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Review Article
Can Marine Products Improve Alzheimer's Disease

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Abstract

Alzheimer's disease is an irreversible chronic neurodegenerative disease which is the most common cause of dementia among older adults. According to amyloid hypothesis, cholin neurotransmitters have important roles in CNS memory function, therefore cholinesterase inhibitors can improve the Alzheimer's symptoms. In recent decades, marine creatures have become interested for their huge medicinal effects and potential of pharmaceutical preparations. Marine classifications contain pharmacologically active compounds with capibilities for improvement of cognitive disorders. This article provides a comprehensive overview of cholinesterase inhibitors from marines in 4 categories contain seaweeds, marine sponges, coelenterates and other invertebrates over the 47 years from 1970 to 2017 which resulted into important bioactive extracts and isolated compounds which representing a diverse range of structural classes such as pyrrole derivatives, sesquiterpene acetates, tetrazacyclopentazulene, bromotyrosine derivatives, plastoquinones, farnesylacetones and poly-alkylpyridinium polymers (Poly-APS). For each structural group, the important compounds with cholinesterase inhibition activities were introduced. The result showed marins can be considered as important sources to discover new cholinesterase inhibitiors.

Keywords: Marine; Alzheimer's disease; Acetylcholinesterase; Butyrylcholinesterase.

Introduction

Alzheimer's disease (AD) is a progressive and neurodegenerative disorder of hyppocampus and neocortex. AD is characterized by the deficits in the cholinergic system and absence of beta amyloid (Aβ) in the form of amyloid plaques. The significant role of cholinergic system is the regulation of learning, memory and emotional responces. Brain atrophy is the most obvious clinical observation in AD that the level of acetylcholin (ACh), as a neurotransmitter, is decreased due to rapid hydrolysis by acetylcholinesterase (AChE) [1, 2]. According to amyloid hypothesis, AChE involves in non-cholinergic secondary functions that change the position of Aβ in the senile plaques which resulted to dysfunction of cholinergic neurons in the basal forebrain moiety and cognitive decline in AD patients [3, 4]. Additionaly, In AD, the abnormal phosphorylation of specific sites on tau inhibit

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microtubules binding ability and Aβ aggregation [5]. On the other hand, some reports indicate that the pathogenesis of Alzheimer's disease is linked to the abnormal metal interaction with Aβ as well as metal-mediated oxidative stress. Formation and accumulation of ROS within cells can exacerbate the disease pathogenesis by lipid, protein, DNA and RNA damage [6, 7]. These mechanisms cause the loss of brain neurons involved in cognitive disease [8]. *In general, AD is an age-related disorder and a prevalent factor of dementia in elderly people.* Therefore, the inhibition of AChE enzyme, which catalyzes the breakdown of ACh, is one of the most prescribed treatment strategies for AD [9, 10]. Hodges et al. showed that inhibition of AChE plays a key role not only in enhancing the cholinergic neruotransimission, but also in reducing the aggregation of Aβ in AD [11, 12]. The use of cholinesterase inhibitors (ChEIs) has been proven as the most useful therapeutic strategy for this type of dementia [13]. The brain of mamals contains two major forms of cholinesterases including AChE and butyrylcholinesterase (BuChE) that play important roles in cholinergic signaling. In human brain, BuChE is placed in glial cells and neurons [14, 15]. Nature is a rich and diverse source for discovery of new biological and chemical substances. In many type of traditional medicine systems, numerous plant's remedies have been used for traetment of cognitive disorders [16]. Natural products provide significant clues to develop medications which can be considered as novel lead compounds. They possess good biological activity against a wide range of unexplored diseases [17]. Some of the biological targetings of natural products are on slowing down the progress of Alzheimer's disease [18]. Galantamine and rivastigmine are among the plant-based AChE inhibitors, which have been approved by FDA [19]. Marine organisms are the wide resources for exploring novel compounds leading a new generation of drugs into the market for treatment of diseases with novel mechanism of action [20]. Ziconotide has been the first marine-derived peptide drug on the market as a reversible N-type voltage-sensitive calcium channel blocker [20, 21]. The pharmacological activities of marine compounds in the nervous system involve three areas contains stimulation of neurogenesis, targeting of receptors and neuron specific molecules [22]. Numerous marine invertebrates have shown biological activities and are helpful for the discovery of bioactive agents [23]. Among near to 7000 nomenclatured marine natural products, 25% classified into algae, 33% sponges, 18 % coelenterates (sea whips, sea fans and soft corals), and 24% from other invertebrate phyla such as ascidians (called tunicates), opisthobranch molluscs (nudibranchs, sea hares), echinoderms (starfish, sea cucumbers) and bryozoans [24, 25].

The first compound with AChE inhibitory activity obtained from marine sources was 4-acetoxy-plakinamine B (stigmastane) (36), an steroidal alkaloid from marine sponge *Corticium* sp. [22, 26]. Over the last decades significant investigations have been carried out to identify new marine-derivatives. These initiatives have been accompanied by specific programs directed towards the collection and characterization of marine natural compounds [27]. The present review focuses on AChEIs from marine resources with a brief available information of their chemical structures.

Seaweeds (marine Algae)

Seaweeds are a diverse macroscopic, saltwater-dwelling type of plants which attacks the rocks in the intertidal zone on the substratum they can grow. According to seaweeds pigmentation, they broadly classified into Chlorophyceae (green algae), Phaeophyceae (brown algae) and Rhodophyta (red algae) [28, 29]. Algae are unicellular or multicellular organisms which have chlorophyll A and the accessory pigment β-carotene. They are tubular and surrounded by membranes [30]. Algae are known to be one of the most important producers of biomass in the marine environment and have been known to produce biological active secondary metabolites that might be used in the pharmaceutical industry [31].Two farnesylacetone (1-2) isolated from Korean brown algae, *Sargassum sagamianum,* showed moderate AChE inhibitory effect [32]. Phlorotannins including dieckol (3) and phlorofucofuroeckol (PFF) (4) found in brown *Eisenia* and *Ecklonia* algae, have abilities to inhibit the activity of AChE. Myung *et al.* showed that these compounds regulate the level of major central neurotransmitters in brain and may improve the cognitive performance in patients with neurodegenerative disorders [33]. Furthermore, Yoon *et al.* studied the ethanolic extracts of 27 Korean marine algae, for their AChE inhibitory activities. Among those the extract of *Ecklonia stolonifera* showed a significant inhibition. Two sterols and eight phlorotannins were isolated from *E. stolonifera*. eckstolonol (7) and phlorofucofuroeckol-A (8), exhibited inhibitory effects toward both AChE and BuChE while eckol (5), 6,6'-bieckol (11), 2-phloroeckol (6) and 7-phloroeckol (9) demonstrated selective dose dependent inhibitory activities. However, phloroglucinol and triphlorethol-A, did not inhibit the cholinesterase enzymes. It may assume that degree of polymerization and closed-ring structure of phlorotannins is important for the inhibitory potential on cholinesterase inhibition [34-36]. Seven

seaweeds collected by Wendy *et al.* in South Africa such as *Caulerpa racemosa var. laetevirens, Codium capitatum, Halimeda cuneata* represented AChE inhibitory effects [37, 38]. Two plastoquinones, sargaquinoic acid (12) and sargachromenol (13),were isolated from *Sargassum sagamianum* showed moderate AChE inhibition [39]. In an experiment performed by kartal *et al.*, the extracts of 13 algae, two fresh-water plants and one sea grass were assessed for AChE inhibition. Among them, *Spirogyra gratiana* possessed the highest activity at concentration of 2.0 mg/ml [40]. The investigation on 11 seaweeds collected from Hare Island, Gulf of Mannar, Tamil Nadu in India, represented high inhibitory activities on AChE for the methanol extracts of *Gracilaria gracilis*, *Cladophora fasicularis and Sargassum* sp. as well as BuChE inhibition effects for *Gracilaria gracilis, Gracilaria edulis* and *Sargassum* sp. [41]. Fucoidan is a sulfated marine-derived polysaccharide [42]. Gao *et al*. showed excellent neuroprotective effects of fucoidan against Aβ-induced learning and memory impairment due to regulating the cholinergic system, reducing oxidative stress and inhibiting the cell apoptosis in AD model of rats [43]. Suganthy *et al.* examined the methanol extracts of 8 seaweeds, collected from Hare Island, Gulf of Mannar, Marine Biosphere Reserve, Tamil Nadu, India for cholinesterase inhibition. *Hypnea valentiae, Ulva retiuclata* showed dual cholinergic inhibition on both AChE and BuChE [13, 44]. Investigation on AChE inhibition of the enzyme-assisted extracts from *Enteromorpha prolifera* was carried out by Ahn *et al*. The extract of flavourzyme, a type of protease, showed the highest AChE inhibitory activity (89.92%) followed by neutrase extract (83.18%) and protamex extract (80.82%) as well as alcalase extract (78.84%). In the carbohydrase types, the extracts from promozyme (93.64%), maltogenase (92.22%), viscozyme (86.08%), termamyl (78.68%) and celluclast (78.35%) showed potent inhibitory activities [45]. The study on the edible brown alga, *Eisenia bicyclis* and its active components showed the oxidative stress and reduced neuronal cell death, may have potential to be used as a dietary neuroprotective agent in AD. Among six phlorotannins, eckol and 7-phloroeckol (9) significantly decreased Aβ-induced cell death [34-36, 46]. In the recent studies, the correlation between antioxidant and cholinesterase inhibitory activity were verified [47]. A molecular docking study performed by Jung and colleagues in 2010 on phlorotannins from *E. bicyclis* for human beta-secretase1 inhibitory activity (hBACE1) showed these compounds have beneficial use in prevention and improvement of AD [48]. Furthermore, the EtOAc and n-BuOH fractions exhibited higher antioxidant and cholinesterase inhibiting activities [49]. Fang *et al.* identified four new glycolipids in *n*-hexane and dichloromethane fractions of *Capsosiphon fulvescens* that capsofulvesin A-C (14-16), exhibited AChE inhibitory activities [50]. Syad and colleagues showed that benzene extract of *Gelidiella acerosa* had significant inhibitory activities on both AChE and BuChE [51]. Kawee-ai *et al.* revealed that fucoxanthin (17) purified from microalga *Phaeodactylum tricornutum* expressed strong selective activity on BuChE versus AChE inhibition. Fucoxanthin is a marine carotenoid in brown seaweeds interacts with the peripheral anionic site of AChE and inhibits within non-competitive manner [52]. A comparison among the extracts of eight different types of seaweeds from Persian Gulf by Ghannadi *et al*. showed highest AChE inhibitory activity for *Sargassum boveanum* while *Cystoseira indica* exhibited the least effect. The species from Rhodophyta (*Gracilaria corticata* and *Gracilaria salicornia*) represented moderate activities [53]. Syad *et al*. suggested that presence of triterpenoid in the dichloromethane extract of *S*argassum *wightii* might be the possible reason for its potential antioxidant and anti-cholinesterase activities [54]. Chitosan, a linear polysaccharide obtained from deacetylation of chitin, has low solubility and must be converting to oligosaccharide, chitooligosaccharides (COS) [55-57]. Lee and colleagues, studied the AChE inhibitiry activities of six kinds of COS with different molecular weights (MW) from 50 to 90% of chitosan deacetylation. These findings suggest the degree of deacetylation of COS is a key factor for AChE inhibition [58]. In another study, Yoon *et al.* synthesized three COS derivatives aminoethyl-COS, dimethylaminoethyl-COS and diethylaminoethyl-COS. Then their AChE inhibitory activities were evaluated [59]. Seven classes of marine metabolites had reported to have anti-cholinesterase activity such as: sesquiterpene acetates [60-62], pyrrole derivatives [63, 64], tetraza cyclopentazulenes [65], bromo tyrosines [66-68], plastoquinones [39], farnesyl acetones [33] and poly alkylpyridinium polymers [69-71]. These classes of marine metabolites also were evaluated by a docking simulation study to determine the most probable mechanism of inhibition leading to development of anti-cholinesterase drugs with dual functions as AChE and Aβ-aggregation inhibitors [72]. In another study, the inhibitory activities of three Malaysian seaweeds (*Padina australis, Sargassum polycystum*, *Caulerpa racemosa*) were assessed on cholinesterase inhibition. *S. polycystum* and *C. racemosa* exhibited AChE inhibitory activities. Moreover, *C. racemosa* and *P. australis* were effective on BuChE inhibition [53, 73]. Murugan *et al.*

demonstrated that *Padina australis* possesses an appreciable amount of polyphenols with AChEI properties [74]. Bianco and colleagues, evaluated the AChE activities of 14 seaweeds (six Rhodophyta, six Ochrophyta and two Chlorophyta), eleven sponges, two ascidians, one bryozoan and one sea anemone species collected along the Brazilian and Spanish coast. Although all species showed AChE inhibition, the results indidated that extracts from seaweeds are more effective than marine invertebrates. *Hypnea musciformis*, *Laurencia translucida* and *Palisada perforata* exhibited the highest activities [75]. Machado *et al.* documented the chemical composition of *Ochtodes secundiramea* extract containing halogenated monoterpenes by GC–MS. This extract showed 48% AChE inhibition at the concentration of 400 µg/ml [76]. In some other studies, monoterpenes identified as a reversible competitive inhibitors of AChE [77, 78]. Due to amyloid hypothesis that Aβ-aggregation disrupts the brain cells and resulting in complete degeneration of neurons [3, 4, 11, 51, 72], Syad *et al.* demonstrated that *Gelidiella acerosa* might have direct interaction with Aβ 25–35 and prevention the aggregation process [79]. A review about neuroprotective activities of marine organisms in the experimental models of Alzheimer, Parkinson and ischemic brain stroke presented by Choi in 2015 demonstrated their molecular targets and mechanism of actions [33, 35, 39, 48, 49, 80]. Rengasamy *et al*. collected eight seaweeds from the intertidal region in KwaZulu-Natal, South Africa for AChE inhibition. The result showed *Halimeda cuneata* exhibited the highest activity [81]. Shanmuganathan and colleaguse evaluated the anti-cholinesterase activities of marine seaweed *Padina gymnospora* that the acetone extract showed the highest inhibitory activity. The assessment of amyloidogenic potential for *P. gymnospora* was performed with the same authors. The results suggested that the bioactive compound α-bisabolol (18) isolated from algae had a significant inhibition for both AChE and BuChE comparing to donepezil and support its potential for the treatment of neurological disorders [82, 83]. Screening of cholinesterase inhibitory activity from microalgae were evaluated by kumar and colleagues that chloroform extract of *Oscillatoria* sp. exhibited the highest inhibition (87%) on AChE while acetone extract of *Phormidium* sp. showed maximum inhibition (36%) for BuChE [84]. In 2016, Alghazwi *et al.* focused on macroalgae-derived compounds with neuroprotective activities for prevention and treatment of neurodegenerative diseases such as AD [85]. Syad *et al.* demonstrated the neuroprotective effect of macroalga *Gelidiella acerosa* and determined the AChE and BuChE inhibitory activities by Ellman method [86, 87]. The results revealed the active component, phytol (35), has cholinesterase inhibitory potential at 5–25 mg/ml [51]. All the cholinesterase inhibitor substances from seaweeds are presented in Table 1 and the structures are shown in Figure 1.

Table 1. Cholinesterase inhibitory activities of compounds from seaweeds

Marine source	Type	Structure Number	Compound(s)/Classification	AChE inh. (IC_{50} or %)	BuChE inh. (IC_{50} or %)	Ref.
Sargassum sagamianum	Brown alga	1	(5E,10Z)-6,10,14-trimethylpentadeca-5,10-dien-2,12-dione/farnesylacetone	65 µM	34 µM	[32, 39]
Sargassum sagamianum	Brown alga	2	(5E,9E,13E)-6,10,4-trimethylpentadeca-5,9,13-trien-2,12-dione/farnesylacetone	48 µM	23 µM	[32, 39]
***Eisenia* & *Ecklonia* sp.**	Brown algae	3	dieckol/phlorotannin	17.1 µM	-	[33, 34]
***Eisenia* & *Ecklonia* sp.**	Brown algae	4	phlorofucofuroeckol/phlorotannin	27.4 µM	-	[33, 34]
Ecklonia stolonifera	Brown alga	5	eckol/phlorotannin	20.5 µM	-	[33, 34]
Ecklonia stolonifera	Brown alga	6	2-phloroeckol/phlorotannin	38.1 µM	-	[33, 34]
Ecklonia stolonifera	Brown alga	7	eckstolonol/phlorotannin	42.6 µM	0.27 µM	[33, 34]
Ecklonia stolonifera	Brown alga	8	phlorofucofuroeckol-A/phlorotannin	4.9 µM	136.7 µM	[33, 34]
Ecklonia stolonifera	Brown alga	9	7-phloroeckol/phlorotannin	21.1 µM	-	[33, 34]
Ecklonia cava	Brown alga	10	phlorofucofuroeckol-A/phlorotannin	16 to 96.3 µM	0.95 µM	[35]
Ishige okamurae	Brown alga	11	6,6'-bieckol/phlorotannin	46.42 µM	-	[36]

Table 1. Ctd

Marine source	Type	Structure Number	Compound(s)/Classification	AChE inh. (IC_{50} or %)	BuChE inh. (IC_{50} or %)	Ref.
Caulerpa racemosa	Green alga	-	Crude extract	<9 mg/ml	-	[35]
Codium capitatum	Green alga	-	Crude extract	<9 mg/ml	-	[35]
Halimeda cuneata	Green alga	-	Crude extract	<9 mg/ml	-	[35]
Ulva fasciata	Green alga	-	Crude extract	<9 mg/ml	-	[35]
Amphiroa bowerbankii	Red alga	-	Crude extract	<9 mg/ml	-	[35]
Amphiroa ephedraea	Red alga	-	Crude extract	<9 mg/ml	-	[35]
Dictyota humifusa	Brown alga	-	Crude extract	<9 mg/ml	-	[35]
Sargassum sagamianum	Brown alga	12	Sargaquinoic acid/plastoquinone	23.2 µM	-	[39]
Sargassum sagamianum	Brown alga	13	Sargachromenol/plastoquinone	32.7 µM	-	[39]
Spirogyra gratiana	Green alga	-	Crude extract	42.5 %	-	[40]
Gracilaria gracilis	Red alga	-	Crude extract	1.5 mg/ml	1.5 mg/ml	[41]
***Sargassum* sp.**	Brown alga	-	Crude extract	1 mg/ml	0.6 mg/ml	[41]
Cladophora fasicularis	Green alga	-	Crude extract	2 mg/ml	-	[41]
Gracilaria edulis	Red alga	-	Crude extract	3 mg/ml	1.3 mg/ml	[41]
Hypnea valentiae	Red alga	-	Crude extract	2.6 mg/ml	3.9 mg/ml	[9,42]
Ulva retiuclata	Green alga	-	Crude extract	10 mg/ml	6.5 mg/ml	[13, 44]
Capsosiphon fulvescens	Green alga	14	(2S)-1-O-(6Z,9Z,12Z,15Z-octadecatetraenoyl)-2-O-(4Z,7Z,10Z,13Z-hexadecatetraenoyl)-3-O-β-D-galactopyranosyl glycerol (capsofulvesin A)/glycolipid	53.1 mg/ml	>132 mg/ml	[50]
Capsosiphon fulvescens	Green alga	15	(2S)-l-O-(9Z,12Z,15Z-octadecatrienoyl)-2-O-(10Z,13Z-hexadecadienoyl)-3-O-β-D-galactopyranosyl glycerol/(capsofulvesin B)/glycolipid	51.3 µM	114 µM	[50]
Capsosiphon fulvescens	Green alga	16	(2S)-1-O-(6Z,9Z,12Z,15Z-octadecatetraenoyl)-3-O-β-D-galacatopyranosyl glycerol/ (capsofulvesin C)/glycolipid	825 µM	185.5 µM	[50]
Gelidiella acerosa	Red alga	-	Crude extract	54.2 %	78.4 %	[51]
Phaeodactylum tricornutum	Micro alga	17	Fucoxanthin/xanthophyll	-	1.9 mM	[52]
Sargassum boveanum	Brown alga	-	Crude extract	1 mg/ml	-	[53]
Sargassum oligocystum	Brown alga	-	Crude extract	2.5 mg/ml	-	[53]
Sargassum wightii	Brown alga		Petroleum ether extract	19.3 mg/ml	17.9 mg/ml	[54]
Sargassum wightii	Brown alga		Hexane extract	46.8 mg/ml	32.7 mg/ml	[54]
Sargassum wightii	Brown alga		Benzene extract	27.2 mg/ml	12.9 mg/ml	[54]
Sargassum wightii	Brown alga		Dichloromethane extract	50.5 mg/ml	36.1 mg/ml	[54]
Padina australis	Brown alga	-	Dichloromethane extract	0.5 mg/ml	>0.2 mg/ml	[73]
Sargassum polycystum	Brown alga	-	Hexane extract	0.1 mg/ml	>0.2 mg/ml	[73]
Caulerpa Racemosa	Green alga	-	Hexane extract	0.1 mg /ml	0.1 mg/ml	[73]
Padina australis	Brown alga	-	Polyphenolic fraction	1.5 mg/ml	-	[74]
Hypnea musciformis	Red alga	-	Crude extract	14.4 µg/ml	-	[75]
Laurencia Translucida	Red alga	-	Crude extract	16.4 µg/ml	-	[75]

Marine sponges, sponge-derived microbes and fungi

Marine sponges belonging to the phylum Porifera, have a high diversity of bioactive components [88, 89]. the sponge-derived chemicals with bioactive properties are prominent candidate for future pharmaceutical applications [90, 91]. Marine sponges contain diverse communities (bacteria, microalgae, fungi) which can comprise up to 40% of the sponge volume [92, 93]. In 1998, Sepčić *et al*. isolated large polymeric 3-alkylpyridinium salts, from marine sponge *Reniera sarai* with AChE inhibitory effect. The polymerization degree and the alkyl chains length, may play important roles for their inhibition activities [69-71].

The steroidal alkaloid, 4-acetoxy-plakinamine B

Table 1. Ctd

Marine source	Type	Structure Number	Compound(s)/Classification	AChE inh. (IC_{50} or %)	BuChE inh. (IC_{50} or %)	Ref.
Porphyra perforata	Red alga	-	crude extract	14.9 µg/ml	-	[75]
Halimeda cuneata	Green alga	-	crude extract	70 µg/ml	-	[81]
Padina gymnospora	Brown alga	-	acetone extract	<150 µg/ml	<150 µg/ml	[82]
Padina gymnospora	Brown alga	18	α-bisabolol/monocyclic sesquiterpene alcohol	<10 µg/ml	<10 µg/ml	[82]
***Oscillatoria* sp.**	Micro alga	-	chloroform extract	87.5 %	-	[84]
***Phormidium* sp.**	Micro alga	-	acetone extract	-	36.1 %	[84]
Gloiopeltis furcate	Red alga	19	2-(3-hydroxy-5-oxotetrahydrofuran-3-yl) acetic acid	1.4 µg/ml	12.6 µg/ml	[143]
Gloiopeltis furcate	Red alga	20	glutaric acid	5.6 µg/ml	41.5 µg /ml	[143]
Gloiopeltis furcate	Red alga	21	succinic acid	5.7 µg /ml	-	[143]
Gloiopeltis furcate	Red alga	22	nicotinic acid	1.1 µg/ml	20.8 µg/ml	[143]
Gloiopeltis furcate	Red alga	23	(E)-4-hydroxyhex-2-enoic acid	12.2 µg/ml	31.5 µg/ml	[143]
Gloiopeltis furcate	Red alga	24	cholesterol/sterol	1.2 µg/ml	-	[143]
Gloiopeltis furcate	Red alga	25	7-hydroxycholesterol/sterol	2.3 µg/ml	5.5 µg/ml	[143]
Gloiopeltis furcate	Red alga	26	uridine/nucleoside	1.6 µg/ml	35.8 µg/ml	[143]
Gloiopeltis furcate	Red alga	27	glycerol/simple polyol	1.6 µg/ml	8 µg/ml	[143]
Gloiopeltis furcate	Red alga	28	5-(hydroxymethyl)-2-methoxybenzene-1,3-diol	7.4 µg/ml	32.6 µg/ml	[143]
Gloiopeltis furcate	Red alga	29	(Z)-3-ethylidene-4 methylpyrrolidine-2,5-dione	4.1 µg/ml	75.2 µg/ml	[143]
Gloiopeltis furcate	Red alga	30	loliolide/carotenoid	7.5 µg/ml	-	[143]
Gloiopeltis furcate	Red alga	31	cholesteryl stearate/sterol	6.3 µg/ml	-	[143]
Gloiopeltis furcate	Red alga	32	cis-5,8,11,14,17 eicosapentaenoic acid/fatty acid	11.5 µg/ml	6.6 µg/ml	[143]
Gloiopeltis furcate	Red alga	33	α-linolenic acid/fatty acid	12.5 µg/ml	15.9 µg/ml	[143]
Gloiopeltis furcate	Red alga	34	dibenzo[1,4]dioxine- 2,4,7,9-tetraol/phlorotannin	84.4 µM	-	[85]
Gelidiella acerosa	Red alga	35	phytol/acyclic diterpene alcohol	2.7 mg/ml	5.8 mg/ml	[144]

(stigmastane) (36), isolated from the methanol extract of Thai sponge *Corticium* sp., showed a prominent AChE inhibitory activity at 0.1 mg/ml [26, 94]. *In a study of* Orhan *and colleagues,* bioactivity of the selected Turkish marine sponges and three compounds from *Agelas oroides* were evaluated for AChE inhibition and only oroidin (37) was active at the concentration of 100 mg/ml [95]. Beedessee *et al.* examined the AChE inhibitory activities of 134 extracts obtained from 45 species of marine sponges collected from Mauritius waters [96].The inhibition was determined by Ellman colorimetric method modified by Eldeen *et al.* [86]. A few number of AChE inhibitor compounds have been isolated from the bacterial associated sponge sources. The first bacterial report on AChEIs was about *Streptomyces antibioticus*. Cyclophostin was another AChEI isolated from *Strepomyces lavendulae* [97, 98]. In the other study, a new pyrroloquinoline alkaloid, marinoquinoline A, was found in a marine gliding bacterium, *Rapidithrix thailandica*. The AChE inhibitory activity of this compound was discovered because of its similarities with tacrine structure. Another research showed a novel marine bacteroidetes member, *Ohtaekwangia kribbensis*, also containes marinoquinoline A [99]. Towards finding novel anti-cholinesterase agents from marine sponges associated strain of *Bacillus subtilis* and other marine bacteria, *Siphonodictyon coralliphagum* was introduced for the highest number of AChEIs. Several alkaloid and terpene derivatives with AChE inhibitory activities have been isolated from sponges. In a previous screening, the compound M18SP4Q, which showed the highest AChE inhibition, was originated from *Bacillus subtilis* [100].

The study performed by Wu and colleagues showed *Talaromyces* sp. strain LF458, a fungus associated with sponge *Aulactinia verrucosa*, produces new oxaphenalenones dimers. Talaromycesone B, the new isopentenyl talaroxanthenone, and the compound AS-186c presented AChE inhibition [101]. In another study, El-Hady *et al*. evaluated tyrosinase and AChE inhibitory potential as well as antioxidant and antimicrobial activities of two fungi (FS_1 and FS_3) isolated from the sponges *Amphimedon viridis* and *Agelas* sp., respectively. The results showed only the mycelial extract from the static culture of FS_3 (identified as *Aspergillus sydowii strain W4-2*) revealed inhibition on AChE [102]. In a mentioned study for investigation on 29 marine species, all the sponges extracts showed AChE inhibitory activities [75]. *Geodia barretti* is a Norwegian coast sponge contains two novel brominated

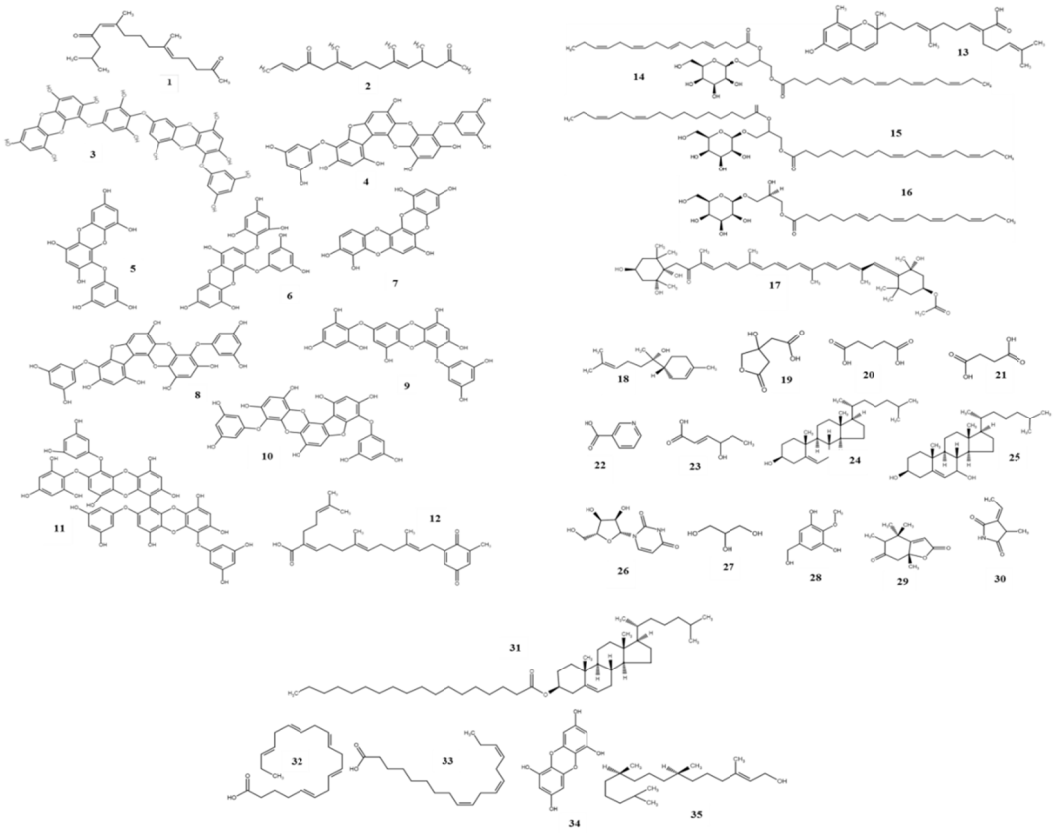

Figure 1. Structures of compounds with cholinesterase inhibitory activities from seaweeds

marine indoles barettin (38) and 8,9-dihydrobarettin (39). The structure–activity investigation was shown the significant AChE inhibitory activity of the brominated indole through combination with natural cationic ligands. The focus on the indole scaffold of barettin and 8,9-dihydrobarettin were not showed any activity against AChE, suggesting that bromine substitution is not enough for bioactivity [103, 104]. Due to reports of brominated compounds isolation (brominated phenylethylamine stryphnusin) by Moodie and co-workers, the authors synthesized some analogues (not shown) which displayed significantly improved anti-cholinesterase activities [104]. From two specimens of genus *Latrunculia*, Botić and colleagues isolated a group of brominated pyrroloiminoquinone alkaloids contains discorhabdin B, L, G and 3-dihydro-7,8-dehydrodiscorhabdin C as a new class of cholinesterase inhibitors. Discorhabdin B (40) and discorhabdin G (41) were the most potent compounds with AChE inhibitory activities [105, 106].

The largest group of alkaloids isolated from marine organisms are pyridoacridines. They have been reported from sponges, ascidians, anemones, tunicates, and mollusk, which are decorated with bright colors. They are in yellow, deep red, orange, blue, and purple colors [107, 108]. Petrosamine (42), a pyridoacridine alkaloid, isolated from a Thai marine sponge, *Petrosia* n.sp., showed an IC_{50} value on a AChE inhibitory assay even lower than galantamine [109]. A group of spirocompounds like aerothionin, homoaerothionin and 11,19-dideoxyfistularin (are not shown) not only block the voltage-dependent calcium channels, but also inhibit AChE and BuChE that both mechanisms are used for treatment of cognitive and neurodegenerative diseases [110]. All the substances with cholinesterase inhibitory activities from sponges are demonestrated in Table 2 and Figure 2, respectively.

Coelenterates, Cnidaria

Marine invertebrates are one of the major groups of biological organisms (Porifera, Cnidaria, Mollusca, Arthropoda, Echinodermata, etc) contains significant number of natural products and secondary metabolites with several pharmacological properties [24]. The

Table 2. Cholinesterase inhibitory activities of compounds from sponges

Marine source	Structure Number	Compound(s)/Classification	AChE inh. (IC_{50} or %)	Ref.
Reniera sarai	-	3-alkylpyridinium salts	3.7 µM	[69, 70]
***Corticium* sp.**	36	4-acetoxy-plakinamine B (stigmastane) /steroidal alkaloid	26.2 %	[22, 94]
Agelas oroides	37	Oroidin/bromopyrrole alkaloid	0.01 mg/ml	[95]
Pericharax heteroraphis	-	Ethyl acetate extract	0.01 mg/ml	[96]
Amphimedon navalis	-	Ethyl acetate extract	36.2 µM	[94]
Geodia barretti	38	Barettin/brominated alkaloid	29.3 µM	[103, 104]
Geodia barretti	39	8,9-dihydrobarettin/brominated alkaloid	1.3 µM	[103, 104]
***Latrunculia* spp.**	40	Discorhabdin B/pyrroloiminoquinone alkaloids	5.7 µM	[105, 106]
***Latrunculia* spp.**	41	Discorhabdin G/pyrroloiminoquinone alkaloids	3.7 µM	[105, 106]
***Petrosia* n. sp.**	42	Petrosamine/pyridoacridine	0.09 µM	[109]

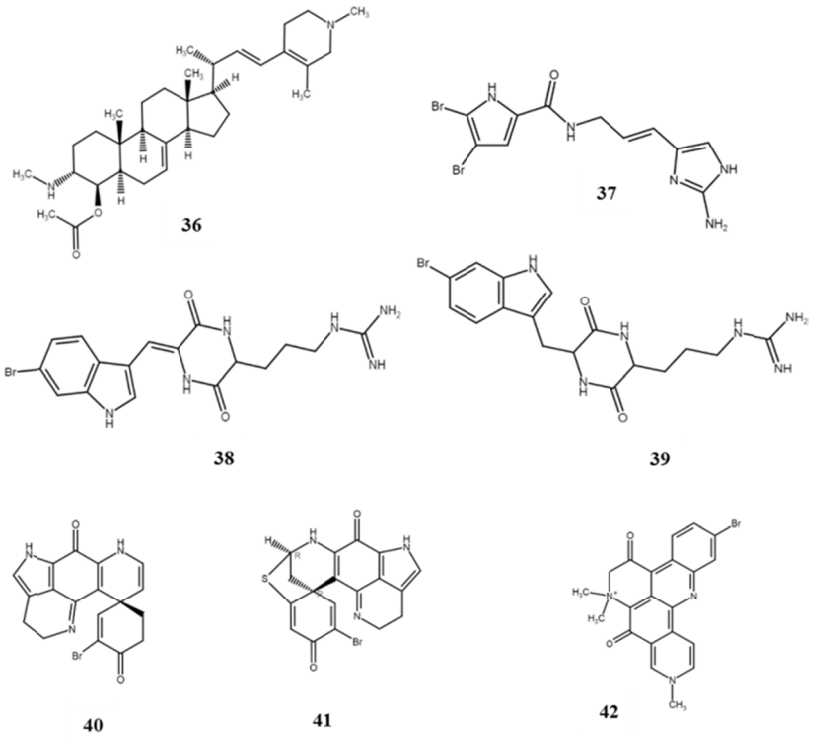

Figure 2. Structures of compounds with cholinesterase inhibitory activities from sponges

phylum Coelenterata is a diverse category of dipoblastic animals which consist of five categories contains a class of Anthozoa and four Medusozoan groups. Anthozoans include sea wasps, sea nettles, sea anemones and corals [111]. Coelenterata includes over 11,000 species that 7500 of them are belonging to the class Anthozoa contains the order Alcyonacea (soft corals) and Gorgonacea (sea fans) with the highest number of bioactive marine compounds. However, the other orders, such as Actiniaria (sea anemones) and Scleractinia (hard corals) have some similar substances [112, 113]. Cnidarians produce two types of alkaloids, zoanthoxanthins and zoanthamine [114-116]. *Turk et al*. isolated several AChE inhibitors from a crust coral *Parazoanthus axinellae* that pseudozoanthoxanthin was the most potent one. In addition parazoanthoxanthin A,

a strong fluorescent pigment synthesized from *P. axinellae* samples obtained from the Bay of Naples, Italy, showed moderate inhibition on AChE from *Electrophorus electricus*, (eeAChE) [65] that may bind to nicotinic acetylcholine receptors (nAChR). Rozman *et al.* used the voltage-clamp technique for evaluation of its effect on Torpedo nAChR (α12βγδ) transplanted to *Xenopus laevis* oocytes [117]. Zooxanthellae are a group of dinoflagellate symbionts living in the tissues of many marine organisms, such as corals, jellyfish and molluscs that make up a large part of the reef widespread. For the use in photosynthesis, the host provides carbon dioxide and other waste products. Scleractinian corals, also called stony or true corals, are members of the phylum Cnidaria, class Anthozoa, order Scleractinia depositing massive amounts of calcium carbonate that make up the structure of coral reefs. Corals (Coelenterata: Alcyonacea) look more like plants than animals, such as sea fans and sea pens which have two roles, secretion of digestive enzymes and absorbtion of digested organic substances from sediments [118]. El-Hady *et al*. separated marine fungus *Emericella unguis* 8429, a coral derived fungus, with AChE inhibitory activity [119]. In another study, the same research group assessed the inhibition of AChE for the soft coral associated fungus *Aspergillus unguis* SPMD-EGY [120]. Alcyonarians are rich sources of unique organic molecules, such as terpenes with significant biological activities [121]. Several new lobane and cembrane diterpenoids were isolated from the soft corals of the genera *Lobophytum* and *Sinularia* with significant AChE-inhibition [122]. Cladidiol (43), a new sesquiterpene from the soft coral genus *Cladiella*, [123], represented AChE-inhibition activity [124]. *Gyrostoma helianthus* is a large anemone which almost be hosted by symbiotic anemone fish [125]. Gomaa and the calleagues were Isolated and characterized a hydrazine derivative with AChE inhibitory activity from *G. helianthus* [126].

Other invertebrates

Bouchet and collegues provided an accurate bibliographical and nomenclatural data for gastropod family-group names. There is not international nomenclature available due to difficulty in establishing the dates and authors. For that reason taxonomist do not insert molluscan family-group names in classifications [127]. Opisthobranches mollusc, *Onchidellu binneyi*, inhabits the rocky intertidal zone, in the Gulf of California. This invertebrate produces a defensive secretion contains onchidal as the major lipid-soluble component [60]. The toxicity of onchidal can be resulted from inhibition of proteins and its structural similarities with acetylcholine. Permanent inhibition of AChE by onchidal, results in potentially deadly cholinergic toxicity. Onchidal and other irreversible inhibitors of AChE are not suitable for direct use as an anti-cholinesterase inhibitors for human diseases but they could have potential for use in insecticides or pesticides [61].

Kigoshi *et al.* isolated turbotoxins A and B from the viscera of the Japanese gastropod, *Turbo marmorata*, that results showed AChE inhibitory effect for turbotoxin A (45) [128]. Bryozoans from the phylum Bryozoa are moss animals, termed zooids that are the most responsible organisms for fouling ship's bottoms and solid surfaces [128]. The perennial marine bryozoan, *Flustra foliacea,* has biologically active brominated alkaloids and monoterpenes as well as some unusual pyrrolo(2,3-*b*)indoles skeleton. Compounds with prenylated physostigmine type marine structures, exhibit AChE inhibitory activities [129-132]. Another study represented the potent BuChE inhibition of isolated debromoflustramine B. Rivera-Becerril and colleagues synthesized both enantiomers of debromoflustramine B. The naturally occurring enantiomer, (-)-176, inhibited human BChE (IC_{50} = 1.37μM) [80, 133, 134]. Marine ascidians are from subphylum Urochordata that their bodies are covered by a substance similar to cellulose, called tunic and considered as a rich source of chemically diverse secondary metabolites [135-138]. Tadesse and colleagues isolated two new dibrominated compounds, pulmonarins A and B, from the sub-arctic ascidian *Synoicum pulmonaria*. Although both of them were non-competitive AChE inhibitors, pulmonarin B (46) was more active [139]. The proposed structures were verified by synthesis. analysis of both compounds revealed their function as reversible, noncompetitive inhibitors. AChE inhibition effects of two new brominated β-carbolines, irenecarbolines A and B (47-48), from solitary ascidian, *Cnemidocarpa irene* were studied by Tadokoro *et al.* The IC_{50} values of tested compounds exhibited concentration-dependent inhibitions [140]. All the cholinesterase inhibitors from invertebrates and the structures are summarized in Table 3 and Figure 3, respectively.

Results

AD is a neurodegenerative disease with multiple etiologies. The inhibition of cholinesterase enzymes are of the most prescribed treatment strategies for AD. The earliest examples of cholinesterase inhibitors, physostigmine and tacrine have been used to treat a range of conditions in AD. Unfortunately, due to the

Table 3. Cholinesterase inhibitory activities of compounds from invertebrates

Marine source	Type	Structure Number	Compound(s)/Classification/Number	AChE inh. (IC_{50} or %)	Ref.
***Cladiella* sp.**	Soft coral	43	Cladidiol/sesquiterpene	67 µM	[123]
Gyrostoma helianthus	Sea Anemone	44	N, N'-bis-(1-methyl-pyridin-2-yl)-hydrazine	43.3 %	[126]
Gyrostoma helianthus	Sea anemone	-	Crude extract	91.9 %	[126]
Turbo marmorata	Gastropod	45	Turbotoxin A	28 µM	[128]
Synoicum pulmonaria	Ascidian	46	Pulmonarin B	20 µM	[139]
Cnemidocarpa irene	Ascidian	47	Irenecarboline A/β-carbolines	0.67 µM	[140]
Cnemidocarpa irene	Ascidian	48	Irenecarboline B/β-carbolines	0.47 µM	[140]

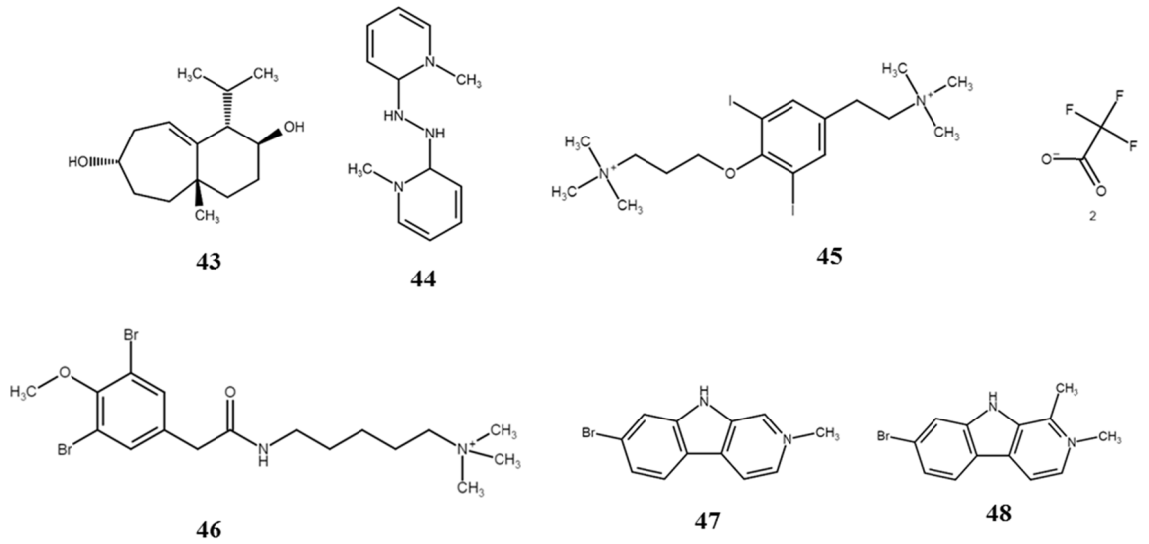

Figure 3. Structures of compounds with cholinesterase inhibitory activities from invertebrates

nature of the biological target and distribution of drugs throughout the body, most of the employed cholinesterase inhibitors induce similar unwanted toxicity and side effects and will face similar challenges to those encountered by drugs that have already advanced to the clinic [141, 142]. For decades, marine environment represent a potential source of new diverse and unique bio-active components. Due to past researches on marine organisms, novel lead ant-icholinesterase compounds with promising activity and structurally diverse, inspirational scaffolds were explored. But there is no marine natural product as AChE inhibitor in clinical uses. Determination of bioactive extracts and lead compounds with novel interaction to AChE, is one of the most promising area to synthesize and discover new drugs for AD treatment and improvment of cognitive disorders. As it was presented in this review, different classes of marine compounds with anti-cholinesterase activity such as pyrrole derivatives, sesquiterpene acetates, tetrazacyclopentazulene, bromotyrosine derivative, plastoquinones, farnesylacetones and poly-alkylpyridinium polymers (Poly-APS) in 4 categories of seaweeds, marine sponges, coelenterates and other invertebrates were discussed. Some of the compound classes presented in this review contains compounds with inhibitory activities comparable to currently approved cholinesterase inhibitors. But this area needs further investigations resulted in the next generation of cholinesterase inhibitors and other useful medicines.

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