Dubai Medical Journal
Volume 7, Issue no. 3, DOI 10.18502/dmj.v7i3.17735
Production and Hosting by KnE Publishing

Review Article

Neurodegenerative Marine Algae Bioactive Compounds: A Viable Cure to Treat Amyotrophic Lateral Sclerosis (ALS): A Review

Ayyandurai Mani, Mathiyazhagan Narayanan*, and V. Rajinikanth

Center for Research and Innovations, Department of Biotechnology, Saveetha School of Engineering, Saveetha Institute of Medical and Technical Science (SIMATS), Chennai-602 105, Tamil Nadu, India

Abstract

Introduction: Amyotrophic lateral sclerosis (ALS), a neurodegenerative disease that causes muscle weakness, paralysis, and death, develops when motor neurons begin to die. There are few proven treatments for ALS, and because the disease is incurable, the exact cause is unknown, making it a devastating condition. According to recent research, marine algae may contain bioactive substances that can be used to treat ALS.

Methods: The comprehensive review of recent publications focused on bioactive compounds extracted from various species of marine algae, including their mechanisms of action against oxidative stress, neuroinflammation, and apoptosis in ALS. The publications were reviewed in scientific journals (ScienceDirect, Springer, Taylor & Francis, and MDPI) and indexed in several databases (Scopus, Web of Science, PubMed, Google Scholar, and so on).

Discussion: Compounds derived from marine algae, including polyunsaturated fatty acids, fucoxanthin, and polysaccharides, exhibit potential neuroprotective effects by modulating neuroinflammation and oxidative stress levels. Fucoxanthin, fucosterol, and alginate demonstrated potential in mitigating oxidative damage and inflammation, which are critical factors in the pathogenesis of ALS.

Conclusion: Bioactive compounds obtained from marine algae demonstrate considerable potential as therapeutic agents for ALS, owing to their capacity to influence multiple pathways linked to oxidative stress and neuroinflammation. Further investigation is required to comprehend their mechanisms and medicinal value, as well as develop novel alternative treatments for ALS.

Keywords: Amyotrophic lateral sclerosis (ALS), neuroinflammation, oxidative stress, polysaccharides, marine bioactive compounds

Corresponding Author:
Mathiyazhagan Narayanan
Email: mathimicro@gmail.com

Received: September 9, 2024
Accepted: October 14, 2024
Published: December 8, 2024

Production and Hosting by Knowledge E

OPEN ACCESS

How to cite this article: Mani A, Narayanan M, and Rajinikanth V. Neurodegenerative Marine Algae Bioactive Compounds: A Viable Cure to Treat Amyotrophic Lateral Sclerosis (ALS): A Review. *Dubai Medical Journal*. 2024;7(3):201–217. DOI 10.18502/dmj.v7i3.17735

1. Introduction

The increasing prevalence of significant neurological diseases globally necessitates the development of novel, appropriate therapeutic strategies. In recent years, natural compounds derived from marine sources have demonstrated significant potential in neuroprotective pharmaceuticals [1]. Degenerative neurological disorders, such as amyotrophic lateral sclerosis (ALS), have a complex etiology that includes behavioral, environmental, and genetic influences. These conditions are becoming more common due to an aging population [2]. ALS is a formidable neurodegenerative disorder that progressively obliterates both upper and lower motor neurons in the brain and spinal cord, leading to a spectrum of clinical manifestations, including respiratory complications, paralysis, and muscular weakness [3]. Despite extensive research, effective treatments for neurodegenerative diseases such as ALS remain elusive [4], underscoring the necessity to investigate innovative therapeutic strategies [5]. ALS progressively diminishes voluntary muscle control by obliterating motor neurons within the neural circuitry of the spinal cord and brain [6]. Respiratory failure is among the leading causes of death, often advancing from initial neurological dysfunction to severe manifestations such as muscular atrophy, bulbar paralysis, and cognitive impairment. Genetic mutations, particularly in the *C9orf72* gene, are pivotal in familial ALS (Figure **1**).

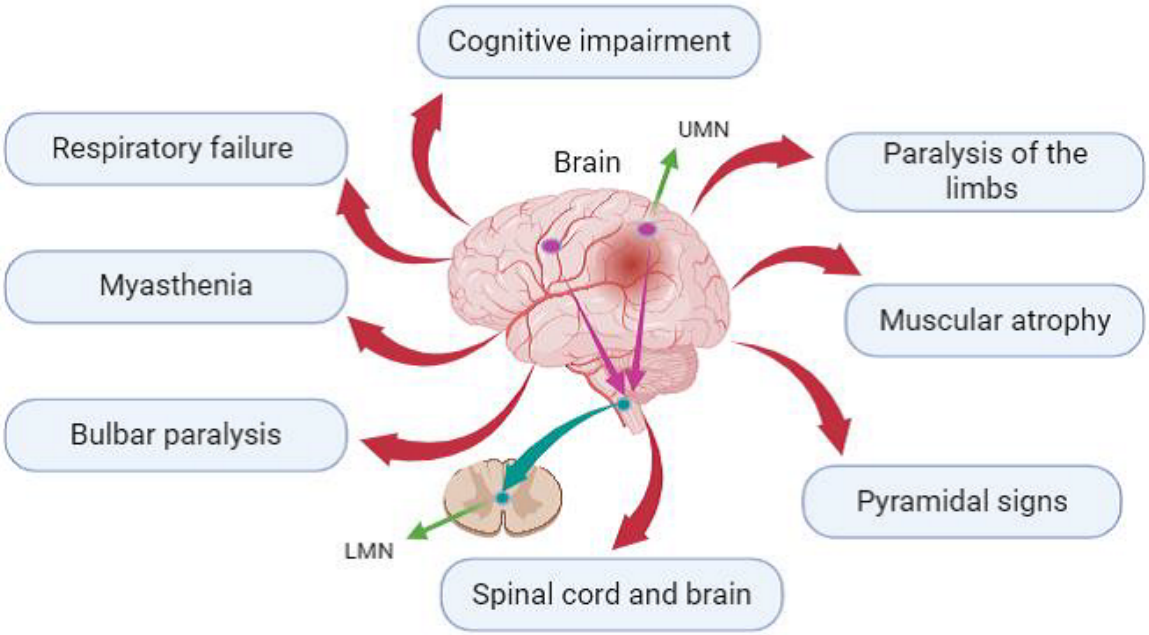

Figure 1: Neurological and muscular symptoms in amyotrophic lateral sclerosis (ALS).

Natural compounds are being evaluated as potential therapeutic agents due to the scarcity of effective prescription medications for neurodegenerative diseases such as ALS [7]. Marine-derived compounds, such as glycans, exhibit considerable potential due to their neuroprotective, anti-inflammatory, anticancer, and antioxidant attributes. A disparity between antioxidants and pro-oxidants in oxidative stress in the central nervous system (CNS) can harm proteins and DNA, leading to lipid oxidation, necrosis, and

apoptosis, which are primary contributors to neuronal death [8]. Marine-derived glycans have emerged as promising candidates for the treatment of neurodegenerative diseases due to their antioxidant properties. Neurodegeneration, affecting multiple CNS disorders, leads to the progressive decline of neuronal populations essential for the proper functioning of neural networks. This loss leads to deficits in brain functions such as memory, cognition, and consciousness, which are characteristics of neurodegenerative diseases [9]. A multitude of biological processes, such as oxidative stress, cerebral inflammation, myocardial dysfunction, protein misfolding, and apoptosis, have been associated with neurodegeneration.

This article provides a comprehensive analysis of the compounds derived from marine algae, detailing their characteristics, mechanisms of action, and therapeutic applications [10]. It underscores potential avenues for the continued exploration and advancement of these compounds as neuroprotective agents. Recognizing the potential of these marine-derived substances may result in novel, effective approaches for treating neurodegenerative diseases [11]. Natural products have been recognized for their therapeutic properties for centuries, and recent research has focused on their bioactive compounds due to their nutritional value, biological activity, and potential medical benefits. The preventive properties of natural products and their constituents have been validated in multiple studies regarding various conditions, including diabetes, cancer, cardiovascular diseases, neurological disorders, and reproductive issues. The following discussion explores the potential use of bioactive compounds from natural products in treating neurodegenerative disorders via their neuroprotective properties.

2. Methods

The examined research concentrated on bioactive compounds sourced from marine environments and their application in treating ALS. Multiple academic platforms were utilized to ascertain the quantity of pertinent publications from 2017 to 2024. Their inclusion comprised ScienceDirect, Springer, Taylor & Francis, and MDPI. To investigate the therapeutic potential of marine bioactive compounds in ALS, we utilized search terms including “ALS marine bioactive compounds,” “neuroprotective bioactive compounds in marine algae,” “neuroinflammation,” and “oxidative stress marine bioactive mechanisms.” Their neuroprotective properties and capacity to diminish neuroinflammation and oxidative stress were specifically investigated. A total of 16,646 publications were identified in our search. We identified 550 pertinent articles according to our search criteria and filters. We further narrowed our selection to 127 articles, which specifically focused on marine bioactive compounds in ALS. We ultimately selected 60 papers for detailed analysis, following a thorough evaluation process. Figure **1** illustrates the selection process and demonstrates the reduction of research papers to those most pertinent to the objectives of our study.

3. Results and Discussion

3.1. Different Species in Marine Algae

Seaweeds, considered marine algae, are vital constituents of the oceanic ecosystem. They offer vital support and habitat for aquatic organisms, aid in carbon sequestration, and possess diverse commercial, medicinal, nutraceutical, and ecological uses. Marine algae are typically categorized into three primary types: brown, red, and green algae [12]. These algae encompass a diverse array of phycobilins, phycocolloids, phycocyanins, vitamins, minerals, polyunsaturated fatty acids, polysaccharides, phytosterols, and soluble dietary fibers, all of which are essential dietary components, including various bioactive constituents, rendering them excellent sources of bioactive materials [13]. Macroalgae, often termed seaweed, are among the most abundant marine organisms and present significant potential as a renewable resource for food and industrial applications. Algal metabolites, encompassing polysaccharides, carotenoids, terpenoids, alkaloids, phenolic compounds, and phytosterols, have garnered significant attention in medicinal chemistry due to their distinctive structures, varied therapeutic properties, and ecological and economic significance [14]. These bioactive compounds exhibit neuroprotective properties in experimental models of cancer, diabetes, obesity, ischemic stroke, brain injury, and neurodegenerative disorders due to their immunomodulatory, anti-inflammatory, or antioxidant effects. Natural substances possessing anti-inflammatory properties are promising candidates for formulating effective treatment strategies, as neuroinflammation significantly contributes to the onset and progression of neurological diseases. The potential of marine algae has garnered heightened interest in recent years, as demonstrated by numerous studies emphasizing the application of bioactive compounds derived from algae in food and medicine. This research has concentrated on the biological attributes of these substances, encompassing their neuroprotective, neurodegenerative, and antioxidant properties.

3.2. Neurodegenerative Mechanisms in ALS

Numerous neurodegenerative conditions, such as Parkinson's disease and Huntington's disease, are characterized by the progressive and selective degeneration of neurons, particularly those susceptible within the CNS, a phenomenon also observed in ALS [15]. In ALS, paralysis and death from respiratory failure results due to the degeneration of upper and lower motor neurons. The precise mechanisms underlying ALS remain incompletely elucidated; however, numerous factors have been correlated with the condition (Figure **2**). In addition to genetic mutations,excitotoxicity, oxidative stress, immunological reactions, diminished axonal transport, neurofilament aggregation, and environmental factors, the disease is also ascribed to mitochondrial dysfunction [16].

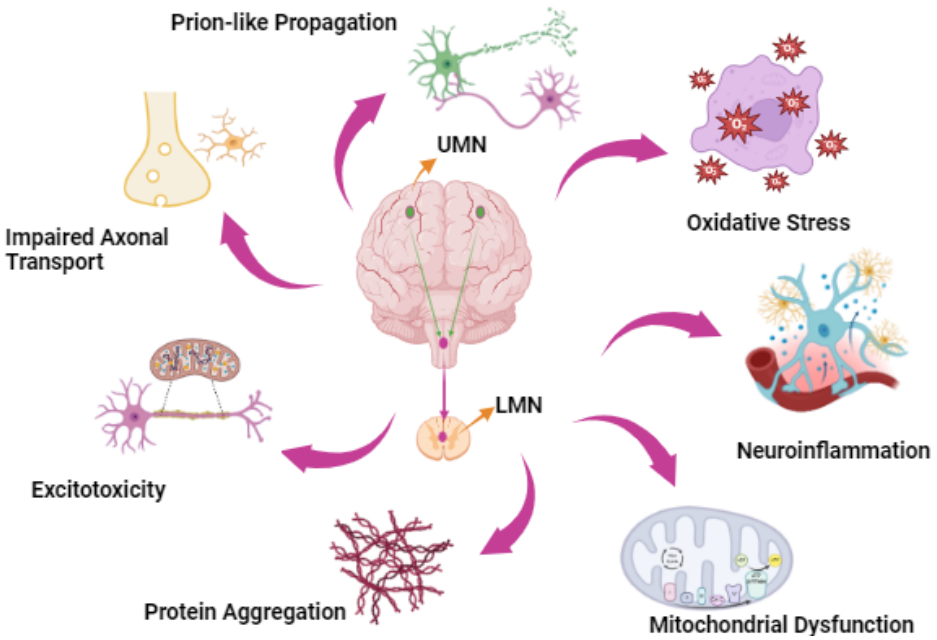

Figure 2: Neurodegeneration in ALS: Unveiling the underlying pathomechanisms.

3.3. Specialist Variations in Genes and Inheritance Affect ALS

This neurological disorder is marked by the gradual degeneration of motor neurons, ultimately leading to paralysis and muscular weakness [17]. The two main types of ALS are sporadic ALS (sALS) and familial ALS (fALS); 40% of cases are sporadic, while the remaining 10% are familial. The disease generally occurs in individuals aged between 50 and 60. Genetic mutations are a significant contributing factor to the onset of ALS. The *SOD1* gene, responsible for encoding the copper/zinc superoxide dismutase-1 enzyme, is one of the most thoroughly studied genetic mutations. The mutations in the *SOD1* gene can compromise the enzyme's capacity to manage oxidative stress, an essential physiological process for preserving cerebral health. Thus, these mutations profoundly affect the pathophysiology of ALS and lead to neuronal damage [18]. The hexanucleotide repeat expansion (GGGGCC) of the *C9orf72* gene is a significant genetic factor in ALS. This mutation is associated with frontotemporal lobar degeneration (FTLD) and ALS. Repeat expansion generates anomalous proteins and deleterious RNA species that interfere with normal cellular functions and promote neurodegeneration. Moreover, mutations in the *FUS* gene, located on chromosome 16, are associated with ALS [19]. The mutations cause the FUS protein to mislocalize in the cytoplasm, disrupting RNA metabolism and other cellular functions, while also increasing neurotoxicity. This mislocalization intensifies neuronal injury [20]. Likewise, RNA metabolism is significantly reliant on the *TARDBP* gene, which is responsible for synthesizing the TDP-43 protein. Anomalies in TDP-43, particularly in its C-terminal region, result in toxic protein aggregates that disrupt normal cellular functions in ALS and FTLD [21]. These aggregates are believed to exemplify the pathophysiology of ALS. This research also indicates that ALS may be influenced by mutations in genes associated with spinal

muscular atrophy (SMA), specifically *SMN1* and *SMN2* [22]. While these mutations primarily pertain to SMA, their involvement exemplifies the intricate genetic landscape that underpins ALS (Figure **3**).

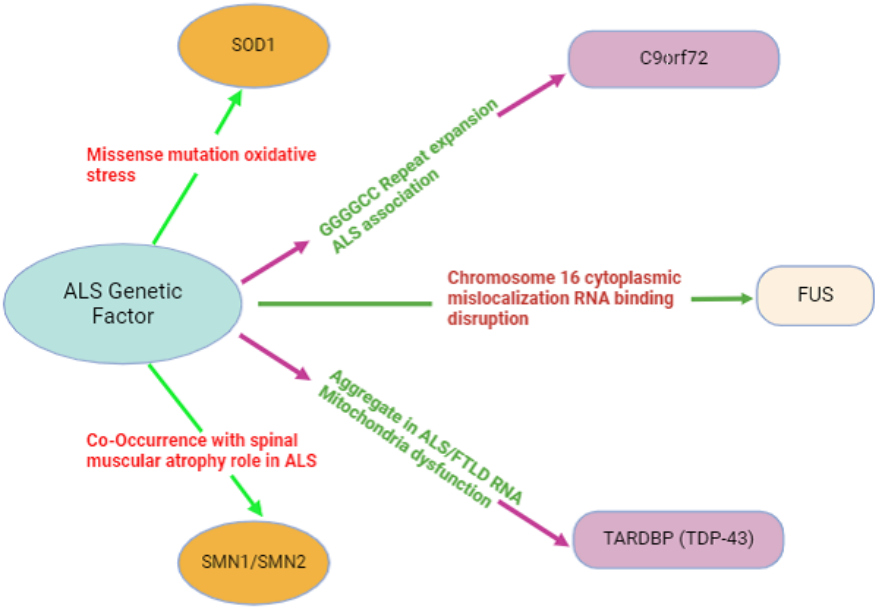

Figure 3: Genetic contribution to ALS.

3.4. Pathogenic Mechanisms Involving Protein Aggregation

Mutations in the *FUS* gene on chromosome 16 are linked to fALS and often lead to the mislocalization of FUS proteins in the cytoplasm, resulting in motor neurondegeneration. The aggregation of mutant FUS causes neuronal toxicity and disrupts normal cellular functions [23].Antisense oligonucleotides (ASOs) directed at the C-terminal region of FUS are under investigation as prospective therapeutic agents to interfere with pathogenic interactions. The development of cytoplasmic inclusions via TDP-43 aggregates is a significant pathogenic characteristic of both FTLD and amyotrophic lateral sclerosis (ALS). The complexes are composed of the TDP-43 protein, essential for RNA metabolic processes such as synthesis, equilibrium, splicing, transport, and translation, encoded by the *TARDBP* gene. Aberrant TDP-43 activity, especially in its C-terminal region, is associated with heightened neurotoxicity and aggregation in FTLD and ALS [24].

3.5. Current Therapeutic Approaches and Challenges

The intricate and varied nature of ALS's etiology complicates the development of effective treatments. The sole medications authorized for the management of ALS are riluzole and edaravone. Riluzole is recognized for mitigating glutamate excitotoxicity, although its exact mechanism of action is not fully understood [25]. Inflammatory markers, such as C-reactive protein, may exacerbate ALS pathogenesis

by activating microglia and increasing blood-brain barrier permeability. Axonal homeostasis depends on the localized translation of specific mRNAs, and the disruption of this process may significantly contribute to neurodegenerative diseases such as ALS, SMA, and Charcot-Marie-Tooth (CMT) disease. These mechanisms are crucial for maintaining axonal integrity, ensuring neuronal survival, and supporting overall function, highlighting the importance of these pathways in neuromuscular disorders. Retrograde transport of locally synthesized proteins to the cell body is crucial during nerve injury [26].

3.6. Potential Marine Bioactive Compounds and Their Mechanisms in ALS

Algae, composed of minerals, vitamins, proteins, lipids, carbohydrates, amino acids, and secondary metabolites including phytosterols, polyphenols, and polysaccharides, demonstrate considerable potential in treating neurodegenerative diseases such as ALS. The chemical composition of different macroalgal species is affected by environmental factors, habitat, and seasonal variations [27]. Compounds from the three principal families of brown, red, and green marine algae have exhibited neuropharmacological properties in diverse in vitro environments.

Multiple cell types, including astrocytes, neutrophils, macrophages, vascular cells, and microglia, play a role in neuroinflammation—a critical element in neurodegenerative disorders. Compounds like fucoxanthin, a pigment found in brown algae such as *Sargassum siliquastrum,* exhibit substantial antioxidant properties that protect against DNA damage induced by oxidative stress [28]. These substances demonstrate immunomodulatory, antiviral, antibacterial, antitumoral, antilipidemic, and antiglycemic properties. Alginate-derived fatty acids from brown algae have demonstrated potential in mitigating neuroinflammation and exhibiting anti-inflammatory, antioxidant, and antimelanogenic properties; furthermore, the marine bioactive compound may have a response to ALS (Figure **4**) [29].

Fucoidan, sourced from the coastal alga *Fucus vesiculosus*, continues to be a viable therapeutic option for neurological disorders, notwithstanding a reduction in bioactivity with decreasing molecular weight [14]. Activated neuroglia can exacerbate neuroinflammation and amyloidogenesis; however, the administration of *Nannochloropsis oceanica* ethanol extract has demonstrated a reduction in inflammatory protein levels (COX-2 and iNOS) within the neural tissues of mice [30]. Fucosterol, predominantly located in brown algae, demonstrates cholinesterase inhibition and anti-inflammatory effects in research concerning *Padina australis, Sargassum polycystum,* and *Caulerpara cemosa.* Fucoxanthin possesses notable neuroprotective properties by mitigating oxidative stress and inflammation, safeguarding DNA from oxidation, and decreasing levels of inflammatory enzymes. The methanol extract of *Ulva conglobata* (green algae) has exhibited anti-inflammatory properties in HT22 hippocampal neurons and BV2 microglia [31]. Furthermore, numerous studies have identified neurological properties as detailed in Table **1**. Phlorotannins, a category of tannins present in brown algae, have demonstrated significant neuroprotective properties by regulating the imbalance of nitric oxide (NO) and reactive oxygen species (ROS). Organic glycerol galactoside

employed by the red algae *Laurencia undulata* oscillates and has been shown to mitigate inflammation-induced neural system damage in vitro [32]. Polyunsaturated fatty acids (PUFAs) are prevalent in marine algae and are advantageous for blood pressure regulation, coagulation, and the support of brain and nervous system functions [33]. Sulfated polysaccharides from seaweed species such as *Ecklonia maxima, Gelidium pristoides, Ulva lactuca, Ulva rigida,* and *Gracilariagracilis* exhibit antineurogenic properties by inhibiting apoptosis, oxidative damage, and acetylcholinesterase activity. Sterols such as fucosterol can traverse the blood-brain barrier and may inhibit neuroinflammation (Table **1**). Fucoidan extracted from algae has demonstrated the capacity to mitigate the neurotoxic effects of amyloid-beta (Aβ) and diminish the downregulation of phosphorylated protein kinase C caused by Aβ, both essential for averting apoptosis-related cell death [14].

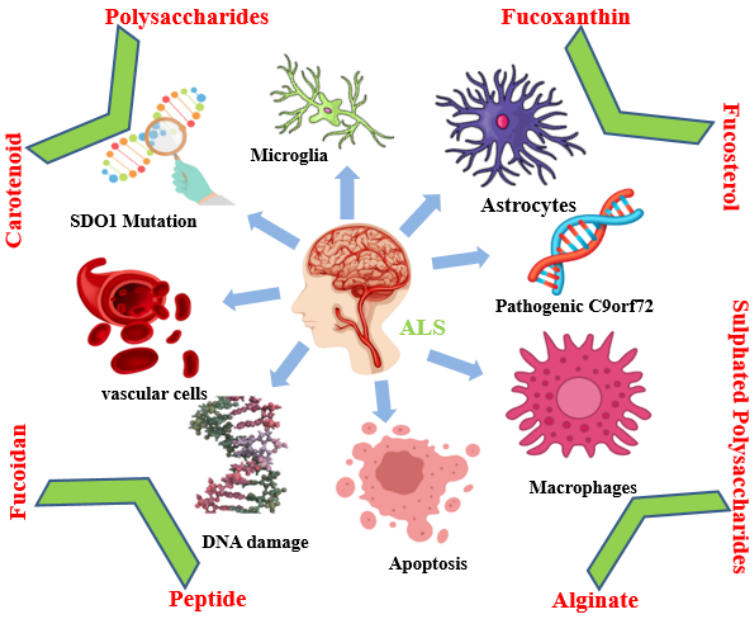

Figure 4: Potential mechanisms of bioactive compounds from marine algae in mediating anti-inflammatory and antioxidant effects.

Table 1: Mechanisms investigation of marine algae's biologically active compounds for neuroprotection.

Bioactive substrates/extract	Marine species	Demonstrative model	References
Fucosterol ethanol extraction	*Padina australis*	The antioxidants and antineuroinflammatory properties lower TNF-α, IL-1β, and IL-6 levels in LPS-stimulated C8-B4 cells.	[34]
Siphonaxanthin methanol extraction	*Codium fragile*	Oxidative and neuroprotective; reduces the generation of ROS and guards against amyloid-beta-induced neurodegeneration.	[35]
Fucoxanthin acetone extraction	*Sargassum siliquastrum*	Protect against immunomodulatory agents, antilipidemic, antiglycemic, and DNA damage imposed on by oxidative stress.	[36]
Eckol methanol extraction	*Ecklonia cava*	Protective of neurons and antioxidants: it decreases glutamate-induced neurotoxicity in hippocampal neurons, scavenges ROS, and prevents lipid peroxidation.	[37]

Table 1: Continued.

Bioactive substrates/extract	Marine species	Demonstrative model	References
Fucoxanthin acetone extraction	*Undaria pinnatifida*	Antioxidant and neuroprotective; lowers tau phosphorylation and Aβ aggregation; guards against neurotoxicity in Alzheimer's models	[37]
Methanol extracts	*Ulva conglobata*	Both microglia BV2 cells and cortical neuronal HT22 cells possess anti-inflammatory properties.	[38]
Alginate-derived oligosaccharides water extraction	*Fucus vesiculosus*	Possesses anti-inflammatory, antioxidant properties, and antimelanogenic qualities; prevents neuronal inflammation	[14]
Natural glycerol galactoside	*Laurencia undulata*	In vitro, it mitigates neuroinflammation-induced neuronal damage and inhibits ROS and NO overloading.	[39]
Fucosterol	*Padina australis, Sargassum polycystum, Caulerpa racemose*	Inhibits cholinesterase and inflammation; lowers ROS and inflammation rates; shields DNA from oxidation; and moderates the rise in inflammatory enzymes.	[40]
Sulfated polysaccharides water extraction	*Maxima Ecklonia, Pristoides gelidium Gracilaria gracilis, Ulva rigida, and Ulva lactuca*	Reduce the amount of phosphorylated protein kinase C that is downregulated in response to Aβ; prevent oxidative stress, acetylcholinesterase activity, and apoptosis; and prevent Aβ from becoming damaging in primary neuronal cells.	[41]
Astaxanthin ethanol extraction	*Haematococcus pluvialis*	Protective and anti-inflammatory; lowers apoptosis in neuronal models, decreases neuroinflammatory indications, and shields neuronal cells from damage caused by oxidative stress.	[42]
Carnosic acid ethanol extraction	*Rosmarinus officinalis*	Antioxidant and protective of neurons; in Parkinson's disease models, it activates the Nrf2 pathway, lowers oxidative stress levels, and stops the death of neurons that produce dopamine.	[30]
Polysaccharides water extraction	*Gracilaria verrucosa*	Neuroprotective and anti-inflammatory; improves brain function in Alzheimer's model mice by lowering apoptosis and oxidative stress in neural cells.	[43]
Phloroglucinol methanol extraction	*Ecklonia cava*	Removes ROS, guards against glutamate-induced neurotoxicity, and stops neuronal cell death. Antioxidant and anti-apoptotic.	[44]
Alpha-bisabolol methanol extraction	*Padina gymnosperm*	Exhibits signs of protection against inflammation and neurotoxicity.	[45]
Sargachromenol methanol extraction	*Sargassum horneri*	Reduces the expression of TNF-α, IL-6, and COX-2 in activated microglia; anti-inflammatory and protective.	[46]
Loliolide hexane extraction	*Sargassumm uticum*	Antioxidant; suppresses the generation of ROS and lessens H_2O_2-induced oxidative injury in neural cells.	[47]
Dieckol ethanol extraction	*Ecklonia stolonifera*	Aβ-induced toxicity is lessened, inflammatory cytokine production is suppressed, and the activity of acetylcholinesterase is inhibited. These properties make it neuroprotective and anti-inflammatory.	[48]
Spirulina polysaccharides water extraction	*Ecklonia stolonifera*	Neuroprotective and antioxidant, it removes free radicals, reduces the peroxidation of lipids, and guards against cognitive impairments.	[49]
Sulfated galactan water extraction	*Codium fragile*	Antioxidant prevents neuroinflammation by lowering cytokine production that promotes inflammation in microglial cells.	[50]

Table 1: Continued.

Bioactive substrates/extract	Marine species	Demonstrative model	References
Docosahexaenoic acid (DHA) hexane extraction	*Crypthecodinium cohnii*	It enhances synaptic plasticity, reduces neuroinflammation, and guards against neurodegeneration with neuroprotective and anti-inflammatory properties.	[51]
Caulerpin methanol extraction	*Cauler palentillifera*	Antioxidants prevent the production of ROS, reduce neuroinflammatory markers, and increase the survival rate of neuronal cells.	[52]
Bryostatin 1 methanol extraction	*Bugula neritina*	In models of cognitive impairment, neuroprotective and synaptogenic substances that stimulate PKC improve synaptic development and function.	[53]
Avrainvilleo ethyl acetate extraction	*Avrainvillea amadelpha*	Antioxidant and prevents the production of ROS and shields neuronal from mitochondrial dysfunction.	[26]
Methanol extraction	*Laminaria japonica*	Anti-amyloidogenic and protective; lowers tau hyperphosphorylation in Alzheimer's models and stops Aβ aggregate.	[54]
Aurantiochytrium-derived omega-3 hexane extraction	*Aurantiochytrium* sp	Anti-inflammatory and protective; improves synapse function, neurogenesis, and neurological inflammation.	[55]
Plocamenone ethanol extraction	*Plocamium cartilaginous*	Anti-inflammatory in nature and neuroprotective; prevents activated microglia from producing TNF-α, IL-1β, and IL-6.	[56]
Stypoldione methanol extract	*Stypopodium zonale*	Protective and neuroprotective; prevents neuronal death, lowers inflammation of the neurons, and reduces microglial activation.	[57]

3.7. Bioactive Peptides and Antioxidant Compounds

Bioactive peptides and amino acids in macroalgae, including taurine, carnosine, glutathione, and mycosporine-like substances, exhibit antiapoptotic and antioxidant properties in the brain. These compounds exhibit diverse biological activities, encompassing immunomodulatory, antioxidant, anticancer, and antihypertensive properties. Subsequent investigations should concentrate on their neuroprotective roles and mechanisms of action [29]. Moreover, polysaccharides derived from *Spirulina platensis* exhibit antioxidant and neuroprotective effects by diminishing lipid peroxidation, neutralizing free radicals, and protecting against cognitive impairments. *Codium fragile* (green algae) contains sulfated galactan, which mitigates neuroinflammation by decreasing the synthesis of pro-inflammatory cytokines in microglial cells [57]. *Crypthecodinium cohnii* (microalgae) synthesizes docosahexaenoic acid (DHA), which improves synaptic plasticity, mitigates neuroinflammation, and safeguards against neurodegeneration [58]. Fucosterol from *Padina australis* diminishes the synthesis of NO, IL-6, and TNF-α in BV-2 cells induced by Aβ42 and inhibits the production of these molecules in C8-B4 cells stimulated by LPS. Eckol, a neuroprotective compound derived from the brown algae *Ecklonia cava*, mitigates glutamate-induced neurotoxicity in hippocampal neurons by scavenging ROS and inhibiting lipid peroxidation [59]. Fucoxanthin derived from *Undaria pinnatifida* (brown algae) mitigates neurotoxicity in ALS's models by

reducing tau phosphorylation and Aβ aggregation. Additional instances encompass astaxanthin derived from *Haematococcus pluvialis* (microalgae), which demonstrates antioxidant and anti-inflammatory characteristics, safeguarding neuronal cells from oxidative stress, inhibiting neuroinflammatory markers, and diminishing apoptosis in neuronal models. Polysaccharides from *Gracilaria verrucosa* (red algae) exhibit antioxidant and neuroprotective characteristics, enhancing cognitive function in ALS models by reducing apoptosis and oxidative stress in neuronal cells. Compounds such as sargachromenol from *Sargassum horneri* and loliolide from *Sargassumm uticum* exhibit neuroprotective and antioxidant properties, mitigating oxidative damage and cerebral inflammation [60]. Marine algae and their bioactive constituents possess considerable neuroprotective potential. Compounds derived from *Sargassumm acrocarpum* and *Jania adhaerens* promote neurite outgrowth, which is crucial for neuronal development and functionality. Phlorotannins derived from brown algae and alpha-bisabolol from *Padina gymnosperma* exhibit protective properties against inflammation and neurotoxicity, positioning them as promising subjects for further investigation[58]. Marine algae provide a substantial reservoir of potential therapeutic agents for neurodegenerative disorders such as ALS by addressing mechanisms associated with neuroinflammation, oxidative stress, and neuroprotection, highlighting the necessity for ongoing research in the formulation of effective natural therapies for ALS and analogous conditions.

3.8. Clinical Trial on Marine Algae-based Bioactive Compounds

Previous investigations indicate that algal sterols, specifically fucosterol derived from *Ecklonia cava* and *Fucus vesiculosus*, possess neuroprotective potential; however, additional clinical trials are necessary to validate their effectiveness in the treatment of ALS. Clinical trials included examining the neuroprotective qualities of Omega-3 fatty acids (*Schizochytrium* and *Nannochloropsis*) in relation to ALS. Research on ALS remains in the preclinical phase; however, fucoxanthin (derived from *Undaria pinnatifida, Sargassum,* and *Laminaria*) shows promise in mitigating inflammation as well as oxidative stress, positioning it as a candidate for additional study in neurodegenerative therapies. Certain studies indicate that they may impede the disease's progression, although results remain under assessment. Although researches on ALS remain in the preclinical stage, fucoidans (*Fucus vesiculosus* and *Laminaria japonica*) are being investigated for their neuroprotective effects in various neurodegenerative disorders. These attributes render them promising subjects for advanced ALS research. Despite the absence of clinical trials exclusively aimed at ALS, laminarin (*Laminaria* sp.) is being studied for its neuroprotective characteristics, especially its capacity to mitigate neuroinflammation. Interest in phycocyanin (Spirulina) for ALS is increasing due to its neuroprotective properties, although research remains in its preliminary phases. Research on neurodegenerative disease models indicates it may mitigate neuronal damage, positioning it as a viable candidate for ALS trials. Although studies have examined the neuroprotective properties of astaxanthin (*Haematococcus pluvialis*) in various neurodegenerative diseases, current

research is concentrated on ALS models. Astaxanthin dosage has demonstrated potential in enhancing motor function and safeguarding motor neurons from oxidative damage in animal models. However, these clinical trials are not completed yet, they are all under process. In future, the compounds that pass the clinical trials will be commercialized to treat ALS.

4. Conclusion

Marine algae contain a wide range of bioactive compounds with promising potential for treating neurological disorders such as ALS. These compounds including carotenoids, peptides, polysaccharides, sterols, and amino acids have demonstrated significant neuroprotective, anti-inflammatory, and antioxidant properties. By targeting key mechanisms involved in neuronal damage, oxidative stress, and neuroinflammation, marine-derived substances offer a natural and multifaceted approach to neuroprotection. Continued research is crucial to elucidate further the specific pathways and mechanisms through which these compounds act, ultimately paving the way for the development of effective treatments for ALS and other neurodegenerative diseases.

Acknowledgment

The author would like to acknowledge the Center for Research and Innovations, Saveetha School of Engineering, Saveetha Institute of Medical and Technical Science (SIMATS), Chennai-602 105, Tamil Nadu, India for constant support in completing this work.

Ethical Statement

The research is exclusively based on published literature, Ethical Approval is not required.

Conflict of Interest

The authors declare that there is no conflict of interest.

Artificial Intelligence (AI) Disclosure Statement

AI-unassisted work.

Funding

No funding

Author Contribution

Mani Ayyandurai: Conceptualization, data analysis, writing, and reviewing the manuscript. Mathiyazhagan Narayanan: Writing, and reviewing the manuscript, supervision, and administration. V. Rajinikanth: Writing and reviewing the manuscript.

Data Sharing Statement

All data generated during this report have been included in the article.

References

[1] Al-Araby SQ, Rahman MA, Chowdhury MA, Das RR, Chowdhury TA, Hasan CM, et al. Padina tenuis (marine alga) attenuates oxidative stress and streptozotocin-induced type 2 diabetic indices in Wistar albino rats. S Afr J Bot. 2020;128:87–100.

[2] Nowicka N, Juranek J, Juranek JK, Wojtkiewicz J. Risk factors and emerging therapies in amyotrophic lateral sclerosis. Int J Mol Sci. 2019 May;20(11):2616.

[3] Štětkářová I, Ehler E. Diagnostics of amyotrophic lateral sclerosis: Up to date. Diagnostics (Basel). 2021 Feb;11(2):231.

[4] Akhtar A, Andleeb A, Waris TS, Bazzar M, Moradi AR, Awan NR, et al. Neurodegenerative diseases and effective drug delivery: A review of challenges and novel therapeutics. J Control Release. 2021 Feb;330:1152–1167.

[5] Teleanu RI, Niculescu AG, Roza E, Vladâcenco O, Grumezescu AM, Teleanu DM. Neurotransmitters—key factors in neurological and neurodegenerative disorders of the central nervous system. Int J Mol Sci. 2022 May;23(11):5954.

[6] Smeyers J, Banchi EG, Latouche M. C9ORF72: What it is, what it does, and why it matters. Front Cell Neurosci. 2021 May;15:661447.

[7] Pal D, Raj K. Biological activities of marine products and nutritional importance. Bioact Nat Prod Pharm Appl. 2021;587–616. https://doi.org/10.1007/978-3-030-54027-2_17.

[8] Veeman D, Dhamodharan D, Surendhar GJ, Natrayan L, Stalin B, Shanmugam R, et al. Systematic review on nine hallmarks of neurodegenerative disease. Indian J Biochem Biophys. 2022;59:249–257.

[9] Bălașa AF, Chircov C, Grumezescu AM. Marine biocompounds for neuroprotection—A review. Mar Drugs. 2020 May;18(6):290.

[10] Catanesi M, Caioni G, Castelli V, Benedetti E, d'Angelo M, Cimini A. Benefits under the sea: the role of marine compounds in neurodegenerative disorders. Mar Drugs. 2021 Jan;19(1):24.

[11] Cotas J, Lomartire S, Pereira L, Valado A, Marques JC, Gonçalves AM. Seaweeds as nutraceutical elements and drugs for diabetes mellitus: Future Perspectives. Mar Drugs. 2024 Apr;22(4):168.

[12] Aziz E, Batool R, Khan MU, Rauf A, Akhtar W, Heydari M, et al. An overview on red algae bioactive compounds and their pharmaceutical applications. J Complement Integr Med. 2020 Jul;17(4):20190203.

[13] Kaur M, Bhatia S, Gupta U, Decker E, Tak Y, Bali M, et al. Microalgal bioactive metabolites as promising implements in nutraceuticals and pharmaceuticals: Inspiring therapy for health benefits. Phytochem Rev. 2023 Jan;22(4):1–31.

[14] Sathishkumar K, Sathuvan M. Brown algal bioactive molecules: A new frontier in oral cancer treatment. Nat Prod Res. 2024 Jun;:1–3.

[15] Elmansy MF, Reidl CT, Rahaman M, Özdinler PH, Silverman RB. Small molecules targeting different cellular pathologies for the treatment of amyotrophic lateral sclerosis. Med Res Rev. 2023 Nov;43(6):2260–2302.

[16] Hemerková P, Vališ M. Role of oxidative stress in the pathogenesis of amyotrophic lateral sclerosis: Antioxidant metalloenzymes and therapeutic strategies. Biomolecules. 2021 Mar;11(3):437.

[17] Masrori P, Van Damme P. Amyotrophic lateral sclerosis: a clinical review. Eur J Neurol. 2020 Oct;27(10):1918–1929.

[18] Noorbakhsh Varnosfaderani SM, Sadat Haeri M, Arian AS, Yousefi Rad A, Yazdanpour M, Mojahedian F, et al. Fighting against amyotrophic lateral sclerosis (ALS) with flavonoids: a computational approach to inhibit superoxide dismutase (SOD1) mutant aggregation. J Biomol Struct Dyn. 2023 Nov;:1–18.

[19] Geng Y, Cai Q. Role of *C9orf72* hexanucleotide repeat expansions in ALS/FTD pathogenesis. Front Mol Neurosci. 2024 Jan;17:1322720.

[20] Aksoy YA, Deng W, Stoddart J, Chung R, Guillemin G, Cole NJ, et al. “STRESSED OUT”: The role of FUS and TDP-43 in amyotrophic lateral sclerosis. Int J Biochem Cell Biol. 2020 Sep;126:105821.

[21] Huang C, Yan S, Zhang Z. Maintaining the balance of TDP-43, mitochondria, and autophagy: A promising therapeutic strategy for neurodegenerative diseases. Transl Neurodegener. 2020 Oct;9(1):40.

[22] Peng Y, Ren D, Song Y, Hu Y, Wu L, Wang Q, et al. Effects of a combined fucoidan and traditional Chinese medicine formula on hyperglycaemia and diabetic nephropathy in a type II diabetes mellitus rat model. Int J Biol Macromol. 2020 Mar;147:408–419.

[23] Kang J, Lim L, Lu Y, Song J. A unified mechanism for LLPS of ALS/FTLD-causing FUS as well as its modulation by ATP and oligonucleic acids. PLoS Biol. 2019 Jun;17(6):e3000327.

[24] Saini A, Chawla PA. Breaking barriers with tofersen: Enhancing therapeutic opportunities in amyotrophic lateral sclerosis. Eur J Neurol. 2024 Feb;31(2):e16140.

[25] Appel SH, Beers DR, Zhao W. The role of inflammation in neurodegenerative diseases. Neurobiol Brain Disord. 2023:403–421. https://doi.org/10.1016/B978-0-323-85654-6.00036-8

[26] Sarangi NV, Harini AB, Rajkumar R, Veeramuthu A. Evaluation of chemical constituents of Stoechospermum marginatum and its potential for antioxidant and antimicrobial activity. Biomass Convers Biorefin. 2023 Feb;:1–2.

[27] Kwon HS, Koh SH. Neuroinflammation in neurodegenerative disorders: The roles of microglia and astrocytes. Transl Neurodegener. 2020 Nov;9(1):42.

[28] Afzal S, Yadav AK, Poonia AK, Choure K, Yadav AN, Pandey A. Antimicrobial therapeutics isolated from algal source: Retrospect and prospect. Biologia (Bratisl). 2023;78(2):291–305.

[29] Menaa F, Wijesinghe U, Thiripuranathar G, Althobaiti NA, Albalawi AE, Khan BA, et al. Marine algae-derived bioactive compounds: A new wave of nanodrugs? Mar Drugs. 2021 Aug;19(9):484.

[30] Venkatachalam J, Jeyadoss VS, Bose KS, Subramanian R. Marine seaweed endophytic fungi-derived active metabolites promote reactive oxygen species-induced cell cycle arrest and apoptosis in human breast cancer cells. Mol Biol Rep. 2024 May;51(1):611.

[31] Lomartire S, Gonçalves AM. Marine macroalgae polyphenols as potential neuroprotective antioxidants in neurodegenerative diseases. Mar Drugs. 2023 Apr;21(5):261.

[32] Kapoor B, Kapoor D, Gautam S, Singh R, Bhardwaj S. Dietary polyunsaturated fatty acids (PUFAs): Uses and potential health benefits. Curr Nutr Rep. 2021 Sep;10(3):232–242.

[33] Šimat V, Čagalj M, Phadke GG, Rathod NB, Hassoun A. The sea as a source of neuroprotective and other health-protective molecules. Natural Molecules in Neuroprotection and Neurotoxicity. Elsevier; 2024. pp. 29–60.

[34] Olasehinde TA, Olaniran AO, Okoh AI. Therapeutic potentials of microalgae in the treatment of Alzheimer's disease. Molecules. 2017 Mar;22(3):480.

[35] Wong CH, Gan SY, Tan SC, Gany SA, Ying T, Gray AI, et al. Fucosterol inhibits cholinesterase activities and reduces the release of pro-inflammatory mediators in lipopolysaccharide and amyloid-induced microglial cells. J Appl Phycol. 2018;30(6):3261–3270.

[36] Hannan MA, Dash R, Haque MN, Mohibbullah M, Sohag AA, Rahman MA, et al. Neuroprotective potentials of marine algae and their bioactive metabolites: Pharmacological insights and therapeutic advances. Mar Drugs. 2020 Jul;18(7):347.

[37] Besednova NN, Andryukov BG, Zaporozhets TS, Kuznetsova TA, Kryzhanovsky SP, Ermakova SP, et al. Molecular targets of brown algae phlorotannins for the therapy of inflammatory processes of various origins. Mar Drugs. 2022 Mar;20(4):243.

[38] Cikoš AM, Šubarić D, Roje M, Babić J, Jerković I, Jokić S. Recent advances on macroalgal pigments and their biological activities (2016–2021). Algal Res. 2022;65:102748.

[39] Mumu M, Das A, Emran TB, Mitra S, Islam F, Roy A, et al. Fucoxanthin: A promising phytochemical on diverse pharmacological targets. Front Pharmacol. 2022 Aug;13:929442.

[40] Nho JA, Shin YS, Jeong HR, Cho S, Heo HJ, Kim GH, et al. Neuroprotective effects of phlorotannin-rich extract from brown seaweed Ecklonia cava on neuronal PC-12 and SH-SY5Y cells with oxidative stress. J Microbiol Biotechnol. 2020 Mar;30(3):359–367.

[41] Paranthaman S, Palraj P. Bioactive Compounds of algae: Potential neuroprotective agents in neurodegenerative disorders. Neuroprotective effects of phytochemicals in brain ageing. Singapore: Springer Nature Singapore; 2024. pp. 257–88.

[42] Bairagi S, Banerjee S, Mulvihill DM, Ahmed S, Wazed A. Extraction, structural properties, and applications of sodium alginate. Natural Gums. Elsevier; 2023. pp. 599–618.

[43] Viswanathan S, Palaniyandi T, Shanmugam R, Karunakaran S, Pandi M, Wahab MR, et al. Synthesis, characterization, cytotoxicity, and antimicrobial studies of green synthesized silver nanoparticles using red seaweed Champia parvula. Biomass Convers Biorefin. 2024 Mar;14(6):7387–7400.

[44] Han HJ, Park SK, Kang JY, Kim JM, Yoo SK, Kim DO, et al. Mixture of phlorotannin and fucoidan from Ecklonia cava prevents the aβ-induced cognitive decline with mitochondrial and cholinergic activation. Mar Drugs. 2021 Jul;19(8):434.

[45] Jafari Z, Bigham A, Sadeghi S, Dehdashti SM, Rabiee N, Abedivash A, et al. Nanotechnology-abetted astaxanthin formulations in multimodel therapeutic and biomedical applications. J Med Chem. 2022 Jan;65(1):2–36.

[46] Kosmopoulou D, Lafara MP, Adamantidi T, Ofrydopoulou A, Grabrucker AM, Tsoupras A. Neuroprotective Benefits of Rosmarinus officinalis and Its Bioactives against Alzheimer's and Parkinson's Diseases. Appl Sci (Basel). 2024;14(15):6417.

[47] Kojima-Yuasa A. Biological and pharmacological effects of polyphenolic compounds from Ecklonia cava. Polyphenols: Mechanisms of action in human health and disease. Elsevier; 2018. pp. 41–52.

[48] Sathya S, Shanmuganathan B, Devi KP. Deciphering the anti-apoptotic potential of α-bisabolol loaded solid lipid nanoparticles against Aβ induced neurotoxicity in Neuro-2a cells. Colloids Surf B Biointerfaces. 2020 Jun;190:110948.

[49] Ghallab DS, Ibrahim RS, Mohyeldin MM, Shawky E. Marine algae: A treasure trove of bioactive anti-inflammatory compounds. Mar Pollut Bull. 2024 Feb;199:116023.

[50] Catarino MD, Silva-Reis R, Chouh A, Silva S, Braga SS, Silva AM, et al. Applications of antioxidant secondary metabolites of Sargassum spp. Mar Drugs. 2023 Mar;21(3):172.

[51] Lee JY, Wong CY, Koh RY, Lim CL, Kok YY, Chye SM. Natural bioactive compounds from macroalgae and microalgae for the treatment of Alzheimer's disease: A review. Yale J Biol Med. 2024 Jun;97(2):205–24.

[52] El-Beltagi HS, Mohamed AA, Mohamed HI, Ramadan KM, Barqawi AA, Mansour AT. Phytochemical and potential properties of seaweeds and their recent applications: A review. Mar Drugs. 2022 May;20(6):342.

[53] Elbandy M. Anti-inflammatory effects of marine bioactive compounds and their potential as functional food ingredients in the prevention and treatment of neuroinflammatory disorders. Molecules. 2022 Dec;28(1):2.

[54] Madhubalaji CK, Ravikumar N, Gadde Venkata S, Surendranatha Reddy EC. Algae as a potential vegetative source of PUFA for the prevention of neurological disorders. Role of Nutrients in Neurological Disorders. Springer; 2022. pp. 201–21.

[55] Hamid MA, Yeap CH, Mustapha WA, Martony O, Fatmawati F. Effects of different solvents on the antioxidant activity of several seaweed species from Semporna, Sabah, Malaysia. ILMU Kelaut Indones J Mar Sci. 2024;29(1):29–36.

[56] Silva M, Seijas P, Otero P. Exploitation of marine molecules to manage Alzheimer's disease. Mar Drugs. 2021 Jun;19(7):373.

[57] Pedrosa RP, Gaudêncio S, Vasconcelos V. XVI international symposium on marine natural products XI European conference on marine natural products. 2020;18(1). https://doi.org/10.3390/md18010040

[58] Sasaki K, Geribaldi-Doldán N, Wu Q, Davies J, Szele FG, Isoda H. Microalgae Aurantiochytrium Sp. increases neurogenesis and improves spatial learning and memory in senescence-accelerated mouse-prone 8 mice. Front Cell Dev Biol. 2021 Feb;8:600575.

[59] Meinita MD, Harwanto D, Choi JS. Seaweed exhibits therapeutic properties against chronic diseases: an overview. Appl Sci (Basel). 2022;12(5):2638.

[60] Conde T, Lopes D, Łuczaj W, Neves B, Pinto B, Maurício T, et al. Algal lipids as modulators of skin disease: A critical review. Metabolites. 2022 Jan;12(2):96.