# A Review on Drugs from Marine Source for Alzheimer's disease

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**ABSTRACT:**
**The most prevalent cause of dementia is Alzheimer's disease, a neurodegenerative condition. Memory and cognitive capacity are equally impacted by Alzheimer's disease. Amyloid plaques and neurofibrillary tangles are the two main symptoms of Alzheimer's disease (NFTs). The pathogenesis of Alzheimer's disease is described in this review, along with treatments for the condition. In a recent article published in the journal Marine Drugs, docosahexaenoic acid (DHA) and DHA-rich phospholipids (DH-PL), which are derived from fisheries and aquaculture wastes, are reviewed with an emphasis on how these substances may assist treat Alzheimer's disease (AD).**

***Keywords: Amyloid-β (Aβ) plaques,Neurofibrillary tangles (NFTs) ,Docosahexaenoic acid (DHA), treatment.***

## INTRODUCTION:

According to the Alzheimer's Association (2019), Alzheimer's disease (AD) dementia describes a specific age-related start and course of cognitive and functional deterioration that ultimately leads to death.When Alois Alzheimer first observed Auguste Deter, a 51-year-old lady with cognitive impairment, disorientation, delusions, and other behavioural problems in 1901, he first wrote about her case in 1906.Mrs. Deter passed away in 1906, 4.5 years later. According to Alzheimer's neuropathologic examination, there were "specific alterations in cortical cell clusters" as well as diffuse brain shrinkage. In a speech "on the unusual illness process of the cerebral cortex," he presented his research findings (Moller and Graeber, 1998).Although Alzheimer initially qualitatively described the disease in 1906, it wasn't until the middle of the 1980s that the molecular identities of the disease's two defining pathologies—beta amyloid peptide found in plaques and hyperphosphorylated tau protein found in neurofibrillary tangles (NFTs)—were demonstrated (Brion et al., 1985; Grundke-Iqbal et al., 1986; Kosik et al., 1986; Pollock et al., 1986; Glenner and Wong, 1984a,b).[1] A leading contributor to dementia, Alzheimer's disease (AD) is a progressive neurological condition. Memory loss, issues with thinking, language, and problem-solving abilities are all symptoms of dementia. According to the WHO update on epidemiology of AD in 2013, the number of dementia sufferers globally, which was around 35.6 million in 2010, is predicted to quadruple by 2050. Age is a factor in dementia incidence; those over 65 years old are afflicted at a rate of 5-8%, and those over 85 years old are impacted at a rate of 25–50%. Men had an AD prevalence that was 19–29% lower than women's did. According to the USFDA (2013) , the nine nations with the highest number of dementia cases in 2010 were China, the USA, India, Japan, Germany, Russia, France, and Brazil. In the brain, a protein is produced that results in the development of plaques and tangles. Indicators of AD can be seen under a microscope as neurotic plaques generating amyloid beta peptide (Aβ42) and neurofibrillary tangles (NFTs) made of hyperphosphorylated tau. These proteins serve as the building blocks for the eventual death of nerve cells and loss of brain tissue by causing the loss of connections between nerve cells.

## PATHOGENISIS:

The most frequent cause of dementia, accounting for 60–80% of all dementia cases, is Alzheimer's disease (AD). Only six FDA-approved medications are currently used to treat AD symptoms, including cholinesterase inhibitors, NMDA receptor antagonists, and other neuromodulatory drugs that are currently prescribed to AD patients to ease the cognitive symptoms, despite the disease's widespread prevalence and rising incidence. Aducanumab, the most recent medication to receive FDA approval, is an immunotherapy that uses antibodies to treat amyloid-β (Aβ) plaques. This new medication's clinical effectiveness is in question, which prevents it from being used on patients with severe AD. Developing efficient therapies to stop the destructive course of AD and the related neurodegeneration is urgently needed, in general. Synaptic dysfunction, neurodegeneration, neuro inflammation, and vascular dysfunction are all features of AD at the cellular level. The final impairment in cognition observed in AD patients is thought to be caused by this confluence of neuronal loss accompanied by an aggravated inflammatory state. Extracellular amyloid-β (Aβ) plaques and intracellular neurofibrillary tangles (NFTs) made of aggregated tau protein are the main neuropathological indicators of AD.

## PATHOLOGIC HALLMARKS OF ALZHEIMER'S DISEASE:

### 1) Aβplaque-related neural degeneration:

This theory states that A plaques develop and are deposited in various parts of the brain. The brain recognises these plaques as foreign substances, triggering an inflammatory and immunological response that eventually results in cell death and neurodegeneration by activating microglia and releasing cytokines. The Aβ plaque is made up of Aβ peptides that are produced by enzymatic cleavage of the APP by secretases (α, β and γ). Amyloid precursor protein (APP) is cleaved by β-secretase to produce a

C-terminal membrane connected with fragments of 89 or 99 amino acids, which is the main process in the formation of Aβ plaque.This β -secretase contains BACE 1, also known as Asp2 or memapsin2, a site-specific APP cleaving enzyme. BACE 1 cleaves APP at the β-sites Asp1 and Glu11. γ-secretase continues to cleave the 99 amino acid residue C-terminal membrane-bound segment to provide the Aβ1-40 and Aβ1-42 isoforms. Presenilin 1 (PS1) or Presenilin 2 are the two most common γ-secretases (PS2).The typical soluble isoform is Aβ1-40, but if the pattern of cleavage shifts, Aβ1-42 may result. This isoform aggregates readily and forms plaque because it contains two additional amino acids, isoleucine and alanine.

Mutations in the APP gene, presenelin 1 or 2 genes, or the apolipoprotein E (APOE4) gene cause this shift in the cleavage pattern.Numerous neuropeptides, in addition to genetic mutations, are likely to play a role in the development of the plaque. For instance, low levels of corticotrophin-releasing hormone (CRH), somatostatin, and neuropeptide Y are likely to contribute to plaque formation, whereas higher levels of angiotensin II may be responsible for either irregular cleavage of the APP or impaired removal of the Aβ1-42 fragment .Tau and Aβ both agglomerate, impede synaptic plasticity, and result in neuronal cell death .The validity of this theory has been hotly debated, and a recent study suggests that amyloid plaque-inhibiting medications have little effect on slowing or preventing cognitive decline. This shows that either the theory is flawed or that the brain develops resistant to therapy with time. Therefore, the search for treatment approaches that affect non-amyloid targets including tau proteins, inflammation, oxidative stress, etc. should be prioritised.

**2) Neurofibrillary Degeneration:**

Neuronal microtubular proteins are known as tau proteins. The microtubule binding domain of tau proteins is involved in the polymerization and stabilisation of the microtubule assembly to sustain the cytoskeleton's structural integrity. The phosphorylation of the serine/threonine residues in this interaction is controlled by a number of kinases, including Fyn Kinase, glycogen synthase kinase-3β (GSKβ3) and cyclin-dependent kinase-5 (CDK5). Potentially contributing to the development of neurofibrillary tangles is CDK5. Calpain is activated by Aβ, and p35, a CDK5 activator, is disrupted. Due to an excess of cytosolic calcium, p35 breaks into p25, which activates CDK5 excessively and causes tau to be hyperphosphorylated.

The tau proteins' affinity for microtubules is diminished as a result of hyperphosphorylation.NFTs are created by hyperphosphorylated tau and are deposited in the cytosol and can no longer carry out the task of keeping the cell's structure. Additionally, this depositiondisrupts regular cellular processes like signal transduction, axonal transport, and synaptic transmission, and causes cells to gradually deteriorate. A tau gene mutation or the dysregulation of the kinases listed below and the phosphatases, which catalyse the phosphorylation process, are cited as the causes of the hyperphosphorylation.

**3) APOE4:**

In AD, there are complications with brain glucose uptake and metabolism.According to metabolic profiling, a subtype of AD specifically linked to the APOE4 variation is associated with reduced brain glucose uptake. In mice, GLUT1 impairment reduces brain glucose uptake, encourages increased amyloid plaque buildup, reduces amyloid clearance, and results in widespread neuronal death and dysfunction resembling AD. Tau tangle development is also caused by impaired brain glucose absorption.Humans have three main APOE alleles: alleles 2 (APOE2), 3 (APOE3), and 4 (APOE4), each of which confers a different level of illness risk.

**CURRENT ALZHEIMER'S DRUG TREATMENT:**

Whereas the number of AD patients is expanding, there are only five acknowledged medications now in use for AD therapy in the United States. As for the European Union, An antagonist of N-methyl-D-aspartate receptor is used in four of the five standard-of-care treatments for AD.Cholinesterase inhibitors (rivastigmine, galantamine, and donepezil) and N-methyl-D aspartate receptor (memantine) . Unfortunately, no medication on the market today can stop or change AD. Rather, these medications reduce the symptoms of AD for a brief period of time and in a restricted number of patients. The first drug that the FDA approved was tacrine (in 1993), and due to its liver toxicity, it has currently been discontinued. Then, donepezil was authorised in 1996 by the FDA. The FDA authorised memantine and galantamine in 2003 and 2004, respectively. Rivastigmine ultimately obtained FDA clearance in 2006. The fifth therapeutic option involving a fixed-dose combination of memantine and donepezil got approval in 2014 to treat patients with milder AD who were receiving a stable therapy with donepezil.

Over the previous 15 years, most of the medication candidates under research have failed. Although AD is a fatal neurodegenerative condition, there is still no viable medication that can heal this condition. Moreover, there is an increasing awareness regarding AD intricacy, its Different pathogenetic mechanisms and the dynamic interaction of the constituent parts are involved in AD. Furthermore, positive findings found from immunisation trials in transgenic animal studies have fostered the discovery of immunotherapeutic agents for AD treatment. There are numerous monoclonal and polyclonal antibodies available are undergoing clinical studies against A. Novel experimental approaches, including single-chain differential fragment antibodies, antibodies specifically targeting conformational epitopes, or intrabodies bring optimism for further medication development for AD. Therefore, additional research taking into account the complexity of AD is needed in order to create potent and unique anti-AD therapeutic molecules.

**DRUGS FROM MARINE SOURCE:**

Numerous studies discovered a vast supply of unusual and diverse structures that are biologically and pharmacologically active in the marine environment. Marine bioactive substances contain distinct biological activities and chemical characteristics not seen in terrestrial products. As a result, these sources are being researched more and more in the search for new drugs to treat various human

disorders.More than 70% of the Earth's surface is covered by marine ecosystems, which also hold around half of the world's diversity. Marine organisms can produce a wide variety of secondary metabolites that exhibit a variety of bioactivities, including antioxidant, antimicrobial, anticancer, neuroprotective, and antidiabetic activity to the various conditions in the marine environment, such as temperature, pressure, salinity, and light.

The structural diversity of the neuroprotective marine chemicals includes polysaccharides, glycosaminoglycans, glycoproteins, lipids and glycolipids, pigments, and polysaccharides. Corals, sponges, algae, tunicates, or marine bacteria are examples of marine resources that produce active secondary metabolites. Consuming fish is also linked to a decline in AD symptoms and incidence. Numerous fish species, particularly docosahexaenoic acid-rich ones like mackerel, tuna, and sardines, are excellent sources of omega-3 PUFAs (DHA).

**DHA:**

Docosahexaenoic acid (DHA) is a polyunsaturated omega-3 fatty acid with a long chain. The n-3 polyunsaturated fatty acids (PUFAs) are lipids that can be found as triacylglycerols, phospholipids, free fatty acids, and cholesterol esters (CEs). DHA is found in the cold-water fish meat, including salmon, cod liver, mackerel, herring, tuna, halibut, seal blubber, and whale blubber. DHA should not be confused with EPA (Eicosapentaenoic Acid). They both exist in fish oil, but they are not the same. DHA can be converted into EPA in the body. DHA is also used as a supplement for premature babies and as an ingredient in baby formula during the first four months of life to promote better mental development. This practice probably started because DHA is found naturally in breast milk. DHA is also used in combination with Arachidonic Acid during the first four to six months of life for this purpose. Postnatal DHA improves vision and some cognitive functions in infants and toddlers.

They are crucial for cell membrane structure, cholesterol transport, and energy storage. As the most prevalent n-3 PUFA in the grey matter of the brain and retina, DHA contributes significantly to the phospholipid membrane, accounting for more than 30% (brain) and 90% (retina) of all n-3 PUFAs respectively. DHA deficiency in the brain has been linked to a number of neurological conditions, including Alzheimer's and Parkinson's.Fish oils, krill oil, algae, and other marine sources are excellent exogenous sources of DHA. Endogenous sources include the bioconversion of ALA into DHA.

The liver is where the elongase and desaturase enzymes that are needed to make DHA are most highly expressed.Numerous studies have shown that DHA has a number of health advantages, such as helping to develop an infant's brain and eyes, preventing preterm birth, being crucial for the health and development of the brain, lowering the risk of tumours and some cancers, inhibiting many inflammatory processes, and preventing cardiovascular disease when consumed. DHA's ability to control lipid metabolism, vascular function, cell membrane dynamics, as well as anti-inflammatory and antioxidant responses, contributes to its cardioprotective benefits.

DHA plays a important role in the development of eye and nerve tissues. DHA is also used to reduce the risk of heart and circulatory disease by decreasing the thickness of the blood, reducing swelling (inflammation), and lowering blood levels of triglycerides.

**HOMOTAURINE: (Tramiprosate)**

Proteoglycans play a role in the development of amyloid fibrils and Aβ-aggregation. The sulfated glycosaminoglycan chains, which are parts of proteoglycans, link to the Aβ peptide and help it change from a random-coil to a β-sheet conformation, which aids in the fibrillogenesis process. To replicate the ionic characteristics required for glycosaminoglycans to bind to Aβ, a selection of low-molecular- weight sulfated molecules was created. A tiny amino sulfonate called homotaurine (3-amino-1-propanesulfonic acid) was found in marine red algae, and it was demonstrated that it inhibited Aβ aggregation and fibrillogenesis in vitro.

By interacting with the Aβ monomers and keeping them in a stable shape, this glycosaminoglycan mimic inhibits the amyloid cascade from developing. Phase III clinical trials using homotaurine to treat mild to moderate AD had mixed findings because of its lower clinical efficacy. Although this medication has a large interindividual pharmacokinetic fluctuation and can elicit nausea and vomiting in vulnerable AD groups, this is likely due to direct gastrointestinal irritation. It was decided to create ALZ-801, or (S)-3-(2-amino-3-methylbutanamido)propane-1-sulfonic acid. The valine moiety of this medication is quickly broken down by amidases in the digestive tract, yielding homotaurine. In comparison to homotaurine, the prodrug had a prolonged half-life and less variability in its pharmacokinetics. Tramiprosate's mechanisms of action include its interaction on amyloid. The GABA-A receptor is connected to the mechanism of action (GABA-AR). Tramiprosate functions as a functional agonist and shares a chemical structure with the neurotransmitter γ -amino butyric acid (GABA).Tramiprosate, a partial agonist of the central GABA receptor, enhances cortical cholinergic transmissions and regulates inhibitory cortical activity in AD patients.

**ANABASEINE:**

Nicotinic acetylcholine receptors (nAChRs) are ligand-gated ion channel receptors that are pentameric membrane proteins. They are made up of various combinations of five subunits subunits (α, β, γ, δ and ε) that form cysteine-loop ligand-gated cation channels permeable to $Na^+$, $K^+$, and varying levels of $Ca^{2+}$ . The most numerous subunits in the brain are the homomeric α7 subtype and the heteromeric α4 β2 subtype, both of which are substantially expressed in brain regions that develop AD neuropathology. The channel rearranges after activation, resulting in a lack of physiologic responsiveness. Because Aβ binds to these receptors, particularly the α7 subtype, and can change the normal functionalization of the receptor, leading to the initiation of Aβ, the nAChR is a target for AD.

Anabaseine, a naturally occurring nicotine-related pyridine alkaloid, was the first to be isolated and recognised as a nemertine alkaloid. It was discovered in certain ants after being isolated from a marine worm. The molecular structure is identical to that of nicotine, except it includes an Instead of a saturated piperidine ring, an imine double bond is used. Anabaseine is a non-specific nicotinic agonist that, like nicotine, stimulates all nAChRs with varying affinities, with anabaseine having a higher affinity for α7 nAChRs. When a benzylidene substituent is added to the 3-position of the anabaseine tetrahydropyridine ring, a benzylidene-substituted anabaseine with functional selectivity for α7 nAChRs is formed.

**BRYOSTATIN:**

Bryostatins include anticancer and immunological modulatory activities, and they have also been shown to improve memory and learning. A powerful PKC modulator, bryostatin-1 is a macrolide lactone with 11 chiral centres that is essential for cell differentiation and signal transduction. It was discovered that PKC, a member of the PKC isozymes family, was lacking in fresh frozen hippocampus brain samples from AD patients and was important in learning and memory. In order to downregulate the protein, bryostatin-1 activates PKC by attaching to the N-terminal C1 domains of PKC and triggering autophosphorylation, protein translocation, and ubiquitination.

The activation of PKCε results in the breakdown of Aβ, the activation of α-secretase, the production of the synaptogenic, non-toxic soluble amyloid-β protein precursor α, and a decrease in GSK3-β activity, hence reducing tau hyperphosphorylation. Its capacity to stimulate synaptogenesis by raising the concentrations of synaptic growth factors inside the brain may be responsible for its neuroprotective effects. Bugulaneritina extract was used to isolate bryostatin for the first time (brown bryozoans). Colonies of aquatic organisms are seen in both tropical and subtropical waters. Bryostatin regulates protein kinase C to carry out its neuroprotective effects (PKC).

**CONCLUSION:**

With the advancement of technology, such as MRI and fMRI, and PET and SPET scans, used in conjunction with neuropsychological tests administered at key time points including followups, the clinician is better placed to make a more reliable diagnosis and prognosis than in the past. It is hope that this will also enlighten service providers in widening access to people with learning disabilities who also have dementia. There are four stages of Alzheimer disease in series i.e., predementia, mild, moderate and severe. Pneumonia is the most common cause of death in Alzheimer disease, followed by myocardial infarction and septicaemia. Various risks factors like age, genetics, education etc. are associated with Alzheimer disease. In addition, environmental factors, vascular factors and psychosocial factors also contribute to Alzheimer disease. Many of the drugs are formulated and evaluated for the treatment of alzhiemer's disease and also the marine source contains the active materials used in the treatment of dementia.

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