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Seaweed Secondary Metabolites as a therapeutic approach for Alzheimer's disease: In Silico Approach

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ABSTRACT

Alzheimer's disease (AD) is the most common type of dementia, presenting significant and escalating global challenges. AD is a progressive neurodegenerative disorder characterized by the cognitive decline, memory loss, and impaired daily functioning. The pathology of AD is characterized by the accumulation of amyloid beta aggregates and hyperphosphorylated tau protein tangles in the brain, along with neuroinflammation, impaired synaptic function and cholinergic dysfunction. Current pharmacological interventions such as donepezil, rivastigmine, and galantamine provide only symptomatic relief and are often associated with adverse effects, underscoring the need for alternative therapeutics. The present study employs an *in silico* approach to identify potential anti-Alzheimer's candidates among secondary metabolites derived from seaweeds. A total of 1072 compounds from the Seaweed Metabolite Database (SWMD) were screened against key AD-associated targets acetylcholinesterase (AChE), butyrylcholinesterase (BChE), and beta-amyloid peptides. Protein structures were refined and validated using RAMPAGE, and active binding sites were predicted using CASTp. Molecular docking using PyRx revealed several potent interactions, with BB002, RR010, RR035, and GC601 exhibiting strong binding affinities and stable hydrogen bond formation within the active sites. ADMET profiling confirmed favorable pharmacokinetic parameters and non-toxic properties of these compounds. These findings suggest that specific seaweed-derived secondary metabolites exhibit significant potential to modulate cholinesterase activity and amyloid aggregation, highlighting their promise as natural leads for the development of neuroprotective therapeutics against AD.

Keywords: *Alzheimer's disease; Seaweed secondary metabolites; Acetylcholinesterase (AChE); Butyrylcholinesterase (BChE); Beta-amyloid; Molecular docking; ADMET; Neuroprotection; Marine natural products; In silico drug discovery*

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1. INTRODUCTION

The most prevalent neurological illness associated with aging is Alzheimer's disease (AD). AD is a progressive neurodegenerative disorder characterized by cognitive impairment, memory loss, and altered behaviour and personality, that are severe enough to strongly interfere with daily life and activities. AD is the most widespread form of dementia, contributing to at least two-thirds of dementia cases among individuals aged 65 and older. More than 11 million people are predicted to be affected by this condition annually by 2050, which will increase the cost and burden on public health and society (1, 2). AD, which is marked by progressive memory loss and cognitive impairment, causes motor function decline and personality changes before to death. Neuropathologically, AD is characterized by the accumulation of extracellular

senile plaques (SPs) and intracellular neurofibrillary tangles (NFTs), which induce neuronal and synaptic loss and, eventually, brain atrophy (3). Amyloid β (A□) peptides aggregate and deposit as SPs, whereas abnormally hyperphosphorylated microtubule associated protein (MAP) tau aggregate to produce NFTs (4).

Acetylcholine (ACh), the brain's most important neurotransmitter, has a role in memory consolidation, language, logical reasoning, and focus. In contrast, acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) enzymes greatly inhibit ACh activity (5). Inhibition of the cholinesterase enzymes (AChE and BChE) can alleviate symptoms associated with the progressive damage of cholinergic function in AD by raising AChE levels in various brain regions. According to research, increased AChE concentration in the brain enhances the production of nicotinic AChE receptors, which are associated with cognitive performance. This mechanism could help Alzheimer's patients create new memories and recall old ones. As a result of the "cholinergic hypothesis," AChE and BChE inhibition have been identified as the primary therapeutic targets (6, 7). While dementia currently has no cure, the US Food and Drug Administration (FDA) has approved various cognition-enhancing medications aimed at managing the symptoms of AD. These drugs primarily work to maintain cognitive and functional abilities, alleviate symptoms and severity in the advanced stages (8). The majority of the medications now licensed for AD are cholinesterase inhibitors, including donepezil, rivastigmine, galantamine, and the NMDA antagonist memantine (9, 10). Only donepezil, one of the most commonly used AChE inhibitors, has been approved for the treatment of all phases of AD. However, this medicine causes a number of major adverse effects, including gastrointestinal (GI) abnormalities, liver problems, and GI disturbances (11). Given these limitation, it is worthwhile to look for new lead compounds from natural products. Natural substances have shown promise as AChE inhibitors. Galantamine and rivastigmine, two currently approved AD medicines, are plant-derived alkaloids that give symptomatic alleviation (12, 13) Natural products and their derivatives are valuable sources of medications (14). A wide variety of organisms, including plants, marine species and terrestrial microbes, have been studied as potential sources of new compounds with biological activities or compounds that could be good lead drugs (including ChE inhibitors) for the pharmaceutical industry (14-16). Currently, plants and marine species represent at least 30% of the leading twenty medicinal products. At present, there are 175 approved small molecules in the market to treat cancer; of them, approximately 49% are derived from natural products (14). Researchers interested in the extraction as well as the analysis of macroalgae have found a multitude of seaweed compounds exhibiting significant biological properties, such as antimicrobial, antihypertensive, anti-inflammatory, and anticancer activity. Macroalgae are increasingly being recognized as a source of secondary metabolites with tremendous promise for the invention of new medications (15-19).

In spite of being consumed as food, seaweeds are often recognized as an important source of novel natural products that might include key concepts for future medication research and development, including the prevention of cardiovascular and cancer therapies (16-18).

Considering this development, *in vitro* research is merely the first step in a lengthy process, while *in vivo* studies and clinical trials are the most informative stages of the factual potential and limits that a secondary metabolite may have as a novel medication (18-23). Seaweeds contribute significantly to ocean biodiversity and contain green, brown, and red algae. Seaweed secondary metabolites exhibit promising bioactivities (24-29). In recent years, researchers discovered that seaweed metabolites contain abundant with terpenoids and alkaloids, polyphenols, steroids, pigments, and polysaccharides. According to research, chemicals derived from marine algae have a variety of biological actions, including those that are anticoagulant (30), antiviral (31) and antioxidant (32) as well as anti-allergic (33), anti-cancer (34), anti-inflammatory (35), and anti-obesity (36). Additionally, a number of research investigations have shed light on the neuroprotective qualities of marine algae. For a very long time, Eastern nations and, more recently, European and American countries have utilized a variety of marine algae species in their traditional diets and medicinal practices. Therefore, there is a lot of promise for using marine algae in neuroprotection (37). According to a number of recent scientific studies, marine algae have a great deal of potential for use in pharmaceuticals, nutraceuticals, and functional foods for their biological activities and neuroprotective effects. These activities include antioxidant, anti-neuroinflammatory, cholinesterase inhibitory activity, and the inhibition of neuronal death (38,39).

In this *in-silico* work, virtual screening is performed on proteins involved in AD pathogenesis using an open-access database of secondary metabolites from seaweeds (1191 molecules). Furthermore, molecular docking experiments were carried out on active compounds. To better understand protein-ligand interactions, the four most active complexes were chosen for free energy and molecular dynamics studies (40).

2. MATERIALS AND METHODS

Ligand preparation

The 3-D Structure of the secondary metabolites of seaweeds were retrieved from an open-access database of secondary metabolites from seaweeds (https://www.swmd.co.in/) (37,38). Before carrying out the molecular docking studies, the geometry of all the structures was cleaned using ArgusLab program.

Protein Preparation

The three-dimensional structure of the proteins AChE, BChE and Beta amyloid were reterived from the Protein Data Bank (PDB). In addition, the non-standard amino acids attached to the proteins have been eliminated or altered using Pymol software (Fig 1).

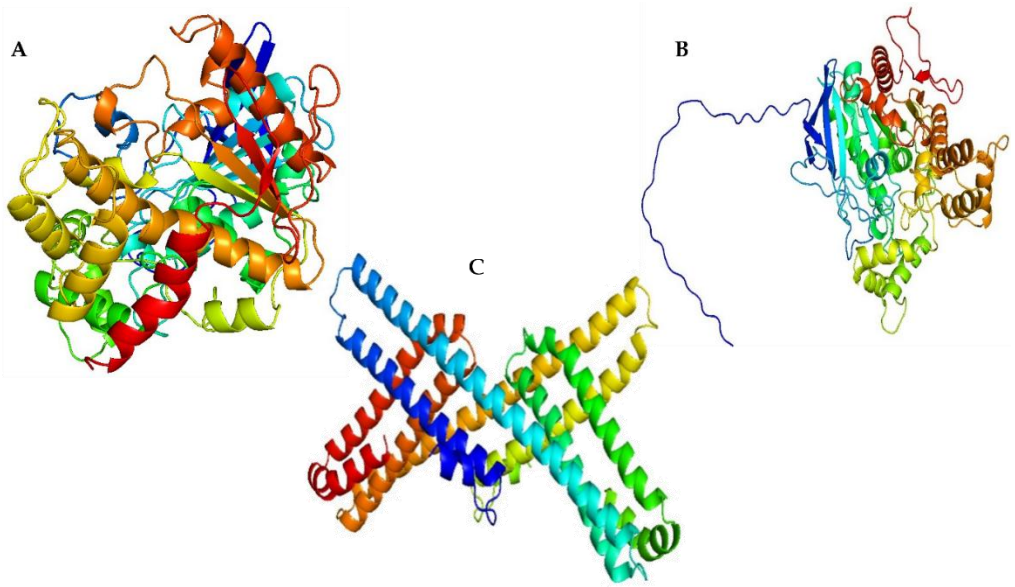


Figure 1: 3-Dimensional Structure of (a) AChE, (b)BChE (c) Beta amyloid peptide purification and structural Validation

The Mod Refiner server was used to refine the protein structures. (https://zhanglab.ccmb.med.umich.edu/ModRefiner/). The Ramachandran plot was used to validate and evaluate the refined protein structures of proteins AChE, BChE and Beta amyloid, revealing that the energetically allowed protein structures regions for backbone dihedral angles towards amino acid residues were found. RAMPAGE was used to generate the plots. The PROCHECK RAMPAGE results revealed that the structure of the protein AChE, BChE, Beta amyloid is stable (39).

Binding Pockets prediction

The binding pockets of AChE, BChE and Beta amyloid peptide-ligand binding were predicted with *in silico* tool CASTp (http://sts.bioe.uic.edu/in, (accessed on 11 August 2021)).

Molecular Docking Studies and Visualization

The pyrx version 0.8 open access docking program was used for the better understanding of molecular interaction and the docking between the AChE, BChE and Beta amyloid peptide and Secondary metabolites of seaweeds. The PDB format proteins was selected, the ligands were uploaded, and the grid box was marked to shield the active site residues, ready to be preferred binding residues to achieve the maximum orientation with the lowest binding affinity (Kcal/mol) values. The BIOVIA Discovery Studio Visualizer were used to visualize the 2-D and 3-D docked conformation of the ligand against the AChE, BChE and Beta amyloid peptide.

ADMET

Investigations into the pharmacokinetic and toxicity (ADMET) profiles of seaweeds' identified secondary metabolites were conducted. It is well known that pharmaceutical activity can be negatively impacted by inadequate ADMET (absorption, distribution, metabolism, excretion, and toxicity) characteristics. Additionally, *in silico* techniques were used to assess ADMET features in order to ascertain whether the seaweed's tested secondary metabolites would be good candidates for appropriate therapy. Toxicity and inappropriate pharmacokinetics are real-world factors why drugs fail. Understanding this during the clinical stage is costly. Based on AMES toxicity, all evaluated phytobioactives derived from various medicinal plants have a toxicity profile. Based on the bioavailability and drug-resemblance of these three compounds, the outcomes of most effective secondary metabolites of seaweeds appropriate for drug discovery.

3. RESULTS

Protein Structure Validation

The of AChE, BChE and Beta amyloid protein structures validation were studied using RAMPAGE. The initial validation were 88.8%, 85.0% and 91% respectively (Table 1 & Figure 2) of residues in a favourable region, and thus the protein could be considered for further docking.

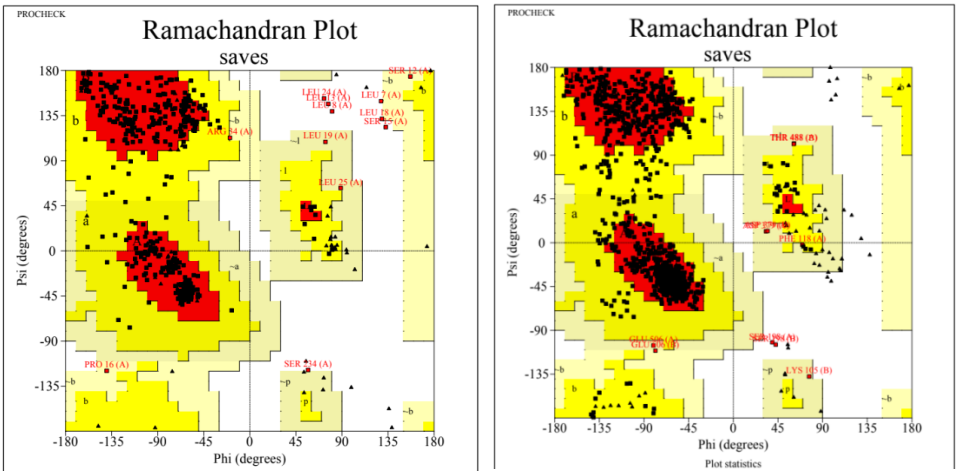


Figure 2. The Ramachandran plot produced using RAMPAGE. The energetically acceptable regions for backbone dihedral angles ψvs are depicted by the Ramachandran plot. ϕamino acid residues in AChE, BChE and Beta amyloid protein structures.

Table 3. The values found from RAMPAGE represents the number of residues in favored region, allowed region and outliner regions through Ramachandran plot evaluation centre and the outliner regions through the RAMPAGE evaluation center.

Sl No	Protein Structures	Number of Residues in Favored Regions (%)	Number of Residues in Allowed Regions (%)	Number of Residues in Disallowed Regions (%)
1	AChE	88.8	8.7	1.6
2	BChE	85.0	13.9	0.2
3	Beta-amyloid	90.8	7.4	1.3

Protein-Ligand Interaction

The significance of this work and the top docked position of the multiplicity of subatomic docked compounds was considered, based on their binding affinity were illustrated in Figure 3. These docked molecules were viewed and studied with BIOVIA Discovery Studio Visualizer software, revealing the neighboring tagged residues.

The AChE, BChE, and Beta-amyloid proteins are found sharing hydrogen bonds that are less than 2.75 long, with semi-surrounded hydrophobic interactions with the selected molecules.

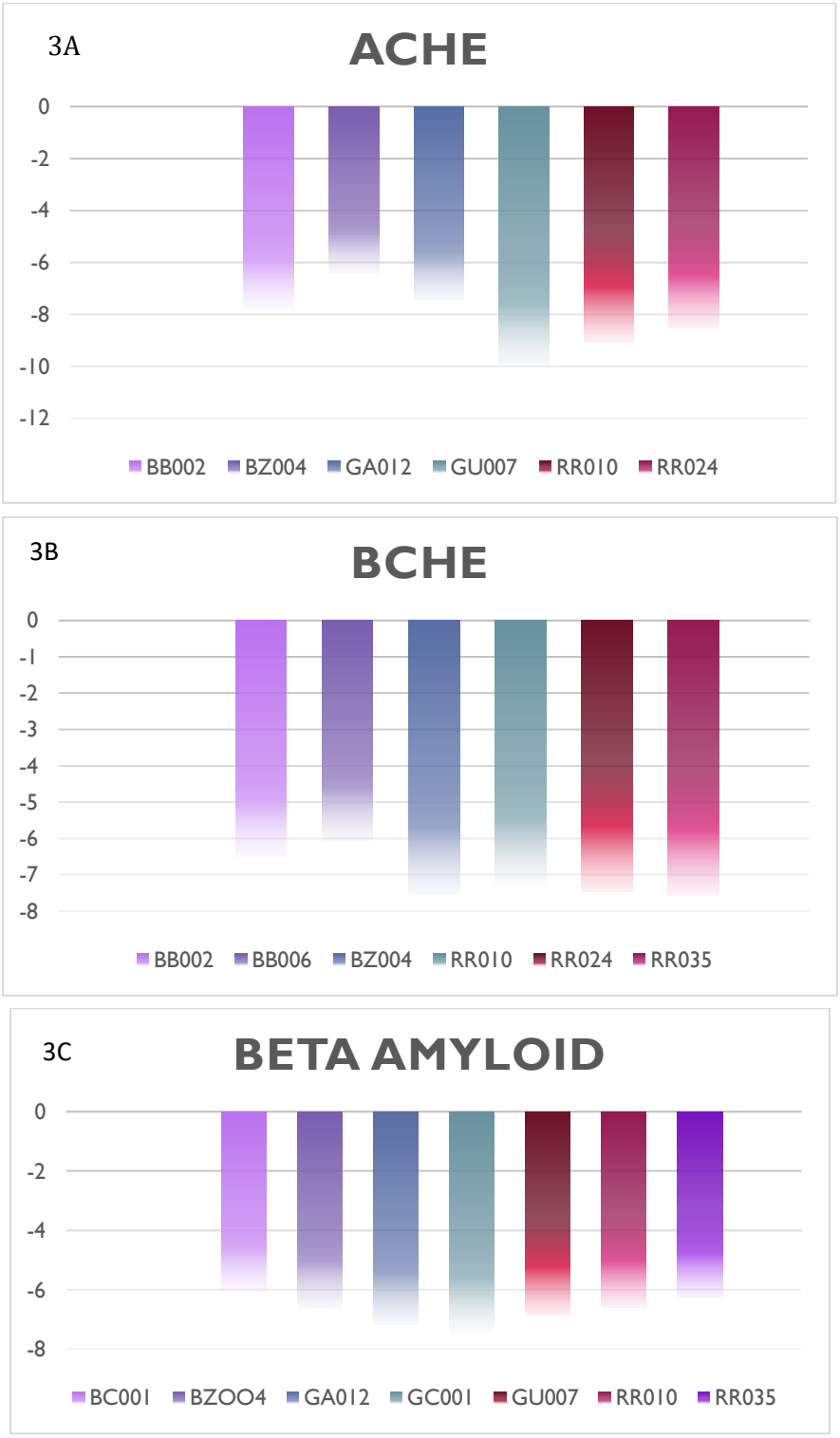


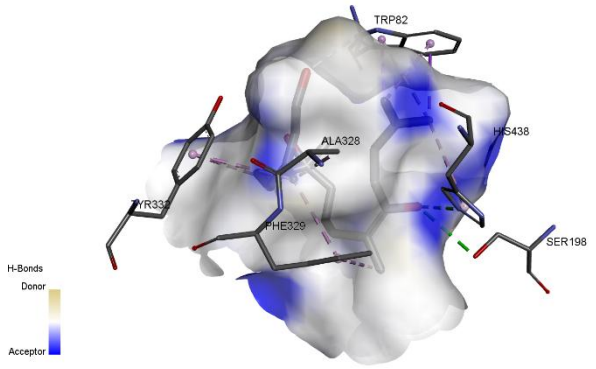
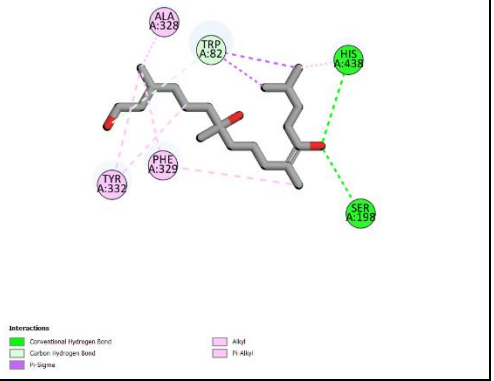
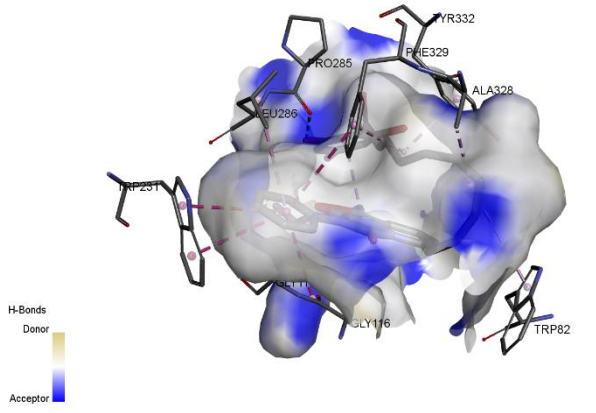
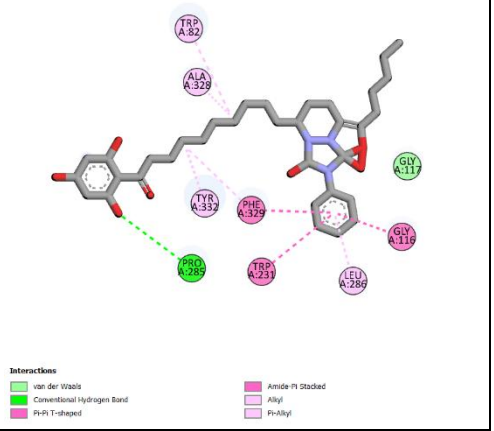
Figure 3. Histogram showing the Molecular Docking results between A) AChE B) BChE and C) Beta amyloid against selective Secondary metabolites of Seaweeds (the binding energy value δG is shown in minus kcal/mol).

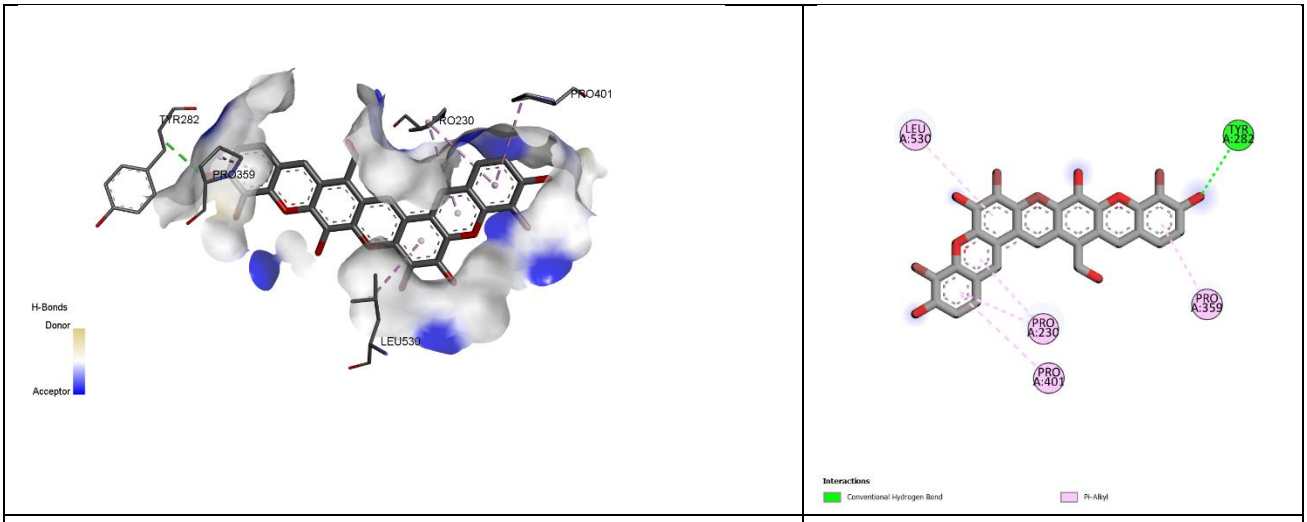
4. MOLECULAR DOCKING INTERACTIONS

Molecular docking is an often utilized strategy in drug discovery that results in little or no side effects. It is a two-step approach, originating with geometrical optimization of the ligand and target biomolecule. Molecular docking is an essential part of bioinformatics that deals with protein-ligand interactions, binding conformations, and affinity predictions. It is a widely adopted approach in drug discovery and has shown to be a rapid, easy, and cost-effective method in industrial and

academic research environments. This has created a great impact in minimizing the cost and time involved in the drug discovery process. It is a two-step approach, originating with geometrical optimization of the ligand and target biomolecule. The visualization of the secondary metabolites of seaweeds in two and three dimensions, docked against the Ache, BChE, and beta amyloid proteins, is depicted in Table 2. It demonstrates hydrogen bonding as well as other lower interactions such as Van der Waals force, π–π stacked, π–πT-shaped, π-alkyl, and carbon-hydrogen bond. Using the Molecular Docking (in silico) technique, we investigated the interaction between the Ache, BChE, and beta amyloid proteins and a secondary metabolite of a seaweed substance. Among the selected compounds, BB002 was found to be more potent against AChE, RR035 has expressed better interaction compared to others with BChE and GC601 with Beta amyloid. These results implicate that Secondary metabolite of Seaweeds binding with key proteins of AD pathogenesis like Ache, BChE and Beta amyloid is very strong as compared to other compounds.

Table 2: 2D and 3D Structural Visualization of Docked molecules

AchE	
BB002	
	
BZ004	
	
GA012	



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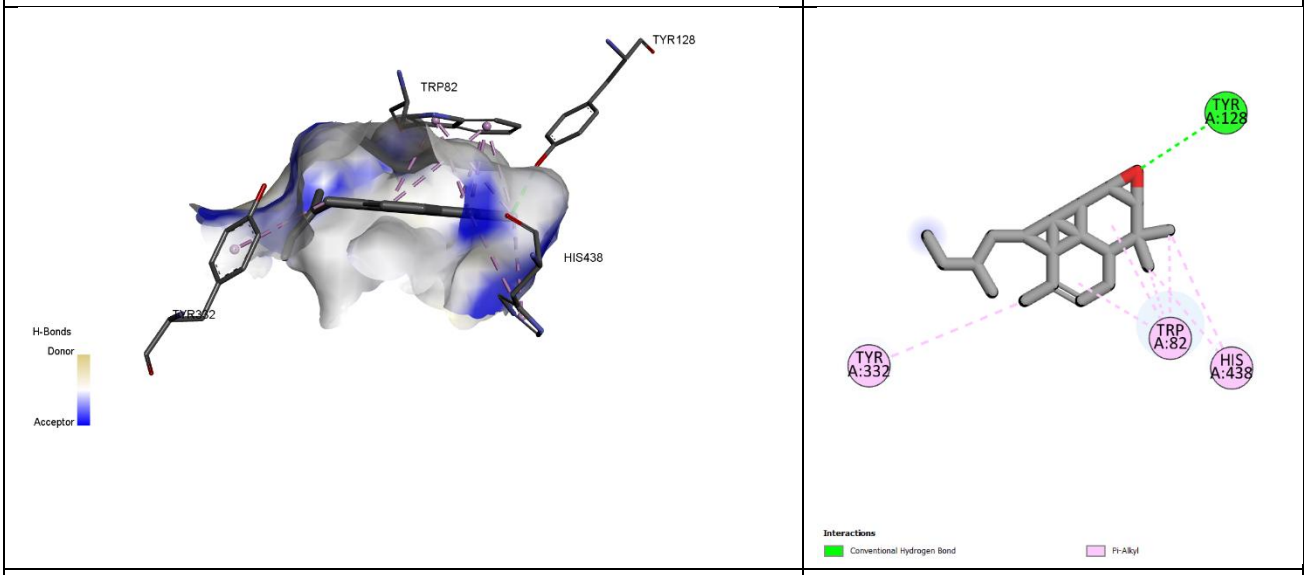
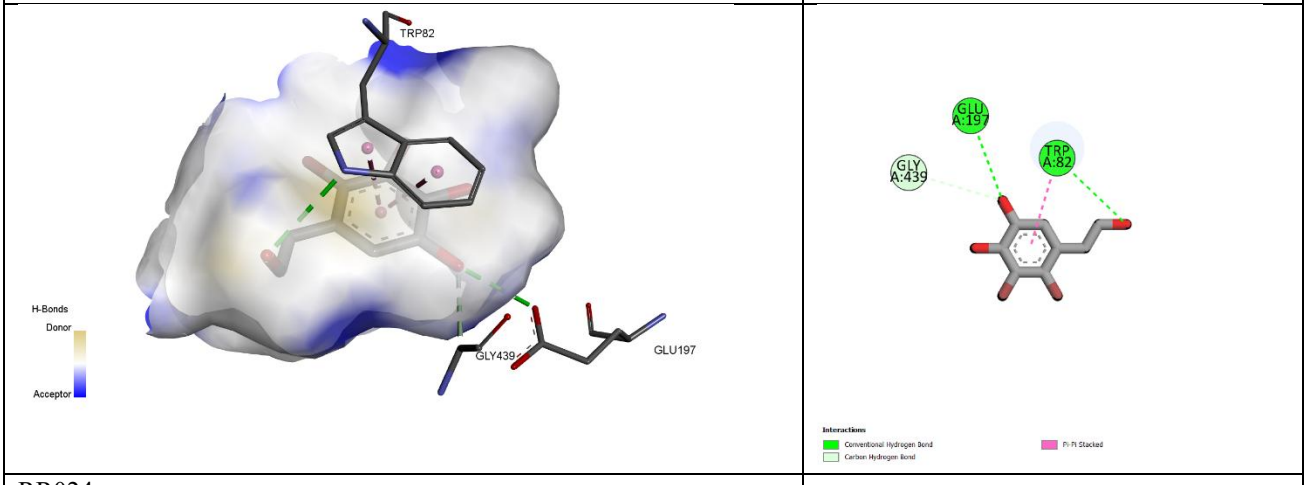
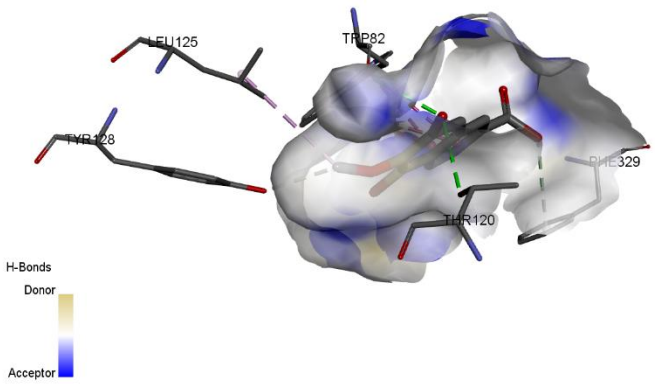
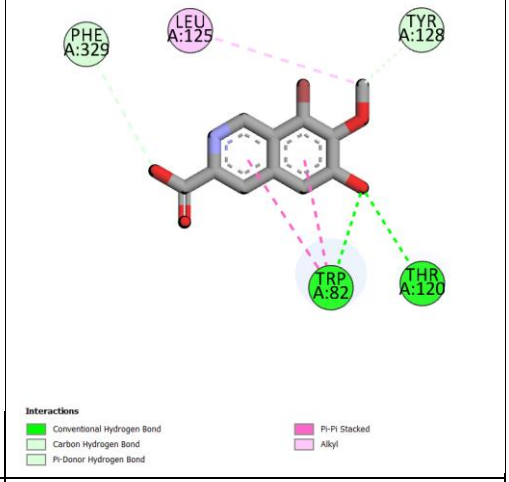


RR010

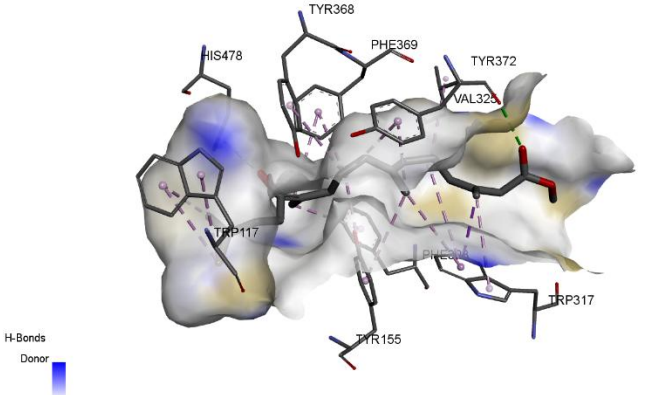


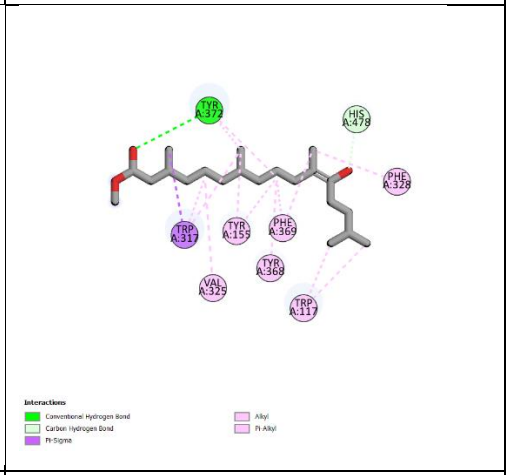
RR024





BB06





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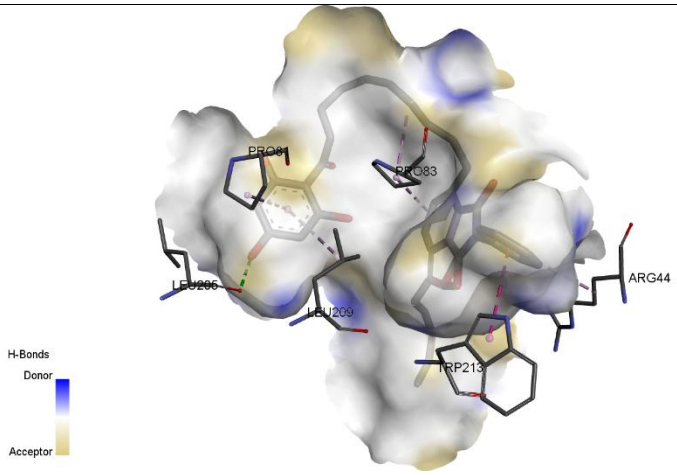

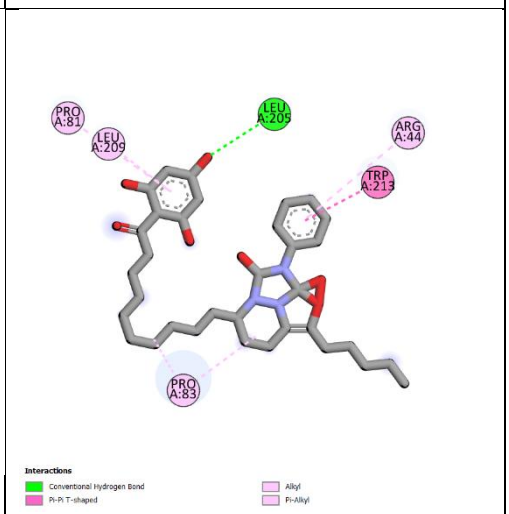

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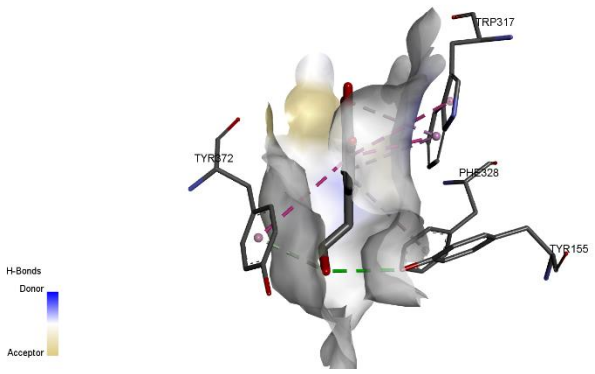

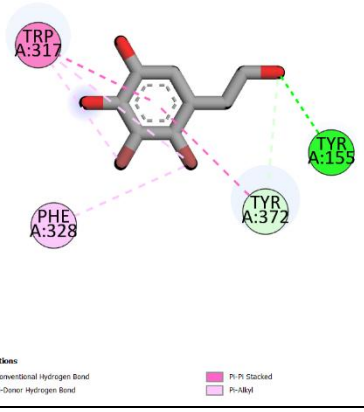

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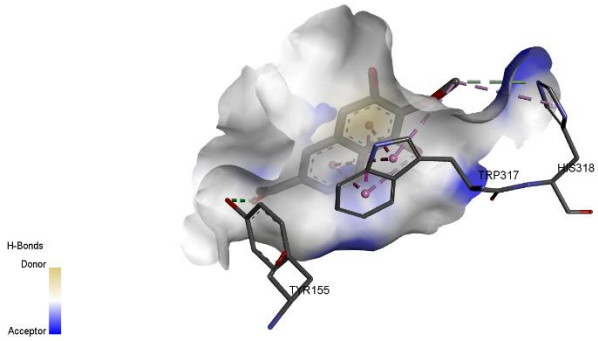

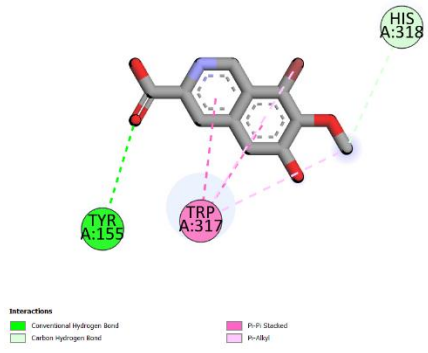

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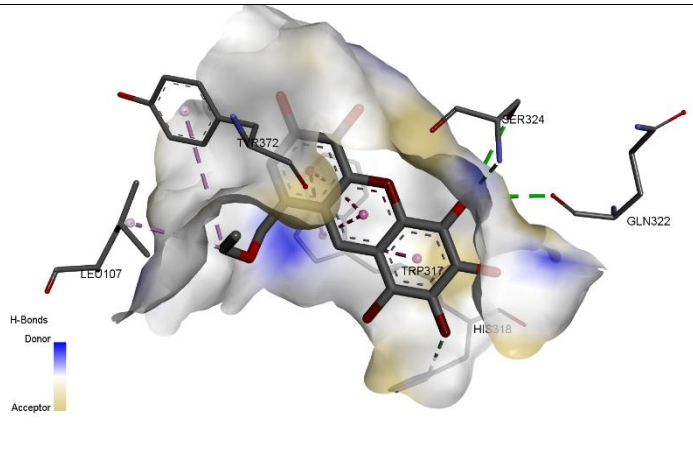
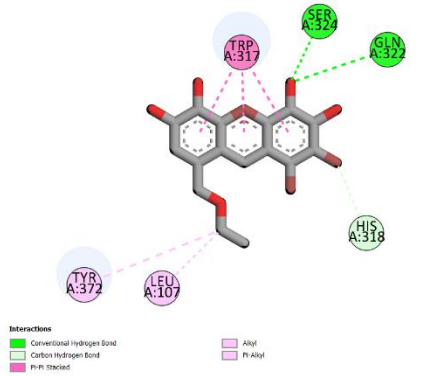
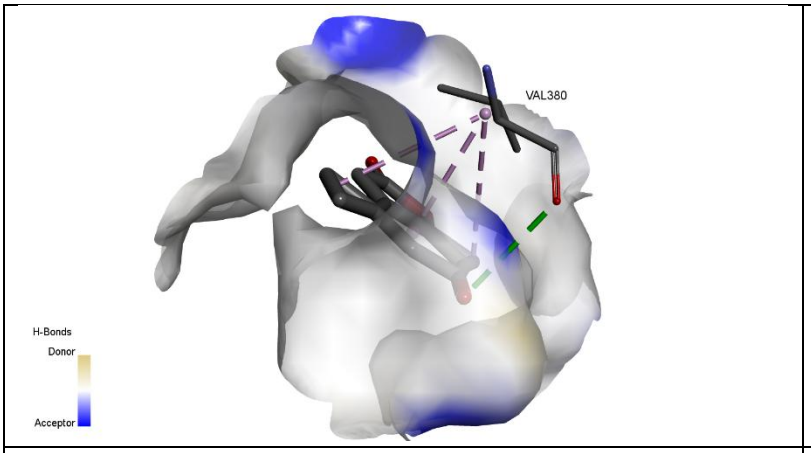
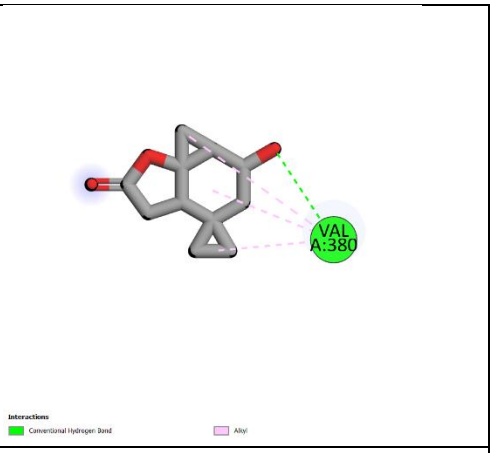




BETA AMYLOID

BC001





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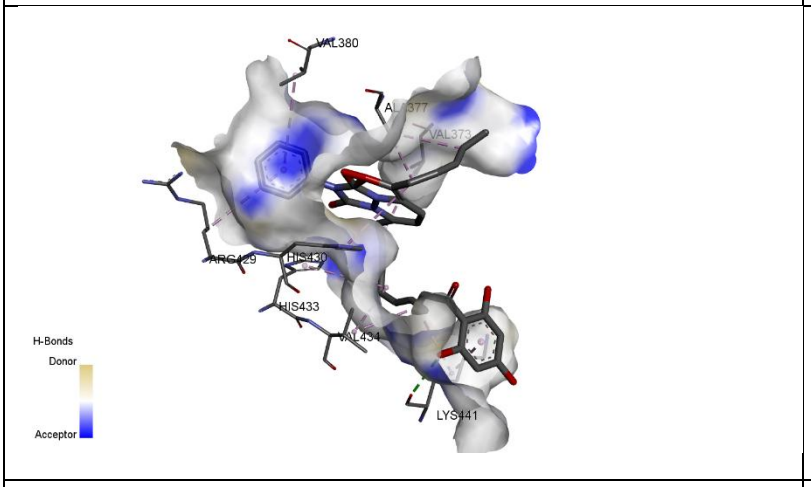

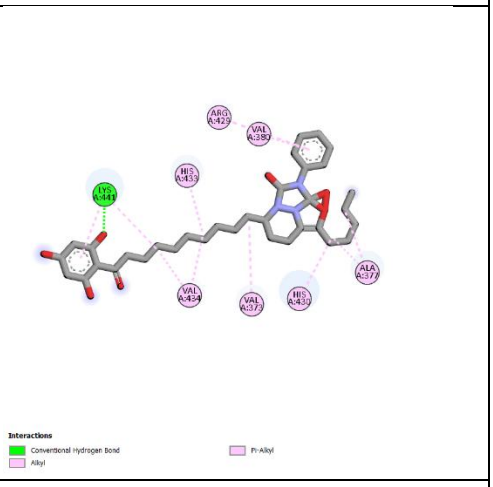

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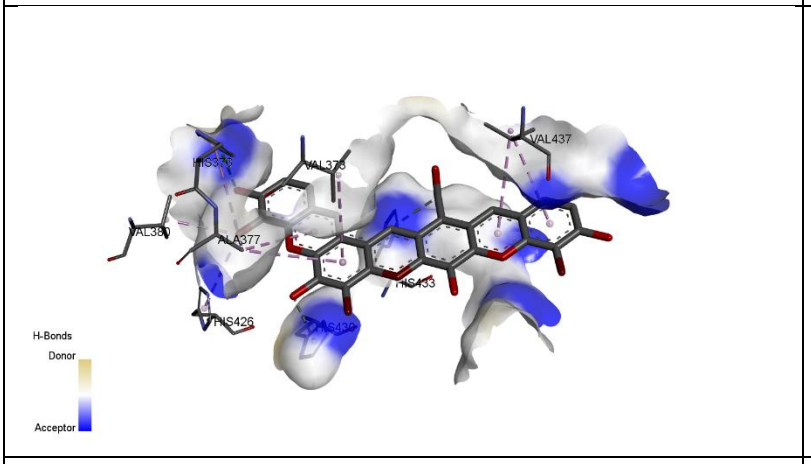

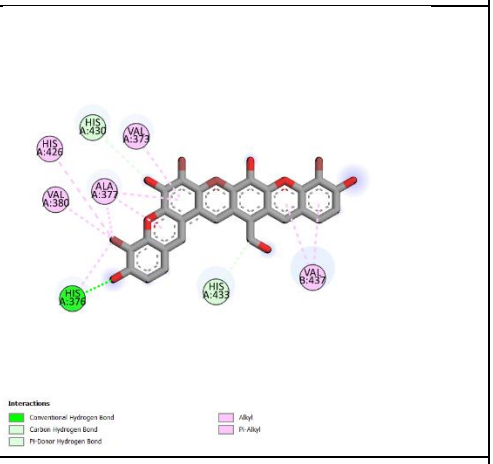

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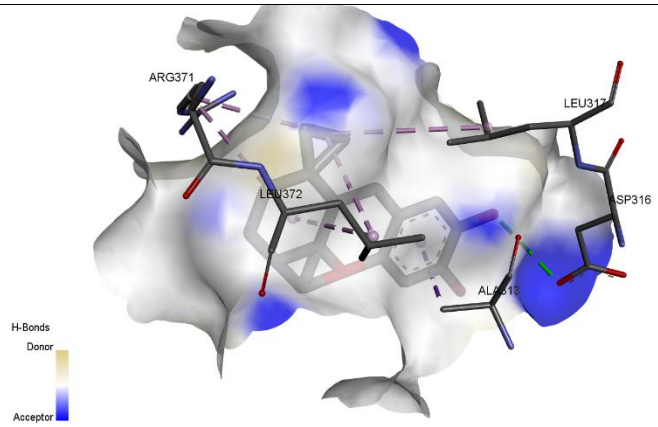

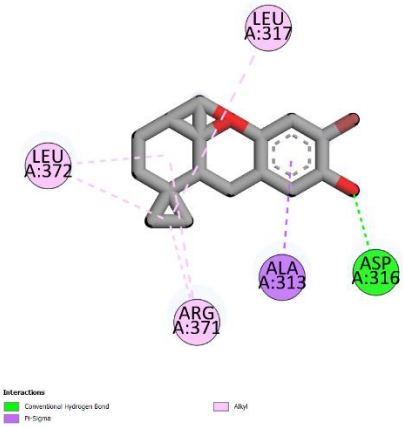

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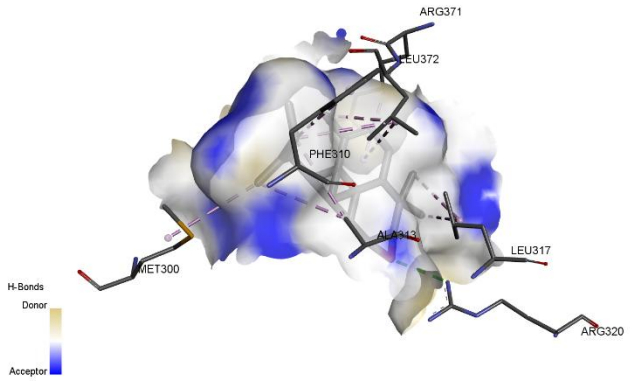

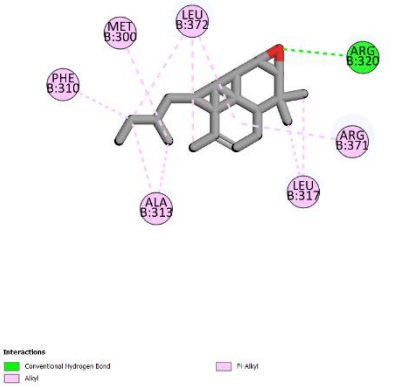

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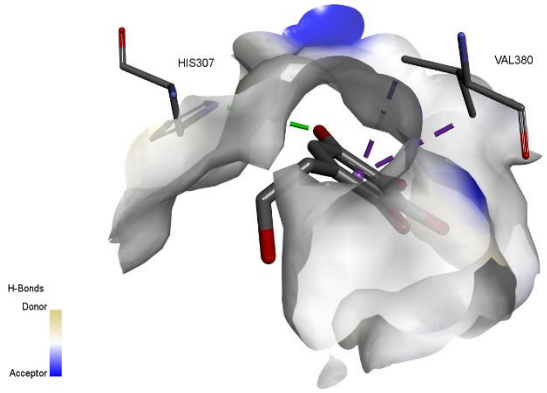
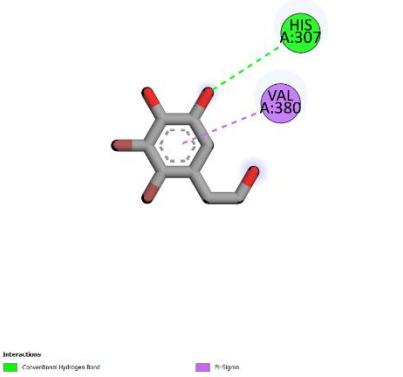
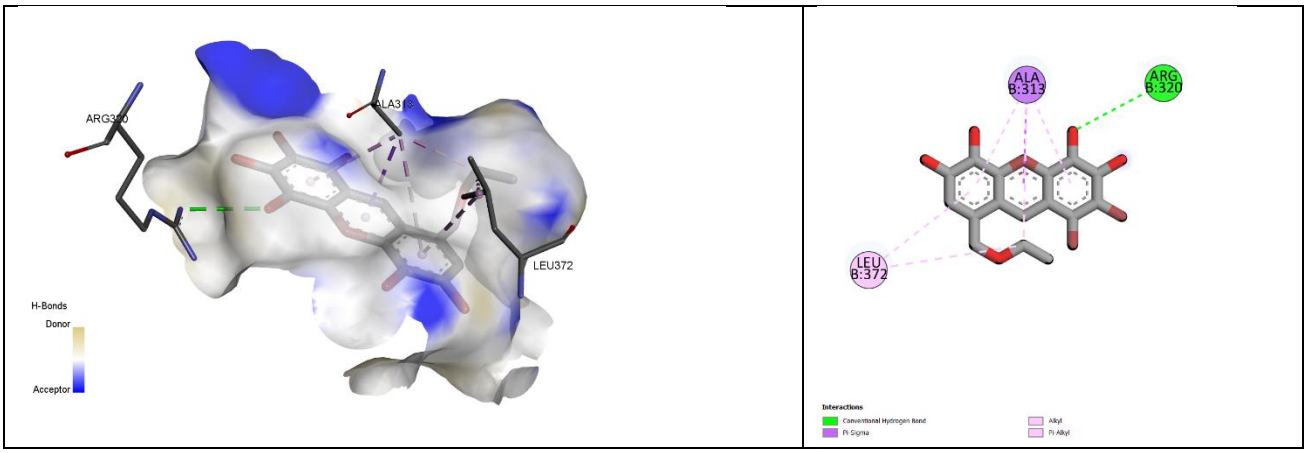




RR035



ADMET

Pharmacokinetic and Toxicity (ADMET) profiles of identified phytobioactives from various medicinal plants were undertaken. It is generally established that poor ADMET (absorption, distribution, metabolism, excretion, and toxicity) qualities can degrade pharmacological activity. Furthermore, ADMET characteristics were examined using *in silico* methods to determine whether the screened phytobioactives would be good candidates for suitable medication. Unwanted pharmacokinetics and toxicity are practical causes of drug failure. This is expensive to discover at the clinical phase. The toxicity profile of all screened phytobioactives from various medicinal plants is based on AMES toxicity. Based on the bioavailability and drug-likeness of these three compounds, the results of more potent phytobioactives suitable for drug discovery are shown in Table 3.

Table 3. ADMET identified properties of top 5 Seaweed compounds.

ADMET Entry	BB002	RR010	RR035	GC601	RR024
	Drug Likeness				
Lipinski	Yes	Yes	Yes	Yes	No
Bioavailability Score	0.55	0.55	0.55	0.55	0.55
	Solubility				
Water Solubility	Yes	Yes	Yes	Yes	No
	Absorption				
Intestinal Absorption	High	High	High	High	Low
Skin Permeability	−9.14	6.88	6.59	−6.96	−9.14
P-glycoprotein Substrate	No	No	No	No	No
	Distribution				
BBB Permeability	No	No	Yes	No	No
CYP1SA2 Inhibitor	No	Yes	Yes	No	No
CYP12C19 Inhibitor	No	No	No	No	No

ADMET Entry	BB002	RR010	RR035	GC601	RR024
CYP2C9 Inhibitor	No	No	No	No	No
CYP2D6 Inhibitor	No	No	No	No	No
CYP3A4 Inhibitor	No	No	No	No	No
	Toxicity				
AMES Toxicity	No	No	No	No	No

5. DISCUSSION

The molecular docking and ADMET analyses in this study demonstrate that seaweed-derived secondary metabolites can effectively interact with major proteins involved in AD pathogenesis. Among the screened molecules, BB002, RR010, RR035, and GC601 displayed the most promising docking scores with AChE, BChE, and beta-amyloid, suggesting a multifaceted mechanism of neuroprotection through cholinesterase inhibition and interfering amyloid aggregation.

The cholinergic hypothesis of AD suggests that decreased acetylcholine levels contribute to cognitive decline (5). Compounds that inhibit AChE and BChE can increase acetylcholine concentration in the synaptic cleft, improving memory and cognition (6). The high binding affinities observed in this study imply that these seaweed metabolites might mimic the pharmacological action of known AChE inhibitors but with potentially fewer adverse effects due to their natural origin.

Furthermore, interaction with beta-amyloid peptide indicates a possible role in mitigating amyloid plaque formation, a hallmark of AD pathology. These dual-target interactions are crucial for designing multitarget-directed ligands (MTDLs), a modern approach in neurodegenerative drug discovery (40).

ADMET evaluation further supports the therapeutic potential of these molecules, revealing good oral bioavailability, absence of Ames toxicity, and compliance with Lipinski's Rule of Five, suggesting drug-likeness. Notably, RR035 showed blood-brain barrier permeability, an essential feature for CNS-targeting drugs.

The results align with prior reports of seaweed metabolites possessing antioxidant, anti-inflammatory, and neuroprotective properties. Their diverse chemical nature-comprising alkaloids, polyphenols, and terpenoids may synergistically contribute to neuroprotection through radical scavenging, modulation of cholinesterase activity, and reduction of neuroinflammation (15-20). Although, *in silico* analyses provide valuable predictive insights, the experimental validation through *in vitro* enzymatic assays, cell culture studies, and *in vivo* neurobehavioral models are essential to confirm efficacy and safety. Despite this limitation, *in silico* analysis remains a powerful tool for identifying novel therapeutic candidates. Advancements in molecular docking tools and algorithms are expected to enhance the accuracy and efficiency of target discovery. Moreover, integrating molecular docking with complementary computational approaches - such as network analysis and machine learning -could yield deeper insights into the complex interactions of seaweed-derived secondary metabolites, potentially accelerating the drug development process while reducing resource demands.

6. CONCLUSION

The present study identifies seaweed-derived secondary metabolites—particularly BB002, RR010, RR035, and GC601 as promising inhibitors of AChE, BChE, and beta-amyloid proteins, key targets in Alzheimer's disease. Their favorable binding affinities, stable protein-ligand interactions, and positive ADMET profiles suggest strong therapeutic potential as natural cholinesterase inhibitors and anti-amyloid agents. These findings underscore the vast and largely untapped potential of marine-derived metabolites in neurodegenerative drug discovery. Future work involving molecular dynamics simulations, 3D-QSAR, and pharmacophore modeling, followed by *in vitro* and *in vivo* validations, could pave the way for the development of novel, safe, and effective natural therapeutics for treating Alzheimer's disease

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