Chapter

# Nutraceuticals from Microbes of Marine Sources

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## Abstract

Therapeutic compounds can be derived from various natural sources like plants, animals, marine organisms, and microorganisms. Although the marine biota accounts for around 50% of the total world biodiversity, but their potential as a rich source of bioactive products and their applications in both pharmaceutical and nutraceutical industries have only recently been identified through several scientific studies. Marine biotechnology is an upcoming area that involves about the study of marine microorganisms and animals including algae, sponges, and coral as a novel source of bioactive substances that can be used in the treatment of various human diseases like cancer, anemia, diarrhea, obesity, diabetes, atopic dermatitis, Crohn's disease, etc. They are also potential sources of natural antioxidants, colors, immunosuppressants, enzyme inhibitors, hypocholesterolemic agents, vitamins, enzymes, and antibiotics. However, marine microorganisms have not yet been given the attention they deserve and a very limited scientific data is available on bioactive potential of marine microorganisms. There is still scope for a higher magnitude of research and investigation to explore the potential of both marine organisms and marine microorganisms as producers of novel drugs. This chapter deals with the exploitation of microbes from marine sources as potential sources for various nutraceuticals and their possibilities for applications in variety of diseases and as functional food supplement.

**Keywords:** microbes, nutraceuticals, marine organisms, functional food, bioactive compounds

## 1. Introduction

It is well-known that more than 70% of our planet's surface is covered by oceans. Experts estimate that the biological diversity in marine environment is higher than in tropical rain forests. Marine water contains enormous amounts of biodiversity which makes it as a source of huge amounts and wide varieties of novel bioactive compounds. The majority of the marine microbiota is soft bodied and follows a sedentary life style, thus requiring the other means of defense systems mainly by producing certain biochemical compounds that are generally toxic to the other animals. These toxic substances also aid them in detecting their harmful predators, and help them to protect themselves from their competitors or they can even paralyze their enemies. The biodiversity of marine microflora is overwhelming and there is an urgent need to explore and exploit their potential as biotherapeutic agents. These biotherapeutic compounds are usually synthesized as secondary metabolites by the marine microflora and fauna. The disadvantage is that since these natural products are synthesized and released extracellularly into the water so they are rapidly diluted and, therefore, their potency should be very high to show any effect. It is well-known that a large number of novel bioactive natural compounds are found in the oceans, and deep sea possessing various biological properties that can be exploited for discovering various drugs with improved efficacy and action in the treatment of various human diseases like cancer, anemia, diarrhea, obesity, diabetes, atopic dermatitis, Crohn's disease, etc. [1, 2].

The oceans are the source of a large group of structurally unique natural products that are mainly accumulated in invertebrates such as sponges, tunicates, bryozoans, and mollusks.

Macroalgae (or seaweed) are one of the most well-known types of algae used in the production of various nutraceuticals or dietary supplements. They are a rich source of valuable bioactive substances with both therapeutic and preventative effect. They have been used to develop a great variety of food and food ingredients, especially in Asian countries including Korea, Japan, and China. It is estimated that China and Indonesia are by far the largest seaweed producers with over 23 million tons of aggregated production in 2014 [3]. About 2400 natural products have been isolated from macroalgae belonging to the classes Rhodophyceae, Phaeophyceae, and Chlorophyceae [4]. Presently, seaweeds constitute commercially important marine renewable resources which are providing valuable ideas for the development of new drugs against diabetes, microbial infections, and inflammations [5]. Algal constituents include acids, alkaloids, amines, antibacterial, antifungal, antiviral substances, lipids, sterols, steroids, fatty acids, phenolic compounds, phytochromes, pigments, proteins, peptides, amino acids, sugar, alcohols, and vitamins. *Gracilaria opuntia* belongs to the family Rhodophyceae (Red algae) and possesses various biological activities.

The potential of marine microorganisms in producing various bioactive metabolites is due to their unique biochemical and physicochemical properties inherited by them in order to survive in extreme environmental conditions in the marine environment. These unique bioactive "bioceuticals" have tremendous potential for use as active pharmaceutical ingredient (API) and in food supplements to design various nutraceuticals [6].

Most of the bioactive compounds are having numerous biological activities which are found to act as nutraceuticals for humans and animals. Thus, the marine microflora contributes an important source of various bioactive constituents. Due to the great diversity of the marine flora, the chemistry of its associated bioactive compounds is also novel [7]. The marine flora includes a wide range of organisms from sponges, tunicates, bryozoans, mollusks to bacteria, microalgae, macroalgae, and cyanobacteria. The bioactive metabolites produced as a result of their metabolic activity is therefore effective in treatment of both infectious and non-infectious diseases.

Marine microflora including algae are widely used in the development of various nutraceuticals and are also used as food source or food ingredients [8]. Algae include both the micro- and macroforms and both the types are used as nutraceuticals. Microalgae are the most primitive and simply organized algae present in marine environment. They are the rich sources of various food nutrients and vitamins such as beta-carotene (vitamin A), vitamin C, E, H, $B_1$, $B_2$, $B_6$, and $B_{12}$, astaxanthin, polysaccharides, and polyunsaturated fatty acids [9]. These bioactive compounds are extracted from the microalgae and are used as food additives, fortifying infant milk, and other dietary supplements [10]. These compounds (especially the tunicate metabolite ET-743) have also shown good pharmacological properties and can be used to develop new drugs for cancer treatment. Some other compounds such as ziconotide obtained from the mollusk (*Conus magus*) are used as analgesics and anti-inflammatory. Natural products localized in symbiotic bacteria or cyanobacteria from marine invertebrates exhibits striking structural similarities with the known microbial metabolites; suggesting that bacteria and microalgae are involved in their biosynthesis and are the true sources of these metabolites. Nowadays, molecular techniques are used to study the microbial diversity in marine sponges and to study the involvement of bacteria in the biosynthesis of the bryostatins in the bryozoan *Bugula neritina* [2].

## 2. Marine microorganisms as source of nutraceuticals

A study reported that some unidentified prokaryotic communities, such as the JS1 and DSAG groups, occur widely in organic rich deep marine sediments associated with methane hydrates along the Pacific Ocean margin. The microflora is present in deep marine sediments and their community structure is affected by the surrounding geochemical and geological settings. Various studies have shown that many classes of microorganisms exist only in the sea [11]. Thus, limited scientific data is available on the growth media and culture techniques for culturing these marine microbes.

Many pharmaceutical industries have not been able to fully utilize this important resource. There is a general belief that marine microorganisms are difficult to culture; however, now there are a number of reports that showed that these marine microorganisms can be successfully cultured [12]. Thus, now many of the developed and underdeveloped countries have shifted their research focus on the marine habitat and new marine-oriented projects are emerging worldwide. Majority of microbes belonging to class bacteria and fungi are now the target of biomedical study. The coastal bacterial samples that grow under saline conditions are a source of novel antibiotics, antitumor, and anti-inflammatory compounds [13]. The symbiotic microbial consortia have also been proven to be a rich source of bioactive compounds with pharmaceutical potential. Many bacteria and fungi have been sampled from the surfaces of marine plants and the internal tissues of invertebrates, and they have been found to be of increasing interest [14].

### 2.1 Marine bacteria

Marine bacteria are prolific producers of valuable secondary metabolites as they thrive in harsh oceanic climates. The marine isolate *Pseudomonas*, Gram-negative, γ-proteo-bacteria is not well explored and only a limited number have been reported as producers of bioactive compounds. A bacterium strain KMM 3042 that is aerobic, non-pigmented, produces some bioactive substances such as pyrroles, pseudopeptide pyrrolidinedione, phloroglucinol, phenazine, benzaldehyde, quinoline, quinolone, phenanthren, phthalate, andrimid, moiramides, zafrin, and bushrin [15]. Some of these bioactive compounds are antimicrobial agents, and dibutyl phthalate and di-(2-ethylhexyl) phthalate have been reported to be cathepsin-B inhibitors [16].

*Stenotrophomonas* strains isolated from sponge, sea urchin, and ophiura specimens showed remarkable antimicrobial and antifungal inhibitory activity. However, they showed negligible activity against *Candida albicans*, but these strains could substantially inhibit Gram-positive microorganisms. Though *Stenotrophomonas maltophilia* is an opportunistic pathogen, it also possesses biocontrolling capabilities [17]. Low molecular weight antimicrobial metabolites have also been reported from marine ark shell *Anadara broughtoni* associated heterotrophic bacteria (butanol extracts) that exhibit strong antimicrobial, hemolytic, and surface activities [18]. Another recently discovered genus of bioactive substance producing marine bacteria is *Pseudoalteromonas*, the seawater species *P. phenolica* was reported to inhibit methicillin-resistant *Staphylococcus aureus* (MRSA) strains due to the presence of a brominated biphenyl compound, 3,3″,5,5″-tetrabromo-2,2″-diphenyldiol [19]. Some strains of *Pseudoalteromonas luteoviolacea* have also been shown to inhibit the growth of protists [20]. Other marine invertebrates have also been shown to be a source of novel bioactive compound which was later identified as a tambjamine (4-methoxypyrrole-containing bioactive compounds) like alkaloid and re-designated as YP1 [21]. *Pseudoalteromonas tunicate* is associated with them and produces a yellow pigment that possesses antifungal activity [20, 22]. These tambjamines are also known to possess antimicrobial, antitumorigenic, immunosuppressive, antiproliferative, and ichthyo-deterrent activities [20]. There are other evidences that points toward the colonizing bacteria present at the surface of higher organisms as the source of these compounds [23]. These studies have been further proven by Burke and colleagues by elucidation of YP1 biosynthetic pathway in *Pseudoalteromonas tunicata* [24].

### 2.2 Marine-derived fungi

Marine fungi have been known to produce a wide variety of bioactive metabolites that possess anticancer, antibacterial, antiplasmodial, anti-inflammatory, and antiviral activity [25, 26]. This is due to the presence of some unique and exceptional carbon frameworks in them. These novel compounds are used as new lead structures for medicine and for plant protection. The detailed procedure for their isolation and cultivation from various marine organisms (sponges, algae, and mangrove plants) has been given by Kjer et al. [27]. They have also elucidated the structure of secondary metabolites produced by these fungi. A novel anthraquinone derivative with naphtho [1,2,3-de]chromene-2,7-dione skeleton was isolated from a marine filamentous fungus, *Aspergillus glaucus* in the Fujian province of China and named aspergiolide A [28]. It was found to exhibit cytotoxicity against K562 and P388 cell lines. Similarly, *Penicillium* sp., isolated from deep ocean sediment was found to exhibit antitumor activities in their alkaloid-rich extracts due to the presence of meleagrin D and E and roquefortine H and I. However, they exhibited weak cytotoxicity in comparison to the previously reported meleagrin B and meleagrin that functions by inducing HL-60 cell apoptosis and can also arrest the cell cycle through G2/M phase, respectively. The mode of action was the distinct substitutions on the imidazole ring that have a significant influence on the cytotoxicity of these alkaloids [29]. Some other novel compounds and metabolites were also isolated and characterized from marine fungi *Ampelomyces* sp. that possesses potent antimicrobial and antifouling compounds. The antilarvicidal effect was due to the presence of compound 3-chloro-2,5-dihydroxybenzyl alcohol that effectively inhibited larval settlement of the tubeworm *Hydroides elegans* and of cyprids of the barnacle *Balanus amphitrite.* The compound is non-toxic and is also a potent antifoulant and/or antibiotic agent [30]. Another example of marine-derived fungus *Cladosporium* sp. also exhibited antibiotic and antifouling activity. It was later named as strain F14. The fungus produced the bioactive compounds in nutrient enriched cultivation media, in the presence of glucose or xylose [31]. Another study reported the marine-derived fungus *Fusarium* sp. (strain 05JANF165) to possess novel antimitotic and antifungal activity from its ethanol extracts. This compound was later identified and named as Fusarielin E [32].

Another marine-derived fungus of the genus *Pseudallescheria* was reported to produce a novel antibacterial dioxopiperazine, dehydroxybisdethiobis-methylthiogliotoxin from its broth. All three compounds exhibited potent antibacterial activity against the methicillin-resistant and multidrug-resistant *Staphylococcus* *aureus*, whereas Gliotoxin showed a significant radical scavenging activity against 1,1-diphenyl-2-picrylhydrazyl (DPPH) [33].

A marine isolate of the fungus *Exophiala* was also reported to exhibit a mild antibacterial activity against *Staphylococcus aureus* due to the presence of two novel antibacterial aspyrone derivatives, viz., Chlorohydroaspyrones A and B, and the previously described aspyrone, asperlactone, and penicillic acid from its broth [34].

Marine fungi also exhibited nematicidal effect along with antimicrobial activity. The same activity has also been reported from marine ascomycete *Lachnum papyraceum* (Karst.) [35].

Another marine-derived *Phoma herbarum* strain was reported with significant radical scavenging activity against DPPH due to the presence of halogenated benzoquinones (bromochlorogentisylquinones A and B) [36].

### 2.3 Marine-derived actinomycetes

Actinomycetes are well-known to be the producers of secondary metabolites. Many well-known antibiotics, such as streptomycin, erythromycin, and tetracycline, with potent biological activities are produced by them [37]. Many marine-derived actinomycetes were found to be the producers of novel antitumor [38], antimalarial [39], and antimicrobial compounds [40, 41]. Another marine-derived actinomycete namely *Nocardiopsis lucentensis* produced four novel 3-methyl-4-ethylideneproline-containing peptides called as Lucentamycins A-D from their fermentation broth [42]. Only compound Lucentamycins A and B exhibited strong *in vitro* cytotoxicity against HCT-116 human colon carcinoma [42]. In a similar study, marine-derived isolate of *Streptomyces* sp. were found to produce four new derivatives, Mansouramycin A-D, and the known 3-methyl-7-(methylamino)-5,8-isoquinolinedione from their ethyl acetate extract. These bioactive compounds, exhibited strong cytotoxicity with great degree of selectivity for non-small cell lung cancer, breast cancer, melanoma, and prostate cancer cells [43] suggesting their potential as anticancer drugs. Similarly, Perez and coworkers [44] isolated a macrodiolide Tartrolon D from the fermentation broths of *Streptomyces* sp. MDG-04-17-069. The isolated tartrolon was found to exhibit strong cytotoxic activity against three human tumor cell lines, viz., lung (A549), colon (HT29), and breast (MDA-MB-231) [44]. In yet another study, the secondary metabolites of a marine *Saccharomonospora* sp. yielded a novel alkaloid Lodopyridone, was found to be cytotoxic to HCT-116 human colon cancer cells [45].

Besides their antitumor and anticancerous potential, marine actinomycetes are also known for their antimicrobial activities also. A marine actinomycete, *Marinispora* was used to isolate a series of chlorinated bisindole pyrroles, Lynamicins A–E that exhibited a broad-spectrum antimicrobial activity against both the groups of Gram-positive and Gram-negative bacteria. These compounds were also effective against important drug-resistant pathogens, such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus faecium* [41]. In a similar study, Carlson et al. [46] isolated the two novel bioactive compounds namely dienoyl tetramic acids tirandamycin C and D from the marine environmental isolate *Streptomyces* sp. These compounds were effective against vancomycin-resistant *Enterococcus faecalis* and are structurally similar to the previously identified compounds Tirandamycins A and B with a slight variation in the pattern of pendant oxygenation on the bicyclic ketal system.

Similarly, ethyl acetate extract of *Streptomyces* sp. isolate B8652 was used to isolate Trioxacarcins A, B, and C along with three new derivatives designated as Trioxacarcins D, E, and F [47]. These types of trioxacarcins exhibited good antimicrobial, antitumor, and antimalarial activity. Similarly, the crude extract of a marine *Streptomyces* strain that was isolated from deep sea sediments, exhibited potent antifouling activity [48].

In yet another study, a marine-derived *Actinomyces* strain (NPS554) that was isolated from Japan yielded two trialkyl-substituted aromatic acids, Lorneic acid A and B. It was observed that Lorneic acid-A had significant inhibition activity against phosphodiesterase (PDE)5 [49]. PDE5 inhibitors are of great pharmacological importance as they are used in erectile dysfunctions and pulmonary hypertension.

### 2.4 Marine-derived microalgae

Cyanobacteria are a diverse group of Gram-Negative bacteria, also known as blue-green algae that produce an array of secondary metabolites with antifungal, antiviral, antibiotic, and other properties. They also exhibit selective bioactivity against vertebrates, invertebrates, plants, microalgae, fungi, bacteria, viruses, and cell lines [50]. Thus, they are of great pharmaceutical value. Besides, there are other anticancer compounds, which were initially thought to be obtained from marine sources, are now known to be produced by cyanobacteria [51]. Ulithiacyclamide and Patellamide A belong to Cyanobactins, produced by cyanobacteria; possess potent antimalarial, antitumor, and multidrug reversing activities [52].

Some other examples of marine cyanobacterial bioactive natural products are viridamides A and B. It was observed that Viridamide A produced by a blackish-green, mat-forming, filamentous cyanobacterium *Oscillatoria nigroviridis* showed antitrypanosomal, and antileishmanial activity [53]. In yet another study, the crude extracts of four green marine algae (*Cladophora rupestris*, *Codium fragile sp. tomentosoides*, *Ulva intestinalis*, and *Ulva lactuca*) were found to exhibit antiprotozoal activity [54]. All the algal extracts were active against *T. brucei rhodesiense*, and exhibited potent leishmanicidal activity [54]. This study was reportedly the first study to show antiprotozoal activity of British marine algae. Further, Desbois et al. [55] isolated an antibacterial polyunsaturated fatty acid, eicosapentaenoic acid (EPA) from the marine diatom, *Phaeodactylum tricornutum Bohlin*, which showed activity against a range of both Gram-positive and Gram-negative bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA) [55].

Both micro- and macroalgae are used as nutraceuticals. Studies have shown that microalgae are rich sources of all the vital nutrients such as beta-carotene, vitamins C, A, E, H, $B_1$, $B_2$, $B_6$, and $B_{12}$, astaxanthin, polysaccharides, and polyunsaturated fatty acids [9]. Thus, their bioactive molecules are produced commercially for use as food additives, infant milk formulations, and dietary supplements [10].

Macroalgae, are also commonly known as seaweeds. They are the most popular type of algae in the nutraceutical industry and are used in a great variety of food and food ingredients, especially in Asian countries like Korea, Japan, and China. Macroalgae are also well-known for the production of agarose. They are also an important source of many bioactive metabolites and natural products that possess many nutritional and therapeutic functions. Some of the examples of bioactive constituents are proteins, furanone, polyunsaturated fatty acids (PUFA), L-α kainic acid, phenotics, pigments, phlorotannins, phyco-colloids (carrageenan and agar), and minerals. Likewise, red and brown seaweeds are also good sources of many vitamins, minerals, proteins, and essential fatty acids [56, 57]. They are also used to prepare bioactive peptides and to improve protein digestibility. Further, antihypertensive bioactive peptides have also been isolated that can act as angiotensin-converting enzyme (ACE) inhibitors [58].

### 2.5 Symbiotic interaction between marine microbes

Symbiosis is the mutual association between any two organisms for their mutual benefit that can be in terms of their nutritional needs or protection from prey.

Research studies have shown that a variety of secondary metabolites are produced as a result of this association especially obtained from algae and invertebrates. Their associated microbes perform various biological activities [59]. Some of the various marine fungi isolated are *Haliclona simulans*, *Agaricomycotina*, *Mucoromycotina*, *Saccharomycotina*, and *Pezizomycotina* [60]. A variety of media were used for their isolation and identification and their antimicrobial activities were also determined. Some of these isolates exhibited antimicrobial activity against *Escherichia coli*, *Bacillus* sp., *Staphylococcus aureus*, and *Candida glabrata* [60]. It has been found that sponge-microbial association is a potential chemical and ecological phenomenon that can serve as a sustainable resource for generating novel pharmaceutical leads. Thus, sponge microsymbionts are an important focus nowadays [61, 62]. In yet another study, a marine-derived fungal strain named M-3 was isolated from marine red alga *Porphyra yezoensis.* It was assessed for its antifungal activity against *Pyricularia oryzae* [63]. As a result, a novel compound diketopiperazine was isolated from the culture extracts and its structure was also elucidated by spectroscopic methods.

In another study, the butanol extracts of algal associated species *Pseudoalteromonas issachenkonii* were reported to show hemolysis and inhibition of *Candida albicans*. Their ethyl acetate extracts were also subjected to spectroscopic studies and revealed the presence of indole-2,3-dione, a type of isatin that was responsible for its antifungal activity [63]. In another study, a red-brown hemolytic pigment was also discovered [64]. Coral reefs widely prevalent in oceans are also unexplored source of novel bioactive compounds [65].

In another study, a marine gorgonian associated bacterium *Bacillus amyloliquefaciens* was isolated from the South China Sea gorgonian, *Junceella juncea.* The studies showed their antibacterial against *Escherichia coli*, *Bacillus subtilis*, and *Staphyloccocus aureus* and antilarval properties against the larvae of bryozoan *Bugula neritina*. In yet another study, an antimicrobial activity of about 42 marine bacterial strains belonging to genera *Alteromonas*, *Pseudomonas*, *Bacillus*, and *Flavobacterium* was reported [66]. Besides this, certain mycoparasitic and fungicolous fungi were also shown to colonize other fungal physiological structures and were known to produce various bioactive agents [67]. In a study, five new natural products, Phomadecalins A, B, C, D, and Phomapentenone A, were reported from cultures of *Phoma* sp., a mitosporic fungal colonist isolated from the stromata of *Hypoxylon* sp. These bioactive compounds were found to be active against Gram-positive bacteria, *Bacillus subtilis* (ATCC 6051) and *Staphylococcus aureus* (ATCC 29213) [68].

## 3. Classification of marine nutraceuticals on the basis of chemical nature

Marine nutraceuticals can be broadly classified into Marine lipids (microalgal origin), polysaccharides derived from macro algae, marine probiotics, marine natural pigments, chitin and other related products, bioactive marine peptides/enzymes, and vitamins.

### 3.1 Lipids

Lipids derived from marine microalgae are used in larval nutrition of aquaculture, especially for enrichment of live feeds. Their other biological properties are anti-inflammatory, antiallergic, antiviral, and therapeutic. The wide spectrum of the properties is due to the presence of various components like polyunsaturated fatty acids (PUFA), highly unsaturated fatty acids (HUFA), and other substances. Various microalgal originated lipid/fatty acids and their activities [69] are given in **Table 1**.

| Microalgal lipid/fatty acid | Biological action/function |
|---|---|
| Eicosapentaenoic acid (EPA) | Nutraceutical; antimicrobial and anti-inflammatory |
| Gamma-linolenic acid (GLA) | Integrity of tissue and delay of aging |
| Arachidonic acid (ARA) | Aggregative and vasoconstrictive of platelets |
| Docosahexaenoic acid (DHA) | Nutraceutical and brain development |
| Brassicasterol and stingmasterol | Hypercholesterolemic |
| Gamma-amino-butyric acid (GABA) | Neuro-transmitter, antioxidant and anti-inflammatory |
| Okadaic acid | Antifungal and promotion of the secretion of nerve growth factor (NGF) |
| Microcolin-A | Immunosuppressive |

**Table 1.**
*Microalgal lipid/fatty acids and their activity.*

### 3.2 Polysaccharides

Generally, bacterial capsules contain polysaccharides. They form one of the important classes of secondary metabolites that are also important from pharmaceutical point of view. Research studies have shown that these exopolysaccharides (EPS) particularly from marine bacteria can be used in various pharmaceutical and food processing agents. They can also be used in industries as thickeners, coagulating agents, adhesive agents, stabilizers, and as gelling agents. The exopolysaccharides possess good viscosity and pseudo-plastic properties that impart them ability to resist extremes of temperature, pH, and salinity. This increases their potential to be used as an industry friendly resource [70]. In a study, exopolysaccharides have been shown to possess immunomodulatory and antiviral properties on immunocompetent cells in a marine bacteria *Geobacillus thermodenitrificans* that was isolated from a shallow marine vent of Volcano Island (Italy). This bacterium not only produced secondary metabolites against other organisms, but also produced certain compounds which help in bioremediation [71]. Certain other marine bacterial species are known as prolific producers of biosurfactants, bioemulsifiers, and exopolysaccharides.

Some polysaccharides are also derived from macroalgae. Seaweeds contain higher amounts of the polysaccharides like agar, alginates, and carrageenan. These act as food fiber and are collectively called phyco-colloids or hydrocolloids. Being rich in fiber, seaweeds exhibit health benefits like reducing the absorption of toxins, anticarcinogenic, and antioxidant properties. Example of the few important bioactive polysaccharides isolated from macroalgae (seaweeds) that possess the potential to be used as nutraceuticals are Fucoidan, Sphinganine amide, and caulerpicin (green algae), Carrageenan, Alginic acid and xylofucans, Hyperoxaluria, Sulfated polysaccharides, and Alginates. All these compounds possess wide range of biological properties such as antioxidant, antiangiogenic, antibacterial, antiviral and antitumor activities anticoagulant, immuno-modulating, hypolipidemic, and anti-inflammatory [72]. In addition to the phyco-colloids, seaweeds are sources of biologically active phytochemicals like carotenoids, phycobilins, fatty acids, vitamins, sterols, tocopherol, phycocyanins, and others.

Macroalgae are also rich sources of insoluble and soluble dietary fiber. They contain chiefly indigestible sulfated polysaccharides. Some of the notable examples of structural and storage polysaccharides are fucan, agar, laminaran, carrageenan, and alginates that are found both in red and brown seaweeds. The alginates obtained from brown seaweeds are used as hydrocolloids and fucans from brown seaweeds are used in both food and cosmetics industries [73].

A research highlighted the role of marine bacteria *Bacillus circulans* in the biodegradation of anthracene (a polyaromatic hydrocarbon) [74]. The said bacteria also produced a novel type of biosurfactant that exhibited excellent emulsification properties. It was shown that *Bacillus circulans* utilized anthracene as a sole carbon source for the production of biosurfactant. The researchers also reported the production of another biosurfactant by an unnamed marine bacteria that has the ability to remove metal from solutions [75].

### 3.3 Bryostatins: bryozoan origin

The marine bryozoan, *Bugula neritina*, is the sole source of the bryostatins, a family of macrocyclic lactones with anticancer activity. Bryostatins are actually the bacterial products as *B. neritina* harbors the uncultivated gamma proteobacterial symbiont *Candidatus Endobugula sertula*. The clinical studies of bryostatins are also under going to study their potential for the treatment of leukemias, lymphomas, melanomas, and solid tumors [76]. Their mode of action is that they act through protein kinase C signal transduction to alter cellular activity.

### 3.4 Probiotics: marine lactic acid bacteria (LAB) origin

Microbial diversity of marine environments is very rich and can be helpful to develop safe and effective probiotics. Novel marine probiotics can be an effective alternative for fighting the antibiotic resistance. *Lactobacillus* and *Bifidobacterium* are found to possess antimutagenic [77] and immunomodulatory [78] activity in host animal. Different strains of marine probiotic bacteria are *Lactobacillus* (*L. casei*, *L. acidophilus*, *L. rhamnosus* GG (ATCC 53013), *L. johnsonii* La-1), *Bifidobacterium* (*B. bifidum*, *B. longum*, *B. infantis*, *B. breve*, *B. adolescentis*), *Leuconostoc* spp. (*Ln. lactis*, *Ln. mesenteroides subsp. cremoris*, *Ln. mesenteroides subsp. dextranicum*), and *Streptococcus* spp. (*S. salivarius subsp. thermophiles*).

The problem posed during the development of new marine probiotics is the isolation and identification of potential strain. Application of biotechnological and molecular biological tactics is necessary for the development of marine probiotic strains for use of aquatic industry [72].

### 3.5 Pigments: marine algae

Besides polysaccharides and lipids, marine macro- and microalgae also provide various types of the bioactive natural pigments. The natural pigments of the marine algae provide food by photosynthesis and also provide the pigmentation. In addition to these, the natural pigments are also found to exhibit health benefits which make them one of the important marine nutraceuticals. Chlorophyll-a, Lutein, zeaxanthin, and canthaxanthin possess antimutagenic properties; pheophytin-a exhibits neuroprotective, and anti-inflammatory action; Chlorophyll-a, Pheophorbide-a, Pyropheophytin-a, Phycoerythrobilin, Lutein, Fucoxanthin, Phycocyanin, Astaxanthin, Zeaxanthin, and Canthaxanthin are all good antioxidants. Alpha-Carotene is also used as a food additive [72].

### 3.6 Chitosan: chitin

Chitosan is a natural polymer derived from chitin and it is the second most abundant polysaccharide after cellulose. Chitin is recovered from processing discards of shrimp, crab, lobster, and crayfish following de-proteinization and demineralization. The chitin so obtained may then be deacetylated to afford chitosan.

Fungal cell walls are also rich in chitin. Chitin and chitosan are used as biomaterials in a variety of application in edible film industry, additives, for improving nutritional quality, recovery of solid materials from food processing waste, in purification of water, etc. The other biological properties of chitosan are antioxidant, hypocholesterolemic, antimicrobial, and anti-inflammatory activities [79].

Chitosan disrupts the barrier properties of the outer membrane of Gram-negative bacteria due to ionic interaction between the cationic groups of the chitosan molecules and the anionic groups of the microbial cell membrane, which can rupture the cell membrane. Chitosan can also function as an antifungal agent by forming gas-permeable coats, interference with fungal growth and stimulation of various defense processes like, build-up of chitinases, production of proteinase inhibitors, and stimulators of callous synthesis.

The antioxidant property could be attributed to the ability of chitosan to chelate metals and combine with lipids. Derivatives of chitosan, namely, N,O-carboxymethyl chitosan, N,O-carboxymethyl chitosan lactate, N,O-carboxymethyl chitosan acetate, and N,O-carboxymethyl chitosan pyrrolidine carboxylate had also exhibited the antioxidant activity. Chitosan possesses special properties for use in pharmaceutical, biomedical, food industry, health, and agriculture due to its biocompatibility, biodegradability, and non-toxic nature. Through encapsulation, it is being used as a vehicle for nutraceutical compounds and pharmacological compounds. Chitosan derivatives may also be produced in order to obtain more effective products for certain applications [72].

### 3.7 Bioactive peptides/enzymes: marine origin

Peptides refer to the specific protein fragments that exhibit a specific biological activity. Some of the peptides may exhibit multifunctional properties like opioid, immunomodulatory, antibacterial, antithrombotic, and antihypertensive activity. Biofunctional peptides have a size range of 2–20 amino acid residues and are encrypted within the sequence of the parent protein and are released during processing. They can be formed either by acid or alkaline hydrolysis. The major bioactivities of peptides are antihypertensive (ACE inhibitory), antioxidant, antimicrobial, antihypoallergenic activity, and cell immunity [80].

Proteins isolated from bacteria such as *Dunaliella*, *Phaeodactylum tricornutum*, and *Arthrospira platensis* possess potent antioxidant and anti-inflammatory activity which can be effectively used in aquaculture practices. Similarly, enzymes such as superoxide dismutase and carbonic anhydrase derived from *Porphyridium*, *Anabaena*, *Isochrysis galbana*, and *Amphidinium carterae* play an important role in regulating the metabolite waste ($CO_2$).

### 3.8 Vitamins: marine microalgal origin

Marine microalgae are also known to have good amount of alpha-carotene. Microalgae like, *Arthrospira*, *Isochrysis galbana*, *Porphyridium cruentum*, and *Tetraselmis* are rich in vitamin C, K, A, E, and alpha-carotene which possess strong antioxidant activity. Vitamins A specially provitamin-A or alpha-carotene and vitamin E or alpha-tocopherol function as source of strong antioxidant compounds and protect the cells from free radical damage by quenching these free radicals. Vitamin E, together with vitamin C and alpha-carotene, helps in improving antioxidant defenses in the body. Fat soluble vitamin K isolated from Pavlova helps in blood clotting or coagulation. The role of antioxidant vitamins in health and disease control has been well documented [73]. Some of the important marine microorganisms, their bioactive metabolites and biological activity are highlighted in **Table 2** [20].

| Microorganism | Marine microbial metabolites | Biological activity |
|---|---|---|
| Cyanobacteria | Dolastatin-10 | Antimicrotubule; and the synthetic analog, TZT-1027, as antitumor |
| | Dolastatin-15 | Antimicrotubule; and the synthetic analog, ILX-651, as antitumor |
| | Curacin A | Antimicrotubule |
| | Toyocamycin | Antifungal |
| Actinomycetes | Resistoflavine | Anticancerous and antibacterial |
| | Marinomycin A | Antitumor and antibiotic |
| | Daryamide C | Antitumor |
| | Violacein | Antiprotozoal |
| Bacteria | Macrolactin S | Antibacterial |
| | Pyrone I and II | Antibacterial |
| | MC21-B | Antibacterial |
| Fungi | Meleagrin | Antitumor |
| | Oxaline | Antitumor |
| | Alternaramide | Antibacterial |
| Algae | Norharman | Enzyme inhibitor |
| | Calothrixin-A | Antimalarial and anticancerous |
| | Eicosapentanoic acid (EPA) | Treats heart disease, anti-inflammatory agent (rheumatoid arthritis and immunodeficiency diseases) |
| Symbiotic microbes | Macrolactin V | Antibacterial and antilarval |
| | DAPG | Antibacterial (anti-MRSA, anti-VRSA and anti-VRE) |
| | BE-43472B | Antibacterial (anti-MRSA and anti-VRE) |

**Table 2.**
*Name and biological activity of some of the marine microbial metabolites.*

## 4. Classical examples of some marine microflora and their nutraceutical potential

The oceans harbor one of the most diverse flora and fauna on our earth surface. Its biodiversity serves as an inexhaustible source of variety of biologically active compounds such as antibiotic, antimicrobial, anti-inflammatory, anticancer, antioxidant, antimicrotubule, cytotoxic, photo-protective, and antifouling properties. A variety of novel range of microorganisms, such as bacteria (both free living and symbiotic), fungi, actinomycetes, microalgae-cyanobacteria, and diatoms, are found in the marine environment that are potent producers of important therapeutic compounds. They have also been found effective against many deadly infectious diseases such as AIDS, drug-resistant bacteria, including conditions of multiple bacterial infections. Only little research has been done on the biophysical and biochemical properties, their chemical structures and biotechnological applications of these marine bioactive substances, and their potential utilization in both cosmeceuticals and nutraceuticals. Some of the research studies on bioactive molecules from marine sources are discussed below.

Seaweeds provide a rich source of bioactive molecules. In this study, the antimicrobial potential of Red sea weed, *Gracilaria opuntia* was investigated against clinically important microorganism such as *Escherichia coli*, *Staphylococcus aureus*, *Klebsiella pneumonia*, and *Pseudomonas putida* that cause diseases in diabetic patients. Crude extracts prepared from aqueous, ethanol, and methanol extraction procedures revealed that aqueous extraction procedure have a wide range of antimicrobial activity against all the test pathogens. The overall antibacterial activity assessed from the above results indicates the presence of active constituents in the extractions of seaweeds, which can be explored for the production of significant molecules that could be used in pharmaceutical industry [81].

In a similar another study on *Gracilaria edulis*, their phytochemical, antibacterial, and antifungal activities of crude extracts were investigated. The methanol and aqueous extracts of *Gracilaria edulis* showed the presence of a number of metabolites such as alkaloids, saponin, phenols, terpenoids, proteins, flavonoids, glycosides, coumarins, and tannins. The red algae showed the significant antibacterial activity against the clinical pathogens of *Pseudomonas aeroginosa*, *Staphylococcus aureus*, *Bacillus cereus*, *Bacillus subtilis*, *Streptococcus pyogenes*, *Salmonella typhi* as well as the fungus *Aspergillus niger*, *Aspergillus flavus*, *Rhizopus indicus*, and *Candida albicans*. The methanol extract showed the broader spectrum of antibacterial and antifungal activity when compared with aqueous extract [82].

In yet another study, the phytochemical and biological evaluation of some *Sargassum* species from Persian Gulf was also studied. These plants contain important phytochemical constituents and have various potential biological activities. The study investigated the presence of phytochemical constituents and total phenolic quantity of the seaweeds *Sargassum angustifolium*, *Sargassum oligocystum*, and *Sargassum boveanum*. Cytotoxicity and antioxidant potential of these three *Sargassum* species was also analyzed. *Sargassum angustifolium* had the highest content of total phenolics and showed the highest antioxidant activity. Cytotoxic results showed that all species could inhibit cell growth effectively, for *S. oligocystum*, *S. angustifolium*, and *S. boveanum*, respectively. Thus considerable phytochemicals and moderate cytotoxic activity of *S. angustifolium*, *S. oligocystum*, and *S. boveanum* make them appropriate candidate for further studies and identification of their bioactive principles [83].

Further study on screening the algae for their phytochemicals from their extracts and testing on their antibacterial, antifungal and antioxidant potential was carried out. The algal strains were *Tetraselmis* sp., *Dunaliella* sp., *Chlorella* sp., *Synechocystis* sp., and *Oscillatoria* sp. Their extracts were prepared in an organic solvent and were used to screen for the presence of any phytochemicals. Later, their antimicrobial activity was also assessed against some selected bacterial and fungal species. Their antioxidant activity was also determined by DPPH scavenging assay and confirmed the presence of flavonoids in majority of the solvent extracts. In addition, the microalgal strains exhibited better antifungal activity as compared to bacterial. The solvent acetone from *Dunaliella* sp. showed highest antioxidant activity. The results showed the presence of Octadecanoic acid-4-hydroxy-methyl ester, benzoic acid, hexadecanoic acid, and Tetradecanoic acid, confirming the bioactive compounds in the algal extracts [84].

## 5. Other marine sources of nutraceuticals

Besides the microbes (which contributes around 19%), there are other marine flora and fauna, such as sponges (38%), coelenterates (23%), algae (10%), echinoderms (7%), tunicates (7%), mollusks (3%), and bryozoans (2%), have also shown to exhibit their potential to produce various therapeutic compounds including some novel anticancer substances. These compounds can also work against infectious diseases and inflammation [85].

## 6. Current market of nutraceuticals

Nutraceuticals, including functional foods and dietary supplements, have tremendous market potential. It has been estimated that the consumer demand of these health foods were around $250 billion only in 2014 alone and this figure is continue to rise and is expected to reach around $385 billion by 2020 [86].

Nutraceutical products are in demand throughout the world especially in developed countries, including United States of America (USA), Europe, Japan, Asia Pacific, Middle East, and Latin America. In particular, the global market is dominated by the United States of America, Europe, and Japan, which account for more than 85% of the market [87]. As per the Mintel survey carried out in the United Kingdom on vitamins and minerals supplements, it was observed that 25% of all adult populations were satisfied with the results of the nutraceutical products. The percentage of the usage varied according to the age of the consumers like the consumption of nutraceutical products was more common in elderly population as compared with the younger generation. There is a strong belief that in the coming years, nutraceutical industry would remain at the forefront market including the Asian countries such as India and China. This is because of greater consumer awareness toward their health, increasing income levels and greater confidence in traditional and complimentary medicines [73].

The consumption of nutraceutical products in the USA is comparatively higher and accounts for approx. 40% of adults; in Spain, the nutraceuticals are consumed by the population aged between 35 and 80 years, and only around 9% consume dietary supplements as the source of vitamins and minerals. Besides, about 72% educated women that are of age between 35 and 49 years are more likely to choose nutraceuticals and dietary supplements [88].

In addition, the geriatric populations are also the most common consumers of these health supplements as they are more prone to micronutrient deficiencies. Due to the steady rise of geriatric population in developed countries, there is an urgent need to encourage and maintain a healthy lifespan and prevent chronic illnesses associated with aging [89].

Thus individuals with healthy lifestyles are more commonly the users of nutraceutical products.

## 7. Conclusion

From the above discussion, it is quite pertinent to conclude that the marine environment harbors variety of microbial flora that have capability to produce a wide array of bioactive metabolites that can be used both in nutrition and pharmaceuticals to formulate new drugs that are effective against various drug-resistant pathogens. Though the saga of marine microbial bioactive metabolites is continuing with new compounds being added day by day, our knowledge is still a miniscule of what exists deep in the oceans. Interdisciplinary research and collaborative endeavors are required amongst scientists, medical practitioners, marine microbiologists, and biotechnologists, to provide innovative approaches to marine based biomedical research. Thus, it is imperative to utilize our marine biodiversity and their bioactive metabolites for discovering new therapeutic compounds of nutraceutical importance. Recent biomedical tools, such as metabolomics and genetic engineering, can also be applied to increase their yield.

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## Conflict of interest

The author(s) confirm that this article content has no conflict of interest.

## Ethical issues

There is none to be declared.

## Abbreviations

| | |
|---|---|
| γ | gamma |
| DPPH | 1,1-diphenyl-2-picrylhydrazyl |
| PDE | phosphodiesterase |
| EPA | eicosapentaenoic acid |
| MRSA | methicillin-resistant *Staphylococcus aureus* |
| ACE | angiotensin-converting enzyme |
| ATCC | American Type Culture Collection |
| PUFA | polyunsaturated fatty acids |
| HUFA | highly unsaturated fatty acids |
| GLA | gamma-linolenic acid |
| ARA | arachidonic acid |
| DHA | docosahexaenoic acid |
| GABA | gamma-amino-butyric acid |
| EPS | exopolysaccharides |
| LAB | lactic acid bacteria |
| $CO_2$ | carbon-di-oxide |
| HIV | Human Immunodeficiency Virus |

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