Marine derived bioactive compounds for treatment of Alzheimer’s disease

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1. ABSTRACT

   Alzheimer’s disease (AD) is mounting as social and economic encumbrance which are accompanied by deficits in cognition and memory. Over the past decades, Alzheimer’s disease (AD) holds the frontline as one of the biggest healthcare issues in the world. AD is an age related neurodegenerative disorder marked by a decline in memory and an impairment of cognition. Inspite of tedious scientific effort, AD is still devoid of pharmacotherapeutic strategies for treatment as well as prevention. Current treatment strategies using drugs are symbolic in nature as they treat disease manifestation though are found effective in treating cognition. Inclination of science towards naturopathic treatments aiming at preventing the disease is highly vocal. Application of marine-derived bioactive compounds, has been gaining attention as mode of therapies against AD. Inspired by the vastness and biodiversity richness of the marine environment, role of marine metabolites in developing new therapies targeting brain with special emphasis to neurodegeneration is heading as an arable field. This review summarizes select-few examples highlighted as therapeutical applications for neurodegenerative disorders with special emphasis on AD.

2. INTRODUCTION

   Aging is an implacable and unavoidable stage of entropy where one comes across diseases and disabilities- a collective consequence of genetic, environmental and lifestyle factors (1). Aging is considered as a main risk factor for a myriad of diseases including inflammatory and metabolic disorders, cancer and neurodegenerative diseases. The coequal hands in the hub of neurodegenerative diseases, Alzheimer’s disease (AD), Parkinson’s disease (PD), and Huntington’s disease (HD) are often life threatening and regarded as social as well
Neuritic plaques of amyloid-β (Aβ) peptide and neurofibrillary tangles of hyper-phosphorylated tau proteins are the two major characteristic pathological hallmarks of AD (fig 1) (5,6).

Extracellular neuritic plaques formed by abnormal aggregation of β-amyloid (Aβ) peptide, is the prime factor which is highly contributing towards neuronal death in AD. Oligomeric Aβ (1-42) is considered as highly toxic among the Aβ species and Aβ (1-42) induced oxidative stress tightly floors the pathogenesis of AD (7). Enzymes β and γ-secretase catalyzes the formation of Aβ peptide from amyloid precursor protein (APP). β-secretase, the rate limiting enzyme of the reaction and is also attributed to β-secretase 1 (BACE1) protein in the brain (5,8).

APP expression, increased APP metabolism, failure in removal of Aβ from the brain etc. all contribute to an elevated amount of Aβ peptide through major contributors like aging, diet and metabolism, genetic and pathogenic alterations. (9). Toxic soluble oligomeric Aβ peptide depositions contribute to plaque formation and is found responsible for enhanced neuronal loss and cholinergic dysfunctions resulting in loss of memory (amnesia) (10,11).

The second lesion in AD brain is neurofibrillary tangles (NFT) formed by hyper-phosphorylation of tau, a microtubule associated proteins (6). Phosphorylation of tau alters microtubule assembly of brain by inhibiting polymerization of tubulin into microtubules. Hyper-phosphorylated tau oligomerize/aggregate to the formation of tangles in AD subjects (12). Misfolding of hyper-phosphorylated tau protein in both synaptic nerve terminals cause synaptic dysfunctions (13), which in turn contribute to neuro-degeneration and dementia. Tau exists as a predominant factor in many additional neurodegenerative diseases other than AD.
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as Taupathies (14). Apart from these main causatives, AD is also contributed by mitochondrial dysfunctions, oxidative stress, inflammatory responses, etc., ending with difficulties in social and personal living owing to minimal communication (aphasia) and weakness to perform day-to-day activities (apraxia) and defective sensory output (agnosias) (15,16).

3. MECHANISMS LEADING TO AD

A number of scientific hypotheses are embracing the explanations of various mechanisms underlying AD. The populously backing hypotheses are described below:

3.1. The amyloid cascade hypothesis

According to this hypothesis, deposition of Aβ protein as amyloid plaques in brain tissues is the hallmark for neuro-degeneration in AD. An imbalance of Aβ production and disposal result in the disease phenomenon including formation of neurofibrillary tangles by tau proteins. The increased plaque formation leads to synaptic dysfunctions, memory impairments and brain damage (5). Aβ is generated by proteolytic cleavage of APP by β and γ – secretase. BACE 1, β site APP cleaving enzyme cleaves APP to form a membrane bound soluble C-terminal fragment, which gets subsequently cleaved by γ-secretase to form Aβ-40 and Aβ-42. Even though, plaques consist of both, Aβ-42 is more neurotoxic and aggregate to a higher extent (17).

3.2. Cholinergic hypothesis

Cholinergic hypothesis is based on presynaptic deficits in the brains of AD patients. According to this hypothesis, cognitive dysfunctions seen in AD patients are contributed by degeneration of cholinergic neurons in forebrain accompanied by loss of cholinergic neurotransmission in cerebral cortex. It has been observed that activities of choline acetyltransferase (ChAT) and Acetylcholine esterase (AchE) are decreased. Failure in cholinergic system results in imperfections in learning and impairment in memory (18).

3.3. The glutametergic hypothesis

The hypothesis is based on abnormal alterations in the GluN2A-containing N-methyl-D-aspartate receptors (NMDARs) resulting in improper synaptic functioning which also result in development of neurotoxicity through GluN2B-containing NMDARs (19).

4. CURRENT THERAPEUTICS

Since AD is a complicated multifaceted disease involving multiple biological pathways, an equally complex therapeutic approach is necessary for its treatment. High number of AD victims in the society urges a well-fabricated treatment strategy for AD. Despite enormous scientific efforts that are focused on the prevention side of AD, until now, no pharmaco-therapeutic agents are available either for prevention or for treatment of AD. If at all, “so called” established treatments are reliable only in symptomatic cure of the disease. There are five drugs namely- Tacrine, Rivastigmine, Donepezil, Galantamine and Memantine-approved by Food and Drug administration (FDA) for AD as first line drugs. Except memantine, a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist, the other four are choline esterase inhibitors (20). While treating the elderly, many reports have come up with disadvantages and side effects for these drugs, which proved their unsuccessful application as medications. Symptoms like hepatotoxicity, renal failure, abdominal pain, anorexia, nausea and variation of blood levels of drugs led to discontinuation of treatment in AD patients (21). Apart from these facts, none of these drugs have proved their potential role in effective treatment of Mild Cognitive Impairment (MCI), ‘symptomatic pre-dementia stage’ which often progress mainly towards AD dementia (22). On the flip side, new drug development or better implementation of old drugs through clinical trials are really challenging. Aβ peptide and the enzymes β and γ-secretase that generate Aβ peptide comprise the drug development targets. Clinical trials for these targets with developing drugs show a frailty to get successful outcome. Experimental mouse models recapitulate only a small fraction of human diseases (9). Such kind of discrepancies also stays as ramparts on the prevention strategies.

5. MARINE DERIVED BIOACTIVE COMPOUNDS FOR TREATMENT OF ALZHEIMER’S DISEASE

For the past decades, science is more inclined towards natural remedies to treat AD and found beneficial without side effects. Obviously herbs were the major focus initially- like Murraya koenigii, Ginkgo biloba, Moringa oleifera, Bacopa monnieri, Phyllanthus emblica, Daucus carota, are considered on the top of the list of herbs providing bioactive compounds against neuroprotection (24). In parallel, the investigations of unique bioactive compounds from marine creatures were also extensively rising. Increased explorations of marine bioactive compounds were seemed highly demanding as the society urge for novel remedies which are more reliable and less cost with long-term retention. Anticancer, anticoagulant, anti-hypercholesterolemic, antioxidant, anti-inflammatory activities etc. of marine bioactive materials were found applicable in reducing the gravity of highly prevailing noncommunicable diseases (NCDs) like cancer, cardiovascular diseases,
neurodegenerative disorders, diabetes and many more diseases (25). The present review puts forward the role of selected few marine bioactive compounds towards neuro-protection with prime emphasis on Alzheimer’s disease (Table 1).

5.1. Bryostatin

Bryostatin was first isolated from the extract of Bugulaneritina (brown bryzoans). The aquatic organism colonies are distributed in tropical and subtropical waters. (26). Previous studies on the clinical applications of Bryostatin demonstrated neuroprotection where repeated administration of Bryostatin following middle cerebral artery occlusion (MCAO) in aged rats reduced ischemic brain injury resulting in improved survival and neurological function (27). Bryostatin enacts its neuroprotective properties through the modulation of protein kinase C (PKC). They can interact with the diacylglycerol/phorbol ester-binding pocket of its C1 domain. The interaction between mammalian Unc13 isoforms and Bryostatin provides a novel molecular target that could be utilized to modulate neuronal synapses under dysfunctional synaptic conditions (28). Bryostatin-1 is also heading to pre-clinical studies with Niemann-Pick type C (NPC) mice. With respect to neuropathological symptoms like neurofibrillary tangles and deregulated Aβ metabolism NPC is reported to have similarities with AD. This will support the treatment of both diseases with Bryostatin-1 (30).

5.2. Chitosan

Chitosan is a derivative of chitin, a bioactive molecule from fish waste. Chitosan is a linear polysaccharide that consists of β-(1→4)-2-acetamido-d-glucose and β-(1→4)-2-amino-d-glucose units derived from partial deacetylation of chitin. However chitosan has limitations in biomedical applications owing to its poor solubility. Hence for many studies, chitosan is converted to chito-oligosaccharides (COS) which is readily soluble in water (31,32). Chitosan as well as COS exert biological activities including anti-inflammatory, antioxidant, anti-diabetic, antibacterial, anti-HIV and immunomodulatory properties (33). Protective effect of chitosan in AD is supported by studies indicating chitosan controlling the Aβ level by BACE-1 inhibition activity (27, 33). COS is also utilized as AchEI and again proved as beneficial material in preventing AD (33). Chitosan nanofiber (CNfib) were prepared from ionic gelation technique and electro-spinning process to release the donepezil drug quickly for Alzheimer’s disease and thus play a potential role in drug delivery in AD studied under both in vitro and in vivo conditions (35).
5.3. Gracilins

Gracilins are isolated from marine sponge *Spongionella gracilis*. Gracilins are able to inhibit \(\beta\)-secretase 1 (BACE1), reduce tau hyperphosphorylation and inhibit extracellular-signal-regulated kinase (ERK). Leiriós et al. (2014), demonstrated that the gracilins exhibit excellent neuroprotection by protecting the neurons from oxidative damage (36). Gracilin exert a neuroprotective effect in primary neurons with a restored mitochondrial membrane potential and an inhibition of the alterations produced by the mitochondrial uncoupler carbonyl cyanide-p-trifluoromethoxyphenylhydrazone (FCCP) (37). Expression of nuclear factor erythroid 2 (NFE2)-related factor 2 (Nrf2) in the nucleus is elicited and enhanced by Gracilin which is related with the antioxidant pathway activation. Gracilin is a potential anti-inflammatory drug due to their capacity of phospholipase A2 (PLA2) inhibition (38) which in turn diminishes amyloid \(\beta\)-induced reactive oxygen species (ROS) production (39). The antioxidant properties open up the specific interactions of gracilins with kinases involved in apoptosis or in the Nrf2-Keap1-ARE signal pathway, assuring their mechanism of action over Nrf2 levels in the nucleus. These bioactives would be interesting for the development of novel drugs for neurodegenerative diseases such as AD, PD, HD and ALS.

5.4. Bastadins and galantamine

Bastadins, isolated from the marine sponge *Lanthella basta* Pallas (family *Lanthellidae*), inhibits the enzymatic activity of \(\beta\)-secretase on APP with an inhibitory concentration of 0.3 \(\mu\)M (40). *Lanthella basta* Pallas is commonly known as elephant ear sponge, which represent the *Lanthellidae* family. Bastadin is considered as a potential anti-amyloidogenic factor able to reduce amyloid precursor protein (APP) processing through inhibitory activity on BACE1 (40).

Galantamine, an alkaloid found in the marine *Amaryllidaceae* family. It is under Phase III clinical trial and is predicted to cross the blood-brain barrier (BBB) (41). Galantamine has a unique dual mode of action. Galantamine treat symptoms of mild to moderate dementia in AD patients. It exerts reversible, competitive inhibition of acetylcholinesterase (AChE) and allosteric modulation of nicotinic ACh receptors (42). Further; studies are needed to elucidate the efficiency of acetylcholinesterase (AChE) inhibitor from sponges.

5.5. Manzamine A

Manzamine A is a marine alkaloid obtained from *Okinawan sponge Haliclonasp*. It is a potent glycosgen synthase kinase 3 (GSK3) inhibitor at a concentration of 25 mM. GSK3 is involved in the phosphorylation of tau and it’s over activity leads to memory impairment, tau hyper phosphorylation, increased inflammation and amyloid production (43). GSK-3 is a serine/threonine kinase and phosphorylates intracellular targets, including \(\beta\)-catenin, glycogen synthase, elf2Be, GATA4, myocardin, c-Jun, cyclin D1, and N-Myc, thereby regulating various key biological processes, including glucose regulation, apoptosis, protein synthesis, cell signaling, cellular transport, gene transcription, proliferation, and intracellular communication (44). GSK-3\(\beta\) is also associated with several neurodegenerative diseases including AD and PD (45,46,47).

Manzamine A inhibits GSK-3\(\beta\) and CDK5, and reduces tau phosphorylation in human neuroblastoma cells (43). Manzamine A interacts with the protein FKB12, resulting in inhibition of the mTOR complex and up regulation of autophagy. Manzamine A increases autophagy which activates autophagy through an mTOR-independent pathway (48). mTORC1 and mTORC2 are two signaling complexes in the mammalian target of rapamycin (mTOR) pathway that regulates autophagy. mTOR is activated downstream of PI3KAKT, a pathway that is commonly dysregulated in neurodegeneration. Cellular stress leads to downregulation of mTOR1 activity that triggers autophagy and mTOR inhibitors, including rapamycin, have been shown to induce autophagy in neurodegeneration (49).

Manzamine A has the ability to inhibit several different kinases (GSK-3\(\beta\), GSK-3\(\alpha\), CDK1, PKA, MAPK, and CDK5) and decrease the hyperphosphorylation of tau protein mediated by GSK-3 in human neuroblastoma cell cultures (43). Manzamine A specifically inhibits GSK-3\(\beta\) and CDK5 (the two key players in the hyperphosphorylation of tau protein in AD) and is ineffective toward others kinases tested. Kinetic studies indicated an ATP non-competitive inhibition regarding GSK-3 (43) while substrate competitive inhibition has been experimentally investigated (50). Manzamine A is a noncompetitive inhibits GSK-3\(\beta\) via a site distinct from the ATP binding pocket (51). Further studies are required to elucidate the efficacy of inhibitors of GSK3 derived from sponges.

Marine sponges serve as alternative source to synthetic ingredients that can contribute to neuroprotection by being a part of pharmaceuticals and functional foods. The wide range of biological activities associated with natural compounds derived from marine sponge such as gracilins, bastadins, galantamine and manzamine A increase the potential to expand the neuroprotective effects and health beneficial values of marine sponge in the pharmaceutical industry. Most of the biological and neuroprotective activities of marine sponge and its natural compounds have been observed in vitro or in vivo. Further research
studies and clinical trials are in need to investigate neuroprotective activities of sponges in humans.

5.6. Tramiprosate (Homotaurine)

Tramiprosate occurs in seaweed. It is a glycosaminoglycan that can prevent the formation of Aβ fibrils in TgCRND8 mice (52). It crosses the murine blood-brain barrier (BBB) to exert its activity. Tramiprosate, which targets soluble amyloid β (Aβ) peptide, represents a new and promising therapeutic class of drugs for the treatment of AD. It is a sulfated glycosaminoglycan mimetic preventing aggregation of Aβ peptide (53).

Homotaurine was reported to exhibit synergistic properties; neuro-protection associated with reduced calpain activity, up-regulation of the phosphoinositide 3-kinase (PI3K)/Akt pathway, and inhibition of glycogen synthase kinase-3β (GSK-3β) (54,55). Homotaurine isolated from red marine algae was evaluated in phase III clinical trials in mild-to-moderate AD (56), being found having no sufficient clinical efficacy (57). Homotaurine in preclinical models possess neuroprotective effect inhibiting Aβ activity and by γ-aminobutyric acid type A receptor affinity. It has been suggested that homotaurine-dependent effects, related to changes of cortical GABA transmission, may ameliorate the cholinergic transmission (58).

Safety for human subjects is a highly concerned fact in drug development. One of the potential drawbacks associated with SIRT1 activation is the over consumption of NAD+, an important bio-

Figure 2. A hypothetical model depicting cell signaling pathways in the neuroprotective actions of the marine algae Manzamine A with special emphasis towards Alzheimer disease (AD). A group of Manzamine A products appear to activate unknown signaling pathways (dotted lines) to activate neurotrophic (CREB) and antioxidant (Nrf2-ARE) defense systems in neurons. Fibroblast growth factors (FGFs) activate FGFR1 induces Ras-MEK and PLCγ-PKC signaling pathways which in turn activate CREB and Nrf2. Brain derived neurotrophic factor (BDNF) and Manzamine A activate TrkB induces PLCγ-PKC and PI3K-Akt signaling pathways that activate CREB and may activate Nrf2. Insulin receptors (IRs) activated by insulin or IGFs induce IRS-1-PI3K-Akt signaling pathway that activatesCREB and maybe Nrf2. Activated Akt inhibits mTOR to activate autophagy, increases APP excretion and IDE expression to reduce Aβ peptides, and inhibits GSK3β to reduce phosphorylated tau. Activated CREB enhances synaptic transmission, neuron survival, and learning and memory. Increase in the expression of antioxidant and detoxifying enzymes involved in Fe2+ homeostasis, redox regulation, and GSH synthesis and metabolism is activated by Nrf2-ARE complex. Activated Nrf2 also enhances mitochondrial biogenesis by increasing the expression of PGC1α, TFAM, Nrf1, and Bcl-2. (↑: increases; blue arrows: activate/cause; red lines: inhibit; light blue dotted arrows: may activate) (23).
energetic molecule in the cell. Energy depletion has also been suggested to play a major role in neuronal cell-death in the neurodegenerative diseases (59). Homotaurine has the ability to activate sirtuin-1 (SIRT1), a member of the mammalian sirtuins that are important for neuronal plasticity, cognitive functions, as well as protection against aging-associated neuronal degeneration, and cognitive decline (60). The clinical efficacy of homotaurine has been extensively studied in several randomized, double-blind, placebo-controlled phase I, II, and III clinical trials, showing significant positive effects on secondary endpoints in patients with AD (56). Thus, the compounds that are capable to activate the sirtuins might be potential lead therapeutics in neurodegeneration.

5.7. Fucoidan

Fucoidan isolated from brown swage Fucus vesiculosus, protect rat cholinergic neuronal death induced by Aβ1–42 (61). Caspase-9 and caspase-3 are two of several central components of the machinery responsible for apoptosis. Therefore, the ability of fucoidan to block the activation of caspase-9 and caspase-3 suggest that inhibition of neuronal death by fucoidan mainly occurs through apoptotic inhibition.

In neurodegenerative diseases, apoptosis might be pathogenic, and targeting this process might mitigate neurodegenerative diseases (62,63). Fucoidan treatment is found to reduce the inhibitory effect of Aβ on the phosphorylation of protein kinase C (PKC) which has been demonstrated to prevent Aβ neurotoxicity and stimulate the survival of neurons. PKC causes GSK-3β inactivation and this inactivation in turn leads to the accumulation of cytoplasmic β-catenin and the subsequent translocation of β-catenin to the nucleus, causing TCF/LEF-1-dependent transcriptional activation of growth and differentiation related genes, which is required to stimulate neuronal survival (64).

Luo et al. demonstrated that fucoidan protect against 1-methyl-4-phenyl-1, 2,3,6-tetrahydropyridine (MPTP) induced neurotoxicity in animal model of Parkinsonism (C57/BL mice) and dopaminergic (MN9D) cells (65). The mechanisms of protection provided by fucoidan may partly relate to its anti-oxidative activity. Role of fucoidan to protect human neuronal (NT2) cells against H$_2$O$_2$-induced neurotoxicity have also been demonstrated (66). Lee et al. demonstrated fucoidan treatment resulted in an increase in cell proliferation of human neuroblastoma (SH-SYSY) cell induced by Aβ (67). Fucoidan was able to protect PC12 cells.
against $H_2O_2$-induced apoptosis via reduction of reactive oxygen species (ROS) levels and activation of phosphatidylinositol-3-kinase (PI3K)/Akt survival pathway (68). Fucoidan exhibits anti-inflammatory property in the brain (69) and it can be able to inhibit cellular and neurotoxic effects of Aβ in rat cholinergic basal forebrain neurons via blocking the generation of ROS. Fucoidan could be beneficial for maintaining the locomotor activities, striatal dopamine and survival of nigral dopaminergic neurons degeneration in MPTP-induced Parkinsonism in C57/BL mice (61)

Sirtuin (SIRT)1 has been linked to the control of metabolic processes in adipose tissue, liver and muscle through the regulation of the nuclear receptor peroxisome-proliferator activated receptor-γ (PPARγ) and its transcriptional co-activator PPARγ co-activator-1α (PGC-1α) (70). The neuroprotective effect of fucoidan might be partly mediated by enhancing mitochondrial respiratory function through the PGC-1α/NRF2 pathway. Further studies are needed to investigate the useful effect of fucoidan in the neurodegenerative diseased states.

5.8. Phlorotannins

Phlorotannins are tannins found in brown algae family such as Alariaceae, Fucaceae and Sargassaceae in the species of *E. cava*. It is related with the increment of major central neurotransmitters in the brain, particularly of ACh, by inhibiting the activity of acetylcholinesterase (AChE). It has inhibitory activity against AChE and butyrylcholinesterase (BuChE) (71). Phlorotannins have been demonstrated to inhibit BACE-1 (72). The currently available medicines for AD are AChE inhibitors and suppression of BACE-1 by phlorotannins is anticipated to enhance the medications for AD patients.

6. CONCLUSION

Alzheimer’s disease (AD) is the most prevalent neurodegenerative disease heading as one of the major social and economic hurdles in the society. Being devoid of any specific diagnostic as well as treatment practices, AD is facing rampant in the curative strategies. Commercially available drugs stay selective in relieving symptoms like memory deficits, are unable to revert or stop the onset or delay the progression of the disease. High cost and adverse side effects of drugs in aged individuals under treatment, entail scientific research to fall on natural treatment practices encircling bioactive compounds from herbal as well as marine resources. Beneficence of marine bioactive compounds in exerting neuroprotection so far, is highly applauded yet it is an arduous task. Future studies should continue to probe marine environment for infinite wellspring of neuroprotective drugs combining innovative technologies and place a perpetual spot in scientific and pharmaceutical application.

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