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Prospecting Marine Natural Products as the Disease-Modifying Treatment of Alzheimer's Diseases

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Abstract

Alzheimer's disease (AD) is a severe and high costs health problem all over the world. To date, there is no therapy capable of curing AD, making drug discovery a challenging and intriguing field to explore. Targeting marine natural products (MNPs) as a source of drug leads is a suitable choice considering the content of bioactive compounds and promising pharmacological benefits. This article aims to look at MNPs with prospects in several prime targets in AD pathology to cure AD. Marine vertebrates (fishes), marine invertebrates (sponges, tunicates, ascidian, clams, scallops, sand dollars, crabs, cockle, sea cucumber, shrimp, bryozoa, marine worm), algae/seaweed, and marine microorganisms (marine fungi, bacterium, dinoflagellata, microalgae) can be potentially used as disease-modifying treatments (DMTs) for AD. By targeting multiple aspects of AD pathology, these MNPs offer a multifaceted approach to treating and potentially modifying the disease course. This result is an intriguing gap for researchers in the discovery and development of new drugs that can improve AD pathology.

Keywords: Alzheimer's disease; marine; natural products; drug lead; treatment.

Abbreviations: Aβ: amyloid β; AChEIs: acetylcholinesterase inhibitors; AD: Alzheimer's Disease; AGEs: Advanced Glycation Endproducts; APP: Amyloid protein precursor; APOE-4: apolipoprotein E4; BACE-1: β-secretase enzyme; BChE: butyrylcholinesterase; CNS: central nervous system; DMTs: disease-modifying treatments; FDA: Food and Drug Administration; GSK-3β: Glycogen synthase kinase 3β; MAPT: microtubule-associated protein tau; MNPs: marine natural products; NMDA: N-methyl-D-aspartate; NFTs: intracellular tau neurofibrillary tangles; nAChRs: nicotinic acetylcholine receptors; PKC: protein kinase C; PSEN: presenilin.

INTRODUCTION

AD is the most common type of dementia experienced by individuals over the age of 65 (Nugraha et al., 2023). *Dementia* is a disease characterized by a group of symptoms consisting of memory impairment, behavioural disturbances, impaired thinking, and social abilities (Lyu et al., 2021). In severe stages, individuals with this disease will experience a reduced quality of life and may become unable to carry out activities independently (Nugraha et al., 2023). The number of individuals with dementia worldwide is estimated to continue increasing alongside the ageing population. In 2019, 55 million people were suffering from dementia, this number is expected to rise to 139 million by 2050 (Rivarti et al., 2023). The costs incurred for dementia care amounted to approximately 818 billion dollars in 2015 and are projected to continue increasing by 35% every five years. The social impact is also experienced by individuals with the disease and their families who care for them (Bălașa et al., 2020). Thus, AD has become a severe public health issue with high medical costs and reported no cure (Hu et al., 2023).

AD therapies that have been used and approved by the U.S. Food and Drug Administration (FDA) are acetylcholinesterase inhibitors (AChEIs) (such as donepezil, rivastigmine, and galantamine) and N-methyl-D-aspartate (NMDA) receptor antagonist (memantine), which only aim to improve AD symptoms (Li et al., 2019; Cummings et al., 2019; Kim et al., 2022). Afterwards, there has not been any therapy approved by the FDA over the past two decades (Kim et al., 2022). The discovery of disease-modifying treatments (DMTs), a therapeutic strategy that changes the disease course by addressing the underlying biological pathway, faces many challenges. DMTs inhibiting the production and aggregation of amyloid β (Aβ) have seen many failures during clinical trials. Clinical trial phases for verubecestat, crenezumab, lanabecestat, and solanezumab failed and were discontinued due to ineffectiveness and negative risk/benefit ratio

(Cummings et al., 2019; Dog et al., 2019). The failure to find effective DMTs for AD is caused by the wrong main target of treatment, loss of follow-up during long-term clinical trials, inappropriate drug doses, and too-late starting of therapies in disease development (Mehta et al., 2017; Kim et al., 2022).

The main objections currently faced in AD treatment are a profound understanding of the disease and its pathological mechanisms, reliable biomarkers to enable early diagnosis, identification and development of new drugs and therapeutic strategies that slow disease progression, and the development of prevention protocols that can be used at high-risk populations (Cacabelos, 2022). Since AD is caused by various molecular processes, identifying a drug capable of modulating more than one target is one of the best strategies in drug discovery and development (Martins et al., 2020). To date, marine natural products (MNPs) have been demonstrated to be the most promising candidates for therapy of various diseases and are known to have more excellent biological activity than terrestrial natural sources (Bălașa et al., 2020). Therefore, this article aims to review the prime targets for DMTs of AD and MNPs prospecting for AD treatment focusing on these targets.

PRIME TARGETS FOR DISEASE-MODIFYING TREATMENTS (DMTs) IN AD

The failure to find an effective therapy for AD is primarily due to a lack of drug discoveries focusing on multiple targets associated with the complex pathophysiology of AD (Rivarti et al., 2023). The pathogenesis of AD is inconclusive, but atypical deposition of amyloid and hyperphosphorylation of tau protein in the brain have been key targets for drug discovery for the disease (Hu et al., 2023). The main targets for DMTs in AD are extracellular amyloid plaques and intracellular Tau neurofibrillary tangles (NFTs), where β-secretase enzyme (BACE-1) activation, neuroinflammation, oxidation, and tau hyperphosphorylation are elements involved in the process (Figure 1) (Park et al., 2019; Kim et al., 2022; Rivarti et al., 2023).

Extracellular Amyloid Plaques

Amyloid is an appealing therapeutic target as it is extraneuronal and is associated with environment toxicity (Mehta et al., 2017). The inhibition of amyloid-β (Aβ) production and plaque formation, as well as the escalation of Aβ degradation and clearance, are the main goals in therapy (Martins et al., 2020). Amyloid protein precursor (APP) cleavage by protease enzymes (β-secretase and then γ-secretase), resulting in the production of amyloidogenic Aβ peptides (Aβ40, Aβ42, and Aβ43) (Cummings et al., 2019; Martins et al., 2020). Aβ peptides accumulate in the central nervous system (CNS), then undergo oligomerization and fibrillization before forming Aβ plaques (Fereira et al., 2022). The accumulation of Aβ plaques causes synaptic dysfunction and neurodegeneration (Martins et al., 2020).

Overexpression of β-secretase 1 (BACE-1) limits the rate at the β site APP, thus reducing the production of amyloidogenic peptides (Koelsch, 2017; Martins et al., 2020). Therefore, inhibiting BACE-1 and γ-secretase is necessary to prevent the formation of Aβ. APP can also be cleaved via the non-amyloidogenic pathway involving the enzyme α-secretase. Conversely, increasing α-secretase activity is required to enhance the formation of α-APP, a potential neuroprotective protein (Koelsch, 2017; Martins et al., 2020).

Mutations of the APP gene, which codes for APP substrates, contribute to the increase of Aβ fibrillogenesis and total Aβ levels. Meanwhile, mutations of the presenilin (PSEN-1 and PSEN-2) genes which code for proteases for cutting APP are known to cause abnormalities and Aβ deposition. In addition, the presence of the apolipoprotein E4 (APOE-4) allele decreases Aβ clearance in brain tissue which leads to the accumulation of Aβ plaque (Cacabelos, 2022).

The initialization of Aβ plaques can occur due to the binding of Aβ to nicotinic acetylcholine receptors (nAChRs), especially the α7 subtype, leading to a decrease in the normal function of these receptors. Oligomerization of Aβ resulting from nAChR activation is also known to induce phosphorylation of tau proteins (Kabir et al., 2021). Therefore, nicotinic agonists can be used as therapeutic agents for AD (Martins et al., 2020).

The Aβ plaque and the persistent single shot of pro-inflammatory cytokines damage neurons and lead to cell death (Martins et al., 2020; Hu et al., 2023). For this reason, therapy targeted at reducing Aβ accumulation and slowing the decline in cognitive function in pre-symptomatic or mild AD is an appropriate pharmacological intervention.

Intracellular Tau Neurofibrillary Tangles (NFTs)

Neurofibrillary tangles (NFTs) are twisted fibres composed of hyperphosphorylated tau (the microtubule-associated) protein that accumulates inside neurons. The presence of NFTs blocks the transport of nutrients and other essential elements into the neuron, resulting in cell death. Glycogen synthase kinase 3β (GSK-3β) is the main enzyme that plays a vital role in the phosphorylation of tau protein (Martins et al., 2020; Silva et al., 2021; Sayas & Ávila, 2021). GSK-3β is also a molecular connection between Aβ and tau in AD pathogenesis. Polymerization of Aβ peptides activates GSK-3β, promoting tau protein phosphorylation (Hu et al., 2023). On the other hand, GSK-3β also regulates APP metabolism and Aβ production, reducing Aβ deposition and plaque formation. Therefore, inhibiting GSK-3β becomes one of the critical targets in the development of AD treatment (Sayas & Ávila, 2021).

GSK-3β can be inhibited by activation of protein kinase C (PKC), one of which can be stimulated by acetylcholine (ACh). Thus, an increase in ACh levels can indirectly inhibit GSK-3β (Martins et al., 2020). In addition, tau protein is encoded by a single-copy gene called microtubule-associated protein tau (MAPT). This gene mutation can lead to NFT formation (Cacabelos, 2022).

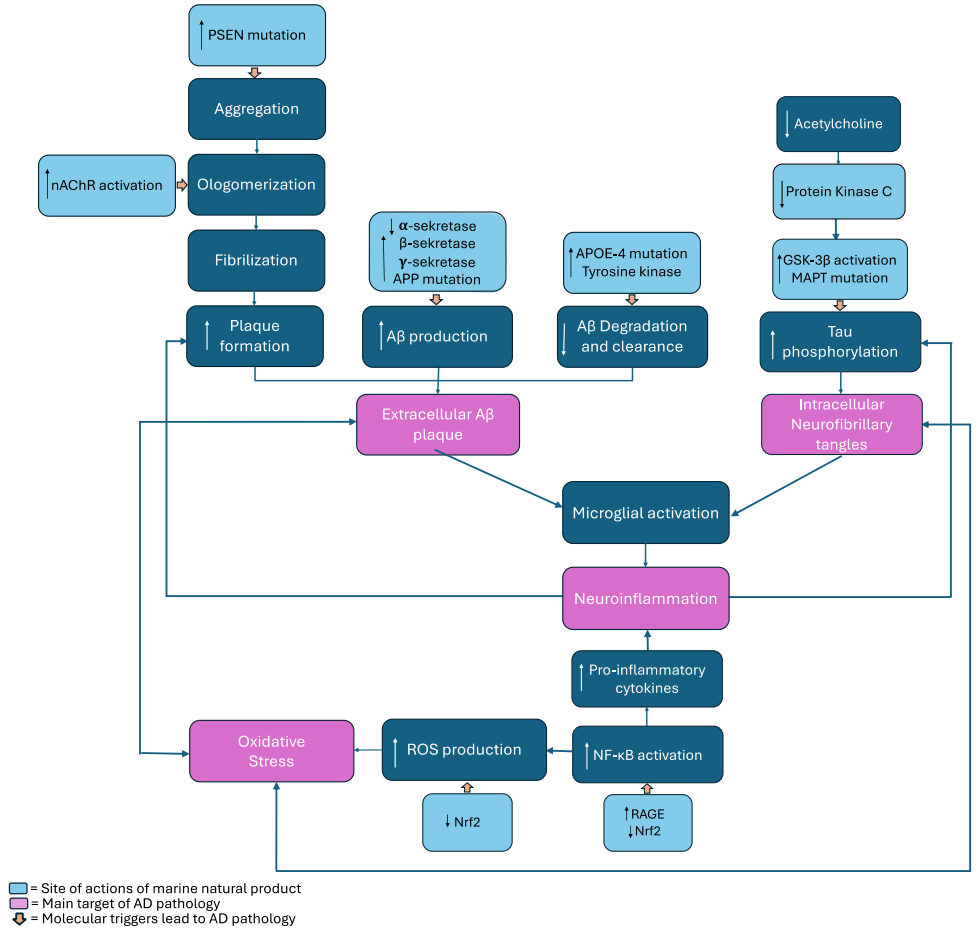

Figure 1. The main target for marine natural products (MNPs) as drug-modifying treatment (DMTs) for alzheimer's disease (AD). These targets are: (1) extracellular amyloid plaque, (2) intracellular neurofibrillary tangles, (3) neuroinflammation, and (4) oxidative stress.

Neuroinflammation

Aβ plaques and NFTs cause an immune system response that activates microglia (Martins et al., 2020; Hu et al., 2023). Microglia cells are gathered to remove the noxious compounds, but when elimination is overwhelmed by excessive production, inflammation occurs (Martins et al., 2020). Long-term microglia activation leads to the accumulation of Aβ and prolonged inflammation that damages neurons and causes excessive phosphorylation of tau protein (Hu et al., 2023). Down-regulation of tyrosine kinase represents a valid mechanism for improving autophagic clearance of neurotoxic elements such Aβ and mitigating microglial-mediated inflammation (Stevenson et al., 2022).

Neuroinflammation is known to be mediated by Advanced Glycation Endproducts (AGEs). AGEs can bind to their receptor called RAGE (Receptors for Advanced Glycation Endproducts), leading to the activation of NFκB, a pro-inflammatory transcription factor. NFκB activation can affect two things, namely inducing the expression of pro-inflammatory cytokines such as interleukin (IL)-1β, IL-6, and tumour necrosis factor-alpha (TNFα), and in turn, can increase oxidative stress due to the production of reactive oxygen species (ROS) induced by the inflammatory response. On the other hand, this oxidative stress, in a cyclic manner, can cause a dramatic increase in the amount of AGEs (Kong et al., 2020; Reddy et al., 2023). Therefore, preventing AGE-RAGE interactions with RAGE antagonists will attenuate AD progression.

Oxidative Stress

An abnormal increase in the production of ROS leads to oxidative stress, another major contributor to the development of AD (Martins et al., 2020). In addition to binding with AGE, RAGE can also bind to Aβ, forming

ROS and increasing the secretion of nitric oxide synthase (NOS), thereby enhancing the deposition of Aβ in the brain (Kong et al., 2020).

Increased ROS production causes the translocation of Nrf2 from the cytoplasm to the nucleus. This translocation activates the transcription of genes that lead to antioxidant responses. Nrf2 activation also leads to increased autophagy, which enhances the clearance of APP and tau. Nrf2 activators can suppress NF-κB activity, thus also affecting the inflammatory cascade. High levels of Nrf2 can ameliorate oxidative stress damage (Osama et al., 2020; Plano et al., 2023). On the other hand, high levels of Aβ and tau can be the cause of oxidative stress.

CURRENT PHARMACOLOGICAL INTERVENTION

AD therapies that have been used and approved by the FDA are therapies that only relieve the symptoms of AD, such as acetylcholinesterase inhibitors (AChEIs) and N-methyl-D-aspartate (NMDA) receptor antagonists.

AChEIs (donepezil, galantamine, and rivastigmine)

Cholinergic dysfunction occurs in the early stages of AD, leading to a decrease in the levels of various neurotransmitters such as acetylcholine, serotonin, dopamine, norepinephrine, etc. Acetylcholine (ACh) is an important neurotransmitter that mediates communication between neurons. Decreased levels and availability of ACh can directly lead to cell damage, thereby reducing the level of serotonin and intensifying the development of NFTs. The decrease in ACh levels is influenced by the following enzymes: acetylcholinesterase (AChE), which plays a role in breaking down acetylcholine, and butyrylcholinesterase (BChE), which is responsible for the degradation of acetylcholine (Metha et al., 2017). Inhibition of AChE and BChE is associated with delaying the cognitive decline in AD patients. AChE inhibitors (AChEIs) such as donepezil and galantamine, as well as pseudo-irreversible AChEI and BChE inhibitors (BChEIs) like rivastigmine are symptomatic therapy approved and still in use to date for AD. Nevertheless, these drugs are believed to only improve the symptoms of AD without restoring it to its original state (Yiannopoulou et al., 2019).

NMDA Receptor Antagonist (memantine)

Insufficient synaptic NMDAR signalling compromises neuronal cell survival, but excessive stimulation of glutamatergic signalling leads to excitotoxicity, resulting in damage and death of neurons. NMDA receptor antagonists such as memantine are noncompetitive low-affinity NMDA receptor open-channel blockers that inhibit glutamatergic transmissions, leading to decreased glutamate levels and prevention of neuronal dysfunction (Wang & Reddy, 2017).

MARINE NATURAL PRODUCTS (MNPs) PROSPECT FOR AD TREATMENT

About 70% of the earth's surface is the sea and half of global diversity is found in marine ecosystems (Ferreira et al., 2022). Marine organisms, both marine macro-organisms (sponges, ascidians/tunicates, echinoderms, gorgonians/octocorals, algae, mangroves) and marine microorganisms (marine fungi and marine bacteria) are known to possess diverse bioactive compounds with significant pharmacological efficacy (Bălașa et al., 2020; Nugraha et al., 2023). MNPs show 10 times greater biological activity than terrestrial natural sources, making them attractive for continuous exploration (Bălașa et al., 2020). MNPs have been demonstrated to be the most prospective candidates for therapy of various diseases. The first marine-derived drug to receive FDA approval in 1969 was an anticancer therapy Cytarabine from the Caribbean sponge *Tethya crypta*. Subsequently, vidarabine (1976) from the same source was recognized for its antiviral effects. Ziconotide, a synthetic compound similar to a peptide isolated from the venom of the cone snail *Conus magus*, attained FDA approval in 2004 for its potent analgesic effect. Trabectedin from the marine tunicate *Ecteinascidia turbinate* received FDA recognition for second-line treatment of liposarcoma or leiomyosarcoma in 2015. In 2016, eribulin mesylate, a synthetic analogue of halichondrin B isolated from the marine sponge *Halichondria okadai* was approved as a chemotherapy agent (Montaser & Luesch, 2011; Altmann, 2017). Limitless discoveries continue, with ongoing exploration of MNPs to produce novel therapies for multifarious diseases (Altmann, 2017). Despite the many studies showing the potential of MNPs for AD therapy, development studies of MNPs for DMTs in AD are still limited to the first stage of the FDA drug development process. Therefore, this remains a challenge and a fertile ground for further studies in discovering new drugs. Table 1 shows the group of MNPs with multiple potential targets in AD treatment.

Marine Vertebrae

Every type of fish is a rich source of n−3 polyunsaturated fatty acids (PUFAs), especially docosahexaenoic acid (DHA) (Ferreira et al., 2022). Marine fishes such as blackmouth catshark (*Galeus melastomus*) and the brown meagre/ corb (*Sciaena umbra*) contain marine-derived glycosaminoglycans, namely chondroitin sulfate. Chondroitin sulfate can combat toxicity caused by AGEs, which impact Aβ aggregation, oxidative stress, and neuroinflammation (Iannuzzi et al., 2019; Bălașa et al., 2020). The liver oil of cod fish especially *Gadus Morrhua L*. consists of polyunsaturated fatty acids, especially ω-3 fatty acids, which have benefits in

reducing Aβ toxicity through increased degradation and clearance (Bălaşa et al., 2020).

Marine Invertebrae

Marine invertebrates include sponges, ascidians/tunicates, echinoderms, gorgonians/octocorals, molluscs (such as octopuses, squids, clams, snails), and arthropods (such as crabs, shrimp, and lobsters). Marine sponges *Spongionella gracilis* contains Gracilin (diterpenoid), which exhibits activity to inhibit BACE-1. Gracilin has anti-inflammatory and antioxidant effects through the induction of Nrf2, thereby inhibiting hyperphosphorylation of tau proteins. Marine sponges *Haliclona sp.* and *Acanthostrongylophora* contain manzamine (an alkaloid) which can inhibit GSK-3 and reduce hyperphosphorylation of tau proteins (Hu et al., 2013; Kabir et al., 2021). From the marine sponge *Fascaplysinopsis bergquist* sp., an alkaloid called Fascaplysin has been isolated, which is known to increase the efflux or clearance of Aβ by increasing the level of P-glycoprotein. A synthetic derivative of Fascaplysin, 9-methylfascaplysin, has more significant potential in inhibiting the formation of Aβ peptide, fibrillation of Aβ, and AChE. Additionally, this derivative compound has the potential to activate antioxidant enzymes that counteract ROS, reduce neuroinflammation, and decrease hyperphosphorylation of tau (Martins et al., 2020).

Maldives sponge *Spongia* sp. impact the reduction of tau pathology due to the presence of Dictyostatine (marine derived macrolide) inside (Xia et al., 2019; Kabir et al., 2021). From the marine sponge *Haliclona moorei* and the tunicate *Aplidium conicum*, a natural alkaloid compound that resembles nicotine, called anabasine, has been isolated. This compound and its synthetic analogues are known to have neuroprotective effects by inhibiting apoptosis and necrosis in neurons. Additionally, one of its analogues, GTS-21, can reduce the amount of Aβ, inhibit the activity of γ-secretase, and promote Aβ clearance through phagocytosis (Martins et al., 2020).

Ascidian *Styela plicata* contains heparin, which influences neuronal cell death by reducing Aβ. Sea cucumber *Acaudina molpadioides*, which belongs to the class Echinodermata, is known to contain a mixture of glycosphingolipids that can reduce cognitive deficits caused by the Aβ1–42 peptide (Carroll et al., 2021). Various species of clams (*Anomalocardia brasiliana*, *Tivela mactroides*, *Donax striatus*, and *Tapes phlippinarum*), scallop *Nodipecten nodosus*, sand dollar *Mellita quinquisperforata*, and cockle *Cerastoderma edule* are known to contain heparin, which influences neuronal cell death by reducing Aβ.

White leg shrimp *Litopenaeus vannamei* and crabs (*Goniopsis cruentata* and *Ucides cordatus*), are also known to contain heparin (Bălaşa et al., 2020). Glycosaminoglicans including chondroitin sulphate (CS), heparan sulfate (HS), and dermatan sulphate (DS), from *Litopenaeus vannamei* demonstrates the ability to reduce cognitive and AD related memory impairments by inhibiting the BACE-1 activity (Carroll et al., 2021; Mycroft-West et al., 2021). *Bugula neritina* contains bryostatin-1, a macrolide lactone that can modulate PKCε, leading to the degradation of Aβ, activation of α-secretase, and reduction of tau hyperphosphorylation through GSK-3β activity (Martins et al., 2020; Kabir et al., 2021; Botelho et al., 2022). Marine worm nemertines have anabasaine that can stimulate various animal nAChR (Kabir et al., 2021).

Algae

In the effort to develop marine-derived medicines as neuroprotective agents, the brown algae *Ecklonia cava* has been studied and is known to reduce the production of Aβ, tau hyperphosphorylation, and neuroinflammatory markers (NFκB and STAT3) due to its fucoidan content (Park et al., 2019; Jo et al., 2023). The phlorotannin content of *Ecklonia cava*, including dieckol, eckol, and 8,8′-bieckol, has inhibitory effects on BACE-1 and anti-inflammatory effects through the inactivation of the NF-κB pathway. Dieckol is known for its high ability to inhibit the accumulation of Aβ peptide through the regulation of APP proteolysis and Aβ production via the GSK-3β signalling pathway (Mehta et al., 2017).

Ecklonia spp. is also known to contain mannuronate oligosaccharides that inhibit Aβ aggregation and inhibit BACE-1 production, thereby reducing Aβ levels (Botelho et al., 2022). Brown algae *Panida australis* and *Sargassum horridum* contain fucosterol (sterol), which can prevent Aβ oligomerization, exhibit anti-inflammatory and anti-BACE1 properties. on the other hand, brown algae such as *Sargassum siliquastrum* contain fucoxanthin, known for its antioxidant and anti-inflammatory effects (Hu et al., 2023). Brown alga *Dictyota coriacea* isolated compound, dictyospiromide (a diterpenoid-maleimide) is known to have cytoprotective properties and antioxidant effects through activation of Nrf2/ARE signaling (Carroll et al., 2021). From the brown algae Dictyopteris spp., Zonarol has been isolated, which can protect neurons from damage due to oxidative stress (Botelho et al., 2022).

Edible brown algae such as *Laminaria hyperborea*, *Laminaria digitata*, *Macrocystis pyrifera*, *Ascophyllum nodosum*, and *Laminaria japonica* contain polymannuronate (polysaccharide). An alginate-derived polymannuronate, namely seleno-polymannuronate, can inhibit Aβ aggregation and reduce APP and BACE-1. This demonstrates that products from these MNPs have the potential as neuroprotective agents.[5,34] Various marine red algae are known as sources of homotaurine, an amino sulfonate that can inhibit Aβ aggregation and oligomerization, also amyloid fibril deposition.[5,12] In addition, the green alga *Haematococcus pluvialis* contains Astaxanthin (carotenoid), which has been used in the supplementary due to its effects in reducing the production of NF-κB transcription factors and pro-

inflammatory cytokines.[5] Dead man's finger (*Codium fragile*) is a green seaweed that contains mannan, a polysaccharide known to inhibit BACE-1.[5] Some seaweeds are isolated sources of betaine, which is a potent antioxidant.[32]

Marine Microorganism

Marine fungi are fungi isolated from marine habitats, either as obligate microorganisms or as facultative microorganisms (Nugraha et al., 2023). *Streptomyces sp*. contains indole, a type of alkaloid that can inhibit the formation of Aβ plaque through the activation of Nrf2 (Hu et al., 2023). *Streptomyces caniferus* and *Phylum Actinobacteria* produce caniferolide A which can reduce neuroinflammation, oxidative stress, blockage BACE-1, inhibit Aβ and tau pathology, and is referred to as a potential compound in AD therapy (Carroll et al, 2021; Hu et al., 2023). Furthermore, Streptomyces-derived compounds Anhydroexfoliamycin and undecylprodigiosin are Nrf2 inducers, thus able to suppress oxidative stress. Anhydroexfoliamycin also significantly suppresses GSK-3β and reduces tau hyperphosphorylation (Kabir et al., 2021). Rifamycin from the marine bacterium Salinispora, extracted from the marine sponge *Pseudoceratina clavate*, exhibits neuroinflammatory activity and potential antioxidant activity in inhibiting the production, aggregation, and fibrillation of Aβ, including increasing Aβ clearance (Kabir et al., 2021).

Marine dinoflagellate *Alexandrium ostenfeldii* contains 13-Desmethyl Spirolide-C, which influences tau hyperphosphorylation by intervening in GSK-3β and Aβ accumulation, especially within cells (Kabir et al., 2021). Meanwhile, some dinoflagellate species are known to produce compounds that are potent in reducing Aβ plaques and tau hyperphosphorylation. *Protoceratium reticulatum*, *Lingulodinium polyedrum*, and *Gonyaulax spinifera* are known to produce yessotoxins, polyether sulfate compounds that can reduce hyperphosphorylated tau and Aβ accumulation through PKC activation. *Karenia selliformis* also produces the toxin Gymnodimine, which can reduce intracellular Aβ accumulation and inhibit GSK-3. Additionally, Gambierol obtained from *Gambierdiscus toxicus* can reduce the levels of Aβ1-42, inhibit BACE-1, and increase GSK-3β inactivation (Botelho et al., 2022).

Microalgae have several types of polyunsaturated fatty acids such as DHA, eicosatetraenoic acid, α-linolenic acid, arachidonic acid, linoleic acid, and oleic acid, which are known to inhibit Aβ-40 and Aβ-42 fibrillogenesis, thus having anti-aggregation effects (Shatshat et al., 2019). The DHA can reduce Aβ deposition, tau phosphorylation, and BACE-1 also γ-secretase activity. Neuroprotectin D1 is a derivative of DHA that has strong anti-inflammatory effects through the inhibition of proinflammatory cytokines, anti-amyloidogenic effects through the activation of α-secretase and downregulation of BACE-1, and anti-apoptotic effects (Martins et al., 2020).

Table 1. MNPs and their multitarget prospects in AD pathology.

Source		Species	Bioactive Compoud	Site of Action
Marine Vertebrae	Fishes	- Blackmouth catshark (*Galeus melastomus*) - The brown meagre/ corb (*Sciaena umbra*)	Chondroitin sulfate (glycosaminoglycans)	- Combat toxicity caused by AGEs - Impact Aβ aggregation - Oxidative stress - Neuroinflammation
		cod fish (*Gadus Morrhua L*)	ω-3 fatty acids	Increase Aβ degradation and clearance
Marine Invertebrae	Sponges	*Spongionella gracilis*	Gracilin (diterpenoid)	- Inhibit BACE-1 - Induction Nrf2 anti-inflammatory and antioxidant effects - Hyperphosphorylation of tau
		- Haliclona sp. - Acanthostrongylophora	Manzamine (alkaloid)	- Inhibit GSK3 - Reduce hyperphosphorylation of tau
		Fascaplysinopsis bergquist sp	Fascaplysin (alkaloid)	Increase Aβ clearance
			9-methylfascaplysin (synthetic derivate)	- inhibit Aβ peptide formation, Aβ fibrillation and AChE - activate antioxidant enzymes - reduce neuroinflammation - decrease hyperphosphorylation of tau
		Spongia sp.	Dictyostatine (macrolide)	Reduce tau pathology
		Haliclona moorei	Anabasaine (alkaloid)	Inhibit apoptosis and necrosis of neurons
			GTS-21 (nicotine	- Reduce Aβ

			analog)	- Inhibit γ-secretase - Promote Aβ clearance
	Tunicate	*Aplidium conicum*	Anabasaine (alkaloid)	Inhibit apoptosis and necrosis of neurons
	Ascidian	*Styela plicata*	Heparan sulfate (Natural Glycosaminoglicans)	Reduce Aβ
	Clams	- *Anomalocardia brasiliana* - *Tivela mactroides* - *Donax striatus* - *Tapes phlippinarum*		
	Scallop	*Nodipecten nodosus*		
	Sand dollar	*Mellita quinquisperforata*		
	Crabs	- *Goniopsis cruentata* - *Ucides cordatus*		
	Cockle	*Cerastoderma edule*		
	Sea cucumber	*Acaudina molpadioides*	Mixture of glycosphingolipids	Reduce Aβ1–42 peptide
	White leg shrimp	*Litopenaeus vannamei*	Natural Glycosaminoglicans: - Chondroitin sulphate - Heparan sulfate - Dermatan sulphate	Inhibit BACE-1
	Bryozoa	*Bugula neritina*	Bryostatin-1 (Macrolide lactone)	- Modulate PKCε - Degradate Aβ - Activate α-secretase - Interfere GSK-3β - Reduce tau hyperphosphorylation
	Marine worm	Nemertines	Anabasaine	Stimulate nAChR
Algae/ Seaweed	Brown algae	*Ecklonia cava*	Fucoidan	- Reduce Aβ production - Reduce tau hyperphosphorylation - Reduce NFκB and STAT3
			Phlorotannin (dieckol, eckol, and 8,8′-bieckol)	- Inhibit BACE-1 - Inactivate NF-κB - Inhibit Aβ peptide accumulation - Interfere Aβ production
		Ecklonia spp.	Mannuronate (oligosaccharides)	- Inhibit Aβ aggregation - Inhibit BACE-1 production
		- *Panida australis* - *Sargassum horridum*	Fucosterol (sterol)	- Prevent Aβ oligomerization - Anti-inflammatory - Anti-BACE1
		Sargassum siliquastrum	Fucoxanthin	- Antioxidant - Anti-inflammatory
		Dictyota coriacea	Dictyospiromide (diterpenoid-maleimide)	- Activate of Nrf2/ARE signaling - Antioxidant - Cytoprotective
		Dictyopteris spp.	Zonarol	Antioxidant
		- *Laminaria hyperborea* - *Laminaria digitata* - *Macrocystis pyrifera* - *Ascophyllum nodosum* - *Laminaria japonica*	Polymannuronate (polysaccharide) Seleno-polymannuronate	- Reduce APP - Inhibit BACE-1 - Reduce Aβ aggregation
	Marine red algae		Homotaurine (amino sulfonate)	- Inhibit Aβ aggregation and oligomerization - Inhibit amyloid fibril deposition
	Green alga	*Haematococcus pluvialis*	Astaxanthin (carotenoid)	Reduce production of NF-κB and pro-inflammatory cytokines
	Green seaweed	Dead man's finger (*Codium fragile*)	Mannan (polysaccharide)	Inhibit BACE-1
	Some seaweeds		Betaine	Potent antioxidant
Marine microorganism	Fungi	*Streptomyces sp.*	Indole (alkaloid)	- Activate Nrf2 - Inhibit Aβ plaque formation
			Anhydroexfoliamycin	- Induce Nrf2 - Suppresses GSK-3β - Reduces tau hyperphosphorylation
			Undecylprodigiosin	Induce Nrf2

	- *Streptomyces caniferus* - *Phylum Actinobacteria*	Caniferolide A	- Reduce neuroinflammation - Reduce oxidative stress - Blockage BACE-1 - Inhibit Aβ and tau pathology
Marine bacterium	Salinispora	Rifamycin	- Neuroinflammatory - Antioxidant - Inhibit Aβ production, aggregation, and fibrillation - Increase Aβ clearance
Dinoflagellate	*Alexandrium ostenfeldii*	13-Desmethyl Spirolide-C	- Interfere GSK-3β - Influence tau hyperphosphorylation - Reduce intracelular Aβ accumulation
	- *Protoceratium reticulatum* - *Lingulodinium polyedrum* - *Gonyaulax spinifera*	Yessotoxins (polyether sulfate)	- Reduce hyperphosphorylated tau - Reduce Aβ accumulation
	Karenia selliformis	Gymnodimine	- Reduce intracellular Aβ accumulation - Inhibit GSK-3
	Gambierdiscus toxicus	Gambierol	- Reduce Aβ1-42 - Inhibit BACE-1 - Inactivating GSK-3β
Microalgae	Several species	- DHA - eicosatetraenoic acid - α-linolenic acid - arachidonic acid - linoleic acid - oleic acid	- Inhibit Aβ-40 and Aβ-42 fibrillogenesis - Anti-aggregation - Reduce Aβ deposition - Reduce tau phosphorylation - Anti-BACE-1 - Reduce γ-secretase
		Neuroprotectin D1 (DHA derivate)	- Inhibit proinflammatory cytokines - Activate α-secretase - Downregulate BACE-1 - Anti-apoptotic

CONCLUSIONS

Marine natural products from marine vertebrates, marine invertebrates, algae/seaweed, and marine microorganisms can be utilized for their potential as they can play a role in several therapeutic targets in AD pathology. These findings can be further utilized in drug discovery and development.

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REFERENCES

Altmann KH. (2017). Drugs from the Oceans: Marine Natural Products as Leads for Drug Discovery. *Chimia (Aarau)*, 71(10): 646-652. doi.org/10.2533/chimia.2017.646.

Bălașa AF, Chircov C, Grumezescu AM. (2020). Marine Biocompounds for Neuroprotection—A Review. *Marine Drugs*, 18(6): 1-24. doi.org/10.3390/md18060290.

Bi D, Li X, Li T, Li X, Lin Z, Yao L, Li H, Xu H, Hu Z, Zhang Z, Liu Q, Xu X. (2020). Characterization and Neuroprotection Potential of Seleno-Polymannuronate. *Front Pharmacol*. 20: 11-21. doi.org/10.3389/fphar.2020.00021.

Botelho MJ, Milinovic J, Bandarra NM, Vale C. (2020). Alzheimer's Disease and Toxins Produced by Marine Dinoflagellates: An Issue to Explore. *Marine Drugs*, 20(4):253. doi.org/10.3390/md20040253.

Cacabelos, R. (2022). What have we learnt from past failures in Alzheimer's disease drug discovery?. *Expert Opinion on Drug Discovery*, 17(4): 309–323. doi.org/10.1080/17460441.2022.2033724.

Carroll AR, Copp BR, Davis RA, Keyzers RA, Prinsep MR. (2021). Marine natural products. *Natural Product Reports*, 38(2): 362-413. doi.org/10.1039/D0NP00089B.

Cummings JL, Tong G, Ballard C. (2019). Treatment Combinations for Alzheimer's Disease: Current and Future Pharmacotherapy Options. *J Alzheimers Dis*, 67(3): 779-794. doi.org/10.3233/JAD-180766.

De Plano LM, Calabrese G, Rizzo MG, Oddo S, Caccamo A. (2023). The Role of the Transcription Factor Nrf2 in Alzheimer's Disease: Therapeutic Opportunities. *Biomolecules*, 13(3):549. doi.org/10.3390/biom13030549.

Dong Y, Li X, Cheng J, Hou L. (2019). Drug development for alzheimer's disease: Microglia induced neuroinflammation as a target?. *Int J Mol Sci*, 20(3): 558. doi.org/10.3390/ijms20030558.

Ferreira I, Rauter AP, Bandarra NM. (2022). Marine Sources of DHA-Rich Phospholipids with Anti-Alzheimer Effect. *Marine Drugs*. 2022, 20(11): 662. doi.org/10.3390/md20110662.

Hu D, Jin Y, Hou X, Zhu Y, Chen D, Tai J, Chen Q, Shi C, Ya J, Wu M, et al. (2023). Application of Marine Natural Products Against Alzheimer's Disease: Past, Present and Future. *Marine Drugs*, 21(1): 43. doi.org/10.3390/md21010043.

Iannuzzi C, Borriello M, D'Agostino A, Cimini D, Schiraldi C, Sirangelo I. (2019). Protective effect of extractive and biotechnological chondroitin in insulin amyloid and advanced glycation end product-induced toxicity. *J Cell Physiol*, 234(4): 3814-3828. doi.org/10.1002/jcp.27153.

Jo S-L, Yang H, Jeong K-J, Lee H-W, Hong E-J. (2023). Neuroprotective Effects of Ecklonia cava in a Chronic Neuroinflammatory Disease Model. Nutrients. 15(8): 2007. doi.org/10.3390/nu15082007.

Kabir MT, Uddin MS, Jeandet P, Emran TB, Mitra S, Albadrani GM, Sayed AA, Abdel-Daim MM, Simal-Gandara J. (2021). Anti-Alzheimer's Molecules Derived from Marine Life: Understanding Molecular Mechanisms and Therapeutic Potential. *Marine Drugs*, 19(5):251. doi.org/10.3390/md19050251

Kim CK, Lee YR, Ong L, Gold M, Kalali A, Sarkar J. (2022). Alzheimer's Disease: Key Insights from Two Decades of Clinical Trial Failures. *J Alzheimers Dis*, 87(1): 83-100. doi.org/10.3233/JAD-215699.

Koelsch G. (2017). BACE1 Function and Inhibition: Implications of Intervention in the Amyloid Pathway of Alzheimer's Disease Pathology. *Molecules*, 22(10):1723. doi.org/10.3390/molecules22101723.

Kong Y, Liu C, Zhou Y, Qi J, Zhang C, Sun B, Wang J, Guan Y. (2020). Progress of RAGE Molecular Imaging in Alzheimer's Disease. *Front. Aging Neurosci, Alzheimer's Disease and Related Dementias*, 2020(12): 1-9. doi.org/10.3389/fnagi.2020.00227.

Li DD, Zhang YH, Zhang W, Zhao P. (2019). Meta-analysis of randomized controlled trials on the efficacy and safety of donepezil, galantamine, rivastigmine, and memantine for the treatment of Alzheimer's disease. *Front Neurosci*, 2019(13): 1-18. doi.org/10.3389/fnins.2019.00472.

Lyu, C, Chen T, Qiang B, Liu N, Wang H, Zhang L, Liu Z. (2021). CMNPD: a Comprehensive Marine Natural Products Database Towards Facilitating Drug Discovery from the Ocean. *Nucleic Acids Res*, 49(1), 509-515. doi: 10.1093/nar/gkaa763.

Martins M, Silva R, M. M. Pinto M, Sousa E. (2020). Marine Natural Products, Multitarget Therapy and Repurposed Agents in Alzheimer's Disease. *Pharmaceuticals*, 13(9): 242. doi.org/10.3390/ph13090242.

Mehta D, Jackson R, Paul G, Shi J, Sabbagh, M. (2017). Why do trials for Alzheimer's disease drugs keep failing? A discontinued drug perspective for 2010-2015. *Expert Opinion on Investigational Drugs*, 26(6): 735–739. doi.org/10.1080/13543784.2017.1323868.

Montaser R, Luesch H. (2011). Marine natural products: a new wave of drugs? *Future Med Chem*, 3(12):1475-89. doi.org/10.4155/fmc.11.118.

Mycroft-West CJ, Devlin AJ, Cooper LC, Guimond SE, Procter P, Guerrini M, Miller GJ, Fernig DG, Yates EA, Lima MA, et al. (2021). Glycosaminoglycans from Litopenaeus vannamei Inhibit the Alzheimer's Disease β Secretase, BACE1. *Marine Drugs*, 19(4): 203. doi.org/10.3390/md19040203

Nugraha AS, Firli LN, Rani DM, et al. (2023). Indonesian Marine and Its Medicinal Contribution. *Nat. Prod. Bioprospect*, 13(38): 1-27. doi.org/10.1007/s13659-023-00403-1.

Osama A, Zhang J, Yao J, Yao X, Fang J. (2020). Nrf2: a dark horse in Alzheimer's disease treatment. *Ageing Research Reviews*, 64: 1-45. doi.org/10.1016/j.arr.2020.101206.

Park SK, Kang JY, Kim JM, Yoo SK, Han HJ, Chung DH, Kim D-O, Kim G-H, Heo HJ. (2019). Fucoidan-Rich Substances from Ecklonia cava Improve Trimethyltin-Induced Cognitive Dysfunction via Down-Regulation of Amyloid β Production/Tau Hyperphosphorylation. *Marine Drugs*, 17(10): 591. doi.org/10.3390/md17100591

Reddy VP, Aryal P, Soni P. (2023). RAGE Inhibitors in Neurodegenerative Diseases. *Biomedicines*, 11(4):1131. doi.org/10.3390/biomedicines11041131.

Rivarti AW, Saputri LO, Harahap HS, Permatasari, L. (2023). Alzheimer's disease from a diabetic brain: Exploring the molecular process to determine the potential therapy target from marine sources. *Pharmacy Education*, 23(4): 189-195. doi.org/10.46542/pe.2023.234.189195.

Sayas CL, Ávila J. (2021). GSK-3 and Tau: A Key Duet in Alzheimer's Disease. Cells. 10(4): 721. doi.org/10.3390/cells10040721

Shatshat AL, Pham AT, Rao PPN. (2019). Interactions of polyunsaturated fatty acids with amyloid peptides Aβ40 and Aβ42. *Archives of Biochemistry and Biophysics*, 663(15): 34-43. doi.org/10.1016/j.abb.2018.12.027.

Silva M, Seijas P, Otero P. (2021). Exploitation of Marine Molecules to Manage Alzheimer's Disease. *Mar Drugs*, 19(7): 373. doi.org/10.3390/md19070373.

Stevenson, ME, Hebron M, Liu X, Kavulu B, Wolf C, Moussa, CEH. (2022). Inhibiting tyrosine kinase c-KIT as a therapeutic strategy for Alzheimer's Disease. *Alzheimer's Dement*., 18(10): 1. doi.org/10.1002/alz.068944

Wang R, Reddy PH. (2017). Role of Glutamate and NMDA Receptors in Alzheimer's Disease. *J Alzheimers Dis*. 57(4): 1041-1048. doi: 10.3233/JAD-160763.

Xia Y, Sorrentino ZA, Kim JD, Strang KH, Riffe CJ, Giasson BI. (2019). Impaired tau–microtubule interactions are prevalent among pathogenic tau variants arising from missense mutation tau mutants impair microtubule interaction. *Journal of Biological Chemistry*. 294 (48): 18488-18503. doi.org/ 10.1074/jbc.RA119.010178

Yiannopoulou KG, Anastasiou AI, Zachariou V, Pelidou SH. (2019). Reasons for Failed Trials of Disease-Modifying Treatments for Alzheimer Disease and Their Contribution in Recent Research. *Biomedicines*, 7(4):97. doi.org/10.3390/biomedicines7040097.

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