CHAPTER

06

CLASSIFICATION OF ORGANIC COMPOUNDS WITH REFERENCE TO NATURAL PRODUCTS FROM SEAWEEDS

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Abstract

Seaweeds, integral to coastal ecosystems, are recognized for pharmacologically active compounds, gaining prominence for pharmaceutical potential. Scientific reports endorse seaweed-based foods for health benefits. Global seaweed production reached 30.1 million tons in 2016, with India contributing 22,000 tons annually. Non-toxic, cost-effective, and easily cultivable, seaweeds offer alternatives to synthetic compounds. They house diverse bioactive molecules, exhibiting antihypertensive, anticarcinogenic, antimicrobial, and anti-inflammatory properties. Seaweeds contain compounds like phenolics, carotenoids, polysaccharides, terpenoids, sterols, proteins, terpenes, acetogenins, peptides, and alkaloids. Marine organisms produce chemical classes, including Terpenes, Shikimates, Polyketides, Acetogenins, Peptides, and Alkaloids, serving as chemical defenses. Seaweed-derived secondary metabolites, progressing into clinical trials, display antibacterial, antiviral, antitumor, antiparasitic, anticoagulant, antimicrobial, anti-inflammatory, and cardiovascular properties. Exploration continues, unveiling promising therapeutic avenues in medicine and beyond.

Key words: Seaweeds, Terpenes, Alkaloids, Polyphenols, Polysaccharides

INTRODUCTION

Seaweeds, an indispensable component of coastal ecosystems, form a captivating marine phylum renowned for its pharmacologically active compounds. Often lauded as the ocean's wonder herbs, seaweeds are gaining increasing recognition for their pharmaceutical potential. The consumption of seaweed-based foods is experiencing a surge, supported by scientific reports that affirm their efficacy in health management. As of 2016, global seaweed production reached an impressive 30.1 million wet tons (FAO, 2018), with India contributing approximately 22,000 tonnes annually through both aquaculture and wild sources. The allure of seaweeds lies in their non-toxic, cost-effective, and easily cultivable attributes, positioning macroalgae as promising alternatives to synthetic compounds.

Seaweeds not only serve as repositories of essential nutrients but also harbor a rich assortment of bioactive molecules and secondary metabolites. Extracted functional compounds exhibit diverse biological activities, spanning antihypertensive, anticarcinogenic, antimicrobial, and anti-inflammatory properties. The spectrum of bioactive compounds found in seaweeds encompasses phenolics, carotenoids, polysaccharides, terpenoids, sterols, proteins, terpenes, acetogenins, peptides, and alkaloids.

The vast diversity of marine organisms and their habitats gives rise to an extensive array of chemical classes within marine natural products. These classes, which include Terpenes, Shikimates, Polyketides, Acetogenins, Peptides, and Alkaloids, showcase diverse structures and a plethora of compounds resulting from mixed biosynthesis processes. Predominantly categorized as secondary metabolites, these marine natural products play a pivotal role in enhancing survival fitness and often function as chemical defenses against bacteria, fungi, viruses, and various aquatic organisms.

Of particular interest to the pharmaceutical industry are the secondary metabolites derived from seaweeds, with many of these compounds progressing into clinical trials as experimental drugs. Over the past five decades, the isolation of numerous novel compounds from seaweed has unveiled a rich repertoire of biological activities. These activities span a wide spectrum, encompassing antibacterial, antiviral, antitumor, antiparasitic, anticoagulant, antimicrobial, anti-inflammatory, and cardiovascular properties. The exploration of marine natural products continues to unveil promising avenues for the development of novel therapeutic agents with diverse applications in medicine and beyond.

BIODIVERSITY OF THE MARINE ENVIRONMENT - A SOURCE OF CHEMICAL DIVERSITY

Within the marine environment, organisms undergo diverse biosynthetic conditions, promote the growth genetic diversity and, consequently, a rich tapestry of chemical diversity. This varied chemical landscape holds considerable potential for the discovery and development of novel drugs. The unique and often demanding circumstances of the marine species, characterized by factors like light and oxygen synergy, can subject marine species, including mollusks and seaweeds, to elevated stress levels. This stress prompts oxidative responses, culminating in the formation of reactive oxygen species (ROS) and other potent oxidizing agents.

Despite the challenges posed by these stressors, marine organisms, particularly seaweeds, exhibit remarkable resilience. They boast robust anti-inflammatory and antioxidant systems, evident in their capacity to thwart oxidative damage in structural components and effectively neutralize toxic ROS. Seaweed species sourced from tropical regions, such as the coasts of Quintana Roo and Yucatan, showcase notable antioxidant and anti-inflammatory activities. This suggests the development of an efficient antioxidant defense system in response to the intense UV radiation prevalent in tropical environments. This resilience not only underscores the adaptability of marine life but also unveils potential avenues for harnessing their bioactive compounds in the pursuit of innovative therapeutic solutions.

CHEMISTRY OF MARINE NATURAL PRODUCTS

The area of marine natural products chemistry has witnessed substantial evolution, progressing through various stages. Technological advancements, such as the use of scuba diving for more accessible material collection from the deep seas, have streamlined the isolation of potent compounds. The new instrumentation techniques, including nuclear magnetic resonance, mass spectrometry, and X-ray diffraction, have played pivotal roles in resolving intricate structural and stereochemical challenges. While this segment does not claim to encompass all bioactive compounds comprehensively, its aim is to illuminate the diverse spectrum of bioactive marine natural products. Huge efforts have been invested to ensure the inclusion of major classes of bioactive compounds, acknowledging the ongoing significance of exploring the chemical richness within the marine ecosystem.

BIOACTIVE SECONDARY METABOLITES OF SEAWEEDS

BIOACTIVE MARINE STEROLS

Sterols, commonly referred to as steroid alcohols, constitute a subset of steroids distributed widely across marine invertebrates, plants, and fungi. Marine algae also harbor sterols, with distinct distributions among various types. Brown algae (Phaeophyceae) are predominantly characterized by the presence of fucosterol and its derivatives. In contrast, red algae (Rhodophyceae) primarily contain cholesterol and cholesterol derivatives, while green algae (Chlorophyceae) are characterized by the presence of ergosterol and 24-ethylcholesterol. Sterols sourced from marine environments have been identified for their varied bioactivities, encompassing antiproliferative, cytotoxic, anti-fouling, and antibacterial activity

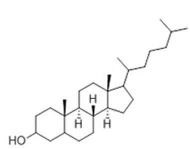
The 6 sterols derived from *Dictyotadichotoma* and *Sargassum granuliferum* possess good antibacterial and antifouling properties. They are coprostanol (1), campesterol (2), stigmasterol (3), fucosterol (4), epicoprostanol (5), and 5β-cholestan-3-one (6). All sterol compounds derived exhibited superior inhibitory effects against Gram-negative bacteria (*V. alginolyticus, V. parahaemolyticus, V. mimicus,* and *P. aeruginosa*). When compared to their impact on Gram-positive bacteria (*B. subtilis*). Epicoprostanol demonstrated the highest level of inhibition, affecting two Gram-positive bacteria, whereas other compounds only exhibited inhibition against one Gram-positive bacterium. The sterol compound extracted from these two seaweeds can be used as a potential natural antifouling substance. There has been a report of isolation of a phytosterol 24-propylidene-cholest-5-en-3–ol(8) (24-branched Δ5 sterols) from extract of red seaweed *L. papillosaas* antibacterial agent. The sterols from marine algae are reported to be non-toxic and have the ability to reduce blood cholesterol level. They are also reported to reduce the tendency to form a fatty liver and excessive fat deposition in the heart.

Li et al. (2009) identified fucosterol, ergosterol, and cholesterol from the extracts of *Ecklonia cava*, a brown species. Similarly, Yoon et al. (2008) made the groundbreaking discovery of 24-hydroperoxy-24-vinylcholesterol in *Ecklonia stolonifera*, demonstrated a certain level of inhibition against butyrylcholinesterase-an enzyme associated with Alzheimer's disease.

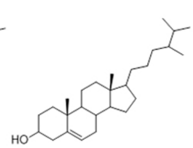
Reports indicate that saringosterol, extracted from brown algae *Sargassum ringgoldianum*, exhibits antitubercular activity (Ikekawa et al., 1968). The minimum inhibition concentration (MIC) against *M. tuberculosis* H37Rv was determined to be 0.25 mg/mL, marking the lowest value among plant-derived natural products. This compares favorably to the tuberculosis drug rifampicin, which displayed a MIC of 0.25 mg/mL in the same assay. Importantly, even at low concentrations, saringosterol demonstrated no toxicity in monkey kidney epithelial (Vero) cells.

Research findings indicate that fucosterol, isolated from the marine algae Pelvetiasiliquosa, possesses antioxidant properties. Fucosterol induces a significant enhancement in the activities of free radical scavenging enzymes, including superoxide dismutase (SOD), catalase, and glutathione peroxidase (GSH-px).The observed rise in catalase activity, particularly in comparison to CCl4 treatment, suggests that fucosterol may play a crucial role in scavenging hydrogen peroxide. The increased SOD activity implies that fucosterol contributes to cellular defense mechanisms by preventing oxidation of cell membranes. Furthermore, the elevated glutathione peroxidase activity suggests that fucosterol aids in the restoration of essential molecules such as cytochrome and glutathione.Fucosterol also posses good antidiabetic activity.

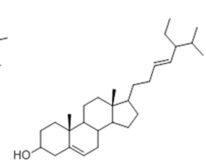
Sterol glycoside 3-O-b-glucopyranosyl clerosterol (7) isolated from *Ulva lactuca* collected from Alexandrian shores had shown the anti-inflammatory activity. The doses at 1000 and 1500 µg/ear gave significant inhibition of oedema of 62.25% and 72.18%, respectively.



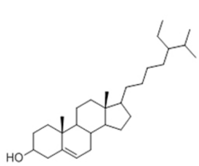
Coprostanol(**1**)



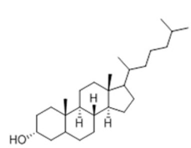
Campesterol(**2**)



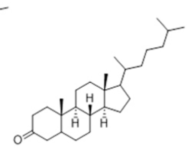
Stigmasterol(**3**)



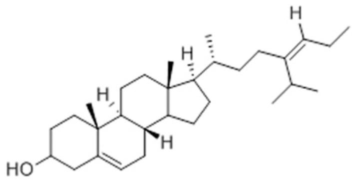
Fucosterol



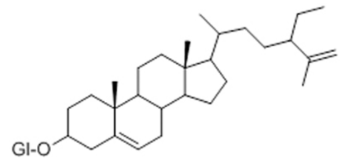
Epicoprostanol(**5**)



5B-Cholestan-3-one(**6**)



24-propylidene-cholest-5-en-3-ol(**7**)



3-O-b-glucopyranosyl clerosterol(**8**)

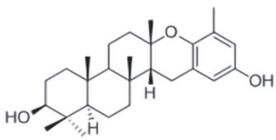
Sterols from different seaweeds

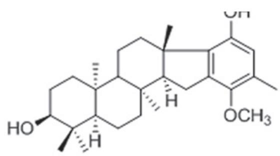
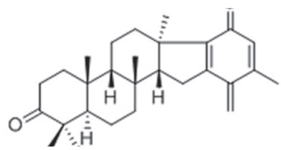
BIOACTIVE TERPENOIDS

These compounds are derived from a five-carbon isoprene structure, and depending on the combination of units, can be subdivided into biogenetic classes such as monoterpenes, sesquiterpenes, diterpenes, sesterpenes, triterpenes (steroids), and tertraterpenes (carotenoids). The green algae of the genera Halimeda, Penicillus and Udotea are found to contain highly active but unstable sesquiterpenoids and diterpenoids. Some of these diterpenoids exhibit cytotoxic and antimicrobial activities.

Meroditerpenes, a class of polycyclic diterpenes with a mixed biogenesis featuring a methyl hydroquinone nucleus linked to a diterpenic chain, have been documented in various marine organisms. Specifically, they have been identified in *Lobophora papenfussii, Taonia atomaria, Stypopodium zonale, Stypopodium flabelliforme* and *Stypopodium schimperii*.

Stypopodium flabelliforme, a member of this genus, has been reported to contain meroditerpene compounds. The *Stypopodium* genus, predominantly found in tropical and warm temperate regions, comprises six accepted species, including *S. flabelliforme, S. schimperii, and S. zonale*, which have been subject to chemical investigations. The meroditerpenes identified in these genera have demonstrated diverse biological activities, including cytotoxic, anti-inflammatory, insecticidal, and antiviral properties.

Product	Source	Activity
	*Stypopodium flabelliforme*	insecticidal

	*Stypopodium flabelliforme*	sodium channel blocking activity
	*Taonia atomaria*	antitumoral

Terpenoids from different seaweeds

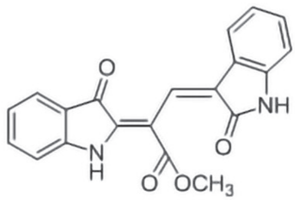
BIOACTIVE MARINE ALKALOID

Alkaloids can be defined as "cyclic organic compounds with nitrogen in a negative oxidation state, exhibiting a restricted distribution among living organisms". Within various categories of secondary metabolites, alkaloids manifest as extensive and intricately structured compounds. The nitrogen present in the molecular structure imparts biological activity to numerous compounds within this class.

Within the marine environment, diverse bisindole alkaloids are synthesized, with green algae (Chlorophyta) serving as a primary contributor to their production. From the green alga Caulerpa racemosa, two recently discovered bisindole alkaloids, namely racemosins A(1) and B(2), were isolated. Additionally, a familiar pigment known as caulerpin was also identified in the same algal source.

Racemosin A , as well as racemosin B , showed neuroprotective action for Aβ25–35-induced SH-SY5Y cell damage, increasing cell viability with 14.6%, at a concentration of 10 Mm. Compounds like racemosin C(3) and caulersin(4) demonstrated PTP1B significant inhibitory activity with IC_{50} values of 5.86 ± 0.57 and 7.14 ± 1.00 µM, respectively.Caulerpin, derived from the lipid extract of *Caulerpa racemose* algae, exhibited anti-inflammatory effects in mice when orally administered at a concentration of 100 µmol/kg. The extensive array of reported biological properties, including its role as an anti-inflammatory agent and antinociceptive, is likely attributed to its bisindolic pharmacophoric nucleus.

Red algae of the genus Gracilaria have also been described as important sources of alkaloids with anti-inflammatory activity.An alkaloid known as azocinyl morpholinone(4) isolated from Gracilaria opuntia, demonstrated anti-inflammatory properties in a murine model featuring carrageenan-induced paw edema. The compound effectively diminished edema formation within 6 hours and displayed a specific inhibitory impact on the activities of COX-2 and 5-LOX.



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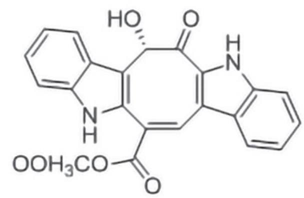

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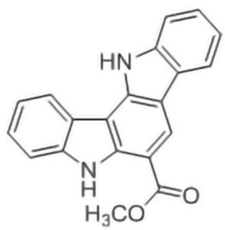

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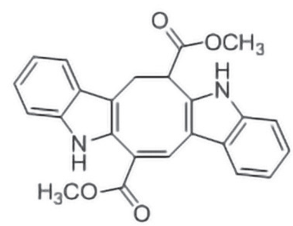

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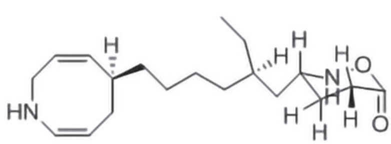

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Alkaloids from different seaweeds

SEAWEED PROTEINS AND PEPTIDES

GLYCOPROTEINS

Glycoproteins are proteins chemically bonded to various oligosaccharide chains, commonly known as glycans. Within glycoproteins, two primary types of sugar chains exist, distinguished by N-glycosyl or O-glycosyl linkages . These glycoproteins are situated on the cell wall, cell surface, or are released freely post-secretion, playing crucial roles in intercellular interactions and recognition processes. The proportions of proteins and sugars within glycoproteins vary among different algae species. For instance, Glycoproteins-rich fractions from Ulva species. exhibited a protein content of up to 33.4% . In contrast, Codium decorticatum, featuring glycoproteins with a molecular weight (MW) around 48 kDa, displayed a protein proportion as high as 60% . Regarding the composition of the prosthetic fraction, it appears that seaweed glycoproteins predominantly consist of mannose.

PBPs

PBPs, or phycobiliproteins, are water-soluble chromophore proteins found primarily in cyanobacteria and red seaweeds. Their main role is to absorb light during photosynthesis, aiding in metabolic processes . There are four classes of PBPs, each with distinct colors: phycocyanin (blue, λmax: 610-620 nm), phycoerythrocyanin (magenta, λmax: 575 nm), allophycocyanin (bluish-green, λmax: 652 nm), and phycoerythrin (deep red or pink, λmax: 540-570 nm) . In red seaweeds, the major PBP is phycoerythrin, with phycoerythrobilin as its primary prosthetic group.

PBPs serve as natural pigments in food, replacing synthetic dyes, and function as fluorescent probes in research . Beyond these applications, ongoing studies explore the potential of PBPs for nutraceutical development, given their bioactivities, including anti-viral, anti-cancer, antioxidant, and anti-inflammatory properties.

Peptides derived from seaweeds, often referred to as Seaweed Bioactive Peptides (BAPs), are short chains of amino acids with notable bioactive properties. Extracted from various seaweed species, these peptides have gained attention for their diverse biological activities, including antioxidant, anti-inflammatory, and antimicrobial effects. Due to their potential health benefits, seaweed peptides are being explored for use in functional foods, nutraceuticals, and cosmetics. Their unique composition and bioactive functions make them a promising area of research for applications in improving human health and well-being.

Trypsin obtained from *Gracilariopsis lemaneiformis* shows ACE inhibitory activity with IC_{50} value 0.25 mg/mL. α-Chymotrypsin obtained from the same species possess DPPH radical scavenging activity with EC_{50} 1.51 mg/mL.

PHENOLIC COMPOUNDS

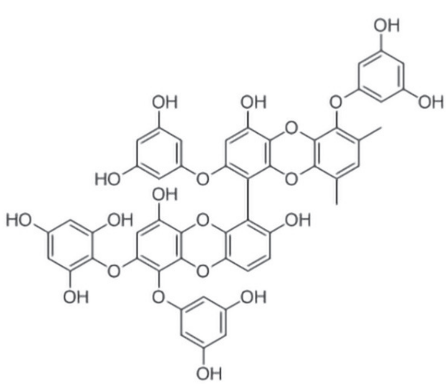
Marine macroalgae serve as a significant reservoir of polyphenolic compounds, including catechins, flavonols, and notably, phlorotannins. Green and red algae predominantly contain bromophenols, phenolic acids, and flavonoids among their phenolic compounds. In contrast, marine brown algae stand out for containing phlorotannins, a group of intricate polymers derived from phloroglucinol (1,3,5-trihydroxybenzene) .

Phlorotannins, distinctive to brown algae, are categorized into six primary subclasses: eckols, fuhalols, fucophlorethols, phlorethols, fucols, and ishofuhalols. These compounds manifest in both soluble and cell-wall-bound forms, playing a crucial role in maintaining the physiological integrity of algae. Furthermore, they contribute to various secondary functions. They exhibit potential health benefits across a spectrum of human diseases, attributed to their enzyme inhibitory effects, as well as their antioxidant antimicrobial, antiviral, anticancer, antidiabetic, antiallergic, and anti-inflammatory activities.

The capacity of naturally existing polyphenols and phlorotannins extracted from specific brown seaweed species (*Ascophyllum nodosum, Fucus vesiculosus, Ishige foliacea)* to inhibit α-amylase and α-glucosidase enzymes in laboratory settings is associated with a decrease in carbohydrate absorption observed in living organisms. These discoveries underscore the promising prospect of employing these compounds as potential agents in the management of type 2 diabetes.

The ethyl-acetate extract derived from Fucus distichus, containing phloratannin oligomers, has been documented to impede lipid accumulation by enhancing lipolysis within cells. Moreover, in adipocytes, the extract demonstrated a dose-dependent reduction in the gene expression levels of pro-inflammatory markers such as TNF-α (tumor necrosis factor alpha), MCP-1 (monocyte chemoattractant protein-1), ICAM (intercellular adhesion molecule 1), and the adipokine leptin. Simultaneously, it increased the expression of the anti-inflammatory adipokine adiponectin. These observed alterations suggest that the phenolic-enriched extract holds potential in alleviating the inflammatory conditions associated with adipose tissue, a factor contributing significantly to the development of cardiovascular events in individuals with obesity.

The phlorotannins 2,7″-phloroglucinol-6,6′-bieckol(1), phlorofucofuroeckol A(2) and diphlorethohydroxycarmalol have been reported to reduce postprandial hyperglycaemia in diabetic mice, an effect most probably related to their ability to inhibit α-amylase or α-glycosidase.



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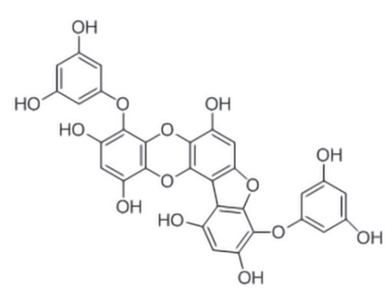

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Polyphenols from different seaweeds

CARBOHYDRATES IN SEAWEEDS

Polysaccharides derived from seaweeds, commonly known as marine algae, display a diverse array of biological activities, rendering them valuable in multiple sectors, including pharmaceuticals, nutraceuticals, and cosmeceuticals. The distinct polysaccharides found in various types of seaweeds contribute to their wide-ranging biological effects. Alginate, sourced from brown seaweeds like kelp and brown algae, exhibits exceptional gelling and thickening properties, making it beneficial in the food industry. Additionally, its wound healing and anti-inflammatory characteristics have spurred investigations into its potential for drug delivery systems owing to its biocompatibility.

Carrageenan(1), obtained from red seaweeds such as Irish moss and red algae, serves as a prominent thickening and gelling agent in the food industry. Beyond its culinary applications, carrageenan demonstrates antiviral and anti-inflammatory properties, prompting research into its potential as an anticoagulant and treatment for respiratory infections.

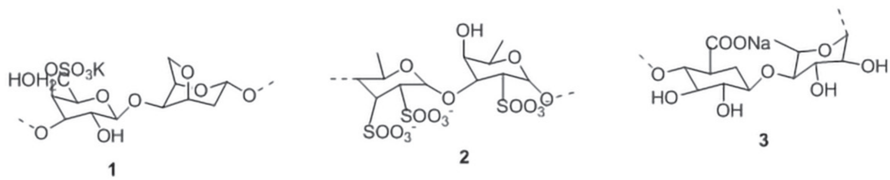
Fucoidan(2), derived from brown seaweeds like bladderwrack and kombu, boasts a plethora of biological activities, including anticoagulant, anti-inflammatory, antioxidant, antiviral, and anti-cancer properties. This versatility positions fucoidan for potential applications in cardiovascular health, immune system modulation, and cancer prevention.

Ulvan(3), sourced from green seaweeds like Ulva species, showcases antioxidant, anticoagulant, and immunostimulatory properties. Its potential applications in the pharmaceutical and nutraceutical industries stem from its role in preventing oxidative stress and promoting immune health.

Agar, extracted from red seaweeds such as Gracilaria and Gelidium species, is widely utilized in the food industry for its gelling properties. Its investigated potential encompasses antiviral, antimicrobial, and anti-inflammatory effects, with agar-based hydrogels under scrutiny for drug delivery applications.

Laminarin, originating from brown seaweeds like kelp and brown algae, exhibits immunomodulatory effects by activating macrophages and natural killer cells. Ongoing research explores its potential in enhancing the immune system.

These diverse biological activities position seaweed-derived polysaccharides as promising candidates for applications in medicine, biotechnology, and the food industry. It is crucial to recognize that the specific activities vary based on seaweed species, extraction methods, and polysaccharide chemical structures. Ongoing research endeavors aim to uncover new applications and deepen our understanding of the mechanisms underpinning these beneficial effects.



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Polysaccharides from different seaweeds

CONCLUSION

Marine natural products derived from seaweeds represent a vast and valuable resource with diverse applications in various industries. Seaweeds, or marine algae, are rich repositories of bioactive compounds, including polysaccharides, peptides, polyphenols, and phycobiliproteins, among others. These compounds exhibit a wide range of biological activities, making them of immense interest in pharmaceuticals, nutraceuticals, cosmeceuticals, and other fields. The polysaccharides found in seaweeds, such as alginate, carrageenan, fucoidan, ulvan, agar, and laminarin, display remarkable properties such as gelling, thickening, and immunomodulation. These polysaccharides have been explored for their potential in wound healing, drug delivery systems, and various health applications. Additionally, the specific biological activities vary among seaweed species, highlighting the need for further research to understand their mechanisms and optimize their utilization. Phycobiliproteins (PBPs) are hydrosoluble chromophore proteins mainly found in cyanobacteria and red seaweeds. With classes like phycocyanin, phycoerythrocyanin, allophycocyanin, and phycoerythrin, PBPs serve as natural pigments in food, replacing synthetic dyes, and as fluorescent probes in research. The bioactive potential of PBPs, including anti-viral, anti-cancer, antioxidant, and anti-inflammatory properties, has sparked interest in their development for nutraceutical applications. Furthermore, the marine natural products from seaweeds are gaining recognition for their sustainability and eco-friendly characteristics. Seaweeds are abundant in the world's oceans, and their cultivation requires minimal freshwater and arable land. As the demand for sustainable and environmentally friendly alternatives increases, seaweed-derived products offer a promising solution. The exploration of marine natural products from seaweeds is an ongoing and dynamic field of research. The diversity of compounds and their versatile applications underscore the significance of continued investigation. Researchers are delving into unexplored seaweed species, optimizing extraction methods, and elucidating molecular mechanisms to unlockthe full potential of thesemarine resources. The integration of advanced technologies, such as genomics and metabolomics, enhances our understanding of the chemical composition and biological activities of seaweed-derived compounds, paving the way for innovative applications. In summary, marine natural products from seaweeds stand at the intersection of biodiversity, sustainability, and technological innovation. Their multifaceted benefits contribute to the development of novel products with the potential to address various health, environmental, and industrial challenges, making them a promising frontier in the ongoing quest for sustainable and bioactive resources.

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