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Marine Organisms with Anti-Amyloid Effect Through Their Role as BACE1 Inhibitors for Preventive Effort in Alzheimer's Disease: A Literature Review

Made Raditya Arhya Putra[1*], Legis Ocktaviana Saputri[2], Teguh Budi Wicaksono[1], Kadek Nandita Nugraha[1], Ajeng Ayu Putri[1], Rika Kamila Salsabila[1], Puspa Zalika Fidelia[1]

[1]Medical Education Study Program, Faculty of Medicine and Health Sciences, The University of Mataram, Mataram, Indonesia;

[2]Department of Pharmacology, Faculty of Medicine and Health Sciences, The University of Mataram, Mataram, Indonesia;

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*Corresponding Author:
Made Raditya Arhya Putra, Medical Education Study Program, Faculty of Medicine and Health Sciences, The University of Mataram, Mataram, Indonesia;
Email: radityaarhya@gmail.com

Abstract: Alzheimer's Disease (AD) is a gradually worsening neurodegenerative condition characterized by the build-up of beta-amyloid proteins, resulting in a decline in cognitive abilities. β-site amyloid precursor protein cleaving enzyme-1 (BACE1) is known to play a role in the formation of beta-amyloid plaques. Thus, theoretically, inhibiting BACE1 can potentially prevent and slow down the accumulation of these plaques. This study is a literature review that compiles data from various research examining the inhibitory effects of compounds from marine organisms on the BACE1 enzyme. A comprehensive analysis was conducted on the available literature to evaluate the potential of these compounds. 19 marine organisms and 40 compounds were identified with low IC50 values, five compounds with notably low IC50 values were identified: (1) 8,8'-Bieckol [1.62 µM] from *Ecklonia cava*, (2) Phlorofucofuroeckol A [2.13 µM] and (3a) Dieckol [2.21 µM] from *Eisenia bicyclis*, (4) bis-(2,3,6-tribromo-4,5-dihydroxybenzyl) ether [2.32 µM] from *Symphyocladia latiuscula*, (3b) another Dieckol [2.34 µM] also from *Ecklonia cava* and (5) Heparan sulfate [2.89 µM] from *Portunus pelagicus*. These findings underscore the therapeutic potential of marine compounds as BACE1 inhibitors for AD. However, further research is needed to explore their bioavailability and clinical efficacy for practical application in preventing and treating Alzheimer's Disease.

Keywords: Alzheimer's Disease (AD), anti-amyloid, BACE1 Inhibitor, IC50, marine organism.

Introduction

Alzheimer's Disease (AD) is a progressive neurodegenerative disorder that is a leading cause of dementia (García-Morales *et al*., 2021; Mycroft-West *et al*., 2019). It is characterized by a decline in cognitive and memory functions, significantly impairing an individual's ability to respond to their surroundings and perform daily activities (Breijyeh & Karaman, 2020; Folch *et al*., 2018). AD is a complex multifactorial disease, with risk factors including aging, genetic factors, and vascular diseases, and it carries a high prevalence and socioeconomic burden (Breijyeh & Karaman, 2020; Folch *et al*., 2018; García-Morales *et al*., 2021; Yang & Qiu, 2024). In Indonesia, over 4.2 million people have dementia, with approximately 27.9% affected by Alzheimer's disease (KEMKES, 2023). According to a 2023 Indonesian Ministry of Health report, there are 50 million individuals with Alzheimer's worldwide, with prevalence rates of 4-9% among those over 60.

The number of affected individuals is projected to rise to 152.8 million by 2050, with age being a significant risk factor, especially in low and middle-income countries (KEMKES, 2023). Several pathophysiological hypotheses

exist for AD, including the amyloid cascade hypothesis. According to this hypothesis, AD occurs due to the accumulation of beta-amyloid plaques in brain tissue, which are central to the onset of AD (Folch *et al*., 2018). Usually, β-amyloid does not form disruptive plaques. However, excessive accumulation can stimulate nerve cell atrophy, neurofibrillary tangles, and increased oxidative stress, resulting in impaired functionality (Breijyeh & Karaman, 2020; García-Morales *et al*., 2021). The enzyme β-secretase, specifically β-site amyloid precursor protein cleaving enzyme-1 (BACE1), is crucial in the formation of β-amyloid plaques by breaking down amyloid precursor protein (APP) into β-amyloid, inhibiting that enzyme making it a promising candidate for treatment and preventive target for AD (Cai *et al*., 2001; Hannan *et al*., 2020; Mycroft-West *et al*., 2019).

Therapies to slow AD progression and improve life quality become essential (KEMKES, 2023). However, current treatment options are limited and often ineffective at significantly halting disease progression. At present, the FDA has authorized just a pair of medication categories for AD management: medications that block cholinesterase and compounds that antagonize NMDA receptors. BACE1 inhibitors as anti-amyloid-beta (Aβ) therapies are being explored. However, no BACE1 inhibitor drug class has yet been approved and is still in clinical trials, such as verubecestat, lanabecestat, atabecestat, elenbecestat, and CNP520 (Bazzari & Bazzari, 2022; Das & Yan, 2019). Natural materials have long been used as therapeutic agents for various diseases, with marine products being among the most significant and untapped sources (Catanesi *et al*., 2021).

Research by Zhu *et al*. (2018) observed that bioactive compounds from terrestrial and marine environments contain many metabolites with varied neurological effects (Zhu *et al*., 2018). Metabolites from seaweed, sponges, and tunicates show potential as neuroprotective, anti-inflammatory, and antioxidant agents that can counteract amyloid toxicity (Sheokand *et al*., 2024). The marine environment is abundant in structurally unique compounds that possess significant biological and pharmacological activity, featuring novel mechanisms of action, prompting researchers to focus on identifying neuroprotectant compounds from marine resources (Hafez Ghoran & Kijjoa, 2021; Hannan *et al*., 2020; Syad *et al*., 2016).

Although a growing body of research is exploring the neuroprotective potential of marine products, the discovery of new marine-derived compounds specifically acting as BACE1 inhibitors is still limited and needs further exploration. Most literature currently identifies organisms with potential compounds for BACE1 inhibitors, but none comprehensively discuss all organisms and their compounds. Considering the urgent need for enhanced treatment options for Alzheimer's disease (AD), this literature review aims to identify and analyze natural substances derived from marine life that can inhibit BACE1. In addition to identifying these compounds, this review will also evaluate their BACE1 inhibition potential through IC50 values. This literature is expected to significantly advance the discovery of more potent therapeutic and preventive approaches against AD, with a particular focus on BACE1 inhibitors.

Materials And Methods

Methods

This study is a comprehensive literature review aimed at evaluating the potential of marine organisms as inhibitors of the BACE1 enzyme. The methodology involved the collection and analysis of published studies concerning how substances extracted from marine life suppress or modulate BACE1 activity.

Search strategy and selection criteria

Literature research was performed across multiple online scientific repositories and academic platforms. The search terms used included combinations of "marine organisms," "BACE1 inhibitors," "Alzheimer's Disease," "beta-amyloid," and related keywords. Studies included in the review were those published in English. Both in vitro and in vivo studies reporting specific inhibition metrics such as IC50 values were considered.

Data extraction

Relevant data were extracted from the selected articles, including type of marine organism, specific compounds tested,

experimental models (in vitro, in vivo), mechanisms of action, IC50 values, and other pertinent pharmacological data. The extracted data were tabulated to synthesize the findings and to facilitate comparison across different studies.

Data synthesis and analysis

The collected data were analyzed to determine the overall potential of marine-derived compounds as BACE1 inhibitors. This involved a comparative analysis of IC50 values, the examination of the mechanisms of inhibition, and the potential therapeutic implications of the findings. Special attention was given to compounds with the lowest IC50 values and their respective marine sources.

Ethical considerations

Given the nature of the review, primary ethical considerations related to the original studies were noted, particularly in terms of sourcing of marine organisms and the ethical treatment of animals in in-vivo experiments.

Results and Discussion

Results

Research into compounds derived from ocean-dwelling species that can inhibit BACE1 has revealed promising directions in developing treatments for AD. The extensive diversity of marine life provides numerous bioactive substances with possible protective effects on nerve cells. In our review of the literature, we identified numerous compounds from various marine species that demonstrate significant BACE1 inhibitory activity. These compounds, ranging from phlorotannins in algae to peptides in cyanobacteria, exhibit varying degrees of potency in inhibiting BACE1. The effectiveness of these compounds is typically quantified through their half-maximal inhibitory concentration, indicating the amount needed to reduce enzyme function by half. Lower IC50 values indicate higher potency, making such compounds particularly interesting for further research and potential drug development. The data visualization below summarizes our findings, comparing the IC50 values of different marine-derived compounds against BACE1.

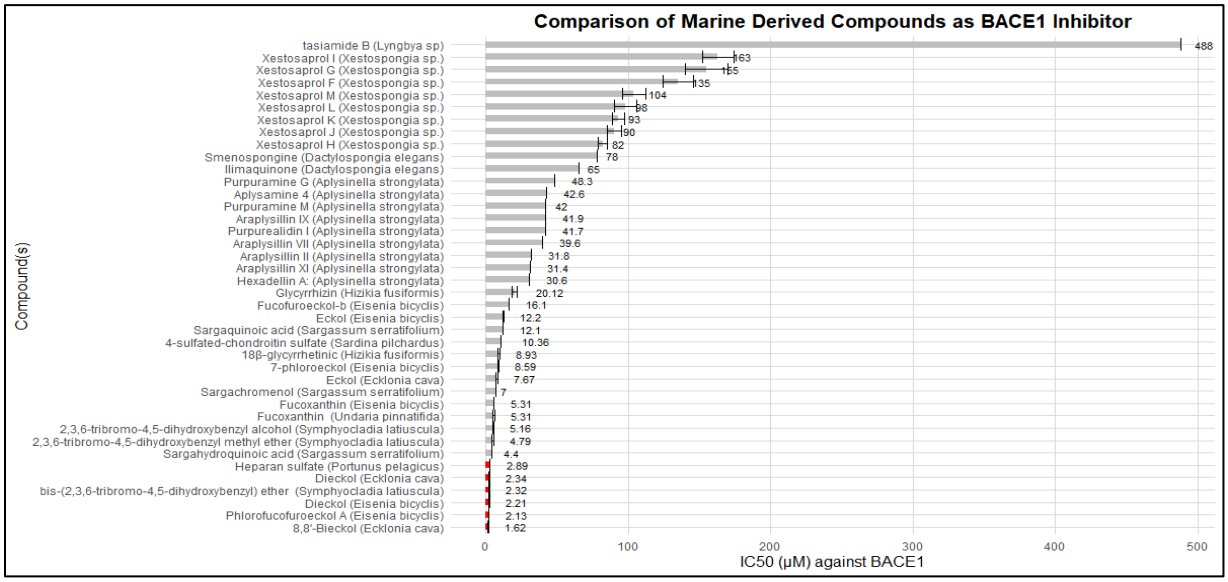
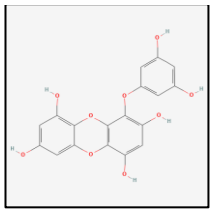
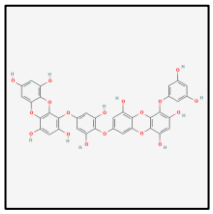
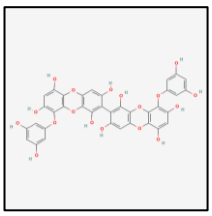
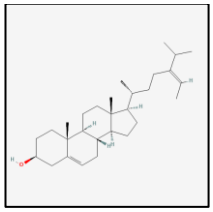
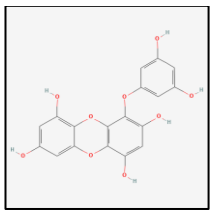
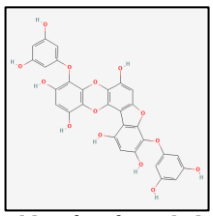
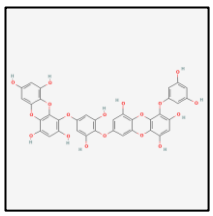
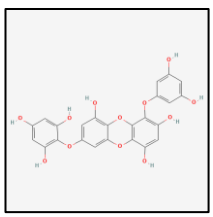
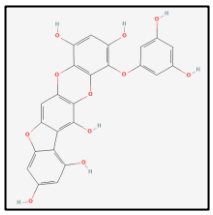


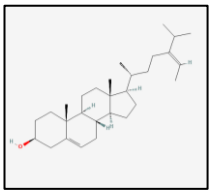
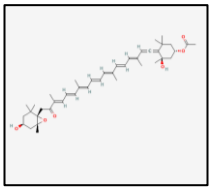
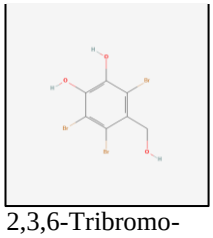
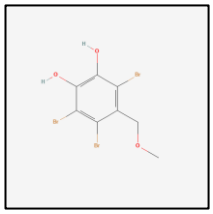
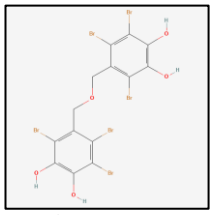
Figure 1. Comparison of each marine derived compound's IC50 test against BACE1. Five compounds with low IC50 values were identified: (1) 8,8'-Bieckol [1.62 µM], (2) Phlorofucofuroeckol A [2.13 µM], (3) Dieckol [2.21 µM and 2.34 µM], (4) bis-(2,3,6-tribromo-4,5-dihydroxybenzyl) ether [2.32 µM], and (5) Heparan sulfate [2.89 µM]. These compounds were found in the following organisms: (1) *Ecklonia cava*, (2) *Eisenia bicyclis*, (3) *Eisenia bicyclis* and *Ecklonia cava*, (4) *Symphyocladia latiuscula*, and (5) *Portunus pelagicus*. The IC50 test indicates the concentration of a substance required to inhibit another compound by 50%. Some organisms were excluded from this chart due to lack of IC50 evidence or too high data variability, including (1) *Haematococcus pluvialis*, (2) *Euphausia superba*, (3) *Symploca sp*., (4) *Ianthella basta Pallas*, (5) *Ecklonia stolonifera*, and (6) *Spongionella gracilis*. Organism names are in brackets.

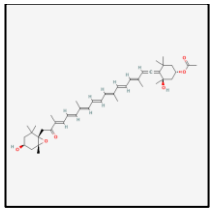
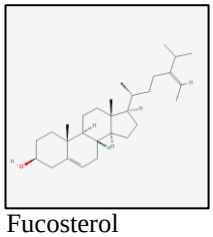
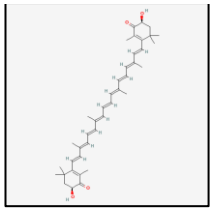
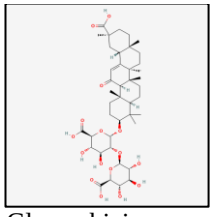
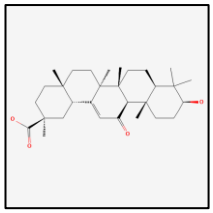
The benefits of studying ocean-dwelling species for AD research goes beyond just BACE1 inhibition. Many compounds extracted from marine sources demonstrate multiple protective effects on nerve cells, such as reducing oxidative stress and inflammation, which could enhance their therapeutic value. Our review has uncovered a diverse array of marine organisms - from microscopic algae to complex invertebrates - that produce compounds with promising anti-Alzheimer's properties. These organisms employ various mechanisms to inhibit BACE1, ranging from direct enzyme inhibition to modulation of gene expression. Understanding these mechanisms is crucial for advancing our knowledge and developing targeted therapies. For a detailed presentation of the research results, the accompanying **Table 1** provides comprehensive data about the marine organisms, their bioactive compounds, proposed mechanisms of action, and experimental data. This table serves as a valuable resource, offering insights into the current state of research on marine-derived compounds for Alzheimer's disease and highlighting promising directions for future investigations.

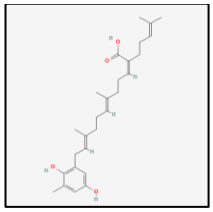
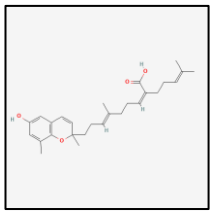
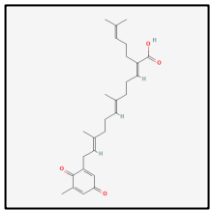
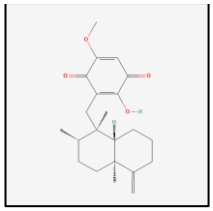
Table 1. Summary of effective doses (based on IC50), experimental models, and action mechanisms of marine organisms against BACE1 inhibitory effects

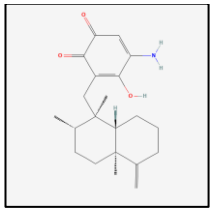
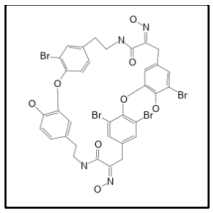
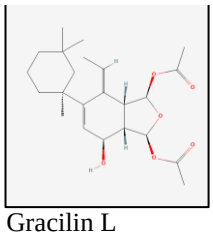
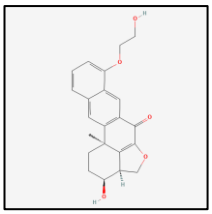
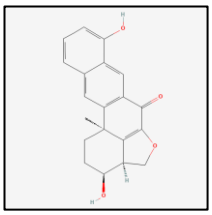
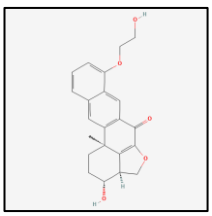
Organism	Compound & Structure	Mechanism of Action	Experimental Model	Compound Effective Concentration (IC50)	Reference(s)
Marine Algae					
Ecklonia cava	 Eckol  Dieckol  8,8'-Bieckol	Non-competitive inhibition through the binding of phlorotannins at the allosteric site of BACE1, stabilizing the enzyme in an inactive form	In vitro and in silico docking	. Eckol: 7.67 ± 0.71 µM . Dieckol: 2.34 ± 0.10 µM . 8,8'-Bieckol: 1.62 ± 0.14 µM	(Klose *et al*., 2022; Lee & Jun, 2019; Rivarti *et al*., 2023)

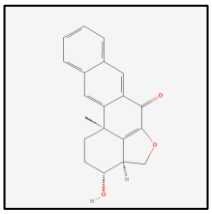
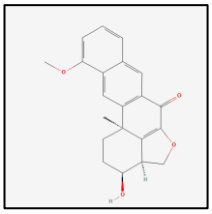
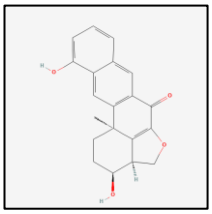
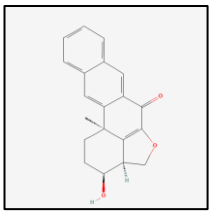
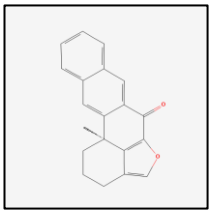
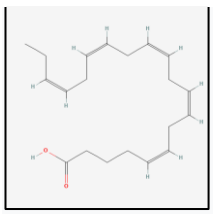
Ecklonia stolonifera	 Fucosterol	BACE1 inhibition through modulation of the BDNF-TrkB-ERK1/2 pathway, reducing ER stress and enhancing BDNF expression	In vitro and in vivo	. Fucosterol: 64.12 ± 1.0 mM	(Jung *et al.*, 2016; Hannan *et al.*, 2020; Klose *et al.*, 2022; Men *et al.*, 2022)
Eisenia bicyclis	 Eckol  Phlorofucofuroeckol A  Dieckol  7-Phloroeckol  Fucofuroeckol-b	Neuroprotective effects through reduction of ROS and intracellular Ca2+ concentration, inhibiting Aβ toxicity	In vitro, PC12 cells (rat pheochromocytoma)	. Eckol: 12.20 µM . PhlorofucofuroeckolA: 2.13 µM . Dieckol: 2.21 µM . 7-Phloroeckol: 8.59 µM . Fucofuroeckol-b: 16.1µM . Fucosterol: 64.12 µM . Fucoxanthin: 5.31 µM	(Ahn *et al.*, 2012; Hannan *et al.*, 2020; Jung *et al.*, 2010; Sheokand *et al.*, 2024)

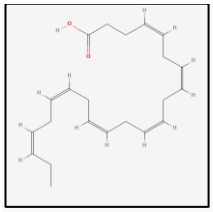
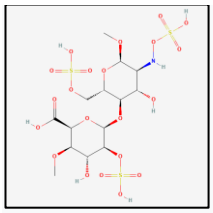
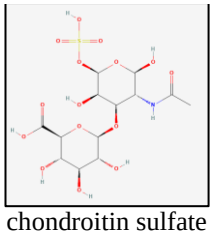
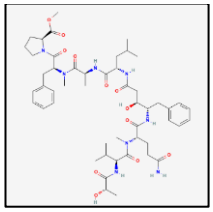
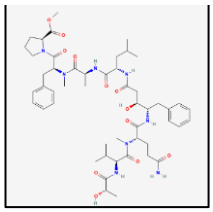
	 Fucosterol  Fucoxanthin				
Symphyocladia latiuscula	 2,3,6-Tribromo-4,5-Dihydroxybenzyl Alcohol  2,3,6-Tribromo-4,5-Dihydroxybenzyl Methyl Ether (PubChem, 2024a)  Bis-(2,3,6-Tribromo-4,5-Dihydroxybenzyl) Ether	Inhibition of BACE1 through halogen interactions and hydrogen bonds that stabilize the enzyme-ligand complex	In vitro and in silico docking	1. 2,3,6-Tribromo-4,5-Dihydroxybenzyl Alcohol: 5.16 ± 0.60 µM 2. 2,3,6-Tribromo-4,5-Dihydroxybenzyl Methyl Ether: 4.79 ± 0.82 µM 3. Bis-(2,3,6-Tribromo-4,5-Dihydroxybenzyl) Ether: 2.32 ± 0.10 µM	(Paudel *et al.*, 2019)

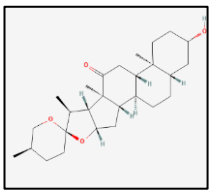
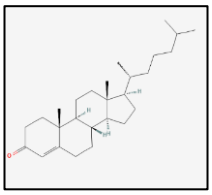
Undaria pinnatifida	 Fucoxanthin  Fucosterol	Non-competitive and mixed-type BACE1 inhibition through hydrogen and hydrophobic interactions	In vitro, enzyme inhibition assay, enzyme kinetics, and molecular docking simulation	. Fucoxanthin: 5.31 ± 0.9 µM . Fucosterol: 64.12 ± 1.0 µM	(Hannan *et al.*, 2020; Jung *et al.*, 2016; Klose *et al.*, 2022; Rafiquzzaman *et al.*, 2015; Xiang *et al.*, 2017)
Haematococcus pluvialis	 Astaxanthin	Inhibition of BACE1 and prevention of amyloid-beta aggregation	In vitro and in vivo, cell-free and cell-based assays, transgenic animal models	-	(Chakraborty *et al.*, 2022; X. Chen *et al.*, 2021)
		Seaweed			
Hizikia fusiformis	 Glycyrrhizin  18β-Glycyrrhetinic Acid	Glycyrrhizin exhibits non-competitive inhibition at the allosteric site, while 18β-Glycyrrhetinic Acid shows competitive inhibition at the catalytic site of BACE1	In vitro, enzyme assay, and in silico docking simulation	. Glycyrrhizin: 20.12 ± 1.87 µM . 18β-Glycyrrhetinic Acid: 8.93 ± 0.69 µM	

Sargassum serratifolium	 Sargahydroquinoic Acid  Sargachromenol  Sargaquinoic Acid	Sargahydroquinoic Acid and Sargaquinoic Acid exhibit mixed-type inhibition at the catalytic and allosteric sites of BACE1, while Sargachromenol shows non-competitive inhibition at the allosteric site	In vitro, enzyme assay and in silico docking simulation	1. Sargahydroquinoic Acid: 4.4 ± 0.31 µM 2. Sargachromenol: 7.0 ± 0.55 µM 3. Sargaquinoic Acid: 12.1 ± 0.87 µM	(Hannan *et al*., 2020; Seong *et al*., 2017)
Marine Sponge					
Aplysinella strongylata	Purpuramine G Purpuramine M Araplysillin II Araplysillin VII, Araplysillin IX, Araplysillin XI, Hexadellin A, Purpurealidin I, Aplysamine 4	-	-	1. Purpuramine G: 48.3 µM 2. Purpuramine M: 42.0 µM 3. Araplysillin II: 31.8 µM 4. Araplysillin VII: 39.6 µM 5. Araplysillin IX: 41.9 µM 6. Araplysillin XI: 31.4 µM 7. Hexadellin A: 30.6 µM 8. Purpurealidin I: 41.7 µM 9. Aplysamine 4: 42.6 µM	(Hafez Ghoran & Kijjoa, 2021)
Dactylospongia elegans	 Ilimaquinone	-	In vitro, BACE1 inhibition assay and cytotoxicity tests on human glioma cells (U251MG) and human	1. Limaquinone: 65 µM, 2. Smenospongine: 78 µM	(Neupane *et al*., 2019)

	 Smenospongia		pancreatic carcinoma cells (Panc-1)		
Ianthella basta Pallas	 Bastadin 9	Oxime-based inhibition of BACE1, interacting with the enzyme's active site | In vitro, EFC assay and LC-MS homogeneous affinity assay	In vitro, EFC assay and LC-MS homogeneous affinity assay	A 50 µg/mL fixed concentration showed>90% inhibition of BACE1 in 7% of the extracts tested.	(Lakshmi *et al*., 2018; Williams *et al*., 2010)
Spongionella gracilis	 Gracilin L	-	In vitro, BE(2)-M17 and SH-SY5Y-TMHT441 neuroblastoma cells; In vivo, 3xTg-AD mouse model	In vitro: 1 µM reduces BACE1 activity by 24.6% In vivo: 0.4 mg/kg and 0.04 mg/kg decrease Aβ42 levels.	(Abbasov *et al*., 2019; Hafez Ghoran & Kijjoa, 2021; Lakshmi *et al*., 2018; Leirós *et al*., 2015; Russo *et al*., 2016)
Xestospongia sp.	 Xestosaprols F  Xestosaprols G  Xestosaprols H	Inhibition of BACE1 through interactions with the enzyme's active site reduces the enzyme's ability to break down amyloid precursor protein	In vitro, BACE1 enzyme assay in a 96-well plate with test compounds dissolved in DMSO	. Xestosaprol F: 135 ± 11 µM . Xestosaprol G: 155 ± 15 µM . Xestosaprol H: 82 ± 3 µM . Xestosaprol I: 163 ± 11 µM . Xestosaprol J: 90 ± 5 µM . Xestosaprol K: 93 ± 4 µM . Xestosaprol L: 98 ± 8 µM . Xestosaprol M: 104 ± 8 µM	(Catanesi *et al*., 2021; J. Dai *et al*., 2010)

	 Xestosaprols I				
	 Xestosaprols J				
	 Xestosaprols K				
	 Xestosaprols L				
	 Xestosaprols M				
Crustaceans					
Euphausia superba	 EPA	-	In vivo (AD mouse model) and in vitro (BV-2 microglial cells)	EPA and DHA reduce LPS-induced production of nitric oxide and ROS, expression of COX-2 and iNOS, and NF-κB activity; Krill oil at 80 mg/kg/day for one month.	(Choi *et al.*, 2017)

	 DHA				
Portunus pelagicus	 Heparan Sulfate (PubChem, 2024c)	Interaction with the BACE1 structure, causing changes in secondary and tertiary structures and thermal destabilization of BACE1	In vitro, FRET assay, circular dichroism (CD) spectroscopy, differential scanning fluorimetry (DSF), prothrombin time (PT) assay, and activated partial thromboplastin time (aPTT) assay	IC50: 1.9 µg/mL; Maximum inhibition: 90.7% at a concentration of 5 µg/mL	(Mycroft-West *et al.*, 2019; Rivarti *et al.*, 2023)
Sardina pilchardus	 chondroitin sulfate 4-sulfate(PubChem, 2024b)	Destabilization of BACE1 structure, reducing the enzyme's thermal stability, similar to the mechanism of heparin	In vitro, Förster resonance energy transfer (FRET) assay, differential scanning fluorimetry (DSF)	IC50: 4.8 µg/mL; Maximum inhibition: concentration >10 µg/mL.	(Mycroft-West *et al.*, 2020; Rivarti *et al.*, 2023)
		Others			
Lyngbya sp.	 Tasiamide B	Inhibition of BACE1, preventing the formation of Aβ peptides from amyloid precursor protein (APP)	In vitro, enzymatic assay	IC50 = 48.8 nM	(Klose *et al.*, 2022; Liu *et al.*, 2012)
Symploca sp.	 Tasiamide B	Inhibition of BACE1, preventing the formation of Aβ peptides from amyloid precursor protein (APP),	In vitro (enzymatic assay), in vivo (mouse model)	. Compound 5: IC50 in the low nanomolar range, . Compounds 12 & 13: IC50 sub-micromolar, . Compound 13 shows significant	(Catanesi *et al.*, 2021; Hafez Ghoran & Kijjoa, 2021; Klose *et al.*, 2022; Liu *et al.*, 2012)

		featuring a typical statin core unit		efficacy in vivo	
Urechis unicinctus	 Hecogenin  Cholest-4-en-3-one	Hecogenin and Cholest-4-en-3-one exhibit inhibitory activity against BACE1, reducing β-amyloid production	In vitro, Fluorescence Resonance Energy Transfer (FRET)-based assay	. Hecogenin: EC50 = 116.3 µM, . Cholest-4-en-3-one: EC50 = 390.6 µM.	(Naushad *et al*., 2019; Rivarti *et al*., 2023; Zhu *et al*., 2018)

Discussions

Current Understanding in AD

AD represents a challenging neurological disorder with multiple contributing factors that demands comprehensive insight into its disease mechanisms for treatment development. Several theories explain the emergence of AD, with key concepts encompassing beta-amyloid accumulation, tau protein abnormalities, acetylcholine deficiency, metal ion imbalances, and inflammatory responses in the brain. (R. Dai *et al*., 2022; García-Morales *et al*., 2021). All of which are interrelated and influence each other as depicted in the **Figure 2**.

Amyloid Cascade Hypothesis

AD, particularly the autosomal dominant form with early onset, is characterized by beta-amyloid (Aβ) plaques in various brain areas, primarily due to overproduction or failure to clear Aβ peptides. (**Figure 3**). Research indicates that Alzheimer's pathogenesis is closely connected to how APP is broken down and utilized in the body. Typically, APP undergoes processing by a trio of distinct enzyme groups in the brain: α, β, and γ secretases. α-secretase processes APP into soluble sAPPα then by γ-secretase is processed into a 3-kD peptide (p3) fragment that is soluble by the Golgi apparatus and non-toxic; this path also known as non-amyloidogenic pathway which has neuroprotective properties and inhibits β-γ secretase activity, enhancing synaptic signaling and neural plasticity (Tiwari *et al*., 2019; Zhou *et al*., 2018). Through the disease-causing pathway, the enzyme BACE-1 transforms APP into sAPPβ and CTFβ fragments. These fragments are then further processed by γ-secretase, resulting in toxic, insoluble peptides. These peptides, specifically the 40 and 42 amino acid variants, combine to form oligomers (oAβ). These oligomers then form insoluble amyloid plaques, a hallmark of AD. Additionally, the apolipoprotein E4 (APOE4) gene's expression correlates with an increased risk of memory-related disorders associated with this disease (Guo *et al*., 2020).

Tau Hypothesis

Mitochondrial dysfunction, associated with Aβ plaque accumulation in nerve cell mitochondria, is critical in AD pathology. These plaques alter mitochondrial structure and block ion channels, disrupting calcium homeostasis. This disruption reduces mitochondrial respiratory capacity and ATP synthesis, impairing cellular function and energy metabolism. Besides its impact on mitochondria, Aβ, particularly Aβ42, also triggers pathologies related to tau protein. Among AD patients, tau, which stabilizes microtubules, becomes hyperphosphorylated due to high levels of Aβ42, then aggregate to form straight, insoluble tau

filaments and fibrils, known as neurofibrillary tangles (NFTs). NFTs accumulate within nerve cells, forming cytoplasmic deposits that disrupt cellular function. The formation of NFTs disrupts microtubule structure, leads to synaptic loss, and impairs neuronal signaling. This process contributes to neuronal apoptosis, damaging brain tissue and exacerbating Alzheimer's clinical symptoms. (Cheong *et al*., 2022).

Cholinergic Hypothesis

The buildup of Aβ40/42 can interfere with the function of channels that transport ACh across cell membranes. ACh serves as a key chemical messenger in the brain that enables learning and memory processes. The central cholinergic system can alter the amount of ACh by controlling its production and release (Bekdash, 2021). The nerve cells that produce acetylcholine in the basal forebrain are essential for cognitive functions, memory formation, and learning abilities. The survival and development of BFCNs depend significantly on nerve growth factor (NGF) found in cortical and hippocampal areas (Latina *et al*., 2018). In AD patients, these acetylcholine-producing neurons undergo substantial deterioration, typically occurring in the disease's early stages. This neurodegeneration is followed by a drastic decrease in ACh production and release and a decrease in acetylcholine transferase activity, exacerbating the condition of ACh deficiency. Recent clinical studies have shown that AD patient's brains have a significant reduction in cholinergic neurons and severe ACh deficiency, indicating widespread damage to the cholinergic system due to Aβ accumulation. This condition results in substantial cognitive function decline and is a potential target for pharmacological intervention to restore cholinergic function or slow neuron degeneration (Chen *et al*., 2022; Cheong *et al*., 2022).

Metal Ion Disturbance Hypothesis

The proper balance of metal ions is essential for optimal brain performance. In AD, disrupted metal ion levels in the brain contribute substantially to disease development. Fluctuations in metal ion concentrations, both increases and decreases and mislocalization have been identified as critical factors contributing to Aβ deposition and tau hyperphosphorylation in AD patients (Adlard & Bush, 2018). Metal ion accumulation in various brain areas disrupts mitochondrial function, causing oxidative stress and potentially leading to pathogenic consequences. High levels of metal ions can enhance the formation of toxic proteins by influencing various enzymes and creating oxidative damage. These ions can modify cellular cleanup processes through their interaction with autophagy proteins, leading to impaired waste removal. The synaptic release of specific metal ions is necessary for proper synaptic plasticity and function. When metal ions are improperly distributed or processed, it leads to compromised communication between neurons in AD, which is closely linked to energy production at nerve cell junctions (L.-L. Chen *et al*., 2023; Wang *et al*., 2020).

Neuroinflammation Hypothesis

Inflammatory processes in the nervous system are linked to every stage of AD development. Recent findings indicate that glial cell-mediated nerve inflammation is a key driver of neurodegenerative processes and cognitive impairments in AD patients. Inflammation in the nervous system contributes to the initial development of AD, heightening the interest of medical researchers in exploring its crucial role in AD progression. Among the various beta-amyloid forms, immune cells in the brain responding to smaller protein clusters show more destructive effects compared to larger aggregates, ultimately leading to neuron death. The relationship between Aβ and nerve inflammation has been widely studied to support the "amyloid cascade hypothesis," whereas research on the connection between microglia and tau is still limited. Under normal conditions, tau helps organize cellular structure by binding to tubulin proteins; in AD, tau becomes insoluble after detaching from microtubules, resulting in the formation of neurofibrillary tangles and an increase in reactive microglia around tau. Research has demonstrated that neurodegenerative microglia (MGnD) excessively produce p-tau + EV alongside the reduction of Aβ plaques and tau NP elimination (Wang *et al*., 2020).

The diagnosis of Alzheimer's disease (AD) is established based on the presence of dementia syndrome without other neurological or

psychiatric disorders, such as memory decline, aphasia, apraxia, agnosia, or other systemic disorders that are not the cause of dementia (Bermejo-Pareja & del Ser, 2024; Breijyeh & Karaman, 2020). The diagnosis is also based on laboratory tests, MRI, and CT scans (Breijyeh & Karaman, 2020; J. Huang, 2023). Brain imaging with radioactive tracers helps identify the buildup of abnormal protein deposits. MRI is used to look for evidence of brain atrophy (Breijyeh & Karaman, 2020).

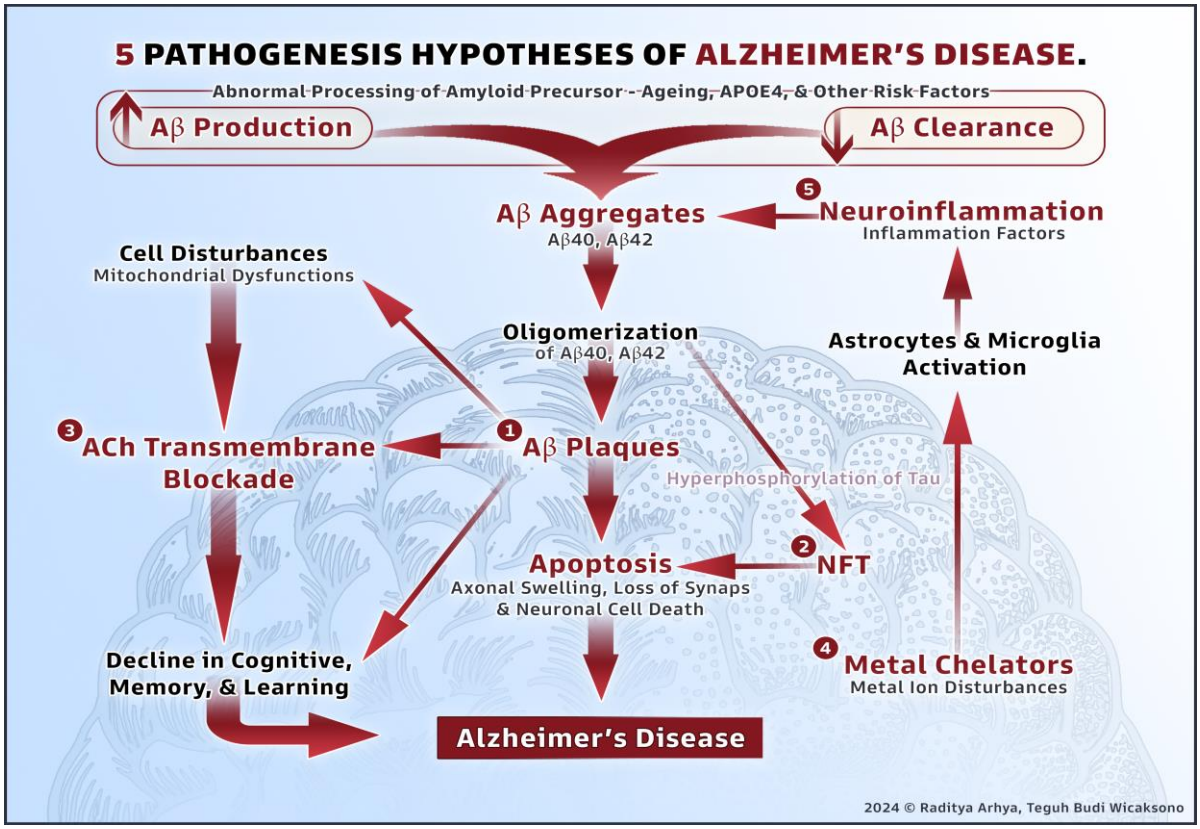


Figure 2. Hypothesis of Alzheimer's Disease Pathogenesis. Amyloid Beta (Aβ); Neurofibrillary Tangle (NFT); Achetilecoline (ACh); Apolipoprotein E (APOE4).

Current Management of Alzheimer's and Developments

Currently, there are four primary mechanisms for the latest control and treatment of AD. These approaches target acetylcholinesterase inhibition, control of beta-amyloid protein levels, risk factor management, and disease progression prevention (García-Morales *et al*., 2021). However, medical authorities have authorized just two categories of medications for AD management: drugs that inhibit cholinesterase and compounds that block NMDA receptors. One type of cholinesterase inhibitor is the acetylcholinesterase inhibitor (AChEI), which prevents the natural breakdown of the neurotransmitter acetylcholine, resulting in higher levels between nerve cells. NMDA antagonists work by preventing excessive activation of glutamate receptors, thus protecting against cell death caused by excessive Ca2+ influx (Breijyeh & Karaman, 2020).

The pathogenesis mechanisms of AD are known to be interconnected and overlap, ranging from genetic etiology, metabolism, and environment. The complex pathogenesis makes conventional single therapies, such as memantine monotherapy (an NMDA class) for treating severe AD symptoms, insufficiently effective (Cheong *et al*., 2022). Combining memantine with donepezil is one of the FDA-approved combination therapies targeting these proteins (Pardo-Moreno *et al*., 2022). Additionally, no pharmacodynamic or pharmacokinetic interactions have been observed between donepezil and memantine, making it a safe therapy combination (Knorz & Quante, 2022).

Therefore, some researchers consider combinations more effective, especially drugs targeting tau and amyloid-beta (Aβ) proteins (Miculas *et al*., 2023).

Current AD treatment developments target various pathogenesis pathways. Anti-amyloid-beta (Aβ) therapy is one anticipated pathway with mechanisms including enzymes that block gamma-secretase, inhibit beta-secretase, modify alpha-secretase activity, and prevent protein clumping (Pardo-Moreno *et al*., 2022). Aducanumab, donanemab, lecanemab, and aducanumab are drugs currently in clinical trials with antibody components that inhibit the amyloid aggregation process. PTI-125 is an experimental compound that binds to a structural protein that helps maintain connections between dissolved Aβ42 and certain acetylcholine receptors. Varoglutamstat (PQ912) works as a glutaminyl cyclase inhibitor, reducing the formation of pGlu-Aβ. This enzyme transforms exposed glutamate molecules on Aβ proteins into a circular form, creating harmful pGlu-Aβ that makes up a significant portion of amyloid deposits (L.-K. Huang *et al*., 2023).

BACE1 inhibitors as anti-amyloid-beta (Aβ) therapy are another pathway being explored. BACE1 is inhibited through post-translational mechanisms targeting the 5'UTR gene code, microRNA, and non-coding sense RNA (Pardo-Moreno *et al*., 2022; Yang & Qiu, 2024). However, many pharmaceutical companies have experienced failures in clinical trial phases, such as safety issues and efficacy problems in the development of BACE1 inhibitors (Bazzari & Bazzari, 2022). Despite this, several BACE1 inhibitors undergo phase 2-3 trials, including verubecestat, lanabecestat, atabecestat, elenbecestat, and CNP520. BACE1 inhibitors continue to be developed due to their potential to delay and slow AD progression. Combining BACE1 with other therapies may be more effective in enhancing cognition and preventive therapy in AD (Das & Yan, 2019).

Potential of Marine Organisms as BACE1 Inhibitors

This literature review identified 19 marine organisms containing 40 compounds with potential as BACE1 inhibitors. These organisms were categorized into marine algae, seaweeds, marine sponges, crustaceans, and other marine organisms.

Marine Algae

Ecklonia cava

This brown algae (*Phaeophyta*), found in the waters of Japan and southern Korea, is known for its active phlorotannin content, which is usually not found in terrestrial plants. Studies by (Lee & Jun, 2019) showed that *E. cava* contains compounds such as Eckol, Dieckol, and 8,8'-Bieckol with inhibitory effects on BACE1. The average IC50 values were found for Eckol [7.67 ± 0.71 μM], Dieckol [2.34 ± 0.10 μM], and 8,8'-Bieckol [1.62 ± 0.14 μM]. Among these, 8,8'-Bieckol showed the best inhibitory effect due to its lower IC50 against BACE1. The study indicated that the phlorotannin content binds non-competitively at the allosteric site of the BACE1 enzyme through hydrogen bonding, inactivating the enzyme BACE1 (Klose *et al*., 2022; Lee & Jun, 2019; Rivarti *et al*., 2023; Wijesekara *et al*., 2010).

Ecklonia stolonifera

Distributed in areas around Korea and Japan and known locally as "turuarame," *E. stolonifera* typically grows at depths of 2-10 meters and exhibits good reproductive and adaptive capabilities to environmental changes (Men *et al*., 2022). *E. stolonifera* contains active substances such as Fucosterol, Fucoxanthin, and Phlorotannin, with anti-inflammatory and anti-adipogenic effects. Fucosterol, for example, was found to have a BACE1 or anti-beta-secretase-1 inhibitory effect (IC50: 64.12 ± 1.0 mM) (Hannan *et al*., 2020; Jung *et al*., 2016; KEMKES, 2023; Men *et al*., 2022).

Eisenia bicyclis

Eisenia bicyclis, a type of brown algae in the Laminariaceae family, is a perennial species commonly found along the mid-Pacific coast, particularly around Korea and Japan. It contains various compounds, including phlorotannins such as eckol, phlorofucofuroeckol A, dieckol, 7-phloroeckol, Fucofuroeckol-b, Fucoxanthin, and fukosterol. Studies have shown that methanol extracts of *E. bicyclis* and its ethyl acetate and n-butanol soluble fractions have significant inhibitory activity against BACE1. In IC50 tests, compounds such as phlorofucofuroeckol,

dieckol, 7-phloroeckol, fucofuroeckol-b, fucosterol, fucoxanthin, and eckol exhibited IC50 values of 2.13 µM, 2.21 µM, 8.59 µM, 16.1 µM, 64.12 µM, 5.31 µM, and 12.20 µM, respectively, demonstrated strong non-competitive inhibition of the BACE1 enzyme, with phlorofucofuroeckol A showing the best effect due to the lowest IC50 followed by dieckol (Ahn *et al*., 2012; Hannan *et al*., 2020; Jung *et al*., 2010; Sheokand *et al*., 2024).

Symphyocladia latiuscula

Symphyocladia *latiuscula* contains several bromophenol derivatives, including (1) 2,3,6-tribromo-4,5-dihydroxybenzyl alcohol, (2) 2,3,6-tribromo-4,5-dihydroxybenzyl methyl ether, and (3) bis-(2,3,6-tribromo-4,5-dihydroxybenzyl) ether. Studies indicate that these bromophenol derivatives inhibit through mechanisms involving halogen and hydrogen interactions that stabilize the enzyme-ligand complex, leading to effective inhibition. The bis-(2,3,6-tribromo-4,5-dihydroxybenzyl) ether (3) shows the highest inhibition due to multiple bond interactions within the enzyme's catalytic site. The IC50 (concentration required to inhibit 50% of enzyme activity) for BACE1 is as follows:

- 2,3,6-tribromo-4,5-dihydroxybenzyl alcohol: IC50 = 5.16 ± 0.60 µM
- 2,3,6-tribromo-4,5-dihydroxybenzyl methyl ether: IC50 = 4.79 ± 0.82 µM
- bis-(2,3,6-tribromo-4,5-dihydroxybenzyl) ether: IC50 = 2.32 ± 0.10 µM

The maximum inhibition effect observed for the most potent compound, bis-(2,3,6-tribromo-4,5-dihydroxybenzyl) ether (3), was significantly higher than the other tested bromophenols. At a concentration of 20 µM, bromophenol 1, 2, and 3 showed more than 50% inhibition of self-induced Aβ25−35 aggregation, with compound 1 exhibiting the highest inhibition at 66.79%, followed by compound 3 at 58.49% and compound 2 at 56.69% (Paudel *et al*., 2019).

Undaria pinnatifida

Known as "wakame," *Undaria pinnatifida* is a brown alga widely consumed in Japan, China, and Korea, renowned for its high content of fucoxanthin and fucosterol, which have various health benefits. *U. pinnatifida* contains active compounds fucoxanthin and fucosterol. The inhibition mechanism of BACE1 by these compounds involves non-competitive and mixed-type inhibition. Molecular docking studies show that these compounds interact with specific residues of BACE1, forming hydrogen bonds and hydrophobic interactions that stabilize the enzyme's open form, thus inhibiting its activity. These compounds show increasing effectiveness at blocking BACE1 as their concentration rises. Tests revealed that fucoxanthin could achieve 50% enzyme inhibition at 5.31 ± 0.9 µM, while fucosterol required a higher concentration of 64.12 ± 1.0 µM to achieve the same effect. The inhibition constant (Ki) was also determined, with fucosterol showing a Ki of 64.59 µM and fucoxanthin at 7.19 µM. The maximum inhibition effect for the most potent compound, fucoxanthin, indicates that this compound has high potential in inhibiting BACE1 activity and protecting nerve cells from damage induced by oxidative stress and inflammation (Hannan *et al*., 2020; Jung *et al*., 2016; Klose *et al*., 2022; Rafiquzzaman *et al*., 2015; Xiang *et al*., 2017).

Haematococcus pluvialis

Haematococcus pluvialis is a freshwater microalga cultivated for its high content of astaxanthin. When exposed to environmental challenges, including intense light or limited nutrients, *H. pluvialis* accumulates large amounts of astaxanthin, giving the algae its reddish color. *H. pluvialis* contains astaxanthin as its main compound. Astaxanthin has been shown to have an inhibitory effect on BACE1 activity. Laboratory experiments have shown astaxanthin's ability to reduce BACE1 enzyme activity and prevent harmful protein accumulation in both isolated proteins and cellular systems. In vivo, studies using animal models, such as transgenic mice exhibiting Alzheimer-like symptoms, have demonstrated astaxanthin's ability to penetrate the protective barrier surrounding the brain, reduce amyloid-beta levels, and enhance cognitive function in these animal models (Chakraborty *et al*., 2022; Chen *et al*., 2021).

Seaweed

Hizikia fusiformis

Hizikia fusiformis is a brown seaweed extensively used in Korea and Japan. This algae

contains various active therapeutic constituents. *H. fusiformis* includes glycyrrhizin and its metabolite, 18β-glycyrrhetinic acid, both of which show selective inhibitory activity against BACE1. 18β-Glycyrrhetinic acid exhibits competitive inhibition with a solid binding affinity at the catalytic site of BACE1. Glycyrrhizin shows non-competitive inhibition, which binds at an allosteric site and alters the enzyme's shape. The IC50 value for glycyrrhizin is 20.12 ± 1.87 µM, while 18β-glycyrrhetinic acid has an IC50 of 8.93 ± 0.69 µM, showing a more potent inhibitory effect compared to glycyrrhizin. The inhibition mechanism involves interactions of halogen and hydrogen bonds that stabilize the enzyme-ligand complex. 18β-Glycyrrhetinic acid displays potent competitive inhibition with high binding affinity at the catalytic site of BACE1, whereas glycyrrhizin shows non-competitive inhibition by binding at an allosteric site, altering the enzyme's shape (Wagle *et al*., 2018).

Sargassum serratifolium

Sargassum serratifolium represents a species of marine algae indigenous to Korean and Japanese coastal waters. This algae is known for its meroterpenoid content, which has various health benefits, including anti-Alzheimer's activity. *S. serratifolium* contains several meroterpenoid compounds, specifically three key substances: sargahydroquinoic acid, sargachromenol, and sargaquinoic acid. These compounds block BACE1 activity by binding to specific protein regions, including the enzyme's active center and regulatory sites. Two of these compounds - sargahydroquinoic acid and sargaquinoic acid - show dual-site binding patterns, while sargachromenol operates solely through regulatory site interactions. Sargahydroquinoic acid has an IC50 of 4.4 ± 0.31 µM with an inhibition constant (Ki) of 1.6 µM. Sargachromenol has an IC50 of 7.0 ± 0.55 µM with a Ki of 2.9 µM, and sargaquinoic acid has an IC50 of 12.1 ± 0.87 µM with a Ki of 4.0 µM. Kinetic analyses reveal that these compounds have high binding affinities to BACE1, making them effective inhibitors (Hannan *et al*., 2020; Seong *et al*., 2017).

Marine Sponges

Aplysinella strongylata

Aplysinella strongylata is a marine sponge found in the waters of Bali, Indonesia. This sponge contains a variety of alkaloids derived from bromotyrosine that engage in diverse biological activities. *A. strongylata* contains several alkaloids derived from bromotyrosine, including Purpuramine G, Purpuramine M, Araplysillin II, Araplysillin VII, Araplysillin IX, Araplysillin XI, Hexadellin A, Purpurealidin I, and Aplysamine 4. These compounds exhibit inhibitory activity against BACE1 with IC50 values ranging from 30.6 µM to 48.3 µM. Purpuramine G has an IC50 of 48.3 µM, Purpuramine M at 42.0 µM, Araplysillin II at 31.8 µM, Araplysillin VII at 39.6 µM, Araplysillin IX at 41.9 µM, Araplysillin XI at 31.4 µM, Hexadellin A at 30.6 µM, Purpurealidin I at 41.7 µM, and Aplysamine 4 at 42.6 µM. Based on these IC50 values, the most effective molecule as a BACE1 inhibitor from *A. strongylata* is Hexadellin-A, with an IC50 of 30.6 µM, indicating that this compound has the most potent inhibitory activity against BACE1 among all tested compounds (Hafez Ghoran & Kijjoa, 2021).

Dactylospongia elegans

Dactylospongia elegans is a marine sponge found in the waters of Hawaii. This sponge contains several bioactive compounds with diverse biological activities. *D. elegans* contains several alkaloids derived from sesquiterpenoids, including Ilimaquinone and Smenospongine. These compounds show inhibitory activity against BACE1. Based on the IC50 values for BACE1 inhibition, Ilimaquinone is more effective than Smenospongine. Ilimaquinone has an IC50 of 65 µM, while Smenospongine has an IC50 of 78 µM. The lower IC50 value indicates more vigorous inhibitory activity against the BACE1 enzyme, making Ilimaquinone better in terms of BACE1 inhibition effectiveness than Smenospongine (Neupane *et al*., 2019).

Xestospongia sp.

Xestospongia sp. is a marine sponge collected from coral reef habitats in Sangalaki, Indonesia. This sponge is known for producing various bioactive compounds with diverse effects. *Xestospongia sp.* contains compounds

derived from xestosaprol, including xestosaprols F-M (8 components). These compounds exhibit moderate inhibitory activity against the BACE1 enzyme involved in Alzheimer's disease. These substances work by binding to specific regions within the enzyme where it normally processes proteins, thereby preventing it from generating harmful amyloid-beta fragments. The inhibitory activities of compounds from *Xestospongia sp.* against BACE1 are as follows:

- Xestosaprol F: IC50 = 135 ± 11 µM
- Xestosaprol G: IC50 = 155 ± 15 µM
- Xestosaprol H: IC50 = 82 ± 3 µM
- Xestosaprol I: IC50 = 163 ± 11 µM
- Xestosaprol J: IC50 = 90 ± 5 µM
- Xestosaprol K: IC50 = 93 ± 4 µM
- Xestosaprol L: IC50 = 98 ± 8 µM
- Xestosaprol M: IC50 = 104 ± 8 µM

Based on the IC50 values for BACE1 inhibition, the molecule Xestosaprol H is the most effective from *Xestospongia sp.*, with an IC50 of 82 ± 3 µM, indicating it has the highest inhibitory potential among the xestosaprol compounds tested (Catanesi *et al*., 2021; J. Dai *et al*., 2010).

Ianthella basta Pallas

Ianthella basta Pallas, the elephant ear sponge, is found in various tropical and subtropical waters. This sponge is known for its bastadins contentidentified as a new class of oxime-based BACE1 inhibitors. Bastadin 9, one of the compounds isolated from this marine sponge, exhibits significant inhibitory activity against BACE1. It functions as an oxime-based inhibitor that interacts with the enzyme's active site, reducing its ability to break down amyloid precursor protein and thereby decreasing the production of amyloid-beta peptides. In initial EFC assay screening, extracts were tested at a fixed concentration of 50 µg/mL. Results indicated that 7% of the tested extracts inhibited more than 90% of BACE1 activity, and an additional 11% reduced BACE1 activity by 70-89%. Bastadin 9 was identified as a new and significant BACE1 inhibitor, showing vigorous inhibitory activity and being the most effective molecule among those isolated from *Ianthella basta Pallas* (Lakshmi *et al*., 2018; Williams *et al*., 2010).

Spongionella gracilis

Spongionella gracilis contains the compound gracilin L, which has demonstrated inhibitory activity against BACE1. This compound was identified through a BACE1 inhibition assay and showed a significant reduction in BACE1 activity at a concentration of 1 µM, decreasing enzyme activity by 24.6%. Gracilin L exhibits inhibitory activity against BACE1 by reducing the enzyme's ability to break down amyloid precursor protein, thus decreasing the production of amyloid-beta peptides. The inhibition mechanism involves direct interactions with the active site of the enzyme BACE1 (Abbasov *et al*., 2019; Hafez Ghoran & Kijjoa, 2021; Lakshmi *et al*., 2018; Leirós *et al*., 2015; Russo *et al*., 2016)

Crustaceans

Portunus pelagicus

Portunus pelagicus, the blue swimmer crab or flower crab, is a crustacean commonly found in tropical and subtropical waters. This crab contains glycosaminoglycans, particularly heparan sulfate, which exhibit various biological activities. The heparan sulfate in *P. pelagicus* demonstrates inhibitory activity against BACE1. The inhibition mechanism involves glycosaminoglycan interactions with the BACE1 structure, causing changes in the enzyme's secondary and tertiary structures as observed through circular dichroism (CD) spectroscopy. These structural changes are consistent with a shift towards a less active form of the enzyme. Differential scanning fluorimetry (DSF) studies show that glycosaminoglycan extracts decrease the thermal stability of BACE1, indicating that glycosaminoglycan binding destabilizes the enzyme, thus inhibiting its activity. The IC50 value of *P. pelagicus* F5 for inhibiting BACE1 is 1.9 µg/mL, indicating the concentration at which the extract inhibits 50% of BACE1 activity. A maximum inhibition level of 90.7% against BACE1 activity was observed at a 5 µg/mL concentration of *P. pelagicus* F5 (Mycroft-West *et al*., 2019; Rivarti *et al*., 2023).

Sardina pilchardus

Sardina pilchardus, or the European sardine, is a marine fish containing glycosaminoglycans, mainly chondroitin sulfate (CS). The molecular structure of CS features

alternating sugar units - glucuronic acid and N-acetylgalactosamine - with sulfate groups attached at different locations. This compound plays a key role in maintaining the framework outside cells, helping preserve the structure of various body tissues including cartilage, bones, skin, and blood vessels. Chondroitin sulfate from *S. pilchardus* shows inhibitory activity against BACE1. The inhibition mechanism involves destabilizing the structure of BACE1, as shown by differential scanning fluorimetry (DSF) analysis, which demonstrates that the enzyme becomes less stable at higher temperatures when mixed with CS extract. This destabilization is similar to that observed with heparin, indicating a similar mechanism of action for glycosaminoglycans in inhibiting BACE1. CS extract from *S. pilchardus* exhibits maximal inhibition of BACE1 at concentrations greater than 10 µg/mL, with an IC50 value of 4.8 µg/mL. This inhibition concentration is slightly higher than pig mucosal heparin (PMH), which has an IC50 of 2.6 µg/mL. DSF analysis shows a concentration-dependent response in destabilizing BACE1, supporting the inhibitory effect of CS extract (Mycroft-West *et al*., 2019; Rivarti *et al*., 2023).

Euphausia superba

Euphausia superba, known as Antarctic krill, is an abundant crustacean species in Antarctic waters. Krill oil extracted from *E. superba* contains high levels of specific omega-3 fatty acids that demonstrate multiple health benefits. Research indicates that krill oil at a concentration of 80 mg/kg/day for one month protects against brain damage caused by inflammation and harmful reactive molecules in mice engineered to exhibit Alzheimer's-like symptoms. Krill oil reduces the formation of harmful protein fragments by suppressing the genes responsible for producing both the precursor protein (amyloid-beta peptide 1-42) and the enzyme that processes it in the brain tissue of mice treated with LPS (Choi *et al*., 2017).

Others

Lyngbya sp.

Lyngbya sp. is a marine cyanobacteria known for producing a variety of modified peptides with significant biological activity. One such peptide is tasiamide B, which has been identified as a BACE1 inhibitor. This compound contains a core statin unit (γ-amino-β-hydroxy acid) typical for aspartate protease inhibition. Tasiamide B and its analogs have shown inhibitory activity against BACE1 with varying IC50 values. The most effective compound in this study, compound 11, has an IC50 of 48.8 nM, demonstrating high potential as a BACE1 inhibitor (Klose *et al*., 2022; Liu *et al*., 2012).

Urechis unicinctus

Urechis unicinctus, also known as the innkeeper worm that contains several steroidal compounds with significant biological activity. *U. unicinctus* contains two primary steroid compounds - hecogenin and cholest-4-en-3-one - that can reduce the activity of the BACE1 enzyme, which creates beta-amyloid proteins, a key factor in the development of AD. These steroidal molecules demonstrate varying levels of effectiveness at blocking BACE1, with different EC50 values (1) Hecogenin (EC50 = 116.3 µM), and (2) Cholest-4-en-3-one (EC50 390.6 µM). In this study, hecogenin was identified as the most effective BACE1 inhibitor from *U. unicinctus*, with an EC50 of 116.3 µM, indicating more potent inhibitory activity compared to cholest-4-en-3-one (Naushad *et al*., 2019; Rivarti *et al*., 2023; Zhu *et al*., 2018).

Symploca sp.

Symploca sp. is a marine cyanobacteria known for producing a variety of peptides with significant biological activity. One such peptide is tasiamide B, which has been identified as a BACE1 inhibitor. Tasiamide B and its analogs show inhibitory effects on BACE1. Its inhibition mechanism involves interactions with the active site of BACE1, preventing the enzyme's action and reducing the formation of Aβ peptides. Tasiamide B and its analogs have shown varying IC50 values for inhibitory activity against BACE1. For example, the most effective tasiamide B analog in this study, compound 11, has an IC50 of 48.8 nM. Compounds 12 and 13, designed by combining tasiamide B with an isophthalic acid group, demonstrated strong cellular activity with sub-micromolar IC50 values, and compound 13 showed significant effectiveness in reducing Aβ levels in vivo:

- Compound 11: IC50 = 48.8 nM

- Compound 12: IC50 sub-micromolar
- Compound 13: IC50 sub-micromolar

In this study, synthetic compound 11 was identified as the most effective BACE1 inhibitor from *Symploca sp.*, with an IC50 of 48.8 nM (Catanesi *et al*., 2021; Hafez Ghoran & Kijjoa, 2021; Klose *et al*., 2022; Liu *et al*., 2012).

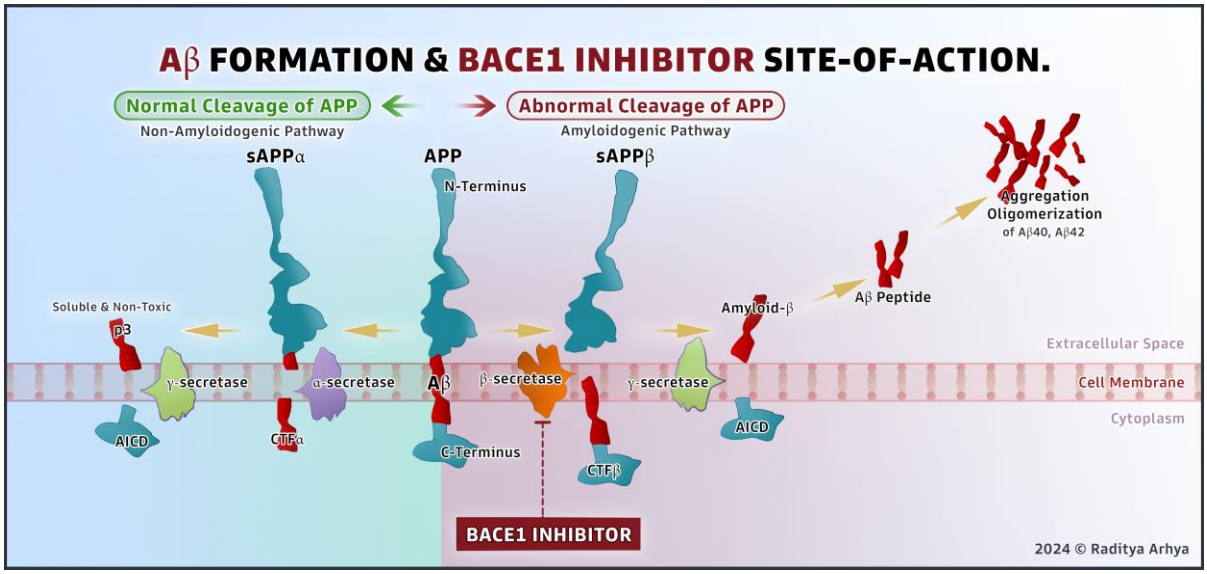


Figure 3. Amyloidogenic and non-amyloidogenic pathway of amyloid β (Aβ) generation and a potential site of action for BACE1 inhibitors derived from marine organisms. Inhibition of BACE1 can prevent and reduce the formation of sAPPβ, which theoretically may diminish the development of amyloid plaques, thus serving as a potential preventive therapy. Amyloid β (Aβ); β-site amyloid precursor protein cleaving enzyme-1 (BACE1); amyloid precursor protein (APP); the soluble ectodomain of APP (sAPP); C-terminal fragment alpha/beta (CTF alpha/beta); 3-kD peptide (p3); APP intracellular domain (AICD).

Preventive Potential and Site of Action

Marine organisms are critical in Alzheimer's disease prevention strategies, categorized into primary and secondary types. Primary prevention aims to obstruct the initiation of the disease by protecting neurons and reducing major risk factors such as oxidative stress and inflammation. Conversely, secondary preventive strategies focus on halting the disease's progression in individuals with early signs or those at high risk. BACE1 inhibitors derived from marine organisms can potentially prevent and reduce the formation of sAPPβ and subsequent amyloid plaques. Compounds from marine sources such as 8,8'-Bieckol, Phlorofucofuroeckol A, and Dieckol, found in species like *Ecklonia cava* and *Eisenia bicyclis*, have shown promising results due to their low IC50 values, indicating strong inhibitory effects on BACE1. These compounds inhibit BACE1 activity through non-competitive binding at the allosteric site, stabilizing the enzyme in an inactive form, thus reducing the production of neurotoxic Aβ peptides. The pathogenesis of Alzheimer's, based on the amyloid cascade hypothesis, suggests that excessive accumulation of β-amyloid stimulates neurodegeneration, oxidative stress, and neurofibrillary tangles. By inhibiting BACE1, these marine-derived compounds can theoretically halt the initiation and progression of amyloid plaque formation, offering a preventive strategy against AD. Additionally, their neuroprotective, anti-inflammatory, and antioxidant properties further contribute to their preventive potential by mitigating oxidative stress and inflammation, which are major risk factors for AD. Thus, using marine organisms to develop preventive strategies promises to enhance the quality of life and offers a safe and effective approach to combating this neurodegenerative disease.

Conclusions

This comprehensive analysis demonstrates the promising role of natural substances from marine sources as tools to block BACE1 activity and potentially combat AD. This brain disorder,

which progressively damages nerve cells and leads to memory and thinking problems, stems largely from toxic protein deposits in the brain. BACE1, an enzyme critical to the amyloidogenic pathway, facilitates the formation of these plaques. Therefore, inhibiting BACE1 activity presents a viable therapeutic target. Compounds isolated from marine organisms such as Ecklonia cava, Eisenia bicyclis, and Symphyocladia latiuscula demonstrate strong BACE1 inhibitory effects, with low IC50 values indicating high potency. These compounds, including 8,8'-Bieckol, Phlorofucofuroeckol A, and Dieckol, inhibit BACE1 non-competitively, reducing β-amyloid production and potentially mitigating plaque formation.

Furthermore, marine-derived BACE1 inhibitors also exhibit neuroprotective, anti-inflammatory, and antioxidant properties, addressing other AD pathogenesis pathways like oxidative stress and neuroinflammation. The integration of these bioactive marine compounds into therapeutic strategies could enhance preventive measures and improve quality of life for those at risk or in early stages of Alzheimer's disease. In conclusion, the findings underscore the promising role of marine compounds in AD therapy, advocating for further research into their bioavailability, clinical efficacy, and potential for incorporation into comprehensive treatment regimens. The study emphasizes the need for a multidisciplinary approach to develop effective and safe therapies for combating Alzheimer's disease.

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