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Review Article

Cyanobacteria: Their Biological Activities and Interesting Medical Applications: Review

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Abstract

Cyanobacteria possess secondary metabolites that can be used in the field of medicine through biotechnological applications. Recently, these microorganisms have gained more interest from scientists due to the production of bioactive compounds with applications in commercial and medical domains. Also, Cyanobacteria are a distinct class of oxygenic photosynthetic bacteria that live in a variety of settings around the globe. Many bioactive molecules derived from cyanobacteria exhibit a broad spectrum of activities, including antimicrobial, antibacterial, antiviral, anti-inflammatory, antitumor, antimalarial, immunosuppressive, and anti-HIV (Human Immunodeficiency Virus) activities as well as protease inhibition, demonstrating their potential as a good source of new therapeutic lead compounds over the past two decades. Cyanobacteria are advantageous as a microbial source for drug development since they are easier to culture than other microorganisms and need only basic inorganic ingredients for growth. So, it appears that there is room for greater use of cyanobacteria in the drug development process. In addition, because of the wide variety of microbes present, cyanobacterial secondary metabolites may be a rich source of novel substances that can be used to create novel medications. However, a variety of problems with how the cyanophycean species are handled have made it difficult to exploit these species. Now that the majority of these issues have been handled, cyanobacteria may be able to increase the range of natural products derived from microbes. In contrast to other microbial sources of natural products, cyanobacteria have historically received less attention. This, combined with the enormous chemical diversity and biological activities of their products, has made them appealing sources of novel drugs for use in a variety of therapeutic fields. As a result, cyanobacterial strains from still uncharted and harsh habitats can make for excellent candidates in interdisciplinary research on the medicinal potential of cyanobacteria.

Keywords : Cyanobacteria; Bioactive Compounds; Biological Activities; Drug Applications

Introduction

Because of metabolic syndrome, diabetes, chronic cardiovascular disease, obesity, stroke, malignancies, immunological disorders, and chronic respiratory diseases, morbidity and death worldwide have been rising. Changing one's eating habits, living environment, and engaging in physical activity are currently acknowledged as effective ways to prevent or treat many disorders. Additionally, the bioactive compound-containing meals may act as important nutrients. Antibiotics were viewed as miracle cures since they could target the pathogenic bacteria in a specific way [1]. The growth and advancement of antibiotic resistance in pathogenic microorganisms is a major worldwide threat which is increasing at an alarming rate [1,2]. Given antibiotic resistance, the antimicrobial properties of natural products from different sources have gained importance as alternatives to antibiotics.

Cyanobacteria, also known as cyanophytes, have shown tremendous potential for clinical exploitation [3-5]. They possess a diverse array of metabolite registry, which has potential not only to alleviate human pathological condition but also to thwart disease manifestation [6,7]. A lifetime of living involves several major health issues. These include physio-anatomical flaws, physiological toxication, and infections from dangerous bacteria. Cancer and other malignant illnesses stand out among these due to their distinction. One of the deadly diseases, cancer has a high mortality toll and places a significant burden on the healthcare system.

Cyanobacteria (blue-green algae) are a primitive, most diverse, and ubiquitous group of photosynthetic prokaryotes, exhibiting resemblance with green plants in oxygenic photosynthesis,

resembles with Gram-negative bacteria in the cellular organization [8]. Blue-green algae grow and colonize in almost all kinds of terrestrial and aquatic freshwater and marine ecosystems adapting to the various environmental conditions [9]. Microalgal classes are abundant in nature, including *Chlorophyceae* (green algae), *Chrysophyceae* (golden algae), *Cyanophyceae* (blue-green algae), and *Bacillariophyceae* (diatoms) [10]. Because they are abundant in primary and secondary metabolites, microalgae are a natural source of bioactive substances that have been employed in a variety of therapeutic applications. Bioactive substances are molecules that have biological activity that can either have a positive or negative impact on a living thing, tissue, or cell when present in small amounts [11,12].

Recently, a steadily growing inventory of microbes from marine sources has increased the focus on telluric bacteria. The ocean covers the majority of the almost 70%–71% of the Earth that is covered by an aquatic ecosystem. More than 90% of oceanic biomass, which is rich in natural variety resources, is made up of microflora and microalgae. This rich diversity of marine life provides a colossal opportunity for the identification of novel molecular entities with distinct biological functions [3]. This abundance of biomolecules is a tremendous resource for identifying possible medications and treatments that will be more effective and targeted in the management and treatment of diseases. Marine organisms have been the best natural resource for the past billion years of Earth's existence because they create unique compounds with a variety of different structural and functional properties to withstand extremely harsh conditions across a wide range of temperature, salinity, pressure, etc.

Algal extracts containing the bioactive compounds, such as proteins, lipids, polysaccharides, oils, vitamins, terpenes, esters, polyphenols, carotenoids exhibit antibacterial, antifungal, antioxidative, anticancer properties, are essential in the development of new drugs [13]. Cyanobacterial polysaccharides, glycoproteins and molecules like carotenoids, vitamins C and butylated hydroxytoluene (BHT) have been successfully used as immune modulators, anticancer agents, and antioxidants, respectively [14]. Even it was proved that crude polysaccharide extracts have anti-inflammatory effects [15]. Essential fatty acids from cyanobacteria, including as omega-3 fatty acids, linoleic acid, and -linoleic acid, have been shown to have positive benefits on health in the treatment of type 2 diabetes, hypertension, renal illness, coronary heart disease, and chronic obstructive pulmonary disease. The bioactive substance from algae can be extracted using a variety of methods [16]. Clinical trials of the extracted bioactive compounds understand its pharmacokinetics, efficacy, bioavailability, and safety for the development of the new drug in different formulations [16]. The systemic screening and phytochemical investigations of green algae revealed different biologically active molecules against various human disorders [17]. In this chapter, we'll talk about the cyanobacteria's bioactive chemicals that exhibit fascinating biological properties, such as antibacterial, anti-inflammatory, antioxidant, anticoagulant, anti-cancer, anti-protozoal, and antiviral properties. This review also discusses various species of algae and the extraction techniques for the bioactive chemicals that are currently undergoing clinical trials to create a new medicine.

Extraction Process of Bioactive Compounds from Algae

Different ancient, conventional, and modern techniques are used to extract the beneficial substances, including fatty acids, polysaccharides, and colours (carotenoids and polyphenols). Traditional solid-liquid and liquid-liquid extraction methods typically demand a lot of energy, a lot of organic solvent, a lot of money, and a lot of time. Advanced sustainable extraction technology, such as green technologies, demonstrated various advantages over traditional methods in order to address these shortcomings, including lower temperatures of performance, shorter extraction times, and use of less solvent [18].

These techniques offer more selectivity for isolating desired molecules, prevent undesirable reactions during extraction, and provide extensive recovery [19]. Size-dependent method of extraction is used due to the variance in physical and chemical characteristics of bioactive substances. Finding an effective extraction technique and streamlining the extraction process are crucial for obtaining the desired bioactive molecule. Phycobiliproteins (large polysaccharides agar and cellulose) from Rhodophyta are extracted using ultrasonication and other traditional procedures, maceration and homogenization, freezing and maceration in the presence of liquid nitrogen, and thawing was first described [20].

Due to their advantages over traditional methods, modern techniques have been used to extract bioactive compounds, such as ultrasound-assisted extraction (UAE), pressurised liquid extraction (PLE), supercritical fluid extraction (SFE), subcritical water extraction (SWE), and microwave-assisted extraction (MAE) (Table 1). SFE (without the use of enzymes) is a cutting-edge approach that extracts microalgae and their bioactive compounds (-3 fatty acids) utilising fluids under supercritical temperature, pressure, and conditions. Carbon dioxide (CO_2) is the most commonly used SFE solvent to enhance extraction efficiency due to its low cost, safety, and nontoxicity [21]. Carotenoids and chlorophylls have been extracted from microalgae using CO_2 modified ethanol for high-speed extraction in a microscale supercritical extraction apparatus [22]. The bioactive compound taurine was extracted from the *Porphyra yezoensis* by UAE method and provided higher yield [23].

Table 1: Bioactive compounds of algae and cyanobacteria, methods of extraction and their applications.

Algae/Cyanobacteria Spp.	Bioactive Compounds	Extraction Methods	Application
Gelidium pusillum	R-phycoerythrin, R- phycocyanin	Ultrasound- assisted methods	Antioxidant, anticancer, neuroprotective, anti-inflammatory, hepatoprotective, and hypocholesterolemia
Laurencia obtuse	Phenolic compounds		Antioxidant
Hormosira banksii	Polyphenols		Antioxidant
Lyngbya majuscula, Nostoc linckia	Lipopeptides	Solvent extraction and chromatography	Anticancer
Nostoc ellipsosporum	Protein		Antiviral
Scytonema varium	Polypeptide		Antiviral
Spirulina platensis	Sulfated polysaccharide		Antiviral
Nostoc sp. GSV 224	Cyclopeptide		Anticancer
Saccharina japonica	Carotenoids, fucoxanthin, and phlorotannins	Supercritical CO_2 extraction	Antioxidant and anticancer
Botryococcus braunii, Chlorella vulgaris, Dunaliella salina, Arthrospira	Alkadienes carotenoids		
Haematococcus pluvialis	Astaxanthin		Antioxidant
Himanthalia elongata	Polysaccharides	Subcritical water extraction	Antiviral
Cystoseira abies-marina, Sargassum vulgare, Halopitys incurvus, Sargassum muticum, Undaria pinnatifida, Porphyra spp.	Polyphenols, neo- antioxidants, and amino acids		Antimicrobial and Antioxidant
S. japonica	Polyphenols		Antioxidant
Sargassum thunbergii	Polysaccharides	Microwave- assisted extraction	Antioxidant and hypoglycemic
Ulva prolifera	Polysaccharides		Antihyperlipidemic, Antioxidant
Caulerpa racemosa	Polyphenols		Antioxidant

The SFE method that is used for extraction green is mainly being used for the extraction of high-value bioactive compounds such as algal pigments and fatty acids [24]. SFE uses supercritical fluids, short processing time, low degradability of the extracted product and requires minimal solvents when compared to other extraction techniques [24]. Depending on the extracted molecule, the UAE method employs both low- and high-frequency ultrasound, which improves the separation. The UAE approach allows for the maintenance of the extraction temperature through the use of heat-exchange systems, which is particularly useful when extracting substances that are thermally labile, such as carotenoids. Typically, proteins and carotenoids are extracted from micro- and macro-algae using a solvent-extraction process with a variety of solvents (e.g., Soxhlet extraction). The techniques, however, are not environmentally friendly, quite expensive, and utilise a lot of chemicals. With PLE (SWE, superheated water extraction, and pressured hot-water extraction), oxygen and light-sensitive carotenoids are extracted using water as a polar solvent [25].

Microwave radiation can be used with the MAE method to aid analytes dissolve and transfer mass by transferring heat in the extraction medium. The efficiency of MAE is affected by the extraction conditions, algal cell shapes, and microwave treatment [25].

Antibacterial Applications of Algae and Cyanobacteria

Algae produce a wide variety of chemically active metabolites, such as amino acids, terpenoids, phlorotannins, steroids, phenolic compounds, halogenated ketones, alkenes, and cyclic polysulfides, to protect themselves against the other settling organisms [26]. Lauritano and coworkers [27] reported that the organic extracts of two diatoms, *Skeletonema costatum* and *Chaetoceros*

pseudocurvisetus, were nontoxic to standard human cell lines and shown antituberculosis efficacy against *Mycobacterium tuberculosis* and *Mycobacterium bovis*. They were the first diatoms with an antituberculosis property [28]. A list of various bioactive compounds from algae and cyanobacteria is mentioned in Table 2.

Table 2: Bioactive compounds showing antimicrobial properties from various algae/cyanobacteria.

Bioactive Compound	Algae/Cyanobacteria	Action/Microorganisms Affected
Antibacterial		
Phlorotannins	*Sargassum thunbergii*	*Vibrio parahaemolyticus*
Laminarin	*Ascophyllum nodosum, Laminaria hyperborean*	*Escherichia coli, Listeria monocytogenes, Staphylococcus aureus, Salmonella typhimurium*
Amphidinolide Q	*Amphidinium sp.*	*S. aureus, Bacillus subtilis, E. coli*
Phycobiliproteins	*Spirulina fusiformis, Synechocystis sp.*	*Streptococcus pyogenes, S. aureus, Bacillus cereus,E. coli*
C-phycocyanin	Streptomyces platensis	*Klebsiella pneumoniae, E. coli, Pseudomonas aeruginosa, S. aureus*
Peyssonoic acid A and B	*Peyssonnelia sp.*	*Pseudoalteromonas bacteriolytica, Lindra thalassiae*
Bromophycolides P and Q	*Callophycus serratus*	MRSA and vancomycin-resistant *Enterococcus faecium*
Neurymenolides A and B	*Neurymenia fraxinifolia*	MRSA and vancomycin-resistant *E. faecium*
Acetylmajapolene A and B	*Laurencia sp.*	*Proteus mirabilis, Proteus vulgaris, V. parahaemolyticus, Vibrio alginolyticus, Erwinia sp., Chromobacterium violaceum*
Sargafuran	*Sargassum macrocarpum*	*Propionibacterium*
Antifungal		
Butylated hydroxytoluene, hexadecanoic acid, methyl ester	*Microcystis aeruginosa*	*Aspergillus sp.*
Balticidins A–D	*Anabaena cylindrica*	*Candida albicans, Candida krusei, Candida maltosa, Aspergillus fumigatus, Microsporum gypseum, Mucor sp., Microsporum canis*
Amphidinolide Q	*Amphidinium sp.*	*C. albicans*
Phycobiliproteins	*Porphyridium aerugineum, Synechocystis sp.*	*C. albicans*
β-Carotene, chlorophyll a, chlorophyll b	*Chlorococcum humicola*	*C. albicans, Aspergillus flavus, Aspergillus niger*
Antiprotozoal		
Bifurcatriol	*Bifurcaria bifurcata*	*Leishmania donovani*
Atomaric acid	*Stypopodium zonale*	*Leishmania amazonensis*
Fucosterol	*Lessonia vadosa*	*Leishmania infantum*
Pachydictyol A/ isopachydictyol A	*Dictyota menstrualis*	*L. amazonensis*
Alkaloids	*Cladophora crispata*	*Echinococcus granulosus*
Sulfated polysaccharide	*Caulerpa racemosa, Botryocladia occidentalis*	*L. amazonensis*

Phlorotannins isolated from *Sargassum thunbergii* inhibits *Vibrio parahaemolyticus* by destroying its cell wall and cell membrane, which results in membrane destruction and cytoplasm leakage [29]. Propanoic and butanoic acid compounds extracted from *Haematococcus pluvialis* have shown activity against *Aspergillus niger, Candida albicans, Escherichia coli,* and *Staphylococcus aureus* [30]. Laminarin extracted from the brown algae, such as *Laminaria hyperborean*, and *Ascophyllum nodosum*, has shown significant growth inhibition against *E. coli*, *Listeria monocytogenes, S. aureus,* and *Salmonella typhimurium* [31]. Fucoidan- and laminarin-like algal polysaccharides exhibited antibacterial activity against *E. coli* and *S. aureus* and also could inhibit the biofilm formation of *Helicobacter pylori* in the gastric mucosa [32-34].

Amphidinolide Q from the symbiotic dinoflagellate *Amphidinium* sp. was active against *S. aureus, Bacillus subtilis*, and *E. coli* [35]. Phycobiliproteins extracted from *Spirulina fusiformis* showed significant antibacterial activity against *Streptococcus pyogenes* and *S. aureus* [36]. The fatty acid extracts from *Synechocystis* sp. inhibited the growth of *Bacillus cereus, E. coli, and C. albicans*. C-phycocyanin produced by Streptomyces platensis seemed to inhibit the growth of *Klebsiella pneumoniae, E. coli, Pseudomonas aeruginosa, and S. aureus* [37]. The compounds, bromophycolides P and Q, extracted from the Fijian red alga *Callophycus serratus* exhibited antibacterial activity against multiresistant *S. aureus* (MRSA) and vancomycin-resistant Enterococcus faecium (VRE) [38]. Pahayokolide A from *Lyngbya* sp. seemed to inhibit the growth of *Bacillus megaterium* and *B. subtilis* and showed cytotoxicity too. The red alga *Neurymenia fraxinifolia* produced neurymenolides A and B, two -pyrone macrolides that have action against MRSA and VRE (Stout et al., 2009). From *Phaeodactylum tricornutum*, EPA, palmitoleic, and hexadecatrienoic acids may be able to stop the growth of bacteria such *B. cereus, Bacillus weihenstephanensis, S. aureus, Staphylococcus epidermidis*, MRSA, and others. [39,40]. Fatty acids such as a dimorphecolic, coriolic, and linoleic acids from *Oscillatoria redekei* have shown growth inhibition of *B. subtilis, Micrococcus flavus, and S. aureus*. Unsaturated fatty acid–containing lipidic fractions [triglycerides and docosapentaenoic acid (DPA)] from *Chaetoceros muelleri* exhibited antibacterial activity against *E. coli, B. subtilis, and S. aureus* [41,42]. Numerous compounds with antibacterial capabilities have been discovered from the Nostoc genus; noscomin, from the terrestrial Nostoc commune, showed antibacterial activity against *B. cereus, S. epidermidis, and E. coli*. An alkaloid from *Nostoc muscorum* called muscoride A may have antibacterial effects on *B. subtilis and E. coli* [43].

Antifungal Applications of Algae and Cyanobacteria

Mickymaray, et al. [44] reported that the ethanolic fractions of Laurencia paniculata that contain the sesquiterpene molecule aristolene have antifungal properties, particularly in cases of bronchial asthma. The chemicals that were isolated from Microcystis aeruginosa, such as BHT, hexadecanoic acid, and methyl ester, showed antifungal efficacy mostly against *Aspergillus* sp. Marrez and Shishido, et al. [45,46] reported a strong antifungal substance called scytophycin that is found in *Anabaena, Nostoc*, and *Scytonema* sp. They were able to find the antifungal hassallidin from Anabaena species and Nostoc species. From the symbiotic dinoflagellate *Amphidinium* sp., Amphidinolide Q was isolated. has antifungal effects on *C. albicans*. *Porphyridium aerugineum* produces phycobiliproteins, and that could show resistance against *C. albicans*. Organic solvent extracts and pigments, such as β-carotene, chlorophyll a, and chlorophyll b, from *Chlorococcum humicola* could inhibit the growth of *C. albicans, Aspergillus flavus, A. niger*, etc. [47]. Nostofungicidine from *N. commune* exhibited strong antifungal activity against *Aspergillus candidus*. Short-chain fatty acids from *H. pluvialis* exhibited activity against *C. albicans*. Lipidic fractions, such as triglycerides and DPA, from *C. muelleri* showed activity against *C. albicans*, reported by Mendiola, et al. [42]. Lipopeptides called Laxaphicins B and C, which were produced from the Anabaena laxa plant, had fungicidal activity against *C. albicans*, *Saccharomyces cerevisiae*, *Penicillium notatum*, *Aspergillus oryzae*, and *Trichophyton mentagrophytes*. Fisherellin from *Fischerella muscicola* showed antialgal and antifungal properties. Okadaic acid and ciguatoxin are effective antifungal agents produced by *Prorocentrum lima* and *Giardia toxicus*, respectively. Antimycotic activities have been reported for karatungiols, a group of compounds synthesized by the dinoflagellate *Amphidinium*. Hassallidins A and B from *Hassallia sp.* have been showing antifungal activity against *Cryptococcus neoformans*, *Aspergillus sp*., *Fusarium sp*., *Penicillium sp*., *Ustilago maydis*, and *Acremonium strictum*. Welwitindolinone A isonitrile and N-methylwelwitindolinone C isocyanate from *Hapalosiphon welwitschii* and *Westiella* genus have been recognized as fungicidal agents [48-50].

Antiprotozoal Applications of Algae and Cyanobacteria

Lobophora variegata extracts showed antiprotozoal activities against *Trichomonas vaginalis*, *Entamoeba histolytica*, *Leishmania mexicana*, *Trypanosoma cruzi*, *Giardia intestinalis*, etc. [51]. Alkaloids and ethyl acetate compounds isolated from *Cladophora crispata* showed activity against the protoscolices of hydatid cysts of *Echinococcus granulosus*. Extracts from these algal species: *Ochtodes secundiramea*, *Caulerpa cupressoides*, *Anadyomene saldanhae*, *Canistrocarpus cervicornis*, *Padina sp*., and *Dictyota sp*. showed growth inhibition against *Leishmania braziliensis*. Leishmanicidal activity against intracellular amastigotes and anti-human immunodeficiency virus (HIV)-1 activity are both displayed by dolabelladienetriol derived from *Dictyota pfaffii*. Dolabelladienetriol appears to be a viable candidate for leishmaniasis treatment given that the HIV-1 is known to increase

the *Leishmania* burden in macrophage infection [52]. Fucoidan, a polyanionic sulfated polysaccharide (SP), found in many brown algae showed an inhibitory effect on intracellular amastigote of *Leishmania donovani*. Elatol, extracted from the Brazilian red alga *Laurencia dendroidea*, showed antiprotozoal activity against the trypomastigotes and amastigotes of *T. cruzi* and the promastigote and intracellular amastigote forms of *Leishmania amazonensis* [53,54] reported that at 24 hours, the organic extracts of the green algae Udotea conglutinate and *Udotea flabellum* were able to totally suppress *T. cruzi* trypomastigotes. The sargaquinoic acid molecule from *Sargassum hemiphyllum*, which resembles meroterpenoids, has strong in vitro action against *Plasmodium falciparum*. Symplocamide A from *Symploca sp.*, Carmabin A and B isolated from *Lyngbya majuscula*, Venturamide A and B from *Oscillatoria sp.* (, etc., are some of the other bioactive compounds exhibited antimalarial/ antiprotozoal activities [55,56].

Antioxidant Applications of Algae and Cyanobacteria

Globally, there is a growing demand for algal foods, which are promoted as "functional foods" or "nutraceuticals" because of their superior health advantages. By scavenging free radicals and active oxygen, bioactive chemicals from the various types of algae can prevent oxidative damage, which aids in the prevention of cancer [57]. Oxidative stress is the root cause of chronic diseases such as heart disease, stroke, cancer, atherosclerosis, neurodegenerative disorders, infant retinopathy, muscular degeneration, and renal failure and aging. Compounds, such as cyanovirin, oleic acid, linolenic acid, palmitoleic acid, vitamin E, B12, β-carotene, phycocyanin, lutein, and zeaxanthin, from algal sources have an antioxidant property besides the antimicrobial and anti-inflammatory effects in reducing or preventing the diseases [58-61].

Epidemiological studies have established an inverse association with the intake of fruits and vegetables. This phenomenon is attributed to the antioxidant activity of these foods. With their ability to scavenge free radicals and operate as active oxygen or nitrogen scavengers, the phytochemicals and pigments found in cyanobacterium function as antioxidants. The cyanobacteria and algae are frequently exposed to high oxygen and radiation levels. These organisms typically create a defensive mechanism to counteract oxidative damage (based on the production of different antioxidants). Dimethyl sulfoniopropionate and mycosporine amino acids are powerful UV radiation blockers that were identified as antioxidant chemicals from microalgae. In addition, the other compounds, such as pigments, lipids, and polysaccharides, from algae found to have antioxidant activity [62].

Antioxidant Components Possessing Anti-inflammatory Activity

Majority of the algal bioactive molecules show both anti-inflammatory and antioxidant activities, including the pigments such as β-carotene, astaxanthin, lutein, zeaxanthin, and phycobiliproteins. One of the key factors driving the quest for bioactive substances like anti-inflammatory active molecules from natural sources like microalgae is the rising demand for medications with few adverse effects. The cell that showed anti-inflammatory action will accumulate metabolites from the various microalgae. Several research have already shown the chemical makeup, structural details, and biosynthesis routes of the bioactive substances displaying anti-inflammatory chemicals produced by microalgae [63,64]. The compounds such as proteins, phycobiliproteins, phenolic compounds such as flavonoids, carotenoids such as astaxanthin, lutein, the fatty acids DHA, EPA, and SPs synthesized by microalgal metabolism are known to have anti-inflammatory activity.

To be a valuable target product, these bioactive compounds must fulfil two requirements:

i. they must accumulate at relatively high concentrations in cells grown under standard conditions during cultivation

ii. They must be overproduced as an algal response to stressful cultivation conditions or when they are put under chemical or physical stress.

This can be done by imposing different conditions, such as alterations in the physicochemical parameters and the concentration of nutrients, as well as changes in the temperature, pH, light quality, and irradiance [65]. The production of anti-inflammatory compounds mainly depends on the type of algae and the cultivation conditions. A peptide from *P. tricornutum* reached the market based on its anti-inflammatory properties only. The algal pigment carotenoids are found to have a positive impact on anti-inflammatory cellular response mechanisms and immune response modulations. Astaxanthin, a carotenoid produced by microalgae *H. pluvialis* has shown profound anti-inflammatory activity. *D. salina* is an example of extremophilic microalga commercially used for the production of a high-value compound that displays anti-inflammatory activity. The polysaccharides, which are anti-inflammatory chemicals produced by microalgae, have also been demonstrated to exert antioxidant activity. Several excellent reviews published in recent years discuss these molecules' applications and advantages for human health. The antioxidant microalgae polysaccharides isolated from *Porphyridium* and *Rhodella* are excellent examples [66].

Anticancer Applications of Algae and Cyanobacteria

Algae and cyanobacteria, which are photosynthetic microorganisms, have evolved to survive in harsh environments by biochemically creating bioactive substances and secondary metabolites. Secondary metabolites that have been isolated are discovered to have a high medicinal potential and have been further enhanced with active pharmaceutical components for anticancer

activities. A combination of anabolic fatty synthesis and acetyl Co-A synthesis pathways is used by some strains of cyanobacteria, including *Nostoc*, *Spirulina*, and *Oscillatoria*, to create cytotoxic lipopeptides [67]. Recently, marine lipopeptide somocystinamide A isolated from filamentous cyanobacteria *L. majuscula* has shown to trigger caspase-8–dependent apoptotic pathway and induce tumor suppression in various cancer cell lines that include melanoma, leukemia, carcinoma, myeloma, and neuroblastoma types. Other lipopeptides include lyngbyabellins, didemnin, and hectochlorin. Boron-containing metabolite, borophycin produced by *N. spongiaeforme* var. *tenue*, has shown potent cytotoxic effect in human carcinoma [68].

Similarly, apratoxin A, a class of natural metabolites from marine cyanobacteria inhibits signal transducer and activator of transcription (STAT) 3, arrests cancer cells at G1 phase, and induces apoptosis in various cancer cell lines. Nostoc also produces a cyclopeptide, cryptophycin, which has shown immense anticancer potential against multidrug-resistant cells due to their action on cytoskeletal protein-Tubulin. Further, they were found to be highly effective against solid tumors. The mechanism of tumor suppression has been linked to its binding to tubulin, causing microtubule depolymerization and perturb dynamic instability of microtubules leading to cell cycle arrest and apoptosis. A number of chemical analogues were successfully produced and are currently undergoing clinical studies as a result of the multipotent action of cryptophycins. The most effective uses of the 26 cryptophycin-isolated *Nostoc* sp. GSV 224 were described for the treatment of advanced lung cancer and platinum-resistant ovarian cancer [69].

Chemotherapy must take into account the way that cyanobacterial metabolites affect cancer cells. The cells are programmed to die in response to a stimulus because of disrupted homeostasis brought on by oxidants, infections, aberrant proliferation, oncogenic changes, and other factors. The great pharmacological value of metabolite-inducing apoptosis for the treatment of cancer stems from this. Anticancer substances derived from cyanobacterial metabolites interact with a variety of molecular cell targets, such as microtubules, DNA, receptor protein kinases, and cell cycle checkpoint proteins, causing cell cycle arrest, mitochondrial dysfunctions, oxidative damage, activation of caspase and noncaspase cascade, and changes in membrane dynamics [70].

Strong anticancer and apoptotic signalling has been tested for a number of pharmaco-active substances isolated from cyanobacteria. In human cancer (Jurkat) cells, Calothrixin A, a class of indolophenanthridine derived from Calothrix, has demonstrated cell cycle arrest in G2/M phase. Additionally, it boosted the formation of ROS, which was connected to DNA breakage. Dolastatin 10 isolated from *Symploca* found to arrest G2/M phase of the cell cycle and induce apoptosis by DNA damage in human lymphoma cell lines and on lung cancer cells. Lipopeptide and cyclic depsipeptides such as hectochlorin and lyngbyabellin, respectively, belong to *Lyngbya* halt G2/M checkpoint in a human Burkitt lymphoma cell line followed by perturbed microfilaments [71]. Mitochondrial dysfunction was observed in cervical carcinoma cells commonly known as Hela cells and was treated with calothrixin A isolated from the marine cyanobacteria *Calothrix*. DNA fragmentation as a consequence of apoptosis was most observed in cryptophycins 1 and 52 treatments. Concurrently, the apoptotic pathways were attributed to caspase-3 and caspase-1 activation [72], whereas phycobiliprotein, *C-phycocyanin*, from both *Lyngbya* and *Phormidium*, was reported to scavenge peroxyl and hydroxyl radicals. Apart from the abovementioned apoptotic markers, few metabolites such as antillatoxin, a lipopeptide isolated from *L. majuscula* and hermitamides, increases the sodium concentration of the cell, thereby perturbing the osmotic balance [73].

Carotenoids, which are by-products of photosynthesis and include -carotene, xanthene, lutein, and lycopene, are often abundant in algae and cyanobacteria. As scavengers of singlet electron species, or ROS, carotenoids and other terpenoids are crucial. Therefore, these scavengers are used as antioxidants to stop the growth of cancer cells. There are not many reports on carotenoids' ability to fight different types of cancer. However, there have been instances where carotenoids increased the growth of lung cancer in patients, which was later determined to be caused by the effects of smoking. Nevertheless, dietary carotenoidswere found to reduce the risk of cancer proliferation has been reviewed by several authors. Among various types of carotenoids, fucoxanthin exerted a strong inhibitory effect on HL-60, HepG-2, MCF-7, and PC-3 cancer cell lines via apoptotic mechanisms [74,75].

Chemicals such alkaloids, polyphenols, glycoproteins, PUFAs, polysaccharides, lipopeptides, terpenoids, and vitamins are mostly present in aqueous extracts of algae. Many of these compounds have undergone drug development testing and have shown effective at causing an anticancer response. ARS-2, a glycoprotein isolated from *C. vulgaris*, for example, activated nuclear factor-B in human HEK 293 cells and shown anticancer efficacy by antimetastatic immunopotentiation. Few secondary metabolites, such as hormothamnin A from *Hormothamnion Enteromorphoides*, hormothamnione A from *Chrysophaeum taylorii*, and malyngamide D from *L. majuscula* were extracted and reported to exhibit anticancer-type activities in several cancer cell lines. Besides the active compounds, several studies involving crude extracts were also conducted to demonstrate the anticancer activity. Crude fractions of polyunsaturated aldehydes, carotenoid extract, chrysolaminarin (polysaccharide), EPA, crude organic solvent extracts, stigmasterol (phytosterol) and aqueous extract [76,77] (Figure 1).

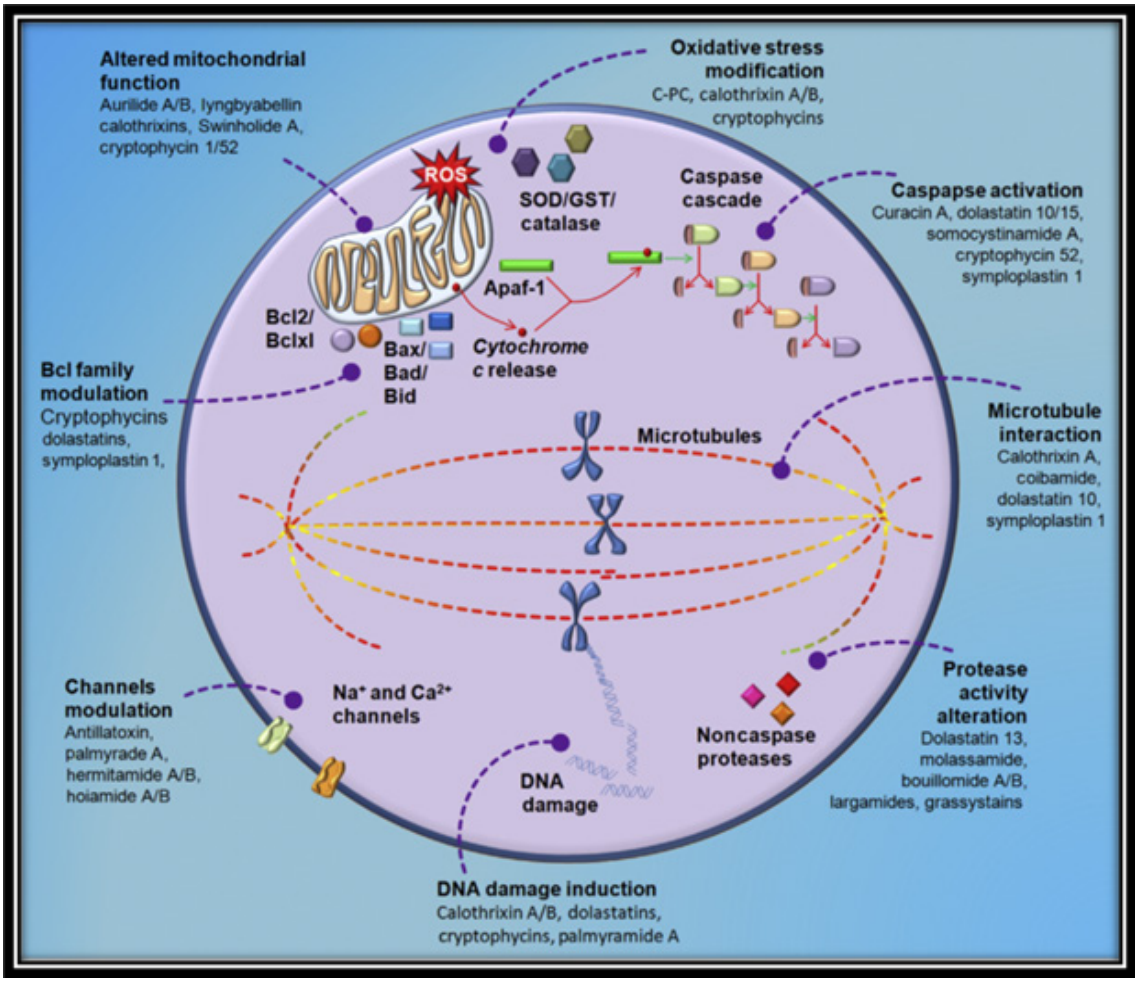

Figure 1: Possible Mechanisms of Anticancer Activity of Cyanobacterial Compounds.

Immunosuppressive Applications of Algae and Cyanobacteria

Table 3: Bioactive substances from blue-green algae with a mechanism of action for immunosuppression.

Algal Compound	Source	Mechanism Action
Lipoproteins, microcolins A 17 and B 18	Green algae *Lyngbya majuscula*	In vitro mouse P388 leukaemia and the murine mixed lymphocyte response
Isorawsonol 30	Tropical green alga *Arrainvilla rawsonii*	Cellular proliferation
Phycocolloid protein hydro-lysates	*Porphyra columbina*	Enhanced IL-10 production during the production of TNFα and IFNγ inhibition on rat splenocytes
Sulfolipids	Blue-green algae	T-cell proliferation assay and rat allogeneic skin graft
MGDG, DGDG, and SQDG	Microalgae	Inhibition of in vitro and in vivo tumor-promoting activity
Polysaccharides	*Phaeodactylum tricornutum*	Rat paw assay, in a phagocytic test, exhibited proinflammatory effects

The immunosuppressive compounds can dampen the immune system, notably T and B lymphocytes with different mechanisms. They are necessary to prolong the survival of allogeneic organ transplantations by suppressing the host immune responses [78]. In a study, SQDG (sulfolipids) from blue-green algae has shown strong immunosuppressive effect in human-mixed lymphocyte reaction, which does not affect the general immunocompetence. Free radical scavenging activity exhibited by the aqueous extract of *Spirulina platensis* showed suppressive potency against cyclophosphamide-induced lipid peroxidation in goat liver homogenates [79]. Blue-green algae *Spirulina* can modulate the production of cytokines by human peripheral blood mononuclear cells, the bioactive

protein present among them stimulates the intestinal immune system by various mechanisms. Therapeutic use of *Spirulina* has been explored, by reducing the levels of glucose and lipids serum, protects the kidney against heavy metals and drugs. β-1,3 glucan from *Chlorella* reduces free radicals and blood cholesterol [80]. Table 3 represents some of the bioactive compounds from blue-green algae with immunosuppressant effect.

Clinical Trial Status of Algae and Cyanobacteria

Clinical trials are helpful to focus efforts on extracted protective bioactive compounds that have certain beneficial characteristics using different model systems. From preclinical validation to Food and Drug Administration (FDA) approval, the process of developing novel molecules as treatments is somewhat time-consuming, difficult, and expensive. A bioactive substance with significant therapeutic promise currently needs to go through preclinical testing, human testing, and regulatory approval by the FDA following post-trial for commercialization and marketing. It is significant to note that not all of the medications found in the library have received FDA approval, but they have all been known to undergo biological activity testing. In addition to the substances that have gained US FDA approval, numerous others have received clinical use approval in other nations but not the US. Clinical trials are carried out utilising various model systems to examine the biological activity of the isolated chemicals at various stages. In vitro cell model and in vivo mouse model revealed potential activities of algal bioactive compounds. Over 18,000 bioactive compounds have been identified as of this writing. Only six marine-derived drugs, however, have received clinical approval and have been put on the market. Additionally, relatively few algal isolates have been recognised clinically. For instance, brentuximab vedotin, an antibody-drug combination developed from the bioactive chemicals extracted from an algal source, is sold under the trade name ADCETRIS as an anticancer medication for non- Hodgkin's lymphoma. The compound was developed as an analog for dolastatin 10 isolated from *Symploca* sp. VP642. Similarly, iota-carrageenan (Carragelose) is the first algal product for antiviral activity isolated from a red edible algae, *Eucheuma*/ *Chondrus*. Subsequently, several dolastatin derivatives, such as depatuxizumab mafodotin, glembatumumab vedotin, and pinatuzumab vedotin, were synthesized and are undergoing varies phases of FDA and EMA clinical trials [81-83].

Clinical trials provide clear evidence for the clinical therapeutic potential of EPA essential amino acids from marine macroalgae in combination with supplementation of DHA extracted from marine microalgae [84]. The products like Tasco TM from *A. nodosum* and *Ocean FeedTM* from macroalgae were already marketed as feed additives and immune stimulators. Double-blind clinical trials with fucoidan extracts show antiaging effects on skin and other benefits in cosmetic applications [85].

Conclusion

The majority of medicinal medications used on a daily basis are derived from natural resources or their synthetic chemical analogues. The pharmacological potency of bioactive chemicals isolated from algae organisms has been thoroughly investigated in recent decades for applications in antibacterial, anti-inflammatory, antioxidant, anticoagulant, anti-cancer, antiprotozoal, and antiviral defence. Through the creation of bioactive chemicals, some algae and cyanobacterial species have evolved innate defence mechanisms to endure in unfavourable environmental conditions. Alkaloids, terpenoids, polysaccharides, peptides, and lipids are examples of bioactive substances that function as toxins to deter predators while simultaneously neutralising stress factors and oxidants. As a result, algal extracts are separated and examined for bioactivity against pathogens such bacteria, protozoa, fungi, and viruses. Additionally, it was shown that algal extracts can suppress the growth of cancer cells while undergoing rigorous clinical trials. Additionally, there are a number of algal and cyanobacterial bases that can endure extremely high temperatures, although the pressure is not yet known. Identification of those species and vigilant cultivation may reveal novel chemical compounds with high potential for therapeutic usefulness.

Modern methods including HPLC, supercritical CO_2 aided ultrasound, and microwave-based extractions have made it possible to describe and isolate pure substances quickly. Despite the fact that several drug isolates are undergoing clinical studies, there is very little clinical evidence available on algal and cyanobacterial treatments because many promising drug candidates fail in clinical trials. Inefficient extraction techniques, low yields, high costs, systemic toxicity, a lack of risk evaluation, etc. are the main causes. Nevertheless, the discovery of bioactive chemicals is made possible by high throughput screening methods. Additionally, to improve clinical efficacy, such pharmacoactive compounds may be altered into analogues, as was the case with dolastatin 10. Animal studies may aid in the assessment and mitigation of toxicity-related problems, while a combination of two or more medications may help in evaluating synergistic, additive, or antagonistic effects in vitro. Algae and cyanobacteria, which may bridge the gap between a clinical trial and human applications, are the most suitable sources for isolating bioactive chemicals for medicinal uses, this review finishes on a higher note.

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Conflict of Interest

None.

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