Exploring Marine Natural Products for Neuroprotection: A Multifaceted Approach to Combat Oxidative Stress and Neuroinflammation

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***Abstract*— Neurodegenerative diseases (NDs), such as Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis, represent a critical global health challenge characterized by progressive neuronal loss and cognitive decline. Central to their pathology are the intertwined mechanisms of neuroinflammation and oxidative stress, which exacerbate neuronal damage. This review explores the emerging potential of marine-derived natural products as neuroprotective agents targeting these processes. Marine ecosystems provide a rich repository of bioactive compounds, including polysaccharides, alkaloids, terpenoids, and polyphenols, which exhibit potent antioxidant and anti-inflammatory activities. Recent advancements in the pharmacological evaluation of these compounds demonstrate their ability to modulate key signaling pathways, enhance mitochondrial function, and mitigate apoptosis, positioning them as promising candidates for neurotherapeutic development. However, challenges related to bioavailability, blood-brain barrier penetration, and clinical translation persist. Innovative strategies, including advanced drug delivery systems and synthetic biology, offer promising solutions to these barriers. This review underscores the therapeutic promise of marine bioactives in addressing the unmet clinical needs of NDs while advocating for sustained interdisciplinary research efforts.**

***Index Terms*- Neurodegenerative diseases, marine-derived natural products, neuroinflammation, oxidative stress, Alzheimer's disease, Parkinson's disease, bioactive compounds, neuroprotection, antioxidant, anti-inflammatory.**

I. INTRODUCTION

Due to their progressive nature and lack of effective treatments, neurodegenerative diseases (NDs), such as amyotrophic lateral sclerosis (ALS), Parkinson's disease (PD), Alzheimer's disease (AD), and Huntington's disease (HD), pose a serious threat to global health [1]. These disorders have a complex etiology, with oxidative stress and neuroinflammation emerging as major contributors that worsen neuronal damage and hasten the course of the disease [2]. Prolonged activation of microglia and astrocytes causes neuroinflammation, which disrupts synaptic function and neuronal homeostasis by causing an excessive release of pro-inflammatory cytokines and neurotoxic mediators [3]. Concurrently, oxidative stress causes lipid peroxidation, DNA damage, and mitochondrial dysfunction in susceptible neuronal populations. Oxidative stress is characterized by an imbalance between the production of reactive oxygen species (ROS) and antioxidant defense mechanisms [4]. A vicious cycle that intensifies neurodegeneration is produced by these interconnected pathological processes, underscoring the critical need for therapeutic agents that can control both oxidative stress and neuroinflammation [5].

Marine ecosystems have drawn a lot of attention lately as a rich source of naturally occurring compounds that are both biologically active and structurally diverse, with potential neuroprotective benefits [6]. In preclinical models of neurodegeneration, marine-derived compounds such as polysaccharides, alkaloids, terpenoids, and polyphenols have shown strong antioxidant and anti-inflammatory properties, making them promising candidates for drug development [7]. Their distinct chemical structures, which are frequently different from those of terrestrial natural products, offer new modes of action that can be used to reduce oxidative damage and neuroinflammatory cascades [8].

The objective of this review is to thoroughly examine recent developments in the identification and pharmacological assessment of natural products derived from marine sources that target oxidative stress and neuroinflammation in neurodegenerative diseases. We hope to shed light on the potential of marine bioactives as next-generation neuroprotective agents by critically evaluating molecular mechanisms, therapeutic efficacy, and clinical translation challenges.

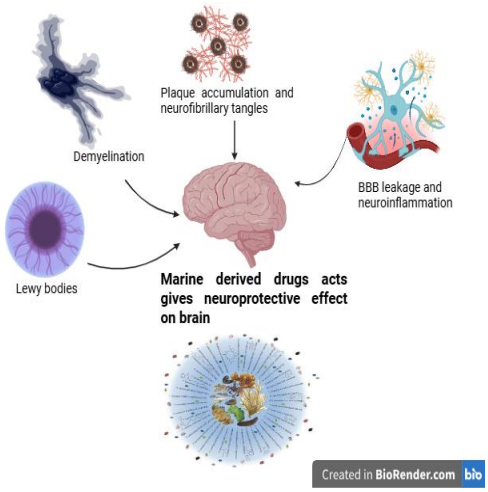

Fig. (1). Neuroprotective actions of marine-derived drugs against neurodegenerative pathologyMarine bioactives mitigate key hallmarks of neurodegeneration, including demyelination, Lewy body formation, plaque accumulation, neurofibrillary tangles, blood-brain barrier (BBB) leakage, and neuroinflammation, thereby exerting protective effects on the brain

II. MATERIALS AND METHODS

This review was conducted by employing a systematic and comprehensive literature search to identify, evaluate, and synthesize relevant studies focusing on the neuroprotective potential of marine-derived natural products in the context of neurodegenerative diseases (NDs). The review adhered to standard scientific reporting practices for narrative reviews in pharmacology.

A. Literature Search Strategy Scientific databases including PubMed, Scopus, Web of Science, and Google Scholar were extensively searched for peer-reviewed articles published between January 2022 and April 2025. The following keywords and Boolean operators were used: “marine-derived natural products”, “neuroprotection”, “oxidative stress”, “neuroinflammation”, “Alzheimer’s disease”, “Parkinson’s disease”, “marine bioactives”, “antioxidants”, “anti-inflammatory compounds”, and “mitochondrial dysfunction”. Filters were applied to include only English-language articles with accessible full texts.

B. Inclusion and Exclusion Criteria Articles were included if they met the following criteria:

Focused on marine organisms (algae, sponges, corals, marine microbes, etc.) and their bioactive compounds. Reported neuroprotective effects related to oxidative stress, neuroinflammation, apoptosis, or mitochondrial protection. Included in vitro, in vivo, or mechanistic studies, or high-quality reviews with relevant mechanistic insights. Published between 2022 and 2025.

C. *Data Extraction and Analysis*

The selected articles were screened for information pertaining to the molecular mechanisms, therapeutic efficacy, targeted pathways, and clinical potential of marine-derived compounds. Special emphasis was placed on:

Antioxidant and anti-inflammatory mechanisms (e.g., Nrf2, NF-κB, MAPK, PI3K/Akt pathways),
Neurotrophic support (e.g., BDNF, CREB),
Apoptosis modulation (e.g., Bcl-2, caspase signaling),
Mitochondrial protection and energy metabolism.

III. OXIDATIVE STRESS AND NEUROINFLAMMATION IN NEURODEGENERATIVE DISORDERS

In the central nervous system (CNS), neuroinflammation is a persistent immune response that is largely controlled by resident glial cells, such as astrocytes and microglia. Under typical physiological circumstances, microglia protects the CNS by monitoring its surroundings. However, in neurodegenerative diseases (NDs), these cells become pathologically activated in response to oxidative damage, neuronal debris, and misfolded proteins such as tau, α-synuclein, or amyloid-β. This shift toward a pro-inflammatory (M1) phenotype leads to the release of inflammatory mediators such as reactive oxygen/nitrogen species (ROS/RNS), interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) [9]. Astrocytes further amplify this response by increasing cytokine production, altering neurotransmitter regulation, and disrupting the blood-brain barrier (BBB), thereby allowing peripheral immune cells to infiltrate the CNS [10]. This chronic inflammatory state causes excitotoxicity, synaptic dysfunction, and reduced availability of neurotrophic factors, forming a feedback loop of glial activation and neuronal stress [11]. Eventually, this leads to apoptosis and progressive neuronal loss.

The activation of inflammasomes, particularly the NLRP3 complex, plays a central role in this process. It regulates the maturation of IL-1β and IL-18 and is crucial in neurodegenerative conditions like Parkinson's and Alzheimer's diseases [12].

A. *Relationship Between Oxidative Stress and Neuroinflammation*

Oxidative stress occurs when the production of ROS exceeds the capacity of the body's antioxidant defenses, which include enzymes like glutathione peroxidase, catalase, and superoxide dismutase (SOD). In neurodegenerative diseases, elevated oxidative stress is driven by chronic inflammation, mitochondrial dysfunction, and glutamate-induced excitotoxicity. These processes collectively increase ROS and RNS production, damaging proteins, lipids, and nucleic acids and disrupting neuronal homeostasis [13]. Protein oxidation alters enzymatic function and impairs signaling, while lipid peroxidation—one of the hallmarks of oxidative stress—compromises neuronal membrane integrity. Oxidative DNA damage contributes to genomic instability and impaired transcription, reducing neuronal repair and survival [14]. Moreover, ROS also act as signaling molecules that trigger further activation of microglia and astrocytes, reinforcing a cycle of neuroinflammation and oxidative stress [15]. Mitochondria are major intracellular sources of ROS. Damage to components of the electron transport chain leads to reduced ATP synthesis and increased electron leakage, thereby intensifying oxidative stress.

A. Pathways of Molecular Signaling

The development of neurodegenerative diseases is significantly influenced by cellular signaling pathways that mediate oxidative stress and neuroinflammation. One of the most crucial pathways is NF-κB (nuclear factor-kappa B**)**, which regulates the expression of various genes involved in inflammatory responses triggered by oxidative stimuli and pro-inflammatory cytokines [16].

Another important signaling system is the mitogen-activated protein kinase (MAPK) pathway, including the JNK and p38 subtypes. These are activated by stress signals and mediate cellular responses such as inflammation, apoptosis, and oxidative damage [17].

Among the antioxidant regulatory mechanisms, Nrf2 (nuclear factor erythroid 2-related factor 2**)** plays a central role. Under oxidative stress, Nrf2 detaches from its inhibitor Keap1, translocates to the nucleus, and binds to antioxidant response elements (ARE) to promote the expression of cytoprotective enzymes like HO-1, SOD, and GPx. However, in chronic neurodegeneration, Nrf2 activity is often impaired, compromising antioxidant defense mechanisms [18].

B. Therapeutic Consequences

The interplay between oxidative stress and neuroinflammation has encouraged the development of dual-action therapeutic agents. These include:

ROS scavengers
Nrf2 activators
NF-κB and inflammasome inhibitors
Microglial activation suppressors [19]

Marine-derived compounds offer distinct advantages due to their multifaceted activities. Their natural ability to modulate oxidative, inflammatory, apoptotic, and mitochondrial pathways places them at the forefront of emerging neuroprotective strategies [20].

IV. NATURAL PRODUCTS DERIVED FROM MARINE ENVIRONMENTS

Marine environments host a remarkable diversity of organisms that produce unique bioactive compounds with neuroprotective potential. These natural products can modulate oxidative stress, inflammation, mitochondrial function, and apoptotic pathways, making them strong candidates for therapeutic development in neurodegenerative diseases [21].

A. Marine Natural Product Sources

Marine organisms such as algae, sponges, corals, bacteria, fungi, and cyanobacteria are prolific producers of structurally diverse secondary metabolites with strong biological activity [21].

Marine Algae: Macro- and microalgae synthesize polysaccharides, carotenoids, and phenolic compounds with potent antioxidant and anti-inflammatory properties. For example, fucoidan, extracted from brown algae, is known to inhibit microglial activation and reduce pro-inflammatory cytokines [21].

Marine Sponges: These sessile invertebrates produce a wide range of terpenoids, peptides, and alkaloids that inhibit

inflammatory enzymes such as cyclooxygenase (COX) and lipoxygenase (LOX), key players in neuroinflammation [21].

*Marine Microorganisms***:** Bacteria and fungi from marine environments produce neuroprotective compounds such as polyketides and peptides. These compounds act via antioxidative and anti-inflammatory pathways [22].

B. Neuroprotective Properties of Marine Natural Products

Marine bioactives provide neuronal protection through several mechanisms, including antioxidant effects, anti-inflammatory modulation, mitochondrial support, and anti-apoptotic activity [23].

Effects of Antioxidants

Marine compounds can neutralize excess ROS and RNS. For instance, phenolic compounds such as phlorotannins from brown algae effectively scavenge free radicals and activate Nrf2 signaling to enhance endogenous antioxidant defense [23].

Inhibition of Inflammation

Several marine compounds inhibit the activation of microglia and astrocytes, thereby decreasing the release of TNF-α, IL-1β, and IL-6. Fucoxanthin, a carotenoid from microalgae, reduces neuroinflammatory signaling by downregulating the NF-κB pathway [24].

Neurotrophic and Anti-apoptotic Impacts: Marine peptides influence neuronal survival by modulating Bcl-2 family proteins and caspase pathways. They also enhance synaptic plasticity and regeneration by upregulating neurotrophic factors such as BDNF [25].

Protection of Mitochondria: Mitochondrial dysfunction is a hallmark of neurodegeneration. Sulfated polysaccharides from marine sources preserve mitochondrial membrane potential, reduce ROS production, and improve ATP synthesis [26].

V. UNDERSTANDING HOW MARINE-DERIVED NATURAL PRODUCTS PROTECT THE NERVOUS SYSTEM

Natural products from marine sources are increasingly recognized as promising candidates for neurotherapeutics due to their structural diversity and multifunctional biological activities. Their ability to simultaneously modulate multiple pathological mechanisms—including neuroinflammation, oxidative stress, mitochondrial dysfunction, and apoptosis—is central to their neuroprotective effects [6], [7].

A. Boosting Antioxidant Defense

One of the primary neuroprotective actions of marine compounds is their strong antioxidant capacity. Excess reactive oxygen species (ROS) damage neuronal lipids, proteins, and DNA, contributing to cell death. Compounds like fucoxanthin, phlorotannins, and sulfated polysaccharides act as free radical scavengers, reducing ROS levels and lipid peroxidation [5], [23].

Additionally, these marine bioactives activate **Nrf2**, a master regulator of the antioxidant response. Upon activation, Nrf2 translocates to the nucleus and promotes the transcription of detoxifying enzymes such as glutathione peroxidase (GPx), superoxide dismutase (SOD), and heme oxygenase-1 (HO-1) [4], [35].

B. Neuroinflammatory Pathway Modification

Chronic activation of astrocytes and microglia leads to excessive production of inflammatory cytokines and neurotoxic mediators. Marine natural products mitigate this by inhibiting key pro-inflammatory signaling pathways, particularly **N**F-κB and MAPK [3]. For instance, fucoxanthin and manoalide have been shown to suppress NF-κB nuclear translocation, thereby reducing TNF-α, IL-1β, and iNOS levels [2], [36]. This results in a dampened inflammatory response and reduced neuronal damage.

C. Mitochondrial Protection

Mitochondrial dysfunction, a key event in neurodegeneration, disrupts ATP production and increases ROS generation. Marine-derived polysaccharides help stabilize mitochondrial membrane potential, reduce ROS formation, and prevent cytochrome c release [4], [26].

By supporting mitochondrial integrity, these compounds enhance neuronal survival and maintain cellular energy metabolism.

D. Inhibition of Apoptosis

Apoptosis is a tightly regulated form of cell death implicated in neuronal loss during neurodegeneration. Marine bioactives can modulate this pathway by Inhibiting pro-apoptotic proteins (e.g., Bax, caspase-3), Enhancing anti-apoptotic proteins (e.g., Bcl-2) [5], [25]. Peptides from marine sponges have demonstrated the ability to suppress caspase-3 activity and preserve neuronal function in oxidative stress models [8].

E. Enhancement of Synaptic Plasticity and Neurotrophic Factors

Marine compounds can improve synaptic function by upregulating neurotrophic factors like BDNF and NGF**,** which are essential for neuronal growth, survival, and synaptic plasticity [6]. Improved BDNF signaling can promote neurogenesis and circuit repair, critical for slowing or reversing the progression of cognitive decline in disorders such as Alzheimer's and Parkinson's disease.

VI. DISCUSSION

Marine-derived natural products have emerged as potent multi-target agents for the treatment of neurodegenerative diseases (NDs), largely due to their ability to address two core pathological features: oxidative stress and neuroinflammation. The compounds highlighted in this review—including fucoidan**,** fucoxanthin**,** phlorotannins**,** and marine peptides—have demonstrated mechanisms that involve: Activation of antioxidant pathways (e.g., Nrf2/HO-1**).** Inhibition of inflammatory cascades (e.g., NF-κB**,** MAPK). Stabilization of mitochondria and enhancement of ATP production, Modulation of apoptotic signals such as Bcl-2 and caspase-3
Promotion of neurotrophic signaling via BDNF**,** NGF, and CREB [6], [19], [25], [35]. While the preclinical data is encouraging, clinical translation faces challenges: Poor pharmacokinetic properties (e.g., low bioavailability and poor BBB penetration). Difficulty in synthetic replication, Environmental sustainability concerns. However, innovative technologies such as nanoparticle-based drug delivery**,** PEGylation**,** and synthetic biology offer solutions that can enhance drug-like properties and ensure sustainable sourcing [31], [32], [33]. Furthermore, marine natural products have shown the ability not only to delay disease progression but also to modify the disease course. By restoring redox balance, protecting mitochondrial integrity, reducing inflammation, and preserving synaptic function, they demonstrate potential as disease-modifying therapeutics rather than symptomatic agents alone. Moving forward, rigorous pharmacokinetic studies**,** toxicity profiling**,** and well-designed clinical trials are essential to validate the efficacy and safety of these compounds in humans. The convergence of disciplines—including marine biology, neuropharmacology, medicinal chemistry, and nanotechnology—will be critical to unlocking the full therapeutic potential of the sea.

VII. CONCLUSION

Marine-derived natural products represent a promising and versatile class of bioactive compounds with strong neuroprotective potential in combating neurodegenerative diseases characterized by oxidative stress and neuroinflammation. Their ability to simultaneously: Scavenge reactive oxygen species, Activate endogenous antioxidant pathways (e.g., Nrf2/HO-1), Suppress pro-inflammatory signaling (e.g., NF-κB, MAPK), Stabilize mitochondria, and Inhibit apoptotic cascades, demonstrates their multifaceted mechanism of action [6], [7], [35], [38].
Despite compelling preclinical evidence, the journey from bench to bedside remains constrained by challenges related to bioavailability, BBB permeability, pharmacokinetics, and manufacturing scalability. Recent advances in drug delivery technologies, synthetic biology, and formulation **science** offer strategic pathways to overcome these hurdles [31], [32], [33]. Future success lies in integrating interdisciplinary research to validate the clinical efficacy and safety of these compounds. If realized, marine bioactives could offer next-generation therapeutics to delay or prevent neurodegeneration and improve the quality of life for millions affected by these disorders.

LIST OF ABBREVIATIONS

- **AD**: Alzheimer's Disease

ALS: Amyotrophic Lateral Sclerosis
ATP: Adenosine Triphosphate
BDNF: Brain-Derived Neurotrophic Factor
BBB: Blood-Brain Barrier
CNS: Central Nervous System
CREB: cAMP Response Element-Binding Protein
HO-1: Heme Oxygenase-1
IL-1β/IL-6: Interleukin-1 Beta / Interleukin-6

MAPK: Mitogen-Activated Protein Kinase
NDs: Neurodegenerative Diseases
NF-κB: Nuclear Factor Kappa-light-chain-enhancer of Activated B cells
NGF: Nerve Growth Factor
Nrf2: Nuclear Factor Erythroid 2–Related Factor 2
PD: Parkinson's Disease
ROS/RNS: Reactive Oxygen/Nitrogen Species
SOD: Superoxide Dismutase
TNF-α: Tumor Necrosis Factor-alpha

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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