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Recent Advances in the Exploration of Bioactive Phytochemicals of Seaweeds for Neuroprotection

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Abstract

Seaweed, an abundant marine resource, is a rich source of bioactive phytochemicals with neuroprotective properties. This review explores the neuroprotective effects of various bioactive compounds found in seaweed, including polyphenols, polysaccharides, carotenoids, and sterols. These compounds exhibit a range of biological activities, including antioxidant, anti-inflammatory, and anti-apoptotic effects, which contribute to their potential in preventing and mitigating neurodegenerative diseases such as Alzheimer's and Parkinson's disease. The mechanisms underlying these effects involve modulation of oxidative stress, inflammatory pathways, and neuronal cell survival. Despite promising in vitro and in vivo studies, further research is required to fully understand the therapeutic potential and safety of these phytochemicals in the clinical setting. Developing seaweed-based nutraceuticals could offer a natural and sustainable approach to neuroprotection and management of neurodegenerative conditions.

Keywords: Seaweeds; Neuroprotection; Phytochemical; Bioactive compounds; Antioxidants

Introduction

Seaweeds, an integral part of marine ecosystems, have garnered significant attention because of their diverse array of bioactive phytochemicals [1]. These marine plants are classified into three major groups: green (Chlorophyta), brown (Phaeophyta), and red (Rhodophyta) algae, which contain many compounds with notable health benefits [2]. Among various applications, the potential neuroprotective effects of seaweed-derived bioactive compounds have become a focus of research in recent years [3]. Neuroprotection refers to the strategies and mechanisms that protect the nervous system from injury and degeneration, which is crucial in the context of neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease, and Huntington's disease [4]. These diseases are characterized by progressive neuronal loss and cognitive decline. Current treatments for these conditions are limited and primarily focus on symptom management, rather than disease modification or prevention [5]. Seaweeds, often known as edible marine algae, are an abundant source of phytosterols, carotenoids, and polysaccharides among other bioactive substances. In recent years, components produced from seaweed have been shown to not only live in the bloodstream but also pass through the blood-brain barrier and perform neuroactive tasks in both pathological and homeostatic settings [6]. As a result, owing to their neuro-immunomodulatory and neuroprotective properties, components produced from seaweed are becoming increasingly popular as potential treatments for a variety of neurodegenerative diseases. Because they exhibit anti-inflammatory properties, improve phagocytic clearance of neurotoxic peptides, and stimulate neuroplasticity, phytosterols produced from seaweed have drawn particular attention as potential treatments for neurodegenerative diseases. However, there has been a recent increase in interest in the anti-inflammatory and antioxidative qualities of other substances, such as carotenoids, phenols, and polysaccharides [7]. During ischemic stroke, other brain traumas, or pathological or physiological aging, the supporting cells and neurons of the brain undergo degenerative changes. Alzheimer's disease (AD) and Parkinson's disease (PD) are examples of degenerative brain disorders that result from abnormal brain ageing, characterized by the loss of neurons in specific regions of the brain [8]. These illnesses are the main cause of dementia in the elderly worldwide [9]. These brain disorders share some pathophysiology, including oxidative stress (OS), neuroinflammation, mitochondrial dysfunction, protein misfolding, and a malfunctioning protein clearance mechanism, which further complicates the disease, even though the precise etiologies of these disorders are still unknown [10,11].

More than 70% of the Earth's surface is made up of a marine ecosystem, which is home to a vast range of macro- and microorganisms. Inherent to their unique nutritional makeup, sea algae are particularly interesting among these organisms because of their therapeutic characteristics. By differentiating themselves from terrestrial plants, marine algae are rich in bioactive chemicals and secondary metabolites including peptides, lectins, carotenoids, polysaccharides, fatty acids, flavonoids, and phytosterols [12-14]. A vast range of macro- and microorganisms can be found in marine ecosystems, which make up over 70% of the planet's surface [1]. Among these species, marine algae are particularly interesting because of their unique nutritional makeup, which has led to the attribution of their therapeutic capabilities. Marine algae differ from terrestrial plants in that they are a rich source of secondary metabolites and bioactive chemicals, including peptides, lectins, carotenoids, polysaccharides, fatty acids, flavonoids, and phytosterols [15]. Seaweeds live in both intertidal and subtidal waters because they need 0.1% photosynthetic light to survive. Since the potential medical benefits of seaweed have long been investigated in traditional East Asian medicine, China and Indonesia are currently the two countries that cultivate and consume the most seaweed [7].

Therefore, there is a pressing need for novel therapeutic approaches that offer neuroprotection and slow or halt disease progression. Seaweeds are a rich source of a variety of bioactive compounds, including polyphenols, polysaccharides, carotenoids, and sterols [16,17]. These compounds exhibit a range of biological activities that are beneficial for neuroprotection, including antioxidant, anti-inflammatory, and anti-apoptotic effects. Antioxidants, for instance, can neutralize reactive oxygen species (ROS) and reduce oxidative stress, which is a major contributor to neuronal damage in neurodegenerative diseases [18,19]. Anti-inflammatory compounds can mitigate chronic inflammation in the brain, which is another key factor in neurodegeneration [20]. Furthermore, anti-apoptotic agents can help preserve neuronal integrity by preventing programmed cell death [21]. This review explores the neuroprotective potential of various bioactive phytochemicals found in seaweed. This review discusses the mechanisms through which these compounds exert their effects, presents evidence from both in vitro and in vivo studies, and considers the potential applications of seaweed-based nutraceuticals in the prevention and treatment of neurodegenerative diseases. By examining the current state of research and identifying future directions, this review highlights the promising role of seaweed phytochemicals in neuroprotection and their potential to contribute to innovative therapeutic strategies for neurodegenerative conditions.

Bioactive Phytochemicals in Seaweed

Seaweeds or marine macroalgae are rich sources of bioactive phytochemicals. These compounds are produced as secondary metabolites and play crucial roles in the growth, reproduction, and defence mechanisms of seaweeds. The study of these bioactive phytochemicals has garnered significant attention because of their potential health benefits and applications in various industries. They can be classified into several categories, including polysaccharides, polyphenols, carotenoids, alkaloids, and sterols. Each compound exhibits unique biological activities that can be harnessed for therapeutic, nutritional, and industrial purposes. The chemical composition of algae is species-specific, location-specific, weather-dependent, and harvesting-time-dependent. Seaweeds are currently regarded as potential organisms for contributing new physiologically active chemicals to the manufacture of innovative foods (nutraceuticals), cosmetics (cosmeceuticals), and medicinal compounds because of their wide range of molecules. A wide range of bioactive substances have been identified, including polyphenolic compounds, carotenoids, minerals, vitamins, phlorotannins, peptides, tocotrienols, proteins, tocopherols, and carbohydrates (polysaccharides).

A multitude of bioactive chemicals found in seaweeds have the potential to be utilized in the development of innovative functional food ingredients as well as in the treatment or prevention of chronic illnesses (Table 1). As consumers are becoming more aware of natural bioactive compounds as functional ingredients in foods, seaweeds may provide an alternative source of synthetic chemicals that could improve consumer well-being when added to new functional foods or drugs. However, eating seaweed requires knowledge of the risks to human health because of the likely presence of dangerous pollutants, such as heavy metals or their high iodine content. Seaweeds have been used as a source of bioactive secondary metabolites with potential applications in medicine (Figure 1). Significant advancements have been made in specific seaweed chemicals, focusing on their composition and use in animal and human nutrition. Seaweeds are used as animal feed and have been employed in energy, fertilizers, pharmaceuticals, cosmetics, industrial agar, and alginate biosynthesis. The inclusion of minerals, vitamins, phenols, polysaccharides, sterols, and various other bioactive components is primarily responsible for the health benefits of seaweeds. Antioxidant, anti-inflammatory, anticancer, antibacterial, and antidiabetic properties appear to be present in these substances [22].

Extraction and Analysis of Phytochemicals

The extraction of bioactive phytochemicals from seaweed involves various methods, including solvent extraction, supercritical fluid extraction, and enzymatic extraction. Analytical techniques such as high-performance liquid chromatography (HPLC), gas chromatography-mass spectrometry (GC-MS), and nuclear magnetic resonance (NMR) spectroscopy have been employed to identify and quantify these compounds [23,24]. Non-nutritive plant compounds with anti-inflammatory or disease-preventive properties are called phytochemicals. Human consumption is required. Nevertheless, it has been demonstrated that these substances safeguard both plants and the people who consume them. A variety of distinct phytochemicals found only in seaweeds are absent in terrestrial plants. Therefore, edible seaweed may be the only significant dietary source for some of these criteria. Numerous studies have reported the high antioxidant contents of various edible seaweeds. Antioxidant enzymes, polyphenolic chemicals, and sulfated polysaccharides all contribute to this ability. The secondary metabolites found in seaweeds used as medicines are abundant and comprise alkaloids, glycosides, flavonoids, saponins, tannins, steroids, and other related active metabolites. These metabolites exhibit significant therapeutic efficacy [25].

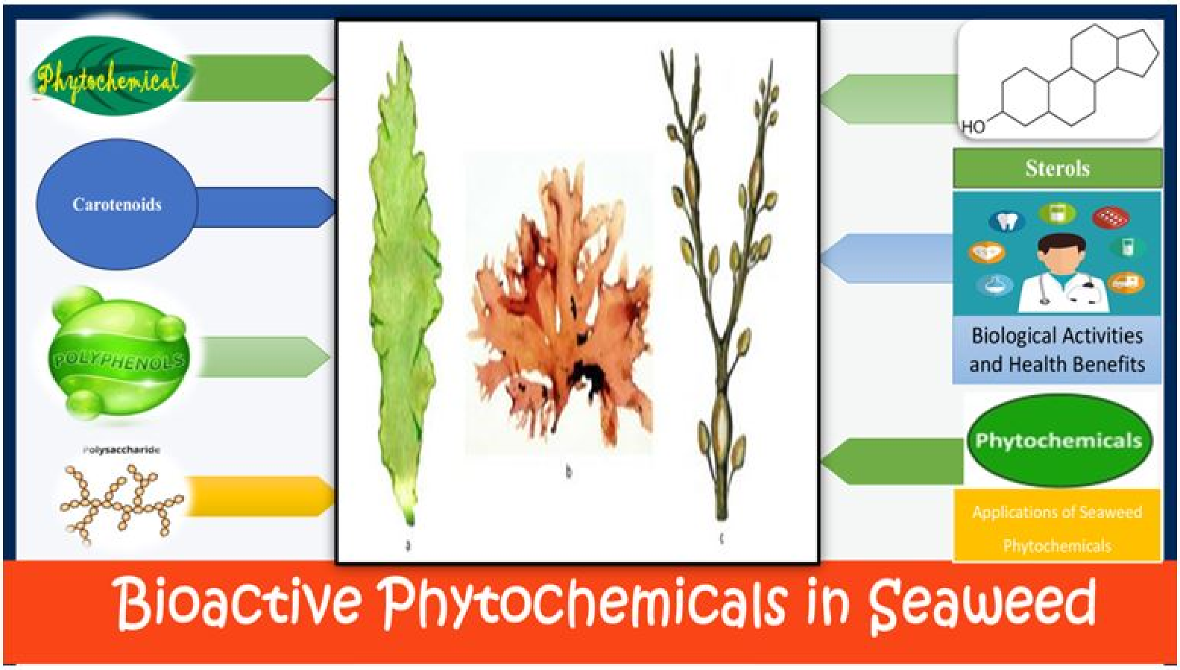

Figure 1: An illustration of the different bioactive phytochemicals present in the seaweeds

Table 1: A list of the different bioactive compounds of seaweed and their therapeutic potential

Sr. No.	Name of Seaweed	Isolated Bioactive Compounds	Effect and Potential
1	*Laminaria japonica*	Fucoxanthins	Antitumoral activity on lung cancer cells
2	*Colpomenia sinuosa, Sargassum prismaticum*	Fucoxanthins	Antitumoral activity on lung cancer cells
3	*Undaria pinnatifida*	Fucoxanthins	Antitumoral activity on SiHa, Malme-3M cells
4	*Cladosiphon okamuranus*	Fucoxanthins	Antimicrobial activity
5	*Laminaria japonica*	Fucoxanthins	Antimicrobial activity
6	*Fucus vesiculosus*	Fucoxanthins	Antimicrobial activity
7	*Fucus evanescens*	Fucoxanthins	Antiviral activity against ECHO-1, HIV-1, HSV-1, HSV-2
8	*Sargassum patens*	Sulfate polysaccharide	Antiviral activity against HSV-1, HSV-2
9	*Gracilaria lemaneiformis*	Sulfate polysaccharide	Anti-obesity, antidiabetic activities
10	*Ecklonia cava*	Phloroglucinol	Anti-inflammatory activity
11	*Padina tetrastromatica*	Carrageenan	Anti-inflammation
12	*Ulva sp.*	Ulvans	Anti-aging
13	*Laminaria japonica*	Laminaran	Antioxidant activity

Alginate, agar, and carrageenan are carbohydrates that constitute seaweed and can be isolated and refined into hydrocolloids. The physicochemical characteristics of carbohydrates vary, and hydrocolloids can gel when dissolved in water. Conventional extraction techniques as well as several environmentally friendly extraction techniques have been suggested and explored to obtain targeted hydrocolloids for certain uses and functions (Table 2). Solvent extraction (SLE) is a conventional extraction method. On the other hand, green extraction techniques include reactive extrusion, which automatically selectively presented as a promising method for extracting hydrocolloids from seaweed, microwave-assisted extraction (MAE), ultrasound-assisted extraction (UAE), supercritical fluid extraction (SFE), and pressurized solvent extraction (PSE) [26].

Table 2: depicts the various extraction processes of phytochemicals from seaweeds along with their pros and cons

Sr. no.	Method	Advantages	Disadvantages
1	Conventional Extraction	The method has been tested initially.	Long extraction time, using a lot of solvents, acids and bases resulted in the degradation of polysaccharide
2	Microwave-Assisted Extraction (MAE)	Short extraction time with a relatively small amount of solvent.	High heat causes the degradation of polyphenols.
3	Ultrasound-Assisted Extraction (UAE)	The extraction time is short. The method works at low temperatures using a relatively little solvent.	Degradation and changes in the structure of polysaccharides.
4	Supercritical Fluid Extraction (SFE)	CO was removed from the extract easily and did not cause structural degradation of the compound.	High pressure to retain solvent which hurts the compound.
5	Pressurized Solvent Extraction (PSE)	The method is similar to Soxhlet extraction, but the solvent has high extraction properties.	The combination of high temperature and pressure to increase the solubility and diffusion of the solvent is difficult.
6	Enzyme-Assisted Extraction (EAE)	Does not use organic solvents but high yield. Extraction results depend on the time, pH, and enzyme temperature. Efficiency depends on the nature of the enzyme.	Does not use organic solvents but high yield. Extraction results depend on the time, pH, and enzyme temperature. Efficiency depends on the nature of the enzyme.

Polyphenols

Polyphenols are a diverse group of phytochemicals found in seaweed that exhibit potent antioxidant properties. They play a significant role in protecting the cells from oxidative stress by scavenging free radicals. Common polyphenols in seaweeds include phlorotannins, flavonoids, and phenolic acids. These compounds have been linked to various health benefits, such as anti-inflammatory, anticancer, and cardiovascular protective effects [23,24].

Polysaccharides

Seaweed is rich in polysaccharides, which are long chains of carbohydrates. The key polysaccharides found in seaweeds include fucoidan, alginate, and carrageenan. These compounds are known for their bioactive properties, including antiviral, anticoagulant, and immunomodulatory activity. Fucoidan, for instance, has been shown to enhance immune responses and inhibit cancer cell growth [23,24].

Carotenoids

Carotenoids are pigment compounds that give seaweeds distinctive colours. Fucoxanthin, a prominent carotenoid in brown seaweed, has garnered attention owing to its antioxidant and anti-obesity effects. Carotenoids also play a role in protecting seaweeds from the damage caused by UV radiation. Their potential health benefits include reducing the risk of chronic diseases such as cancer and cardiovascular disorders [23,24].

Sterols

Sterols are a class of lipids found in seaweeds that resemble cholesterol in structure. Fucosterol is the most abundant sterol in seaweed and has various biological activities, including anti-inflammatory and antioxidant effects. Sterols from seaweed can contribute to lowering cholesterol levels in humans and have potential applications in treating metabolic disorders [23,24].

Biological Activities and Health Benefits

Research has demonstrated that seaweed-derived phytochemicals exhibit a range of biological activities including antioxidant, anti-inflammatory, antimicrobial, and anticancer properties. These compounds can help reduce oxidative stress, inhibit the growth of pathogenic microorganisms, and prevent cancer cell proliferation. Additionally, they have been shown to improve cardiovascular health and boost the immune system [23,24].

Applications of Seaweed Phytochemicals

Bioactive phytochemicals from seaweeds have diverse applications in nutraceuticals, pharmaceuticals, cosmetics, and agriculture. They are used in the formulation of functional foods and dietary supplements, development of therapeutic drugs, production of skincare and anti-aging products, and enhancement of livestock feed [23,24]. Although thousands of bioactive compounds have been identified, the number of new diseases and the urgent need for innovative therapeutic chemical-resistant varieties of microbes and foods high in phytochemicals need to undoubtedly be a component of a well-balanced diet. Beyond nutrition, the human body can fight oxidative stress through various physiological, biochemical, and enzymatic mechanisms. The path taken by a large range of phenolic chemicals to enter the bloodstream, their bioavailability, and the distribution and half-life of certain elements in the human body are poorly understood. Prior research on intervention studies involving dietary antioxidant consumption has increased, but there has not been a corresponding shift in the body's overall antioxidant capacity. body. Although this calls into question the value of increasing polyphenolic consumption to reduce oxidative stress, it must be noted that such compounds may have other physiological effects [25].

Mechanisms of Neuroprotection

Antioxidant Effects

The presence of free radicals, including reactive nitrogen species (RNS) and reactive oxygen species (ROS), within the human body can lead to cellular damage or apoptosis, contributing to premature aging and conditions such as liver cirrhosis. Antioxidants play a crucial role in mitigating the detrimental effects induced by these free radicals. Antioxidant effects are a key mechanism of neuroprotection, involving scavenging of free radicals and reduction of oxidative stress in neuronal cells. Neuroprotective agents with antioxidant properties help neutralize ROS, thereby preventing cellular damage and maintaining neuronal health. These effects are crucial in mitigating the progression of neurodegenerative diseases such as Alzheimer's and Parkinson’s disease [27]. Recent studies have highlighted the potential of metal and metal oxide nanoparticles synthesized from brown seaweeds as effective antioxidants. For instance, gold nanoparticles derived from *Sargassum longifolium* have demonstrated significant antioxidant properties, showcasing their ability to scavenge free radicals effectively [28]. Similarly, iron oxide nanoparticles synthesized from *Spatoglossum asperum* have also been reported to exhibit notable antioxidant activities [29]. These findings underscore the therapeutic potential of seaweed-derived nanoparticles in combating oxidative stress-related disorders. The potential mechanism of the antioxidative effects of seaweed derived compounds for neuroprotection is given in the figure 2.

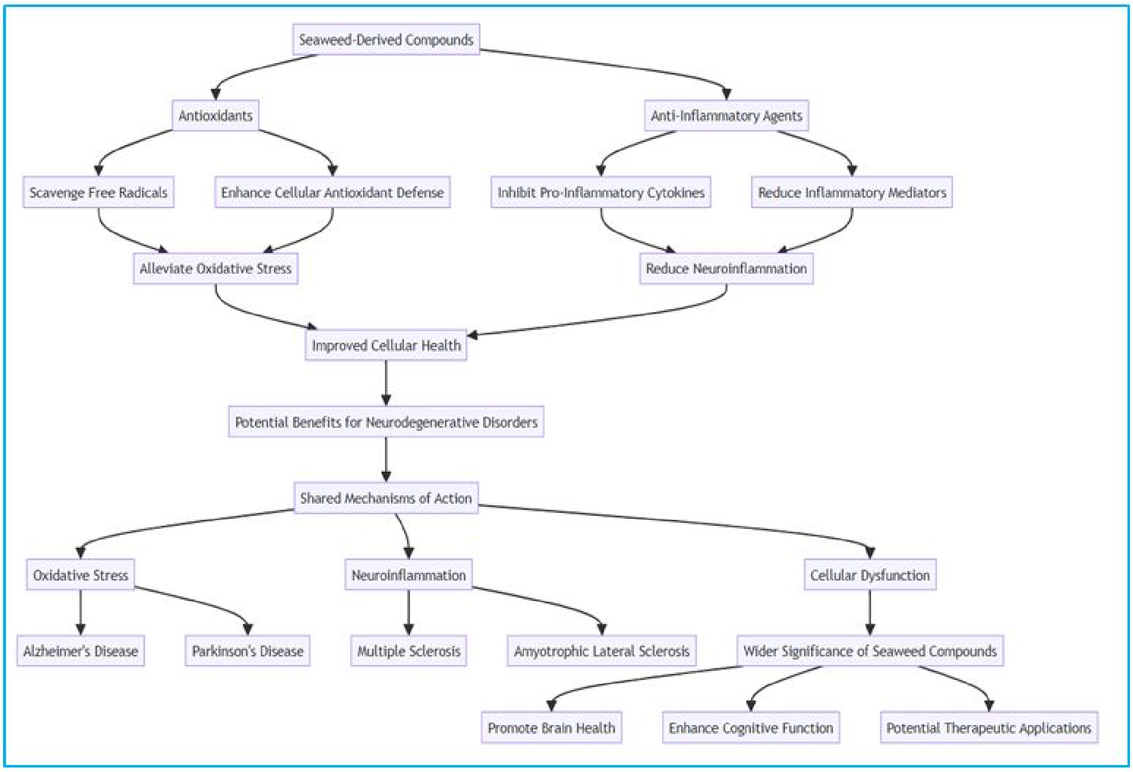

Figure 2: Shows the wider significance of the compounds derived from seaweed

Anti-inflammatory Effects

Inflammation plays a significant role in the pathogenesis of several neurodegenerative diseases. Anti-inflammatory effects involve inhibition of pro-inflammatory cytokines and pathways that contribute to neuronal damage. Neuroprotective agents that exert anti-inflammatory effects can reduce inflammation in the central nervous system, thereby protecting neurons from inflammation-induced damage and improving overall brain health [30].

Anti-apoptotic Effects

Apoptosis or programmed cell death is a natural process that can be exacerbated in neurodegenerative diseases, leading to excessive neuronal loss. Anti-apoptotic effects refer to the ability of neuroprotective agents to prevent or delay apoptosis of neuronal cells. This can be achieved through the modulation of apoptotic pathways and inhibition of key pro-apoptotic factors, thereby promoting neuronal survival and function [31].

Alzheimer’s Disease

Alzheimer's disease (AD) is characterized by progressive cognitive decline and memory loss. Potential applications of neuroprotective agents in Alzheimer's disease include the use of antioxidants to reduce oxidative stress, anti-inflammatory agents to decrease neuroinflammation, and anti-apoptotic compounds to prevent neuronal death (Figure 1). These approaches aim to slow disease progression and improve the quality of life of patients [31].

Parkinson's Disease

Parkinson's disease primarily affects motor function due to the degeneration of dopaminergic neurons in the substantia nigra. Neuroprotective strategies in Parkinson's disease focus on antioxidant therapy to mitigate oxidative damage, anti-inflammatory treatments to reduce neuroinflammation, and anti-apoptotic agents to protect dopaminergic neurons. These interventions have the potential to preserve motor function and delay disease progression [30].

Other Neurodegenerative Conditions

Other neurodegenerative conditions such as amyotrophic lateral sclerosis (ALS), Huntington's disease, and multiple sclerosis (MS) also benefit from neuroprotective approaches (Figure 3). These include the use of compounds that target oxidative stress, inflammation, and apoptotic pathways to protect neurons and support neural functions. The application of neuroprotective agents in these conditions aims to alleviate symptoms, improve patient outcomes, and enhance quality of life [27].

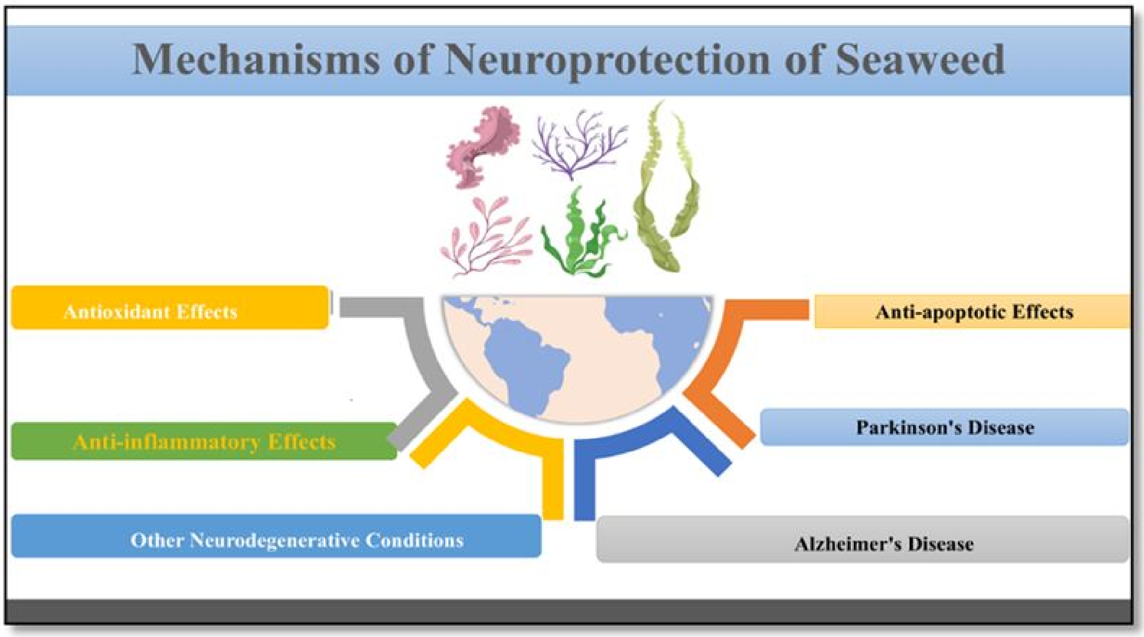

Figure 3: Neuroprotective potential of seaweeds

Therapeutic Potential of Seaweeds

Seaweeds represent an emerging resource of significant therapeutic potential due to their abundance, ecological sustainability, and rich composition of bioactive compounds. These marine organisms have been extensively studied for their role in combating a wide array of diseases, ranging from cancer and inflammatory disorders to metabolic and neurodegenerative conditions. The genus Sargassum has been a major focus of research due to its diverse bioactive compounds. Fucoidan, a sulfated polysaccharide found in *Sargassum* spp., exhibits potent anti-cancer properties by inducing apoptosis, modulating the Bax/Bcl-2 expression ratio, and suppressing tumor angiogenesis through VEGF inhibition [32]. Additionally, fucoidan protects keratinocytes from UV-induced oxidative damage and has shown anti-inflammatory and antioxidant effects relevant to diabetes, neurological diseases, and other chronic disorders [33]. Another compound, mojabanchromanol, demonstrates anti-inflammatory and anti-cancer potential by suppressing inflammatory cytokines and proteins like COX-2, iNOS, and NF-κB [34]. Fucosterol, also from *Sargassum* spp., has been shown to modulate pathways involved in inflammation and oxidative stress, including NF-κB/MAPK and Nrf2/HO-1 [35]. Beyond *Sargassum*, other seaweeds like *Ecklonia* spp., *Undaria pinnatifida*, and *Ulva* spp. have shown promise. *Ecklonia* spp. is rich in phlorotannins, which exhibit anti-inflammatory properties by inhibiting MAPK and NF-κB signaling. These compounds also reduce acetylcholinesterase activity, suggesting potential in Alzheimer's disease treatment [36,37]. Sulfated polysaccharides such as ulvans and fucoidans have neuroprotective effects, scavenging free radicals and reducing oxidative stress, thereby preventing neuronal damage [38].

Seaweeds also exhibit significant benefits in metabolic health. Polysaccharides like fucoidan and laminarin from *Sargassum* and other species help regulate blood sugar levels and modulate gut microbiota, enhancing gut health and addressing obesity and diabetes [39]. These compounds promote the growth of beneficial bacteria such as Bifidobacterium while inhibiting harmful microbes [40]. Protein hydrolysates from seaweeds like *Palmaria palmata* and *Gracilariopsis lemaneiformis* show cardioprotective properties by inhibiting angiotensin-1 converting enzyme (ACE) and dipeptidyl peptidase, contributing to the management of hypertension and diabetes [41]. Furthermore, seaweed-derived compounds have applications in cancer therapy. Studies highlight their roles in reducing oxidative stress, modulating apoptosis, and regulating pathways like ERK/MAPK, making them promising candidates for skin, liver, and colorectal cancers [35,42]. Their ability to modulate inflammatory and immune responses positions them as valuable agents in managing chronic diseases and enhancing general health [43,44].

Nanoencapsulation of seaweed bioactives

Nanoencapsulation involves enclosing bioactive compounds within nanocarriers to protect them from environmental degradation and enhance their delivery to target sites in the body [45]. Nanoencapsulation protects bioactive compounds from degradation caused by heat, light, and oxygen exposure during storage and digestion. By facilitating better absorption through the gastrointestinal tract, nanoencapsulated seaweed bioactives can achieve higher concentrations in systemic circulation, enhancing their therapeutic effects [46]. The encapsulation process can be designed to allow for a sustained release of bioactives over time, beneficial for chronic conditions like neurodegenerative disorders where prolonged exposure to therapeutic agents is desirable [47].

Antioxidants derived from seaweeds may help reduce amyloid plaque formation and oxidative stress associated with Alzheimer's pathology. For example, *Ecklonia cava* extracts have shown promise in inhibiting acetylcholinesterase (AChE), an enzyme linked to cholinergic dysfunction in AD [48]. Compounds like fucoidan from *Fucus vesiculosus* have demonstrated neuroprotective effects against dopaminergic neuron degeneration in PD models by modulating inflammatory responses [49]. Certain seaweed extracts have been noted for their calming effects; for instance, *Sargassum fusiforme* has been associated with reduced anxiety-like behaviors in animal studies due to its antioxidant properties [50]. Undoubtedly, the nanoencapsulation of seaweed bioactives presents a promising strategy for enhancing the efficacy of natural compounds in treating nervous disorders. By improving stability, bioavailability, and controlled release profiles, these advanced formulations can potentially lead to more effective therapeutic interventions. Future research should focus on clinical trials to validate the safety and efficacy of these nanoencapsulated formulations in human subjects suffering from neurological conditions. The integration of marine-derived compounds into therapeutic strategies could significantly impact the management of neurodegenerative diseases and related disorders.

Challenges and Future Directions

Seaweeds are a rich source of bioactive phytochemicals, including polyphenols, polysaccharides, carotenoids, and sterols, which have demonstrated potential neuroprotective properties. These compounds can mitigate neurodegeneration through antioxidant, anti-inflammatory, and anti-apoptotic mechanisms. Their diverse bioactivities make seaweed-derived phytochemicals promising candidates for the development of neuroprotective therapies. Efficient and cost-effective extraction methods must be developed to isolate bioactive compounds from seaweeds. Additionally, standardizing these extracts to ensure consistent bioactivity and dosage remains a significant challenge because many bioactive compounds from seaweed have low bioavailability, which limits their effectiveness. Innovative delivery systems are required to enhance the absorption and bioavailability of these compounds in the human body [30]. Regulatory approval for the use of bioactive seaweed compounds in neuroprotective therapies is a lengthy and complex process. It is essential to ensure the safety and efficacy of these compounds through rigorous clinical trials. Sustainable harvesting and cultivation of seaweed is crucial to prevent overexploitation and ensure a steady supply of raw materials for extraction. Environmental impact and ethical considerations must be addressed. Continued research on the neuroprotective mechanisms of seaweed bioactive compounds is essential. This includes identifying new compounds, understanding their modes of action, and optimizing the extraction and formulation methods [27]. Conducting well-designed clinical trials to validate the neuroprotective effects of bioactive seaweed compounds is critical. These trials should focus on efficacy, safety, and potential therapeutic applications in neurodegenerative diseases. The development of advanced delivery systems, such as nanoparticles, liposomes, and encapsulation techniques, can improve the bioavailability and targeted delivery of seaweed-derived neuroprotective compounds. Advanced delivery systems, such as nanoparticles, liposomes, and encapsulation techniques, are pivotal in optimizing the bioavailability and targeted delivery of neuroprotective compounds sourced from seaweed. Nanoparticles facilitate the effective transport of these compounds across the blood-brain barrier, ensuring precise delivery to therapeutic targets. Liposomes offer a biocompatible and versatile platform for encapsulating bioactive substances, safeguarding them from degradation and enabling controlled release. Encapsulation techniques further improve stability and solubility, enhancing the overall efficacy of these neuroprotective agents.

To address the regulatory challenges associated with these advanced delivery systems, a systematic approach is imperative. This entails conducting comprehensive preclinical studies to evaluate the safety, efficacy, and pharmacokinetics of the delivery systems in relevant animal models. Following positive preclinical outcomes, a detailed clinical trial protocol should be developed, specifying the objectives, design, and methodology for human trials. Early engagement with regulatory authorities, such as the FDA or EMA, is essential to incorporate their feedback and ensure adherence to safety and efficacy standards. Conducting clinical trials in phases—starting with small-scale Phase I trials to assess safety, followed by larger Phase II and III trials to evaluate efficacy—will facilitate a thorough assessment of the delivery systems. By adhering to these structured steps, researchers can effectively navigate the regulatory landscape, promoting the successful clinical application of seaweed-derived neuroprotective compounds.

Conclusions

Bioactive phytochemicals in seaweed represent a promising frontier for neuroprotection. A diverse array of compounds, including polyphenols, polysaccharides, carotenoids, and sterols, have shown significant potential for mitigating neurodegenerative processes through their antioxidant, anti-inflammatory, and anti-apoptotic properties. The therapeutic potential of these compounds is substantial, offering potential interventions for a range of neurodegenerative diseases, such as Alzheimer's and Parkinson's disease. However, several challenges must be addressed to fully harness the neuroprotective potential of bioactive phytochemicals in seaweed. These include the need for efficient and cost-effective extraction methods, improved bioavailability and delivery systems, rigorous regulatory and safety assessments, and sustainable harvesting practices. Overcoming these challenges requires a concerted effort from researchers, industry stakeholders, and policymakers. Looking forward, future directions should focus on continued research and development to uncover new bioactive compounds and elucidate their mechanisms of action. Conducting well-designed clinical trials is essential to validate the efficacy and safety of these compounds in neuroprotective therapies. Additionally, innovative delivery systems need to be developed to enhance the bioavailability of these compounds, ensuring their therapeutic effectiveness. Collaboration across sectors will be crucial to promote sustainable practices and facilitate the translation of these promising compounds into viable therapeutic agents. In conclusion, seaweed bioactive phytochemicals offer a rich and largely untapped resource for neuroprotection. By addressing the existing challenges and focusing on future research and development, we can unlock the full potential of these compounds, paving the way for new and effective treatments for neurodegenerative diseases.

Declarations

The authors declare they have no conflict of interest.

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Author Contributions

Mukul M. Barwant: Conceptualization, Writing – review & editing. Mudasir A. Dar: Conceptualization, Funding acquisition, Writing – review & editing. Murad Muhammad: Investigation, Writing – review & editing. Maheswari Behera: Software, Formal analysis, Writing – review & editing. Vanita C. Karande: Conceptualization, Investigation, Writing – review & editing. All authors read and approved the manuscript.

References

1. Pereira L, Valado A (2023) From the ocean to the brain: harnessing the power of marine algae for neuroprotection and therapeutic advances. Exploration of Neuroprotective Therapy, 3: 409-28.

2. Jannat K, Balakrishnan R, Han JH, Yu YJ, Kim GW, Choi DK (2023) The neuropharmacological evaluation of seaweed: A potential therapeutic source. Cells, 12: 2652.

3. Yordi GE, Pérez Martínez A, Radice M, Scalvenzi L, Abreu-Naranjo R, Uriarte E, Santana L, Matos MJ (2024) Seaweeds as Source of Bioactive Pigments with Neuroprotective and/or Anti-Neurodegenerative Activities: Astaxanthin and Fucoxanthin. Marine Drugs, 22: 327.

4. Khairinisa MA, Latarissa IR, Athaya NS, Charlie V, Musyaffa HA, Prasedya ES, Puspitasari IM (2023) Potential application of marine algae and their bioactive metabolites in brain disease treatment: Pharmacognosy and pharmacology insights for therapeutic advances. Brain Sciences, 13: 1686.

5. Cummings J, Lee G, Ritter A, Sabbagh M, Zhong K (2019) Alzheimer's disease drug development pipeline: 2019. Alzheimer's & Dementia: Translational Research & Clinical Interventions, 5: 272-93.

6. Patel AK, Albarico FPJB, Perumal PK, Vadrale AP, Nian CT, Chau HTB, Anwar C, et al. (2022) Algae as an emerging source of bioactive pigments. Bioresource technology, 351: 126910.

7. Schepers M, Martens N, Tiane A, Vanbrabant K, Liu HB, Lütjohann D, Mulder M, Vanmierlo T (2020) Edible seaweed-derived constituents: An undisclosed source of neuroprotective compounds. Neural regeneration research, 15: 790-5.

8. Vasili E, Dominguez-Meijide A, Outeiro TF (2019) Spreading of α-synuclein and tau: A systematic comparison of the mechanisms involved. Frontiers in molecular neuroscience, 12: 107.

9. Chi H, Chang HY, Sang TK (2018) Neuronal cell death mechanisms in major neurodegenerative diseases. International journal of molecular sciences, 19: 3082.

10. Hannan MA, Dash R, Haque MN, Mohibbullah M, Sohag AAM, Rahman MA, Uddin MJ, Alam M (2020) Moon IS. Neuroprotective potentials of marine algae and their bioactive metabolites: Pharmacological insights and therapeutic advances. Marine drugs, 18: 347.

11. Ganguly G, Chakrabarti S, Chatterjee U, Saso L (2017) Proteinopathy, oxidative stress and mitochondrial dysfunction: cross talk in Alzheimer's disease and Parkinson's disease. Drug design, development and therapy, 2017; 797-810.

12. Rengasamy KR, Mahomoodally MF, Aumeeruddy MZ, Zengin G, Xiao J, Kim DH. Bioactive compounds in seaweeds: An overview of their biological properties and safety. Food and Chemical Toxicology, 135: 111013.

13. Lomartire S, Gonçalves AM (2022) An overview of potential seaweed-derived bioactive compounds for pharmaceutical applications. Marine Drugs, 20: 141.

14. Das S, Behera M, Das SR, Behera KC, Singh L (2024) Green Seaweeds as a Potential Source of Biomolecules and Bioactive Peptides: Recent Progress and Applications–A Review. Chemistry & Biodiversity, 202401695.

15. Lomartire S, Gonçalves AM (2023) Marine macroalgae polyphenols as potential neuroprotective antioxidants in neurodegenerative diseases. Marine drugs, 21: 261.

16. Meinita MDN, Harwanto D, Choi JS (2022) Seaweed exhibits therapeutic properties against chronic diseases: An overview. Applied Sciences, 12: 2638.

17. Kim SK. ed. (2011) Handbook of marine macroalgae: biotechnology and applied phycology. John Wiley & Sons.

18. Silva J, Alves C, Freitas R, Martins A, Pinteus S, Ribeiro J, Gaspar H, Alfonso A, Pedrosa R (2019) Antioxidant and neuroprotective potential of the brown seaweed Bifurcaria bifurcata in an in vitro Parkinson's disease model. Marine drugs, 17: 85.

19. Emerit J, Edeas M, Bricaire F (2004) Neurodegenera-

tive diseases and oxidative stress. Biomedicine & pharmacotherapy, 58: 39-46.

20. Glass CK, Saijo K, Winner B, Marchetto MC, Gage FH (2010) Mechanisms underlying inflammation in neurodegeneration. Cell, 140: 918-34.

21. Mattson MP (2000) Apoptosis in neurodegenerative disorders. Nature reviews Molecular cell biology, 1: 120-30.

22. El-Beltagi HS, Mohamed AA, Mohamed HI, Ramadan KM, Barqawi AA, Mansour AT (2022) Phytochemical and potential properties of seaweeds and their recent applications: A review. Marine drugs, 20: 342.

23. Habeebullah SFK, Alagarsamy S (2023) Bioactive secondary metabolites from marine macroalgae. In Algal Metabolites, 339-400. Apple Academic Press.

24. El-Sheekh M, Fathy AA, Saber H, Saber A (2023). Medicinal and pharmaceutical applications of seaweeds. Egyptian Journal of Botany, 63: 1-29.

25. Janarthanan M, Kumar MS (2013) Qualitative and quantitative analysis of phytochemical studies on selected seaweeds Acanthopora spicifera and Sargassum wightii. International Journal of Engineering Research and Development, 7: 11-5.

26. Dulanlebit YH, Hernani H (2023) Overview of extraction methods for extracting seaweed and its applications. Jurnal Penelitian Pendidikan IPA, 9: 817-24.

27. Ryan M, Tan VT, Thompson N, Guévremont D, Mockett BG, Tate WP, Abraham WC, Hughes SM, Williams J (2021) Lentivirus-mediated expression of human secreted amyloid precursor protein-alpha promotes long-term induction of neuroprotective genes and pathways in a mouse model of Alzheimer's disease. Journal of Alzheimer's Disease, 79: 1075-90.

28. Rajeshkumar S, Parameswari RP, Jayapriya J, et al. (2022) Apoptotic and antioxidant activity of gold nanoparticles synthesized using marine brown seaweed: an in vitro study. Biomed Res Int, e5746761.

29. Palaniyandi T et al. (2023) Biosynthesis of iron nanoparticles using brown algae Spatoglossum asperum and its antioxidant and anticancer activities through in vitro and in silico studies. Part Sci Technol. 41: 916-29.

30. Williams-Karnesky RL, Stenzel-Poore MP (2009) Adenosine and stroke: maximizing the therapeutic potential of adenosine as a prophylactic and acute neuroprotectant. Current neuropharmacology, 7: 217-27.

31. Aghili-Mehrizi S, Williams E, Yan S, Willman M, Willman J, Lucke-Wold B (2022) Secondary mechanisms of neurotrauma: a closer look at the evidence. Diseases, 10: 30.

32. Saeed M, et al. (2021) A comprehensive review on the health benefits and nutritional significance of fucoidan polysaccharide derived from brown seaweeds in human, animals and aquatic organisms, Aquac. Nutr. 27: 633-54.

33. Liu J. et al. (2020) Therapeutic and nutraceutical potentials of a brown seaweed Sargassum fusiforme, Food Sci. Nutr. 8: 5195-205.

34. Herath K.H.I.N.M. et al. (2020) Mojabanchromanol Isolated from Sargassum horneri Attenuates Particulate Matter Induced Inflammatory Responses via Suppressing TLR2/4/7-MAPK Signaling in MLE-12 Cells, Mar. Drugs, 18: 355.

35. Kirindage K.G.I.S. et al. (2022) Fucosterol isolated from dietary brown alga sargassum horneri protects TNF-α/IFN-γ-stimulated human dermal fibroblasts via regulating Nrf2/HO-1 and NF-κB/MAPK pathways, Antioxid. Basel Switz. 11: 1429.

36. Nagahawatta D.P, N.M. Liyanage, H.H.A.C.K. Jayawardhana, H.G. Lee, T. U. Jayawardena, Y.J. Jeon (2022) Anti-fine dust effect of fucoidan extracted from ecklonia maxima laves in macrophages via inhibiting inflammatory signaling pathways, Mar. Drugs, 20: 413.

37. Shah MD, Venmathi Maran BA, Shaleh SRM, Zuldin WH, Gnanaraj C, Yong YS (2022) Therapeutic potential and nutraceutical profiling of north bornean seaweeds: A review. Marine Drugs, 20: 101.

38. Bauer S, W. Jin, F. Zhang, R.J. Linhardt (2021) The application of seaweed polysaccharides and their derived products with potential for the treatment of alzheimer's disease, Mar. Drugs, 19: 89.

39. Cui Y. et al. (2021) Structure of a laminarin-type β-(1→3)-glucan from brown algae Sargassum henslowianum and its potential on regulating gut microbiota, Carbohydr. Polym. 255: 117389,

40. Chen X, Drew J, Berney W, Lei W (2021) Neuroprotective natural products for Alzheimer's disease. Cells, 10: 1309.

41. Mousaie M., M. Khodadadi, M. Tadayoni (2022) Hydrolysate protein from brown macroalgae (Sargassum ilicifolium): antioxidant, antitumor, antibacterial, and ACE inhibitory activities, J. Food Process. Preserv. 46: e17020.

42. Atashrazm F, R.M. Lowenthal, G.M. Woods, A.F. Holloway, J.L. Dickinson (2015) Fucoidan and cancer: a multifunctional molecule with anti-tumor potential, Mar. Drugs, 13: 2327–46.

43. Praveen MA, K.R.K. Parvathy, P. Balasubramanian, R. Jayabalan (2019) An overview of extraction and purification techniques of seaweed dietaary fibers for immunomodulation on gut microbiota, Trends Food Sci. Technol. 92: 46-64.

44. Wang L et al. (2021) In vitro and in vivo anti-inflammatory effects of sulfated polysaccharides isolated from the edible brown seaweed, sargassum fulvellum. Mar. Drugs, 19: 277.

45. Lomartire S, Gonçalves AMM (2022) An Overview of Potential Seaweed-Derived Bioactive Compounds for Pharmaceutical Applications. Mar Drugs. 20: 141.

46. Maghraby YR, Farag MA, Kontominas MG, et al. (2022) Nanoencapsulated Extract of a Red Seaweed (Rhodophyta) Species as a Promising Source of Natural Antioxidants. ACS Omega, 7: 6539-48.

47. Jaison J.P., Balasubramanian B., Gangwar J. et al. (2024) Bioactive nanoparticles derived from marine brown seaweeds and their biological applications: a review. Bioprocess Biosyst Eng. 47: 1605-18.

48. Thiurunavukkarau R, Shanmugam S, Subramanian K. et al. (2022) Silver nanoparticles synthesized from the seaweed Sargassum polycystum and screening for their biological potential. Sci Rep. 12: 14757.

49. Koo SY, Hwang KT, Hwang S, et al. (2023) Nanoencapsulation enhances the bioavailability of fucoxanthin in microalga Phaeodactylum tricornutum extract. Food Chemistry, 403: 134348.

50. Kumar Y, Ayon T, Badgujar PC (2021) Seaweed as a Source of Natural Antioxidants: Therapeutic Activity and Food Applications, Journal of Food Quality, 17: 5753391.

51. Bauer S, Jin W, Zhang F, Linhardt RJ (2021) The application of seaweed polysaccharides and their derived products with potential for the treatment of Alzheimer's disease. Marine drugs, 19: 89.

52. Chen X, et al. (2018) In vitro prebiotic effects of seaweed polysaccharides, J. Oceanol. Limnol. 36: 926-32.

53. Coelho M, Duarte AP, Pinto S, Botelho HM, Reis CP, Serralheiro ML, Pacheco R (2023) Edible seaweeds extracts: characterization and functional properties for health conditions. Antioxidants, 12: 684.

54. Corsetto PA, Montorfano G, Zava S, Colombo I, Ingadottir B, Jonsdottir R, Sveinsdottir K, Rizzo AM (2020) Characterization of antioxidant potential of seaweed extracts for enrichment of convenience food. Antioxidants, 9: 249.

55. Custodio L, Silvestre L, Rocha MI, Rodrigues MJ, Vizetto-Duarte C, Pereira H, Barreira L, Varela J (2016) Methanol extracts from Cystoseira tamariscifolia and Cystoseira nodicaulis are able to inhibit cholinesterases and protect a human dopaminergic cell line from hydrogen peroxide-induced cytotoxicity. Pharmaceutical Biology, 54: 1687-96.

56. Liyanage NM, Nagahawatta DP, Jayawardena TU, Jeon YJ (2023) The role of seaweed polysaccharides in gastrointestinal health: Protective effect against inflammatory bowel disease. Life, 13: 1026.

57. Lourenço-Lopes C, Fraga-Corral M, Soria-Lopez A, Nuñes-Estevez B, Barral-Martinez M, et al. Fucoxanthin's optimization from Undaria pinnatifida using conventional heat extraction, bioactivity assays and in silico studies. Antioxidants, 11: 1296.

58. Luo C, Wei X, Song J, Xu X, Huang H, Fan S, Zhang D, Han L, Lin J (2022) Interactions between gut microbiota and polyphenols: new insights into the treatment of fatigue.

Molecules, 27: 7377.

59. Oh JH, Nam TJ (2019) Hydrophilic glycoproteins of an edible green alga Capsosiphon fulvescens prevent aging-induced spatial memory impairment by suppressing GSK-3β--mediated ER stress in dorsal hippocampus. Marine drugs, 17: 168.

60. Sathya R, Kanaga N, Sankar P, Jeeva S (2017) Antioxidant properties of phlorotannins from brown seaweed Cystoseira trinodis (Forsskål) C. Agardh. Arabian Journal of Chemistry, 10: S2608-14.

61. Shah M.D, B.A. Venmathi Maran, S.R.M. Shaleh, W.H. Zuldin, C. Gnanaraj, Y. S. Yong (2022) Therapeutic potential and nutraceutical profiling of north Bornean seaweeds: a review, Mar. Drugs, 20.

62. Zhang Z, Wang X, Pan Y, Wang G, Mao G (2020) The degraded polysaccharide from Pyropia haitanensis represses amyloid beta peptide-induced neurotoxicity and memory in vivo. International journal of biological macromolecules, 146: 725-9.

63. Zheng H, Zhao Y, Guo, L (2022) A bioactive substance derived from brown seaweeds: Phlorotannins. Marine Drugs, 20: 742.