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MARINE DRUG: ALZHEIMER'S DISEASE THERAPEUTICS AGENTS: A REVIEW

Shivanshu Kushwaha*[1], Navneet Kumar Verma[1], Shekhar Singh[1]

[1*]Suyash Institute of Pharmacy, Hakkabad, Gorakhpur, Uttar Pradesh, India.

ABSTRACT

Alzheimer's disease (AD), a neurodegenerative disease, is one of the most difficult illnesses to treat among the elderly. Clinically manifested as various impairments in memory, language, cognition, visuospatial skills, executive function and so on, the symptoms progressively worsened over time. The drugs currently in clinical use can slow the progression of Alzheimer's disease and alleviate symptoms, but they cannot cure it completely. The drugs are primarily acetylcholinesterase inhibitors (AChEIs) and noncompetitive N-methyl-D-aspartate receptor (NDMAR) antagonists. Although the pathogenesis of Alzheimer's disease is unknown, it is frequently linked to beta-amyloid expression. Previous, current, and future drug development for the disease has focused on abnormal amyloid deposition and hyperphosphorylation of tau protein in the brain. Researchers are currently focusing increasingly on the extraction of natural compounds that may be effective against Alzheimer's disease and other neurodegenerative disorders. Marine natural products have been shown to be the most promising candidates among these compounds, with some exhibiting significant neuroprotective properties. Consequently, we aim to elucidate the potential effects of bioactive compounds derived from marine organisms, including polysaccharides, carotenoids, polyphenols, sterols and alkaloids, as drug candidates, to facilitate the discovery of novel and efficacious therapeutic agents effective against Alzheimer's disease.

KEYWORDS

Alzheimer's disease, Neurodegenerative disease, Therapeutic, Pathogenesis and Marine natural products.

Author for Correspondence:

Shivanshu Kushwaha,
Suyash Institute of Pharmacy,
Hakkabad, Gorakhpur, Uttar Pradesh, India.

Email: shivanshukushwaha012@gmail.com

INTRODUCTION

Alzheimer's disease (AD) is widely recognized as the predominant cause of dementia, predominantly affecting older adults[1,2]. AD is characterized by behavioral disturbances, neuronal death, memory loss, cognitive deficits, and cholinergic dysfunction. The pathogenesis of Alzheimer's disease involves intricate processes and a deficiency in the neural pathways related to memory function[3]. Early-onset Alzheimer's disease has been identified in

individuals aged over 65 years. Nonetheless, over 90% of diagnosed cases are associated with late-onset Alzheimer's Disease, typically observed in individuals over 65 years old[4]. Conversely, the presenilin 1 (PSEN1) mutation (P117L) is associated with familial Alzheimer's disease (FAD) and may result in mortality as early as 28 years of age[5]. Numerous genetic mutations, specifically in the genes for amyloid precursor protein (APP), PSEN1, and preselinin 2 (PSEN2), have been linked to the development of AD at an early age[6]. About 5-10% of cases of early-onset AD that are diagnosed may have dysregulated expression of these genes[4,6]. In fact, both early-onset and late-onset AD are significantly influenced by polymorphic alleles of apolipoprotein E (APOE)[7,8]. Furthermore, during normal aging, the presence of APOE4 alleles is associated with an increased risk of age-associated cognitive deficit and cerebral amyloid angiopathy[9].

Intracellular neurofibrillary tangles (NFTs), extracellular amyloid plaques, and nerve cell death are the main neuropathological characteristics of AD[10-14]. The amyloidogenic pathway and the non-amyloidogenic pathway are the two pathways through which sequential APP cleavage occurs[15]. Amyloid beta (Aβ), which is produced by the amyloidogenic APP cleavage, is the building block of amyloid plaques. This pathway produces Aβ by cleaving APP via β-secretase (BACE1) and then γ-secretase[14]. An association between FAD mutations and an elevated Aβ42/40 ratio has been found[16,17], suggesting that elevated Aβ42 levels (in comparison to Aβ40) are important in the pathophysiology of AD, potentially by serving as the core for Aβ assembly into amyloidogenic plaques, fibrils, and oligomers[18,19]. Aβ accumulation may occur in the elderly as a result of altered APP cleavage. According to reports, non-amyloidogenic APP processing may be decreased by excessive age-linked acetylation of the α-secretase gene[20]. Amyloidogenic APP processing was found to be elevated in early AD brain tissue due to increased BACE1 activity[21,22]. Aβ monomers gradually aggregate into oligomers, insoluble amyloid plaques, and fibrils[10].

The histopathological hallmark of AD is NFTs, which are made of hyperphosphorylated tau[23]. Under typical circumstances, tau can mediate microtubule stabilization. On the other hand, tau can form tangles composed of paired helical filaments when it is hyperphosphorylated[11]. According to the amyloid cascade hypothesis, Aβ buildup can mediate the intracellular environment for the formation of NFTs by dysregulating neuronal and synaptic function, ultimately leading to neuronal loss and further decline in neurotransmitter activity[10]. Marine organisms are used to extract pharmacologically active substances, which are then transformed into forms that humans can use. In fact, the ocean is a reservoir of many bioactive compounds, but the ocean remains relatively unexploited[24-27]. It was revealed through the isolation of soft corals that marine-organisms can be an important source for novel drugs containing novel chemical structures and an increased level of therapeutic value. Moreover, the marine ecosystem is a significant source for discovering effective therapeutic agents, and marine organisms are associated with half of the Earth's biodiversity[28,29]. The occurrence of new infections, metabolic disorders, and the increased rate of lifestyle and aging- associated diseases suggest that there is value in the constant exploration for more effective and highly selective drugs, utilizing both modern and traditional methods for designing and developing novel drugs. Microorganisms, invertebrates, and algae are rich sources of several important drugs[30]. Large research areas for the extraction of bioactive compounds from seas and oceans have been made possible by modern technologies[31]. Numerous marine-derived secondary metabolites with substantial therapeutic potential have already been found in a variety of sessile marine invertebrates, such as sponges, bryozoans and tunicates. The discovery of several new metabolites, such as bryostatin, indicates that the ocean is a rich source of many significant therapeutic candidates[32,33]. One to two hours after the start of infusion, bryostatin concentrations peaked in a phase IIa clinical trial[34]. Within an hour

of the infusion beginning, the blood's maximum bryostatin levels were accompanied by an increase in the concentration of PBMC protein kinase C epsilon (PKCε). Additionally, bryostatin was found to improve Mini-Mental State Examination (MMSE) scores. Additionally, bryostatin was found to be well tolerated and no adverse drug reactions were reported in AD patients. Furthermore, research on animals showed that bryostatine increased levels of brain-derived neurotrophic factor (BDNF), postsynaptic density protein 95 (PSD-95) and effective PKCε. initiation. All of these results pointed to bryostatin 1 as a successful treatment for AD[35]. The medications made from marine organisms that may be helpful in treating AD are the main topic of this review. Additionally, we provide an overview of the therapeutic agents currently used to treat AD.

Facts and features of Alzheimer's disease

The World Health Organization (WHO) has identified Alzheimer's disease (AD) as a global health priority[36]. It is anticipated that by 2050, there will be roughly one million new cases of AD annually, with a new case being diagnosed every 33 seconds[37]. It is believed that AD, a neurodegenerative disease, begins years before its symptoms, which include language and memory loss, manifest. The degeneration or injury of neurons involved in cognitive function is linked to the onset of the symptoms. Walking and swallowing are two abilities that become impossible as AD worsens, necessitating 24-hour care[38]. Known risk factors for AD include advanced age, family history, the genotype of the apolipoprotein E (APOE) ε4 allele, lifestyle, psychosocial factors, cardiovascular disease risk factors and illiteracy[38]. The presence of intracellular neurofibrillary tangles (NFT), extracellular amyloid plaques and nerve cell death, which results in brain atrophy, are the hallmarks of AD[38,39]. β-Amyloid (Aβ) plaques may contribute to cell death by interfering with the communication at synapses between neurons, while NFTs block the transport of nutrients and other essential molecules within neurons[38]. Amyloid precursor protein (APP) cleavage produces Aβ peptides, which make up the majority of amyloid plaques. Three secretases can cleave APP through two different metabolic pathways: the amyloidogenic and the non-amyloiddogenic pathways (Figure No.1). The non-amyloidogenic pathway, The enzymes that are involved are α-secretase and γ-secretase. α-secretase first cleaves APP, producing a soluble fragment called α-APP and a smaller peptide that is 83 amino acids (a.a.) long. γ-secretase then cleaves the smaller peptide into two non-amyloidogenic peptides. Because the cleavage takes place at the fragment's N-terminus, the second pathway is the one that produces Aβ peptides. When APP is broken down by β-secretase (BACE-1), two fragments are produced: β-APP, a soluble fragment, and a longer 99 a.a. peptide, which is subsequently broken down by γ- secretase into different lengths of amylogenic peptides, such as Aβ40, Aβ42, and Aβ43[40].

NFTs are formed from hyperphosphorylated tau protein, a protein that stabilizes the microtubules but which, when hyperphosphorylated, accumulates into tangles[38,41]. The main enzyme involved in the process is glycogen synthase kinase 3β (GSK-3β) and its inhibition can lead to a reduction in tau hyperphosphorylation. GSK-3β can be inhibited by protein kinase C (PKC), which is stimulated by muscarinic receptor 1 (M1) agonists such as acetylcholine[40]. The presence of toxic Aβ peptides and tau proteins causes an immune system response that activates microglia. These cells try to eliminate the toxic compounds, and when the production is higher than the clearance, inflammation occurs[38]. An abnormal increase in the production of reactive oxygen species (ROS) leads to oxidative stress, which is another major contributor to the development of AD. The presence of certain metal ions, such as aluminum (Al3+), iron (Fe2+), copper (Cu2+), zinc (Zn2+) and mercury (Hg2+), and mitochondrial dysfunction, also contribute to the pathogenesis of AD[42]. Recently, studies in mice investigating the possibility that Aβ peptide from the intestinal microbiome might be a trigger leading to AD opened a new avenue of research in this area[43,44]. Therefore, AD can be caused by several

mechanisms, leading to the possibility of being treated by different pathways, which are outlined in Figure No.2[45].

Current Drug Therapy for Alzheimer's

There are currently only five approved medications used to treat AD in the United States, despite the fact that the number of AD patients is increasing[46]. An antagonist of the N-methylD-aspartate receptor (memantine) and cholinesterase inhibitors (rivastigmine, galantamine, and donepezil) are part of four of the five standard-of-care treatments for AD in the European Union[39,47-49]. Unfortunately, there are currently no medications that can stop or change the progression of AD; instead, they only temporarily alleviate the symptoms of AD in a small percentage of patients[50,51]. Tacrine, which was the first FDA-approved medication in 1993, is no longer in use because of liver toxicity. In 1996, the FDA approved donepezil. The FDA approved galantamine in 2004 and memantine in 2003[52]. The FDA finally approved rivastigmine in 2006[53] and the fifth therapeutic option, which consists of a fixed-dose combination of memantine and donepezil, was approved in 2014 to treat patients with moderate-severe AD who were receiving a stable therapy with donepezil[54-56]. Most of the drug candidates under development have failed over the past 15 years, but there is still no effective drug that can cure AD, despite growing knowledge of the disease's complexity, its various pathogenetic modes, and the dynamic interaction between the constituents that cause AD[57]. Additionally, encouraging results from vaccination trials in transgenic animal models have prompted the development of immunotherapeutic agents for the treatment of AD[58]. Numerous monoclonal and polyclonal antibodies have been created to combat Aβ, and they are presently undergoing clinical testing. There is hope for additional AD medication development thanks to novel experimental techniques like intrabodies, antibodies that recognize particular conformational epitopes and single-chain variable fragment antibodies[59]. Therefore, more research is needed to develop novel and effective anti-AD therapeutic molecules, taking into account the complex nature of AD.

Potential Therapeutic Uses of Anti-Alzheimer's Molecules Derived from Marine Sources

Bryostatin-1

The marine invertebrate Buculaneritina is the source of the macrocyclic lactone bryostatin 1[60]. It has nanomolar potency for PKC1ε and α isotypes and is a strong activator of members of the protein kinase C family. Moreover, bryostatin 1 mediates PKC activation, which causes the central nervous system to produce and release more BDNF, a synaptic growth factor linked to memory and learning[61]. Additionally, bryostatin 1 activates the amyloid precursor protein's non-amyloidogenic α-secretase processing pathway[62]. In AD transgenic mouse models, preclinical research showed that intraperitoneal bryostatin 1 administration activates PKCε in the brain and inhibits Aβ accumulation, synaptic loss and memory deficit[63]. Additionally, in rodent models of Fragile X syndrome and stroke as well as aged rat models, bryostatin 1 mediates synaptic preservation and improves memory[64,65]. Additionally, bryostatin taken orally has been shown to improve memory and learning in an AD mouse model[66]. In a mouse model of multiple sclerosis, bryostatin also improves the anti-inflammatory immune response and neurological decline[67].

Clinical Proof

A single intravenous administration of bryostatin increased the Mini-Mental State Examination (MMSE) score of six AD individuals compared to three placebo-receiving individuals, according to a phase II clinical study[68]. In fact, bryostatin was found to be well tolerated in these AD patients, and no notable side effects were noted. After an hour of infusion, peak blood levels of bryostatin were found, along with elevated peripheral blood mononuclear cells (PKC) levels. Long-term bryostatin treatment caused PKC down regulation. That depended on the dosage levels and length of treatment. The administration of maximum doses (25μg/m2) for five or six consecutive weeks resulted in a significant down regulation of PKCɢ[68].

Additionally, this study suggested that bryostatin could be a useful medication option for treating AD. In another phase II clinical study, bryostatin was used to treat cognitive function loss in 150 patients with advanced AD. It demonstrated better efficacy, tolerability, and safety. Remarkably, the full analysis set (FAS) did not yield any significant primary endpoints. Nevertheless, the bryostatin (20µg)-treated group outperformed the placebo group in pre-specified and post hoc exploratory analyses, as well as primary and secondary analyses in the completer analysis set (CAS). All of these results point to the need for additional clinical research to ascertain the effectiveness of bryostatin (20µg) in the treatment of AD[69]. In June 2018, a separate phase II study involving 108 patients was initiated. Figure No.1. Mechanism of action of different bioactive compounds derived from marine sources in Alzheimer's disease. DHA stands for docosahexaenoic acid; GSK3β for glycogen synthase kinase 3 beta; nAChR for nicotinic acetylcholine receptor; NFTs for neurofibrillary tangles; NF-κB for nuclear factor-kappa B; PKC for protein kinase C; ROS for reactive oxygen species; and Aβ for amyloid beta. 3.1.2. Evidence from Clinical Practice A single intravenous administration of bryostatin increased the Mini-Mental State Examination (MMSE) score of six AD individuals compared to three placebo-receiving individuals, according to a phase II clinical study[34]. In fact, bryostatin was found to be well tolerated in these AD patients, and no notable side effects were noted. After an hour of infusion, peak blood bryostatin concentrations were found along with elevated PKCε levels in peripheral blood mononuclear cells. Prolonged bryostatin treatment caused PKCεdownregulation, which depended on the dosage and length of treatment. When maximum doses (25µg/m2) were given for five or six weeks in a row, a significant downregulation of PKCε was seen[68]. Additionally, this study suggested that bryostatin could be a useful medication option for treating AD. In another phase II clinical study, bryostatin was used to treat cognitive function loss in 150 patients with advanced AD. It demonstrated better efficacy, tolerability and safety[69]. Remarkably, in the entire analysis set, no significant primary endpoint was reached.

(FAS) Nevertheless, the bryostatin (20µg)-treated group outperformed the placebo group in pre-specified and post hoc exploratory analyses, as well as primary and secondary analyses in the completer analysis set (CAS). All of these results point to the need for additional clinical research to ascertain the effectiveness of bryostatin (20µg) in the treatment of AD[69]. In June 2018, 108 AD patients who were not on memantine participated in a separate phase II trial. According to their MMSE scores, patients in that study were split into two groups: those with scores between 10 and 15 and those with scores between 4 and 9. These groups were then randomly assigned to receive bryostatin (20µg) or a placebo. Over the course of twelve weeks, a total of seven doses were given[70]. Unfortunately, this study's findings were unsatisfactory.

Preclinical Evidence for Homotaurine

Numerous species of red marine algae contain the natural amino acid homotaurine (tramiprosate)[71]. Despite having an extra carbon in its chain, this compound is comparable to taurine. Preclinical research has shown that tramiprosate reduces the production of Aβ oligomers and the accumulation of amyloid fibrils as plaques in a mouse model of AD. Treatment with trimiprosate decreased the amount of soluble amyloid proteins and the amount of amyloid plaques that formed in the brain[72]. Plasma levels of Aβ decreased in a dose-dependent manner, which further implies that tramiprosate may have a role in brain Aβ transport or metabolism[73]. Tramiprosate mediates the polymerization of tau in fibrillar aggregates, according to a preclinical study; however, in neuronal cell cultures, these tau aggregates had no harmful effects. Furthermore, tramiprosate mediated the reduction of tau-actin complexes that might be harmful to cells rather than affecting tau's ability to bind with microtubules[73].

Clinical Proof

Tramiprosate has been shown in a phase II clinical trial to safely lower Aβ42 levels in the

cerebrospinal fluid (CSF) of people with mild-to-moderate AD. Indeed, these decreased levels of Aβ42 reported in CSF and long-term clinical observations, which suggests a role for tramiprosate in disease modification. Additionally, tramiprosate was found to be safe and well tolerated after three months of treatment[74]. The results of this study were inexplicably inconsistent, despite the fact that trimiprosate did not show any discernible differences in the later phase III study (Alphase study)[75]. Additionally, taking into account the distribution of the ApoE4 allele, a pooled analysis of the two phase III trials conducted among 2025 mild-to-moderate AD patients showed that homozygote individuals (who received 150mg twice a day) had significant differences in their ADAS-cog scores and a positive trend in their Clinical Dementia Rating Scale Sum of Boxes scores (CDR-SB). It's interesting to note that APOE4 heterozygotes demonstrated an intermediate level of efficacy, while non-APOE4 individuals showed no clinical benefits[76]. The homozygote individuals, who were at the mildest clinical stage of the disease, exhibited the greatest efficacies, according to subsequent re-analyses of these data (MMSE, 22-26). When compared to the placebo group, tramiprosate showed advantages in those individuals' disability assessment for dementia (DAD), CDR-SB, and ADAS-cog. While functional (DAD) and cognitive (ADAS-cog) effects increased over time, cognitive stabilization was observed in ADAS-cog over 78 weeks[77].

Anabaseine and Its Substance Preclinical Evidence for GTS-21

Nemertines, a phylum of carnivores (especially marineworms), produce the alkaloid toxin anabaseine (3, 4, 5, 6-Tetrahydro-2, 3'-bipyridine)[78]. It has been discovered that the synthetic anabaseine derivative GTS-21 functions as a partialagonist in neural nicotinic acetylcholine receptors[79]. Anabaseine can, in fact, function as a potent agonist at the level of muscle alpha-bungarotoxin-sensitive nicotinic receptors and neurons[80].

Ionotropic cholinergic receptors that are sensitive to nicotine activation are known as nicotinic acetylcholine receptors (nAChRs). In addition to strongly activating α7 subtypes, GTS-21 can bind to both α7 and α4β2 subtypes[81]. The hippocampus and the pre- and frontal cortex are the primary brain regions where α7 nAChR is expressed. Important cognitive processes like judgment, language, orientation, calculation, learning capacity, comprehension, thinking, and memory are also linked to α7-nAChR. It was discovered that Aβ inhibits or activates the α7-nAChR in a manner that is dependent on Aβ concentration. Additionally, tauvia activation of α7-nAChR is phosphorylated by Aβ oligomers. Thus, agonists of α7-nAChR and/or positive allosteric modulators of α7-nAChR may be useful in treating AD[82].

Clinical Evidence

The effects, pharmacokinetics, tolerability, and safety of GTS-21 on cognitive functions in healthy male subjects have been established by Kitagawa, *et al*[83]. A total of 18 subjects were randomized to receive either placebo or GTS-21 at doses of 150, 75, or 25mg (three times a day for the first four days, once on the fifth day) for three five-day sessions. At doses up to 450 mg/day, GTS-21 was found to be well-tolerated and to have no clinically significant safety issues. The area under the plasma drug concentration and Cmax of GTS-21 and its metabolite, 4-OH-GTS-21, increased in a dose-dependent manner, but there was a significant intersubjective variability that decreased with continuous dosin, encompassing working memory, attention, and episodic secondary memory, in contrast to a placebo. Furthermore, a correlation between the degree of the cognitive response and GTS-21 exposure was noted, with doses ranging from 150 to 75 mg three times a day approaching a maximum effect. All of these results point to the potential efficacy of GTS-21 as a novel dementia treatment[83].

Preclinical Evidence for Rifampicin

The broad-spectrum antibiotic rifamycin was originally isolated from the Gram-positive bacterial species Amycolatopsis. Additionally, Salinispora, a marine bacterium, is isolated from Pseudoceratinaclavata, a marine sponge, to yield

rifamycin[84]. Apart from its typical anti-infectious properties, rifampicin has demonstrated significant neuroprotective effects in a number of studies. Additionally, it lessens neuroinflammation and free radical damage, which further produces notable neuroprotective effects (Table No.1)[85]. The production of Aβ is also significantly influenced by the generation of free radicals[86]. Antioxidants have already demonstrated therapeutic efficacy in treating Aβ plaque-associated neurotoxicity in AD in a number of studies. According to the study by Tomiyama *et al*[87], rifampicin prevents neurotoxic effects in pheochromocytoma PC12 rat cells and inhibits fibril formation and aggregation of synthetic Aβ1-40 in a dose-dependent manner. It was discovered that rifampicin suppressed Aβaggregation 10-100 times more effectively than vitamins. A different study found that while the lipophilicity of rifampicin's sana-chain is important for drug transport into the brain *in vivo*, it is not necessary for suppressing Aβ aggregation[88]. Numerous *in vitro* investigations have demonstrated the anti-amyloid properties of rifampicin, including the inhibition of the formation of amyloid fibrils[89]. The observed suppressive activity was mediated by rifampicin binding with peptide fibrils rather than their potential intracellular antioxidant effect, according to several studies that also assessed the anti-amyloid activity of rifampicin on the aggregation of amylin fibrin and related toxicity[90].

According to Umeda *et al*, study, rifampicin significantly reduces the accumulation of tau oligomers and Aβ in a variety of transgenic mouse models. After a month of treatment, rifampicin dramatically reduced tau and amyloid toxicity, which was associated with improved microglial activation and synapse loss. In addition, rifampicin ameliorated memory loss and suppressed apoptotic pathways, such as by activating caspase 3 and releasing cytochrome c in the hippocampus. Autophagy-lysosomal activity was also restored by rifampicin. The results indicated that rifampicin exhibits significant inhibitory effects on apoptotic pathways, microglial activation, hyperphosphorylation of tau and accumulation of tau and Aβ oligomers, all of which are positively correlated with neurocognitive outcomes, despite some minor variations in Aβ deposition in different transgenic mouse models (such as AD, amyloid oligomers and tauopathy model)[91].

Clinical Proof

In contrast with preclinical results, only a small number of clinical studies have assessed the activity, efficacy and outcomes ofrifampicin in AD patients. Namba *et al*[92] examined 16 brains from leprosy patients without dementia and compared the senile plaques and neurofibrillary tangles using immunohistochemical staining in 140 elderly Japanese volunteers who were not dementia-afflicted. According to their research, elderly non-demented leprosy patients who were given rifampicin showed an unusual lack of senile plaques in their brains when compared to age-matched controls[92]. Regretfully, these results have not been confirmed in later research, which implies that rifampicin has no effect on the prevalence of AD in leprosy patients[93]. Although follow-up studies were intended to demonstrate the causal anti-dementia action of rifampicin, they were unable to produce definitive clinical results. Loeb *et al*[94] showed that rifampicin (oral administration of 300 mg/day for three months) had anti-dementia effects in 101 patients with mild-to-moderate AD. A standardized ADAS-Cog (SADAS-cog) score was used to measure cognitive function, and the results showed a significant improvement. However, these auspicious findings could not be confirmed in a study involving a rifampicin treatment for 12 months[95].

In another study, Iizuka *et al*[96] showed that the preventive activity of rifampicin requires a minimum dose of 450 mg/day for one year, even for the period of predementia. These authors also revealed in a retrospective fluorodeoxyglucose (FDG)-positron emission tomography (PET) study that a treatment with rifampicin markedly ameliorated cognitive and metabolic (posterior cingulate gyrus) deficits at the predementia stage in the long-term follow up. Rifampicin treatment significantly improved the uptake of FDG in the

posterior cingulate gyrus region at a dose of 450mg/day for more than a year, and this was also evident in the MMSE scores.

Preclinical Evidence for Dictyostatin

The Maldivian marine sponge, Spongia sp., was the source of the first extraction of dictyostatin, a marine-derived macrolide[97]. According to reports, AD patients have abnormally high tau levels[98]. Makani *et al*[99] used a PS19 tau Tg mouse model to estimate the effectiveness of dictyostatin. In comparison to vehicle-treated PS19 mouse models, dictyostatin-treated PS19 mouse models were found to exhibit improved microtubule density, reduced axonal dystrophy, a lower level of tau pathology, and a propensity for an increased survival rate of hippocampus neurons[99]. The idea that microtubule-stabilizing molecules might be useful in treating AD was supported by the practical positive results observed on the brain effect in aged PS19 mouse models treated with dictyostatin.

Clinical Proof

The effects of doxycycline and rifampicin were assessed in a clinical trial involving 101 patients with probable AD and mild-to-moderate dementia[97]. According to that study, rifampicin and doxycycline treatment may be helpful for mild-to-moderate AD patients.

Another clinical study was also conducted to refute or confirm these findings[100]. When compared to a placebo, SADAScog showed a noticeable decline over time when taking doxycycline and rifampicin. When compared to a placebo, there was no statistically significant decline or deterioration overall (n = 305). Additionally, neither rifampicin nor doxycycline significantly affected the Clinical Dementia Rating Scale SumofBoxes scores (CDR-SB). Secondary outcomes also showed similar trends. According to the study's findings, treating AD patients with rifampicin or doxycycline for a year, either separately or in combination, had no positive effects on function or cognition[100].

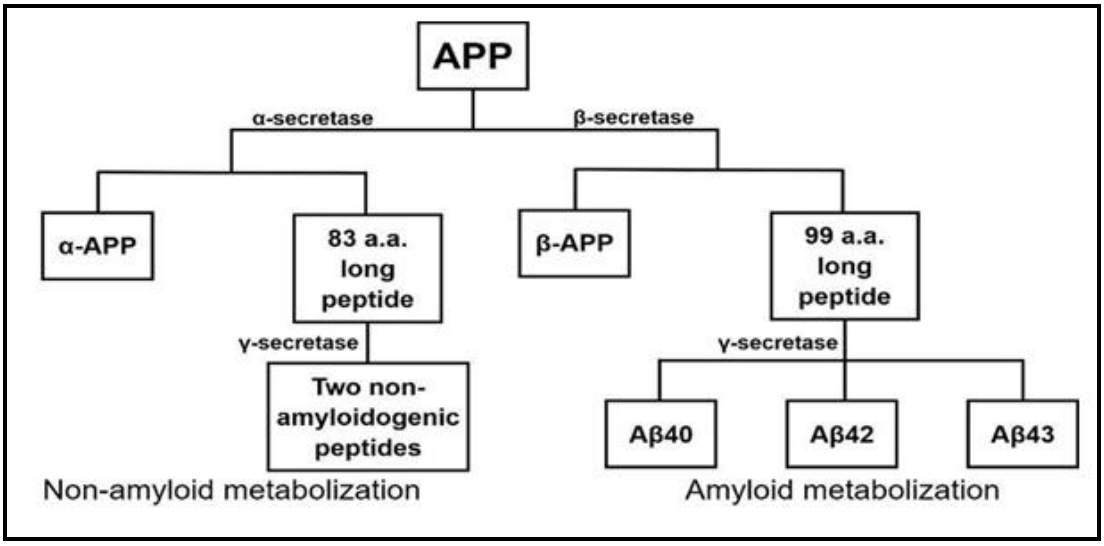

Figure No.1: Shows the two possible metabolic pathways for the cleavage of amyloid precursor protein (APP): nonamyloid metabolism and amyloid metabolism modified[40]

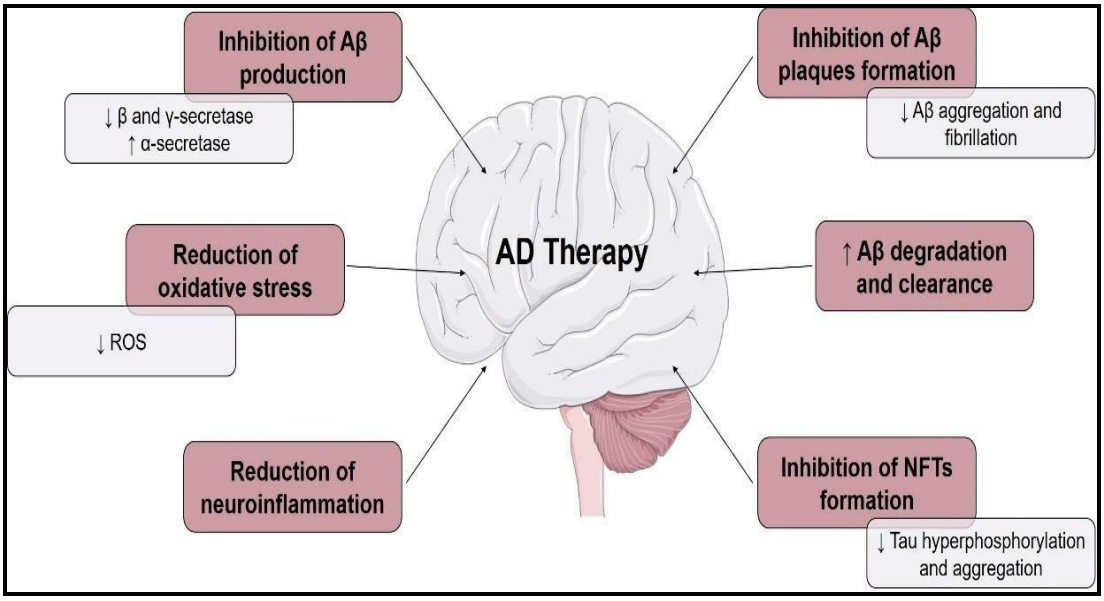

Figure No.2: Various approaches to treating Alzheimer's disease (AD). Up and down arrows, respectively, indicate increase and decrease, modified from[45]

CONCLUSION

Novel, safe and effective treatments for AD are desperately needed. Marine organism-derived natural products have the potential to be a great source for expanding the pharmaceutical pipeline. In numerous *in vitro* and *in vivo* investigations, a variety of novel compounds originating from marine organisms have demonstrated noteworthy effects against the pathogenesis of AD. According to research, there are many compounds in nature that can be used to treat AD. Thanks to technological advancements in sample harvesting, product purification and characterization, it is now possible to create effective bioactive compounds from marine sources. Therefore, in order to create new and efficient therapeutic agents to treat AD, more research on marine organisms is needed.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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