Neurophysiology
https://doi.org/10.1007/s11062-025-09953-1

Bioactive compounds from marine macroalgae in the treatment and prevention of neurodegenerative diseases

M. Fernanda C. Leal[1,2,3] · Rúben J. G. Duarte[1] · Inês L. Cardoso[1,2,3] · Rita I. L. Catarino[1,2,3] · Adriana M. Pimenta[1,2,3] · M. Renata S. Souto[1,2,3]

Received: 20 January 2025 / Accepted: 17 March 2025

Abstract
To date, neurodegenerative diseases, such as Alzheimer's and Parkinson's diseases, have no cure. The identification of natural compounds that can be used to treat and prevent neurodegeneration is of growing scientific interest. Marine macroalgae are associated with added value in the areas of therapeutics, food, and industry, and are unexplored sources of bioactive compounds including phlorotannins, terpenes, pigments, phytosterols, and polysaccharides, with beneficial properties for human health. Their antioxidant, anti-inflammatory, and anti-amyloidogenic properties increasingly reinforce their great neuroprotective potential, acting to protect against oxidative stress, neuroinflammation, and mitochondrial dysfunction, which are related to the pathophysiology of neurodegenerative diseases. Few compounds from marine macroalgae have been studied in clinical trials to date. However, the recent approval in China by the National Medical Products Administration of a marine macroalgae oligosaccharide, sodium oligomannate, for the treatment of Alzheimer's disease has paved the way for the discovery of drugs with potential for the treatment and prevention of neurodegenerative diseases based on marine macroalgae. This manuscript reviews the mechanisms of neurodegeneration characteristic of diseases such as Alzheimer's and Parkinson's diseases, and the bioactive compounds of marine macroalgae that exhibit neuroprotective effects, as well as their application in the treatment and prevention of neurodegenerative diseases.

Keywords Bioactive compounds · Marine macroalgae · Neurodegenerative diseases · Alzheimer's disease · Parkinson's disease

Introduction

Neurodegenerative diseases, projected to be the second leading cause of death among the elderly population by 2040, are a set of pathological phenomena associated with neuronal degeneration and microvascular dysfunction in the brain [1]. According to the World Health Organization (WHO), there are around 50 million people with dementia, a number that could triple by 2050, rising to 150 million. The increase in average life expectancy, in combination with an unhealthy lifestyle, is directly related to new health problems, accompanied by an increase in the incidence of neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease, and frontotemporal dementia. In Portugal, it is estimated that by the year 2050, a third of the population will be over 65 years old, the age at which this type of condition will become more common. In addition to age, risk factors such as alcohol consumption, tobacco use, an unbalanced diet, environmental pollution, and conditions such as diabetes and obesity contribute to a greater incidence in the development of neurodegenerative diseases [2].

Numerous studies have reported a strong relationship between unbalanced nutrition and the appearance of neurodegenerative diseases. Thus, in recent years, awareness about preventive behaviors through physical and mental exercises, as well as through a balanced diet, has increased, along with the search for new compounds for the treatment

✉ M. Fernanda C. Leal
fleal@ufp.edu.pt

1 FCS-UFP, Faculty of Health Sciences, Fernando Pessoa University, Fernando Pessoa Teaching and Culture Foundation, Rua Carlos da Maia 296, 4200–150 Porto, Portugal

2 RISE-Health, Faculty of Health Sciences, Fernando Pessoa University, Fernando Pessoa Teaching and Culture Foundation, Rua Carlos da Maia 296, 4200–150 Porto, Portugal

3 FP-I3ID, FP-BHS, Fernando Pessoa University, Fernando Pessoa Teaching and Culture Foundation, Praça de 9 de Abril 349, 4249–004 Porto, Portugal

Published online: 10 July 2025

and prevention of neurodegenerative diseases, which has grown exponentially. This search has led to the emergence of more studies of marine species, as their value as a therapeutic and preventive tool becomes increasingly evident [3].

Marine macroalgae are marine organisms and large reservoirs of natural bioactive compounds. They are the largest primitive photoautotrophic and polyphyletic group of eukaryotes, which carry out more than 50% of photosynthesis on our planet [4]. Different types of macroalgae can be found, including Phaeophyceae, Chlorophyta, and Rhodophyta (brown, green, and red algae, respectively), characterized based on the type of pigments that make them up [5]. The vast majority of brown algae thrive in moderate and cold waters, while green and red algae are mainly found in tropical and subtropical waters [6]. Despite being an abundant resource on our planet, the rapid demand and need for these marine organisms, as well as the concern for the preservation of the earth's natural resources, have led to the rapid expansion of the seaweed farming sector. In 2015, global seaweed production resulted in 30.4 million tons, with natural cultivation totaling 1.0 million tons and agricultural cultivation 29.4 million tons [7].

There is a historical association between the potential of seaweed and herbal treatments, particularly in Asian countries, where seaweed has been traditionally consumed and used for hundreds of years [8]. Countries such as China, Japan, Indonesia, the Philippines, South Korea, and North Korea have been exploring the therapeutic properties of these organisms for several generations, using them in traditional Asian medicine. Recently, they have begun to gain a reputation in Western countries, also through the introduction of Asian cuisine, drawing attention to the potential benefits in various areas of health. These marine organisms contain enormous amounts of phytonutrients, including fiber, omega-3, β-carotene, astaxanthin, vitamin C, and other compounds beneficial to human health. In the marine world, with its vast biodiversity, macroalgae have evolved by producing a variety of enzymes and defensive metabolites in diverse environments, including cold coastlines and tropical coral reefs, thus surviving in extreme conditions of nature [9].

The scientific community is increasingly demonstrating and recognizing the interest in the role of these organisms and their therapeutic capacity [10], especially in the anti-inflammatory, antioxidant, immunomodulatory [11], antitumor [12], antidiabetic [13], and neuroprotective fields, where their potential is already recognized. Understanding the role of marine macroalgae in the prevention and treatment of neurodegenerative diseases is an increasingly important and necessary challenge, with the incidence of this type of condition rising. This manuscript will address bioactive compounds with neuroprotective potential, understanding neuroprotection as any activity related to the protection of neurons in the central nervous system (CNS) or peripheral nervous system, which prevents degradation, degeneration, dysfunction, or apoptosis.

Neurodegenerative mechanisms

The study of neurodegenerative mechanisms, as well as their prevention, has been the subject of increasing research in recent times. The term neurodegenerative disease is a general term that refers to certain clinical conditions that cause the degeneration of neurons in the CNS, leading to neuronal dysfunction, loss of brain function, and eventual cell death [14]. These processes occur progressively and continuously and are characterized by being the foundation of many neurodegenerative diseases such as Alzheimer's and Parkinson's diseases and multiple sclerosis. They are the most common neurodegenerative diseases, and future forecasts show a progressive worsening of these pathologies, especially in aging countries such as Portugal. Neurodegenerative diseases are triggered by a diverse number of factors, including oxidative stress, impaired mitochondrial function, abnormal protein aggregation, deficiencies in the proteostasis process, and neuroinflammation.

Alzheimer's disease neurodegenerative mechanisms. Alzheimer's disease is a type of dementia, the most common type accounting for 50 to 70% of all cases. Therefore, followed by Parkinson's disease, it is the most prevalent neurodegenerative disease in the world. According to "Health at a Glance", a report by the Organization for Economic Cooperation and Development [15], Portugal ranks as the 4th country with the most cases (19.9 for every 1000 inhabitants).

Alois Alzheimer first described this condition in 1906, and this data was published in 1907 [16]. This dementia is morphologically characterized by the abnormal extracellular arrangement of amyloid plaques between nerve cells. It is also characterized by the intraneural accumulation of hyperphosphorylated tau protein, resulting in the formation of intracellular neurofibrillary tangles, oxidative stress, neuroinflammation, ferroptosis, and synaptic dysfunction [17]. The relationship between these two phenomena and the way they act synergistically in the progression of neurodegenerative processes makes their study multifactorial and complex [18].

Regarding biochemical aspects, the most significant change in a patient with Alzheimer's is the reduction in acetylcholine (ACh) levels in the hippocampus and cortex of the brain. A marked deterioration occurs, with a decrease in the number of neurons responsible for cognition, memory, and neuronal processes. Many non-genetic fac-

tors can contribute to this state of dementia, including diabetes, dyslipidemia, smoking, traumatic brain injuries, stress, depression, inadequate sleep, blood pressure issues, and cardiovascular disease, among others [19]. The main symptoms of these patients include persistent and recurrent memory problems, speech difficulties, emotional instability, lack of understanding of questions and directions, as well as the need for support with basic tasks, hygiene, and social habits [20]. This disease gradually and progressively destroys nervous tissue, leading to a state of confusion and disorientation in space and time [21].

Amyloid-β (Aβ) and the accumulation of amyloid plaques. Amyloid plaques are globular deposits composed of extracellular clusters of the amyloid-β (Aβ) peptide, resulting from the improper cleavage of the amyloid precursor protein (APP) [22]. The extracellular deposition of these peptides is one of the distinctive characteristics of Alzheimer's disease. APP is a transmembrane protein located in the synapses of neurons and participates in the regulation and formation of synapses, as well as in the processes of neuroplasticity, neuronal growth and repair, and intracellular transport, among others [23].

APP cleavage involves three enzymes: α-, β-, and γ-secretases, and can occur through two pathways. In normal and physiological non-amyloidogenic processing, APP is cleaved by the α-secretase pathway, specifically between residues 16 and 17 of the Aβ domain, yielding a soluble fragment, sAPPα, that has a neuroprotective function. The presence of sAPPα is associated with adequate synaptic plasticity, learning, memory, emotional behavior, and neuronal survival [24]. A remaining C-terminal fragment of APP (C83), bound to the membrane, is then cleaved by γ-secretase to release a non-toxic extracellular peptide called P3 [25], which is soluble and has a normal synaptic signaling function.

In the amyloidogenic pathway, APP is cleaved by β-site amyloid precursor protein-cleaving enzyme 1, or β-secretase 1 (BACE1), cleaving APP initially below the α-secretase cleavage site at the *N*-terminus, yielding sAPPβ and removing most of the extracellular portion of the protein. A membrane-bound C-terminal fragment, CTFβ or C99, is then cleaved by γ-secretase, resulting in the formation of insoluble and neurotoxic Aβ fragments, which, in the extracellular fluid, are capable of forming large agglomerates, giving rise to amyloid plaques [23, 26]. Ultimately, the formation of these plaques induces a pathway of cell death, which is one of the original causes of disease progression. This accumulation process can occur decades before the onset of symptoms.

Aβ is present in all humans, comprising Aβ fragments 40 and 42, with Aβ40 being the most common. Although physiological levels of Aβ are crucial for plasticity, neuronal survival, neurotransmission, and memory, high concentrations are associated with neuronal death [27]. Neuronal toxicity is mainly caused by Aβ1-42, increasing the tendency for plaque formation and aggregation [28]. In Alzheimer's disease, an anomalous enzymatic action of this peptide occurs, leading to its accumulation and the formation of senile plaques, which are the main biomarker of this disease.

Hyperphosphorylation of tau protein and formation of neurofibrillary tangles. Another characteristic alteration present in Alzheimer's disease is the dysregulation of the phosphorylation of tau protein, a protein that is encoded by the *MAPT* gene located on chromosome 17. Tau protein plays an important role in the formation and maintenance (binding function) of microtubules [29], which are intracellular structures of the neuronal cytoskeleton whose function is to conduct elements of the cell body (such as neurotransmitter precursors, neuropeptides, among others) from the neuron to the synaptic terminal. Any anomaly in tau protein can lead to neuronal degeneration. In a healthy brain, the phosphorylation of this protein is a balanced process between kinases and phosphatases, resulting in 2–3 phosphorylated tau amino acid residues. However, when there is an imbalance, on average, around 9 residues are phosphorylated, which can result in the dissociation of tau protein from microtubules, leading to their accumulation and aggregation into oligomers, as seen in Alzheimer's disease [30]. This aggregation of oligomers has toxic potential, being considered the main neurotoxin responsible for inducing neuronal loss in patients with Alzheimer's [31]. Moreover, these oligomers can promote the spread of the disease by being released into the extracellular space and taken up by healthy neurons. These oligomers can also activate microglial cells that induce neuroinflammation [32].

Hyperphosphorylation results in the loss of the microtubule-binding function of tau protein and the formation of insoluble neurofibrillary tangles that accumulate within the neurons of patients with Alzheimer's disease. These neurofibrillary tangles cause damage to microtubules, affect transport within neurons, and lead to loss of synapses and cell death. This hyperphosphorylation may originate from changes in the activity of tau phosphatases and kinases; thus, a possible therapeutic approach may involve the inhibition of tau kinases such as GSK-3β, CDK5, CK-1, PKA, CaMK II, and MAPK, thus reducing hyperphosphorylation and its pathogenic effect [29].

Parkinson's disease neurodegenerative mechanisms. Parkinson's disease is a neurodegenerative condition, first described by James Parkinson in 1817 [33], that affects the CNS. It is the second most prevalent neurodegenerative disease in the world's population, affecting approximately 2 to

3% of the population over 65 years. According to the Portuguese Society of Neurology, in 2017, there were around 20,000 people diagnosed in Portugal, based on the prevalence reported by a national study [34], a number that has been growing in more developed countries, usually appearing between 50 and 80 years of age. According to a 2016 study, it is estimated that there are around 6.1 million people diagnosed worldwide, compared to just 2.5 million in 1990 [35].

Parkinson's disease is characterized by the progressive loss of dopamine-producing neurons in the substantia nigra, a region of the brain that regulates movement, and by the aggregation of intraneuronal α-synuclein. The consequent neuronal death leads to a decrease in dopamine levels, resulting in symptoms such as tremors, rigidity, bradykinesia, and fragile posture, as well as other motor symptoms such as gait blockages, hypomimia, hypophonia, and dysphagia [36].

Lewy bodies and α-synuclein accumulation. Although the exact etiology of Parkinson's disease is not yet fully known, it is believed to be caused by a combination of hereditary and environmental factors. Lewy bodies, abnormal aggregates of proteins that accumulate in brain neurons, are one of the main pathological features of Parkinson's disease. Lewy bodies, which in turn induce the degeneration and death of dopamine-producing neurons, include insoluble α-synuclein aggregates, the accumulation of which is a key factor in the onset and progression of the disease [37]. This accumulation occurs abnormally in neuronal tissue, evolving and spreading to different areas of the nervous system, mainly in the substantia nigra pars compacta. From there, the loss of dopaminergic neurons and consequent motor weaknesses characteristic of the disease occur [38].

Pathological α-synuclein triggers neurodegenerative mechanisms such as microglial activation, and according to several authors, its oligomerization is related to the production of reactive oxygen species (ROS) and the release of proinflammatory cytokines [39–41]. It is also believed that the formation of α-synuclein deposits is a cofactor in mitochondrial dysfunction [42], genomic instability, and that presynaptic aggregates of α-synuclein contribute to synaptic loss and cognitive dysfunction [43].

Phosphorylation of α-synuclein by protein kinases can erroneously modify the unfolded protein response signaling pathway and the lysosomal signaling pathway, inhibiting α-synuclein degradation and increasing its toxicity. In addition to this phosphorylation contributing to increased ROS production, it can also obstruct mitochondrial metabolism, leading to its dysfunction. This process can also cause obstruction of the endoplasmic reticulum, leading to an influx of calcium that can potentiate even more α-synuclein aggregation and ROS production [44].

Alzheimer's and Parkinson's disease similar neurodegenerative mechanisms. Neurodegenerative diseases, despite being individually complex, share similarities in some mechanisms, such as neuroinflammation, oxidative damage caused by ROS and reactive nitrogen species (RNS), loss of synaptic function, mitochondrial dysfunction, ferroptosis, and poor protein folding, among others [45]. Although the pathophysiology of these brain diseases is not exactly known, it has been shown in several studies that oxidative stress, neuroinflammation, mitochondrial dysfunction, and protein misfolding play a significant role in their development [46]. Oxidative stress and neuroinflammation are two distinct processes that occur in diverse pathological events that interact with each other throughout the disease process. Thus, by inhibiting neuroinflammation, it is possible to reduce oxidative stress and vice versa.

Oxidative stress. Oxidative stress refers to a state of high intercellular levels of ROS and RNS that cause damage to lipids, proteins, and DNA. It is closely linked to a large number of pathologies [47] and occurs when antioxidant defenses are not sufficient to maintain ROS and RNS concentrations at a moderate level. When this phenomenon occurs and the production of ROS and RNS exceeds the antioxidant capacities, certain mechanisms are created that culminate in cellular degeneration. Due to a large consumption of oxygen and lipid content, the CNS is more sensitive to this phenomenon compared to other parts of the human body, resulting in a cascade of events that leads to cell death in neurodegenerative pathologies. Therefore, several studies have stated that this process and lack of antioxidant balance are involved in the pathogenesis of neurodegenerative diseases [48].

Free radicals generated in mitochondria help cells fight infections but can also damage the cell membrane of neurons or the DNA [49]. Neuronal cells are rich in polyunsaturated fatty acids, which are highly sensitive to peroxidation. Cells use antioxidant mechanisms through enzymes such as superoxide dismutase (SOD) and glutathione (GSH) to protect against cellular oxidation, inhibit damage to cellular DNA, and prevent apoptosis.

Oxidative imbalance accelerates the progression of Alzheimer's disease, and the ROS accumulation caused is correlated to the accumulation of Aβ aggregates. In Parkinson's disease, mitochondrial dysfunction caused by this imbalance is also related to the progression of the disease, generating excessive ROS and inducing neuronal apoptosis [50].

Being one of the main causes of aging and a precursor of various types of pathologies, such as cardiovascular diseases, diabetes, and cancer, in addition to the already mentioned neurodegenerative diseases, oxidative stress is also aggravated by environmental and lifestyle factors, such

as stress, diet, smoking, alcohol consumption, and pollution, making the human body's natural defenses insufficient against these external aggressions and the overproduction of ROS. In this context, antioxidants are important for supporting the endogenous mechanisms of the human body.

Neuroinflammation. Inflammation is the pathophysiological mechanism underlying many chronic diseases, such as cardiovascular disease, diabetes, certain types of cancer, arthritis, and neurodegenerative diseases. Although it is a normal process of the body's immune response to injury or infection, chronic inflammation has been linked to neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease. Inflammatory molecules and activated immune cells can contribute to the degeneration of neurons and the formation of characteristic protein aggregates in the brain, contributing to the progression and development of neurodegenerative diseases. Although other types of cells are also involved in neurodegeneration-mediated inflammation, glial cells, namely astrocytes and microglia, which are chronically activated in the brain, are considered critical components of immunological aggression to neurons, acting in the triggering and progression of these diseases [51].

Astrocytes, responsible for providing structural support to neurons and regulating the chemical environment, when activated by an inflammatory response, can release pro-inflammatory substances and contribute to the inflammatory response in the CNS. Unlike other immune cells such as macrophages, microglia permanently reside in the CNS, being the main immune cells of the CNS. These cells play a role in surveillance and have the ability to detect and respond to changes in the brain environment, including damage, infections, and the accumulation of anomalous proteins [52].

Several studies observe that the chronic activation of these cells and the excessive release of pro-inflammatory mediators trigger the development of neurological degeneration and thus contribute to the pathogenesis of Parkinson's disease, Alzheimer's disease, and multiple sclerosis [53]. Some examples of pro-inflammatory factors are nitric oxide (NO), a toxic molecule that can lead to oxidative stress and DNA damage, prostaglandin E2 (PGE2), an inflammatory mediator, as well as inflammatory cytokines such as interleukin (IL)-1β, IL-6, and tumor necrosis factor (TNF)-α, which trigger inflammatory responses and may contribute to cell death [54]. Understanding the interactions between glial cells, neurons, and the immune system is crucial for developing therapies aimed at modulating inflammation in the brain.

Degradation of cholinergic neurons. Alzheimer's disease is closely associated with decompensation caused by the degradation of cholinergic neurons, accelerating the neurodegenerative process. However, recent studies have shown that this phenomenon also occurs severely in cases of dementia associated with Parkinson's disease. Cholinergic neurons, which have an extensive distribution in the brain, play a fundamental role in human cognition. These produce ACh, a neuro-mediator involved in signal transduction related to memory and learning capacity [55]. ACh is synthesized by acetyltransferase and is essential for the suppression of inflammation processes. In neuronal signaling, human acetylcholinesterase (AChE) is an important enzyme responsible for the degradation of ACh, which in turn blocks the transmission of the postsynaptic signal. Reduced levels of the neuromediators ACh and butyrylcholine (BCh) have been observed in the brains of patients with Alzheimer's disease. For this reason, the inhibition of the enzymes AChE and butyrylcholinesterase (BChE), responsible for the hydrolysis of ACh and BCh respectively, has become a treatment option for these types of neurodegenerative diseases [56].

Accumulation of metals. Iron is involved in several processes such as transport, storage, and activation of oxygen, being a central element of hemoglobin, responsible for transporting oxygen throughout the body. It is essential for cellular respiration and an important component in enzymes involved in the electron transport chain and energy production. It also plays a role in the processes of regulating dopamine and serotonin neurotransmitters in the brain [48, 57].

Based on several studies, there is a growing relationship between iron accumulation and neuroinflammation processes and the progression of neurodegenerative diseases [58, 59]. When poorly regulated, excess iron can aggravate oxidative stress processes that degrade lipids, proteins, and cells such as astrocytes, microglia, and neuronal cells, and is also associated with mitochondrial dysfunction that leads to an energy deficit and increased production of ROS through the Fenton reaction, initiating the process of oxidative stress and the inflammatory cascade [60, 61].

Several studies [62, 63] have also reported a link between disorders in iron metabolism and the promotion of protein aggregation, as well as their malformation, accelerating the aggregation and deposition of the Aβ peptide and hyperphosphorylation of the tau protein in Alzheimer's disease, as well as the accumulation of α-synuclein in Parkinson's disease, with the ability to accelerate the rate of aggregation and formation of Lewy compounds. This discovery points to the importance of the bond between iron and α-synuclein for the development of Parkinson's disease.

According to several scientific studies, iron deposition may not be an initial process in Parkinson's disease but plays a major role in the degeneration of the substantia nigra, a heterogeneous portion of the midbrain responsible

for the production of dopamine in the brain [64]. While the initial causes of the disease are not yet well defined, the substantia nigra of patients with Parkinson's disease, where the loss of dopaminergic neurons occurs, shows an increase in the content of this metal. Neuromelanin, a granular pigment present in dopaminergic neurons, binds to iron in the form of Fe^{3+} and has a chelating effect on this metal, blocking it and thus preventing the formation of free radicals by the Fenton reaction as well as the dopaminergic oxidation resulting from oxidative processes. However, excessive ROS production resulting from the saturation of neuromelanin chelating sites has been detected in patients with Parkinson's disease [65]. The use of iron chelators has been proven effective in preventing neurodegeneration in several animal models, highlighting the pivotal role of iron as a mediator of neuronal death in Parkinson's disease [66].

In patients with Alzheimer's disease, elevated levels of copper have also been detected, which may promote hyperphosphorylation of tau protein and deposition of Aβ. Studies involving copper chelating agents resulted in an attenuation of tau protein hyperphosphorylation in human neuroblastoma cells and suppressed levels of copper. According to some studies, this led to a significant attenuation of tau protein hyperphosphorylation in transgenic mice [58, 67]. Copper chelators can also inhibit the activity of the β-secretase enzyme [66, 68, 69].

Regarding zinc, this metal plays an essential role in the brain and its normal functioning. However, imbalances in zinc levels may contribute to the development of Alzheimer's disease since it is involved in the processing and degradation of the Aβ peptide [58, 70]. Some studies have reported increased zinc levels in senile plaques, while other studies have reported reduced zinc content in specific brain regions of patients with Alzheimer's disease [69]. The reasons for this discrepancy are still unclear, but it suggests that normal zinc levels in the brain are important for neuronal functions, while deviations from its normal level are detrimental [69]. In pathological conditions, excess zinc is released from presynaptic neurons and astrocytes, causing increased ROS production and microglial activation, leading to neurodegeneration [71].

Studies have also shown that intracellular calcium dysregulation is an early manifestation of Alzheimer's disease and that calcium concentrations in Aβ deposits are significantly increased. Ca^{2+} can promote the production of Aβ and its toxicity, while Aβ also contributes to the increase in intracellular calcium, resulting in an exacerbated development of neurodegeneration in patients with Alzheimer's disease [72, 73]. Its role as a potentiator of oxidative stress and high production of free radicals is also known, with activation of microglia and astrocytes in the brain, leading to dose-dependent production of glutamate and calcium influx, resulting in neuronal death.

Dysregulation of cholesterol metabolism. Cholesterol is a major constituent of the CNS, accounting for 25% of all cholesterol in the human body [74]. It plays a crucial role in the CNS and is primarily involved in the formation of myelin sheaths, which surround axons. Cholesterol-rich myelin sheaths serve as insulators and are essential for the proper functioning of the nervous system, as they protect axons and allow efficient transmission of nerve impulses [75].

Liver X receptors (LXRs) have been shown to control cholesterol homeostasis in the brain at different stages by negatively regulating cholesterol uptake from neurons through degradation of the low-density lipoprotein receptor (LDLR) by an inducible degrader of LDLR (IDOL), increasing cholesterol efflux from neurons through activation of LXRs by a synthetic agonist, and finally regulating the supply of cholesterol from astrocytes to neurons. It is now known that the latter is the main source of cholesterol for neurons [76]. In the plasma membranes of patients with Alzheimer's disease, cholesterol levels appear to increase throughout the development of the disease, and studies indicate that this accumulation of cholesterol triggers an increase in Aβ production by increasing BACE1 activity on APP [77].

Apolipoprotein E (APOE) plays a key role throughout the body by helping to transport cholesterol and other lipid molecules. The gene coding for APOE exists in different allelic forms, the most common being the *APOE3* allele. The most prominent is the *APOE4* gene, which has long been linked to an increased risk of dementia in Alzheimer's disease. People who inherit one copy of the *APOE4* gene (heterozygous condition) have up to a fourfold increased risk of developing dementia. Inheriting two copies of *APOE4* (homozygous state) increases the risk up to twelvefold. However, despite years of study, there is still little understanding of how the isoenzyme APOE4 affects the human brain and increases the risk of dementia [78].

Dysregulation of intestinal microbiota. Recent studies have been exploring the potential of modulating intestinal microbiota to reduce the risk of neurodegenerative damage and its use as an effective strategy for controlling and improving associated symptoms. These studies are possible thanks to advanced sequencing techniques that allow the identification of different bacterial communities residing in the intestines of healthy individuals and allow comparison with other individuals, with a reduced diversity of the intestinal microbiome being associated with the etiology of Alzheimer's and Parkinson's diseases [79, 80].

The gastrointestinal nervous system, which contains between 200 and 500 million neurons, is in constant contact with the central nervous system, and this two-way communication is referred to as the "gut-brain axis", con-

sisting of neurochemical, endocrine, and immunological interactions. Adopting certain types of diet can increase the prevalence of certain bacterial communities associated with the production of metabolites beneficial to the intestinal microbiota. In relation to neurodegenerative diseases, certain studies have detected large differences in the diversity of the gut microbiota of patients with Alzheimer's and Parkinson's when compared with healthy controls [81, 82]. It is estimated that there is an imbalance in the microbiome of around 1000 different species of bacteria. This imbalance is normally characterized by an abnormal abundance of pathogenic bacteria, capable of releasing endotoxins that promote inflammation and compromise the integrity of physiological barriers. Most (80%) of the microbiome composition is from the *Bacteroidetes* and *Firmicutes* families, while in a healthy human, pathogenic species such as *Campylobacter jejuni, Salmonella enterica*, and *Bacteroides fragilis* exist at a prevalence below 0.1% [83].

Braniste et al. [84] showed that the integrity of the blood-brain barrier and the intestinal epithelial barrier also depends on the composition of the intestinal microbiota and that the lack of diversity of this microbiota leads to defects in microglial maturation, differentiation, and function, as well as in the permeation and entry of immune cells peripheral to the brain and secondary metabolites from the intestinal microbiota. These researchers also suggest that this deficient permeation allows the passage of large amounts of amyloid derivatives and lipopolysaccharides (LPS) that can indirectly cross these physiological barriers through other pro-inflammatory molecules that normally transit, thus contributing to neurodegenerative pathology. The reduced presence of species such as *Faecalibacterium prausnitzii* and *Eubacterium rectale*, as well as the abundance of the *Escherichia* and *Shigella* genera, appears to be directly related to the brain accumulation of Aβ in Alzheimer's disease [85].

A more detailed narrative review investigating the role of microbiota in Alzheimer's disease was conducted by Bairamian et al. [86], which concluded that bacteria of the genus *Firmicutes* are reduced in patients with Alzheimer's and reported an association between microbiome dysbiosis and an increase in pro-inflammatory microbes, as well as a decrease in anti-inflammatory commensals.

In a meta-analysis obtained from several healthy individuals, it is possible to observe a high abundance of bacteria from the *Firmicutes* and *Bacteroidetes* families, as well as *Actinobacteria* and *Proteobacteria* [87]. The idea that a set of microorganisms in the intestine can affect the brain may seem surprising. However, several animal studies report the importance of this 'gut-brain axis' in processes such as neuroinflammation, suggesting that certain foods help reduce inflammation by being converted into short-chain fatty acids with anti-inflammatory activity, proving to be able to improve memory [88]. In a study that tested the effects of a high-fiber diet and its effect on microglia, both in adult and aged rats, it was observed that the diet altered their intestinal microbiome, increased the production of short-chain fatty acids, and reduced the expression of several genes related to neuroinflammation. In older rats, the dysregulated microglia returned to their normal and healthy state, comparable to younger rats [89].

In another meta-analysis, associations were found between Parkinson's disease and changes in the numbers of certain bacterial species, including an increase in the genera *Lactobacillus, Akkermansia*, and *Bifidobacterium*, as well as a reduction in the family *Lachnospiraceae* and the genus *Faecalibacterium*, both described as producers of short-chain fatty acids [90], important microbial mediators of the gut-brain axis [91]. In clinical studies of Parkinson's disease, two studies with patients showed a relationship between severe decline in motor skills over time and decreased abundance of short-chain fatty acid-producing bacteria (*Prevotella* and *Barnesiella*), when compared to patients with less decline in motor skills [92, 93].

In general, as demonstrated by the review carried out by Fakhri et al. [94], carotenoids, polysaccharides, phytosterols, terpenoids, and other bioactive compounds extracted from marine macroalgae have biological activities capable of modulating the intestinal microbiota and having a neuroprotective effect by modulating dysregulated pathways in neurodegenerative conditions.

Neuroprotective activity of bioactive compounds from marine macroalgae

Phlorotannins. Phlorotannins, phenolic compounds exclusive to brown macroalgae (such as *Ecklonia cava, Ecklonia maxima, Eisenia bicyclis*, and *Ishige okamurae*), are distinguished by the peculiar polymerization of phloroglucinol (1,3,5-trihydroxybenzene) units and can be classified into different groups depending on the number of hydroxyl groups present. They are found mainly in cell walls and play an important role in protecting cells against environmental aggression, such as high levels of salinity, limited availability of light and nutrients, microorganisms, and UV radiation. These phenolic compounds have been studied for their potential health benefits in various contexts, such as antioxidant, anti-inflammatory, antiviral, and anticancer, but their ability to act as neuroprotective agents opens up new research opportunities [95].

Due to their therapeutic properties and the prevention of some pathologies, polyphenols, such as phlorotannins, have gained attention from the scientific community among secondary metabolites. Studies demonstrate the therapeutic capacity of phlorotannins isolated from *Ecklonia cava*,

specifically their anti-HIV activity, inhibiting the reverse transcriptase enzyme [96]. Phlorotannins also demonstrate bactericidal capacity against several bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA) and *Escherichia coli* [97]. Fucofuroeckol A has demonstrated strong in vitro bactericidal potential, working in synergy with streptomycin [98].

In another context, it was demonstrated that phlorotannins can act in the conversion of angiotensin I to angiotensin II, inhibiting the angiotensin-converting enzyme. It has also been shown that phlorofucofuroeckol A has the greatest inhibitory action, and although it does not reach the potential of captopril, it may be a valuable approach in the treatment of hypertension [99]. Its use as a skin lightener in pigmentation problems is also known, and recent examples, such as the case of a phlorotannin temporarily named 974-A (due to its molecular weight being 974), were identified for the first time as a potent inhibitor of tyrosinase, an enzyme involved in melanin synthesis [100].

Of the approximately 150 phlorotannins reported from brown algae, dieckol, present in macroalgae such as *Ecklonia cava* and *Eisenia bicyclis*, together with phlorofucofuroeckol A, contributed positively to the increase in neurotransmitters in the brain of an animal model, especially ACh, by inhibiting the activity of AChE, as well as stimulating memory [101, 102]. In another study, the neuroprotective action of dieckol was observed through the elimination of ROS, activating the transcription factor Nrf2, which is involved in the regulation of cellular response to oxidative stress, and activating heme oxygenase I (HO-1), an enzyme also responsible for mitigating oxidative stress, inflammation, and cellular damage [103].

Dieckol and eckol extracted from *Eisenia bicyclis*, also known as wire algae or sea oak, have shown their effectiveness by inhibiting monoamine oxidase (MAO)-A and MAO-B, enzymes that degrade endogenous monoamines such as dopamine, serotonin, noradrenaline, and adrenaline. Since in Alzheimer's disease, serotonin and noradrenaline are reduced, and in Parkinson's disease, the same happens with dopamine levels, this neuroprotective action of dieckol and eckol allows initial control of the progression of these pathologies and exhibits antidepressant activity [104].

Recently, Yoon et al. [105] reported the ability of dieckol to act as a potent inhibitor of Aβ production by regulating several protein kinases (PI3K, Akt, and GSK-3β). The discovery of phlorotannins such as dieckol, eckol, and 8.8'-bieckol, which have neuroprotective effects by inhibiting the BACE1 enzyme, can synergistically improve the drug action and treatment of patients with Alzheimer's disease. Consistent with this study, another by Lee & Jun [106] states that, in terms of the structure-activity relationship, the quantity and location of hydroxyl groups on the phenolic ring are generally responsible for the neuroprotective properties of phenolic compounds. It was shown that dieckol (IC50 of 2.2 μM) had an inhibitory effect on BACE1 five times higher than eckol (IC50 of 12.2 μM) [106]. In a study where these compounds were also evaluated against Aβ25–35-mediated cytotoxicity in animal cells, they all suppressed the inflammatory response by inactivating the NF-κB transcription factor [107]. The same effect was confirmed by Jung in relation to dieckol, as it reduced the expression of pro-inflammatory mediators and cytokines [108].

A similar study demonstrated that six phlorotannins, including phloroglucinol, eckstolonol (dioxinodehydroeckol), 7-phloroeckol, eckol, phlorofucofuroeckol A, and dieckol, extracted from *Eisenia bicyclis*, showed a protective action against Aβ by reducing ROS generation and Ca^{2+} release in PC12 cells (a cell line derived from a rat adrenal medulla pheochromocytoma). The two compounds with the greatest neuroprotective activity are 7-phloroeckol and phlorofucofuroeckol A. This neuroprotective activity against Aβ cytotoxicity seems to be directly related to molecular size and the number of hydroxyl groups [109]. In a study by Jung et al. [110] with the same compounds also isolated from *Eisenia bicyclis*, researchers confirmed that the anti-inflammatory effects were in sufficient quantity to inhibit nitric oxide (NO) production by reducing the levels of nitric oxide synthase (NOS) and cyclooxygenase-2 (COX-2) and ROS production induced by tert-butyl hydroperoxide in RAW 264.7 macrophages.

In a study conducted to evaluate the neuroprotective activities of phloroglucinol, the results of the cell viability assay showed that phloroglucinol protected SH-SY5Y cells from hydrogen peroxide-induced cell death. In addition, intracellular levels of ROS and oxidation markers in the cells were reduced by pretreatment with phloroglucinol [111]. Phloroglucinol, which is found in large quantities in the brown seaweed *Ecklonia cava*, was also studied by Yang and demonstrated the ability to attenuate Aβ-induced ROS accumulation in HT-22 cells, as well as to attenuate the reduction in the density of dendritic spines, crucial for synaptic connections and neuronal communication, in rat hippocampal neurons caused by Aβ, thus preventing cognitive degeneration in this animal model [112]. The same authors conducted a study that demonstrated the efficacy of oral administration of phloroglucinol from *Ecklonia cava* in 6-month-old mice expressing the human APP and PSEN1 transgenes, with a total of five mutations related to Alzheimer's disease (5XFAD mice). The treatment resulted in a significant decrease in the number of amyloid plaques and in the protein level of BACE1, and in accordance with the previous study, a decrease in the density of dendritic spines and the number of mature dendritic spines in the hippocampus was observed [113].

In a study by Kannan et al. [114], the use of AChE inhibitors was investigated as an approach to treat symptoms of neurodegenerative diseases, as well as other strategies to halt the progression of neurodegeneration. In this study, several phlorotannins were isolated from *Ecklonia maxima*, a brown seaweed abundant on the South African coast and used to produce alginate, animal feed, food supplements, and fertilizers. These compounds were observed to have inhibitory activity on AChE. Of the tested compounds, 1,4-dioxine-2,4,7,9-tetraol and eckol exerted a more effective action compared to phloroglucinol [114].

In another study by Yoon et al. [115], substances extracted from the seaweed *Ishige okamurae* were examined, and phlorotannins such as 6,6'-bieckol and diphlorethohydroxycarmalol (DPHC) demonstrated strong inhibitory capacity of AChE and a reasonable action on BChE [115]. This was reinforced in a recent study, where DPHC isolated from the brown seaweed *Ishige foliacea* increased cell viability and exerted a protective effect against hydrogen peroxide-induced damage in HT22 cells (rat hippocampal neuronal cell line used for studies of glutamate-induced toxicity in neuronal cells), in addition to attenuating ROS production, lipid peroxidation, and intracellular Ca^{2+} levels [116].

When it comes to breaking the amyloidogenic process related to diseases such as Alzheimer's, phlorotannins could slow down the production of Aβ [106]. Shrestha et al. [117], using phlorotannin-rich extracts from *Ecklonia radiata*, namely dibenzodioxin-fucodiphloroethol, tested in PC-12 cells, explored the neuroprotective capacity through the inhibition of Aβ aggregation, AChE activity, as well as the inhibition of ROS formation, proving to be a neuroprotective compound through several mechanisms.

Table 1 summarizes the neuroprotective activity observed in the mentioned studies for phlorotannins extracted from different marine macroalgae species.

Terpenes. Terpene is a general term for hydrocarbons and their derivatives, obtained through the polymerization of isoprene units. According to their structures and biological functions, they are usually divided into monoterpenes, sesquiterpenes, diterpenes, and polyterpenes [118]. Brown macroalgae are considered one of the main sources of biologically and ecologically relevant terpenes, mainly diterpenes and meroditerpenes [119]. Meroterpenoids are predominant in the genus *Sargassum*, with sargachromenol being the best known.

In a study on the effects of sargachromenol isolated from the macroalgae *Sargassum macrocarpum*, the ability to promote neuronal growth factor (NGF), which has a crucial role in neuronal differentiation, survival, and regeneration, was demonstrated [120]. In another study [121], two known meroterpenoids, sargaquinoic acid and sargachromenol, were isolated from the macroalgae *Sargassum sagamianum*. Both compounds exerted a moderate inhibitory role on the AChE enzyme, while sargaquinoic acid demonstrated remarkable inhibition of BChE.

In a different study [122], it was proven that *Caulerpa* species (*Caulerpa racemosa* and *Caulerpa prolifera*) are rich in terpenoids and that their most relevant sesquiterpene can be easily extracted and used as an inhibitor of lipoxygenase, a family of ferric enzymes increased in Alzheimer's disease [123].

In an investigation into electrophilic compounds capable of exerting neuroprotection, a sesquiterpene of interest, zonarol, extracted from the brown macroalgae *Dictyopteris undulata*, stood out by exerting, through the activation of the Nrf2/ARE pathway, an intrinsic defense mechanism against oxidative stress, being the first electrophilic compound reported from marine macroalgae. At a concentration of 1 µM, zonarol almost completely prevented cell death induced by 5–20 mM glutamate in HT22 cells, highlighting its protective and therapeutic potential as a target for future studies. Glutamate induces cell death by depleting intracellular glutathione levels [124].

A recent study of the brown macroalgae *Bifurcaria bifurcata*, mainly found on the Atlantic coast, demonstrated the antioxidant and neuroprotective capacity of its two main diterpenes through the determination of mitochondrial membrane potential, H_2O_2 production, and caspase-3 activity. The fraction with the greatest neuroprotective action was subjected to a purification process, revealing the well-known eleganolone and eleganonal, both exhibiting great antioxidant potential and proving to be excellent candidates for further studies in the prevention and/or treatment of Parkinson's disease [125].

A study that aimed to deepen the therapeutic effects of the bioactive compounds of *Sargassum serratifolium*, in addition to the already known antimicrobial, anti-inflammatory [126], and anti-carcinogenic effects [127] and known efficacy in pathologies related to hyperpigmentation [128], focused on evaluating meroterpenoids isolated from this species and assessing their neuroprotective capacities. It concluded that these compounds inhibited AChE, BChE, and BACE1, and may be beneficial for the treatment of Alzheimer's disease [129].

Table 2 summarizes the neuroprotective activity observed in the mentioned studies for terpenes extracted from different marine macroalgae species.

Pigments. In addition to their ecological relevance, pigments have gained enormous attention within the extensive repertoire of bioactive compounds of marine algae, given that they are also directly related to the taxonomy and classification of marine organisms. These pigments, responsible for the vibrant colors presented by macroalgae, have been

Table 1 Neuroprotective activity of phlorotannins extracted from marine macroalgae

Species	Extracted compounds	Effect	Assay	Reference
Ecklonia cava	Dieckol, Eckol, 8,8'-Bieckol	Inhibition of Aβ production by expressing the PI3K/Akt and GSK-3β pathways	N2a cells (mutant APP overexpressed)	Yoon et al. [105]
	Dieckol	↓ ROS production ↓ pro-inflammatory mediators ↑i-NOS and COX-2	LPS-stimulated BC2 microglial cells	Jung et al. [108]
	Dieckol, Eckol 8,8'-Bieckol	Potent inhibitory capacity of AChE and BChE	–	Lee et al. [106]
	Phloroglucinol	↓ Amyloid plaques ↓ BACE1 ↓ Density of dendritic spines	Mice with increased APP and PSEN1 transgenes	Yang et al. [113]
		↓ Density of dendritic spines ↓ Intracellular ROS	HT-22 cells, induction of Aβ toxicity	Yang et al. [112]
	Phloroglucinol, Eckstolonol, 7-Phloroeckol, Eckol, Phlorofucofuroeckol A, Dieckol, fucosterol	↓ NO production ↑i-NOS and COX-2 ↓ ROS production Suppression of the NF-kB pathway	RAW 264.7 macrophages	Jung et al. [110]
	Dieckol, Phlorofucofuroeckol A	Increased neurotransmitters (ACh) Memory stimulation	Mice pretreated with ethanol	Myung et al. [102]
Ecklonia radiata	Dibenzodioxin-fucodiphloroethol	↓ Aβ41–42 aggregation ↓AChE activity ↑ ROS scavenging capacity	PC12 cells	Shrestha et al. [117]
Ecklonia maxima	1,4-Dioxine-2,4,7,9-tetraol, Eckol	↓ AChE activity	–	Kannan et al. [114]
Eisenia bicyclis	Dieckol, Eckol	Protection of primary neurons and HT22 cells ↓ Oxidative stress Nrf-2/HO-1 activation (↑ antioxidant defenses) Inhibition of MAO-A and -B	HT22 cells (cellular model to evaluate glutamate-induced toxicity in neuronal cells)	Cui et al. [103] Jung et al. [104]
	Phloroglucinol, Eckstolonol, 7-Phloroeckol, Eckol, Phlorofucofuroeckol A, Dieckol, Fucosterol	↓ NO production ↑ i-NOS and COX-2 ↓ ROS production Suppression of the NF-kB pathway	RAW 264.7 macrophages	Jung et al. [110]
	7-Phloroeckol, Phlorofucofuroeckol A, Dieckol	↓ ROS production ↓ Ca^{2+} release (only 7-phloroeckol and phlorofucofuroeckol A)	PC12 cells	Ahn et al. [109]
Ishige foliacea	DPHC	Prevention of cell damage caused by H_2O_2 ↓ Proteins mediating cell apoptosis ↓ ROS production ↓ Lipid peroxidation ↓ Ca^{2+} release	HT22 cells	Heo et al. [116]
Ishige okamurae	6,6'-Bieckol, DPHC	Strong AChE inhibitory capacity (6.6'-bieckol) ↓ BChE activity (DPHC)	–	Yoon et al. [115]

the subject of extensive research, covering a spectrum of chemically diverse compounds belonging to classes such as chlorophylls, carotenoids (carotenes and xanthophylls), and phycobilins [130], each with distinct particularities. There is growing interest in their applications in the food sector, where these pigments are used to replace synthetic products, as well as in cosmetics and pharmaceuticals due to their proven antioxidant, anti-inflammatory, and biotechnological potential.

Carotenoids are derived from isoprene units, which are small units of 5 carbons, and these units are enzymatically polymerized to form larger, highly conjugated structures known as tetraterpenes, with a total of 40 carbons. They can be divided into two classes according to their polarity: carotenes and xanthophylls. They function as light energy

Table 2 Neuroprotective activity of terpenes extracted from marine macroalgae

Species	Extracted compounds	Effect	Assay	Reference
Sargassum serratifolium	Sargaquinoic acid, Sargahydroquinoic acid, Sargachromenol	Moderate inhibition of AChE Potent inhibition of BChE and BACE1	Enzyme inhibition assays	Seong et al. [129]
Sargassum macrocarpum	Sargachromenol	↑ Neuronal growth factor ↑ Neuronal differentiation	PC12 cells	Tsang et al. [120]
Sargassum sagamianum	Sargaquinoic acid, Sargachromenol	Moderate inhibition of AChE Notable inhibition of BChE (sargaquinoic acid only)	Enzyme inhibition assays	Choi et al. [121]
Bifurcaria bifurcata	Eleganolone	Antioxidant potential ↓ H_2O_2 production	SH-SY5Y cells	Silva et al. [125]
	Eleganonal	Mitochondrial membrane protection Inhibition of caspase-3 activity		
Dictyopteris undulata	Zonarol	Prevention of cell death after glutamate exposure	HT22 cells	Shimizu et al. [124]
Caulerpa racemosa *Caulerpa prolifera*	Sesquiterpene	Lipoxygenase inhibition	Enzyme inhibition assays	Cengiz et al. [122]

harvesters, absorbing light at different wavelengths and expanding the range of light that algae can use for photosynthesis [131].

Humans cannot synthesize carotenoids and must obtain them through the diet [132]. The basis of carotenoids is a "backbone" of polyenes consisting of a series of conjugated C =C bonds. This characteristic contributes to their ability to interact with reactive molecules and their antioxidant property, inactivating ROS formed as a result of exposure to light and oxygen [133]. The antioxidant property of carotenoids has inspired many epidemiological and clinical studies that have investigated whether these compounds are capable of preventing various disorders mediated by ROS, such as cancer [134], inflammation, retinal degeneration [135], and neurodegenerative diseases.

As already proven, xanthophylls such as fucoxanthin, zeaxanthin, and astaxanthin have been associated with beneficial properties in the field of health and prevention of neurodegeneration, diabetes, obesity, cancer, cardiovascular, and inflammatory diseases [136] and have been studied due to their antioxidant characteristics. Brown macroalgae are known for their fucoxanthin [137] content. *Undaria pinnatifida*, a macroalga widely used in traditional Chinese medicine, is rich in fucoxanthin, which, in addition to its antioxidant properties, also has effects against inflammation, cancer, diabetes, and obesity [138]. Although it is not directly biofunctional in the human body, it is metabolized in the intestinal tract with the help of pancreatic lipases, being released in its functional form, fucoxanthinol [139]. A pioneering study of the action of this compound, isolated from *Undaria pinnatifida*, demonstrated its neuroprotective potential by preventing hypoxia-induced oxidative stress in neuronal cells [140].

In an evaluation by Jang et al. [141], both β-carotene and fucoxanthin isolated from *Laminaria japonica* demonstrated the ability to protect against the formation of ROS in response to oxidative damage caused by arachidonic acid. Purified fucoxanthin from *Sargassum horneri* showed the ability to inhibit neurotoxicity related to Aβ oligomers in SH-SY5Y cortical neurons and also reduce intracellular ROS induced by them [31]. Co-incubation of fucoxanthin with Aβ41–42 oligomers resulted in the formation of relatively less toxic modified oligomers in SH-SY5Y cells, proving that fucoxanthin has the ability to structurally affect these compounds, reducing their toxicity [142].

The use of fucoxanthin in the pharmaceutical industry and in the production of nutraceuticals depends on its purity. Unlike astaxanthin, which, when incubated at high concentrations (50 µM) with PC12 cells, did not show any cytotoxicity, studies on the toxicity and activity of fucoxanthin by oral route showed that high concentrations of fucoxanthin impair the viability of human cells such as keratinocytes (HaCaT) when treated with 40 µM for 16 h, PC12 neuronal cells at concentrations above 5 µM, and human lymphocytes when treated with 10 µM [143]. However, fucoxanthin did not show any toxicity in rats when treated with 1000 and 2000 mg/kg. According to this study, and in agreement with previous studies [31, 142], 1 µM fucoxanthin was able to increase the cell viability of cells compromised by Aβ1–42 from 67 to 98.5% in PC12 cells and from 55 to 80% in SH-SY5Y cells, suggesting its neuroprotective capacity against Aβ-induced cytotoxicity. This study also demonstrated the ability to reduce Aβ aggregation by 50% at a concentration of 1 µM in PC12 cells. At a concentration of 2 µM, it was able to significantly protect cell viability against toxicity exerted by H2O2 [143].

Table 3 Neuroprotective activity of pigments extracted from marine macroalgae

Species	Extracted compounds	Effect	Assay	Reference
Sargassum siliquastrum	Fucoxanthin	↑ Significant increase in the survival rate of cells damaged by the Aβ25–35 fragment	PC12 cells	Alghazwi et al. [147]
		↓ Aβ1–42 clustering		
		↓ H_2O_2-induced toxicity	Vero cells	Heo et al. [146]
Sargassum horneri	Fucoxanthin	↓ Oxidative stress and neurotoxicity associated with Aβ oligomers	SH-SY5Y cortical neurons	Lin et al. [31]
		↓ Intracellular ROS		
		Prevention of Aβ1–42 cluster inhibition, and transformation of oligomers into less toxic forms	Synthetic Aβ1–42 peptides in rats	Xiang et al. [142]
		Improvement of several cognitive factors		
		Reversal of reduction in SOD, GSH and CAT		
Sargassum oligocystum	Fucoxanthin	Inhibition of AChE	C6 glial research cells	Hong et al. [145]
		↓ Oxidative stress		
		Regulation of antioxidant enzyme expression and increased ROS scavenging		
Sargassum muticum	Apo-9'-fucoxanthinone	↓ Production of inflammatory mediators	LPS-stimulated RAW 264.7 macrophages	Kim et al. [144]
		↓ COX-2 and iNOS		
Undaria pinnatifida	Fucoxanthin	↓ Hypoxia-induced oxidative stress	Neuronal cells	Mohibbullah et al. [140]
Laminaria japonica	β-carotene Fucoxanthin	↓ ROS formation and pathological changes potentiated by arachidonic acid and alteration of apoptotic proteins	HepG2 cells	Jang et al. [141]

Apo-9'-fucoxanthinone, extracted from the macroalgae *Sargassum muticum*, inhibited the production of PGE2 and NO in RAW 264.7 macrophages stimulated by LPS, as well as the expression of COX-2. PGE2 and NO are inflammatory mediators that participate in the immune and inflammatory response, and iNOS and COX-2 are important enzymes in the inflammatory process responsible for the production of NO and synthesis of prostaglandins, respectively. The inhibition of their production suggests that apo-9'-fucoxanthinone may have anti-inflammatory properties and may be beneficial in modulating the inflammatory responses of the immune system [144].

Fucoxanthin isolated from *Sargassum oligocystum* demonstrated a neuroprotective effect against neurotoxicity induced by H_2O_2 and Aβ25–35, exhibiting greater protective potency at concentrations of 50 and 100 µg/mL, presenting AChE inhibitory capabilities, as well as a positive effect in reducing oxidative stress by regulating the expression of antioxidant enzymes (catalase (CAT) and glutathione-peroxidase) and contributing to the elimination of free radicals [145].

In a study conducted by [146], fucoxanthin isolated from the seaweed *Sargassum siliquastrum*, at concentrations of 5 to 200 µM, was shown to be effective in reducing H_2O_2-induced toxicity in Vero cells. Furthermore, in another study conducted by [143], it was demonstrated that pretreatment with fucoxanthin at concentrations of 0.1 to 2 µM significantly increased the survival rate of cells damaged by the Aβ25–35 fragment, with survival rates ranging from 67 to 98.5%, evidencing its neuroprotective capabilities in the prevention and treatment of Alzheimer's disease.

Table 3 presents the neuroprotective activity observed in the mentioned studies for pigments extracted from different marine macroalgae species.

Phytosterols. Sterols play crucial roles in the structure and function of cell membranes in various organisms. These organic compounds are very common in macroalgae, earning the name phytosterols. The structure and functions of seaweed phytosterols are very similar to those of cholesterol. Due to their structural similarity and shared absorption pathway, sterols cause a reduction in intestinal cholesterol absorption and play a significant role in maintaining homeostasis, which, if disturbed, can be implicated in the appearance and development of neurodegenerative diseases [148]. Phytosterols have the ability to cross the blood-brain barrier and accumulate in the CNS, which allows them to exert neuromodulatory effects. However, most studies on these compounds focus on those of terrestrial origin, rather than those of aquatic origin.

β-Sitosterol, isolated from *Sargassum fusiforme*, a macroalga widely used in traditional Chinese medicine for its anti-atherosclerotic properties, is able to alter macrophage function, increasing their polarization toward an anti-inflammatory phenotype. This ability suggests an interesting

approach for the treatment of neurodegenerative diseases [149].

Also derived from seaweed, 24 (S)-saringosterol isolated from *Sargassum fusiforme* can activate LXRs [150]. LXRs are important transcription factors for controlling and regulating immunomodulatory processes. They are also important in maintaining synaptic integrity and stimulating synaptic remodeling, and neurons, especially distal axons, require a local source to support their functions and structure [151]. The dysregulation of cholesterol metabolism is closely linked to neurodegenerative diseases, and LXRs act as metabolic sensors, inducing LXR-responsive genes essential for regulating the cellular "turnover" of cholesterol from astrocytes to neurons. This ability is essential, as adult neurons depend on the ability to take up cholesterol synthesized by neighboring glial cells to maintain membrane plasticity and cellular function [76]. There are two LXR receptors in the brain, LXRβ and LXRα, and activation of LXRβ results in improvements in cognition and reduction of Aβ plaques in Alzheimer's patients, while activation of LXRα can lead to hypertriglyceridemia and hepatic steatosis, making it a difficult treatment route.

In a study by Zelcer et al. [152], extracts of 24 (S)-saringosterol caused relevant activation of LXRβ and, to a limited extent, LXRα. In this study, the tested rats showed a significant improvement in memory and cognition compared to the control group. In an analysis of several phytosterols isolated from *Sargassum fusiforme*, saringosterol proved to be the most potent by stimulating the transcriptional activities of LXRα by approximately 4-fold and LXRβ by 14-fold. An epimer derivative of the original compound has been shown to be a more effective LXRβ agonist and a potent reducer of cholesterol levels [153].

Fucosterol, one of the most abundant sterols in seaweed, has a QPlogBB (blood-brain barrier permeability parameter) within the recommended range and is able to cross the blood-brain barrier. In addition, it also complies with Lipinski's rule of five, used to assess whether the physicochemical characteristics of a given chemical compound with pharmacological activity make it viable for oral administration [148].

As previously mentioned, in neuroinflammation processes, overexpression of NOS, COX-2, and secretion of inflammatory mediators such as TNF-α, IL-6, and IL-1β are characteristic, which can stimulate neurons to cause neurodegeneration. In a study using several extracts of the macroalga *Eisenia bicyclis* in RAW 264.7 macrophages stimulated by LPS, there was a decrease in the activity of COX-2 and NOS, as well as the suppression of NF-kB signaling, a protein complex that performs transcription functions responsible for facilitating morbidities and the production of several factors associated with the development of Alzheimer's disease [154]. The extract with strong anti-inflammatory capacity was purified and revealed a high content of fucosterol [110].

Fucosterol isolated from *Undaria pinnatifida* suppressed the transcription of iNOS, TNF-α, and IL-6, consequently inhibiting their production. Its ability to attenuate the activation of the MAPK signaling pathway was also confirmed, with a consequent reduction in the release of pro-inflammatory cytokines [155]. In another study, fucosterol also demonstrated dose-dependent inhibitory capacity against AChE and BchE, conferring protection against Aβ-mediated neuroinflammation by inhibiting the production of pro-inflammatory mediators [156].

Another mechanism by which fucosterol can be used as a therapeutic weapon for Alzheimer's disease is its ability to non-competitively inhibit β-secretase, making it an effective and safe candidate, as evidenced by a study in which fucosterol was isolated from *Ecklonia stolonifera* and *Undaria pinnatifida* [157]. The same author previously demonstrated that fucosterol inhibited ROS production in RAW 264.7 cells induced with tert-butyl hydroperoxide [110]. The same occurred with fucosterol extracted from *Ecklonia stolonifera*, in which, in addition to inhibiting ROS production, an increase in glutathione levels was recorded in HepG2 cells, conferring protection against oxidative damage [158]. When derived from *Sargassum binderi*, fucosterol demonstrated protective effects against oxidative stress in lung epithelial cells by increasing the expression of the antioxidant enzymes SOD, CAT, and HO-1, in addition to increasing the transcription factor Nrf2 [159].

Finally, in a recent study, six European marine macroalgae were selected for their saringosterol and fucosterol content and compared with the known effects of *Sargassum fusiforme*. Results showed a greater efficacy of *Himanthalia elongata* extract in activating LXRs, being able to increase the secretion of ApoE4-containing particles by astrocytes in a comparable way to *Sargassum fusiforme*. The described effect was obtained specifically through the induction of the expression of *ABCA1* and *ABCG1*, genes that play an important role in lipid metabolism by promoting cholesterol efflux and by suppression of genes involved in the synthesis of cholesterol and fatty acids [160]. According to Wang et al. [161], the removal of ApoE4 markedly protects against tau-mediated neurodegeneration and microglial phagocytosis of synaptic elements. Previous studies reported the known ability of *Sargassum fusiforme* to improve cognitive performance and symptomatology of Alzheimer's disease. Therefore, *Himanthalia elongata* may be a promising alternative for preventing this type of condition.

Table 4 presents the neuroprotective activity observed in the mentioned studies for phytosterols extracted from different marine macroalgae species.

Table 4 Neuroprotective activity of phytosterols extracted from marine macroalgae

Species	Extracted compounds	Effect	Assay	Reference
Undaria pinnatifida	Fucosterol	Inhibition of inflammatory mediator production by Aβ	Enzyme inhibition assays	Wong et al. [156]
		Reversal of SOD, CAT and GSH reduction		
		Non-competitive inhibition of β-secretase	RAW 264.7 macrophages induced with tert-butyl hydroperoxide	Jung et al. [157]
		↓ ROS production	RAW 264.7 macrophages induced with tert-butyl hydroperoxide	Jung et al. [110]
		↓ Dose-dependent AChE and BChE activity	RAW 264.7 macrophages	Yoo et al. [155]
Ecklonia stolonifera	Fucosterol	Non-competitive inhibition of β-secretase	RAW 264.7 macrophages induced with tert-butyl hydroperoxide	Jung et al. [157]
		↓ ROS production ↑ Glutathione level	HepG2 cells	Choi et al. [158]
		↓ ROS production	RAW 264.7 macrophages induced with tert-butyl hydroperoxide	Jung et al. [110]
Sargassum binderi	Fucosterol	↑ Expression of antioxidant enzymes ↑ Transcription factor Nrf2	Lung epithelial cells	Fernando et al. [159]
Sargassum fusiforme	24(S)-saringosterol	Activation of LXRs, mainly LXRβ (maintenance of neuronal function and reduction of Aβ plaques)	LXR receptors assays	Zelcer et al. [152]
Himanthalia elongata	Saringosterol Fucosterol	↑ LXR activation ↑ Secretion of ApoE4-containing particles	LXR receptors assays	Alghazwi et al. [147]
Eisenia bicyclis	Fucosterol	↓ COX-2 and NOS activity Suppression of the NF-kB signaling pathway	LPS-stimulated RAW 264.7 macrophages	Jung et al. [110]

Polysaccharides. Polysaccharides isolated from marine macroalgae are found mainly in sulfated and non-sulfated forms and can constitute 4 to 76% of their total dry weight. Polysaccharides derived from marine algae, such as agar, alginates, and carrageenans, are used in various processes in the food industry, mainly due to their viscosifying capacity [162].

These compounds have antioxidant activity that is influenced by several factors, such as the high number of hydroxyl groups and the presence of carboxylic groups that give high efficiency in neutralizing free radicals. The sulfate content and its position are also characteristics of their antioxidant capacity, as well as their low molecular weight [163]. A study was able to demonstrate that derivatives of the seaweed *Ulva pertusa* with low molecular weight exhibited stronger antioxidant activity than plant polysaccharides with a higher molecular weight [164].

Ulvan, a polysaccharide isolated from green algae of the genus *Ulva*, can prevent Aβ fibrillation, inhibit the development of A11-reactive Aβ oligomers, a significant toxic species of Aβ, and consequently reduce its cytotoxicity. The same study demonstrated its efficacy in protecting PC12 cells and reducing intracellular ROS levels [165].

In another study [166], several fractions of constituents of the macroalga *Ecklonia radiata*, one of which was the polysaccharide fraction, were evaluated in several neuroprotection assays. All fractions demonstrated antioxidant properties against toxic effects induced by hydrogen peroxide. High activity in reducing apoptosis induced by Aβ1-42 in PC12 cells was also observed, which may be due to their high fucoidan content. These findings highlight their neuroprotective effects and suggest that these extracts should be tested as potential dietary supplements and functional food. The polysaccharide fraction was also the most potent in causing stimulation of neurite outgrowth, associated with its high fucose content [166].

Porphyran, a metabolite of the red macroalga *Porphyra haitanensis*, can protect neurons from the neurotoxic effects of Alzheimer's disease, namely the effect exerted by Aβ1–40, that affects learning and memory. Furthermore, it appears that porphyran works by decreasing the activity of enzymes related to ACh, a crucial neurotransmitter in the brain [167]. In another in vitro study, the same compound extracted from *Porphyra yezoensis* showed hydroxyl radical and superoxide anion scavenging activity in RAW 264.7 cells stimulated by LPS [168].

Sulfated fucoidans and galactans are the most studied sulfated polysaccharides present in the literature. The physiological and pharmacological effects of these sulfated polysaccharides include antithrombotic, anticoagulant, antioxidant, anti-inflammatory, antitumor, immunomodulatory, and antiviral properties [169]. Fucoidans are a complex series of sulfated polysaccharides found both intercellularly

and in the cell wall of brown macroalgae and may represent between 5 and 20% of their composition [170, 171].

In a study by Wei et al. [172], the ability of fucoidan to protect cells from induced apoptosis was investigated. Fucoidan exerted a protective action against neurotoxicity exerted by Aβ25–35 in PC12 cells by reducing oxidative stress. It also blocked cell apoptosis by inhibiting caspase activation and increasing the expression of apoptosis inhibitor proteins. This compound was also able to decrease AChE activity and, through the activation of SOD and GSH, improve antioxidant activity.

Park et al. [173] studied the impact of fucoidan-rich extracts isolated from *Ecklonia cava* and concluded that fucoidan extract and a polyphenol:fucoidan extract in a 4:6 ratio improved learning, cognitive function, and memory, as well as reducing tau protein hyperphosphorylation and Aβ accumulation.

Fucoidan obtained from *Laminaria japonica* has also been shown to significantly improve locomotor capacity, protect against striatal dopamine depletion in vivo, reduce the loss of dopaminergic neurons, and contribute to the maintenance of antioxidant capacity in the substantia nigra pars compacta of rats with 1-methyl-4-phenyl-1.2.3.6-tetrahydropyridine (MPTP)-induced Parkinson's disease [174]. Other studies of fucoidan extracted from *Laminaria japonica* have shown its ability to alleviate the symptoms of Parkinson's disease by reducing the loss of dopaminergic neurons, oxidative stress, and suppressing the production of inflammatory mediators through dysregulation of the MAPK and NF-κB signaling pathway [175]. It also inhibits the increase in NADPH oxidase 1 (NOX1), oxidative stress, and microglial activation in the substantia nigra pars compacta [176].

In several cellular and animal models of neurotoxicity, fucoidans isolated from the macroalgae *Fucus vesiculosus* and *Undaria pinnatifida* have been shown to be neuroprotective by reducing lipid peroxidation, strengthening antioxidant defenses, preventing mitochondrial membrane disruption, and caspase-3 activation under neurotoxic conditions. They regulate cholinergic systems, prevent apoptosis, and improve cell viability and antioxidant capacity, resulting in improved memory and reduced Aβ deposition in animal models [172]. In a study by Alghazwi et al. [147], the activity of fucoidans extracted from these same species caused a decrease in Aβ aggregation and hydrogen peroxide-induced cytotoxicity in PC12 cells.

In a study [177] where sulfated polysaccharides were extracted from *Ecklonia maxima* (PKPM), *Gelidium pristoides* (PMNP), and *Ulva rigida* (PURL), the inhibition capacities of AChE, BChE, and β-secretase were evaluated. The three extracts revealed AChE inhibitory capacity, with the PKPM extract being the most effective (98.75 µg/mL), followed by PURL (118.23 µg/mL), and the PMNP extract showing the weakest inhibition (< 50%). Concerning BChE inhibition, the PKPM extract was also the most effective. The co-inhibition of AChE and BChE has been identified as a therapeutic approach in the treatment of cholinergic deficit in Alzheimer's disease. Regarding β-secretase inhibition, the PKPM (2.83 mg/mL), PMNP (4.86 mg/mL) and PURL extracts (3.66 mg/mL), inhibited β-secretase by 87.55, 70.66 and 50.66% respectively. Regarding the aggregation of Aβ1–42, present in the control group, they contrasted with the elimination or disaggregation induced by sulfated polysaccharides observed in the treatment group through fluorescence, preventing their accumulation, indicating their neuroprotective potential in the control of Alzheimer's disease. Fluorescence emission increases when thioflavin-T binds to Aβ fibrils and after 48 h of incubation, in relation to the control group, the intensities of co-incubation with the various extracts decreased, occurring a variation of 35.66–7.33 AU (PKPM), 35.66–5.33 AU (PURL) and 35.66–14.01 AU (PMNP), with AU being the measure of fluorescence intensity (< 50%). Concerning BChE inhibition, the PKPM extract was also the most effective. The co-inhibition of AChE and BChE has been identified as a therapeutic approach in the treatment of cholinergic deficit in Alzheimer's disease. Regarding β-secretase inhibition, the PKPM (2.83 mg/mL), PMNP (4.86 mg/mL), and PURL extracts (3.66 mg/mL) inhibited β-secretase by 87.55, 70.66, and 50.66%, respectively. Regarding the aggregation of Aβ1–42 present in the control group, they contrasted with the elimination or disaggregation induced by sulfated polysaccharides observed in the treatment group through fluorescence, preventing their accumulation, indicating their neuroprotective potential in the control of Alzheimer's disease. Fluorescence emission increases when thioflavin-T binds to Aβ fibrils, and after 48 h of incubation, in relation to the control group, the intensities of co-incubation with the various extracts decreased, occurring a variation of 35.66–7.33 AU (PKPM), 35.66–5.33 AU (PURL), and 35.66–14.01 AU (PMNP), with AU being the measure of fluorescence intensity.

Table 5 presents the neuroprotective activity observed in the mentioned studies for polysaccharides extracted from different marine macroalgae species.

Sodium oligomannate. In preclinical studies, sodium oligomannate, an oligosaccharide prepared from the extract of brown marine macroalgae, demonstrated neuroprotective capacity against Aβ-induced neurotoxicity and improved memory in transgenic mice with five mutations associated with Alzheimer's disease [178].

Recently, sodium oligomannate was used to develop a new drug (GV-971) against Alzheimer's disease, which has been successfully applied in clinical practice. It was developed by the Shanghai Institute of Materia Medica in

Table 5 Neuroprotective activity of polysaccharides extracted from marine macroalgae

Species	Extracted compounds	Effect	Assay	Reference
Laminaria japonica	Fucoidan	↓ Loss of dopaminergic neurons ↓ Oxidative stress ↓ Production of inflammatory mediators	Models of rats with MPTP-induced Parkinson's	Liyanage et al. [175]
		↑ Locomotor capacity ↓ Dopamine depletion ↓ Loss of dopaminergic neurons ↑ Antioxidant capacity	Models of rats with MPTP-induced Parkinson's	Zhang et al. [174]
		↓ NOX1 ↓ Oxidative stress	Models of rats with MPTP-induced Parkinson's	Zhang et al. [176]
Ecklonia radiata	Polysaccharide fraction	↓ COX-2 and NOS Suppression of the NF-kB signaling pathway	Neurotoxicity assay in PC12 cells	Alghazwi et al. [166]
	Fucoidan	↓ Hyperphosphorylation of tau protein ↓ Aβ accumulation ↑ Cognitive function and memory	Behavioral tests (Y-Maze test, Morris Water Maze test) and examination of brain tissue in rats	Park et al. [173]
		↑ ACh ↓AChE ↑ SOD and GSH ↓ Oxidative stress and cellular apoptosis	PC12 cells	Wei et al. [172]
Fucus vesiculosus	Fucoidan	↓ Aβ aggregation	PC12 cells induced with hydrogen peroxide	Alghazwi et al. [147]
Undaria pinnatifida		↓ Cytotoxicity ↓ Lipid peroxidation ↓ Caspase activation ↑ Cognitive function resulting from reduced Aβ deposition	Animal models	Wei et al. [172]
Porphyra haitanensis	Porphyran	↓AChE and BChE dose-dependent ↑Cortical and hippocampal ACh	Models of rats with Alzheimer's injected with toxic fragment Aβ1–40	Zhang et al. [167]
Porphyra yezoensis	Porphyran	↓ Hydroxyl radicals ↓ Superoxide anions	Enzyme inhibition assays	Isaka et al. [168]
Ulva sp	Ulvan	↓Aβ toxicity ↓Aβ-induced cell apoptosis ↑Neurite growth	Tau protein aggregation assays in PC12 cells	Liu et al. [165]
Ecklonia maxima	Sulfated polysaccharides	↓ Aβ1–42 aggregation	Enzyme inhibition assays	Olashinde et al. [177]
Gelidium pristoides		↑Inhibitory capacity of cholinesterase and β-secretase (principally in *Ecklonia maxima*)	Aβ aggregation assays	
Ulva rigida		↑Capacity to scavenge free radicals and exert chelating activity on Fe^{2+}		

China, where the phase III clinical trial was completed, proving to be safe, well-tolerated, and effective in improving cognition throughout the 36 weeks of the study [179].

In animal models of Alzheimer's disease, alterations in the intestinal microbiota led to peripheral accumulation of phenylalanine and isoleucine, which stimulated the proliferation of proinflammatory Th1 cells. GV-971 was able to attenuate neuroinflammation by suppressing intestinal dysbiosis, reversing the previously described effects. After oral administration, the majority of the compound is retained in the intestine, and hence its main mechanisms act through the reconstitution of the microbiota, reducing the peripheral infiltration of immune cells driven by bacterial metabolites to the brain and inhibiting neuroinflammation. The ability to bind to multiple subregions of Aβ and inhibit the formation of Aβ plaques and transform them into non-toxic monomers is also due to its ability to partially cross the blood-brain barrier [180]. The randomized, double-blind, multisite clinical trial consisted of administering two 450 mg doses of

Table 6 Neuroprotective activity of GV-971 in *in-vivo* and human trials

Species	Extracted compounds	Effect	Assay	Reference
Ecklonia kurome	Sodium oligomannate (GV-971)	↑ADAS-Cog12 score, compared to placebo group	Phase III Human Clinical Trial (Oral administration of 450 mg twice daily, for 36 weeks)	Xiao et al. [179]
Ecklonia kurome	Sodium oligomannate (GV-971)	Normalization of fecal and blood concentrations of phenylalanine and isoleucine	Oral administration (100 mg/kg) for 1 month in transgenic (Alzheimer's) rats	–
		↓ Th1 cells ↓ Reactive microglia ↓ Deposition of Aβ plaques ↓ Tau phosphorylation in the brain		Wang et al. [180]
		↑Cognitive functions and memory capacity	Oral administration (50 and 100 mg/kg) for 3 months in transgenic (Alzheimer's) rats	

GV-971 to 408 Chinese patients and a control group of 410 additional patients, all between 50–85 years of age and with mild to moderate Alzheimer's disease. This drug could modulate intestinal microbiota, leading to a decrease in neuroinflammation [181].

In the study by Xiao et al. [179], the Alzheimer's Disease Assessment Scale, cognitive subscale (ADAS-Cog) was used. It is a neuropsychological scale developed to assess the cognitive status of Alzheimer's patients that ranges from 0–70 points. Results above 18 are indicative of a strong cognitive impairment. Many regulatory entities consider, for example, a difference of 4 negative points in a 6-month study as an indication of a severe decline in clinical status [182]. This scale is divided into two assessment parameters, the first targeting language, identification ability, comprehension, and quality of speech. The second parameter consists of the assessment of memory, construction and idealization ability, recognition of words and names, among others [183]. In the study in question [179], a significant improvement was demonstrated with a difference of –2.15 points (95% confidence interval) between the treatment group and the group administered placebo after 36 weeks of investigation, with this score increasing throughout the treatment, being 2.70 for the GV-971 group and –0.16 for the placebo group.

In conclusion, and as mentioned, although all the mechanisms are not yet understood, the results of existing studies show the ability of GV-971 to attenuate phenylalanine and isoleucine levels, thus causing a decrease in Th1 cells, which promote neuroinflammation. Researchers believe that this compound acts by modulating the intestinal microbiome in the correct direction, preventing intestinal dysbiosis, reducing inflammation, and reversing cognitive impairment. The simultaneous administration of antibiotics has been shown to nullify these effects, demonstrating that the mechanism of GV-971 may involve alteration of the intestinal microbiota, as well as the balance of amino acid metabolism, especially phenylalanine and isoleucine [180], which is dysregulated in patients with Alzheimer's disease [184].

In December 2019, GV-971 went on sale in China for around 488 euros for one month of treatment, twice the price of AChE inhibitors. In December 2021, it began to be subsidized by the government, reducing the cost to around 80 euros. In the genesis of its approval in China, many doubts arose regarding the existing scientific information, given the short period of time in which clinical trials on humans took place. Hoping to expand and gain legitimacy internationally with European entities and the Food and Drug Administration (FDA), Green Valley (producer of the drug) embarked on an investment of around US$600 million for a global phase III clinical study, with 2000 patients from the United States, China, and Europe. This study was terminated due to limitations imposed by the emergence of coronavirus disease 2019 (COVID-19) and lack of investment. Two phase IV clinical trials to evaluate the long-term safety and efficacy of GV-971 capsules are currently still ongoing in China, ending in 2025 (NCT05181475).

Table 6 presents the neuroprotective activity of GV-971, observed in the mentioned *in vivo* and human trials.

Conclusions

Neurodegenerative diseases and their complex mechanisms are still largely unknown. Several mechanisms of neurodegeneration, such as neuroinflammation and oxidative stress, are closely related in the pathological process, representing a great challenge in the discovery of new effective alternatives capable of diverse neuroprotective mechanisms.

Increasing exponentially year after year, research into the marine world is accelerating as seaweed proves to be a valuable resource of interest to the food, energy, and cosmetics industries. To date, there are 163 industries producing macroalgae in Europe alone, with the largest markets lo-

cated in France, Ireland, and Spain, a market that, in global terms, is projected to reach 33.5 billion euros.

There are more than 11,000 known species of marine macroalgae. In order to adapt to their habitat and sometimes extreme conditions, macroalgae produce several metabolites that are of interest for use in various industries, particularly the pharmaceutical industry. They are the source of 50 to 80% of the planet's oxygen, in addition to absorbing huge amounts of carbon dioxide from the atmosphere. A major use of seaweed is phycocolloids such as alginate, agar, or carrageenan, which are used as food additives, in the medical industry for mold making, in cosmetics as thickening agents, in the agricultural industry as fertilizers, or in the energy industry for biofuel production, being held back only by the still high cost of the processes involved in its production and the difficulty in large-scale production.

This review addresses several classes of bioactive compounds extracted from marine macroalgae that have demonstrated preventive or protective capabilities against neurodegenerative processes. Compounds that simultaneously exhibit anti-inflammatory and antioxidant activities are excellent candidates for future research due to their multiple pathways of action. Compared to synthetic therapies, the use of natural drugs produces well-tolerated effects and is more than just a treatment mechanism with low or no adverse effects. Furthermore, since neurodegenerative diseases are directly related to poor nutrition, research into the compounds discussed here as potential nutraceuticals or supplements can be used as adjuvant therapy or in the prevention of these diseases.

There is currently a wide variety of in vitro and in vivo studies in animal models reported in the literature, and studies in humans are needed to strengthen the position of these bioactive compounds from marine macroalgae as potential nutraceuticals and targets for the development of new therapeutics. The development of new solutions for human brain health can pass through our marine life, with a new horizon in sight for the conservation of quality of life and human health.

The recent approval of a new monoclonal antibody, aducanumab, by the FDA for the treatment of Alzheimer's disease has encouraged progress and the development of new therapies in the field of neurodegenerative diseases. However, concerns regarding safety have prevented commercialization in Europe. Thus, approaches focused on natural compounds have gained even greater relevance for the prevention of neurodegenerative diseases. Among the most notable examples, GV-971 emerged as one of the first to address a promising mechanism that is still largely unexplored: the modulation of the intestinal microbiota, which has recently become a new focus in the research and study of new treatments, achieving its approval in China.

Author Contribution All authors contributed to the writing of the manuscript.

Conflict of interest M. F.C. Leal, R.J. G. Duarte, I.L. Cardoso, R.I. L. Catarino, A.M. Pimenta and M. R.S. Souto declare that they have no competing interests.

Ethical approval Not applicable.

References

1. Zlokovic BV. Neurovascular pathways to neurodegeneration in Alzheimer's disease and other disorders. Nat Rev Neurosci. 2011;12(12):723–38.
2. Armstrong R. What causes neurodegenerative disease? Folia Neuropathol. 2020;58(2):93–112.
3. Polidori MC. Preventive benefits of natural nutrition and lifestyle counseling against Alzheimer's disease onset. J Alzheimers Dis. 2014;42(4):S475–82.
4. Menaa F, Wijesinghe PAUI, Thiripuranathar G, Uzair B, Iqbal H, Khan BA, Menaa B. Ecological and industrial implications of dynamic seaweed-associated microbiota interactions. Mar Drugs. 2020;18(12):641.
5. Gomes L, Monteiro P, Cotas J, Gonçalves AMM, Fernandes C, Gonçalves T, Pereira L. Seaweeds' pigments and phenolic compounds with antimicrobial potential. Biomol Concepts. 2022;13(1): 89–102.
6. Rengasamy KR, Kulkarni MG, Stirk WA, Van Staden J. Advances in algal drug research with emphasis on enzyme inhibitors. Biotechnol Adv. 2014;32(8):1364–81.
7. Ferdouse F, Yang Z, Lovstad Holdt S, Murúa P, Smith R. The global status of seaweed production, trade and utilization. 2018.
8. Ganesan AR, Tiwari U, Rajauria G. Seaweed nutraceuticals and their therapeutic role in disease prevention. Food Sci Hum Wellness. 2019;8(3):252–63.
9. Stiger-Pouvreau V, Zubia M. Macroalgal diversity for sustainable biotechnological development in French tropical overseas territories. Bot Mar. 2020;63(1):17–41.
10. Barbosa M, Valentão P, Andrade PB. Bioactive compounds from macroalgae in the new millennium: implications for neurodegenerative diseases. Mar Drugs. 2014;12(9):4934–72.
11. Yahfoufi N, Alsadi N, Jambi M, Matar C. The immunomodulatory and anti-inflammatory role of polyphenols. Nutrients. 2018;10(11):1618.
12. Moussavou G, Kwak DH, Obiang-Obonou BW, Maranguy CAO, Dinzouna-Boutamba S-D, Lee DH, Pissibanganga OGM, Ko K, Seo JI, Choo YK. Anticancer effects of different seaweeds on human colon and breast cancers. Mar Drugs. 2014;12(9):4898–911.
13. Zhao C, Yang C, Liu B, Lin L, Sarker SD, Nahar L, et al. Bioactive compounds from marine macroalgae and their hypoglycemic benefits. Trends Food Sci Technol. 2018;72:1–12.
14. Blamire AM. MR approaches in neurodegenerative disorders. Prog Nucl Magn Reason Spectrosc. 2018;108:1–16.
15. OECD. Health at a glance. 2017.
16. Alzheimer A, Stelzmann RA, Schnitzlein HN, Murtagh FR. "An English translation of Alzheimer's 1907 paper, "Über eine eigenartige Erkankung der Hirnrinde". Clin Anat. 1995;8(6):429–31.
17. Islam BU, Zaidi SK, Kamal MA, Tabrez S. Exploration of various proteins for the treatment of Alzheimer's disease. Curr Drug Metab. 2017;18(9):808–13.
18. Islam BU, Tabrez S. Management of Alzheimer's disease—an insight of the enzymatic and other novel potential targets. Int J Biol Macromol. 2017;97:700–9.
19. Reitz C, Mayeux R. Alzheimer disease: epidemiology, diagnostic criteria, risk factors and biomarkers. Biochem Pharmacol. 2014;88(4):640–51.

20. Breijyeh Z, Karaman R. Comprehensive review on Alzheimer's disease: causes and treatment. Molecules. 2020;25(24):5789.
21. Dhahri M, Alghrably M, Mohammed HA, Badshah SL, Noreen N, Mouffouk F, et al. Natural polysaccharides as preventive and therapeutic horizon for neurodegenerative diseases. Pharmaceutics. 2021;14(1):1.
22. DeTure MA, Dickson DW. The neuropathological diagnosis of Alzheimer's disease. Mol Neurodegener. 2019;14(1):32.
23. Chen G-F, Xu T-H, Yan Y, Zhou Y-R, Jiang Y, Melcher K, Xu HE. Amyloid beta: structure, biology and structure-based therapeutic development. Acta Pharmacol Sin. 2017;38(9):1205–35.
24. Tiwari S, Atluri V, Kaushik A, Yndart A, Nair M. Alzheimer's disease: pathogenesis, diagnostics, and therapeutics. Int J Nanomedicine. 2019;14:5541–54.
25. Nathalie P, Jean-Noël O. Processing of amyloid precursor protein and amyloid peptide neurotoxicity. Curr Alzheimer Res. 2008;5(2):92–9.
26. Tu S, Okamoto S-I, Lipton SA, Xu H. Oligomeric Aβ-induced synaptic dysfunction in Alzheimer's disease. Mol Neurodegener. 2014;9(1):48.
27. Parihar MS, Brewer GJ. Amyloid-β as a modulator of synaptic plasticity. J Alzheimers Dis. 2010;22(3):741–63.
28. Thordardottir S, Stahlbom AK, Almkvist O, Thonberg H, Eriksdotter M, Zetterberg H, Blennow K, Graff C. The effects of different familial Alzheimer's disease mutations on APP processing in vivo. Alzheimers Res Ther. 2017;9(1):9.
29. Medeiros R, Baglietto-Vargas D, LaFerla FM. The role of tau in Alzheimer's disease and related disorders. CNS Neurosci Ther. 2011;17(5):514–24.
30. Chong FP, Ng KY, Koh RY, Chye SM. Tau proteins and tauopathies in Alzheimer's disease. Cell Mol Neurobiol. 2018;38(5):965–80.
31. Lin J, Yu J, Zhao J, Zhang K, Zheng J, Wang J, et al. Fucoxanthin, a marine carotenoid, attenuates β-amyloid oligomer-induced neurotoxicity possibly via regulating the PI3K/Akt and the ERK pathways in SH-SY5Y cells. Oxid Med Cell Longev. 2017; https://doi.org/10.1155/2017/6792543.
32. Vogels T, Murgoci A-N, Hromádka T. Intersection of pathological tau and microglia at the synapse. acta neuropathol commun. 2019;7(1):109.
33. Parkinson J. An essay on the shaking palsy. 1817. J Neuropsychiatry Clin Neurosci. 2002;14(2):223–36.
34. Ferreira JJ, Gonçalves N, Valadas A, Januário C, Silva MR, Nogueira L, Vieira JLM, Lima AB. Prevalence of Parkinson's disease: a population-based study in Portugal. Eur J Neurol. 2017;24(5):748–50.
35. Neurol L. Global, regional, and national burden of Parkinson's disease, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol. 2018;17(11):939–53.
36. Loscalzo J, Fauci A, Kasper D, Hauser S, Longo D, Jameson JL, editors. Harrison's principles of internal medicine. New York, NY: McGraw-Hill; 2022.
37. Singh A, Kukreti R, Saso L, Kukreti S. Oxidative stress: a key modulator in neurodegenerative diseases. Molecules. 2019;24(8):1583.
38. Braak H, Tredici KD, Rüb U, de Vos RAI, Steur ENHJ, Braak E. Staging of brain pathology related to sporadic Parkinson's disease. Neurobiol Aging. 2003;24(2):197–211.
39. Grozdanov V, Bousset L, Hoffmeister M, Bliederhaeuser C, Meier C, Madiona K, et al. Increased immune activation by pathologic α-synuclein in Parkinson's disease. Ann Neurol. 2019;86(4):593–606.
40. Qiao H, He X, Zhang Q, Yuan H, Wang D, Li L, Hui Y, Wu Z, Li W, Zhang N. Alpha-synuclein induces microglial migration via PKM2-dependent glycolysis. Int J Biol Macromol. 2019;129:601–7.
41. Choi I, Zhang Y, Seegobin SP, Pruvost M, Wang Q, Purtell K, Zhang B, Yue Z. Microglia clear neuron-released α-synuclein via selective autophagy and prevent neurodegeneration. Nat Commun. 2020;11(1):1386.
42. Kamp F, Exner N, Lutz AK, Wender N, Hegermann J, Brunner B, et al. Inhibition of mitochondrial fusion by α-synuclein is rescued by PINK1, Parkin and DJ-1. Embo J. 2010;29(20):3571–89.
43. Kramer ML, Schulz-Schaeffer WJ. Presynaptic alpha-synuclein aggregates, not Lewy bodies, cause neurodegeneration in dementia with Lewy bodies. J Neurosci. 2007;27(6):1405–10.
44. Fields CR, Bengoa-Vergniory N, Wade-Martins R. Targeting alpha-synuclein as a therapy for Parkinson's disease. Front Mol Neurosci. 2019;12:299.
45. Liu Z, Zhou T, Ziegler AC, Dimitrion P, Zuo L. Oxidative stress in neurodegenerative diseases: from molecular mechanisms to clinical applications. Oxid Med Cell Longev. 2017; https://doi.org/10.1155/2017/2525967.
46. Hou Y, Dan X, Babbar M, Wei Y, Hasselbalch SG, Croteau DL, Bohr VA. Ageing as a risk factor for neurodegenerative disease. Nat Rev Neurol. 2019;15(10):565–81.
47. Schieber M, Chandel NS. ROS function in redox signaling and oxidative stress. Curr Biol. 2014;24(10):R453–62.
48. Zecca L, Youdim MBH, Riederer P, Connor JR, Crichton RR. Iron, brain ageing and neurodegenerative disorders. Nat Rev Neurosci. 2004;5(11):863–73.
49. Dizdaroglu M, Jaruga P. Mechanisms of free radical-induced damage to DNA. Free Radic Res. 2012;46(4):382–419.
50. Kim GH, Kim JE, Rhie SJ, Yoon S. The role of oxidative stress in neurodegenerative diseases. Exp Neurobiol. 2015;24(4):325–40.
51. Block ML, Zecca L, Hong JS. Microglia-mediated neurotoxicity: uncovering the molecular mechanisms. Nat Rev Neurosci. 2007;8(1):57–69.
52. Allen NJ, Barres BA. Neuroscience: glia—more than just brain glue. Nature. 2009;457(7230):675–7.
53. Lull ME, Block ML. Microglial activation and chronic neurodegeneration. Neurotherapeutics. 2010;7(4):354–65.
54. Badanjak K, Fixemer S, Smajic S, Skupin A, Grünewald A. The contribution of microglia to neuroinflammation in Parkinson's disease. Int J Mol Sci. 2021;22(9):4676.
55. Ferreira-Vieira TH, Guimarães IM, Silva FR, Ribeiro FM. Alzheimer's disease: targeting the cholinergic system. Curr Neuropharmacol. 2016;14(1):101–15.
56. Mushtaq G, Greig NH, Khan JA, Kamal MA. Status of acetylcholinesterase and butyrylcholinesterase in Alzheimer's disease and type 2 diabetes mellitus. CNS Neurol Disord Drug Targets. 2014;13(8):1432–9.
57. Leal MFC, Catarino RIL, Pimenta AM, Souto MRS. The influence of the biometals Cu, Fe, and Zn and the toxic metals Cd and Pb on human health and disease. Trace Elem Electrol. 2023a;40(1):1–22.
58. Leal MFC, Catarino RIL, Pimenta AM, Souto MRS. Roles of metal microelements in neurodegenerative diseases. Neurophysiology. 2020;52(1):80–8.
59. Ward RJ, Dexter DT, Crichton RR. Iron, neuroinflammation and neurodegeneration. Int J Mol Sci. 2022;23(13):7267.
60. El SN, Karakaya S. Radical scavenging and iron-chelating activities of some greens used as traditional dishes in Mediterranean diet. Int J Food Sci Nutr. 2004;55(1):67–74.
61. Weinreb O, Amit T, Mandel S, Youdim MBH. Neuroprotective molecular mechanisms of (-)-epigallocatechin-3-gallate: a reflective outcome of its antioxidant, iron chelating and neuritogenic properties. Genes Nutr. 2009;4(4):283–96.
62. Tahmasebinia F, Emadi S. Effect of metal chelators on the aggregation of beta-amyloid peptides in the presence of copper and iron. Biometals. 2017;30(2):285–93.
63. Galante D, Cavallo E, Perico A, D'Arrigo C. Effect of ferric citrate on amyloid-beta peptides behavior. Biopolymers. 2018;109(6):e23224.

64. Mochizuki H, Choong C-J, Baba K. Parkinson's disease and iron. J Neural Transm. 2020;127(2):181–7.
65. Zucca FA, Segura-Aguilar J, Ferrari E, Muñoz P, Paris I, Sulzer D, Sarna T, Casella L, Zecca L. Interactions of iron, dopamine and neuromelanin pathways in brain aging and Parkinson's disease. Prog Neurobiol. 2017;155:96–119.
66. Leal MFC, Catarino RIL, Pimenta AM, Souto MRS. Metal chelators as part of a strategy for the treatment of neurodegenerative diseases. Trace Elem Electrol. 2023b;40(3):126–38.
67. Voss K, Harris C, Ralle M, Duffy M, Murchison C, Quinn JF. Modulation of tau phosphorylation by environmental copper. Transl Neurodegener. 2014;3(1):24.
68. Lyubartseva G, Smith JL, Markesbery WR, Lovell MA. Alterations of zinc transporter proteins ZnT-1, ZnT-4 and ZnT-6 in preclinical Alzheimer's disease brain. Brain Pathol. 2009;20(2):343–50.
69. Wang Z, Zhang Y-H, Zhang W, Gao H-L, Zhong M-L, Huang T-T, et al. Copper chelators promote nonamyloidogenic processing of AβPP via MT(1/2) /CREB-dependent signaling pathways in AβPP/PS1 transgenic mice. J Pineal Res. 2018;65(3):e12502.
70. Watt NT, Whitehouse IJ, Hooper NM. The role of zinc in Alzheimer's disease. Int J Alzheimers Dis. 2010; https://doi.org/10.4061/2011/971021.
71. Furuta T, Ohshima C, Matsumura M, Takebayashi N, Hirota E, Mawaribuchi T, Nishida K, Nagasawa K. Oxidative stress upregulates zinc uptake activity via Zrt/Irt-like protein 1 (ZIP1) in cultured mouse astrocytes. Life Sci. 2016;151:305–12.
72. Kuchibhotla KV, Goldman ST, Lattarulo CR, Wu H-Y, Hyman BT, Bacskai BJ. Abeta plaques lead to aberrant regulation of calcium homeostasis in vivo resulting in structural and functional disruption of neuronal networks. Neuron. 2008;59(2):214–25.
73. Latulippe J, Lotito D, Murby D. A mathematical model for the effects of amyloid beta on intracellular calcium. PLoS ONE. 2018;13(8):e202503.
74. Hussain G, Wang J, Rasul A, Anwar H, Imran A, Qasim M, et al. Role of cholesterol and sphingolipids in brain development and neurological diseases. Lipids Health Dis. 2019;18(1):26.
75. Vance JE. Dysregulation of cholesterol balance in the brain: contribution to neurodegenerative diseases. Dis Model Mech. 2012;5(6):746–55.
76. Courtney R, Landreth GE. LXR regulation of brain cholesterol: from development to disease. Trends Endocrinol Metab. 2016;27(6):404–14.
77. Marquer C, Devauges V, Cossec J-C, Liot G, Lécart S, Saudou F, et al. Local cholesterol increase triggers amyloid precursor protein-Bace1 clustering in lipid rafts and rapid endocytosis. FASEB J. 2011;25(4):1295–305.
78. Blanchard JW, et al. APOE4 impairs myelination via cholesterol dysregulation in oligodendrocytes. Nature. 2022;611(7937):769–79.
79. Kesika P, Suganthy N, Sivamaruthi BS, Chaiyasut C. Role of gut-brain axis, gut microbial composition, and probiotic intervention in Alzheimer's disease. Life Sci. 2021;264:118627.
80. Yemula N, Dietrich C, Dostal V, Hornberger M. Parkinson's disease and the gut: symptoms, nutrition, and microbiota. J Parkinsons Dis. 2021;11(4):1491–505.
81. Friedland RP, Chapman MR. The role of microbial amyloid in neurodegeneration. PLoS Pathog. 2017;13(12):e1006654.
82. Seo DO, Holtzman DM. Gut microbiota: from the forgotten organ to a potential key player in the pathology of Alzheimer's disease. J Gerontol A Biol Sci Med Sci. 2020;75(7):1232–41.
83. Hillman ET, Lu H, Yao T, Nakatsu CH. Microbial ecology along the gastrointestinal tract. Microbes Environ. 2017;32(4):300–13.
84. Braniste V, Al-Asmakh M, Kowal C, Anuar F, Abbaspour A, Tóth M, et al. The gut microbiota influences blood-brain barrier permeability in mice. Sci Transl Med. 2014;6(263):263.
85. Leylabadlo HE, Ghotaslou R, Feizabadi MM, Farajnia S, Moaddab SY, Ganbarov K, et al. The critical role of faecalibacterium prausnitzii in human health: an overview. Microb Pathog. 2020;149:104344.
86. Bairamian D, Sha S, Rolhion N, Sokol H, Dorothée G, Lemere CA, Krantic S. Microbiota in neuroinflammation and synaptic dysfunction: a focus on Alzheimer's disease. Mol Neurodegener. 2022;17(1):19.
87. Mobeen F, Sharma V, Tulika P. Enterotype variations of the healthy human gut microbiome in different geographical regions. Bioinformation. 2018;14(9):560–73.
88. McGrattan AM, McGuinness B, McKinley MC, Kee F, Passmore P, Woodside JV, McEvoy CT. Diet and inflammation in cognitive ageing and Alzheimer's disease. Curr Nutr Rep. 2019;8(2):53–65.
89. Vailati-Riboni M, Rund L, Caetano-Silva ME, Hutchinson NT, Wang SS, Soto-Díaz K, et al. Dietary fiber as a counterbalance to age-related microglial cell dysfunction. Front Nutr. 2022;9:835824.
90. Romano S, Savva GM, Bedarf JR, Charles IG, Hildebrand F, Narbad A. Meta-analysis of the Parkinson's disease gut microbiome suggests alterations linked to intestinal inflammation. NPJ Park Dis. 2021;7(1):27.
91. Hoyles L, Snelling T, Umlai U-K, Nicholson JK, Carding SR, Glen RC, McArthur S. Microbiome-host systems interactions: protective effects of propionate upon the blood-brain barrier. Microbiome. 2018;1(6):55.
92. Aho VTE, Pereira PAB, Voutilainen S, Paulin L, Pekkonen E, Auvinen P, Scheperians F. Gut microbiota in Parkinson's disease: temporal stability and relations to disease progression. eBioMedicine. 2019;44:691–707.
93. Lubomski M, Xu X, Holmes AJ, Muller S, Yang JYH, Davis RL, Sue CM. The gut microbiome in Parkinson's disease: a longitudinal study of the impacts on disease progression and the use of device-assisted therapies. Front Aging Neurosci. 2022;14:875261.
94. Fakhri S, Yarmohammadi A, Yarmohammadi M, Farzaei MH, Echeverria J. Marine natural products: promising candidates in the modulation of gut-brain axis towards neuroprotection. Mar Drugs. 2021;19(3):165.
95. Barbosa M, Lopes G, Andrade PB, Valentão P. Bioprospecting of brown seaweeds for biotechnological applications: phlorotannin actions in inflammation and allergy network. Trends Food Sci Technol. 2019;86:153–71.
96. Artan M, Li Y, Karadeniz F, Lee S-H, Kim M-M, Kim S-K. Anti-HIV-1 activity of phloroglucinol derivative, 6,6'-bieckol, from Ecklonia cava. Bioorg Med Chem. 2008;16(17):7921–6.
97. Choi JG, Kang O-H, Brice O-O, Lee Y-S, Chae H-S, Oh Y-C, et al. Antibacterial activity of Ecklonia cava against methicillin-resistant Staphylococcus aureus and Salmonella spp. Foodborne Pathog Dis. 2010;7(4):435–41.
98. Eom SH, Kim YM, Kim SK. Antimicrobial effect of phlorotannins from marine brown algae. Food Chem Toxicol. 2012;50(9):3251–5.
99. Wijesekara I, Kim SK. Angiotensin-I-converting enzyme (ACE) inhibitors from marine resources: prospects in the pharmaceutical industry. Mar Drugs. 2010;8(4):1080–93.
100. Manandhar B, Wagle A, Seong SH, Paudel P, Kim H-R, Jung HA, Choi JS. Phlorotannins with potential anti-tyrosinase and antioxidant activity isolated from the marine seaweed Ecklonia stolonifera. Antioxidants. 2019;8(8):240.
101. Jo S-L, Yang H, Jeong K-J, Lee H-W, Hong E-J. Neuroprotective effects of Ecklonia cava in a chronic neuroinflammatory disease model. Nutrients. 2023;15(8):2007.
102. Myung CS, Shin H-C, Bao HY, Yeo SJ, Lee BH, Kang JS. Improvement of memory by dieckol and phlorofucofuroeckol in ethanol-treated mice: possible involvement of the inhibition of acetylcholinesterase. Arch Pharm Res. 2005;28(6):691–8.
103. Cui Y, Amarsanaa K, Lee JH, Rhim J-K, Kwon JM, Kim S-H, Park JM, Jung S-C, Eun S-Y. Neuroprotective mechanisms of dieckol against glutamate toxicity through reactive oxygen species

scavenging and nuclear factor-like 2/heme oxygenase-1 pathway. Korean J Physiol Pharmacol. 2019;23(2):121–30.
104. Jung HA, Roy A, Jung JH, Choi JS. Evaluation of the inhibitory effects of eckol and dieckol isolated from edible brown alga Eisenia bicyclis on human monoamine oxidases A and B. Arch Pharm Res. 2017;40(4):480–91.
105. Yoon J-H, Lee N, Youn K, Jo MR, Kim H-R, Lee D-S, Ho C-T, Jun M. Dieckol ameliorates Aβ production via PI3K/Akt/GSK-3β regulated APP processing in SweAPP N2a cell. Mar Drugs. 2021;19(3):152.
106. Lee J, Jun M. Dual BACE1 and cholinesterase inhibitory effects of Phlorotannins from Ecklonia cava—an in vitro and in silico study. Mar Drugs. 2019;17(2):91.
107. Liu X-Y, Liu D, Lin G-P, Wu Y-J, Gao L-Y, Ai C, et al. Anti-ageing and antioxidant effects of sulfate oligosaccharides from green algae Ulva lactuca and Enteromorpha prolifera in SAMP8 mice. Int J Biol Macromol. 2019b;139:342–51.
108. Jung W-K, Heo S-J, Jeon Y-J, Lee C-M, Park Y-M, Byun H-G, Choi YH, Park S-G, Choi I-W. Inhibitory effects and molecular mechanism of dieckol isolated from marine brown alga on COX-2 and iNOS in microglial cells. J Agric Food Chem. 2009;57(10):4439–46.
109. Ahn BR, Moon HE, Kim HR, Jung HA, Choi JS. Neuroprotective effect of edible brown alga Eisenia bicyclis on amyloid beta peptide-induced toxicity in PC12 cells. Arch Pharm Res. 2012;35(11):1989–98.
110. Jung HA, Jin SE, Ahn BR, Lee CM, Choi JS. Anti-inflammatory activity of edible brown alga Eisenia bicyclis and its constituents fucosterol and phlorotannins in LPS-stimulated RAW264.7 macrophages. Food Chem Toxicol. 2013;59:199–206.
111. Kim HS, Lee K, Kang KA, Lee NH, Hyun JW, Kim H-S. Phloroglucinol exerts protective effects against oxidative stress–induced cell damage in SH-SY5Y cells. J Pharmacol Sci. 2012;119(2):186–92.
112. Yang E-J, Ahn S, Ryu J, Choi M-S, Choi S, Chong YH, et al. Phloroglucinol attenuates the cognitive deficits of the 5XFAD mouse model of Alzheimer's disease. PLoS ONE. 2015;10(8):e135686.
113. Yang E-J, Mahmood U, Kim H, Choi M, Choi Y, Lee J-P, et al. Phloroglucinol ameliorates cognitive impairments by reducing the amyloid β peptide burden and pro-inflammatory cytokines in the hippocampus of 5XFAD mice. Free Radic Biol Med. 2018;126:221–34.
114. Kannan RRR, Aderogba MA, Ndhlala AR, Stirk WA, Van Staden J. Acetylcholinesterase inhibitory activity of phlorotannins isolated from the brown alga, Ecklonia maxima (Osbeck) Papenfuss. Food Res Int. 2013;54(1):1250–4.
115. Yoon NY, Lee S-H, Li Y, Kim S-K. Phlorotannins from Ishige okamurae and their acetyl- and butyrylcholinesterase inhibitory effects. J Funct Foods. 2009;1(4):331–5.
116. Heo S-J, Cha S-H, Kim K-N, Lee S-H, Ahn G, Kang D-H, et al. Neuroprotective effect of phlorotannin isolated from Ishige okamurae against H_2O_2—induced oxidative stress in murine hippocampal neuronal cells, HT22. Appl Biochem Biotechnol. 2012;166(6):1520–32.
117. Shrestha S, Johnston MR, Zhang W, Smid SD. A phlorotannin isolated from Ecklonia radiata, Dibenzodioxin-fucodiphloroethol, inhibits neurotoxicity and aggregation of β-amyloid. Phytomed Plus. 2021;1(4):100125.
118. Rocha DHA, Pinto DCGA, Silva AMS. Macroalgae specialized metabolites: evidence for their anti-inflammatory health benefits. Mar Drugs. 2022;20(12):789.
119. Gaysinski M, Ortalo-Magné A, Thomas OP, Culioli G. Extraction, purification, and NMR analysis of terpenes from brown algae. Methods Mol Biol. 2015;1308:207–23.
120. Tsang CK, Ina A, Goto T, Kamei Y. Sargachromenol, a novel nerve growth factor-potentiating substance isolated from Sargassum macrocarpum, promotes neurite outgrowth and survival via distinct signaling pathways in PC12D cells. Neuroscience. 2005;132(3):633–43.
121. Choi BW, Ryu G, Park SH, Kim ES, Shin J, Roh SS, Shin HC, Lee BH. Anticholinesterase activity of plastoquinones from Sargassum sagamianum: lead compounds for Alzheimer's disease therapy. Phytother Res. 2007;21(5):423–6.
122. Cengiz S, Cavas L, Yurdakoc K, Pohnert G. The Sesquiterpene Caulerpenyne from Caulerpa spp. is a lipoxygenase inhibitor. Mar Biotechnol. 2011;13(2):321–6.
123. Manev H, Chen H, Dzitoyeva S, Manev R. Cyclooxygenases and 5-lipoxygenase in Alzheimer's disease. Prog Neuropsychopharmacol Biol Psychiatry. 2011;35(2):315–9.
124. Shimizu H, Koyama T, Yamada S, Lipton SA, Satoh T. Zonarol, a sesquiterpene from the brown algae Dictyopteris undulata, provides neuroprotection by activating the Nrf2/ARE pathway. Biochem Biophys Res Commun. 2015;457(4):718–22.
125. Silva J, Alves C, Freitas R, Martins A, Pinteus S, Ribeiro J, Gaspar H, Alfonso A, Pedrosa R. Antioxidant and neuroprotective potential of the brown seaweed Bifurcaria bifurcata in an in vitro Parkinson's disease model. Mar Drugs. 2019;17(2):85.
126. Joung E-J, Gwon W-G, Shin T, Jung B-M, Choi J, Kim H-R. Anti-inflammatory action of the ethanolic extract from Sargassum serratifolium on lipopolysaccharide-stimulated mouse peritoneal macrophages and identification of active components. J Appl Phycol. 2017;29(1):563–73.
127. Kang C-W, Park M-S, Kim N-H, Lee J-H, Oh C-W, Kim H-R, Kim G-D. Hexane extract from Sargassum serratifolium inhibits the cell proliferation and metastatic ability of human glioblastoma U87MG cells. Oncol Rep. 2015;34(5):2602–8.
128. Azam MS, Joung E-J, Choi J, Kim H-R. Ethanolic extract from Sargassum serratifolium attenuates hyperpigmentation through CREB/ERK signaling pathways in α-MSH-stimulated B16F10 melanoma cells. J Appl Phycol. 2017; https://doi.org/10.1007/s10811-017-1120-8.
129. Seong SH, Ali MY, Kim H-R, Jung HA, Choi JS. BACE1 inhibitory activity and molecular docking analysis of meroterpenoids from Sargassum serratifolium. Bioorg Med Chem. 2017;25(15):3964–70.
130. Patel AK, Albarico FPJB, Perumal PK, Vadrale AP, Nian CT, Chau HTB, et al. Algae as an emerging source of bioactive pigments. Bioresour Technol. 2022;351:126910.
131. Pangestuti R, Kim S-K. Biological activities and health benefit effects of natural pigments derived from marine algae. J Funct Foods. 2011;3(4):255–66.
132. Chuyen HV, Eun J-B. Marine carotenoids: bioactivities and potential benefits to human health. Crit Rev Food Sci Nutr. 2017;57(12):2600–10.
133. Young AJ, Lowe GL. Carotenoids-antioxidant properties. Antioxidants. 2018;7(2):28.
134. Linnewiel-Hermoni K, Khanin M, Danilenko M, Zango G, Amosi Y, Levy J, Sharoni Y. The anti-cancer effects of carotenoids and other phytonutrients resides in their combined activity. Arch Biochem Biophys. 2015;572:28–35.
135. SanGiovanni J, Chew EY, Clemons TE, Ferris FL 3rd, Gensler G, Lindblad AS, et al. The relationship of dietary carotenoid and vitamin A, E, and C intake with age-related macular degeneration in a case-control study. Arch Ophthalmol. 2007;125(9):1225–32.
136. Aryee ANA, Agyei D, Akanbi TO. Recovery and utilization of seaweed pigments in food processing. Curr Opin Food Sci. 2018;19:113–9.
137. Hu L, Chen W, Tian F, Yuan C, Wang H, Yue H. Neuroprotective role of fucoxanthin against cerebral ischemic/reperfusion injury through activation of Nrf2/HO-1 signaling. Biomed Pharmacother. 2018;106:1484–9.
138. Peng J, Yuan J-P, Wu C-F, Wang J-H. Fucoxanthin, a marine carotenoid present in brown seaweeds and diatoms: metabo-

lism and bioactivities relevant to human health. Mar Drugs. 2011;9(10):1806–28.
139. Yamamoto K, Ishikawa C, Katano H, Yasumoto T, Mori N. Fucoxanthin and its deacetylated product, fucoxanthinol, induce apoptosis of primary effusion lymphomas. Cancer Lett. 2011;300(2):225–34.
140. Mohibbullah M, Haque N, Khan MNA, Park I-S, Moon IS, Hong Y-K. Neuroprotective effects of fucoxanthin and its derivative fucoxanthinol from the phaeophyte Undaria pinnatifida attenuate oxidative stress in hippocampal neurons. J Appl Phycol. 2018;30:3243–52.
141. Jang EJ, Kim SC, Lee J-H, Lee JR, Kim IK, Baek SY, Kim YW. Fucoxanthin, the constituent of Laminaria japonica, triggers AMPK-mediated cytoprotection and autophagy in hepatocytes under oxidative stress. BMC Complement Altern Med. 2018;18(1):97.
142. Xiang S, Liu F, Lin J, Chen H, Huang C, Chen L, et al. Fucoxanthin inhibits β-amyloid assembly and attenuates β-amyloid oligomer-induced cognitive impairments. J Agric Food Chem. 2017;65(20):4092–102.
143. Alghazwi M, Smid S, Musgrave I, Zhang W. In vitro studies of the neuroprotective activities of astaxanthin and fucoxanthin against amyloid beta ($A\beta_{1-42}$) toxicity and aggregation. Neurochem Int. 2019b;124:215–24.
144. Kim E-A, Kim S-Y, Ye B-R, Kim J, Ko S-C, Lee WW, et al. Anti-inflammatory effect of Apo-9'-fucoxanthinone via inhibition of MAPKs and NF-kB signaling pathway in LPS-stimulated RAW 264.7 macrophages and zebrafish model. Int Immunopharmacol. 2018;59:339–46.
145. Hong DD, Thom LT, Ha NC, Thu NTH, Hien HTM, Tam LT, et al. Isolation of Fucoxanthin from Sargassum oligocystum Montagne, 1845 Seaweed in Vietnam and its neuroprotective activity. Biomedicines. 2023;11(8):2310.
146. Heo SJ, Jeon YJ. Protective effect of fucoxanthin isolated from Sargassum siliquastrum on UV-B induced cell damage. J Photochem Photobiol B. 2009;95(2):101–7.
147. Alghazwi M, Smid S, Karpiniec S, Zhang W. Comparative study on neuroprotective activities of fucoidans from Fucus vesiculosus and Undaria pinnatifida. Int J Biol Macromol. 2019a;122:255–64.
148. Rahman MA, Dash R, Sohag AAM, Alam M, Rhim H, Ha H, Moon IS, Uddin J, Hannan A. Prospects of marine sterols against pathobiology of Alzheimer's disease: pharmacological insights and technological advances. Mar Drugs. 2021;19(3):167.
149. Liu R, Hao D, Xu W, Li J, Li X, Shen D, et al. β-Sitosterol modulates macrophage polarization and attenuates rheumatoid inflammation in mice. Pharm Biol. 2019a;57(1):161–8.
150. Bogie J, et al. Dietary Sargassum fusiforme improves memory and reduces amyloid plaque load in an Alzheimer's disease mouse model. Sci Rep. 2019;9(1):4908.
151. Schepers M, Martens N, Tiane A, Vanbrabant K, Liu H-B, Lütjohann D, Mulder M, Vanmierlo T. Edible seaweed-derived constituents: an undisclosed source of neuroprotective compounds. Neural Regen Res. 2020;15(5):790–5.
152. Zelcer N, Khanlou N, Clare R, Jiang Q, Reed-Geaghan EG, Landreth GE, Vinters HV, Tontonoz P. Attenuation of neuroinflammation and Alzheimer's disease pathology by liver x receptors. Proc Natl Acad Sci U S A. 2007;104(25):10601–6.
153. Chen Z, Liu J, Fu Z, Ye C, Zhang R, Song Y, Zhang Y, Li H, et al. 24(S)-Saringosterol from edible marine seaweed Sargassum fusiforme is a novel selective LXRβ agonist. J Agric Food Chem. 2014;62(26):6130–7.
154. Sun E, Motolani A, Campos L, Lu T. The pivotal role of NF-kB in the pathogenesis and therapeutics of Alzheimer's disease. Int J Mol Sci. 2022;23(16):8972.
155. Yoo M-S, Shin J-S, Choi H-E, Cho Y-W, Bang M-H, Baek N-I, Lee K-T. Fucosterol isolated from Undaria pinnatifida inhibits lipopolysaccharide-induced production of nitric oxide and pro-inflammatory cytokines via the inactivation of nuclear factor-κB and p38 mitogen-activated protein kinase in RAW264.7 macrophages. Food Chem. 2012;135(3):967–75.
156. Wong CH, Gan SY, Tan SC, Gany SA, Ying T, Gray AI, Igoli J, Chan EWL, Phang SM. Fucosterol inhibits the cholinesterase activities and reduces the release of pro-inflammatory mediators in lipopolysaccharide and amyloid-induced microglial cells. J Appl Phycol. 2018;30:1–10.
157. Jung HA, Ali MY, Choi RJ, Jeong HO, Chung HY, Choi JS. Kinetics and molecular docking studies of fucosterol and fucoxanthin, BACE1 inhibitors from brown algae Undaria pinnatifida and Ecklonia stolonifera. Food Chem Toxicol. 2016;89:104–11.
158. Choi JS, Han YR, Byeon JS, Choung S-Y, Sohn HS, Jung HA. Protective effect of fucosterol isolated from the edible brown algae, Ecklonia stolonifera and Eisenia bicyclis, on tert-butyl hydroperoxide- and tacrine-induced HepG2 cell injury. J Pharm Pharmacol. 2015;67(8):1170–8.
159. Fernando IPS, Jayawardena TU, Kim H-S, Lee WW, Vaas APJP, De Silva HIC, et al. Beijing urban particulate matter-induced injury and inflammation in human lung epithelial cells and the protective effects of fucosterol from Sargassum binderi (Sonder ex J. Agardh). Environ Res. 2019;172:150–8.
160. Martens N, Zhan N, Voortman G, Leijten FPJ, van Rheenen C, van Leerdam S, et al. Activation of liver X receptors and peroxisome proliferator-activated receptors by lipid extracts of brown seaweeds: a potential application in Alzheimer's Disease? Nutrients. 2023;15(13):3004.
161. Wang C, Xiong M, Gratuze M, Bao X, Shi Y, Andhey PS, et al. Selective removal of astrocytic APOE4 strongly protects against tau-mediated neurodegeneration and decreases synaptic phagocytosis by microglia. Neuron. 2021;109(10):1657–1674.e7.
162. Alba K, Kontogiorgos V. Seaweed polysaccharides (agar, alginate carrageenan). In: Melton L, Shahidi F, Varelis P, editors. Encyclopedia of Food Chemistry. Oxford: Academic Press; 2019. pp. 240–50.
163. Shao P, Pei Y, Fang Z, Sun P. Effects of partial desulfation on antioxidant and inhibition of DLD cancer cell of Ulva fasciata polysaccharide. Int J Biol Macromol. 2014;65:307–13.
164. Qi H, Zhao T, Zhang Q, Li Z, Zhao Z, Xing R. Antioxidant activity of different molecular weight sulfated polysaccharides from Ulva pertusa Kjellm (Chlorophyta). J Appl Phycol. 2005;17:527–34.
165. Liu F, Zhao W, Zhao F, Dong Q, Wang Y, Wei W, Jia L, Lu F. Dual effect of the acidic polysaccharose ulvan on the inhibition of amyloid-β protein fibrillation and disintegration of mature fibrils. ACS Appl Mater Interfaces. 2020;12(37):41167–76.
166. Alghazwi M, Charoensiddhi S, Smid S, Zhang W. Impact of Ecklonia radiata extracts on the neuroprotective activities against amyloid beta (Aβ1–42) toxicity and aggregation. J Funct Foods. 2020;68:103893.
167. Zhang Z, Wang X, Pan Y, Wang G, Mao G. The degraded polysaccharide from Pyropia haitanensis represses amyloid beta peptide-induced neurotoxicity and memory in vivo. Int J Biol Macromol. 2020;146:725–9.
168. Isaka S, Cho K, Nakazono S, Abu R, Ueno M, Kim D, Oda T. Antioxidant and anti-inflammatory activities of porphyran isolated from discolored nori (Porphyra yezoensis). Int J Biol Macromol. 2015;74:68–75.
169. Jin W, Zhang W, Wang J, Yao J, Xie E, Liu D, Duan D, Zhang Q. A study of neuroprotective and antioxidant activities of heteropolysaccharides from six Sargassum species. Int J Biol Macromol. 2014;67:336–42.
170. O'Sullivan L, Murphy B, McLoughlin P, Duggan P, Lawlor PG, Hughes H, Gardiner GE. Prebiotics from marine macroalgae for human and animal health applications. Mar Drugs. 2010;8(7):2038–64.
171. Sanjeewa KKA, Lee J-S, Kim W-S, Jeon Y-J. The potential of brown-algae polysaccharides for the development of anticancer agents: an update on anticancer effects reported for fucoidan and laminaran. Carbohydr Polym. 2017;177:451–9.

172. Wei H, Gao Z, Zheng L, Zhang C, Liu Z, Yang Y, et al. Protective effects of fucoidan on Aβ25-35 and d-Gal-induced neurotoxicity in PC12 cells and d-Gal-induced cognitive dysfunction in mice. Mar Drugs. 2017;15(3):77.
173. Park SK, Kang JY, Kim JM, Yoo SK, Han HJ, Chung DH, Kim D-O, Kim G-H, Heo HJ. Fucoidan-rich substances from Ecklonia cava improve trimethyltin-induced cognitive dysfunction via down-regulation of amyloid β production/Tau hyperphosphorylation. Mar Drugs. 2019;17(10):591.
174. Zhang L, Hao J, Zheng Y, Su R, Liao Y, Gong X, Liu L, Wang X. Fucoidan protects dopaminergic neurons by enhancing the mitochondrial function in a rotenone-induced rat model of Parkinson's disease. Aging Dis. 2018;9(4):590–604.
175. Liyanage NM, Lee H-G, Nagahawatta DP, Jayawardhana HHACK, Song K-M, Choi Y-S, Jeon Y-J, Kang M-C. Fucoidan from Sargassum autumnale inhibits potential inflammatory responses via NF-κB and MAPK pathway suppression in lipopolysaccharide-induced RAW 264.7 macrophages. Mar Drugs. 2023;21(7):374.
176. Zhang FL, He Y, Zheng Y, Zhang W-J, Wang Q, Jia Y-J, et al. Therapeutic effects of fucoidan in 6-hydroxydopamine-lesioned rat model of Parkinson's disease: role of NADPH oxidase-1. CNS Neurosci Ther. 2014;20(12):1036–44.
177. Olasehinde TA, Mabinya LV, Olaniran AO, Okoh AI. Chemical characterization, antioxidant properties, cholinesterase inhibitory and anti-amyloidogenic activities of sulfated polysaccharides from some seaweeds. Bioact Carb Diet Fibre. 2019;18:100182.
178. Jiang RW, et al. Synthesis and bioassay of β-(1,4)-D-mannans as potential agents against Alzheimer's disease. Acta Pharmacol Sin. 2013;34(12):1585–91.
179. Xiao S, Chan P, Wang T, Hong Z, Wang S, Kuang W, et al. A 36-week multicenter, randomized, double-blind, placebo-controlled, parallel-group, phase 3 clinical trial of sodium oligomannate for mild-to-moderate Alzheimer's dementia. Alzheimers Res Ther. 2021;13(1):62.
180. Wang X, Sun G, Feng T, Zhang J, Huang X, Wang T, et al. Sodium oligomannate therapeutically remodels gut microbiota and suppresses gut bacterial amino acids-shaped neuroinflammation to inhibit Alzheimer's disease progression. Cell Res. 2019;29(10):787–803.
181. Gates EJ, Bernath AK, Klegeris A. Modifying the diet and gut microbiota to prevent and manage neurodegenerative diseases. Rev Neurosci. 2022;33(7):767–87.
182. Rockwood K, Fay S, Gorman M, Carver D, Graham JE. The clinical meaningfulness of ADAS-Cog changes in Alzheimer's disease patients treated with donepezil in an open-label trial. BMC Neurol. 2007;7:26.
183. Nogueira J, Freitas S, Duro D, Tábuas-Pereira M, Guerreiro M, Almeida J, Santana I. Alzheimer's disease assessment scale—cognitive subscale (ADAS-cog): normative data for the Portuguese population. Acta Med Port. 2018;31(2):94–100.
184. Liu P, Yang Q, Yu N, Cao Y, Wang X, Wang Z, Qiu W-Y, Ma C. Phenylalanine metabolism is dysregulated in human hippocampus with Alzheimer's disease related pathological changes. J Alzheimers Dis. 2021;83(2):609–22.