioural change with daily activities. Mitigating the effects of brain diseases on human health necessitates holistic strategy that incorporates medical, psychological, social, and community-oriented therapies.[4,5]

Alzheimer's disease is the most common neurodegenerative condition and a significant public health concern, affecting more than 50 million people globally, with forecasts of 152 million cases by 2050.[6,7] India's population is aging rapidly. According to research, almost 8% of the population is already 60 years or older, and this figure is anticipated to rise to about 19% by 2050. Currently, an estimated 5.3 million Indians are living with dementia, and this figure is expected to increase over the next three decades. Alzheimer's disease accounts for between 60 and 70% of all dementia cases. In India, almost 4 million individuals have some dementia. At least 44 million individuals worldwide have dementia, making it a global health epidemic that must be addressed.[8]

Current licensed medications such as acetylcholinesterase inhibitors (Donepezil drug) and N-methyl-D-aspartate (NMDA) receptor antagonists are slow the progression of AD.[9,10] There is no current medicine to cure completely or prevent AD disease. Therefore, there is dire need to find potential drug candidate that address the underlying molecular mechanisms of neurodegeneration. However, scientists are also looking towards development of potential lead phytocompounds from the traditional medicinal plants for the prevention and treatment of AD. Phospholipase D3 (PLD3), a membrane-associated enzyme implicated in phospholipid metabolism, has recently emerged as a potential molecular target in Alzheimer's disease due to its involvement in amyloid precursor protein processing and neuronal signaling. PLD3 is often found in the lysosomes of neurons, particularly within the cortex and hippocampus, and functions as a 5'-3' nuclease to degrade single-stranded DNA (ssDNA). Its deficiency or malfunction may result in the accumulation of mtDNA within lysosomes which induces the activation of the cGAS-STING pathway and causes neuroinflammation, hinders mitophagy, and expedites APP processing into develop amyloid-β (Aβ).Restoring or activating of PLD3 activity could be a new way to stop or slow down completely the development of amyloid precursor protein in Alzheimer's disease.[11]Modulation of PLD3 activity may offer a novel approach to attenuating AD-associated neurodegeneration.PLD3 encodes a phospholipase that may play a role in the digestion of the amyloid precursor protein (APP). This indicates that PLD3 may contribute to reduce the build-up of amyloid plaques, a characteristic feature of Alzheimer's disease.[12]

Traditional Indian systems of medicine, such as Ayurveda, offer an alternative approach to treating brain disorders. Medicinal plants derived phytochemicals have gained increasing attention as potential multi-target therapeutic agents for neurodegenerative diseases. Phytochemicals such as flavonoids, alkaloids, and polyphenols are known to modulate neurotransmitter systems, reduce oxidative stress, suppress neuroinflammation, and interfere with amyloid aggregation.[13]*B. monnieri*, sometimes referred to as brahmi, is a plant extensively utilized in Ayurvedic medicine (Figure 1). The Bacopa in Ayurvedic medicine is known to enhance memory, treat sleeplessness, manage epilepsy, and function as an anxiolytic. Numerous clinical investigations have evidenced that Bacopa has been widely recognized for its cognitive-enhancing, memory development, reducing anxiety and depression, thereby serving as a neuroprotective, antioxidant, and anti-inflammatory. It is commercial available in many formulations as syrup, tablet, capsules to support cognitive function of brain. It has been characterized as a soothing cognitive enhancer. Due to the high demand for herbal supplements for cognitive health, the global market for *Bacopa monnieri* extract was estimated to be worth USD 320 million in 2024 and is expected to reach USD 350 million in 2025[14].It is well reported that *B. monnieri* can reduce Tau aggregation and Tau-mediated toxicity in cells observed in Alzheimer's patients.[15,16]

Therefore, the present study employs a *insilico* approach to investigate the binding potential of between *Bacopa monnieri* phytochemicals and human phospholipase D3. PLD3 a new target protein which has not been earlier investigated in reference to the baccopa phytochemicals.

Figure 1: *Bacopa Monneieri.*

MATERIALS AND METHODS

Selection and preparation of Ligands

Ligands selected for the docking with the phospholipase D3 protein) interactions were based on a literature review of potential neuroprotective phytochemicals *of B. monnieri*. *B. monnieri* phytochemicals that serve as ligands (39 phytochemicals) were retrieved from the Indian Medicinal Plants, Phytochemistry and Therapeutics (IMPPAT https://cb.imsc.res.in/imppat/), summarized in Table 1.[17] The druglikeness and bioavailability scores of all 39 phytochemicals were evaluated using Swiss ADME online (https://www.swissadme.ch/software)[18] and the Molsoft server (https://molsoft.com/mprop/mprop.cgi).[19]

Table 1: List of phytochemicals of *B. Monneri (Source: IMPPAT)*.

IMPPAT ID	Compound name	Canonical smiles	Drug likeness score	Bioavailability score	M.W.
IMPHY006362	Ascorbic acid	C([C@@H]([C@@H]1C(=C(C(=O)O1)O)O)O)O	0.74	0.56	176.03
IMPHY007357	Nicotinic acid	C1=CC(=CN=C1)C(=O)O	0.3	0.85	123.03
IMPHY011710	Apigenin-7-o-glucuro	C1=CC(=CC=C1C2=CC(=O)C3=C(C=C(C=C3O2)O[C@@H]4[C@(	0.67	0.11	446.08
IMPHY015494	Bacopaside I	CC(=C[C@@H]1CO[C@]23C[C@]4(CO2)[C@@H]([C@H]3[C@@	0.08	0.08	978.45
IMPHY004660	Luteolin	C1=CC(=C(C=C1C2=CC(=O)C3=C(C=C(C=C3O2)O)O)O)O	0.38	0.55	286.05
IMPHY004661	Apigenin	C1=CC(=CC=C1C2=CC(=O)C3=C(C=C(C=C3O2)O)O)O	0.39	0.55	270.05
IMPHY007301	Nicotine	CN1CCC[C@H]1C2=CN=CC=C2	0.03	0.55	126.12
IMPHY007325	Plantainoside B	C1=CC(=C(C=C1CCO[C@H]2[C@@H]([C@H]([C@@H]([C@H](O	0.17	0.17	640.2
IMPHY011646	Cynaroside	C1=CC(=C(C=C1C2=CC(=O)C3=C(C=C(C=C3O2)O[C@H]4[C@@	0.6	0.17	448.1
IMPHY012003	Betulinic acid	CC(=C)[C@@H]1CC[C@]2([C@H]1[C@H]3CC[C@@H]4[C@]5(C	0.25	0.85	456.36
IMPHY013594	Bacoside B	CC(=CCC[C@@](C)([C@@H]1[C@H]2CC[C@H]3[C@]([C@@]2(	0.29	0.17	257.11
IMPHY014827	Bacoside A	CC(=CCC[C@@](C)([C@@H]1[C@H]2CC[C@H]3[C@]([C@@]2(	0.55	0.17	768.47
IMPHY014836	beta-Sitosterol	CC[C@H](CC[C@@H](C)[C@H]1CC[C@@H]2[C@@]1(CC[C@H	0.78	0.55	414.39
IMPHY014842	Stigmasterol	CC[C@H](/C=C/[C@@H](C)[C@H]1CC[C@@H]2[C@@]1(CC[C@	0.62	0.55	412.37
IMPHY014899	Stigmastanol	CC[C@H](CC[C@@H](C)[C@H]1CC[C@@H]2[C@@]1(CC[C@H	0.22	0.55	416.4
IMPHY000309	Dotriacontane	CCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCC	-1.03	0.55	450.52
IMPHY001534	Jujubogenin	CC(=C[C@H]1C[C@]([C@@H]2[C@H]3CC[C@@H]4[C@]5(CC[C	0.47	0.55	472.36
IMPHY001896	Heptacosane	CCCCCCCCCCCCCCCCCCCCCCCCCCC	-1.03	0.55	380.44
IMPHY002343	Bacogenin a2	OC[C@@H]1O[C@H]([C@@H]([C@H]1O)O)OC[C@H]([C@H]1O	-0.04	0.14	898.49
IMPHY002389	Bacogenin-a1	OC[C@@]12CC(=O)[C@@H]([C@H]1CC[C@H]1[C@@]2(C)CC[C	0.3	0.55	472.36
IMPHY002708	Pseudojujubogenin	CC1=C(O[C@@H]2[C@H]1[C@@]3([C@@H](C2)[C@@H]4CC[C	0.69	0.55	430.31
IMPHY004187	L-(+)-Arabinose	CC(=O)N[C@H]1CO[C@@H]([C@@H]([C@H]1NC(=O)C)NC(=O)	0.06	0.17	530.23
IMPHY004660	Luteolin	C1=CC(=C(C=C1C2=CC(=O)C3=C(C=C(C=C3O2)O)O)O)O	0.38	0.55	286.05
IMPHY005478	Strychnine	C1CN2CC3=CCO[C@H]4CC(=O)N5[C@H]6[C@H]4[C@H]3C[C@	0.52	0.55	334.17
IMPHY006362	Ascorbic acid	C([C@@H]([C@@H]1C(=C(C(=O)O1)O)O)O)O	0.74	0.56	176.03
IMPHY006699	Bacosine	CC(=C)[C@@H]1CC[C@]2([C@H]1[C@H]3CC[C@@H]4[C@]5(C	0.26	0.85	456.36
IMPHY007301	Nicotine	CN1CCC[C@H]1C2=CN=CC=C2	0.03	0.55	162.12
IMPHY007395	Bacoside A3	CC(=C[C@H]1C[C@]([C@@H]2[C@H]3CC[C@@H]4[C@]5(CC[C	-0.04	0.55	928.5
IMPHY007882	Ebelin lactone	CC(=C/C=C/C(=C/[C@H]1CC[C@@H]2[C@]3(CC[C@@H](C([C@	-0.33	0.55	454.34
IMPHY008910	Hentriacontane	CCCCCCCCCCCCCCCCCCCCCCCCCCCCCCC	-1.03	0.55	436.5
IMPHY009413	Triacontane	CCCCCCCCCCCCCCCCCCCCCCCCCCCCCC	-1.03	0.55	422.49
IMPHY009481	Octacosane	CCCCCCCCCCCCCCCCCCCCCCCCCCCC	-1.03	0.55	394.45
IMPHY009482	Nonacosane	CCCCCCCCCCCCCCCCCCCCCCCCCCCCC	-1.03	0.55	408.47
IMPHY009532	4-Hydroxy-2H-pyrar	C1/C(=C/O)/C(=O)C=CO1	-1.13	0.55	126.03
IMPHY009537	Stigmastenol	C[C@H](CC[C@@H](C=CO)C(C)C)[C@H]1CC[C@@H]2[C@@]1(	0.1	0.55	414.39
IMPHY011711	Apigenin 7-glucuronic	C1=CC(=CC=C1C2=CC(=O)C3=C(C=C(C=C3O2)O[C@H]4[C@@I	0.67	0.11	446.08
IMPHY011729	Mannitol	C([C@H]([C@H]([C@@H]([C@@H](CO)O)O)O)O)O	0.10	0.55	182.08
IMPHY012003	Betulinic acid	CC(=C)[C@@H]1CC[C@]2([C@H]1[C@H]3CC[C@@H]4[C@]5(C	0.25	0.55	456.36
IMPHY014893	D-Glucose	C([C@@H]1[C@H]([C@@H]([C@H](C(O1)O)O)O)O)O	-0.12	0.55	180.06

Screening of phytochemicals

All 39 phytochemicals were screened in an Excel sheet for drug-likeness scores greater than 0.13 and bioavailability scores greater than 0.18. Drug likeness score is an Quantitative Estimate of Drug-likeness (QED), which is measured by combining eight molecule properties: molecular weight, logP, H-bond donors/acceptors, polar surface area, rotatable bonds, aromatic rings, and stereo centers. The bioavailability score indicates the absorption effectiveness of compounds based on data available on the IMPPAT website. The Lipinski Rule of Five is also used to calculate the drug-likeness score (Table 2). Eleven phytochemicals were screened, and their chemical structures (in 2SDF format) were acquired from the IMPPAT database (Figure 2), subsequently transformed to 3D structures (PDB) using BioDiscovery Studio, and utilized for docking analysis. Donepezil, an established acetylcholinesterase inhibitor for Alzheimer's disease, served as a reference ligand for comparing the docking results.

Table 2: Filtration of phytochemicals based on the drug-likeness score and bioavailability score.

S. No.	Pubchem ID	Phytocompounds	Drug likeness score	Bioavailability score	Molecular Weight(g/mol)
1.	54670067	Ascorbic acid	0.74	0.56	176.03
2.	938	Nicotinic acid	0.3	0.85	123.03
3.	5280445	Luteolin	0.38	0.55	286.05
4.	5280443	Apigenin	0.39	0.55	270.05
5.	64971	Betulinic acid	0.25	0.85	456.36

6.	222284	beta-Sitosterol	0.78	0.55	414.39
7.	5280794	Stigmasterol	0.62	0.55	412.37
8.	241572	Stigmastanol	0.22	0.55	416.4
9.	275185179	Bacogenin-a1	0.3	0.55	472.36
10.	7091799	Pseudojujubogenin	0.69	0.55	430.31
11.	71312547	Bacosine	0.26	0.85	456.36
12.	3152	Donepezil (reference drug)	1.56	0.55	379.49

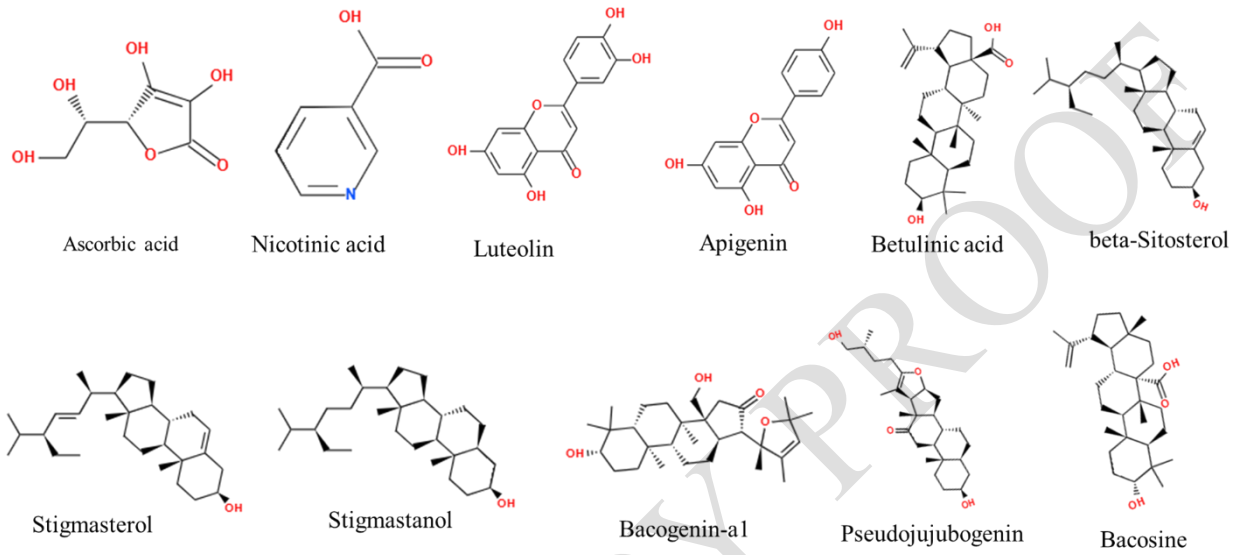

Figure 2: Chemical structure of selected phytochemicals.

ADME of phytochemicals

The SwissADME is an online computer server was used to assess the absorption, distribution, metabolism and excretion (ADME) of a potential phytocompounds using their canonical SMILES [https://www.swissadme.ch/.[20]

Selection and Preparation of Target Protein Phospholipase D3: The crystal structure of the target receptor Phospholipase D3 protein was retrieved (PDB ID 8V5T) from the RCSB Protein DataBank.[21] It contains two chains bound to the non-protein molecule, i.e., 2-acetamido-2-deoxy-β-D-glucopyranose-(1-4)-2-acetamido-2-deoxy-beta-D-glucopyranose, sulfate ion, and glycerol as a heteroatom in the PDB structure (Table 3). The structure was inspected and prepared using BIOVIA Discovery Studio. The chain B, non-essential heteroatoms, and water were removed from the target protein 8V5T. The final clean protein model was saved in PDB format in the docking folder for a subsequent docking experiment (Figure 3).

Table 3.

Molecule	Chains	Sequence Length	Organism
5'-3' exonuclease PLD3	A,B	490	Homo sapiens

Identification of the binding pocket of the target protein-8V5T

The binding pocket of 8V5T was determined using the PrankWeb, a online server (https://prankweb.cz/.[22]The binding pocket residue includes A_125, A_126, A_199, A_201, A_218, A_220, A_222, A_223, A_227, A_327, A_328, A_334, A_335, A_367, A_369, A_411, A_416, A_418, A_432, A_437, A_441 of 8V5T receptor protein.

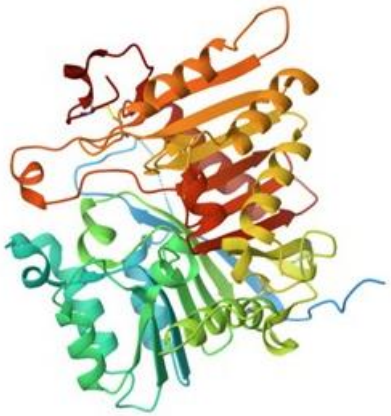

Figure 3: Crystal structure of phospholipase D3 (PDB ID 8V5T).

Molecular Docking

The docking study was carried out using PyRx (Version 0.8 with Virtual Screening and Drug Discovery features), which integrates the AutoDockVina docking engine.[23]The cleaned 8V5T protein receptor was loaded into PyRx and converted to PDBQT format, with added polar hydrogens and charges assigned. All 10 ligands were then exported in PyRx using the OpenBabel module, and the energy of each ligand was calculated. The binding site for docking was defined based on the coordinates of the co-crystallized ligand in Phospholipase D3 protein and a grid box (x =-32.129, y =-38.5316, z =-57.1906). AutoDockVina was used with default exhaustiveness and search parameters to evaluate ligand-protein interactions. For each compound, Vina generated multiple docking poses (10), and he conformation exhibiting the minimal negative binding energy (kcal/mol) was chosen for subsequent study. The docked complexes were viewed and analyzed in BIOVIA Discovery Studio Visualizer to evaluate polar and nonpolar interactions between the ligands and the target receptor protein 8V5T. The docking scores and interaction profiles were documented for the comparative assessment of ligand affinity for Phospholipase D3 protein.

RESULTS AND DISCUSSION

ADME prediction of phytochemicals

The ADME profiling performed in this study offer considerable translational significance.[24]Table 4 shows the ADME (pharmacokinetic behaviour) of some phytochemicals from *Bacopa monnieri*, as studied using SwissADME. It depicts how well phytochemicals would be absorbed and used by the body. Most low-molecular-weight chemicals, such as ascorbic acid, nicotinic acid, luteolin, apigenin, bacogenin-A1, and pseudojujubogenin, were well absorbed by the body after being taken by mouth. Among the phytochemicals, nicotinic acid and pseudojujubogenin were blood–brain barrier permeant (BBB). CYP2C19 and CYP3A4 suppression was found in luteolin and apigenin, whereas pseudojujubogenin inhibited CYP1A2. Stigmasterol, β-sitosterol, stigmastanol, bacogenin-A1, and bacosine showed negligible CYP inhibition, reducing the risk of metabolic drug interactions.

The primary phytochemicals, particularly pseudojujubogenin (with BBB permeability) and bacogenin-A1, displayed favorable drug-like properties and low predicted toxicities. This indicates a significant advantage, as many synthetic neurotherapeutics fail due to poor pharmacokinetics or off-target effects. The potential of these compounds is attributed not only to their affinity for PLD3 but also to the inherent multi-target capabilities of plant-derived molecules.

Table 4: ADME profile of *Bacopa monnieri* phytochemicals.

S.No.	Bacopa monnieri phytochemicals	GI absorption	BBB permeant	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor
1.	Ascorbic acid	High	No	No	No	No	No	No
2.	Nicotinic acid	High	Yes	No	No	No	No	No
3.	Luteolin	High	No	No	Yes	No	No	Yes
4.	Apigenin	High	No	No	Yes	No	No	Yes
5.	Betulinic acid	Low	No	No	No	No	Yes	No
6.	beta-Sitosterol	Low	No	No	No	No	No	No
7.	Stigmasterol	Low	No	No	No	No	Yes	No
8.	Stigmastanol	Low	No	No	No	No	No	No
9.	Bacogenin-a1	High	No	No	No	No	No	No
10.	Pseudojujubogenin	High	Yes	Yes	No	No	No	No
11.	Bacosine	Low	No	No	No	No	No	No

Molecular Docking

The present study investigated the *baccopa monnerie* phytochemicals as potential modulators of human phospholipase D3 (PLD3), which is involved in the progression of amyloid plaque development (PDB: 8V5T). We evaluated docking studies 11 phytochemicals against the target protein, human phospholipase D3, as a therapeutic drug target for the prospective treatment of Alzheimer's disease. **Table 5** presents the binding energies and interactive amino acid residues of the docked complex between the phytochemicals and the human phospholipase D3 protein receptor. Figures4-13 show exhibit the 2D and 3D images of the binding interactions of docking complex (phytochemicals with target protein 8V5T). *B. monnieri* phytochemicals bind strongly to human phospholipase D3's active site, as shown by the 2D and 3D images of the dock complex. Molecule docking results reveal that bacosine had the greatest binding energy (−10.2 kcal/mol), followed by pseudojujubogenin (−9.4 kcal/mol) and bacogenin-A1 (−9.3 kcal/mol). These values were much greater than those for donepezil (−8.0 kcal/mol), indicating greater stability of PLD3 receptor interaction.

Table 5: Binding interactions of complex ligands with the 8V5T protein receptor complex

S. No.	Pubchem ID	Phytocompounds (Ligands)	Binding energy kcal/mol)	Number of polar interactions (H-bonds)	Interactive amino acid residues in H bonds	Number of non-polar bonds	Interactive amino acid residues in Non-polar interactions
1.	71312547	Bacosine	−10.2	4	THR 441, ASN328, PHE335,HIS201	11 (Akyl, Pi-alkyl)	TYR 437, TYR411, TYR125, TYR126, VAL227, PHE125, PHE335 VAL199
2.	7091799	Pseudojujubogenin	−9.4	2	ARG222	07 (Alkyl & Pi alkyl)	HIS135, HIS201, PHE125,MET327,PRO410,TYR411
3.	275185179	Bacogenin-A1	−9.4	0	0	11 (Alkyl, Pi-Alkyl, Pi Sigma Unfavorable donor donor)	PHR 335, TYR 437, PHE 125, TYR126, TYR411, TRP367, HIS416, ASN 436
4.	5280794	Stigmasterol	−9	0	0	05 (Pi sigma and Akyl, Pi alkyl)	TYR326, MET127, HIS416, HIS201
5.	64971	Betulinic acid	− 8.8	0	0	11 (Alkyl, Pi-Akyl and Unfavourble donor donor)	ASN136,PHE335,TYR437 TYR126,TYR411,TRP367 PHE125,VAL199
6.	241572	Stigmastanol	−8.5	0	0	03 (Pi Sigma and Pi alkyl)	TYR411, TYR126
7.	222284	β-Sitosterol	−8.4	0	0	10 (Pi sigma and Pi alkyl)	TYR411, TYR126 HIS 416 HIS369 TRP 367
8.	5280445	Luteolin	−7.9	03	LYS167, SER 166	03 (PiPi stacked, PiPiT shaped, andunfavorval donor donor)	PHE 125, TYR 126 TYR 411, ARG 222
9.	5280443	Apigenin	−7.7	01	ARG222	05 (PiPi T shaped Pi alkyl and PiPi T shaped)	TYR126,PHE125 PRO 168
10.	54670067	Ascorbic acid	−5.7	3	Gly368, ILE 406, ARG413	02 (unfavourable donor donor and Carbon Hydrogen bond)	ASN485, HIS 369
11	938	Nicotinic acid	-5.1	3	GLY368, ILE409, ASN 485	H bonds	ALA402,ALA407, ARG413
12.	3152	Donepezil	−8.0	0	0	06 (carbon H	TYR 437, TYR411, TYR126,

		(Reference drug)				bond Pi-pi Stacked, Pi alkyl and Van der walls)	VAL227, HIS416

The molecular docking analysis indicated that phytochemicals from *B. monnieri* exhibited higher binding affinities than the reference drug, donepezil, against the PLD3 crystal structure (PDB: 8V5T). Bacosine, pseudojujubogenin, and bacogenin-A1 are triterpenoid saponins derived mainly from Bacopamonnieri, a well-known medicinal plant used for cognitive enhancement. Bacosine, pseudojujubogenin, and bacogenin-A1 were identified as the leading possibilities, with binding energies of -10.2, -9.4, and -9.3 kcal/mol, respectively.

Bacosine is a triterpenoid saponin with a hydrophobic aglycone attached to one or more sugar moieties. It is recognized for its ability to augment synaptic plasticity and neural transmission.[25] It demonstrates antioxidant action, reduces lipid peroxidation, and facilitates cholinergic transmission, which is essential for learning and memory in Alzheimer's disease.[26] Figure4 shows 2D and 3D images of docking phytochemicals with the receptor proteins. Bacosine formed 4 hydrogen bonds with the active binding residues TH-R441, ASN328, PHE335, and HIS201 of the target receptor, indicating strong catalytic pocket anchoring and a significant binding energy (−10.2 kcal/mol).

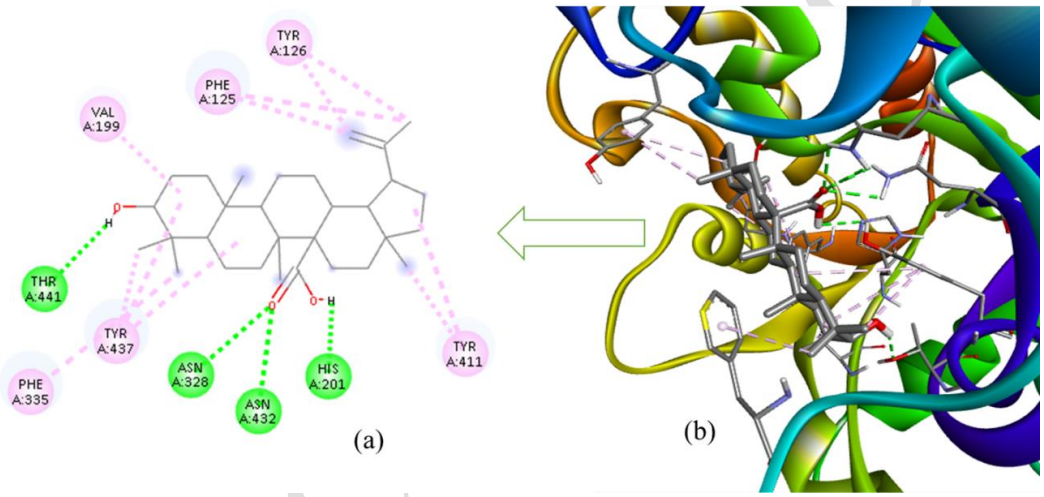

Figure 4: Binding interactions between bacosine and 8V5T (a) 2D binding interactions b) 3D view of docked bacosin- 8V5T complex.

Pseudojujubogenin is a sapogenin, characterized by a steroid-like triterpenoid backbone, representing the non-sugar component of saponins. The inflexible ring shape facilitates interaction with brain receptors and enzymes implicated in neurodegeneration. It demonstrates physiologically neuroprotective and anti-inflammatory properties. It helps reduce oxidative stress and may inhibit amyloid-β formation, a key pathogenic feature of Alzheimer's disease.[27] Figure 5 depicts the molecular docking binding affinity of pseudojujubogenin, hydrogen-bonded with ARG222 and hydrophobically with HIS135 by which it can enhance the activity of PL3 protein.

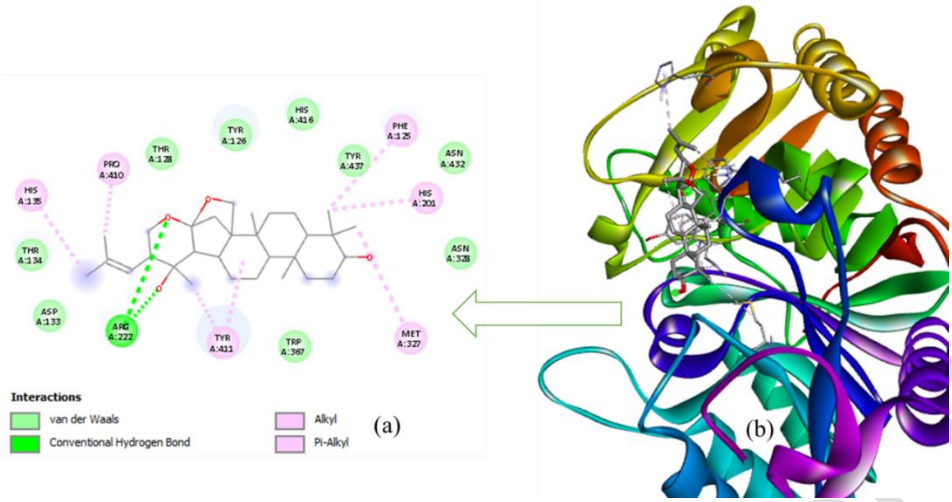

Figure 5: Binding interactions between pseudojujubogenin and 8V5T (a) 2D binding interactions b) 3D view of dock pseudojujubogenin- 8V5T complex.

Bacogenin-A1 is the principal active aglycone and derivative of bacosides, distinguished by a pentacyclic triterpenoid structure.[28,29] Figure 6 shows the binding interactions between bacogeninand 8V5T. It exhibits two nonpolar interactions (Unfavourable donor-donor and Pi Sigma) with the amino acid residues ASN136 and TYR411 of the 8V5 T receptor protein. It is reported that bacogenin-A1 facilitates efficient interaction with neuronal membranes and signaling pathways, thereby preventing neuronal damage. Researchers also reported that bacogenin-A1 acts as a neuroantioxidant and regulates acetylcholinesterase activity, thereby enhancing cognitive function and slowing memory decline in Alzheimer's disease.

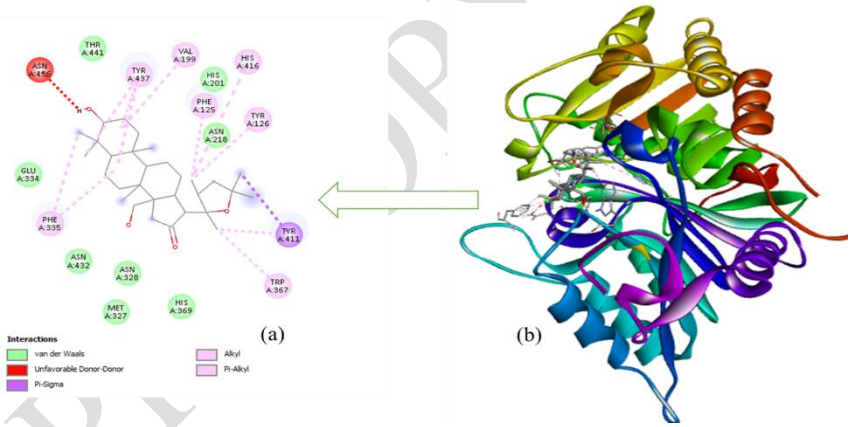

Figure 6: Binding interactions between bacogenin-A1 and 8V5T (a) 2D binding interactions b) 3D view of docked complex (bacogenin-A1 and 8V5T).

These phytochemicals having significant minimum binding energy compare to other docked phytocompounds indicating the stable complex with the binding pocket of target protein 8V5T and such *baccopa monnerie* phytochemcials might be produced synergistically effect to reduce oxidative stress, inhibit neuroinflammation, protect neurons with enhance cholinergic signaling in the biologicals system against amyloid development. The structural features significantly influence their capacity to traverse biological membranes and provide neuroprotective effects, positioning them as promising natural candidates for the management of Alzheimer's disease. The strong affinity of these molecules with target protein PLD3can be attributed to their complex, rigid polycyclic structures, characteristic of triterpenoids. The frameworks, which contain hydroxyl and carbonyl functional groups, provide optimal three-dimensional complementarity to the hydrophobic and polar residues located in the active site pocket of PLD3 (e.g., THR441, ASN328, PHE335, HIS201). This enables various beneficial interactions, including hydrogen bonding and van der Waals forces, which stabilize the ligand-protein complex.

Other phytocompounds such as stigmasterol, stigmastanol, and β-Sitosterol are phytosterols that share structural similarities with cholesterol, characterized by a cyclopentanoperhydrophenanthrene core, a hydroxyl group at C3, and an aliphatic side chain at C17. These exhibited substantial binding, mainly through hydrophobic and π-alkyl interactions with aromatic residues, including TYR411 and TYR126. Their planar,

steroid-like cores, despite lacking polar bonds, appear to effectively occupy the hydrophobic subpockets of PLD3, suggesting a possible restoration of enzymatic activity PLD 3.

In the present study, we found that all three phytochemicals bind to the target protein PLD3. Figure 7, 8 and 9 show the 2D and 3D images of the docking view of stigmasterol, stigmastanol, and β-sitosterol respectively. The docking complex of these phytochemicals has binding energies (-8.4, -9.0, -8.5 kcal/moles, respectively) that are stabilized by hydrophobic and π-alkyl interactions with aromatic residues in the binding site of target 8V5T proteins.

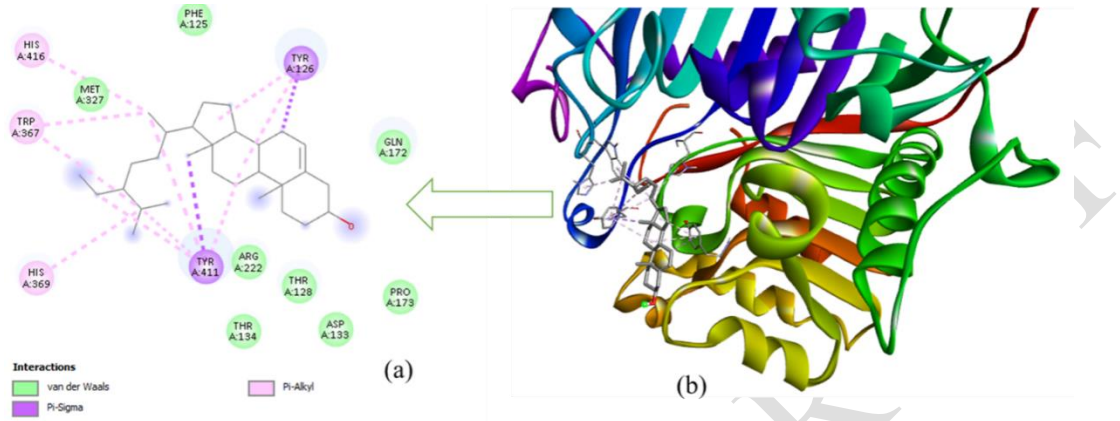

Figure 7: Binding interactions between β-Sitosterol and 8V5T (a) 2D binding interactions b) 3D view of docked complex (β-Sitosterol and 8V5T)

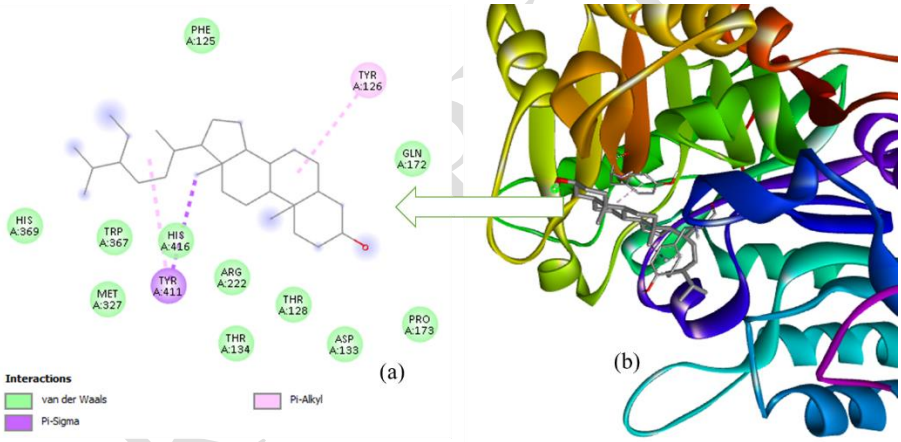

Figure 8: Binding interactions between stigmastanol and 8V5T (a) 2D binding interactions b) 3D view of docked complex (stigmastanol and 8V5T).

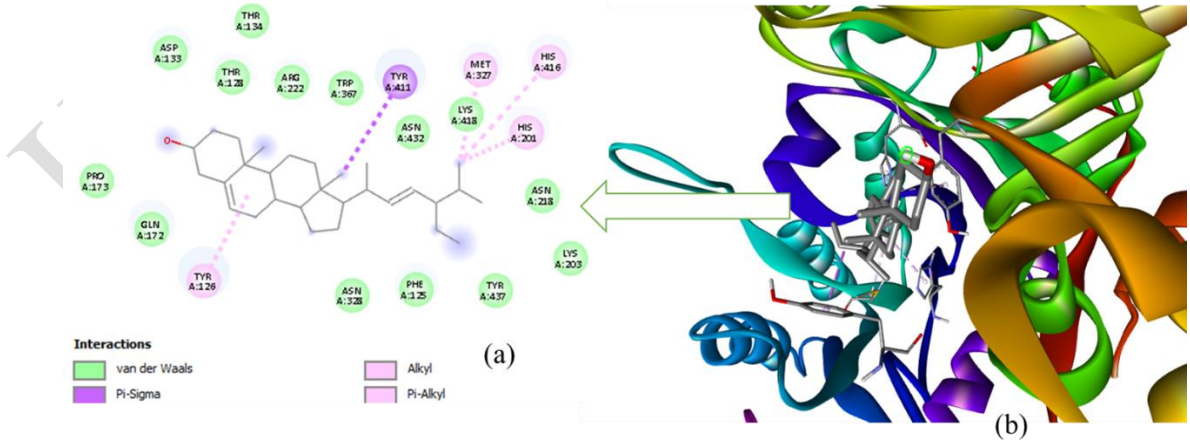

Figure 9: Binding interactions between stigmasterol and 8V5T (a) 2D binding interactions b) 3D view of docked complex (Stigmasterol and 8V5T)

Figure 10 depicts the binding affinity between betulinic acid and PLD3 (8V5T). Betulinic acid has a greater binding affinity (− 8.8 kcal/mol) without hydrogen bonds. It mostly interacted with PLD3 via a modest unfavorable donor–donor interaction with Asn136. The betulinic acid-PLD3 complex is stabilized by hydrophobic interactions and exhibits complementarity within the binding pocket, as evidenced by its high binding energy.

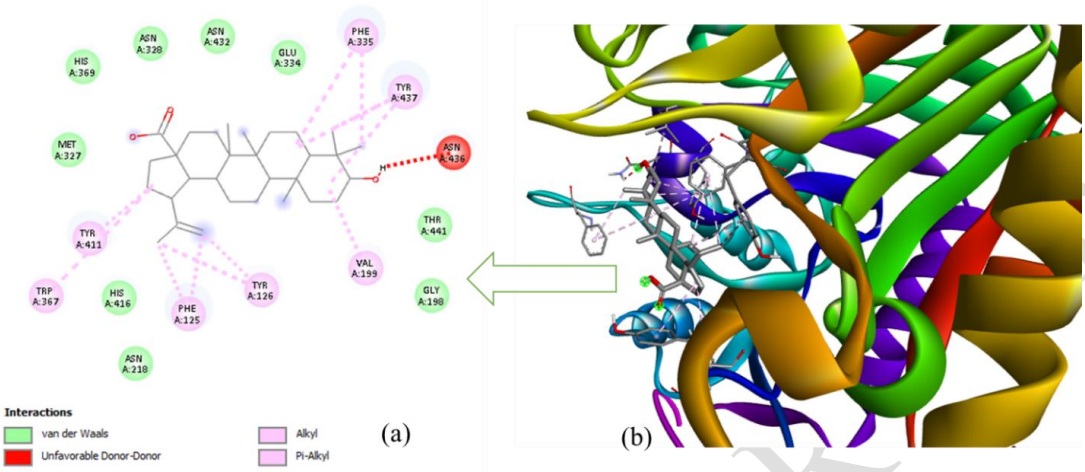

Figure 10: Binding interactions between betulinic acidand8V5T (a) 2D binding interactions b) 3D view of docked complex (betulinic acid and 8V5T).

Luteolin and Apigenin are flavonoids which containa 15-carbon skeleton (C6-C3-C6) with two phenyl rings (A and B) and a heterocyclic pyran ring (C) present in *baccopa monnerie*[32,33]. The hydroxylation pattern on these rings determines their antioxidant capacity and binding specificity to enzymes such as PLD3.Luteolin showed three hydrogen bonding interactions with Lys167 and Ser166 of PLD3 with the binding affinity (−7.9 kcal/mol) (Figure 11). It also exhibits aromatic interactions, including π–π stacking and π–π T-shaped interactions with residues including Phe125, Tyr126, Tyr411, and Arg222, stabilized its binding with the PLD3 protein. Apigenin formed a single hydrogen bond with Arg222 with a binding energy of -7.7 kcal/mol (Figure 12). It has successfully docked with the binding pocket of PLD3 by forming one polar (H bond) and five non-polar interactions, such as π–π T-shaped and π-alkyl interactions with Tyr126, Phe125, and Pro168 (Figure 13). These hydrophobic interactions may involve in stabilizing the apigenin–PLD3 complex. Despite exhibiting substantially reduced binding energies, both luteolin and apigenin interacted with the target protein via a mix of hydrogen bonds and π-π stacking interactions with critical residues, underscoring their potential as frameworks for future enhancement.

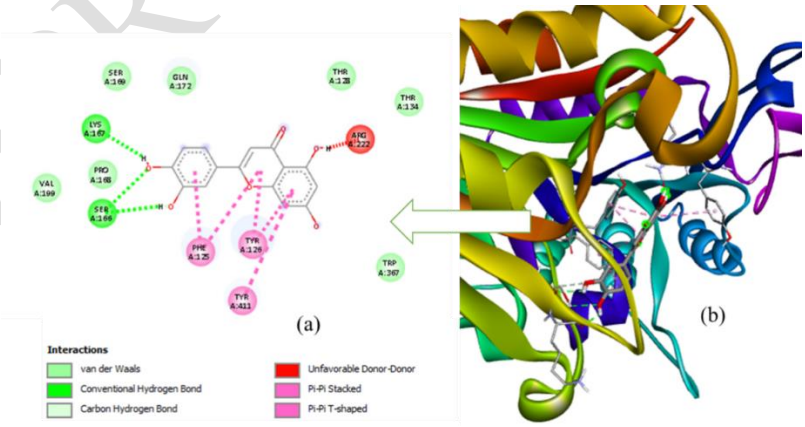

Figure 11: Binding interactions between luteolin and 8V5T (a) 2D binding interactions b) 3D view of docked complex (luteolin and 8V5T)

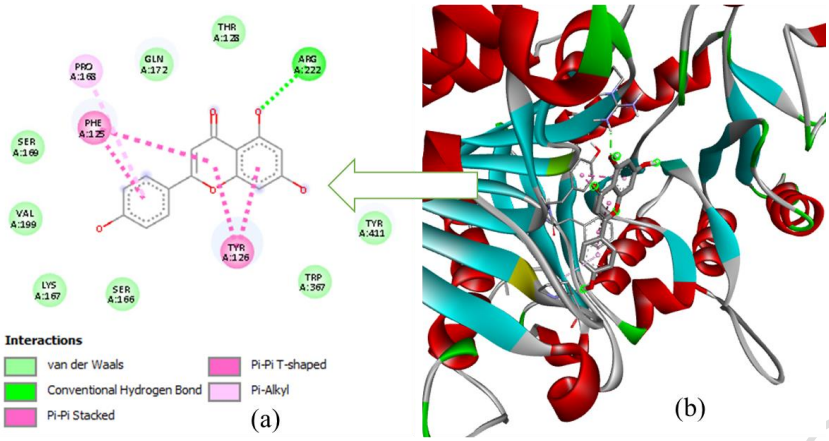

Figure 12: Binding interactions between Apigenin and 8V5T (a) 2D binding interactions b) 3D view of docked complex (Apigenin and 8V5T).

Ascorbic acid is a well-known water-soluble antioxidant vitamin that exhibits both hydrogen and no polar interaction with the binding pocket of PLD 3 due to its antioxidant activity. It shows the BBB permeability.[34]Figure 13 shows the docking interaction of ascorbic acid, which formed three hydrogen bonds with Gly368, Ile406, and Arg413. Asn485 and His369 also formed weak donor–donor and carbon–hydrogen bonds, indicating minimal ligand stability (−5.7 kcal/mol) in the binding pocket.

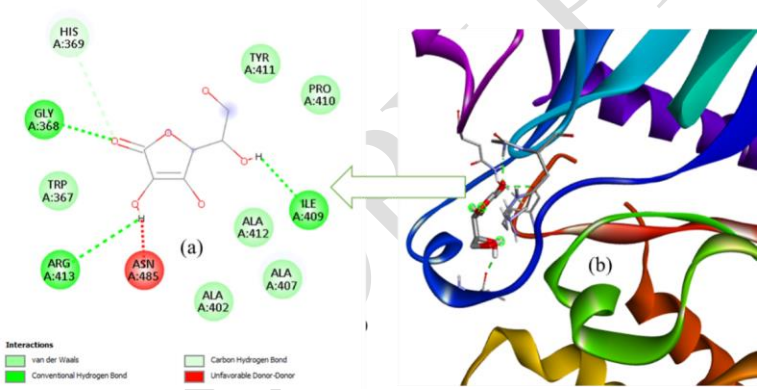

Figure 13: Binding interactions between ascorbic acid and 8V5T (a) 2D binding interactions b) 3D view of docked complex (ascorbic acid and 8V5T)

The baccopa plant contains nicotinic acid, a water-soluble vitamin. By creating three H-bonds and three alkyl interactions, it was able to successfully connect with the binding pocket of the 8V5T protein and demonstrated a binding energy of -5.1 kcal/mol (Figure14). This is niacin, which may function as a cofactor to increase PLD3's catalytic activity.

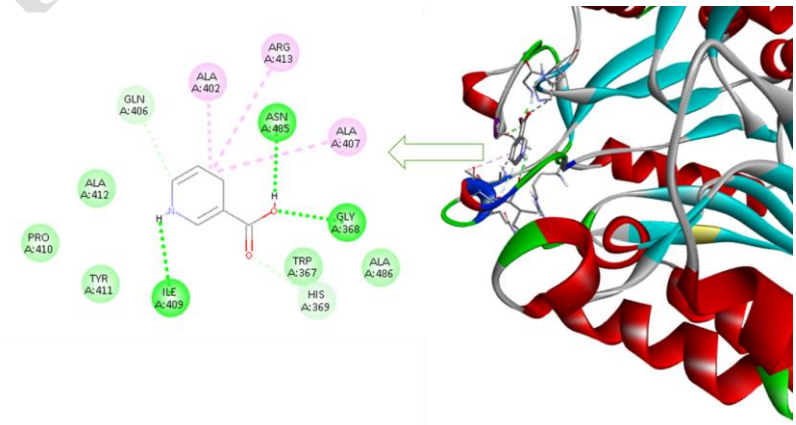

Figure 14: Binding interactions between nicotinic acid and 8V5T (a) 2D binding interactions b) 3D view of docked complex (nicotinic and 8V5T).

Donepezil is well known drug for the management of symptoms of Alzheimer's disease. It primarily inhibits the enzyme activity of acetylcholinesterase (AChE). It is sold as Aricept for the treatment of Alzheimer 's-type dementia.[35] Figure 15 shows the docking interaction between Donepezil and 8V5T. It forms six non-polar interactions ((carbon H bond Pi-pi Stacked, Pi alkyl and Van der walls) with the binding residues TYR 437, TYR411, TYR126, VAL227, HIS416 which have a binding score −8.0 kcal/mol, which is less than bacosine phytochemicals.

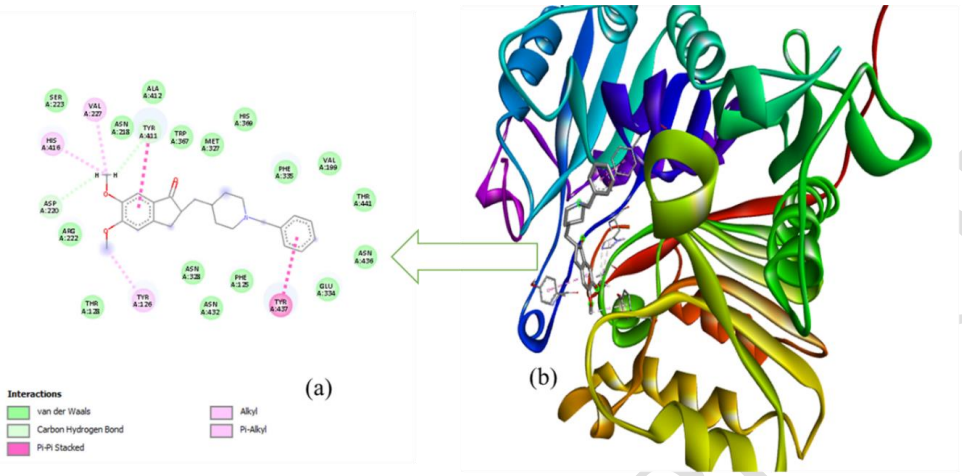

Figure 15: Binding interactions between Donepezil and 8V5T (a) 2D binding interactions b) 3D view of docked complex (Donepezil and 8V5T).

The docking results show that *B. monnieri phytochemicals* have a significant affinity and positive interaction pattern with PLD3 compared with the phytocompounds, suggesting that they could modulate Alzheimer's disease-related amyloid pathways.

LIMITATIONS

There are no wet-laboratory experiments in this study. This study is merely a predictive one that needs experimental confirmation of the phytochemicals in baccopa's modulatory action on the PLD-3 protein receptor in biological models. Potential therapeutic uses of *B. monnieri* phytochemicals as modulatory effects for PLD 3 enzyme activity against Alzheimer's illnesses would benefit from the anticipated research outcome.

CONCLUSION

The molecular docking and ADME studies demonstrate that phytochemicals of *Bacopa monnieri*, specifically bacosine, pseudojujubogenin, and bacogenin-A1, exhibit notable and stable interactions with the human phospholipase D3 (PLD3), a crucial enzyme involved in the metabolism of amyloid-β in Alzheimer's disease. Moreover, other phytochemicals, such as luteolin, apigenin, stigmasterol, stigmastanol, β-sitosterol ascorbic acid and nicotinic acid, demonstrated favorable interactions with the PLD3 protein, indicating their potential to support and complement modulatory enzymatic effects against AD. The combined binding affinity, interaction stability, and favorable ADMET profiles highlight the multitarget therapeutic potential of *B. monnieri* phytochemicals, underscoring the need for further experimental validation for the treatment of Alzheimer’s disease.

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AUTHOR CONTRIBUTIONS

Dr. Arvind Kumar Shakya contributed for experimental work, data acquisition, data analysis, manuscripts writing and editing and Dr. Narendra Kumar helped in editing and checking plagiarism.

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ETHICAL APPROVALS: This study does not involve experiments on animals or human subjects.

USE OF ARTIFICIAL INTELLIGENCE (AI)-ASSISTED TECHNOLOGY: The authors confirm that no artificial intelligence (AI) tools were used in the writing or editing of this manuscript, and all images are unaltered and free from AI-based modifications.

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