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REVIEW

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Natural Bioactive Compounds from Macroalgae and Microalgae for the Treatment of Alzheimer's Disease: A Review

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Neuroinflammation, toxic protein aggregation, oxidative stress, and mitochondrial dysfunction are key pathways in neurodegenerative diseases like Alzheimer's disease (AD). Targeting these mechanisms with antioxidants, anti-inflammatory compounds, and inhibitors of Aβ formation and aggregation is crucial for treatment. Marine algae are rich sources of bioactive compounds, including carbohydrates, phenolics, fatty acids, phycobiliproteins, carotenoids, fatty acids, and vitamins. In recent years, they have attracted interest from the pharmaceutical and nutraceutical industries due to their exceptional biological activities, which include anti-inflammation, antioxidant, anticancer, and anti-apoptosis properties. Multiple lines of evidence have unveiled the potential neuroprotective effects of these multifunctional algal compounds for application in treating and managing AD. This article will provide insight into the molecular mechanisms underlying the neuroprotective effects of bioactive compounds derived from algae based on *in vitro* and *in vivo* models of neuroinflammation and AD. We will also discuss their potential as disease-modifying and symptomatic treatment strategies for AD.

INTRODUCTION

Alzheimer's disease (AD) is the most prevalent form of dementia, accounting for 60-80% of cases [1]. According to the World Health Organization (WHO), about 55 million people worldwide currently live with dementia, and this number is expected to burgeon to 139 million by 2050 [2]. Dementia imposes significant physical, psychological, and financial burdens on both patients and their families [1]. In 2019, global dementia care costs were estimated at approximately $1.3 trillion, with unpaid caregivers bearing about half of this financial burden [1]. The physical and psychological stresses of caregiving also put these individuals at risk of health complications [3].

Current AD treatments are primarily palliative, which aim to delay cognitive deterioration and alleviate symptoms without addressing the underlying pathology [4,5]. FDA-approved drugs like donepezil, rivastigmine, and galantamine are acetylcholinesterase (AChE) inhibitors that increase acetylcholine levels in the brain by preventing its breakdown [6]. However, these treatments can cause adverse effects, therefore slow dose escalation in modest increments is essential for minimizing adverse events [6]. Memantine, another FDA-approved drug, is

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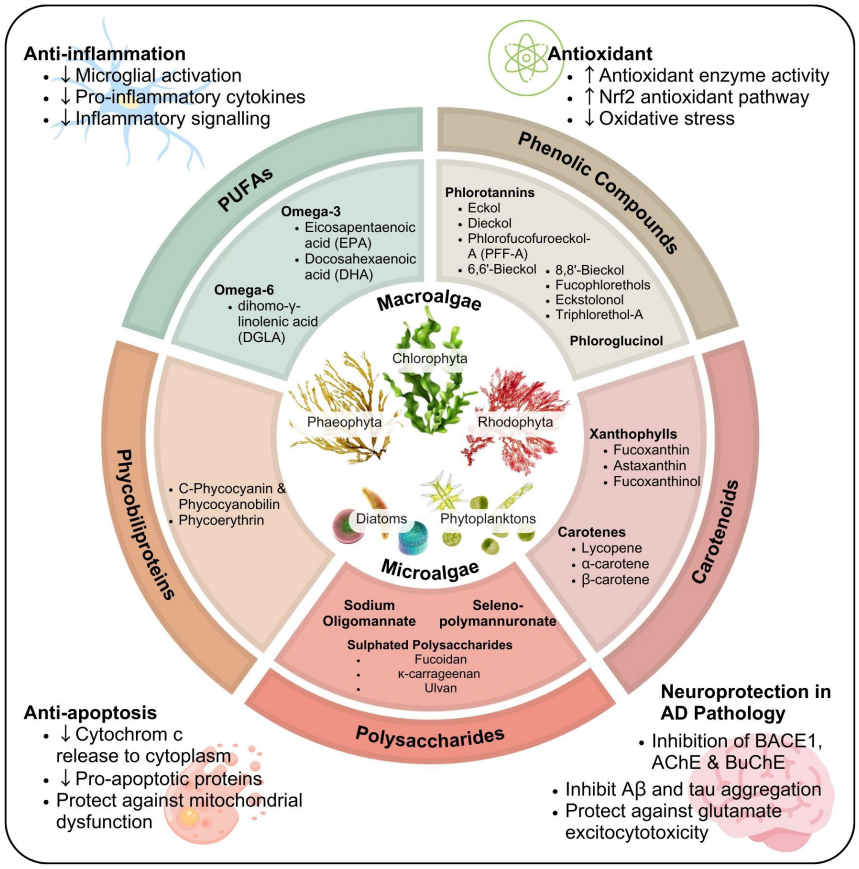
Abbreviations: AD, Alzheimer's disease; AChE, acetylcholinesterase; BBB, blood-brain barrier; ROS, reactive oxygen species; PUFA, polyunsaturated fatty acid.

Keywords: marine algae, bioactive compounds, neuroprotection, beta-secretase, cholinesterase, Alzheimer's disease



Graphical Abstract.

an N-methyl-D-aspartate receptor (NMDAR) antagonist that mitigates neurotoxicity by inhibiting excessive glutamatergic signaling [5]. Recently, a few anti-Aβ monoclonal antibodies including aducanumab and lecanemab have been approved as disease-modifying drugs [7,8] by lowering amyloid burden in AD patients [5,9].

The incomplete understanding of disease etiologies and pathological mechanisms, the difficulty for early diagnosis and intervention, and the limited drug penetration across the blood-brain barrier (BBB) are major impediments to developing effective treatments for neurodegenerative diseases [10,11]. Over the last few decades, research efforts have focused on novel therapeutic strategies, including immunotherapy, gene therapy, treatment with neurotrophic factor, and epigenetic modulation, all of which are still being evaluated in clinical studies [4]. Considering the pivotal roles of the pathological mechanisms (eg, oxidative stress, loss of proteostasis, mitochondrial dysfunction, neuroinflammation, apoptosis) in neurodegenerative diseases, targeting these mechanisms may help manage symptoms and delay disease progression [12]. For instance, antioxidants that reduce reactive oxygen species (ROS) in neurons can mitigate oxidative stress and neuroinflammation, preventing oxidative cell death [13].

Given the limited efficacy and side effects of existing AD drugs [4,6], natural products have garnered attention as potential alternative therapies. Bioactive compounds from macroalgae and microalgae have been extensively studied for their antioxidant, anti-inflammatory, and neuroprotective properties [14]. Macroalgae contain a variety of beneficial metabolites, including phenolic compounds, alkaloids, isoprenoids, polysaccharides, and polyunsaturated fatty acids (PUFAs) [14-16]. Similarly, microalgae produce secondary metabolites such as pigments (eg, phycobiliproteins, carotenoids, chlorophylls), PUFAs (eg, omega-3 and omega-6 fatty acids), carbohydrates, vitamins, amino acids, and sterols with important health-promoting properties [17,18]. This review explores the molecular mechanisms by which bioactive compounds from macroalgae and microalgae exert their anti-inflammatory, antioxidant, and neuroprotective effects in models of neuroinflammation and AD. We will also discuss their potential as symptomatic treatments and disease-modifying approaches for the management of AD.

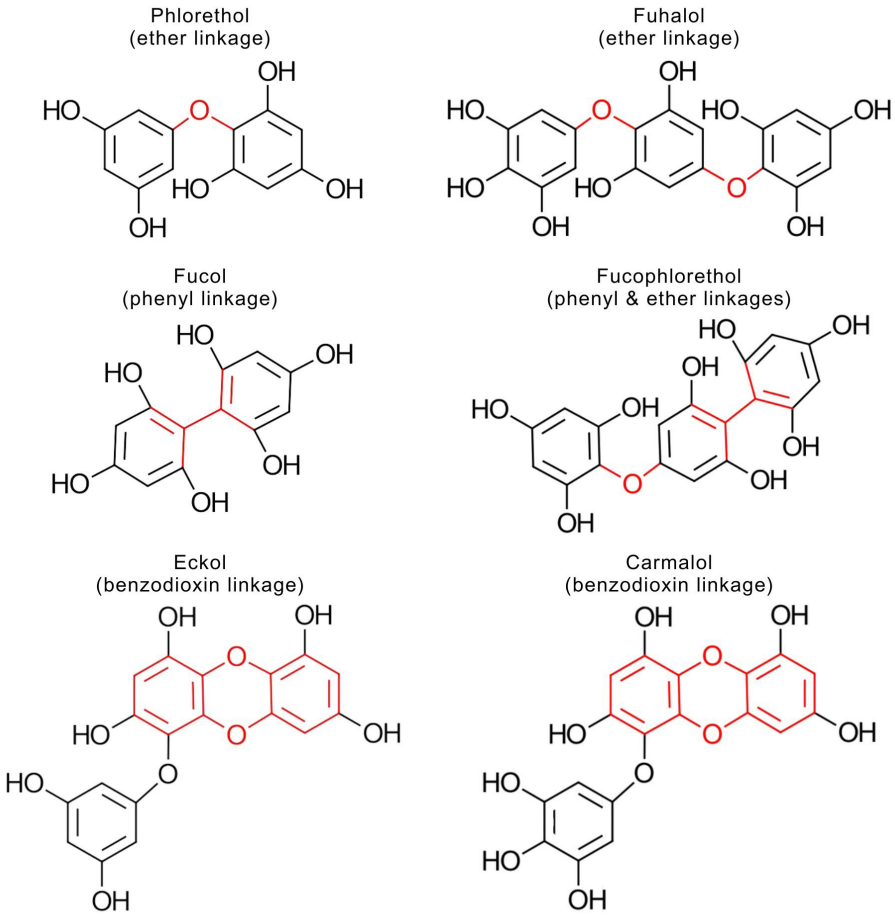


Figure 1. **Chemical structures of phlorotannins isolated from marine algae**. Phlorethol and Fuhalol with ether linkage, Fucol with phenyl linkage, Fucophlorethol with ether and phenyl linkages, Eckol and Carmalol with benzodioxin linkage.

NEUROPROTECTIVE EFFECTS OF MACROALGAE- AND MICROALGAE-DERIVED BIOACTIVE COMPOUNDS AGAINST AD

Algae can be classified by size into macroalgae and microalgae, or by pigments into Chlorophyceae, Phaeophyceae, and Rhodophyceae (green, brown, and red algae, respectively) [19]. Macroalgae, more commonly known as seaweed, are macroscopic multicellular organisms, whereas microalgae are microscopic unicellular prokaryotes (eg, cyanobacteria) or eukaryotes (eg, diatoms, Chlorophyta) [18,19]. Algae thrive in fluctuating and hostile conditions of salinity, light, tidal current, and temperature [20,21]. To survive in extreme environments, they undergo structural, physiological, and biochemical adaptations, resulting in the synthesis of stress-tolerant molecules such as PUFAs, phenolic compounds, carotenoids, chlorophylls, and polysaccharides, which have biological functions in human pathologies [22,23].

Phenolic Compounds

Phloroglucinol: Phloroglucinol, a polyphenol found exclusively in brown macroalgae, is renowned for its antispasmodic properties and has been traditionally used clinically as a spasmolytic agent [24]. Phloroglucinol impedes the breakdown of catecholamines such as dopamine and norepinephrine by inhibiting the catechol-O-methyltransferase (COMT) enzyme, consequently increasing their levels. This increase in neurotransmitter levels activates the sympathetic nervous system in specific smooth muscle tissues, leading to an increased sympathetic tone and subsequent relaxation [24]. Emerging studies have unveiled its neuroprotective potential due to potent antioxidant activities, such as scavenging intracellular free radicals, enhancing the antioxidant system, and reducing oxidative stress [25]. *In vitro* studies using neuronal models of AD showed that phloroglucinol diminished $A\beta_{1\text{-}42}$-induced ROS elevations and accumulations and restored dendritic spine density [26]. *In vivo*, it improved cognitive performance in 5XFAD mice and reduced cognitive im-

pairments, as observed by improved performance in Morris water maze, T-maze, and Y-maze tests, which assess spatial learning and memory. In a study, phloroglucinol, eckol, dieckol, triphlorethol-A, and eckstolonol isolated from *Ecklonia cava* demonstrated neuroprotective effects by lowering intracellular ROS and Ca^{2+} levels, as well as by inhibiting apoptosis in H_2O_2-treated HT22 cells [13].

Phloroglucinol derived from macroalgae has been shown to be a promising anti-inflammatory agent in addition to its antioxidant activities. In a 5XFAD mouse model of AD, phloroglucinol was administered orally and showed reductions in Aβ plaque burden, BACE1 protein levels, and neuroinflammation as indicated by decreased expression of inflammatory markers (Iba-1, GFAP, TNF-α, and IL-6) in the hippocampal dentate gyrus and CA1 subfields [27]. In the study, phloroglucinol-treated AD mice showed improvement in cognitive deficits and synaptic plasticity impairment induced by $A\beta_{1-42}$ and homocysteine (Hcy) aggregates [27]. The anti-neuroinflammatory effects of phloroglucinol may be due to its ability to directly bind to and inhibit the aggregation of $A\beta_{1-42}$ with Hcy seeds and to disassemble the pre-formed amyloid aggregates [28]. These findings suggest a potential therapeutic role for phloroglucinol in AD, although further research is warranted to elucidate the mechanisms underlying its neuroprotective effects and establish its clinical utility. Future investigations could explore its interactions with specific molecular targets involved in AD pathology, such as those involved in the amyloidogenic pathway, oxidative stress pathways, and inflammatory cascades. Notably, phloroglucinol was predicted to cross the BBB [28,29]. In support of this, studies have highlighted the neurological activity of phloroglucinol in the CNS [30,31], and a certain amount of phloroglucinol was detected in the brain shortly after oral administration [27]. Hence, it is imperative to characterize the pharmacokinetic and pharmacodynamic profiles of phloroglucinol in the CNS to help in dosing optimization and understand its distribution and duration of action in the brain. Furthermore, rigorous evaluation of the safety and tolerability of CNS administration of phloroglucinol is essential. This includes the assessment of potential adverse effects, toxicity risk, and long-term safety profiles, especially concerning chronic use.

Phlorotannins: Phlorotannins are the seaweed polyphenol class that has garnered the most attention in both the academic and industry research domains for their multifaceted benefits. They are a major group of polyphenolic secondary metabolites present in large amounts in brown seaweed [25,32]. Phlorotannins possess a wide range of biological activities, including antioxidant, anti-inflammatory, antimicrobial, antiviral, anticancer, antidiabetic, antihypertensive, and hepatoprotective properties [33]. Phlorotannins also exhibit good safety profile and biocompatibility, making them versatile assets in the fields of medicine, food, cosmetics, and agriculture. They are formed by oligomerization of phloroglucinol units and can be further divided into six subgroups: phlorethols, fuhalols, fucols, fucophlorethols, eckols, and carmalols based on the type of structural linkages between aromatic units [14]. For instance, phlorotannins with an ether linkage include fuhalols and phlorethols; eckols and carmalols have a benzodioxin linkage, while fucols and fucophlorethols have an ether and a phenyl linkage [32], as shown in Figure 1.

Collectively, studies have shown that the brown algal phlorotannins especially dieckol (a hexamer), eckol (a closed-chain trimer of phloroglucinol), and phlorofucofuroeckol-A (PFF-A) have potent free radical scavenging activity on 1,1-diphenyl-2-picrylhydrazyl (DPPH), H_2O_2, hydroxyl radical, and superoxide anion [34-39]. A study evaluated the antioxidant capacity of the phlorotannins 974-A and 974-B isolated from *Ecklonia kurome* (*E. kurome*) using the DPPH and the 2′,7′-dichlorofluorescein diacetate (DCFH-DA) intracellular radical scavenging assays [40]. In the study, both compounds exhibited strong DPPH radical scavenging abilities with IC50 values of 10 μM and 11 μM respectively, comparable to other well-known algal phlorotannins like PFF-A and dieckol. Additionally, they showed superior intracellular scavenging activity compared to most tested algal phlorotannins, including phloroglucinol, PFF-B, α-tocopherol, and ascorbic acid. These results suggest that they may be useful as effective antioxidants in neurodegenerative diseases like AD, where oxidative stress plays a crucial role in disease progression. Phlorotannins were recently extracted from the cell walls of *Pelvetia canaliculate* and *Fucus vesiculosus* to examine their antioxidant and neuroprotective effects on cell culture models of AD and Parkinson's Disease (PD) [41]. These cell wall-bound phlorotannins demonstrated comparable neuroprotective effects to their intracellular fractions, with less cytotoxicity but milder antioxidant activity, indicating that they may be promising candidates for therapeutic applications in neurodegenerative diseases [41]. On the other hand, phlorotannins isolated from brown seaweed, such as eckol, dieckol, and bieckol, have been shown to have anti-inflammatory properties. The mechanisms of action include downregulating the NF-κB and MAPKs (p38, JNK, and ERK) inflammatory signaling pathways, which suppresses the production of proinflammatory mediators (eg, iNOS, COX-2, PGE2, TNF-α, and IL-6) and ROS [42-45].

Glutamate toxicity leads to Ca^{2+} overload, which triggers mitochondrial dysfunction, an increase in oxidative and ER stress, and apoptotic signaling, which ultimately results in neuronal cell death in neurodegenerative diseases [46,47]. A study showed that dieckol isolated

from *E. cava* can prevent glutamate-induced cytotoxicity in neuronal cultures by scavenging free radicals in a dose-dependent manner and activating the antioxidative nuclear factor-like 2 (Nrf2)/heme oxygenase-1 (HO-1) pathway [46]. In addition, dieckol pretreatment also protected against mitochondrial dysfunction as it decreased mitochondrial membrane depolarization and increased intracellular adenosine triphosphate (ATP) levels in the glutamate-stimulated neurons [46]. Likewise, PFF-A pretreatment in PC12 cells was demonstrated to prevent the loss of mitochondrial mass and disruption of mitochondrial membrane potential, as well as decrease the rise in intracellular ROS [48].

It has been demonstrated that the polyphenols derived from brown seaweed selectively inhibit BACE1 [49,50]. Butanol extract of *E. cava* was shown to inhibit Aβ synthesis by inhibiting BACE1 activity [51]. This prevents Aβ oligomerization and protects the neurons from Aβ-induced cytotoxicity [51]. In a subsequent study, *E. cava* extract upregulated the α-secretase activity while downregulating the γ-secretase activity, potentially through lower PSEN1 expression, which led to decreased Aβ production in HEK293 APPsw cells [52]. Particularly, PFF-A isolated from *E. cava* demonstrated strong inhibitory activity of around 60% on BACE1, which is comparable to that of a known strong BACE1 inhibitor with 75% inhibitory activity [50]. Taken together, these studies showed that phlorotannins from marine algae may be used as a disease-modifying therapy strategy to treat AD patients by targeting the amyloidogenic pathway.

Dieckol and PFF extracted from *E. cava* were found to improve learning and memory in ICR mice [53]. This is likely due to their inhibitory actions on AChE, which resulted in higher levels of the neurotransmitter ACh in the striatum, hippocampus, and frontal cortex of ICR mice and improved cholinergic signaling [53]. Likewise, PFF-A and dieckol isolated from *E. cava* were identified as the most potent inhibitors of butyrylcholinesterase (BuChE) with IC_{50} values of 0.95 and 2.7 μM respectively, compared to other isolated algal polyphenols including eckol, 6,6'-Bieckol, and 8,8'-Bieckol (IC_{50} values ranging from 3.8 to 29.0 μM) [50]. Notably, all the isolated polyphenols also modestly inhibited AChE and GSK3β [50], indicating their potential to relieve AD pathology and progression. Phlorotannin-rich extract from *E. cava* (PEEC) was also shown to inhibit both AChE and BuChE in a dose-dependent manner [54]. These findings imply that phlorotannins may enhance cognitive functions in older, healthy subjects as well as provide symptomatic relief for AD patients by boosting cholinergic neurotransmission.

However, clinical trials on phlorotannins have primarily focused on anti-obesity, metabolic syndrome management, anti-inflammatory and antioxidant effects [55]. For phlorotannins to advance into clinical trials for neurodegenerative diseases, several barriers must be addressed, including obtaining regulatory approval, recruiting volunteers, and establishing extensive preclinical evidence supporting their potential neuroprotective effects, alongside comprehensive mechanistic studies and safety profiles. Many trials involving phlorotannins face limitations due to small sample sizes, short durations, and lack of long-term efficacy data [55]. In addition, standardization of extraction methods and formulations is essential for precise dosing and reliable study results. Identifying the individual bioactive compounds responsible for observed effects can help elucidate their mechanisms of action and potential health benefits [55]. Optimizing extraction methods to improve yield and purity of phlorotannin extracts is also fundamental to further enhance their potential therapeutic utility.

Carotenoids

Xanthophylls: Fucoxanthin (tetraterpenoid) is an important carotenoid present primarily in brown seaweeds including *Eisenia*, *Undaria*, *Sargassum*, *Laminaria*, *Dictyota*, *Fucus*; and in microalgae such as *Isochrysis*, *Phaeodactylum*, *Cylindrotheca*, *Cyclotella*, *Nitzschia*, *Prymnesium*, *Chaetoceros*, and *Odontella* [56,57]. In bone marrow-derived astrocytes and immune cells, fucoxanthin from the microalga *Phaeodactylum tricornutum* prevented ATP- and LPS-induced activation of NF-κB and NLRP3 inflammasomes [58]. In neurodegenerative diseases, NLRP3 is a crucial regulator of microglia-mediated neuroinflammation [59,60]; NF-κB plays a vital role during the priming step of NLRP3 [61,62]. Moreover, fucoxanthin may be a powerful anti-inflammatory agent as it also suppressed the expressions of cleaved caspase-1, phosphorylated IκBα, and pro-IL-1β, and inhibited the oligomerization of apoptosis-associated speck-like *protein* containing a caspase recruitment domain (ASC), all of which are essential for inflammasome signaling [58]. Several lines of evidence have also indicated that one of the key anti-inflammatory mechanisms of fucoxanthin is the inhibition of MAPK and NF-κB signaling pathways, which reduced the production of inflammatory mediators including TNF-α, IL-6, IL-1β, ROS, and iNOS [63-66].

The neuroprotective activities of the xanthophylls fucoxanthin and astaxanthin in AD have been linked to several processes, including the regulation of antioxidant enzymes such as SOD and CAT through inhibition of the ERK pathway, and inhibition of AChE, BuChE, and BACE-1 [67]. The combined effects of these are decreased Aβ accumulation, improved cholinergic function and diminished neuroinflammation that ultimately prevented neurotoxicity in AD models [67]. A recent study showed that fucoxanthin has antioxidant effects in PC12 cells exposed to Aβ by upregulating the expression of

Nrf2 and the downstream Phase-II antioxidant enzymes, including NADPH: quinone oxidoreductase-1 (NQO-1), glutamate cysteine ligase (GCL), and thioredoxin reductase 1 (TrxR1) [68]. Besides, they found that fucoxanthin upregulated the Akt/GSK-3β/Fyn signaling, which activated the Nrf2-mediated antioxidant system [68]. In the study, the expression of Kelch-like ECH-associated protein 1 (Keap1), a Nrf2 repressor protein, paralleled with the upregulation of Nrf2 expression [68]. An earlier study revealed that fucoxanthin may alter the conformation of Keap1 and encourage the dissociation of the Nrf2-Keap1 complex, which leads to Nrf2's nuclear translocation and subsequent gene transcription, eventually protecting neuronal cells against 6-OHDA-induced cytotoxicity [69].

Fucoxanthin isolated from the microalga *P. tricornutum* exerted strong inhibitory activity against BuChE (IC_{50} = 1.97 mM) in a dose-dependent manner and a relatively weaker inhibition on AChE [70] by interacting with the enzyme's peripheral anionic site (PAS) [71]. In scopolamine-treated mice, fucoxanthin treatment also elevated the expression of hippocampal and cortical (BDNF), which reversed the effects of scopolamine on their cognitive function [71]. Scopolamine is a muscarinic acetylcholine receptor antagonist that inhibits cholinergic neurotransmission, leading to memory impairment in animal models [71]. It impairs cognitive function by causing cholinergic dysfunction, increasing oxidative stress and neuroinflammation in the brain [72,73]. This makes it a valuable experimental model for AD, useful for testing potential drugs that can reverse the cognitive deficits by enhancing cholinergic transmission or mitigate oxidative stress and inflammation to counteract these deficits. Fucoxanthin (and fucosterol) extracted from *Ecklonia stolonifera* and *Undaria pinnatifida* also showed mixed-type inhibition against BACE1 enzyme with an IC_{50} of 5.31 mM, indicating its potential function in delaying the onset of AD [74]. Xiang et al. [75] showed that fucoxanthin can directly bind to and inhibit the aggregation of $A\beta_{1-42}$, which protects SH-SY5Y neuronal cells against Aβ-induced neurotoxicity. In line with this, both fucoxanthin and astaxanthin were shown to exhibit neuroprotective activities by inhibiting the aggregation of Aβ, attenuating $A\beta_{1-42}$ and H_2O_2-induced cytotoxicity, and increasing neurite outgrowth activity in PC-12 neuronal cells [76]. These results suggest that the xanthophyll carotenoids from marine algae also have positive effects on amyloid pathology in the pathogenesis of AD.

Astaxanthin is a marine source xanthophyll carotenoid with potent antioxidant activity that is superior to other carotenoids including, β-carotene, zeaxanthin, and lutein, and to vitamin E [77,78]. According to *in vivo* research, astaxanthin has neuroprotective effects against AD by reducing $A\beta_{1-42}$ level, tau hyperphosphorylation (inhibition of GSK-3β activity), TNF-α level, oxidative stress, and AChE activity [79-81]. Intriguingly, astaxanthin was found to decrease Insulin receptor Substrate-1 (IRS-1) phosphorylation in the hippocampus of AD rats, indicating its significance in preventing Aβ-induced neuronal insulin resistance [79]. Furthermore, it was shown to improve learning and memory deficits in APP/PS1 transgenic mice by activating mTOR signaling, which is essential for synaptic plasticity [82].

Astaxanthin at a dose of 1 mg/kg orally has previously been shown to significantly inhibit AChE activity in AD mice as compared to the group treated with $A\beta_{1-42}$ alone [79]. Hafez et al. [83] showed that astaxanthin could suppress the accumulation of $A\beta_{1-42}$ and malondialdehyde, expression of BACE1, and activities of AChE and MAO. These results are consistent with those of a recent study in which astaxanthin showed potent reversible inhibition of AChE (IC_{50} = 8.64 μmol/L) and increased antioxidant capacities by upregulating the expressions of SOD and catalase in $A\beta_{25-35}$-induced PC12 cells [84]. In an AD-like mouse model induced by hydrated aluminum chloride (AlCl3.6H2O) solution, oral administration of astaxanthin also increased the levels of ACh, serotonin, and expressions of Nrf2 and miRNA-124 [83]. In aggregate, these findings suggest that astaxanthin may be useful in ameliorating cholinergic dysfunction throughout the progression of neurodegenerative diseases. In a 12-week long randomized double-anonymous placebo-controlled study in 96 healthy elderly subjects with forgetfulness, daily supplementation of astaxanthin-rich *Haematococcus pluvialis* extract (6 or 12 mg/day) has also displayed promising clinical benefits in improving cognitive function [85]. In the study, high-dosage astaxanthin (12 mg/day) improved CogHealth battery (a set of tasks to assess working memory, reaction time, and executive function) scores after 12 weeks, while Groton Maze Learning Test (a neuropsychological test used to assess spatial learning and memory) scores improved in astaxanthin-treated groups compared to the placebo group. However, the differences between treated and placebo groups did not reach significance due to small sample size, warranting future clinical trials to include greater sample sizes to get more conclusive results. Similar findings have been observed in another study [86], where the subgroup with subjects aged 45-54 years but not the group ≥ 55 years old supplemented with astaxanthin-rich extract from *Paracoccus carotinifaciens* displayed significant increase in the number of recalled words after 5 min in the Word memory test compared to the placebo group after 8 weeks.

In cyclophosphamide-treated adult male albino rats, a high dose (100 mg/kg) of microalga lutein administered once daily for 10 consecutive days lowered the brain levels of IL-18, IL-1β, cytokine-induced-neutrophil chemoattractant (CINC), and NLRP3 to their normal values [87]. Besides, compared to the cyclophos-

phamide group, it substantially decreased the levels of MMP1, MIP2, and caspase-1 by 51%, 83%, and 79%, respectively, and attenuated neurodegeneration in histomorphometric analysis [87]. In DPPH and hydroxyl radical scavenging experiments, acetone extracts of the green microalga *Botryococcus braunii* at 10 ppm levels of carotenoid displayed potent antioxidant activity [88]. The extract inhibited lipid peroxidation by about 70% in the liver, brain, and kidney of rats as well as in the liposome system (78%) at 10 ppm levels of carotenoid. It is believed that the high concentration of carotenoids in *B. braunii*, particularly lutein (which makes up 75% of total carotenoids), is responsible for the observed antioxidant activity [88]. Fucoxanthinol, which is also a marine microalgae-derived xanthophyll carotenoid, was shown to remarkably downregulate LPS-induced expressions of proinflammatory iNOS and COX-2 and to suppress the production of inflammatory cytokines through a mechanism involving NF-κB, Akt, MAPK, and Nrf2 signaling pathways in BV2 microglia [89]. In summary, microalga-derived xanthophyll carotenoids, such as fucoxanthin, astaxanthin, and lutein hold promise as potential neuroprotective agents against neurodegenerative diseases due to their antioxidant, anti-inflammatory properties, and cholinesterase inhibitory action. Fucoxanthinol, on the other hand, is relatively less studied compared to its parent compound, fucoxanthin, and there remains a gap in understanding its neuroprotective mechanisms beyond anti-inflammation. Future research endeavors should aim to explore the neuroprotective effects of fucoxanthinol in animal models of AD. This exploration should encompass investigating their mechanisms of action in lowering oxidative stress and alleviating AD-associated pathology, as well as their potential influence on cholinergic function, shedding light on their comprehensive neuroprotective effects.

Carotenes: Lycopene exerted anti-neuroinflammation effects in AD by inhibiting the accumulation of Aβ, reducing the levels of APP, and suppressing BACE1 expression while upregulating the expressions of α-secretase ADAM10 [90]. Importantly, the restoration in learning and memory abilities may be attributed to lycopene's ability to downregulate the inflammatory response by suppressing the expressions of proinflammatory cytokines and inhibiting the activation of relevant inflammatory signaling pathways such as MAPKs, NF-κB, and Nrf2 [90-92]. In male albino rats, lycopene treatments have been shown to alleviate acrylamide-induced neurotoxicity by re-establishing the concentrations of serotonin and dopamine as well as the activity of AChE in the brain [93]. In a transgenic mouse model of tauopathy, the combination of lycopene and vitamin E also had synergistic antioxidant effects that significantly reduced tau phosphorylation, increased antioxidant defense, and improved memory impairment, suggesting that this combination of nutrients may have beneficial effects on tau pathology in AD [94].

In a study, 2.05 mg/kg of β-carotene treatment ameliorated streptozotocin-induced memory impairment in AD mice due to its antioxidant properties, inhibitory effects on AChE, and ability to prevent the formation of Aβ aggregates [95]. Earlier *in vitro* research has shown that β-carotene has anti-amyloidogenic and fibril-destabilizing activity, which may have contributed to its antioxidant effects [96]. In a subsequent investigation, the precise mechanism by which β-carotene regulates Aβ aggregation was unveiled, which does not relate to the direct inhibition of Aβ fibrillation or alteration of the morphology of $A\beta_{42}$ aggregates. Instead, they discovered that β-carotene modulates Aβ aggregation by promoting fibrillar polymorphs devoid of the structural order required for the formation of fibrillar aggregates [97]. β-carotene has also been identified as an effective competitive inhibitor for AChE with a binding mode similar to that of rivastigmine and galantamine, suggesting that it may be employed as a natural pharmaceutical for the management of AD [98].

Polysaccharides

Sodium Oligomannate: Sodium oligomannate, also known as oligomannate 971 or GV-971, is an orally administered acidic oligosaccharide derived from the marine alga *E. kurome*, showing promising neuroprotective effects in AD [99]. Although its mechanisms are not fully understood, it is believed to modulate the gut microbiome [99,100] and inhibit Aβ fibrillation [101]. GV-971 developed by Shanghai Green Valley Pharmaceuticals, was first approved in China on November 2, 2019, for treating mild-to-moderate AD [102]. Emerging evidence links gut microbiome dysbiosis with neurodegenerative diseases, including AD [99,100]. Modulating the gut microbiome could potentially impact neuroinflammation, synaptic function, and amyloid deposition in the brain [99,103,104]. In AD mice, sodium oligomannate reconditioned the gut microbiota, which regulated the amino acid metabolism, particularly by lowering phenylalanine and isoleucine levels [99]. This reduced T helper (Th1) cell infiltration and microglial activation in the brain, suppressing AD-associated neuroinflammation [99]. Furthermore, sodium oligomannate can cross the BBB via carrier transporters like the glucose transporter 1 (GLUT1), where it targets Aβ subregions and prevents Aβ fibrillation. Evidently, treatment with sodium oligomannate significantly reduced Aβ plaque aggregation and tau phosphorylation, and enhanced spatial learning and memory in AD mice [99]. Interestingly, a very recent study revealed a sex difference in the reduction of Aβ amyloidosis and reactive microglia of GV-971 in APPPS1-21

mice and 5XFAD mice [100]. In comparison to control male APPPS1-21 mice, treated male mice showed specific reductions in brain Aβ deposition, Clec7a+ plaque-associated microglia activation, neuroinflammation, and alterations in microbiota profiles after receiving GV-971 treatment. Notably, similar effects were not observed in female mice treated with sodium oligomannate. These findings provide insights into interventions targeting the gut-brain axis to influence AD pathology, and underscores the importance of considering sex-specific differences in microbiota composition and treatment responses in AD.

A recent study has shed light on the mechanism by which GV-971 exerts its inhibitory effects on Aβ aggregation [101]. Biochemical and biophysical experiments revealed that GV-971 disrupts Aβ aggregation primarily through electrostatic interactions between its carboxylic groups and histidine residues within Aβ40/Aβ42. This disruption prevents the formation of toxic Aβ aggregates and reduces the flexibility of the histidine-containing fragment of Aβ, further contributing to its inhibitory effects. Synthetic compounds derived from GV-971, including β-(1,4)-D-mannobiose, β-(1,4)-D-mannotriose, and β-(1,4)-D-mannotetraose, likewise showed neuroprotective properties against Aβ peptide toxicity on SH-SY5Y human blastoma cells [105]. Together, these findings show that it is possible to modify the structure of GV-971 without losing its function, which justifies further research into the development of novel neuroprotective compounds.

A randomized, double-anonymous, placebo-controlled phase II clinical trial found that AD patients receiving 600 or 900 mg/day of GV-971 for 24 weeks did not significantly improve on the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-cog12) scores, but that there was a significant improvement on the Clinician's Interview-Based Impression of Change-Plus (CIBIC+) scores in the 900-mg group compared to the placebo group (92.77% vs. 79.52%) [106]. The CIBIC+ test is an interview-based clinical global assessment tool used in clinical trials for AD conducted by experienced clinicians to assess overall changes in cognitive, functional, and behavioral impairment over time through an interview with the patient and caregivers, providing an impression of treatment's clinical benefits [107]. Subsequently, in a phase III, double-anonymous, placebo-controlled trial with mild-to-moderate AD patients, GV-971 significantly improved cognitive functions compared to the placebo group after 4 weeks of treatment, as assessed by ADAS-cog12, and also benefited secondary endpoints like CIBIC+ scores and activities of daily living (ADCS-ADL) scores [108]. The incidence of adverse events was also not statistically different between oligomannate-treated and placebo groups [108], suggesting GV-971 is a potentially effective, safe, and well-tolerated therapeutic agent for symptomatic relief in AD patients. However, more rigorous clinical trials involving larger sample sizes and longer durations should be carried out to determine whether there is a meaningful difference between the drug and placebo groups in the secondary outcomes.

Sulphated Polysaccharides: Marine algae Rhodophyceae, Phaeophyceae, and Chlorophyceae contain sulphated polysaccharides such as carrageenan, fucoidan, and ulvan, respectively [109]. These compounds, particularly carrageenan and fucoidan have been extensively researched for their antioxidant, antitumor, anti-inflammatory, and antimicrobial properties [110].

Fucoidan is a class of sulphated polysaccharides found exclusively in brown algae. The most discussed possible anti-inflammatory mechanism of action of fucoidan in rat microglial cells is the inhibition of NF-κB [111], ERK, and p38 MAPK signaling pathways [111,112]. Downregulation of these inflammatory pathways is brought upon by suppression of NO production and iNOS expression [111,112]. NO production is regulated by components of the signal transduction pathways (eg, tyrosine kinases, protein kinase C) and the MAPK pathways [112]. On the other hand, transcription factors such as NF-κB, CREB, STAT, and activator protein (AP)-1 directly influence the gene expression of iNOS and subsequently the production of NO [113]. Fucoidan has been shown to suppress the activation of p38 MAPK, JAK/STAT, IRF-1, and AP-1 while upregulating the expression of scavenger receptor B1 (SR-B1) [113]. All this results in decreased NO production in the TNF-α- and IFN-γ-stimulated C6 glioma cells [113].

In vitro, fucoidan treatment prevented the release of cytochrome c to the cytoplasm and upregulated the expression of apoptosis inhibitor proteins (IAPs), which in turn rescued PC12 cells from apoptosis induced by $A\beta_{25-35}$ and D-galactose (D-Gal) [114]. Fucoidan treatment improved cholinergic deficiency and antioxidant activity *in vivo*, which reversed the learning and memory deficits in D-gal-induced AD mice [114]. These studies showed that fucoidan could enhance cognitive functions partly due to its ability to inhibit apoptosis and alleviate cholinergic deficiency. A fucoidan isolated from *Sargassum fusiforme*, SFPS65A, was shown to reverse cognitive impairments in ethanol and sodium nitrite-induced mice. Structural analysis revealed that SFP65A has a higher degree of sulphation compared to its homogenous counterpart SFPS65B, which may have largely contributed to its bioactivities for improving cognitive ability [115].

Previously, it was demonstrated that pretreatment of κ-carrageenan and its desulphated derivatives in LPS-induced microglial cells can inhibit microglial cell activation and migration [116], suggesting a possible application in attenuating neuroinflammation in neuro-

generative diseases. Importantly, they discovered that the desulphated derivatives of carrageenan had weaker inhibitory effects on microglial activation, indicating that the sulphate group content in κ-carrageenan is the primary factor affecting its inhibitory function [116]. Similarly, pretreatment of the κ-, ι-, and λ-carrageenan in LPS-stimulated BV2 microglial cells markedly reduced the levels of inflammatory cytokines in a dose-dependent manner [117]. According to the literature, the potential mechanisms of action of k-carrageenan's anti-inflammatory activity are by inhibiting the inflammatory NF-κB, JNK, and MAPK pathways [118,119], as well as the AMPK/ULK1 autophagy pathway [120,121]. In Aβ-induced AD rats, hippocampal infusions of 1% low-MW fucoidan (AD-F-L) and 1% low-MW λ-carrageenan (AD-C-L) substantially improved memory function and increased the expressions of ciliary neurotrophic factor (CNTF) and BDNF. Both AD-F-L and AD-C-L also effectively augmented insulin signaling by enhancing the phosphorylation of AKT, STAT3, and GSK-3β, which may reduce Aβ deposition in the hippocampal region and contribute to improved memory [122].

Alginate-derived Oligosaccharides: After acid hydrolysis, the naturally occurring acidic polysaccharide, alginate, found in brown seaweed, is converted to polymannuronate (PM) [123]. The resulting PM blocks are then degraded by hydrogen peroxide in a process called oxidative degradation, to produce oligomannuronates of various sizes which are then subjected to chromatographic separation and characterization. The purified alginate-derived oligosaccharide (AdO) has shown anti-inflammatory activity in cell culture models by suppressing proinflammatory mediators (iNOS, COX-2, TLR4, and NF-κB) [124,125] and enhancing microglia-mediated Aβ clearance, suggesting its putative role as an anti-inflammatory agent in AD [125].

Seleno-polymannuronate (Se-PM), a seleno-derivative of PM, is synthesized through sulphation and selenylation replacement reactions and has demonstrated antioxidant and anti-inflammatory properties [126-128]. In LPS-stimulated RAW264.7 macrophages, it mitigated the production of ROS, NO, PGE_2, and other proinflammatory mediators, and downregulated the inflammatory NF-κB and MAPK signaling [126]. Similar effects were observed in LPS-activated primary microglia and astrocytes, suggesting its neuroprotective potential [127]. Se-PM has also shown antioxidative effects in the N2a-APP695-sw cell culture model of AD [128]. It decreased ROS production by increasing antioxidant enzymes like superoxide dismutase (SOD) and glutathione peroxidase (GPx) [128]. Importantly, Se-PM prevented apoptosis by restoring mitochondrial membrane potential, upregulating the anti-apoptotic protein Bcl-2, and downregulating cytochrome c [128,129]. It also regulated relevant Aβ pathways via β-amyloid precursor protein (APP) and BACE1, inhibiting $A\beta_{1-42}$ aggregation. Notably, Se-PM was also more effective than PM in that regard, demonstrating the vital role of the selenium element for its antioxidant and anti-inflammatory activities [129].

Phycobiliprotein

C-Phycocyanin and Phycocyanobilin: C-Phycocyanin (C-PC), is composed of polypeptide subunits and three covalently bound, open-chain tetrapyrrole units called Phycocyanobilin (PCB) [130]. C-PC is the primary phycobiliprotein present in the marine cyanobacteria *Spirulina* spp., which has antioxidant, anti-inflammatory, and neurotrophic properties. In H_2O_2-stimulated astrocytes, C-PC upregulated antioxidant enzymes (SOD and catalase) and neurotrophic factors (NGF and BDNF), while decreasing inflammatory markers (IL-6 and IL-1β) [131]. In the Experimental Autoimmune Encephalitis (EAE) model of multiple sclerosis (MS), C-PC promoted remyelination, induced regulatory T cell (Treg) response, enhanced antioxidant status, and modulated genes associated with remyelination [132,133]. They also postulated that part of C-PC's remyelinating activity is caused by its inhibitory actions on COX-2, highlighting its potential therapeutic applications to aid MS patients in recovery [134]. On top of that, C-PC showed neuroprotective properties by sparing SH-SY5Y cells from tert-butylhydroperoxide (t-BOOH)-induced apoptosis *in vitro* and rat retinas from ischemia-reperfusion injury *in vivo* [135], and hippocampal neurons from global cerebral ischemia-reperfusion injury in gerbils [136]. Overall, these investigations amply showed that C-PC can facilitate CNS repair following an ischemic insult and is a viable pharmacological approach to enhance functional recovery following an ischemic stroke.

Generally, the anti-inflammatory activities of C-PC entail the suppression of proinflammatory cytokines production [137,138], inhibition of apoptosis [137,138] and modulation of PI3K/AKT signaling [138]. Importantly, C-PC also attenuated Aβ-induced neuroinflammation by targeting HDAC3 and miR-335, revealing its beneficial effects in preventing neuronal apoptosis by preventing epigenetic dysfunction [137]. In particular, Agrawal et al. [138] found that C-PC effectively reduced AChE activity, which may aid in attenuating the cholinergic deficit in AD patients as a symptomatic treatment. In PC12 neuronal cells, C-PC from *Spirulina maxima* suppressed the $A\beta_{1-42}$-induced neurotoxicity and increases in APP, BACE1, and poly-ADP ribose polymerase-1 (PARP-1) cleavage, and raised the levels of antioxidant defenses [139]. In support of this, C-PC and the red phycobiliprotein phycoerythrin were both identified as potent β-secretase inhibitors [140,141] with great antioxidant activity [142]. These findings uncovered the potential benefits of phy-

cobiliproteins in alleviating AD pathology by interfering with amyloidogenic processing, suppressing Aβ-induced neuroinflammation and oxidative stress, and ultimately averting cell death.

PCB is a covalently attached chromophore to C-PC. A previous study used the oxygen radical absorbance capacity (ORAC) assay to quantify the peroxyl radical scavenging capacity of PC and PCB [143]. They found that both PC and PCB are more potent scavengers of peroxyl radicals compared to a few well-known antioxidant molecules including Trolox, ascorbic acid, and reduced glutathione. Importantly, PCB had the highest ORAC value (22.18 Trolox equivalents), compared to that of PC, GSH, and AA (20.33, 0.57, and 0.75 Trolox equivalents, respectively), suggesting that PCB is the primary compound responsible for the antioxidant activity of PC [143]. Marín-Prida et al. [144]. showed that PCB-modulated genes related to cerebroprotection (Mal, NADH dehydrogenase, Bcl-2a1, Gadd45g, Baiap2 and VEGFA), remyelination/demyelination processes (*Foxp3, TGF-β, TNF-α, IL-17A*, *IL-1β*), and inflammatory processes in a rat cerebral hypoperfusion model. Similar outcomes were also observed in rodent models of EAE [145,146], where PCB suppressed proinflammatory cytokines, and decreased demyelination by modulating myelination-associated genes and stimulating OPC and OD [146]. Notably, when PCB and IFN-β were given prophylactically together, superior outcomes were observed in terms of lowering proinflammatory cytokines and enhancing Treg induction [146].

Neuroprotective Effects of Spirulina spp. on AD: Spirulina spp. are rich sources of proteins, which account for approximately 60-70% of dry weight. They have powerful antioxidant, anti-inflammatory, antimicrobial, antitumor and neuroprotective effects on human health because they are also rich in essential fatty acids, phytopigments (phycobiliproteins, chlorophylls, carotenoids), minerals, and vitamins [147]. At concentrations of 50 and 100 g/ml, *S. maxima* extract inhibited Trimethyltin chloride-induced neurotoxicity in HT-22 hippocampal neuronal cells [148]. It also inhibited PARP cleavage, which prevented neuronal cell apoptosis, and suppressed ROS production and AChE activity, while upregulating the neurotrophic BDNF/CREB signaling [148]. In a relevant study, Koh et al. [149] reported that 70% ethanol extract of *S. maxima* (SM70EE) reduced $A\beta_{1-42}$ levels in the hippocampus and increased the expressions of antioxidant enzymes. Noteworthily, it potentiated the BDNF/PI3K/Akt signaling pathway which suppressed GSK-3β phosphorylation, consequently downregulating BACE1 and APP [149]. Subsequently, a randomized, double-anonymous, placebo-controlled clinical trial was conducted to evaluate the clinical benefits of SM70EE in patients with mild cognitive impairment [150]. According to the study, patients who received 1g/day of SM70EE for 12 weeks showed a substantial improvement in vocabulary, visual learning and visual working memory tests compared to the placebo group, with no significant adverse side effects [150]. Although the result did not reach a significant level, the increase in total antioxidant capacity in the treatment group compared to the placebo group in the trial indicated that further investigations are necessary [150].

In LPS-induced microglial cells, pretreatment with *S. platensis* mitigated upregulation of iNOS expression and generation of IL-1β and TNF-α [151]. Furthermore, it also inhibited NF-κB translocation and upregulated the gene expressions of Nrf2 and HO-1 [151]. In an *in vivo* rat model of $AlCl_3$-induced dementia, *S. platensis* reinstated the antioxidant status to normal and decreased brain TNF-α level [152]. Histopathological observation revealed a reduction in the number of neurodegenerative features and amyloid aggregates in the spirulina-treatment group compared to controls [152].

Polyunsaturated Fatty Acids

Omega-3 and Omega-6 PUFAs for Brain Health: Omega-6 (AA, LA, and dihomo-γ-linolenic acid; DGLA) and omega-3 (ALA, EPA, and DHA) are the primary PUFAs in cell membrane phospholipids [153]. AA, a precursor for inflammatory eicosanoid mediators such as prostaglandins (PGs), leukotrienes (LTs), and thromboxanes, is abundant in human inflammatory cells [153]. Omega-3 supplements, especially EPA, can reduce AA levels in these cells, decreasing the synthesis of inflammatory eicosanoids [154,155]. Reduced substrate availability thereby reduces the synthesis of inflammatory eicosanoids. A study of 13 young adults showed that 30-day supplementation with EPA and docosahexaenoic acid (DHA) reduced plasma AA levels, with EPA enhancing neurocognitive performance more effectively, as indicated by reduced reaction times in the color-word Stroop task [156]. Notably, this improvement was linked to decreased activation in the left anterior cingulate cortex (attention allocation and conflict monitoring) and increased activation in the right precentral gyrus (voluntary movement control), suggesting enhanced neural efficiency. EPA also competes with AA for COX and 5-lipoxygenase (5-LOX) enzymes to produce less inflammatory eicosanoids, such as 3-series prostaglandins and 5-series leukotrienes [157]. Omega-3 fatty acids have also been shown to suppress the COX-2 [158] and 5-LOX [159] pathways in AA metabolism in earlier research. As a result, this reduces the synthesis of potent inflammatory mediators like the 2-series prostaglandins and 4-series leukotrienes [153,157].

Observational studies have consistently revealed that consuming more omega-3 PUFAs regularly through fatty fish and fish oil was linked to a decreased risk of AD [160-163]. Clinical studies on the effects of omega-3

fatty acids in AD, however, revealed that there were only modest benefits on cognitive function and memory, with no significant improvement in the mini-mental state examination (MMSE), ADAS-cog, ADCS-ADL, Hamilton Depression Scale (HDRS), Clinical Dementia Rating (CDR), and Neuropsychiatric Inventory (NPI) scores [164-166]. Instead, omega-3 supplementation mainly improved mood and psychiatric symptoms (improvement in CIBIC-plus score) in mild-to-moderate AD patients [165]. However, when fish oil, carotenoids, and vitamin E are combined, it appears to be more effective at alleviating the symptoms and progression of mild-to-moderate AD, as evidenced by improvements in serum levels of carotenoids, omega-3 fatty acids, and vitamin E, MMSE category results, and clinical collateral memory and mood scores when compared to a placebo group [167]. Similar findings were also observed in a 24-month, double-anonymous, placebo-controlled, randomized clinical trial where adults with healthy brain aging showed improved working memory after supplementing with the three nutrients together, underscoring the potential advantages of this combined micronutrient supplementation for the management of AD [168].

Neuroprotective Effects of Microalgae-derived PUFAs: The market demand for omega-3 PUFA-rich oils has been steadily rising over the past 10 years, particularly EPA and DHA [169]. There is a growing need for alternate sources of omega-3 PUFA-rich oils as the increased demand was unmet by the supply from wild fisheries' catches and aquaculture [169]. Other than environmental impact, regular consumption of fatty fish and fish oil supplements may cause health complications in consumers as some fish species may be contaminated by environmental toxicants including methylmercury, organochlorine pesticides, and polychlorinated biphenyls [170,171]. Moreover, some people may find fish and supplements derived from marine creatures to be unappealing to the taste; they are also not an option for vegetarians and vegans [172]. In view of this, microalgal oils have been extensively explored in the scientific and industrial domains as a sustainable fish oil substitute with a high concentration of omega-3 fatty acids and excellent productivity [169]. According to literature, a variety of species and strains of heterotrophic microalgae, including *Crypthecodinium cohnii*, *Schizochytrium* sp., *Thraustochytrium* spp., and *P. tricornutum* have high omega-3 PUFAs content [172]. Among the three major groups of macroalgae, brown algae are the richest source of PUFAs, followed by red, and green algae [173]. Generally, these algal phyla contain higher levels of EPA and relatively low levels of DHA [173].

Since marine creatures obtain and accumulate PUFAs from seaweed and phytoplankton, which are at the base of the marine food chain, fish oils obtained from marine animals are therefore rich in PUFAs [169]. Hence, it stands to reason that consuming marine algae rich in PUFAs could possibly be just as beneficial as consuming fish oils or fatty fish in attaining the health-promoting effects. Indeed, although both fish oil and DHA-rich microalgal oil (DMO) supplementation restored the brain DHA levels to normal levels in mildly omega-3-deficient rat pups, DMO was marginally more effective in this regard due to its higher total omega-3 PUFA content (about 1.3-fold) than fish oil [174]. Balakrishnan et al. [175] reported that oral supplementation of *Isochrysis* sp. biomass markedly improved serum lipid profiles, brain DHA level, and antioxidant status while diminishing the proinflammatory status in Wistar rats. In their subsequent study, they showed that long-term supplementation of this microalgal-derived PUFA in pregnant female Wistar rats can protect the offspring rats against MSG-induced neurotoxicity [176]. The microalgal-derived PUFA enhanced the accumulation of DHA and AA in the brain, while upregulating CREB/BDNF signaling and inhibiting the NMDAR activation [176]. On the other hand, the DGLA omega-6 derived from the green microalga *Lobosphaera incisa* P127 had an anti-inflammatory effect on the LPS-stimulated RAW264.7 macrophages t drastically reduced the levels of intracellular NO, IL-6, and ROS as well as iNOS expression. It also increased PGE1 secretion in a dose-dependent manner [177]. Based on the data, as microalgae are a superior source of omega-3 PUFAs, particularly EPA and DHA, they may be able to generate favorable outcomes comparable to fish oil supplementation in the management of neurodegenerative diseases including AD and PD.

CONCLUSION

Recent research highlights that macroalgae and microalgae contain natural compounds that could be promising treatments for neurodegenerative diseases like AD. These bioactive compounds show promise in mitigating Aβ (suppression of β- and γ-secretase activity), tau pathologies, and alleviating symptoms by enhancing cholinergic functions and preventing glutamate excitotoxicity. Nevertheless, despite the encouraging results observed in *in vitro* and *in vivo* studies, the underpinning mechanisms of action remain elusive, and there is insufficient clinical evidence to adequately support their application in humans. Currently, sodium oligomannate is the only marine algae-derived compound which has been approved for AD treatment in China. Even though the beneficial biological effects of other algal bioactive compounds have been amply demonstrated, the results of preclinical studies may not necessarily translate to humans and are limited by research evidence to support their advancement into clinical studies. Hence, future re-

search in the field of algae-derived compounds and their potential therapeutic applications in AD should prioritize several key directions. Firstly, thorough mechanistic investigations are required to uncover the neuroprotective effects of these compounds. This includes exploring their interactions with key proteins and pathways associated with AD and investigating alternative pathways, such as gut-brain axis modulation. Examining how these compounds affect pathogenic protein aggregation and their interactions with enzymes and receptors involved in AD is also crucial for identifying potential side effects and unintended consequences. Once robust preclinical evidence is established, the translation of findings to human studies becomes paramount. This involves conducting clinical trials with large, diverse patient cohorts and stringent outcome measures to evaluate the efficacy of algae-derived compounds. Longitudinal studies should assess long-term effects and safety, monitoring disease progression, cognitive function, and quality of life. Pharmacokinetic studies are also essential to understand bioavailability and optimal dosing regimens required for effective treatment. Importantly, these studies should take into consideration variations in disease stages, adaptive mechanisms, dose-dependent effects, as well as genetic factors affecting individual responses to treatment. Another interesting area of research is exploring the synergistic effects of combining algae-derived compounds with existing treatments for AD. This could entail studying combination therapies with conventional medications or other nutraceuticals with complementary mechanisms of action, potentially targeting multiple pathogenic pathways of the diseases. As aforementioned, identifying and studying individual bioactive compounds responsible for observed effects enable specific therapeutic targeting, accurate dose optimization, and synergistic combination therapies. This approach can maximize therapeutic efficacy while minimizing adverse effects. Efforts should also focus on optimizing extraction methods to improve the yield and purity of bioactive compounds from marine algae. Standardizing formulations ensures consistent dosing and comparability across studies, which is essential for enhancing therapeutic potential and gaining regulatory approval for clinical use.

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