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Review

Red Algae Compounds: Potential Neuroprotective Agents for Neurodegenerative Disorders

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Special Issue: Natural Products and Their Bioactive Compounds for Treatment of Neurodegenerative Brain Disorder

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Abstract

This review explores the potential of compounds derived from red algae (Rhodophyta) as promising neuroprotective agents for treating neurodegenerative disorders. Red algae, abundant in marine environments, contain bioactive compounds with diverse chemical structures and functionalities. Sulfated polysaccharides, primarily agar and carrageenans, stand out as the predominant and widely utilized compounds derived from red algae. Additionally, red algae harbor a spectrum of potential molecules such as essential fatty acids, phycobiliproteins, vitamins, minerals, and secondary metabolites. Extensive research has highlighted the diverse biological activities exhibited by these compounds, including anti-oxidative and anti-inflammatory properties. These compounds show various biological

activities that have garnered interest in their therapeutic potential for neurodegenerative diseases. This comprehensive review aims to summarize the current knowledge regarding the extraction, characterization, mechanisms of action, and therapeutic applications of Rhodophyta-derived compounds in the context of neuroprotection and treatment of neurodegenerative disorders.

Keywords
Rhodophyta; bioactive compounds; neuroprotective agents; therapeutic interventions

1. Introduction

Neurodegenerative disorders, characterized by the progressive degeneration of the structure and function of the nervous system, pose significant challenges in the field of medical research and healthcare [1]. As the global prevalence of these disorders continues to rise, there is an urgent need for innovative and effective therapeutic interventions. In recent years, natural compounds derived from marine sources have emerged as promising candidates for developing neuroprotective agents [2].

Among the vast diversity of marine organisms, red algae (Rhodophyta) have gained attention for their rich repertoire of bioactive compounds. These algae, abundant in aquatic environments, offer a source of diverse chemical entities with unique structures and functionalities. Notably, sulfated polysaccharides, such as agar and carrageenans, stand out as predominant and widely studied compounds derived from red algae [3, 4].

In addition to sulfated polysaccharides, red algae harbor an array of bioactive molecules, including essential fatty acids, phycobiliproteins, vitamins, minerals, and various secondary metabolites [5]. Exploring these compounds has revealed various biological activities, particularly anti-oxidative and anti-inflammatory properties. Such characteristics intrigue red algae-derived compounds for their potential therapeutic applications in neurodegenerative diseases [6].

This review aims to provide a comprehensive overview of the current knowledge surrounding the extraction, characterization, mechanisms of action, and therapeutic applications of compounds derived from red algae in the context of neuroprotection and the treatment of neurodegenerative disorders. By synthesizing existing research, we highlight the promising avenues for further exploration and development of red algae compounds as neuroprotective agents. Ultimately, understanding the potential of these marine-derived compounds may contribute to the advancement of novel and effective strategies for combating neurodegenerative disorders.

1.1 Overview of Neurodegenerative Disorders

Neurodegenerative brain disorders represent a group of debilitating conditions characterized by the progressive degeneration and dysfunction of neurons in the central nervous system. These disorders manifest through a gradual decline in cognitive function, motor skills, and, in some cases, behavioral aspects [7]. The prevalence of neurodegenerative disorders, including Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS), has seen a notable increase, posing significant challenges to global healthcare systems [7, 8].

AD is the most prevalent neurodegenerative disorder, characterized by the accumulation of β-amyloid plaques and neurofibrillary tangles in the brain. These pathological changes lead to synaptic dysfunction and neuronal loss, resulting in memory impairment, cognitive decline, and a profound impact on daily functioning [9].

PD is primarily characterized by the degeneration of dopaminergic neurons in the substantia nigra of the brain. The hallmark symptoms include tremors, bradykinesia, rigidity, and postural instability. As the disease progresses, it significantly impairs motor function and may lead to cognitive impairment in later stages [10].

HD is an inherited disorder caused by a mutation in the HTT gene, producing abnormal huntingtin protein. This protein buildup leads to neuronal damage, particularly in the basal ganglia, causing motor dysfunction, cognitive decline, and psychiatric symptoms [11].

Multiple sclerosis (MS) is an autoimmune disease in which the expected propagation of nerve impulses is affected. In this disease, there is damage to myelin, a protein that surrounds nerve cells (neurons) and plays a vital role in the propagation of those impulses. In affected nerves, the propagation of nerve impulses is compromised. MS is the most common nervous system disease in young adults and is more common in women. Symptoms usually begin between 20 and 40 years of age [12].

ALS is a progressive neurodegenerative disorder affecting motor neurons in the spinal cord and brain. This results in muscle weakness, atrophy, and eventual paralysis. ALS is characterized by the degeneration of both upper and lower motor neurons, impacting voluntary muscle control [13].

The etiology of neurodegenerative disorders is multifaceted, involving genetic, environmental, and lifestyle factors. The aging population, in particular, contributes to the increasing prevalence of these conditions. Despite extensive research, effective disease-modifying treatments for neurodegenerative disorders remain elusive, making the exploration of novel therapeutic strategies crucial [14, 15].

Understanding the underlying mechanisms, risk factors, and shared pathways among various neurodegenerative disorders is essential for developing targeted interventions. Recent advances in molecular and cellular neuroscience have shed light on potential therapeutic targets, opening avenues for developing neuroprotective agents to slow or halt the progression of these devastating brain disorders [16]. In this context, exploring natural compounds, such as those derived from red algae, emerges as a promising avenue for innovative therapeutic interventions in neurodegenerative diseases [17, 18].

1.2 Significance of Natural Extracts from Red Algae

Red macroalgae compounds have emerged as promising candidates in neuroprotective agents, particularly in addressing neurodegenerative disorders [19]. Within these seaweeds lies a treasure trove of bioactive elements, including polysaccharides, polyphenols, vitamins, and minerals, which exhibit significant potential in safeguarding neurological health and combating conditions such as Alzheimer's, Parkinson's, and other neurodegenerative ailments [20].

These compounds display remarkable neuroprotective properties by their anti-oxidative, anti-inflammatory, and neuro-regenerative capabilities. Polysaccharides like carrageenans and agar, prevalent in red algae, have shown promise in shielding neurons from oxidative stress, reducing neuroinflammation, and fostering neuronal repair and regeneration [21]. Moreover, certain

polyphenolic compounds derived from these macroalgae demonstrate the ability to inhibit protein aggregation, a hallmark of many neurodegenerative diseases, potentially slowing disease progression [22]. These findings open avenues for developing therapeutic interventions and pharmaceutical formulations harnessing the neuroprotective potential of red algae compounds. Their ability to mitigate neuronal damage, promote neurogenesis, and modulate neuroinflammatory responses offers hope for novel treatments and strategies for managing and potentially preventing neurodegenerative disorders [23].

However, further research, including clinical trials and comprehensive studies, is crucial to elucidate these compounds' precise mechanisms of action, optimal dosage, and long-term effects. This investigation is imperative to harness their full potential and ensure their safe and effective application as neuroprotective agents in treating and managing neurodegenerative conditions [24].

2. Red Algae Compounds: Sources and Extraction

2.1 Has Seaweed Played a Pivotal Role in Shaping Our Current Identity of the Human Species?

Seaweeds hold a significant place in the cultural heritage of Asian nations, more prominently than in their Western counterparts. However, recent archaeological findings have unearthed cooked and partially consumed seaweeds at a 14,000-year-old site in southern Chile, suggesting that seaweeds have been a part of the human diet across various regions [25, 26].

Millions of years ago, a transformative event occurred, enabling early Homo sapiens to diverge from the primitive hominoid family tree. Could this crucial turning point in human evolution be attributed, in part, to seaweed and its rich content of essential nutrients? Over the past 2-2.5 million years, human brains have undergone unprecedented development, resulting in the modern-day human possessing an organ that embodies the qualities defining humanity [27].

The remarkable brain development of our ancestors required abundant energy-rich foods and specific essential nutrients. Nutrients such as magnesium and zinc, crucial for modern brain function, likely played a role in influencing the evolution of the human brain, as suggested by several scientific studies [28, 29]. Without access to these essential nutrients, the development of the human brain into its current form might not have occurred.

The nutrients essential for the transition from primitive ancestors to modern Homo sapiens were, and still are, readily available in seaweeds. Abundant along coastlines, seaweeds were a consistent source of these crucial nutrients for a foraging lifestyle [30]. According to Cornish et al. [29, 30], the divergence of the human lineage from our closest living relatives, chimpanzees, is estimated to have occurred approximately 5-7 million years ago. However, the changing resource distribution linked to the extensive drying and expansion of African savannahs between 2 and 2.5 million years ago prompted a shift in foraging behavior among early members of the genus Homo [31].

The necessity to forage over longer distances for food likely contributed to bipedalism and different body stature, as more extensive ranges had to be traversed. Coastal environments, rich in resources, may have attracted early hominoids searching for food. Our primitive ancestors likely encountered a variety of foods, such as fish, crustaceans, snails, seaweeds, bird eggs, and occasional dead marine vertebrates [32]. However, their understanding of seasonal tidal cycles and their impact on shellfish availability might have been rudimentary [33].

In contrast, seaweeds of various types were accessible across the intertidal zone, from the high-water mark to subtidal regions, making them quickly and repeatedly harvestable for all family

members, including women and children. The nutritional benefits of seaweed weren't confined to our ancestors; even today, seaweed remains as healthy and nutritious for humans as it was millions of years ago [34].

There has been a longstanding suspicion that the abundance of specific nutrients can impact cognitive processes and emotions. Recent insights into the influences of dietary factors on neuronal function and synaptic plasticity have unveiled essential mechanisms underlying the effects of diet on brain health and mental function. Certain gut hormones, either entering the brain or produced within it, have been identified as influencers of cognitive ability [35]. Moreover, established regulators of synaptic plasticity, such as brain-derived neurotrophic factors, can serve as metabolic modulators, responding to external signals like food intake. Unraveling the molecular basis of how food affects cognition is crucial for understanding how to optimize diet to enhance neuronal resilience, withstand insults, and promote mental fitness [36].

2.2 Extraction Methods and Red Algae Compounds Characterization

Red algae, commonly called seaweeds belonging to the Rhodophyta phylum, have chlorophyll a, phycobilins, and some carotenoids as photosynthetic pigments. These macroalgae constitute an abundant source of diverse bioactive compounds [37]. Extracting these compounds involves specific methods tailored to their chemical composition and desired application. Different species of red algae offer varying compositions of bioactive compounds [38].

Efficient extraction methods are crucial to isolate and preserve the bioactive compounds from red algae. Techniques such as solvent extraction, where methanol has been a commonly used solvent, enable the retrieval of neuroprotective agents [39]. Bioactivity-guided experiments aid in the identification and isolation of specific compounds with therapeutic potential. Further studies explore alternative extraction methodologies to enhance efficiency while maintaining the integrity of the neuroprotective compounds [40].

Red algae, commonly found in warmer seas, present diverse bioactive compounds with varying compositions across different species. Notable examples include *Gracilaria, Porphyra* (nori), *Gelidium*, *Chondrus crispus* (Irish moss) (Figure 1), etc. [4]. These red algae are rich sources of polysaccharides like agar and carrageenans, polyphenols including phlorotannins, and pigments such as chlorophylls and carotenoids. Additionally, they contain proteins, vitamins, and minerals, each contributing to their distinct properties and potential applications [41].

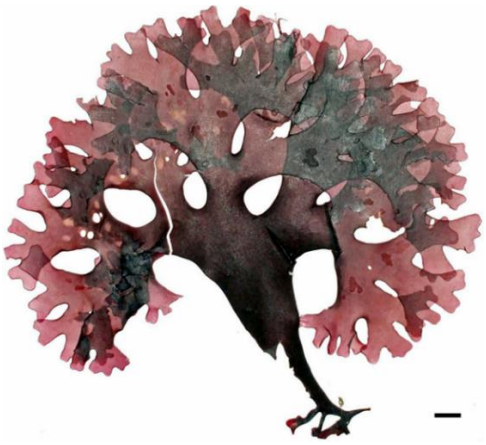


Figure 1 Red alga *Chondrus crispus*. Scale = 1 cm.

When extracting these valuable compounds, several techniques are employed, considering the specific characteristics of the compounds and their intended applications. Water-based extraction methods involve hot water extraction, where macroalgae are boiled to extract soluble compounds, and cold-water extraction, employed to preserve the bioactivity of certain compounds like antioxidants and polysaccharides [42]. Solvent-based extraction methods, on the other hand, utilize organic solvents such as ethanol or methanol [43]. Techniques like Soxhlet extraction or maceration extract a broader range of compounds, including polyphenols and lipids [44]. Supercritical Fluid Extraction (SFE) is another solvent-based method that utilizes supercritical CO_2 to efficiently extract compounds while maintaining their integrity, making it particularly suitable for sensitive bioactive [45]. Enzyme-assisted extraction involves using enzymes like cellulase or pectinase to break down the cell walls of algae, enhancing the release of target compounds, especially polysaccharides [46]. Ultrasound-assisted extraction (UAE) employs ultrasound waves to disrupt cell walls and increase mass transfer, thereby improving compound yield and extraction efficiency [47]. Microwave-assisted extraction (MAE) utilizes microwave energy to expedite the extraction process by promoting the release of compounds from the macroalgae matrix [48].

Following extraction, purification methods such as chromatography or filtration are implemented to refine the extracts, remove impurities, and concentrate the bioactive compounds. These comprehensive extraction techniques ensure the harnessing of the full potential of red algae compounds for various applications, ranging from pharmaceuticals and cosmetics to food and agriculture [49].

Characterizing the compounds found in red algae is a multifaceted exploration that delves into the intricate biochemical makeup of these marine organisms. Among the notable compounds, polysaccharides stand out prominently. Agar and carrageenans are critical polysaccharides found in red seaweeds, contributing not only to the structural integrity of the algae but also possessing valuable properties for applications in food, pharmaceuticals, and biotechnology [19]. For instance, the gel-forming ability of these polysaccharides makes them desirable in the food industry for their textural and stabilizing properties, in addition to their enormous potential in the pharmaceutical industry [50].

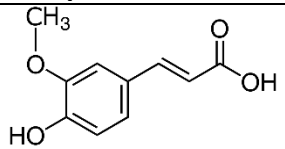
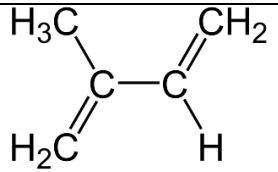
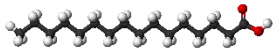
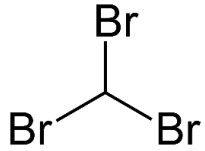
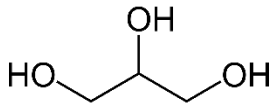
Polyphenols, including phlorotannins, add another layer to characterizing red algae compounds. These compounds exhibit antioxidant, anti-inflammatory, and antiviral properties, making them subjects of interest for pharmaceutical and cosmetic applications [51]. The vibrant pigments present, such as chlorophylls and carotenoids, not only contribute to the visual appeal of red algae but also hold potential as natural colorants and antioxidants [38]. Proteins, vitamins, and minerals further enrich the characterization, offering a holistic view of the nutritional profile of red algae. These components contribute to the health-promoting aspects of seaweed consumption and have implications for developing functional foods and nutraceuticals [52].

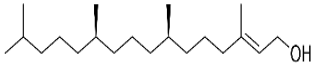
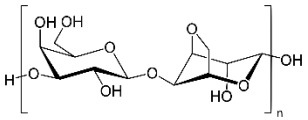
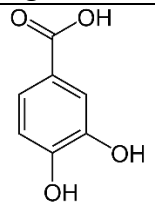
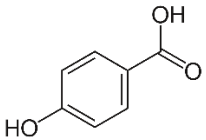
The characterization process extends beyond mere identification to understand the interplay of these compounds within the seaweed matrix. Factors such as extraction methods, geographical location, and environmental conditions influence the composition and bioactivity of these compounds [53]. Advanced analytical techniques, including chromatography, spectroscopy, and mass spectrometry, play a crucial role in unraveling the intricate chemical fingerprint of red seaweed [54].

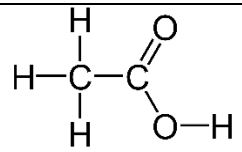
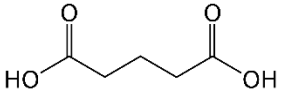
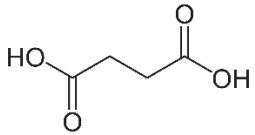
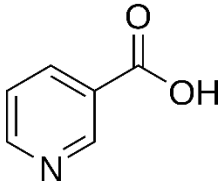
3. Neuroprotective Mechanisms of Some Rhodophyta Compounds

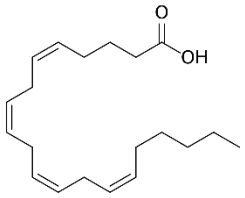
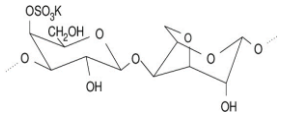
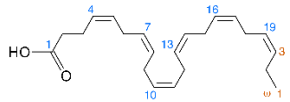
Table 1 presents a comprehensive overview of pure compounds derived from red macroalgae, showcasing diverse neuroprotective activities. Neurodegenerative diseases, typically afflicting adults in mid-life, manifest progressive motor or cognitive symptoms that diminish life expectancy. These diseases can arise from various environmental and genetic factors, ranging from risk-increasing mutations to those directly causing the disorder. Similar to cancer, neurodegeneration may result from dominant or recessive mutations [55].

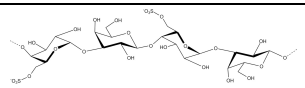
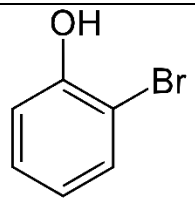
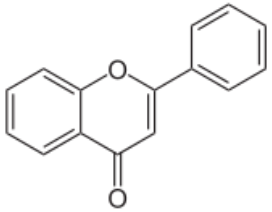
Table 1 Compounds derived from red algae showcasing neuroprotective activities.

Species	Compounds	Extract	Activity	References
Alsidium triquetrum (as *Bryothamnion triquetrum*)	 Ferulic acid	Water extract	Protect GT1-7 cells death produced by severe (180 min.) chemical hypoxia/glycemia insult.	[56]
Amphiroa anceps	 Isoprene (Terpene)	Methanolic extract	Inhibiting AChE IC_{50} = 5.34 +/- 0.14 mg/mL^{-1}	[57]
A. bowerbankii	-	Methanolic extract	Inhibiting AChE IC_{50} = 5.3 mg mL^{-1}	[58]
A. ephedraea	 Palmitic acid (hexadecanoic acid)	Methanolic extract	Inhibiting AChE IC_{50} = 5.1 mg mL^{-1}	[58]
Asparagopsis armata	 Halogenated compounds	Exudate	AChE inhibitory capacity: 58.4% Inhibitory capacity on AChE (58.4% at 10 mg mL^{-1}) of human cells	[59, 60]
Chondrophycus undulatus (as *Laurencia undulata*)	 Glycerol	Glycerol glycosides: Floridoside	Suppress pro-inflammatory responses in microglia by markedly inhibiting the production of nitric oxide (NO) and reactive oxygen species (ROS) IC_{50} = 10 µM	[61]

Chondrus crispus (Figure 1)	-	Methanolic extract	Extract-mediated protection against Parkinson' 's disease pathology	[62]
Gelidiella acerosa	 Phytol	Phytol	Phytol showed significant ($p < 0.05$) antioxidant activities (25-125 µg/mL) with an IC_{50} value of 95.27 ± 1.65 µg/mL and cholinesterase inhibitory potential (5-25 µg/mL) with IC_{50} values of 2.704 ± 0.07 and 5.798 ± 0.72 µg/mL for AChE and BuChE, respectively	[63]
G. acerosa	-	Phytol	*In vitro* and *in vivo* antioxidant activities (25-125 µg mL^{-1}) with an IC_{50} value of 95.27 µg mL^{-1} and cholinesterase inhibitory potential (5-25 µg mL^{-1}) with IC_{50} values of 2.704 and 5.798 µg mL^{-1} for AChE and BuChE, respectively	[63]
Gelidium amansii	 Agarose	Ethanol extract	Neurogenesis (synaptogenesis promotion)	[64]
Gelidium foliaceum	 Protocatechuic acid  4-Hydroxybenzoic acid	50% Aqueous methanol extract	Inhibiting AChE IC_{50} = 0.16 mg mL^{-1}	[65]

Gloiopeltis furcata	 Acetic acid  Glutaric acid  Succinic acid  Nicotinic acid	2-(3-Hydroxy-5-oxo tetrahydrofuran-3-yl) acetic acid, glutaric acid, succinic acid, nicotinic acid, (E)-4-hydroxy hex-2-enoic acid, cholesterol, 7-hydroxycholesterol, uridine, glycerol, phlorotannin, fatty acids	Inhibiting AChE 1.4-12.50 µg mL^{-1} Inhibiting BuChE 6.56-75.25 µg mL^{-1}	[66]
Gracilaria edulis	-	Methanolic extract	Inhibiting AChE IC_{50} = 3 mg mL^{-1}	[67]
G. edulis	-	Methanolic extract	Inhibiting AChE IC_{50} = 3 mg mL^{-1}	[68]
Gracilaria gracilis	-	Methanolic extract	Inhibiting AChE IC_{50} = 1.5 mg mL^{-1}	[67]
Gracilariopsis chorda	-	Ethanolic extract	Neuronal cell viability and cell cytotoxicity testing revealed that the ethanol extract afforded the most neuroprotection at a concentration of 15 µgmL^{-1}, at which *G. chorda* extract significantly increased cell viability to	[69]

			119.0%-3.2% and decreased cell death to 80.5%-10.3%	
G. chorda	 Arachidonic acid	Ethanolic extract	Arachidonic acid (AA) significantly increased the densities of dendritic filopodia and spines	[70]
Hypnea valentiae	-	Methanolic extract	Inhibiting AChE IC_{50} = 2.6 mg mL^{-1}	[68]
Jania pedunculata var. *adhaerens* (as *Jania adhaerens*)	-	Phosphate buffered saline (PBS) extract	Neurite outgrowth-promoting substances will inhibit the degeneration of neurons.	[71]
Kappaphycus alvarezii	 κ-carrageenan	Kappa-carrageenan	Anti-oxidative activity: Inhibit superoxide radicals, hydroxyl radicals, and lipid peroxidation IC_{50} = 0.112, 0.335 and 0.323 mg mL^{-1}, respectively	[72]
K. alvarezii	-	Ethanolic extract	Promotes neurite outgrowth in hippocampal neurons	[73]
Laurencia dendroidea	Elatol	Halogenated sesquiterpenes	Elatol was able to inhibit acetylcholinesterase	[74]
Laurencia snackeyi	 Docosahexaenoic acid	Docosahexaenoic acid	The extract inhibited both acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) with IC_{50} values of 14.45 ± 0.34 µg mL^{-1} and 39.59 ± 0.24 µg mL^{-1}, respectively.	[75]

Ochtodes secundiramea	-	Dichloromethane/methanol extract: Halogenated monoterpenes	The extract showed 48% AChE inhibition at 400 µg mL^{-1}	[76]
Pyropia haitanensis	 Porphyran	Porphyran	Porphyran increased ChAT activity and decreased AChE activity in the cortical and hippocampal tissue.	[77]
Pyropia yezoensis	Porphyran	Ethanolic extract	Increased neurite outgrowth at an optimal concentration of 15 µg mL^{-1}	[78, 79]
Rhodomela confervoides	 Bromophenol	Bromophenols	Antioxidant activity IC_{50} = 5.22-23.60 µM	[80]
Rhodomelopsis africana		50% Aqueous methanol extract	Inhibiting AChE IC_{50} = 0.12 mg mL^{-1}	[81]
Symphyocladia latiuscula	Flavone Bromophenol	Bromophenols	Bromophenols, especially highly brominated, may represent a novel class of anti-Alzheimer's disease drugs.	[82]

Compounds derived from macroalgae, mainly red algae (Rhodophyta), showcase significant neuroprotective potential, holding promise for preventing and treating neurodegenerative diseases such as Alzheimer's, Huntington's, and Parkinson's [19]. Notable bioactive compounds from red algae include α-alkokainic acid isolated from Digenea simplex, demonstrating potent neurophysiological activity in mammals [83, 84]. These neurodegenerative diseases involve extensive loss of neurons, yet their precise etiology remains elusive despite historical documentation [85]. Reactive oxygen species (ROS), such as hydrogen peroxide (H_2O_2), have been implicated in disorders like Alzheimer's, Parkinson's, and Minamata diseases [86]. H_2O_2 exerts neurotoxicity primarily through the formation of the highly reactive hydroxyl (•OH) radical alongside factors like glutathione (GSH) depletion and secondary disruption of calcium homeostasis [87].

While significant research has focused on neurodegenerative diseases, particularly Alzheimer's, effective treatments remain elusive. The identification of genes associated with early-onset Alzheimer's could facilitate early diagnosis and treatment, potentially preventing irreversible brain damage [88]. In Alzheimer's, a deficiency in the neurotransmitter acetylcholine (ACh) has been noted, leading to interest in acetylcholinesterase (AChE) inhibitors as a symptomatic treatment. Marine algae, including *Pyropia haitanensis*, have demonstrated AChE inhibitory activity, suggesting their potential as neuroprotective agents [89].

Predictions indicate that neurodegenerative diseases will surpass cancer as the second leading cause of death among the elderly by the 2040s [90]. Consequently, there is growing interest in safe and effective neuroprotective agents, with natural compounds emerging as potential candidates, particularly those from marine algae. However, developing marine algae as neuroprotective agents faces challenges, including further studies in human subjects, understanding synergistic effects, determining optimal doses, and refining preparation methods [91].

Bromophenols, a distinctive class of bioactive compounds in red algae, show anti-inflammatory effects, as seen in vidalols A and B from *Osmundaria obtusiloba*, inhibiting bee venom-derived phospholipase A2(PLA2) activity [92]. Dysregulation of PLA2 in the brain can lead to oxidative stress and neuroinflammation, contributing to various neurological diseases. Marine algae extracts, such as *Neorhodomela aculeata* and *Alsidium triquetrum* (formerly *Bryothamnion triquetrum*), have demonstrated potential against neuroinflammation and oxidative stress [93].

Natural neuroprotective agents have been identified in extracts from red algae, highlighting their potential significance. The neuroprotective properties of these red algae extracts have been examined through the lens of acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) activities, two enzymes closely associated with Alzheimer's and Parkinson's diseases [73]. For instance, studies have explored AChE activity in various compounds extracted from algae, confirming neuroprotective effects. Examples include phytol extracted from *Gelidiella acerosa*, evaluated through both *in vitro* and *in vivo* experiments [4], as well as methanol extracts from *Hypnea valentiae*, *Gracilaria edulis* [73], and *Gracilaria manilaensis* [94]. Studies on marine algae like *Symphyocladia latiuscula* and *Pyropia yezoensis* (Figure 2) suggest potential neuroprotective effects. *S. latiuscula* and *P. yezoensis* administration increased dopamine levels, indicating possible psychotropic and anxiolytic effects [84, 87]. *Ochtodes secundiramea*, a Brazilian red alga species, provided several compounds, including one with inhibitory activities against AChE [95].

Figure 2 Red macroalga *Pyropia yezoensis*. Scale = 1 cm.

Research efforts, such as those by Mohibbullah et al. [96], have screened edible seaweeds for neuroprotective activity, revealing *Gracilariopsis chorda* (Rhodophyta) and *Undaria pinnatifida* (Phaeophyceae) as promising candidates. Additionally, dietary supplementation with *Chondrus crispus* extract has shown protective effects against α-synuclein accumulation and dopaminergic neurodegeneration in worms, suggesting potential pharmaceutical applications in anti-neurodegenerative drug development [97].

3.1 Molecular Targets and Pathways Involved

Understanding the molecular targets and pathways of neuroprotective compounds derived from red macroalgae is crucial for elucidating their therapeutic mechanisms in neurodegenerative disorders. The molecular targets and pathways implicated in the action of red macroalgae-derived neuroprotective compounds shed light on their potential therapeutic relevance. One of the critical molecular targets identified for red macroalgae-derived neuroprotective compounds is acetylcholinesterase (AChE). AChE inhibition plays a crucial role in the management of neurodegenerative disorders such as Alzheimer's disease by enhancing cholinergic neurotransmission [98].

Neuroinflammation is a hallmark feature of various neurodegenerative disorders and represents a potential target for therapeutic intervention. Red macroalgae-derived compounds have been shown to modulate inflammatory pathways, offering neuroprotective effects. Bromophenols found in red algae, such as vidalols A and B from *Osmundaria obtusiloba*, exhibit anti-inflammatory effects by inhibiting bee venom-derived phospholipase A2 (PLA2) activity [99]. These compounds promise to mitigate neuronal damage associated with neurodegenerative diseases by attenuating neuroinflammation.

Oxidative stress is implicated in the pathogenesis of neurodegenerative disorders, contributing to neuronal dysfunction and degeneration. Red macroalgae-derived compounds possess antioxidant properties, targeting oxidative stress pathways to confer neuroprotection. *Bryothamnion triquetrum* extracts, rich in phenolic compounds, demonstrate potent ROS scavenging activity [100]. Neorhodomela aculeata extracts have also been reported to inhibit oxidative stress-induced lipid peroxidation in brain homogenates [101]. By mitigating oxidative stress, these compounds offer potential therapeutic avenues for neurodegenerative disorders.

Dysregulation of dopaminergic pathways is implicated in the pathophysiology of Parkinson's disease, making it a crucial molecular target for neuroprotective interventions. Methanolic extracts from *Hypnea musciformis* (Figure 3) have increased dopamine levels in rats and mice [102]. This modulation of dopaminergic pathways suggests the potential of red macroalgae-derived compounds in alleviating dopaminergic dysfunction associated with Parkinson's disease.

Figure 3 Red macroalga *Hypnea musciformis*. Scale = 1 cm.

Red macroalgae-derived neuroprotective compounds exert their therapeutic effects through diverse molecular targets and pathways implicated in neurodegenerative disorders. By targeting acetylcholinesterase inhibition, anti-inflammatory pathways, oxidative stress pathways, and dopaminergic pathways, these compounds offer multifaceted mechanisms of neuroprotection. Further elucidation of the molecular mechanisms underlying the action of red macroalgae-derived compounds holds promise for the development of targeted therapies for neurodegenerative disorders [103].

3.2 Evidence of Neuroprotection in Preclinical Studies

Oxidative stress, characterized by an imbalance between pro-oxidants and antioxidants, poses a significant threat to CNS health due to its high oxygen consumption and lipid content. This stress contributes to neurodegenerative diseases like Alzheimer's and Parkinson's. Antioxidants derived from marine algae, such as *Neorhodomela aculeata* (Rhodophyta) and *Halimeda incrassata* (Chlorophyta), exhibit potent scavenging abilities against ROS and lipid peroxidation, attributed to compounds like phenolics and carotenoids. Moreover, marine algae contain sulfated polysaccharides (SPs) with antioxidant potential [104].

Microglia, the immune cells in the CNS, play a crucial role in neuroinflammation, a critical factor in neurodegenerative diseases. Marine algae, including *Solieria filiformis* and *Laurencia undulata* (Rhodophyta), have shown promising anti-neuroinflammatory effects by suppressing pro-inflammatory mediators like nitric oxide (NO) and prostaglandins. These findings underscore the potential of marine algae-derived compounds as therapeutic agents for CNS disorders and call for clinical trials to validate their efficacy. Additionally, the paragraph briefly touches upon the cholinesterase inhibitory activity of certain plants, suggesting a potential avenue for the symptomatic treatment of Alzheimer's disease [66, 105].

The study explored the antioxidant and anti-inflammatory effects of the methanolic extract derived from *Neorhodomela aculeata* (Rhodophyta) on hippocampal and microglial cells [101]. Demonstrating significant neuroprotective capabilities, the *N. aculeata* extract effectively mitigated glutamate-induced neurotoxicity and hindered the generation of ROS within the hippocampal HT22

cell line. Additionally, it exhibited a notable inhibition of lipid peroxidation induced by H_2O_2 in rat brain homogenates. Regarding its anti-inflammatory properties, the extract demonstrated promise in reducing microglial activation triggered by interferon-gamma (IFN-g), decreasing inducible nitric oxide synthase, and subsequent NO levels. These findings collectively indicate the potential of *N. aculeata* as a valuable resource for combating oxidative stress and inflammation associated with neurological disorders [101].

The study delves into the potential of *Palmaria palmata* (Rhodophyta) (Figure 4) as a prebiotic in mitigating MS through the modulation of the gut microbiome community in a mouse model [106]. Multiple sclerosis is a complex autoimmune disorder characterized by the immune system attacking the central nervous system. The research suggests that altering the gut microbiome composition could hold promise in alleviating MS symptoms. By utilizing *P. palmata* as a prebiotic, the study aims to foster a healthier gut microbial environment, which in turn could influence the progression of MS. Prebiotics like *P. palmata* are known to selectively stimulate the growth and activity of beneficial gut bacteria, thereby enhancing gut health and potentially impacting systemic immune responses. The findings underscore the intricate relationship between the gut microbiome and immune function, suggesting that interventions targeting gut microbial communities could offer novel therapeutic avenues for managing autoimmune diseases such as MS. This research contributes to the growing body of evidence supporting the therapeutic potential of prebiotics and highlights the need for further exploration into their mechanisms of action and clinical applications in autoimmune disorders [106].

Figure 4 Red macroalga *Plamaria palmata*. Scale = 1 cm.

The study investigates the neuroprotective effects of agaropentaose (hydrolysates of agarose isolated from red algae) against 6-hydroxydopamine (6-OHDA)-induced neurotoxicity in SH-SY5Y cells. It explores the underlying molecular mechanisms involving the NF-κB and p38MAPK signaling pathways. 6-OHDA is a neurotoxin commonly used to induce PD-like symptoms in cell and animal models [107]. Agaropentaose, a derivative of agar, demonstrates promising neuroprotective properties by attenuating the cytotoxic effects of 6-OHDA on SH-SY5Y cells. The NF-κB and p38MAPK signaling pathways are known to be involved in inflammation and cell death processes associated with neurodegenerative disorders like PD. The study suggests that agaropentaose exerts its protective effects by modulating these pathways, potentially reducing inflammation and apoptosis

induced by 6-OHDA. By elucidating the mechanisms underlying agaropentaose-mediated neuroprotection, the research contributes to our understanding of novel therapeutic strategies for neurodegenerative diseases, particularly Parkinson's disease, and highlights agaropentaose as a promising candidate for further investigation in the development of neuroprotective agents [107].

4. Therapeutic Applications and Efficacy

In neurological protection, studies focusing on marine algae compounds highlight promising avenues for therapeutic development. Derived from various species of brown algae, fucoidan has garnered attention for its neuroprotective properties. Preclinical studies suggest that fucoidan exhibits antioxidant, anti-inflammatory, and anti-apoptotic effects, which may help mitigate neuronal damage and inflammation in neurodegenerative diseases. Challenges include elucidating its mechanisms of action and optimizing delivery methods for clinical translation [108].

Phlorotannins are found in brown algae, demonstrating neuroprotective effects through antioxidant and anti-inflammatory mechanisms. Research suggests that phlorotannins can attenuate oxidative stress, inhibit neuroinflammation, and promote neuronal survival in models of Alzheimer's, Parkinson's, and stroke. Numerous *in vivo* studies using different disease models have demonstrated the potential neuroprotective effects of various phlorotannins. Overcoming bioavailability and dose optimization challenges are crucial for their clinical application [109].

A carotenoid pigment abundant in brown algae, fucoxanthin demonstrates neuroprotective effects attributed to its antioxidant and anti-inflammatory properties. Preclinical studies suggest that fucoxanthin may attenuate neuroinflammation, reduce oxidative stress, and promote neurogenesis in various neurodegenerative conditions. Clinical trials are needed to evaluate its therapeutic potential and safety profile in neurological disorders [21].

These examples illustrate the diverse neuroprotective properties of marine algae compounds and underscore the importance of further research to harness their therapeutic benefits for neurological diseases. Addressing challenges such as formulation optimization, pharmacokinetics, and clinical validation is essential for translating promising preclinical findings into effective patient treatments [17, 19, 20].

5. Conclusions and Future Perspectives

Exploring compounds derived from marine macroalgae as potential neuroprotective agents holds promise for addressing the complex challenges of neurodegenerative disorders. Seaweeds, abundant in aquatic environments, offer a rich source of bioactive compounds with diverse chemical structures and functionalities. Among these compounds, sulfated polysaccharides like agar and carrageenans have garnered significant attention for their therapeutic potential. Additionally, red macroalgae harbor a spectrum of bioactive molecules, including essential fatty acids, phycobiliproteins, vitamins, minerals, and various secondary metabolites, which exhibit anti-oxidative and anti-inflammatory properties [110].

The comprehensive review presented here highlights the current understanding of the extraction, characterization, mechanisms of action, and therapeutic applications of compounds derived from red macroalgae in the context of neuroprotection and the treatment of neurodegenerative disorders. While substantial progress has been made in elucidating the neuroprotective properties of red macroalgae compounds, several avenues for future exploration and development remain.

Further research should focus on elucidating the precise mechanisms of action underlying the neuroprotective effects of seaweed compounds. Understanding these mechanisms will facilitate the identification of optimal dosage regimens and the development of targeted therapeutic interventions for specific neurodegenerative diseases.

Clinical trials and comprehensive studies are needed to evaluate red macroalgae-derived compounds' safety, efficacy, and long-term impact on neurodegenerative disorders. Rigorous scientific investigation is essential to validate the therapeutic potential of these compounds and ensure their safe and practical application in clinical settings.

Moreover, collaborative interdisciplinary efforts between researchers, clinicians, and industry stakeholders are crucial to drive innovation and translate scientific discoveries into tangible therapeutic solutions. By leveraging advances in molecular and cellular neuroscience, biochemistry, and pharmacology, we can harness the full potential of red macroalgae compounds to develop novel and effective strategies for combating neurodegenerative disorders.

In conclusion, exploring compounds derived from marine macroalgae represents a promising frontier in neurodegenerative research. By harnessing the neuroprotective properties of these marine-derived compounds, we can advance our understanding of neurodegenerative diseases and develop innovative therapies to improve patient outcomes and quality of life. Through continued scientific inquiry and collaborative efforts, we can unlock the full therapeutic potential of red macroalgae compounds and pave the way for transformative advancements in neurology and neuroscience.

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Author Contributions

LP: Conceptualization, Writing-original draft, Writing-review & editing, Supervision. AV: Writing-review, Validation. Both authors read and approved the submitted version.

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Competing Interests

The authors have declared that no competing interests exist.

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