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Greener Extraction Techniques and Neuroprotective Compounds from Marine Algae: A New Wave in Neuropharmacology

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ABSTRACT

The increasing prevalence of neurodegenerative diseases, including Alzheimer's and Parkinson's, underscores the urgent need for new therapies with broad mechanisms of action, minimal side effects, and sustainable origins. Marine algae represent a valuable source of neuroprotective compounds, such as phlorotannins, fucoxanthin, omega-3 fatty acids, sulfated polysaccharides, and sterols. These bioactive compounds exhibit antioxidant, anti-inflammatory, anti-amyloidogenic, and neurogenic activities by inhibiting acetylcholinesterase, scavenging reactive oxygen species, suppressing pro-inflammatory cytokines, and enhancing neurotrophic factors such as Brain-Derived Neurotrophic Factor (BDNF). Despite their promise, the therapeutic application of these compounds is restricted by conventional extraction processes that are energy-demanding, environmentally harmful, and inefficient. To overcome these limitations, this review highlights the role of green extraction technologies, such as Ultrasound-Assisted Extraction (UAE), Microwave-Assisted Extraction (MAE), Supercritical Fluid Extraction (SFE), Enzyme-Assisted Extraction (EAE), and Pressurized Liquid Extraction (PLE), which enhance yield, preserve compound integrity, reduce solvent use, and align with the principles of green chemistry. These approaches offer scalable and eco-friendly solutions for marine biomass utilization. The review also addresses challenges related to extraction standardization, bioavailability, and blood–brain barrier permeability, while highlighting advanced delivery systems, such as nanocarriers and intranasal administration. Future directions emphasize sustainability, precision neuropharmacology, and regulatory and ethical considerations, which are discussed in detail in later sections. Marine algae have thus emerged as an underutilized yet sustainable resource for the development of next-generation neurotherapeutics.

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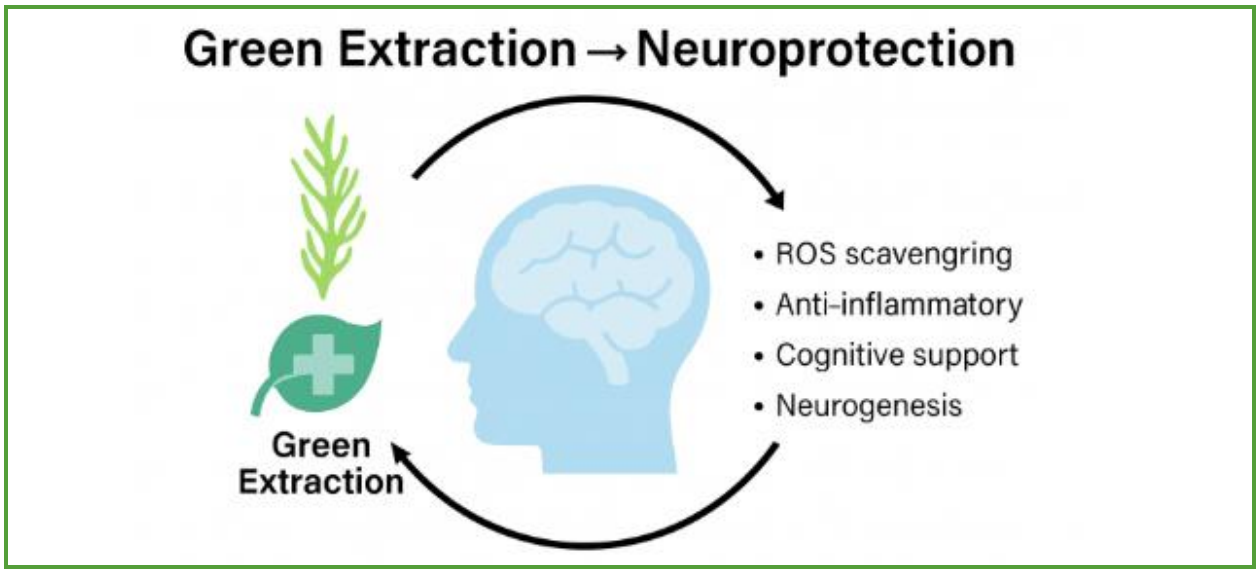
Graphical Abstract



Introduction

Neurodegenerative disorders, including Alzheimer's disease, Parkinson's disease, Huntington's disease, and various forms of dementia, represent significant global health challenges. These conditions are characterized by a progressive loss of neuronal structure or function, leading to cognitive decline, motor dysfunction, and behavioural disturbances. With an aging global population, the prevalence of such diseases is increasing at an alarming rate. According to the World Health Organization (WHO), neurological disorders are among the leading causes of disability and death worldwide [1].

Due to oxidative stress, neuroinflammation, mitochondrial dysfunction, and protein misfolding, the current therapeutic interventions only provide symptomatic relief and do not prevent disease progression [2,3].

This scenario underscores the urgent need for novel, multi-targeted neuroprotective agents that can intervene early in the disease process and potentially restore or maintain neural function [4]. To address these therapeutic limitations, marine algae have become more popular as natural reservoirs of bioactive compounds that can target multiple pathways involved in neurodegeneration. Marine algae, a diverse group of photosynthetic organisms found in oceanic ecosystems, have emerged as promising sources of bioactive compounds with therapeutic potential. Unlike terrestrial plants, marine algae are exposed to extreme environmental conditions, such as UV radiation, salinity, and oxidative stress, prompting them to produce a wide array of secondary metabolites with potent antioxidant, anti-inflammatory, and neurotherapeutic activities [5].

Some compounds such as phlorotannins, fucoxanthin, omega-3 fatty acids (EPA and DHA), sulfated polysaccharides, and sterols have shown significant potential for mitigating the key pathological mechanisms underlying neurodegenerative diseases [6,7].

Preclinical studies have demonstrated the ability of these compounds to inhibit acetylcholinesterase (AChE), suppress pro-inflammatory cytokines, scavenge reactive oxygen species (ROS), and enhance neurogenesis [8-10].

A growing number of studies suggest that marine algae are distinct and unexpolited reservoirs of novel neurotherapeutic agents [11,12].

Despite the pharmacological potential of marine algal compounds, the challenge lies in their efficient and sustainable extraction. Conventional extraction methods often involve prolonged processing times, excessive use of toxic organic solvents, and thermal degradation of sensitive bioactive compounds, which undermine the therapeutic potential and environmental sustainability of the process [13].

In recent years, green extraction technologies have gained momentum as viable alternatives that align with the principles of green chemistry and sustainability [14,15].

These methods, including ultrasound-assisted extraction (UAE), microwave-assisted extraction (MAE), supercritical fluid extraction (SFE), enzyme-assisted extraction (EAE), and pressurized liquid extraction (PLE), offer numerous advantages, such as enhanced extraction yields, reduced solvent consumption, shorter processing times, and preservation of compound integrity [16,17].

The integration of these greener techniques is essential for developing scalable and eco-friendly processes for isolating marine-derived neuroprotectants [18].

“Sustainable drug development” refers to the designing, extracting, producing, and deliverying pharmaceuticals in ways that minimize environmental impacts, conserve resources, and ensure long-term availability. It emphasizes green chemistry, renewable sourcing, ethical compliance, and life cycle thinking, ensuring that therapeutic innovation aligns with ecological responsibility. This review aims to provide a comprehensive analysis of the current advancements in green extraction techniques, specifically applied to marine algae, with a focus on their role in neuropharmacology. It seeks to bridge the gap between sustainable marine bioprocessing and the development of effective neurotherapeutics. This review systematically explores the types of bioactive compounds found in different classes of marine algae, highlights their mechanisms of neuroprotection, and critically evaluates green extraction methodologies that enable their efficient isolation. Furthermore, it outlines the challenges and future perspectives associated with the translation of marine algal compounds into clinically viable neurotherapeutics. This integrative perspective is intended to inform researchers, formulators, and industry stakeholders on how green technologies can be harnessed to unlock the full potential of marine resources for combating neurodegenerative diseases.

Marine Algae and Their Neuroprotective Potentials

Marine macroalgae, commonly referred to as seaweeds, are broadly categorized into three main classes based on their pigmentation, biochemical composition, and habitat: red algae (Rhodophyta), green algae (Chlorophyta), and brown algae (Phaeophyceae) (Table 1) [19].

Red algae are rich in phycoerythrin and phycocyanin pigments, and are known for their high content of sulfated polysaccharides, such as carrageenans and agar. These species thrive in deeper waters and exhibit remarkable antioxidant and anti-inflammatory activities, making them strong candidates for neuroprotective interventions [20,21].

Table 1. Classification and bioactive profile of marine algae

Algae Type	Pigment	Major Bioactives	Neuroprotective Mechanisms	Key Examples
Red (Rhodophyta)	Phycoerythrin and Phycocyanin	Carrageenans and Bromophenols	Anti-inflammatory and AChE inhibition	*Gracilaria spp.* and *Palmaria palmata*
Green (Chlorophyta)	Chlorophyll a, b	Sterols and Carotenoids	Neurotransmitter modulation and Antioxidant	*Ulva lactuca* and *Codium spp.*
Brown (Phaeophyceae)	Fucoxanthin	Phlorotannins, Fucoidan, and Fucosterol	BDNF upregulation and ROS scavenging	*Fucus vesiculosus* and *Laminaria spp.*

Green algae, which typically grow in shallow marine waters, are characterized by the presence of chlorophyll a and b. They contain various neuroactive substances including carotenoids, sterols, vitamins, and unsaturated fatty acids. Some species of green algae also synthesize unique acetylcholinesterase inhibitors and neurostimulatory peptides, which demonstrate promise for cognitive support [22,23].

Brown algae are mostly found in temperate and cold marine environments and are distinguished by pigments, such as fucoxanthin, and polysaccharides, such as laminarin and alginate. This class of algae is particularly notable for its production of phlorotannins and omega-3 polyunsaturated fatty acids (PUFAs), both of which are involved in reducing oxidative and inflammatory stress linked to neurodegeneration [24,25].

The difference between three groups not only lies in their morphology and ecology, but also in the profile and concentration of bioactive constituents they possess, which has a profound impact on their therapeutic potential in neuropharmacology [26].

Bioactive Constituents and Their Roles in Neuroprotection

Marine algae are a prolific source of structurally diverse bioactive metabolites that can target various neurodegenerative mechanisms. Polyphenols, particularly phlorotannins derived from brown algae, possess strong antioxidant capacities, inhibit inflammatory signalling cascades, and attenuate neuronal apoptosis [27].

Carotenoids, such as fucoxanthin and β-carotene, are lipid-soluble antioxidants that neutralize free radicals, reduce oxidative DNA damage, and modulate pathways involved in programmed neuronal death [28,29].

Polysaccharides such as fucoidan (brown), carrageenan (red), and ulvan (green) have demonstrated anti-inflammatory, neuroprotective, and immunomodulatory effects, acting through toll-like receptors and Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF-κB) inhibition [30,31].

Polyunsaturated fatty acids (PUFAs), especially EPA and DHA, enhance synaptic plasticity, protect membrane integrity, and suppress neuroinflammatory cascades, which are pivotal in Alzheimer's and Parkinson's pathologies [32,33].

Sterols, notably fucosterol, not only reduce neuroinflammation, but also facilitate neurotransmitter regulation and memory restoration through enhanced cholinergic signalling [34].

Mechanisms of Action in Neuroprotection

Marine algal bioactives exert neuroprotection primarily through antioxidant and anti-inflammatory pathways, AChE inhibition, and modulation of neurotrophic factors, such as BDNF and NGF. These compounds reduce oxidative stress, suppress pro-inflammatory cytokines, enhance synaptic plasticity, and improve neurotransmission, thereby contributing to their potential in combating neurodegenerative disorders. Figure 1 shows a schematic representation of the neuroprotective mechanisms of the marine algal compounds.

Antioxidant and anti-inflammatory effects

Oxidative stress and neuroinflammation are the hallmark features of neurodegenerative disorders. Algal polyphenols and carotenoids scavenge reactive oxygen species (ROS) and reactive nitrogen species (RNS), thereby preventing neuronal apoptosis, lipid peroxidation, and mitochondrial dysfunction [35]. Moreover, they inhibit NF-κB pathway activation and suppress pro-inflammatory cytokine release (*e.g.,* TNF-α and IL-1β), thereby preserving the neuronal microenvironment [36].

Inhibition of AChE

Increased AChE activity contributes to cholinergic deficits in Alzheimer's disease. Bromophenols, alkaloids, and unique phenolic compounds isolated from red and green algae have shown reversible inhibition of AChE, thereby supported acetylcholine levels and improved memory function [37,38].

Modulation of neurotrophic factors and neurotransmitters

Neurotrophic factors, such as Brain-Derived Neurotrophic Factor (BDNF) and Nerve Growth Factor (NGF), are vital for neuronal survival, differentiation, and plasticity. Algal-derived polysaccharides and sterols have been found to upregulate these growth factors, thereby facilitating neurogenesis and synaptic remodelling [39].

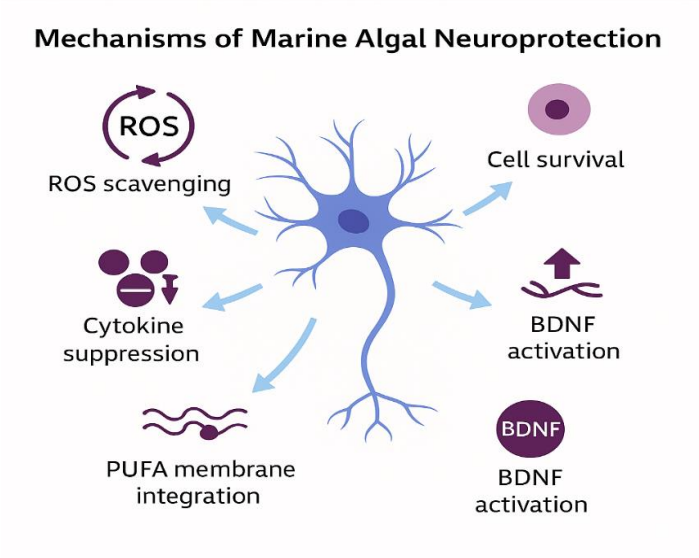


Figure 1. Mechanistic pathways of marine algal neuroprotection, highlighting antioxidant, anti-inflammatory, and anti-apoptotic effects

Furthermore, modulation of dopaminergic and serotonergic pathways by algal metabolites improves mood, reduces anxiety, and supports cognitive performance in animal models of depression [40,41].

Greener Extraction Techniques for Marine Algal Compounds

Greener extraction techniques, such as UAE, MAE, SFE, PLE, and EAE, enable efficient, eco-friendly recovery of neuroprotective compounds from marine algae while preserving bioactivity and minimizing environmental impact, as depicted in Figure 2.

Ultrasound-assisted extraction

Ultrasound-Assisted Extraction (Table 2) utilizes acoustic cavitation generated by high-frequency ultrasonic waves (typically 20–100 kHz) to enhance disruption of algal cell walls and improve solvent penetration. The collapse of cavitation bubbles produces intense local shear forces and microjets that rupture cell membranes, thereby enabling the efficient release of intracellular bioactive molecules. UAE is especially advantageous for the extraction of thermolabile neuroprotective compounds, such as phlorotannins, polyphenols, and fucoxanthin, due to its low-temperature operation. This technique significantly reduces the extraction time and solvent consumption while improving the yield and preserving compound integrity. Its application in brown and red algae has led to the successful recovery of antioxidant and anti-inflammatory compounds, making it a leading green technology for neuroprotective drug discovery from marine biomass.

Microwave-assisted extraction

Microwave-Assisted Extraction (Table 3) involves the use of microwave energy to rapidly heat the moisture inside algal cells, creating an internal pressure that disrupts the cell wall and accelerates mass transfer. This technique operates at frequencies of 300 MHz to 300 GHz and enables a dramatic reduction in extraction time, often within minutes, while minimizing solvent use and degradation of active compounds.

Table 2. Ultrasound-Assisted Extraction (UAE) of marine algae species and their neuroprotective bioactive compounds, highlighting the advantages of UAE in enhancing yield and activity

Marine Algae Species	Target Compounds	Neuroprotective Potential	Ref.
Padina boryana	Phlorotannins, flavonoids	Antioxidant, anti-inflammatory	[42]
Sargassum tenerrimum	Fucoxanthin, tannins	ROS scavenging	[43]
Turbinaria ornata	Phenolics	Anti-neuroinflammatory	[44]
Cystoseira tamariscifolia	Sulfated polysaccharides	AChE inhibition	[45]
Caulerpa racemosa	Pigments, phenolics	Neuroprotection	[46]
Chaetomorpha antennina	Sterols	Cholinergic enhancement	[47]

Table 3. Microwave-assisted extraction (MAE) of marine algae species and their bioactive compounds. The technique enhances recovery of neuroprotective agents with therapeutic potential

Marine Algae Species	Target Compounds	Neuroprotective Potential	Ref.
Enteromorpha compressa	Polysaccharides	Immune modulation	[48]
Acanthophora spicifera	Phenolic acids	Cognitive enhancement	[49]
Gelidiella acerosa	Sterols, pigments	Neurotransmitter modulation	[50]
Cladophora glomerata	Polyphenols	Oxidative stress reduction	[51]
Hypnea musciformis	Flavonoids	Neuroprotection	[52]
Bryothamnion seaforthii	Agar	Anti-inflammatory	[53]

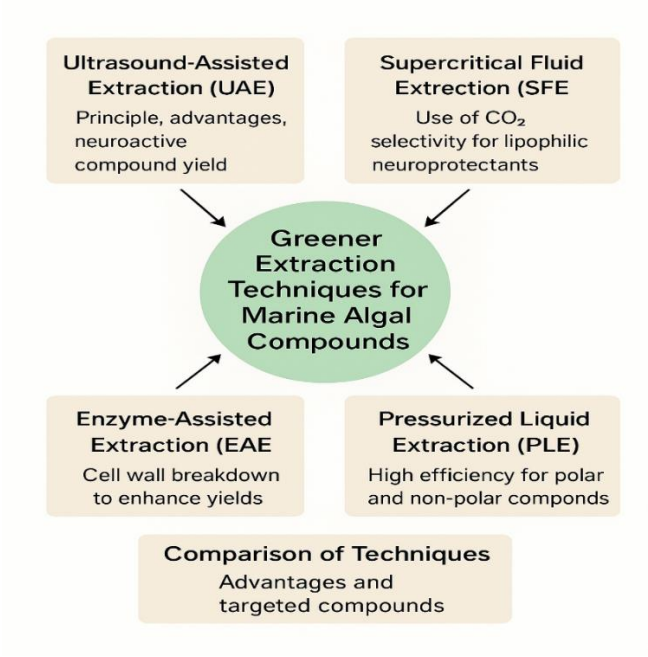


Figure 2. Comparative evaluation of green extraction techniques for marine algal bioactive compounds

MAE is particularly suited for extracting polar compounds, such as sulfated polysaccharides, carotenoids, and sterols, which are known for their neuroprotective roles, including the modulation of neurotransmitters, free radical scavenging, and anti-apoptotic effects. The non-invasive nature and scalability of MAE make it highly effective for producing bioactive-rich extracts with significant potential for treating neurodegenerative disorders.

Supercritical fluid extraction

Supercritical fluid extraction (Table 4) primarily utilizes carbon dioxide (CO_2) above its critical temperature (31.1°C) and pressure (73.8 bar), wherein it behaves as both a gas and a liquid. This supercritical state provides exceptional solvating power, allowing CO_2 to efficiently penetrate algal biomass and selectively dissolve non-polar, lipophilic compounds, such as omega-3 fatty acids (EPA and DHA), fucoxanthin, and marine sterols. Since CO_2 is non-toxic, non-flammable, and leaves no residual solvent, SFE ensures a clean and eco-friendly extraction process with high purity and bioavailability of the extracted compounds. The tunability of the process by adjusting the temperature and pressure further enhances selectivity and efficiency while preserving the bioactivity of sensitive neuroactives. These features make SFE an exemplary green extraction technique for scalable pharmaceutical applications.

Pressurized liquid extraction

Pressurized liquid extraction (Table 5), also referred to as Accelerated Solvent Extraction (ASE), involves the use of solvents at elevated temperatures (typically 50–200 °C) and pressures (10–20 MPa) to enhance the solubility and diffusion of bioactive compounds. Under these controlled conditions, solvents such as ethanol, methanol, or water remain in the liquid phase, allowing faster and more efficient extraction of both polar and nonpolar substances.

PLE is particularly effective for recovering complex neuroprotective constituents, such as polyphenols, sulfated polysaccharides, and mannitol, from various marine algae. These compounds exert antioxidant, anti-inflammatory, and neurogenesis-promoting effects. PLE stands out for its speed, reproducibility, scalability, and alignment with green chemistry principles, making it suitable for large-scale production of marine neuroprotective extracts.

Enzyme-assisted extraction

Enzyme-assisted extraction (Table 6) employs specific hydrolytic enzymes, such as cellulase, protease, and alginase, to break down the structural components of algal cell walls, primarily polysaccharides and glycoproteins. This enzymatic degradation facilitates the gentle and selective release of intracellular compounds, without the need for harsh physical or chemical treatments. EAE is particularly valuable for isolating high-molecular-weight bioactive compounds such as sulfated polysaccharides, protein hydrolysates, and oligosaccharides, which exhibit diverse neuroprotective functions, including synaptic modulation, inhibition of neuroinflammatory pathways, and enhancement of neuronal survival.

Table 4. Supercritical fluid extraction (SFE) of marine algae species and their neuroprotective compounds. SFE ensures high-purity recovery of lipids and carotenoids with brain-protective benefits

Marine Algae Species	Target Compounds	Neuroprotective Potential	Ref.
Spatoglossum asperum	EPA, DHA	Neuronal membrane integrity	[54]
Dictyopteris delicatula	Carotenoids, sterols	Synaptic function	[55]
Botryocladia leptopoda	Lipids	Cognitive function	[56]
Bryopsis plumosa	PUFAs	Neuroinflammation suppression	[57]
Ceramium rubrum	Sterols	Antioxidant	[58]
Derbesia tenuissima	Fucoxanthin	Brain cell protection	[59]

Table 5. Pressurized liquid extraction (PLE) of marine algae species and their neuroactive compounds. PLE offers efficient recovery of phenolics and polysaccharides with neuroprotective effects

Marine Algae Species	Target Compounds	Neuroprotective Potential	Ref.
Centroceras clavulatum	Polyphenols	Oxidative stress reduction	[60]
Hydropuntia edulis	Sulfated polysaccharides	Immune signalling modulation	[61]
Ulva rigida	Phenolic acids	Anti-neurodegenerative	[62]
Spongomorpha indica	Sterols	Neuronal differentiation	[63]
Stoechospermum marginatum	Pigments	Neurotrophic factor modulation	[64]
Zonaria tournefortii	Mannitol	ROS neutralization	[65]

Table 6. Enzyme-assisted extraction (EAE) of marine algae species and their neuroprotective compounds. EAE facilitates targeted release of bioactives with enhanced brain health benefits

Marine Algae Species	Target Compounds	Neuroprotective Potential	Ref.
Grateloupia filicina	Polysaccharide-peptides	Neuroprotective synaptic action	[66]
Jania rubens	Enzyme-extracted flavonoids	AChE inhibition	[67]
Boodlea composita	Enzymatic peptides	Neurotransmission enhancement	[68]
Kappaphycus alvarezii	Carrageenan derivatives	Neuroinflammation reduction	[69]
Ahnfeltia plicata	Protein hydrolysates	Neuronal signalling support	[70]
Halymenia floresii	Enzymatic sugars	Cognition improvement	[71]

The mild operational conditions of EAE preserve the bioactivity of sensitive compounds and support their integration with other techniques, such as UAE or MAE for improved yields. The mild operational conditions of EAE preserve the bioactivity of sensitive compounds and support their integration with other techniques such as UAE or MAE for improved yields. Upon outlining the major greener extraction strategies, attention is now directed toward the role of these marine algal bioactives in neuropharmacology, particularly concerning cognitive enhancement and neuroprotection.

Role of Extracted Compounds in Neuropharmacology

Marine algae are treasure troves of structurally diverse bioactive compounds with significant neuropharmacological properties. These include polyphenols, carotenoids, sterols, sulfated polysaccharides, and alkaloids, which have been extensively studied for their roles in combating neurological disorders, such as Alzheimer's disease, Parkinson's disease, stroke, and age-related cognitive decline. The bioactive compounds found in marine algae are diverse in structure and possess significant neuropharmacological properties, including polyphenols, carotenoids, sterols, sulfated polysaccharides, and alkaloids, which have been extensively studied for their roles in combating neurological disorders such as Alzheimer's disease, Parkinson's disease, stroke, and age-related cognitive decline.

These compounds exhibit a multitude of biological effects, including antioxidative, anti-inflammatory, anti-amyloidogenic, and neuroprotective properties, making them strong candidates for neurotherapeutics.

Cognitive enhancement

Cognitive decline, a hallmark of neurodegenerative conditions and aging, is often associated with cholinergic deficits, oxidative damage, and impaired neuroplasticity. Marine algal extracts, particularly phlorotannins from brown algae (*Ecklonia cava*), have shown remarkable potential in enhancing memory and learning. These compounds inhibit AChE, thereby increasing the synaptic availability of acetylcholine, a neurotransmitter that is crucial for cognition. Additionally, they upregulate BDNF and modulate synaptic signalling pathways such as ERK/CREB, which are essential for long-term potentiation and memory formation. In rodent studies, phlorotannin-rich fractions improved performance in the Morris water maze and passive avoidance tests, suggesting enhanced spatial learning and memory retention [72,73].

Neuroprotection in animal models

Neurodegenerative diseases are characterized by progressive neuronal loss often initiated by oxidative stress, mitochondrial dysfunction, excitotoxicity, and neuroinflammation. Algal-derived compounds such as ulvans from *Ulva lactuca* and carrageenans from Kappaphycus alvarezii have demonstrated protective effects against these pathways. In Parkinson's disease models, these polysaccharides suppressed dopaminergic neuron degeneration by reducing microglial activation and ROS production. Furthermore, fucosterol, a marine sterol from Sargassum fusiforme, protects cortical neurons from glutamate-induced excitotoxicity by regulating intracellular calcium levels and preserving mitochondrial membrane potential [74,75]. Animal studies have revealed that rats treated with fucosterol and related algal sterols show decreased levels of apoptotic markers (*e.g.,* Bax and caspase-3) and enhanced expression of anti-apoptotic proteins such as Bcl-2. These

findings highlight the ability of algal sterols to stabilize neuronal integrity and prevent the apoptotic cascades triggered by ischemic injury or neurotoxins.

Anti-amyloidogenic and anti-inflammatory actions

The aggregation of β-amyloid (Aβ) peptides into plaques is a central pathological feature of Alzheimer's disease. Certain marine polyphenols, such as dieckol and eckol from brown algae (*Eisenia bicyclis*), can inhibit Aβ fibrillogenesis and disaggregate preformed fibrils. These actions are facilitated by their capacity to bind to hydrophobic sites on Aβ peptides, preventing conformational changes that lead to the formation of toxic aggregates [76]. Besides addressing Aβ pathology, algal bioactives modulate key inflammatory signalling pathways. Phlorotannins and sulfated polysaccharides suppress NF-κB translocation and MAPK pathway activation, thereby reducing the expression of pro-inflammatory cytokines, such as TNF-α, IL-1β, and IL-6. These compounds also downregulate inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2), curbing the production of neurotoxic nitric oxide and prostaglandins [77].

Antioxidant defense and mitochondrial protection

Neuronal cells are highly vulnerable to oxidative damage because of their elevated metabolic demands and lipid-rich membranes. Marine algal extracts provide robust antioxidant defence by directly scavenging free radicals, such as superoxide, hydroxyl, and peroxynitrite, while also enhancing endogenous antioxidant enzyme activity, including superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase. For example, fucoxanthin, a carotenoid derived from *Undaria pinnatifida*, has been shown to reduce lipid peroxidation, restore mitochondrial membrane potential, and maintain ATP production during oxidative stress–induced neuronal injury. Besides these direct effects, fucoxanthin modulates the Nrf2/ARE signaling pathway, which serves as a master regulator of cellular antioxidant responses. The activation of this pathway promotes the transcription of detoxifying enzymes and helps counter excessive reactive oxygen species (ROS) accumulation. This dual mechanism—direct radical scavenging combined with indirect gene regulation—positions algae-derived antioxidants as powerful neuroprotectants with significant potential for managing neurodegenerative disorders [78].

Integration of Green Chemistry and Sustainable Drug Development

The growing global interest in safer and more sustainable therapeutics has driven the pharmaceutical sector to adopt environmentally responsible practices in drug development (Table 7). Marine algae, due to their renewable availability and rich secondary metabolite content, are considered excellent resources for next-generation bioactives [79]. Traditional extraction and processing of marine compounds often involve toxic solvents, high energy consumption, and extensive waste generation, which contradicts the principles of sustainability [80]. Integrating green chemistry principles offers a practical solution, minimizing the ecological impact while ensuring economic viability and long-term material access [81].

Eco-friendly processing of marine bioresources

Greener extraction techniques, such as UAE, MAE, PLE, EAE, and SFE, operate under mild conditions to avoid hazardous solvents. Supercritical CO_2 extraction is an eco-friendly

process, offering a recyclable, non-toxic solvent system particularly suited for lipophilic marine neuroactives [81,82].

These methods are particularly effective for extracting heat-sensitive neuroprotectants, such as phlorotannins, fucoxanthin, and polysaccharides. For example, supercritical CO_2 is widely recognized as a safe, recyclable solvent that is ideal for the extraction of lipophilic compounds from species such as *Sargassum* [83]. Additionally, sustainable technologies allow for complete biomass utilization, converting residual algal material into products such as biofertilizers and bioplastics, thus contributing to a circular bioeconomy [84].

Life cycle assessment (LCA) and scalability

Life Cycle Assessment (LCA) is a systematic framework used to evaluate the environmental impact of a product or process across all stages, from raw material acquisition and production to distribution, use, and end-of-life disposal. In the context of marine-derived pharmaceuticals, LCA helps to identify hotspots of energy consumption, greenhouse gas emissions, water usage, and waste generation, enabling more informed decisions regarding sustainability improvements. Ensuring the environmental sustainability of marine-derived drugs requires a full assessment of the product life cycle from cultivation to packaging and disposal. Life Cycle Assessment (LCA) enables quantitative evaluation of energy input, emissions, and waste output throughout this chain [85].

Table 7. Comparative summary of green extraction techniques for marine algal neuroprotective compounds

Technique	Key Features	Advantages	Limitations	Neuroprotective Applications
UAE (Ultrasound-Assisted Extraction)	Uses ultrasonic waves to disrupt cell walls	Low cost, short extraction time, and high efficiency for heat-sensitive compounds	Limited penetration in dense matrices	Effective for phlorotannins, flavonoids, and polysaccharides with antioxidant and anti-inflammatory roles
MAE (Microwave-Assisted Extraction)	Microwaves enhance solvent penetration and heating	Rapid extraction, reduced solvent use, and high yield	Risk of compound degradation at high temperatures	Useful for polyphenols, pigments, and sterols improving cognition and neurotransmission
SFE (Supercritical Fluid Extraction)	Employs CO_2 under supercritical conditions	Eco-friendly, high purity, and selective extraction	High setup cost and limited solubility of polar compounds	Efficient recovery of lipids, carotenoids, and PUFAs for brain protection
PLE (Pressurized Liquid Extraction)	Uses solvents at high pressure and temperature	Fast, automated, efficient extraction with less solvent	Requires specialized equipment and risk of thermal degradation	Recovers polyphenols and polysaccharides for anti-neurodegenerative activity
EAE (Enzyme-Assisted Extraction)	Uses enzymes to break down cell walls	Mild, specific, eco-friendly, and enhances bioavailability	Costly enzymes and longer extraction time	Yields peptides, carrageenan derivatives, and flavonoids with neuroprotective and synaptic effects

Although systems such as open ponds and photobioreactors can capture CO_2 and use non-arable land, the use of fossil fuels and chemical-intensive harvesting may negate these benefits. Thus, integrating renewable energy systems, water recycling, and biodegradable materials into the process is essential for minimizing the total ecological footprint [86]. Scalability remains a challenge for green extraction. Many bench-scale techniques effective at bench scale encounter issues during industrial translation, such as cost, standardization, and batch consistency. Advances such as continuous-flow systems and integrated biorefineries may help bridge this gap, facilitating large-scale production of marine-derived therapeutics in line with green chemistry goals [87]. Both conventional vs green processing of marine bioresources are shown in Table 8.

Table 8. Conventional vs. green processing of marine bioresources

Parameter	Conventional Methods	Green Chemistry Methods
Solvents Used	Organic solvents (*e.g.,* hexane, methanol, and chloroform)	Supercritical CO_2, ethanol, water, and ionic liquids
Energy Requirements	High (reflux, Soxhlet, and long durations)	Low to moderate (UAE, MAE, and EAE need shorter time/heat)
Temperature Sensitivity	Often leads to degradation of thermolabile compounds	Operates at mild temperatures and preserving bioactives
Selectivity for Target Compounds	Low (co-extraction of impurities common)	High (*e.g.,* SFE tuned by pressure/temp. for lipophiles)
Environmental Impact	High – toxic waste generation and solvent loss	Low – recyclable solvents and minimal emissions
Scalability and Sustainability	Poor scalability and non-renewable inputs	Easily scalable with modular bioreactors and renewable energy
Waste Management	Hazardous waste disposal required	Often closed-loop systems or biodegradable waste
Compliance with Green Regulations	Requires remediation technologies	Supports eco-labeling, EHS compliance, and circular economy

Tabe 9. Regulatory and ethical guidelines

Guideline/Framework	Relevance to Green Drug Development
ICH Q8/Q11 (Quality by Design)	Encourages systematic development and design space incorporating eco-efficient parameters
ICH Q12 (Lifecycle Management)	Supports continuous process improvement and LCA integration
EMA Reflection Paper (2020)	Emphasizes use of greener solvents, cleaner manufacturing processes in APIs and excipients
FDA Green Chemistry Guidance (Draft)	Recommends minimizing solvent use, using renewable feedstocks, and reducing toxic intermediates
Nagoya Protocol (CBD-ABS)	Requires prior informed consent and fair benefit-sharing for marine genetic resources
REACH (EU Regulation)	Restricts use of hazardous chemicals; promotes safe use of marine-extracted substances
UN Sustainable Development Goals (SDG 12)	Advocates responsible consumption and production in pharmaceutical manufacturing

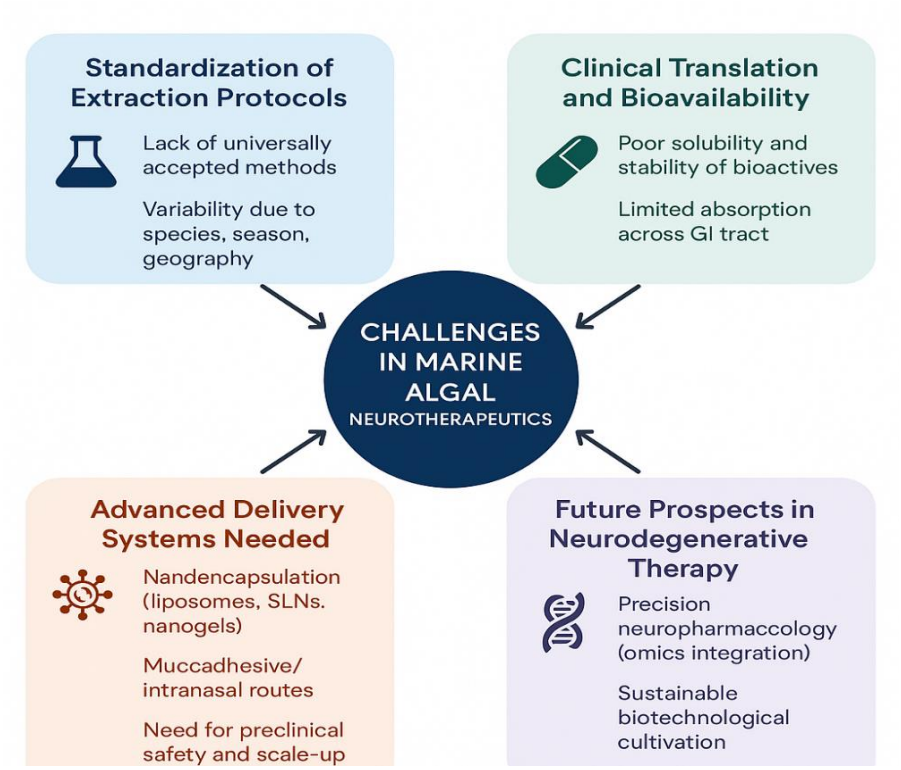


Figure 3. Graphical representation of key challenges in marine algal neurotherapeutics. The major barriers include the lack of standardized extraction protocols, poor bioavailability and limited clinical translation, the need for advanced drug delivery systems, and future prospects emphasizing precision neuropharmacology and sustainable biotechnological approaches

Regulatory and Ethical Considerations

Adopting sustainable drug manufacturing approaches must align with existing regulatory standards and ethical frameworks. Regulatory agencies such as the U.S. FDA and EMA encourage green innovations under programs such as Quality by Design (QbD) and ICH Q12, which advocate process control and risk mitigation [88]. Moreover, ethical sourcing is critical for marine resources (Table 9). Compliance with the Nagoya Protocol ensures fair benefit-sharing and biodiversity preservation, especially when marine genetic resources are commercialized [89].

Respect for indigenous knowledge and marine ecosystems must also be a part of sustainable drug development. Overharvesting marine algae can damage ecosystems; therefore, sourcing strategies should involve community partnerships and ecological restoration. Transparent practices, including eco-labelling and sustainability reporting, enable accountability and help establish trust between regulators and consumers [90,91].

Challenges and Future Directions

Although there is a growing body of evidence supporting the neuroprotective and therapeutic potential of marine algal compounds, there are still several challenges that hinder their clinical translation and commercial viability. Addressing these hurdles is vital for harnessing the full spectrum of marine bioactive compounds for the prevention and treatment of neurodegenerative disorders (Figure 3).

Conclusion

Marine algae have emerged as a sustainable source of neuroprotective compounds, with promising therapeutic potential. Efficient and environmentally conscious extraction methods are necessary for the fulfillment of this promise.Green extraction technologies such as SFE, UAE, and MAE represent a paradigm shift by enhancing yields, reducing solvent use, and preserving thermolabile bioactive compounds. Their integration with advanced delivery systems and sustainable processing strategies ensures that marine-derived therapeutics can be both effective and environmentally responsive; however, significant challenges remain, including the lack of standardized extraction protocols, low oral bioavailability, limited BBB penetration, and regulatory hurdles. The integration of advanced drug delivery systems, such as nanoparticles and transdermal systems, combined with omics-driven precision neuropharmacology can revolutionize the clinical application of marine bioactive materials. Additionally, aligning drug development strategies with environmental regulations, life cycle assessments, and ethical sourcing policies such as the Nagoya Protocol will ensure that marine-derived therapeutics are not only effective, but also sustainable. Thus, the future of neurodegenerative therapy lies in the successful convergence of marine biotechnology, green chemistry, and innovative pharmaceutical designs.

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Authors' Contributions

Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualization; Writing original draft; Writing review and editing by Soumya S. Dharan and Ronald Darwin C.

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