

REVIEW ARTICLE

Marine-derived bioactives as immunomodulators: Potential applications in food and health

Gulsun Akdemir Evrendilek*

University of Maine Cooperative Extension, Orono, Maine, United States of America

Abstract

Marine ecosystems are prolific sources of structurally diverse bioactives—including polysaccharides (e.g., alginate, fucoidan, laminarin, and carrageenan), peptides/proteins, ω -3 long-chain polyunsaturated fatty acids, carotenoids (e.g., astaxanthin and fucoxanthin), steroids, macrolides, and alkaloids—that modulate innate and adaptive immunity through convergent pathways. Evidence across algae, fish, shellfish, microbes, and sponges shows these molecules regulate toll-like receptor signaling, nuclear factor κ B/mitogen-activated protein kinase axes, cyclooxygenase/lipoxygenase-derived eicosanoids, complement activation, and redox tone; rebalance cytokine profiles ($\downarrow$ tumor necrosis factor- α /interleukin (IL)-1 β /IL-6; $\uparrow$ IL-10); and influence effector functions of macrophages, natural killer and T cells. Marine peptides and protein hydrolysates, often generated through enzymatic hydrolysis or fermentation and purified by membrane fractionation and chromatography, display antioxidant, antimicrobial, antihypertensive, antihyperlipidemic, anti-inflammatory, immunostimulatory, and anticancer activities *in vitro* and *in vivo*. Polysaccharide structure (e.g., molecular weight, linkage, and sulfation) and peptide sequence/composition drive bioactivity, whereas ω -3-derived specialized pro-resolving mediators contribute to inflammation resolution. Beyond direct immune effects, several marine bioactives exert prebiotic-like actions that reshape gut microbiota and mucosal defenses. Advances in extraction, stabilization, and delivery are accelerating incorporation into functional foods, nutraceuticals, cosmeceuticals, and medical nutrition. Key translation barriers remain—heterogeneity of sources, batch-to-batch variability, processing stability, bioavailability and pharmacokinetics, allergenicity, and limited standardized immune endpoints and human trials. This review synthesizes mechanistic and application-oriented evidence for marine-derived immunomodulators, outlines safety and regulatory considerations, and prioritizes research needed to enable evidence-based deployment in food and health.

Keywords: Marine bioactives; Immunomodulation; Polysaccharides; Peptides; ω -3 polyunsaturated fatty acids; Carotenoids; Functional foods; Nutraceuticals

***Corresponding author:**
Gulsun Akdemir Evrendilek
(gulsun.akdemir@maine.edu)

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1. Introduction

Marine ecosystems represent an abundant and diverse reservoir of biologically active compounds with significant potential to improve human health. These

molecules—including polysaccharides, peptides, proteins, ω -3 fatty acids, pigments, and phenolic constituents—function as natural bioactives with roles in disease prevention, immune support, and overall well-being (Figure 1). As a result, interest in identifying, characterizing, and incorporating marine-derived compounds into functional foods, nutraceuticals, pharmaceuticals, and dietary supplements has grown steadily.^{1–4} The demand for seafood and marine-origin products continues to rise in parallel with evidence linking marine bioactives to reduced chronic disease risk and enhanced general health.^{3,4}

Oceans cover more than 70% of the Earth's surface and harbor extraordinary biological and chemical diversity. Marine organisms have evolved unique secondary metabolites that allow them to communicate, defend themselves, and adapt to complex ecological gradients shaped by salinity, temperature, currents, and light availability.^{5–9} These structural and functional distinctions make marine bioactives particularly promising as innovative therapeutic leads. Marine animals, plants, algae, and microorganisms produce a wide spectrum of metabolites, including polyunsaturated fatty acids (PUFAs), polysaccharides, peptides, enzymes, pigments, and trace minerals, each contributing distinct biological properties.^{2,4,10}

Marine-derived bioactives have gained increasing attention for their capacity to modulate immune responses, with relevance to inflammation, infection, allergy, and cancer.^{11–15} The human immune system integrates signals from both biotic and abiotic sources, and dysregulation can lead to chronic inflammation, autoimmunity, and disease progression.^{5,16–18} Before activation of cellular immune mechanisms, however, the body relies on physical and

chemical barriers—particularly the multilayered epithelia of the skin and the mucous membranes of the respiratory, gastrointestinal, and urogenital tracts—which constitute the true first line of defense.^{18,19} Only when these barriers are breached do innate immune cells, such as natural killer (NK) cells, neutrophils, and macrophages, become activated to eliminate invading pathogens and coordinate adaptive immunity.⁵

Marine processing by-products—including heads, skins, viscera, and bones—represent more than half of the total seafood biomass and remain underutilized despite being rich in high-value compounds such as PUFAs, phenolics, proteins, and peptides.^{16,17} These bioactive components exhibit diverse functionalities, including antioxidant, anti-inflammatory, antihypertensive, antidiabetic, antimicrobial, anticancer, and wound-healing effects, supporting their application as multifunctional ingredients in the food and health industries.¹⁸

Despite the abundance of promising marine bioactives, significant challenges remain for commercialization. Standardized analytical protocols, sensory evaluation, stability assessment, toxicological characterization, and well-designed clinical trials are necessary to support health claims and ensure product safety. Current gaps in efficacy and safety data have contributed to the underutilization of marine resources.^{20–22}

An additional consideration is the presence of naturally occurring marine toxins. Harmful algal blooms (HABs), which are increasing in frequency and severity due to climate change and nutrient enrichment, produce potent biotoxins such as domoic acid, saxitoxins, brevetoxins, okadaic acid, azaspiracids, and ciguatoxins.²³ Among these, domoic acid, produced by *Pseudo-nitzschia* spp.,

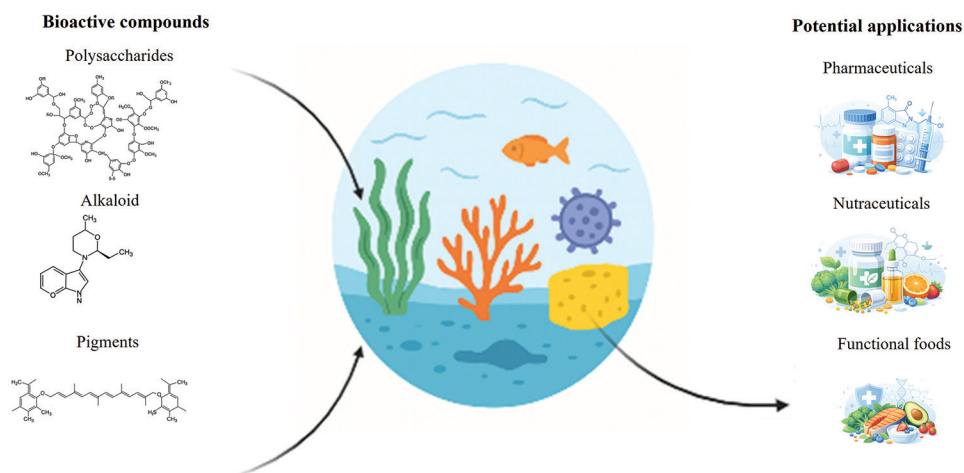


Figure 1. Marine bioactives and their potential applications. Created with BioRender.com. Akdemir Evrendilek, G. (2025) <https://app.biorender.com/profile/template/details/t-693113fc98801763f1db0c08-marine-bioactives>

is associated with amnesic shellfish poisoning and has well-documented neurotoxic and immunotoxic effects in humans and marine wildlife.²⁴ Marine heatwaves and altered upwelling patterns have intensified domoic acid events and increased contamination risks in coastal fisheries.^{25,26} Chronic exposure has been linked to cognitive impairment, endocrine disruption, and neurological damage.^{24,25} Widespread morbidity in sea lions, dolphins, whales, and seabirds further highlights the ecological and public health relevance of HAB toxins.^{24,25} Newly emerging toxins—including pinnatoxins, palytoxins, cyclic imines, and novel ciguatoxins—complicate monitoring and risk assessment, as some species produce multiple toxin classes simultaneously.^{27–30} Ensuring the safety of marine-derived functional ingredients, therefore, requires robust monitoring and regulatory oversight throughout harvesting and processing.

Collectively, marine ecosystems provide a vast chemical repertoire with applications in food, health, and therapeutic innovation. However, translational progress depends on overcoming challenges related to safety, standardization, bioavailability, and clinical validation. This review synthesizes current evidence on marine-derived bioactive compounds, their biological activities, and their potential applications in the food and health sectors, while outlining the barriers that must be addressed for successful development and commercialization.

2. Marine bioactives

Marine ecosystems are among the most abundant and diverse reservoirs of bioactive compounds, offering remarkable potential for applications in human health, nutrition, and various industries. A wide range of marine organisms—including algae, sponges, corals, bacteria, and fungi—synthesize unique secondary metabolites that enable them to adapt and thrive in complex, highly competitive, and constantly changing environmental conditions. These bioactives—ranging from polysaccharides, peptides, lipids, and pigments to novel small molecules—exhibit remarkable antioxidant, antimicrobial, antiviral, anticancer, and anti-inflammatory properties (Figure 2). As interest in natural and sustainable resources grows, marine bioactives are increasingly recognized as valuable ingredients in pharmaceuticals, nutraceuticals, cosmeceuticals, and functional foods, highlighting the ocean's untapped potential as a reservoir for innovation.^{1,31,32}

2.1. Antioxidant agents

Current dietary recommendations for preventing chronic diseases such as cancer and coronary heart disease emphasize consuming more fruits and vegetables, as they

are rich in antioxidants. These foods also have a variety of antiatherogenic properties.^{33–36} Carotenoids, a specific type of antioxidant, do more than protect cells from oxidative damage; they also help regulate gene expression and facilitate communication between cells.³⁷

Carotenoids are widely distributed across nature, occurring in plants, algae, and various microorganisms. These compounds possess the ability to bind heavy metals and other toxic elements, such as arsenic, thereby reducing their accumulation within the human body.^{38,39} Because humans and other animals are unable to synthesize carotenoids endogenously, they must obtain them through dietary intake. Structurally, carotenoids are divided into two major classes: Carotenes and xanthophylls.⁴⁰ Among marine-derived carotenoids, astaxanthin and fucoxanthin stand out for their strong antioxidant activities, primarily through mechanisms involving free radical scavenging and singlet oxygen quenching.^{41,42}

2.2. Astaxanthin

Astaxanthin is a primary marine carotenoid pigment structurally similar to other well-known carotenoids, including β -carotene, zeaxanthin, and lutein. It is naturally produced by several microalgae species—most notably the green alga *Haematococcus pluvialis*, which serves as one of the richest biological sources. This pigment also accumulates through the food chain in a variety of marine organisms, such as salmon, trout, shrimp, and lobster, as well as fish roe, contributing to their characteristic reddish-orange coloration.⁴³

Compared to other carotenoids, astaxanthin possesses two additional oxygenated groups on each of its ring structures, which account for its superior antioxidant activity (Figure 3). Several studies have demonstrated that astaxanthin has even more potent free-radical scavenging and antioxidant properties than vitamin E and β -carotene.⁴⁴ Astaxanthin exhibits a wide range of important biological functions, including protection against ultraviolet radiation, oxidative stress, inflammation, and various age-related conditions. It also plays a role in strengthening immune activity within vital organs such as the liver, kidneys, heart, eyes, and joints. In addition, astaxanthin contributes to prostate health and protects membranous phospholipids and other lipids from oxidative degradation through its strong antioxidant capacity.⁴⁵ Furthermore, it has been associated with the modulation of inflammatory responses, emphasizing its therapeutic relevance in promoting overall health and disease prevention.⁴⁶

Clinical investigations have demonstrated that astaxanthin supplementation can lower biomarkers of oxidative stress and inflammation associated with

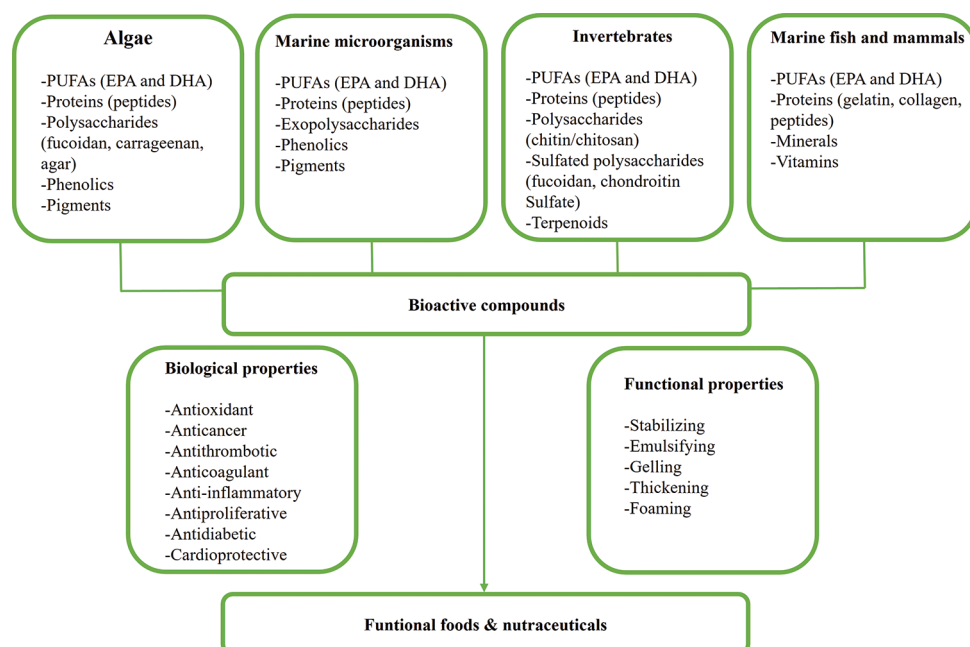


Figure 2. Sources and functional roles of marine-derived bioactive compounds in health and food applications. Modified from Senadheera *et al.*¹ Abbreviations: DHA: Docosahexaenoic acid; EPA: Eicosapentaenoic acid; PUFA: Polyunsaturated fatty acid.

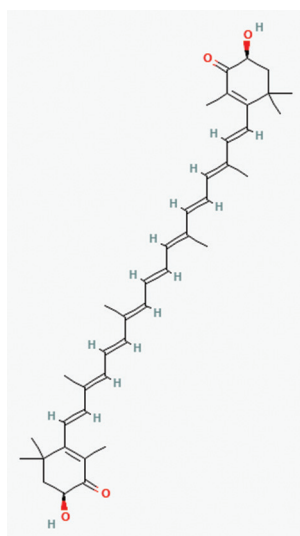


Figure 3. Chemical structure of astaxanthin. The chemical structure was retrieved from PubChem (CID: 5281224).⁴⁷

cardiovascular risk, while simultaneously enhancing overall blood parameters and circulatory health.^{48,49} Owing to its strong antioxidant capacity and ability to stabilize and protect cellular membranes, astaxanthin holds considerable promise in the prevention and management of numerous chronic inflammatory disorders, including cancer, metabolic syndrome, arthritis, diabetes, diabetic nephropathy, and neurodegenerative diseases.⁵⁰ Consequently, regular consumption of astaxanthin may confer broad health benefits, supporting not only

cardiovascular function but also offering protection against other inflammation-related conditions, thereby representing a valuable approach to overall health maintenance and disease prevention.^{51,52}

2.3. Fucoxanthin

Fucoxanthin (Figure 4) is a brown pigment from the xanthophyll class that exhibits antioxidant properties, especially in low-oxygen conditions where other carotenoids are less effective. It functions by donating electrons to quench free radicals.^{53,54} During regular metabolic activity, the body produces heat through thermogenesis. Fucoxanthin has been shown to modulate key enzymes associated with lipid metabolism, thereby promoting enhanced energy expenditure through the breakdown of fat stores.⁵⁵

Fucoxanthin functions as a potent antioxidant that helps protect cells against oxidative damage and provides a wide range of additional health benefits. Reported effects include enhancement of cardiovascular function, reduction of inflammation, lowering of cholesterol and triglyceride (TAG) concentrations, regulation of blood pressure, and promotion of optimal liver health.⁵⁶⁻⁵⁸ Further well-designed clinical studies are necessary to fully elucidate the therapeutic efficacy of marine carotenoids—particularly astaxanthin and fucoxanthin—not only in maintaining vascular health but also in supporting cartilage integrity and joint function in individuals at risk for or suffering from osteoarthritis.

3. Cyclooxygenase (COX) inhibitors

COX inhibitors comprise a group of compounds that suppress the activity of COX enzymes, which are responsible for catalyzing the conversion of arachidonic acid into prostaglandins—lipid mediators that regulate inflammation, pain, fever, and numerous physiological functions. Two major isoforms of these enzymes are recognized: COX-1, which is constitutively expressed and contributes to normal physiological processes such as gastric mucosal protection and platelet aggregation, and COX-2, which is inducible and predominantly associated with inflammatory pathways. Both non-steroidal anti-inflammatory drugs (NSAIDs) and selective COX-2 inhibitors act by targeting these enzymes to alleviate inflammation, reduce pain, and mitigate risks associated with chronic inflammatory diseases, including cardiovascular and neurodegenerative conditions. In this context, marine-derived bioactive compounds exhibiting COX-inhibitory activity have attracted increasing attention as potential natural alternatives to synthetic drugs, offering comparable efficacy with potentially reduced adverse effects.^{60,61}

3.1. Pacifenol

Pacifenol (Figure 5) is a halogenated sesquiterpenoid first isolated in 1971 from the red marine alga *Laurencia claviformis* (Rhodomelaceae) collected in Easter Island, with its chemical structure elucidated through crystallographic and chemical analyses.⁶² Its biosynthetic precursor, prepacifenol, was initially discovered in the Australian red alga *Laurencia filiformis* but later identified in *Laurencia tasmanica* as well.⁶³ Pacifenol represents the earliest reported example of a naturally occurring algal metabolite containing both bromine and chlorine atoms covalently bound.⁶⁴ Interestingly, these compounds are not restricted to algae; they have also been detected in marine invertebrates, such as the digestive system of the

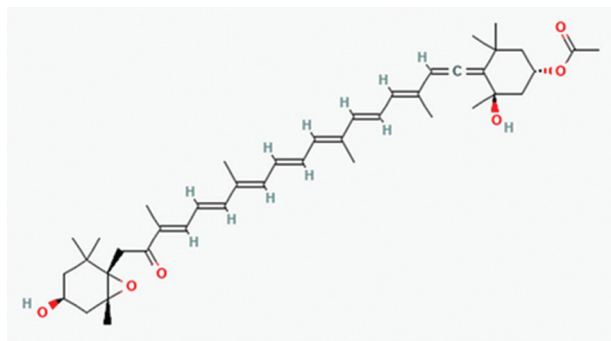


Figure 4. Chemical structure of fucoxanthin. The chemical structure was retrieved from PubChem (CID: 5281239).⁵⁹

sea hare *Aplysia californica*.⁶⁵ Beyond its ecological role, pacifenol and its derivatives exhibit notable antimicrobial activity, particularly against *Streptococcus enteritidis* and *Pseudomonas aeruginosa*.

From a pharmacological perspective, pacifenol is known to reduce leukotriene B4 (LTB4) and thromboxane B2 (TXB2) production, suppress degranulation responses, and inhibit phospholipase A2—thereby modulating the COX pathway.⁶⁶ These actions underpin its anti-inflammatory and anti-allergic effects, highlighting its potential for managing inflammatory and allergic disorders.

3.2. Stypotriol triacetate

Stypotriol triacetate (Figure 6), another polycyclic meroditerpenoid, was isolated from *Stypopodium flabelliforme*.⁶⁸ Its full stereochemical configuration has only recently been resolved.⁶⁹ Due to its instability in air, it must be acetylated during extraction to prevent oxidative degradation before biological testing.⁷⁰ This compound has demonstrated both antifeedant and anti-inflammatory activities.⁷¹ Mechanistically, it inhibits inflammation by reducing elastase release, suppressing phospholipase A2 activity, and decreasing eicosanoid secretion, thus modulating the COX pathway.⁷² These actions are particularly relevant for conditions such as rheumatoid arthritis (RA), where elastase-driven cartilage degradation contributes to joint damage and pain. Stypotriol also shows broad-spectrum antibacterial activity against Gram-positive and Gram-negative species,⁷³ as well as cytotoxic and antiproliferative effects, with significant inhibitory activity against colorectal adenocarcinoma and rat basophilic leukemia cell lines.⁷⁴ Among the meroditerpenoids studied, stypotriol displayed the strongest cytotoxic effects in a dose-dependent manner,

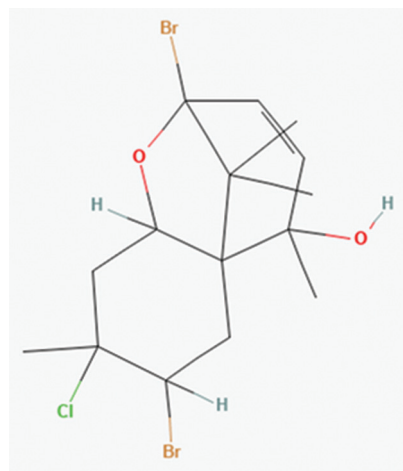


Figure 5. Chemical structure of pacifenol. The chemical structure was retrieved from PubChem (CID: 122808).⁶⁷

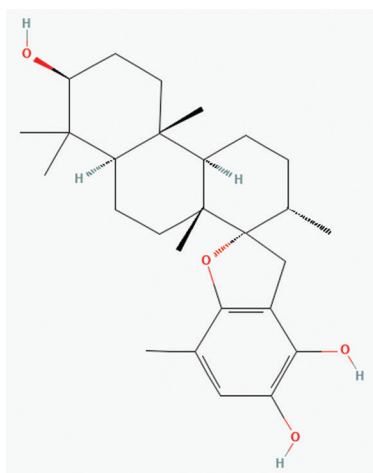


Figure 6. Chemical structure of stypotriol triacetate. The chemical structure was retrieved from PubChem (CID: 23424859).⁷⁶

followed by epitaondiol.⁷⁵

3.3. Epitaondiol

Epitaondiol (Figure 7) is a meroditerpenoid compound isolated from the brown seaweed *S. flabelliforme*, a tropical marine alga commonly found in the coastal waters surrounding Easter Island.⁶⁶ Members of this genus are rich in polycyclic meroditerpenoids with diverse biological activities.⁷⁷ Epitaondiol diacetate has demonstrated cardiovascular effects in rats, producing negative inotropic and chronotropic actions,⁷⁸ while also showing strong anti-inflammatory activity through inhibition of eicosanoid (LTB₄ and TXB₂) release and phospholipase A₂ activity, which reduces arachidonic acid release and subsequent lipid mediator production.⁷² Remarkably, its anti-inflammatory efficacy exceeds that of indomethacin.⁷⁹ Beyond its anti-inflammatory profile, epitaondiol isolated from the Brazilian brown alga *Styopodium zonale* has been shown to possess potent *in vitro* antiviral activity against herpes simplex virus type 1 (HSV-1).⁸⁰ In addition, epitaondiol exhibits gastroprotective effects in murine models, comparable to lansoprazole, by reducing gastric lesions.⁷⁸ This dual functionality—combining anti-inflammatory and gastroprotective effects—positions epitaondiol as a promising therapeutic candidate compared with conventional anti-inflammatory agents, which are frequently linked to gastrointestinal adverse effects. In addition to these properties, epitaondiol has demonstrated notable antimicrobial efficacy against both Gram-positive and Gram-negative bacteria, particularly *Enterococcus faecalis*.⁷³ Furthermore, it exhibits antiviral activity against herpes simplex virus⁶¹ and antiproliferative potential in various cancer cell lines, including human colorectal adenocarcinoma and neuroblastoma.^{57,61} Its derivative, 2 β -3 α -epitaondiol, also demonstrated sodium channel-

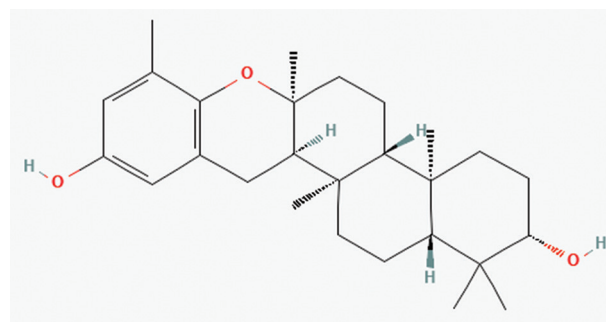


Figure 7. Chemical structure of epitaondiol. The chemical structure was retrieved from PubChem (CID: 156834).⁸³

blocking activity and cytotoxicity against human lung cancer cells,⁸¹ whereas isoeptaondiol showed a radical-scavenging capacity stronger than that of ascorbic acid.⁸² These findings suggest that epitaondiol and its analogs hold promise in targeting both inflammation and oxidative stress, two hallmarks of chronic inflammatory diseases.

4. Marine steroids

Steroidal drugs are well-established in clinical practice and are commonly prescribed for the management of asthma, RA, psoriasis, and numerous inflammatory conditions.⁸⁴ Their therapeutic effects are mainly due to their ability to suppress inflammatory pathways and modulate immune activity, leading to relief of symptoms such as joint pain and stiffness, respiratory distress, skin lesions, and other inflammation-associated manifestations. While most steroids in use today are synthetic, marine organisms—particularly sponges—have emerged as a valuable natural reservoir of structurally unique steroids with potent anti-inflammatory potential.^{33,84,85}

4.1. Clathriols

Clathriols A and B are uncommon polyoxygenated steroidal compounds that have been isolated from the marine sponge *Clathria lissosclera*, which inhabits the coastal waters of New Zealand.⁸⁶ Their structural hallmark is the uncommon 14- β stereochemistry, a feature typical of sponge-derived steroids. While structurally related to contignasterol, clathriols exhibit comparatively weaker inhibition of histamine release.⁸⁷ Nevertheless, both compounds display notable biological activity as moderate anti-allergic and anti-inflammatory agents. In particular, clathriol B has been studied for its capacity to suppress superoxide production in human peripheral blood neutrophils,⁷⁰ an effect relevant to the pathology of chronic inflammatory and degenerative diseases.^{86,88,89} Although their potency is lower than that of contignasterol, clathriols exhibit noteworthy antioxidant and anti-inflammatory activities, making them valuable candidates for further

investigation, particularly for addressing inflammation and oxidative stress associated with chronic diseases.³³

4.2. Xestobergsterol

Xestobergsterol is a pentacyclic, polyhydroxylated steroid that was first isolated in 1992 from the Okinawan marine sponge *Xestospongia bergquistia*.⁹⁰ This compound exhibits strong inhibitory activity against immunoglobulin E (IgE)-mediated histamine release from mast cells,⁹¹ demonstrating greater potency than the clinically used antiallergic drug disodium cromoglicate.⁹² Mechanistically, xestobergsterol A interferes with intracellular signaling by preventing the formation of inositol triphosphate (IP₃) and inhibiting phospholipase C activity, which in turn restricts Ca²⁺ mobilization from internal stores—an essential event in IgE-dependent mediator release.^{33,93}

Due to these mechanisms, xestobergsterol is being explored as a candidate anti-asthma agent with strong pharmacological promise, and synthetic studies have been carried out on its analogs to enhance bioactivity and stability.⁹⁴ Its potent immune-modulatory action places it among the most interesting natural steroid leads for allergy and inflammation control.⁸⁷

4.3. Contignasterol

Contignasterol is a naturally occurring polyoxygenated steroid that was initially isolated from the marine sponge *Petrosia contignata*, which was collected from the coastal waters of Papua New Guinea.⁹⁵ Unlike classical steroids, contignasterol possesses an unusual side chain and a distinctive arrangement of functional groups, making it chemically novel within the steroid class.⁹² Early studies highlighted its therapeutic potential in asthma and other inflammatory diseases.⁸⁷ Functionally, it prevents histamine release from basophils and lung tissue and reduces histamine-induced contraction, potentially through modulation of intracellular signaling and inhibition of phospholipase C activity.⁹³ This action effectively protects against bronchoconstriction.⁷⁰

Beyond respiratory conditions, contignasterol also demonstrated the ability to inhibit platelet aggregation triggered by platelet-activating factor and collagen. This suggests a potential role as an antithrombotic compound. Because of these properties, contignasterol has been proposed as a multifunctional pharmacological agent with applications in cardiovascular disorders, allergic diseases (e.g., asthma, allergic rhinitis, and psoriasis), osteoarthritis, and systemic inflammatory conditions.^{33,96–98}

5. Marine macrolides

The marine environment serves as a prolific reservoir of structurally diverse natural products, among which

macrolides are particularly distinguished for their intricate molecular architecture and potent biological activities. Characterized by a large macrocyclic lactone ring decorated with multiple oxygenated and functional groups, these compounds exhibit remarkable chemical versatility and pharmacological promise. The exploration of marine macrolides began with the discovery of aplysiatoxins—bioactive metabolites isolated in 1974 from the sea hare *Stylocheilus longicauda*. Since then, the structural and functional diversity within this class has expanded substantially, with more than 200 macrolides identified to date, drawing significant attention for their potential therapeutic applications.^{99,100}

The therapeutic significance of marine-derived macrolides lies in their capacity to modulate key cellular mechanisms. Among their most extensively studied properties are their antiproliferative and cytotoxic effects, which are mediated through interactions with multiple molecular targets. This broad spectrum of activity positions marine macrolides as highly promising candidates for the development of novel anticancer agents.^{101,102} Beyond oncology, their immunomodulatory and anti-inflammatory properties are increasingly recognized for applications in treating chronic inflammatory and autoimmune diseases (Table 1).

Contemporary research is pushing the boundaries of marine macrolide applications. While compounds such as dolastatin 19 have shown promise in targeting specific cancer cell lines,¹⁰³ recent efforts are focused on overcoming the challenges of natural product development, such as supply and toxicity. Semisynthetic derivatives of potent macrolides are being engineered to enhance efficacy and reduce side-effect profiles. For example, research into the lobophorin scaffold aims to decouple its potent anti-inflammatory activity from its cytotoxicity, a key step for rheumatologic drug development.¹⁰⁴

Furthermore, the field is being revolutionized by biosynthetic insights. The identification and manipulation of polyketide synthase gene clusters responsible for macrolide production in marine bacteria now allow for the generation of novel “unnatural” natural products through metabolic engineering and combinatorial biosynthesis.^{110,111} This approach provides a sustainable solution to the supply problem and opens up a vast chemical space for discovering new drug candidates.¹¹¹

Marine macrolides offer a rich and structurally unique pharmacopeia. Their demonstrated efficacy as cytotoxic, immunosuppressant, and anti-inflammatory agents underscores their potential not just as anticancer agents but also as transformative therapies for inflammatory and immune-mediated diseases. The convergence of traditional

Table 1. Selected marine macrolides, their mechanisms of action, and biological activities

Compound/class (with source organism)	Primary mechanism of action	Key biological activities
Latrunculins A & B (From the Red Sea sponge <i>Latrunculia magnifica</i>)	Disruption of actin polymerization and microfilament organization ¹⁰²	Antiproliferative effects, cytoskeletal disruption
Sphinxolides (from the New Caledonian sponge <i>Neosiphonia superstes</i>) and scytophycins (from the cyanobacterium <i>Scytonema pseudohofmanni</i>)	Binding to actin filaments and inhibiting their polymerization ¹⁰⁵⁻¹⁰⁷	Potent cytotoxicity and inhibition of proliferation in human cancer cell lines
Lobophorins A & B (from marine actinomycetes associated with the brown alga <i>Lobophora variegata</i>)	Multitarget; potent inhibition of key inflammatory pathways ¹⁰⁸	Antibiotic, anticancer, and significant anti-inflammatory properties (exceeding indomethacin in some assays)
Aplyronines (from the sea hare <i>Aplysia kurodai</i>) ¹⁰⁹ and dolastatin 19 (from the sea hare <i>Dolabella auricularia</i>) ¹⁰³	Interaction with tubulin and inhibition of microtubule assembly	Strong antiproliferative activity, notably in breast and colon cancer cell lines

natural product chemistry with modern synthetic and biosynthetic techniques is poised to unlock the full clinical potential of these remarkable marine molecules.

6. Molecules interfering with nuclear factor (NF- κ B)

The NF- κ B signaling pathway plays a central role in inflammation, immune regulation, and cancer progression. Consequently, natural products that can interfere with NF- κ B activation are of considerable interest as potential anti-inflammatory, immunosuppressive, and anticancer agents. Several marine-derived compounds have shown promising activity in this regard.

6.1. Hymenialdisine

Hymenialdisine (Figure 8) is a marine-derived alkaloid first isolated from sponges such as *Acanthella aurantiaca* and *Stylissa massa*.¹¹² This compound has been extensively investigated for its potent anti-inflammatory activity, particularly its capacity to inhibit NF- κ B signaling and suppress the expression of key pro-inflammatory cytokines, including interleukin (IL)-8, IL-2, and tumor necrosis factor- α (TNF- α). Mechanistically, hymenialdisine acts as a competitive ATP inhibitor targeting several kinases involved in cell cycle regulation, such as glycogen synthase kinase-3 β (GSK-3 β), cyclin-dependent kinases (CDKs), and casein kinase 1 (CK1).¹¹³ By modulating these signaling pathways, hymenialdisine also reduces tau protein phosphorylation—an event associated with Alzheimer's pathology—thereby indicating potential neuroprotective effects against neurodegenerative diseases.¹¹⁴

With regard to inflammation, hymenialdisine is believed to inhibit NF- κ B signaling by blocking protein kinase C and inhibitor of NF- κ B (I κ B) phosphorylation,¹¹⁶ thereby reducing transcription of NF- κ B-dependent inflammatory genes. This results in a reduction of IL-8³³ and IL-1 β production.¹¹⁷ Experimental studies have further demonstrated its protective effects on articular tissues,

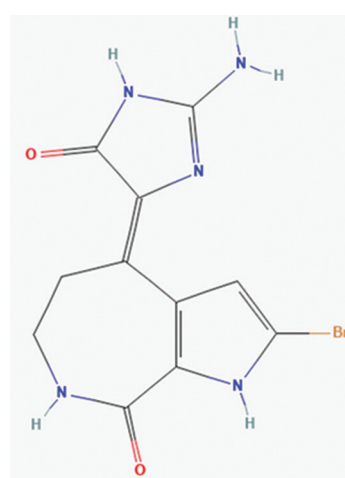


Figure 8. Chemical structure of hymenialdisine. The chemical structure was retrieved from PubChem (CID: 135413546).¹¹⁵

where it inhibited proteoglycan degradation in bovine cartilage in a dose-dependent manner.¹¹⁸ Given the central role of proteoglycan loss in RA, further investigation into its activity on human cartilage could confirm hymenialdisine's potential as a therapeutic agent for RA.¹¹⁹

6.2. Cycloprodigiosin

Cycloprodigiosin, a member of the prodigiosin family, is characterized by a cyclized six-membered side chain.¹²⁰ It is a red pigment synthesized by several marine bacteria, including *Serratia marcescens*, *Zooshikella rubidus*, and *Pseudoalteromonas denitrificans*, and has been reported to exhibit both immunosuppressive activity and pro-apoptotic effects in cancer cells through modulation of the NF- κ B pathway.¹²¹ In particular, the hydrochloride salt of cycloprodigiosin, obtained from *P. denitrificans*, has been shown to induce cytotoxicity and apoptosis in various cancer cell lines, particularly when combined with the pro-inflammatory cytokine TNF- α . Mechanistically, it suppresses NF- κ B-dependent gene transcription,

thereby blocking a key survival pathway in tumor cells.¹²² Experimental evidence demonstrates its ability to induce apoptosis in breast,¹²³ liver, and colon cancer cells through a mechanism involving H⁺/Cl⁻ symporter activity, which promotes cytosolic acidification.¹²³

In addition, cycloprodigiosin has demonstrated therapeutic effects in promyelocytic leukemia by inducing cell differentiation or apoptosis through upregulation of Fas ligand, activation of stress-activated protein kinases, and caspase signaling.¹²³ Its ability to disrupt NF- κ B signaling also confers immunosuppressive effects, as the compound selectively inhibits T-cell proliferation, a property common within the prodigiosin family.^{124,125} Interestingly, it also stimulates nitric oxide (NO) production during hepatic injury by regulating NF- κ B-dependent gene expression, such as inducible NO synthase (iNOS).¹²⁶ Because both NF- κ B inhibition and NO modulation are therapeutic strategies for inflammatory bowel disease, cycloprodigiosin has been proposed as a potential candidate to manage chronic intestinal inflammation.¹²⁷ Furthermore, given that NF- κ B regulates multiple inflammatory mediators implicated in autoimmune disorders, including RA, its suppression by cycloprodigiosin suggests additional anti-inflammatory and anti-arthritic potential.^{128,129}

7. Polysaccharides

Marine polysaccharides are derived from a broad range of organisms, including macroalgae, invertebrates, vertebrates, and microorganisms, each contributing unique structural features that define their functionality^{129–131} (Figure 9).

7.1. Macroalgal polysaccharide

Polysaccharides are major constituents of seaweeds, accounting for a substantial 4–76% of their dry weight. They are primarily located within the cell walls and intercellular spaces, where their specific structural configurations allow for great flexibility, a characteristic pivotal for the algae's adaptation to the dynamic forces of the aquatic environment.¹³³ It is noteworthy that the chemical composition and corresponding bioactive properties of marine-derived compounds are dynamic and can vary considerably depending on multiple factors, such as the species involved, environmental conditions of their habitat, and seasonal fluctuations.¹³⁴

7.1.1. Brown macroalgae (*Phaeophyceae*)

The principal polysaccharides found in brown seaweed are alginate, fucoidan, and laminarin, each with a distinct role and structure.¹³⁵

- Alginate was first identified by E.C.C. Stanford in

1881 and is characterized by its linear copolymer structure composed of β -D-mannuronic acid (M) and α -L-guluronic acid (G) residues linked in a β -(1,4) configuration.^{136,137} The polymer chain is not uniform; it contains homogeneous blocks (MM or GG) and heterogeneous blocks (MG or GM), with the ratio and sequence of these blocks being the primary determinant of its physical properties. Specifically, alginates rich in G-blocks form strong, brittle gels in the presence of divalent cations such as calcium, a phenomenon explained by the “egg-box” model, whereas those rich in M-blocks produce highly viscous solutions.^{133,138} Alginate, which can account for up to 40% of the dry weight of brown seaweeds and generally possesses a molecular weight between 500 and 1000 kDa, is widely utilized in the food and cosmetic industries for its gelling, texturizing, and stabilizing properties.^{133,137–141}

- Fucoidan was first described by Professor Harald Kylin in 1913 and originally named *fucoidin*. Fucoidan is a sulfated, fucose-rich polysaccharide that is characteristic of brown algae.¹³⁴ Its structure is complex and variable, often characterized by a backbone of α -(1,3)-linked fucose or alternating α -(1,3) and α -(1,4) linkages, frequently with sulfate esters at the C2 or C4 positions and potential branching.^{24,40} This structural diversity results in a wide molecular weight range, typically reported between 7 and 2300 kDa, and accounts for 20–25% of the algal dry weight, varying according to species type and environmental conditions.^{133,137,142} Although its exact biological function in algae remains incompletely elucidated, fucoidan is believed to contribute to preventing dehydration and maintaining structural integrity within algal tissues.¹⁴³ Owing to its strong bioactive properties, this polysaccharide has attracted considerable attention for potential use in cosmeceutical and pharmaceutical formulations, particularly as a drug delivery agent or an enhancer of bioavailability in therapeutic products.¹⁴⁴
- Laminarin, also referred to as laminaran, was first characterized in 1885 by Oswald Schmiedeberg from members of the Laminariaceae family.¹³⁴ It is a low-molecular-weight (~5 kDa) β -glucan that serves as the principal energy storage polysaccharide in brown macroalgae, comprising 22–49% of their dry biomass, and is utilized during colder months following accumulation in warmer seasons.¹³⁴ Structurally, laminarin is composed of β -(1,3)-linked *D*-glucose units with occasional β -(1,6)-linked branches and may include a terminal mannitol residue at the reducing end—features that vary depending on algal species

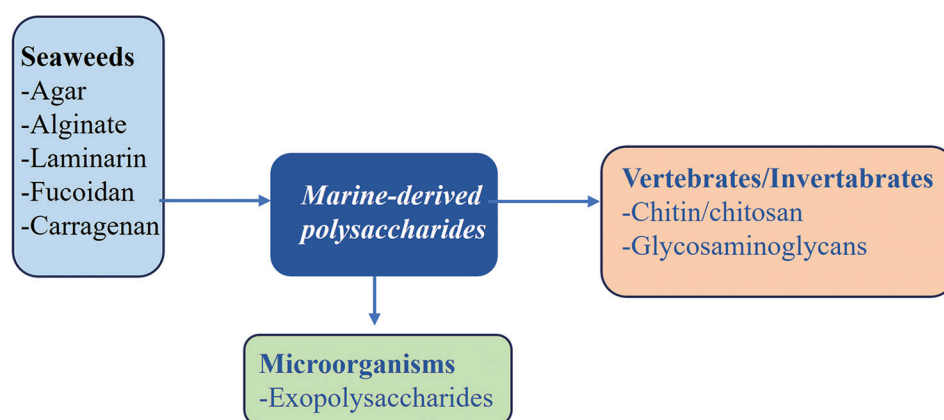


Figure 9. Marine polysaccharides: Properties and potential. Modified from Carrasqueira *et al.*¹³²

and environmental factors.^{133,134,137,145} Its solubility is determined by the degree of branching, and because it cannot be digested by the human gastrointestinal system, it functions as an important dietary fiber.^{137,140} More recent studies have emphasized its potential in biomedical applications, particularly in drug delivery and tissue engineering, owing to its capacity to support cellular functions and facilitate tissue regeneration, making it beneficial in wound healing and repair processes.¹⁴⁶

7.1.2. Red macroalgae (*Rhodophyceae*)

These seaweeds are exceedingly rich in the phycocolloids agar and carrageenan, which account for their high commercial value, constituting 40–50% of the dry weight.^{147,148}

- Agar, first discovered in Japan during the 17th century, contributes to the structural flexibility of red algae, enabling them to endure the mechanical stress of ocean currents.^{148,149} Rather than being a single polymer, agar is a heterogeneous complex composed mainly of two fractions: Agarose—a linear, neutral polysaccharide that can constitute up to 70% of total agar and imparts its strong gelling capacity—and agarpectin, an acidic, branched polysaccharide that enhances viscosity.^{148,150} The agarose component is made up of repeating disaccharide units of 3-O-linked β -D-galactose and 4-O-linked 3,6-anhydro- α -L-galactose (collectively known as agarobiose), which organize into a double-helix structure capable of entrapping water molecules.^{151,152} Gelation occurs through a thermoreversible process mediated by hydrogen bonding. Since agar cannot be digested by the human gastrointestinal system, it has been investigated as a potential prebiotic; however, its principal commercial uses remain in the food sector as a gelling and stabilizing agent and in microbiology

as a solidifying medium for culture preparation.^{147,153}

- Carrageenan is a family of sulfated polygalactans with an ester-sulfate content of 15–40% and a high molecular weight typically over 100 kDa.^{154,155} Its fundamental structure is based on alternating 3-linked β -D-galactose and 4-linked α -D-galactose residues. The three primary types industrially used—kappa (κ -), iota (ι -), and lambda (λ -)—are classified based on the number and position of sulfate ester groups, which directly dictate their functional properties.^{147,154-156} For example, κ -carrageenan (one sulfate group) forms strong, brittle gels, ι -carrageenan (two sulfate groups) forms soft, elastic gels, and λ -carrageenan (three sulfate groups) is a non-gelling thickener. Similar to agar and other polysaccharides, carrageenan is indigestible in the human digestive tract and can only be fermented by the colonic microbiota.¹⁴⁷ They are considered generally recognized as safe (GRAS), inexpensive, non-toxic, and biocompatible, leading to a wide range of applications as gelling agents, thickeners, and stabilizers.^{147,154-156}

7.2. Biological activities and mechanisms of action

The beneficial biological activities of marine polysaccharides stem from the structural complexity and variability of their sugar backbones, which enable multifaceted interactions within physiological systems. These compounds exhibit notable antioxidant potential and play an important role in mitigating oxidative stress—an underlying factor in the development of chronic disorders such as diabetes, cancer, and cardiovascular diseases. Their protective effects arise through multiple pathways, including the direct neutralization of reactive oxygen species (ROS) and the modulation of endogenous antioxidant defenses. Marine polysaccharides have been shown to influence the activity of key antioxidant enzymes, such as superoxide dismutase (SOD) and catalase, as well as support intracellular

glutathione homeostasis.^{102,157} Their efficacy is strongly influenced by structural features such as molecular weight, monosaccharide composition, glycosidic linkages, and particularly, the degree of sulfation, as the sulfate groups are highly effective at donating electrons to stabilize free radicals.¹ For example, thermally processed alginates with reduced molecular weight have demonstrated stronger antioxidant capacity than their unmodified counterparts, a result attributed to the generation of new reactive functional groups during heating.¹⁵⁸ Similarly, fucoidan has been shown to protect renal tissue from oxidative injury and, by limiting oxidative stress-related pathways, it may also reduce the risk of kidney stone formation.¹⁵⁹ In a human study, a high-molecular-weight chitosan supplement (Chitosamin[®]) was shown to decrease lipid hydroperoxide levels and suppress oxidative stress in the systemic circulation, suggesting its utility in treating serious illnesses such as renal failure.¹⁶⁰ Furthermore, exopolysaccharides (EPSs) from marine bacteria, such as EPS273 from *Pseudomonas stutzeri* 273, have demonstrated effective scavenging of hydroxyl and superoxide radicals, indicating their potential as natural antioxidants for food and health products.¹⁶¹

Persistent inflammation underlies the progression of numerous diseases, and marine-derived polysaccharides have been shown to influence these processes through multiple regulatory actions. Many of these biomolecules attenuate inflammatory responses by downregulating the synthesis or secretion of key pro-inflammatory mediators, including cytokines such as TNF- α , IL-1 β , and IL-6, as well as by suppressing the activity of enzymes involved in eicosanoid production, notably COX and lipoxygenase (LOX).¹⁶² The anti-inflammatory potential of marine polysaccharides is closely linked to their structural features, including molecular size, degree of branching, and patterns of sulfation. This relationship is exemplified by alginic acid, which has been reported to curb mast cell degranulation, markedly diminish passive cutaneous anaphylactic responses, and downregulate both the release and gene expression of pro-inflammatory mediators such as IL-1 and TNF- α . These findings highlight its promise as a therapeutic candidate for managing anaphylaxis and other inflammation-related conditions.¹⁶³ Likewise, fucoidan isolated from *Saccharina japonica* has been shown to mitigate oxidative stress and lower inflammation-related markers in animal models of diabetes, indicating its protective effects in metabolically induced inflammatory conditions.¹⁶⁴ Research on laminarin has revealed its anti-inflammatory potential in models of inflammatory bowel disease, making it a candidate for dietary supplementation in such conditions.¹⁶⁵

Beyond algal polysaccharides, those from marine animals show significant promise. For example, the anti-inflammatory effect of chitosan in models of ulcerative colitis has been found to be size-dependent, with larger molecules showing greater efficacy in inhibiting pro-inflammatory cytokine release and regulating the intestinal microbiota.¹⁶⁶ In addition, a sulfated glycosaminoglycan perna viridis polysaccharide (PVP-2) isolated from the Asian green mussel *Perna viridis* demonstrated strong anti-inflammatory properties. It suppressed the activities of COX-1, COX-2, and 5-LOX, lowered NO production *in vitro*, and markedly reduced carrageenan-induced paw edema in animal models.¹⁶⁷

8. Marine-derived bioactive proteins and peptides

Although marine environments harbor extraordinary biological diversity, research on bioactive proteins and peptides has primarily focused on a relatively narrow group of organisms.¹⁶⁸ Most investigations have centered on specific invertebrate groups (such as mollusks, sponges, echinoderms, and cnidarians), finfish, various macroalgae (red, brown, and green species, including *Spirulina*), crustaceans (crabs, lobsters, prawns, and shrimp), and other marine microorganisms.¹⁶⁸ Among these resources, fish represent a major reservoir of nutritionally valuable proteins rich in essential amino acids required for human health. Key structural and functional proteins—including collagen, myoglobin, and actin—are widely distributed across different fish tissues, including the skin, skeleton, scales, and internal organs. Collagen has also been successfully extracted from a range of other marine organisms, such as sea cucumbers, sponges, crustaceans, mollusks, jellyfish, and certain seaweeds.^{22,169-172}

Shellfish—including shrimp, crab, lobster, mussels, and clams—are notable reservoirs of functional peptides exhibiting diverse biological activities. These include opioid peptides (e.g., dynorphins in *Mytilus edulis*, methionine-enkephalins in oysters and clams, and β -endorphins in shrimp), antimicrobial peptides in blue mussels and oysters, angiotensin-converting enzyme (ACE)-inhibitory peptides such as valyl-tyrosine from *Litopenaeus vannamei*, isoleucyl-prolyl-proline from *Crassostrea gigas*, isoleucyl-leucine-proline from *Portunus trituberculatus*, and leucine (Leu)-aspartic acid from *Meretrix meretrix*, as well as immunomodulatory and antioxidant peptides from scallops and mussels.^{20,173-175} Gelatin hydrolysates from fish and other marine organisms have demonstrated antioxidant, antihypertensive, calcium-binding, antimicrobial, and immunoregulatory effects.^{176,177}

Marine microorganisms and invertebrates also yield potent bioactive compounds. Antimicrobial peptides have been identified in *Gadus morhua*, *Scylla paramamosain*, *C. gigas*, *Pelteobagrus fulvidraco*, *M. coruscus*, and *Octopus vulgaris*, many of which are cysteine- or proline-rich and characterized by high bioactivity and biocompatibility.^{178–180} Recent studies highlight the discovery of anticancer peptides such as clavatuside C, a novel cyclopeptide derived from a fungus associated with the hydrothermal vent crab *Xenograpsus testudinatus*.¹⁸¹ Co-culturing bacterial or yeast strains has also proven effective in generating new compounds; for example, *Streptomyces* co-cultured with *Bacillus* produced two piperazic acid-bearing cyclic peptides.^{182–184}

Bioactive peptides are most commonly obtained through enzymatic hydrolysis—a GRAS, eco-friendly, and reproducible technique widely applied in the food, chemical, and pharmaceutical sectors.¹⁸⁵ Proteolytic enzymes derived from plants (e.g., bromelain and papain), animals (e.g., pepsin and trypsin), fungi, and bacteria (e.g., alcalase and neutrase) selectively cleave peptide bonds under controlled pH and temperature. Critical factors such as enzyme type, concentration, hydrolysis time, and temperature influence peptide yield, composition, and functionality. For example, fish protein hydrolysates generated with trypsin and Se-abzyme exhibit variable ACE-inhibitory activity depending on hydrolysis duration.¹⁸⁶ Using response surface methodology, Wang *et al.*¹⁸⁷ optimized *Trichiurus lepturus* surimi hydrolysis with dispase (44.7°C, 12 h), achieving peptides with superior antioxidant activity (29.7 ± 0.9 U/mL). Sequential enzymatic digestion (pepsin → pancreatin or trypsin) further enhances peptide recovery, as shown in *Rachycentron canadum*, *Dunaliella salina*, and *Stichopus japonicus*.¹⁸⁸

Microbial fermentation offers another GRAS-compatible route for peptide production through microbial and enzymatic hydrolysis of proteins. Parameters such as microbial strain, substrate type, temperature, and incubation time influence peptide yield and activity. Interestingly, sequential digestion and fermentation approaches often produce novel compounds with higher total peptide content and stronger biological activity than undigested controls.^{188,189}

Following extraction, purification is essential to enhance peptide purity and bioactivity.¹⁹⁰ Ultrafiltration enables cost-effective, size-based fractionation of peptides under pressure, where smaller fractions (<5 kDa) often show the highest antioxidant effects, as demonstrated in sea cucumber (*S. japonicus*) peptides protecting H₂O₂-exposed Vero cells.¹⁹¹ Further purification commonly involves ion-exchange, gel filtration, affinity, or reverse-phase high-

performance liquid chromatography (RP-HPLC). For example, Jin *et al.*¹⁹² isolated a tetrapeptide with potent antioxidant capacity (EC₅₀ = 0.385 mg/mL), though offering high selectivity and resolution, is typically applied as an analytical complement due to its low throughput.¹⁹³

The identification and functional assessment of purified peptides are increasingly complemented by computational approaches. Techniques such as molecular docking and quantitative structure–activity relationship (QSAR) analysis are commonly used to predict peptide–target interactions, elucidate structure–function relationships, and enhance the efficiency of discovering bioactive candidates.^{1–3} For example, ACE-inhibitory peptides isolated from *Spirulina* protein hydrolysates were characterized using liquid chromatography–mass spectrometry/mass spectrometry and validated via virtual screening and docking simulations.¹⁹⁴

8.1. Bioactivities of marine-derived proteins and peptides

A wide range of marine life—such as finfish, macroalgae, crustaceans, various invertebrates, and marine microorganisms—provides an abundant supply of bioactive proteins and peptides with diverse therapeutic potential.^{19,195} These molecules are generally well tolerated by humans, free from pathogens associated with land animals, and broadly acceptable across different cultural and religious settings. Marine-derived peptides display an extensive array of biological activities, including antihypertensive, antioxidant, anticoagulant, antidiabetic, antimicrobial, anti-inflammatory, anticancer, antithrombotic, and immune-regulating properties.¹⁹

Although oxidative reactions are essential for maintaining normal metabolic functions, they can also generate ROS and other radicals that disrupt cellular balance and initiate oxidative stress. When this imbalance persists, it can lead to structural and functional damage of key biomolecules, thereby contributing to the development of numerous chronic conditions, including cardiovascular disorders, stroke, diabetes, atherosclerosis, and various cancers.^{196–199} In the context of foods, ROS-driven lipid oxidation is a major issue, as it promotes rancidity, off-flavors, and the formation of harmful degradation products that compromise both quality and safety.^{200–202}

Marine-derived peptides exhibit notable antioxidant activity, largely attributed to their ability to neutralize free radicals, bind pro-oxidant metal ions, and support the body's intrinsic antioxidant systems. Their functional properties are typically evaluated using common *in vitro* assays, including 2,2-diphenyl-1-picrylhydrazyl (DPPH), 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid)

(ABTS), hydroxyl and superoxide radical scavenging tests, as well as metal-chelation assays. The underlying antioxidant action generally involves the transfer of hydrogen atoms or electrons from specific amino acid residues, effectively quenching reactive species.^{203,204} Hydrophobic residues—phenylalanine (Phe), tyrosine (Tyr), alanine (Ala), valine (Val), Leu, and tryptophan (Trp)—facilitate interactions with lipid bilayers, while lysine (Lys), aspartic acid (Asp), and glutamic acid (Glu) enhance metal-chelating activity. Aromatic amino acids such as Tyr, Trp, and Phe contribute to direct electron transfer and radical stabilization.²⁰⁵

A substantial body of research has demonstrated the strong antioxidant capacity of proteins and peptides derived from marine organisms. As an example, bioactive peptides obtained from the sea cucumber *Holothuria leucospilota* have shown promising antioxidant effects, suggesting their suitability as natural alternatives for incorporation into food products or pharmaceutical formulations.²⁰⁶ Hydrolysates obtained from *Cucumaria frondosa* using alcalase, corolase, and flavourzyme showed strong ABTS and DPPH radical scavenging, especially with the (flavourzyme + corolase) enzyme combination.²⁰⁷ Similarly, *S. japonicus* hydrolysates protected Vero cells and zebrafish embryos against H₂O₂-induced oxidative damage by reducing lipid peroxidation and ROS. Protein hydrolysates derived from shrimp shell by-products using pepsin, chymotrypsin, and trypsin demonstrated radical scavenging and metal-chelating activities and effectively inhibited DNA damage and low-density lipoprotein (LDL) oxidation.²⁰⁸

Peptides isolated from Antarctic krill (*Euphausia superba*) have demonstrated notable antioxidant capacity, including strong reducing activity and the ability to safeguard plasmid DNA from oxidative damage.²⁰⁹ Similarly, peptides extracted from the mantle of the pearl oyster (*Pinctada martensii*, type V) displayed greater antioxidant effectiveness than collagen derived from tilapia (*Oreochromis niloticus*) scales. In addition, peptides from *M. coruscus* were shown to enhance the viability and structural integrity of human umbilical vein endothelial cells exposed to oxidative stress.²¹⁰ Novel antioxidant peptides isolated from *Pangasius sutchi* myofibrillar protein hydrolysates demonstrated exceptional radical scavenging potential,²¹¹ and peptides from mackerel (*Scomber japonicus*) displayed both DPPH and SOD-like activities.²¹² From tilapia gelatin hydrolysates, Glu-Gly-Leu and Tyr-Gly-Asp-Glu-Tyr showed strong hydroxyl radical scavenging capacity.²¹³ In addition, Saidi *et al.*²¹⁴ identified four antioxidant peptides (YENG, EGYAWN, YIVYPG, and WGDAGGY) from tuna processing waste with potent hydroxyl radical scavenging activity.

Collagen peptides from *Acaudina molpadioides*, particularly Phe-Leu-Ala-Pro, demonstrated high DPPH scavenging at 0.385 mg/mL after neutrase-assisted microwave hydrolysis, potentially due to their low molecular weight and hydrophobicity.¹⁹² A heptapeptide (TCGGQGR) from mackerel by-products also exhibited strong antioxidant potential,²¹⁵ while alcalase-hydrolyzed weakfish by-product protein achieved 60–70% DPPH radical inhibition. Hydrolysis of jellyfish (*Rhopilema esculentum*) with alcalase yielded VKP and VKCFR peptides that enhanced SOD, catalase, and glutathione peroxidase activities and protected rat cerebral microvascular endothelial cells from oxidative injury.^{216,217}

Extensive screening of algal protein hydrolysates revealed substantial antioxidant diversity among taxa. Terriente-Palacios *et al.*²¹⁸ reported that red algae exhibited the strongest DPPH and trolox-equivalent antioxidant capacity (65.7% and 68.5%, respectively), followed by green (58.9% and 60.5% respectively) and brown algae (47.5% and 49.7% respectively). Particularly, *Porphyra* sp., *Caulerpa lentillifera*, *Arthrospira platensis*, *Chlorella vulgaris*, and *Ulva intestinalis* displayed over 70% activity in at least one assay, whereas most brown algae showed lower values except for *Odonella aurita*, *Nannochloropsis* sp., and *Bifurcaria bifurcata*.

Despite substantial evidence supporting the antioxidant activities of peptides obtained from marine organisms, several limitations remain. Variability in enzymatic hydrolysis conditions, purification strategies, and analytical techniques often leads to inconsistent findings and makes cross-study comparisons difficult. Moving forward, research should prioritize the harmonization of extraction and evaluation methods, deeper exploration of structure–activity relationships, and robust *in vivo* studies to clarify bioavailability, underlying mechanisms, and potential therapeutic applications.

8.2. Antimicrobial activity

A growing body of evidence shows that proteins and peptides derived from marine organisms exhibit strong antimicrobial properties against diverse pathogenic microorganisms. These bioactive agents—sourced from fish, crustaceans, chelicerates, mollusks, and various other invertebrates—typically exert their effects by targeting microbial membranes, leading to structural disruption, impaired protein synthesis, or interruption of essential metabolic functions. In addition to their direct antimicrobial actions, many marine peptides also bolster the host's innate immune defenses by modulating immune pathways and promoting protective responses.^{219,220} Because of their wide antimicrobial range, generally low

toxicity, and reduced likelihood of promoting resistance, peptides obtained from marine organisms are increasingly viewed as attractive candidates to replace or complement traditional antibiotics.

Likewise, protein hydrolysates produced from various marine species exhibit notable antibacterial and antifungal activities, a consequence of the rich and diverse array of bioactive metabolites found in aquatic life.²⁰ For example, protein extracts from squid (*Todarodes pacificus*) viscera and ink sacs inhibited bacterial and fungal growth.²²¹ White shrimp (*L. vannamei*) carapaces conjugated with glucosamine exhibited enhanced antibacterial activity, indicating improved bioefficacy through chemical modification.²²² Three antimicrobial peptides (Nv-p1, Nv-p2, Nv-p3) isolated from the mollusk *Nerita versicolor* showed strong activity against *P. aeruginosa*, with Nv-p3 displaying the greatest potency at 1.5 µg/mL.²²² Centrocin 1, a peptide isolated from the sea urchin *Echinus esculentus*, has demonstrated wide-ranging antimicrobial effects. It was active against several clinically relevant pathogens, including *Escherichia coli*, *Staphylococcus aureus*, *Streptococcus pneumoniae*, *E. faecalis*, *Cryptococcus neoformans*, and *Candida albicans*. Its mechanism of action involves compromising microbial membranes and reducing fungal adhesion.^{223,224}

A synthetic 23-residue peptide (GWLIRGAIHAGK AIHGLIHRRRH) derived from *Octopus minor* demonstrated antifungal effects against *C. albicans* (minimum fungicidal concentration [MFC]: 200 µg/mL; minimum inhibitory concentration [MIC]: 50 µg/mL) by compromising membrane integrity and inducing structural deformities.²²⁵ Another *O. minor*-derived peptide, octopromycin, showed strong antibacterial activity against *Acinetobacter baumannii* (minimum bactericidal concentration [MBC]: 200 µg/mL; MIC: 50 µg/mL) through increased membrane permeability and ROS generation.²²⁶ Similarly, a hepcidin-like peptide (Lc-HepL) from yellow croaker (*Larimichthys crocea*) inhibited *Corynebacterium glutamicum*, *Micrococcus lysodeikticus*, and *Photobacterium damsela* via membrane disruption and stimulation of flocculant secretion.²²⁷ The β-defensin peptide from *Plecoglossus altivelis* displayed limited direct bactericidal action against *Vibrio anguillarum* but effectively enhanced immune defense by promoting phagocytosis and ROS-mediated killing.²²⁸

Polyphemusin III, a β-hairpin peptide from the horseshoe crab *Limulus polyphemus*, exhibited strong antimicrobial effects (IC₅₀ < 10 µM) against various bacterial species by destabilizing plasma membranes via a non-apoptotic mechanism.²²⁹ Peptides derived from half-fin anchovy (*Setipinna taty*) hydrolysates—HGM-Hp1 (FEDQLR), HGM-Hp2 (ALERTF), and HGM-Hp3

(RHPEYAVSVLLR)—disrupted bacterial membrane integrity through potassium ion leakage and intracellular ROS induction.²³⁰ Other antimicrobial peptides have been identified in *Barbus barbus* muscle protein hydrolysates and *Sardinella aurita*, reinforcing the potential of fish-derived peptides as functional antimicrobial agents.^{231,232}

Despite extensive evidence supporting the antimicrobial activities of marine-derived peptides and proteins, several obstacles continue to limit their broader application. Challenges such as limited stability, poor bioavailability, and incomplete understanding of their molecular mechanisms hinder progression toward therapeutic use. Additional concerns include the potential for resistance emerging over time, the scarcity of comprehensive *in vivo* studies, and difficulties associated with large-scale production. Future research should prioritize strategies to enhance peptide robustness, explore advanced delivery approaches such as nanoparticle-based carriers, and employ omics-driven methods to clarify their modes of action. Long-term resistance evaluation, effective pairing with existing antibiotics, and the development of recombinant production platforms will be essential for improving manufacturability and expanding their clinical and industrial potential.

8.3. Anti-inflammatory effects

Inflammation represents the body's primary defense against infection or injury, orchestrated by complex signaling among immune cells and mediators such as IL-1, IL-6, TNF-α, prostaglandin E₂ (PGE₂), and enzymes (e.g., COX-2 and iNOS).^{233,234} Although corticosteroids and NSAIDs are widely used and generally effective, their use is often limited by undesirable side effects, such as gastrointestinal complications and elevated cardiovascular risk. These concerns highlight the importance of identifying safer anti-inflammatory agents.²³⁵ Marine organisms produce abundant bioactive peptides capable of modulating key inflammatory pathways, presenting a promising avenue for therapeutic development.²³⁴

Peptides derived from the crab *Charybdis natator* (LGLGA AVL, 713.45 Da) significantly inhibited COX-2 expression in macrophages, demonstrating notable anti-inflammatory potential.²³⁶ Similarly, peptides phenylalanine-proline-glycine-alanine (FPGA) (390.19 Da), threonine-alanine-methionine-tyrosine (TAMY) (484.19 Da), and threonine-tryptophan-proline (TWP) (402.19 Da) from pearl oyster (*P. martensii*) meat hydrolysates reduced NO and pro-inflammatory cytokines (TNF-α, IL-6, and IL-1β) while enhancing IL-10 production.²³⁷ The peptide ELLGDVF (849.43 Da) from the green mussel (*P. viridis*) suppressed COX-2 activation and decreased cytokine and NO levels.²³⁸ A

stable hexapeptide, ALGTWK (690.20 Da), from the mollusk *Harpa ventricosa* attenuated inflammation in lipopolysaccharide (LPS)-stimulated macrophages by reducing NO, TNF- α , and IL-1 β .²³⁹

Sea cucumber peptides from *Acaudina leucoprocta* and *Apostichopus japonicus*—including PQGETGA, GPAGPR, GPSGRP, and GFDGPEGPR—reduced hepatic inflammation in LPS-treated mice by downregulating the mitogen-activated protein kinase (MAPK)/NF- κ B pathway.²⁴⁰ Peptides from *Lateolabrax maculatus* and skipjack tuna (*Katsuwonus pelamis*) inhibited NO and pro-inflammatory cytokine release in macrophages.^{230,241} Likewise, the tripeptide PAY (349.37 Da) from salmon (*Salmo salar*) prevented NO/iNOS and PGE₂/COX-2 pathway activation.²⁴² A peptide isolated from sturgeon (*Acipenser schrenckii*) muscle exerted anti-inflammatory effects through MAPK inhibition.²⁴³

Marine microbes also produce potent anti-inflammatory peptides. Compounds isolated from *Synechococcus* sp.—ALNKTHLIQTK, AILQSYSAGKTK, IPDAHVPK, LLVHAPVK, and VVVLRDGAVQQLGTPR—suppressed pro-inflammatory gene expression, including iNOS, TNF α , COX2, and IL6.²⁴⁴ Similarly, *Porphyridium* sp. peptides (GVYVRF, AIPAAPAGPKLY, and LIHADPPGVGL) inhibited COX-1 and COX-2 activity by 92.14% and 32.25%, respectively.²⁴⁵ Peptides from mollusks such as *M. meretrix* (NPAQDC, 647.55 Da) also reduced NO production and COX-2 activation in macrophages.²³⁹

Marine worms are another valuable source of anti-inflammatory agents. Hydrolysates from the clam worm (*Marphysa sanguinea*) and the peanut worm (*Sipunculus nudus*) suppressed NO and cytokine production in LPS-stimulated macrophages via downregulation of iNOS, TNF- α , IL-6, and COX-2, without inducing cytotoxicity.^{246,247} Similarly, low-molecular-weight (<10 kDa) hydrolysates from sardine (*Sardina pilchardus*) by-products exhibited notable anti-inflammatory effects.²⁴⁸

Peptides of marine origin mitigate inflammatory responses through several key mechanisms, including downregulation of NF- κ B and MAPK signaling, decreased production of NO and its associated enzymes (iNOS), suppression of COX-2-mediated PGE₂ synthesis, and rebalancing of cytokine profiles by lowering TNF- α , IL-1 β , and IL-6 while promoting IL-10. Despite increasing evidence supporting their anti-inflammatory activity, important questions persist regarding their molecular targets, pharmacokinetics, and *in vivo* effectiveness. Moving forward, research efforts should focus on harmonizing extraction and purification protocols, refining structure–activity understanding, and advancing both preclinical and clinical investigations to fully assess

their therapeutic relevance for inflammation-related disorders.^{247,248}

8.4. Antihypertensive effects

Hypertension continues to be a significant worldwide health challenge. Although synthetic ACE inhibitors are commonly prescribed, rates of hypertension-related mortality remain high, prompting growing interest in marine-derived peptides with natural ACE-inhibitory activity. ACE plays a central role in blood pressure regulation by converting angiotensin I into the potent vasoconstrictor angiotensin II and by degrading the vasodilator bradykinin; therefore, blocking ACE activity is a well-established strategy for managing hypertension.²⁴⁹

Marine organisms yield numerous ACE-inhibitory peptides with favorable binding to the ACE active site via hydrogen bonding, electrostatics, and hydrophobic interactions. From blue mussels (*M. edulis*), peptides IK, YEGDP, WF, and SWISS showed strong inhibition (IC₅₀ = 0.77 $\pm$ 0.020, 0.19 $\pm$ 0.010, 0.40 $\pm$ 0.015, and 0.32 $\pm$ 0.017 mg/mL, respectively).¹⁹⁴ Jellyfish (*R. esculentum*) peptides VKP and VKCFR inhibited ACE with IC₅₀ values of 1.3 μ M and 34.5 μ M, respectively; docking indicated coordination within the Zn(II)-containing active site.²¹⁸ Potent activity has also been reported from monkfish (*Lophius litulon*) swim bladder hydrolysates and shortfin scad (*Decapterus macrosoma*) waste (alcalase hydrolysis).²⁵⁰

Marine algae and microalgae are complementary sources. The red algal peptide FQIN[M(O)]CILR from *Gracilariopsis lemaneiformis* lowered blood pressure in spontaneously hypertensive rats (SHRs).²⁵¹ From *Isochrysis zhanjiangensis*, PIZ inhibited ACE non-competitively and attenuated angiotensin II-driven vascular inflammation via NF- κ B/NRF2/MAPK/protein kinase B (AKT) modulation²⁴¹; the tetrapeptide Thr-Tyr-Ile-Ala from *Porphyra dioica* was likewise active.²⁵² In *Laminaria japonica*, eight Tyr-terminal peptides (FY, KY, AKY, GKY, KFKY, KKFY, SKTY, and AKYSY) underscore the role of C-terminal Tyr in potency.²⁰² Dipeptides Ile-Trp, Leu-Trp, and Val-Trp from *Chlorella sorokiniana* highlight the importance of C-terminal Trp plus N-terminal branched hydrophobes.¹⁸⁸ Additional *Isochrysis* peptides included ETT (IC₅₀ = 15.08 μ M; non-competitive), which also suppressed angiotensin II-induced inflammation and apoptosis and lowered blood pressure in SHRs,⁸¹ and PIZ (IC₅₀ = 61.38 μ M; non-competitive).²⁴¹ Spirulina-derived IRDLDDYY (*in silico/in vitro*) further broadened the algal portfolio (IC₅₀ = 1.75 mM) with low cytotoxicity.²⁵³

Crustacean and echinoderm by-products provide scalable sources. Shrimp shell waste yielded <5 kDa fractions (neutral protease) with 84.04% ACE inhibition.²⁴⁹ Sea

cucumber preparations showed robust activity: *Actinopyga lecanora* proteolysate produced *in vivo* antihypertensive effects in Sprague–Dawley rats,²⁵⁴ whereas *Stichopus horrens* peptides EVSQGRP, CRQNTLGHNTQTSLAQ, and VSRHFASYAN inhibited ACE with IC₅₀ values of 0.05, 0.08, and 0.21 mM (hippuryl-*L*-histidyl-*L*-Leu assay), respectively.²⁵⁵

Collectively, marine peptides modulate blood pressure primarily via ACE inhibition, with encouraging *in vivo* data in animal models. To translate these findings, human intervention trials, standardized characterization (sequence, potency, and stability), pharmacokinetics/bioavailability profiling, and food/clinical formulations are needed.

8.5. Anticancer potential

Marine-derived peptides offer multimodal anticancer actions with potential for selectivity and lower systemic toxicity.^{256,257} Mechanistically, they induce intrinsic (mitochondrial) apoptosis via cytochrome-*c* release and caspase activation; modulate B-cell lymphoma 2 (BCL-2) family proteins ($\uparrow$ Bax, $\downarrow$ Bcl-2); inhibit angiogenesis (e.g., vascular endothelial growth factor pathways); and suppress oncogenic signaling (phosphoinositide 3-kinase [PI3K]/Akt and MAPK), thereby sensitizing tumors to therapy.^{257–260}

Fish protein hydrolysates reduce oxidative stress and limit DNA damage, contributing to antiproliferative effects. Fish protein hydrolysates from skins, bones, heads, and viscera inhibited human colon and breast cancer cell growth²⁶¹; cuttlefish (*Sepia pharaonis*) hydrolysates suppressed MDA-231 and T47D proliferation (78.2% and 66.2% inhibition, respectively) while exhibiting antioxidant activity.²⁶² Among fish mucus peptides, pardaxin (33-aa α -helix) from *Pardachirus marmoratus* induces G2/M arrest and triggers apoptosis across multiple tumor types^{263,264}; piscidin-4 causes necrotic death in non-small cell lung cancer cell lines (A549, NCI-H661, NCI-H1975, and HCC827)¹⁵⁷; and epinecidin-1 from *Epinephelus coioides* inhibits lung cancer and glioblastoma via apoptosis/necrosis modulation.²⁶⁵

Bivalves and sponges contribute structurally unique scaffolds. *Cyclina sinensis* hydrolysates generated pentapeptides that induced apoptosis and curtailed DU-145 prostate cancer cell proliferation.²⁶⁶ Sponge-derived cyclo/depsipeptides—including jaspamide, koshikamides, and theonellamide G—showed broad cytotoxicity against prostate and breast carcinomas, acute myeloid leukemia, and colon cancer cells, with distinct non-proteinogenic features.^{267,268} Ascidians yielded turgencin A/B (linear, Cys-rich), which suppressed melanoma A2058

and human fibroblast MRC-5 proliferation.²⁶⁹

Echinoderms also show promise. Sea cucumber hydrolysates inhibited A549 cell proliferation, migration, and invasion; reduced pleural effusion; and limited tumor burden, extending survival in C57BL/6 models.²⁷⁰ *C. frondosa* peptides WPPNYQW and YDWRF bound epidermal growth factor receptor, PI3K, AKT1, and CDK4 in docking/molecular dynamics simulations; WPPNYQW formed stable complexes across targets, suggesting strong anti-breast cancer potential.²⁷¹

Despite compelling *in vitro* and preclinical data, major gaps remain: Bioavailability, metabolic stability, target engagement *in vivo*, scalable synthesis/purification, and cost. Progress will depend on advanced delivery systems (e.g., nanocarriers and conjugates), systematic structure–activity relationship, and integrated computational pipelines (docking and machine learning/artificial intelligence prioritization) to triage candidates. Coordinated efforts among marine biotechnologists, pharmacologists, and clinicians are essential to propel the most promising peptides into well-designed clinical trials.^{132,272}

8.6. Immunomodulatory effects

The immune system safeguards against infection and neoplasia through coordinated cellular and humoral responses. Its performance can be impaired by malnutrition, psychological/oxidative stress, and pathogen or antigen exposure. Pharmacologic immunomodulators (e.g., actinomycin, vincristine, dexamethasone, levamisole, and thymosin α 1) are effective but costly and may cause adverse effects, limiting long-term use. Accordingly, nutrition-based strategies—notably functional foods enriched with immunomodulatory peptides—are attracting interest, although their precise mechanisms remain incompletely defined.²⁷³

Marine organisms produce abundant proteins and peptides with natural immunoregulatory activity, supporting both the innate and adaptive arms of the immune system. A skin hydrolysate from giant croaker (*Nibea japonica*) enhanced cell-mediated immunity (splenocyte proliferation) and humoral responses (increased immunoglobulins).²⁶⁶ From *Stolephorus chinensis*, a <1 kDa fraction containing Tyr-Val-Met-Arg-Phe maximized RAW 264.7 proliferation (relative proliferation rate = 70.03%).^{192,274} Sea cucumber hydrolysates (*A. japonicus*) upregulated NO, TNF- α , and IL-6 in a dose-dependent manner and activated macrophages via NF- κ B and MAPK signaling. Oligopeptides attributed to sea cucumber (*Codonopsis pilosula*) improved cell- and humoral-mediated immunity, macrophage phagocytosis, and NK cell activity in BALB/c mice,²⁷⁵ while an enzymatic

fraction from *Colochirus robustus* increased lymphocyte proliferation, serum albumin, NK activity, and helper T-cell function in C57BL/6 mice.²⁷⁶

Given their capacity to tune innate and adaptive immunity, proteins and peptides are promising candidates for safer immunotherapies. Protein/peptide-based drugs may mitigate adverse immune reactions associated with conventional agents while sustaining efficacy.²⁰

8.7. Antihyperlipidemic properties

Obesity—often driven by high-fat diets—is a significant risk factor for hyperlipidemia, fatty liver, hypertension, and type 2 diabetes.^{277–279} Hyperlipidemia (hypercholesterolemia and/or hypertriglyceridemia) strongly predisposes to cardiovascular disease. Marine-derived peptides and algal glucans show hypocholesterolemic and anti-obesity actions, with additional antioxidant and immune benefits.^{279,280}

Novel peptides (TKY, LIL, FPK, and IAIM) from silver carp muscle lowered cholesterol by inhibiting intestinal absorption and promoting peripheral LDL uptake.²¹⁹ Fish protein hydrolysates from sardine, horse mackerel, axillary seabream, bogue, small-spotted catshark, and blue whiting are promising cholesterol-lowering ingredients. From ark shell protein hydrolysate, LLRLTDL and GYALPCDCL reduced lipid accumulation by ~49% and ~46% at 100 μ M, respectively, via antioxidant/anti-inflammatory actions and modulation of adipocyte differentiation.²⁷⁷

Collagen peptides provide additional metabolic benefits. Great hammerhead shark skin peptides decreased high-fat and alcohol-induced hyperlipidemia by downregulating fatty acid synthase (FAS) and 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR) and upregulating lecithin: cholesterol acyltransferase, reducing hepatic cholesterol.^{31,201,281} *Raja kenojei* collagen peptides suppressed lipogenesis, inhibited adipocyte differentiation, enhanced fatty acid oxidation, and halved adipose mass (3% $\rightarrow$ 1.5%) in high-fat diet-treated mice.^{55,282} Tuna skin collagen peptides limited lipid accumulation in 3T3-L1 cells and improved serum total cholesterol (TC), TAG, LDL, and high-density lipoprotein in obese mice.²⁸³ Two peptides from *Miichthys miiuy* (VIAPW and IRWW) dose-dependently reduced oleic acid-induced lipid buildup and intracellular TAG/TC in HepG2 cells while downregulating sterol regulatory element-binding protein-1c/2, FAS, acetyl-CoA carboxylase, and HMGCR, as well as upregulating peroxisome proliferator-activated receptor α , acyl-coenzyme A oxidase 1, and carnitine palmitoyltransferase 1.¹⁸⁷

Dietary fish hydrolysates also improved lipid and oxidative profiles *in vivo*: *Boops boops* hydrolysate lowered serum lipids and hepatic malondialdehyde and boosted

antioxidant enzymes in high-cholesterol diet rats²⁸⁴; sardine and sardinella hydrolysates reduced lipid peroxidation across serum/tissues and enhanced antioxidant defenses.²⁸⁵

Although current findings are promising, several critical uncertainties persist. These include a limited understanding of the precise molecular mechanisms underlying their lipid-lowering and anti-adipogenic effects, insufficient data on bioavailability, stability, and effective human dosing, and a lack of rigorous clinical evaluations. Future research should focus on identifying more potent peptide sequences, improving formulation and delivery strategies to enhance stability and absorption, and conducting well-designed, large-scale clinical trials to determine their efficacy in managing obesity and metabolic disorders.

8.8. Wound healing and skin health

The epidermis is a frontline barrier essential for tissue homeostasis.²⁸⁶ Burns, infections, scarring, genetic disorders, and chronic conditions complicate repair, which relies on inflammation, re-epithelialization, matrix remodeling, and vascularization. Marine collagen—in peptides, hydrolysates, fibers, and scaffolds—has emerged as an effective wound-healing biomaterial.^{286–288}

Marine collagen peptides accelerated closure in scratch assays at 50 μ g/mL within 12 h, comparable to 10 ng/mL epidermal growth factor; *in vivo*, tilapia-skin peptides hastened rabbit wound healing over 11 days.²⁸⁸ Alaska pollock collagen peptides improved rat wound recovery and increased hydroxyproline (10.6 vs. 9.25 μ g/mg), with complete re-epithelialization and hair follicles by day 12.²⁸⁹ Salmon-skin peptides enhanced wound tensile strength. From the sponge *Chondrosia reniformis*, collagen hydrolysates promoted fibroblast/keratinocyte migration and proliferation, improving gap closure at 6–30 h.²⁹⁰ Acid-soluble collagen from haddock skin supported vascularization, epithelial regeneration, faster closure, and reduced bleeding/clotting times.²⁹¹

Combining astaxanthin with squid collagen accelerated healing in rats (greater epithelialization, angiogenesis, keratinization, and collagen deposition).²⁹² Tilapia collagen and bovine collagen nanofibers likewise improved recovery, elevating fibroblast activity, vascularization, collagen content, and reducing inflammation; hydroxyproline played a key role in re-epithelialization.²⁹³ Collagen-based skin-like scaffolds derived from sea urchin food waste accelerated wound closure in sheep, with increased keratinocyte migration by day 14, less inflammation, and greater granulation tissue.²⁹⁴

Collectively, marine-derived collagens and peptides enhance cell migration, cell proliferation, angiogenesis, matrix deposition, and tensile strength, highlighting

strong potential for pharmaceutical and cosmeceutical applications. Further work should standardize material sourcing and processing, define dose–response and degradation profiles, and advance controlled clinical studies to confirm efficacy and safety.

9. Limitations and future directions

Despite considerable promise of marine bioactives, the field still faces substantial limitations that must be acknowledged to guide future progress. Large-scale, randomized human trials remain scarce, limiting the ability to translate promising preclinical findings into validated clinical recommendations. Many marine-derived compounds face inherent challenges related to poor oral stability, limited absorption, rapid metabolism, and limited tissue bioavailability, all of which complicate their therapeutic use. Furthermore, large-scale production and purification of structurally complex compounds can be technically demanding and costly, raising questions about long-term cost-effectiveness, sustainability, and scalability. Addressing these gaps is essential for de-risking development pipelines and for establishing realistic expectations regarding the commercial and clinical translation of marine-derived bioactives.

Translational success, however, requires addressing several critical gaps. First, rigorous standardization of sourcing, extraction, purification, and structural characterization is essential to establish reproducible structure–function relationships, particularly for complex polysaccharides and multifunctional peptides. Second, advances in formulation science are needed to improve the stability, bioaccessibility, and targeted delivery of marine bioactives, many of which exhibit limited oral bioavailability in their native form. Third, harmonized and clinically meaningful immune endpoints—along with mechanistic dose–response frameworks—must be developed to enable robust evaluation across preclinical and clinical studies. Fourth, a comprehensive safety assessment remains imperative, including evaluation of allergenicity, long-term exposure risks, interactions with pharmaceutical agents, and monitoring for the presence of marine toxins associated with HABs. Finally, human intervention trials integrating pharmacokinetic profiling, microbiome–immune readouts, and precision-nutrition approaches will be indispensable for translating promising preclinical findings into validated health applications.

Leveraging omics technologies, computational design tools (QSAR modeling, molecular docking, and machine learning), and biosynthetic or enzymatic engineering can significantly expand the accessible chemical space,

improve manufacturability, and optimize bioactivity. With sustained interdisciplinary collaboration across marine science, biochemistry, nutrition, pharmacology, and clinical research, marine-derived immunomodulators are well-positioned to advance from a promising research domain to a mature class of evidence-based functional food ingredients, nutraceuticals, and therapeutic adjuncts capable of contributing meaningfully to human health.

10. Conclusion

Marine organisms offer a uniquely rich pharmacopeia of immunomodulatory compounds with complementary mechanisms of action, collectively demonstrating the capacity to dampen maladaptive inflammation, enhance host defense, and support metabolic balance and tissue repair. This review highlights key classes of bioactives—such as sulfated polysaccharides with defined structural motifs, low-molecular-weight peptide fractions enriched in hydrophobic and aromatic residues, ω -3 PUFAs and their specialized pro-resolving mediators, and distinct steroidal and macrolide scaffolds—that act across central immune pathways, including toll-like receptor/NF- κ B/MAPK signaling, COX/LOX-mediated eicosanoid biosynthesis, oxidative stress networks, and mucosal immune regulation. These converging mechanisms underpin a broad spectrum of biological activities relevant to cardiometabolic diseases, infectious conditions, autoimmune and allergic disorders, cancer adjunct therapy, and applications in skin health and wound management. Notably, the valorization of marine processing by-products aligns these discoveries with circular-economy goals, reinforcing the role of marine bioactives in sustainable, food-as-medicine strategies.

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