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BIOACTIVE COMPOUNDS FROM MICROALGAE AND CYANOBACTERIA: UTILITY AND APPLICATIONS

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ABSTRACT

Microalgae and Cyanobacteria (blue-green algae) are photosynthetic prokaryotes used as food by humans. They have gained a lot of attention in recent years because of their potential applications in biotechnology. They have also been recognized as an excellent source of vitamins and proteins and as such are found in health food stores throughout the world. They are reported to be a source of fine chemicals, renewable fuel and bioactive compounds. Bioactive compounds are extra nutritional constituents that typically occur in small quantities in foods. Numerous bioactive compounds appear to have beneficial health effects. Microalgae and Cyanobacteria have been identified as a rich source of biologically active compounds with antiviral, antibacterial, antifungal and anticancer activities. This review is an attempt to consolidate the latest studies and critical research in this field, and to showcase the immense competence of uses of microalgae and cyanobacteria as a potential and promising source of novel compounds.

INTRODUCTION: Microalgae are a diverse group of prokaryotic and eukaryotic photosynthetic micro-organisms that can grow rapidly due to their simple structure. They are microscopic unicellular organisms capable to convert solar energy to chemical energy via photosynthesis.

Phylogenetically, microalgae can be prokaryotic or eukaryotic and, in evolutionary terms, recent or very ancient. This very diversity makes microalgae, as a group, a potentially rich source of a vast array of chemical products with applications in the feed, food, nutritional, cosmetic, pharmaceutical and even fuel industries.

Microalgae are common, normal inhabitants of surface waters and are beneficial to the health of a water body. Low concentrations of microalgae represent primary producers of organic matter which provide food base for most marine and freshwater food chains and plays important role in the equilibrium of aquatic ecosystem [1, 2]. Microalgae can be a very interesting natural source of new compounds with biological activity that could be used as functional ingredients. In fact, some microalgae are organisms that live in complex habitats submitted to extreme conditions (for example, changes of salinity, temperature, nutrients, UV irradiation etc.), therefore, they must adapt rapidly to the new environmental conditions to survive, producing a great variety of secondary (biologically active) metabolites, which cannot be found in other organisms [3].

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Besides its natural character, other important aspects related to the microalgae are their easy cultivation, their rapid growing (for many of the species) and the possibility of controlling the production of some bioactive compounds by manipulating the cultivation conditions.

Among the oldest extant organism on Earth, dating back in the fossil record to nearly 3.5 billion years ago, the cyanobacteria ("blue-green algae") have evolved to produce an impressive array of biologically active compounds. Cyanobacteria are a simple, but primitive and diverse group of microorganisms, with characteristics in common to both bacteria and algae. Cyanobacteria an ancient group of prokaryotic organisms that are found all over the world in environments as diverse as Antarctic soils and volcanic hot springs, often where no other vegetation can exist [4].

Cyanobacteria are cosmopolitan and possess high potential for adoption to diverse environmental factors. Their success as a group in a wide range of habitats has been attributed to their unique physiological characters and high adaptive ability under a wide range of environmental conditions. The potential of cyanobacteria as a source of a variety of compounds such as polysaccharides, lipids, proteins, vitamins, sterols, enzymes, pharmaceuticals and other fine chemicals is well recognized, and their demand is now on an increasing trend.

Cyanobacteria are photosynthetic prokaryotes used as food by humans. They have also been recognized as an excellent source of vitamins and proteins and as such are found in health food stores throughout the world. They are also reported to be a source of fine chemicals, renewable fuel and bioactive compounds. This potential is being realized as data from research in the areas of the physiology and chemistry of these organisms are gathered and the knowledge of cyanobacterial genetics and genetic engineering increased.

One feature of cyanobacteria is their frequent formation of mass growth known as blooms in water bodies creating aesthetic, operational and health problems.

Cyanobacterial blooms may be visible as thick mats or scum on the surface of water and particularly when the scum begins to decay it can be smelly. It can be bluish-green to red in colour and might look like paint on the surface of the water.

Bioactive Compounds from Microalgae: Microalgae are a diverse group of microscopic plants with the wide range of physiological and biochemical characteristics and contain up to 50-70% protein (up to 50% in meat, and 15-17% in wheat), 30% lipids, over 40% glycerol, up to 8-14% carotene and a fairly high concentration of vitamins B1, B2, B3, B6, B12, E, K, D, etc., compared with other plants or animals. The potential of microalgae biomass for big Pharma practical uses is certainly great. The first use of microalgae by humans dates back 2000 years to the Chinese, who used *Nostoc* to survive during famine.

At present around 110 commercial producers of microalgae are in the Asia-Pacific region, with annual production capacity ranging from 3 to 500 tones [5]. The commercially cultivated microalgae include *Chlorella, Spirulina, Dunaliella, Nannochloris, Nitzschia, Crypthecodinium, Schizochytrium, Tetraselmis, Skeletonema* etc. The market survey shows that being developed in the last 20-30 years, the microalgae production volume increased excessively[6]. Second-generation microalgae large scale manufacturing volume sharply increased due to significant influence of food, high-quality perfumery additives related industry development.

Most of the commercially produced algal biomass is being marketed as health food, in the forms of tablets and capsules. Algae and their extract are also included in noodles, wine, beverages, breakfast cereals and cosmetics. So, currently over 75% of pharmaceutical product development is generated by the food supplement production comprising also microalgae. In recent years, microalgae have gained much attention due to their high nutritional value, high-value chemicals (pigments and vitamins), high growth rate as compared to higher plants, and the ability to utilize light energy. In addition, many bioactive compounds have been found in microalgae. For example, dried microalgae could be used as high-protein feeds for animals such as shrimp and fish.

The biotechnology of microalgae has gained considerable importance in recent decades. Applications range from simple biomass production for food and feed to valuable products for ecological applications. Microalgae are a great source of many highly valuable products such as polyunsaturated fatty acids, astaxanthin and bioactive compounds. Large-scale production of these products, however, has been hindered by an inability to obtain high cell densities and productivities in conventional photoautotrophic systems. High cell density processes suitable for heterotrophic cultures of microalgae may provide an alternative means for the large-scale production of algal products of high value.

For most of these applications, the market is still developing and the biotechnological use of microalgae will extend into new areas. Considering the enormous biodiversity of microalgae and recent developments in genetic engineering, this group of organisms represents one of the most promising sources for new products and applications. In *Chlorella* species, the most important compound from a medical point of view is ˙β-1, 3-glucan, an active immunostimulator, a free radical scavenger and a blood lipid reducer. Efficacy of this compound against gastric ulcers, wounds and constipation, preventive action against artherosclerosis and hypercholesterolemia, and antitumor action have also been reported**.**

Microalgae are significant resource for bioactive metabolites, particularly cytotoxic agents with applications in cancer chemotherapy. From the marine microalgae such as from the blooms of *Phaeocystis sp*., antibiotic substances were listed. *Phaeocystis pouchetii* is reported to produce chemicals such as Acrylic acid, which constitutes about 7.0% of the dry weight. The antibiotic substances thus produced are transferred throughout the food chain and found in the digestive tract of Antartic penguins. Production of ß carotene and vitamins by the halotolerant alga *Dunaliella sp.,* is documented.

These compounds have much importance for the Mariculture activities. Microalgae, such as *Ochromonas* sp., *Prymnesium parvum*, and a number of blue-green algae produce toxins that may have potential pharmaceutical applications [7].

The marine cyanobacteria has many potential pharmaceutical activity and they produce novel and biologically active natural products such as acetogenins, bromophenols, fattyacids, terpenes, sterols, alkaloids, etc.. They have potentially useful biological activities such as antibiotic, antifungal, antitumour and anti-inflammatory activities [8]. Various strains of cyanobacteria are known to produce intracellular and extracellular metabolites with diverse biological activities such as antialgal, antibacterial, antifungal and antiviral activity.

Temperature of incubation, pH of the culture medium, incubation period, medium constituents and light intensity are the important factors influencing antimicrobial agent production [9]. The study of Abo-Shady *et al.,* [10] revealed the high efficiency of three algal filtrates (*Anabaena subcylindrica*, *Nostoc muscorum* and *Oscillatoria angusta)* on the control of the isolated pathogenic fungi from the roots, stems and leaves of Faba bean plants. Abedin and Taha [11] found that *Spirulina platensis* and *Anabaena oryzae* had antifungal activity towards the plant pathogenic fungi. Fatty acids are isolated from microalgae that exhibited antibacterial activity [12].

Chlorophyll is one of the valuable bioactive compounds that can be extracted from microalgal biomass. It is used as a natural food colouring agent and has antioxidant as well as antimutagenic properties. Sulfated polysaccharides of microalgae can be used in anti-adhesive therapies against bacterial infections both in cold and warm blooded animals. The use of some microalgal species, especially *Arthrospira* and *Chlorella,* is well established in the skin care market and some cosmeticians have even invested in their own microalgal production system (LVMH, Paris, France and Daniel Jouvance, Carnac, France). Their extracts are found in e.g. anti-aging cream, refreshing or regenerating care products, emollient and as an anti-irritant in peelers and also in sun protection and hair care products.

Some of these products' properties based on algal extracts include: repairing the signs of early skin aging, exerting a skin tightening effect, preventing stria formation and stimulation of collagen synthesis in skin.

Table 1 below represents the microalgal PUFAs of particular interest: however, currently, DHA is the only algal PUFA commercially available. Indeed, even if species have demonstrated industrial production potential of EPA (*Porphyridium purpureum*, *Phaeodactylum tricornutum*, *Isochrysis galbana*, *Nannochloropsis sp*. and *Nitzschia laevis*) [13, 14].

TABLE 1: PARTICULARLY INTERESTING MICROALGAL PUFAS

PUFA	Potential application	Microalgae as producer
γ-Linolenic acid (GLA)	Infant formulas for full-term infants, Nutritional supplements	*Arthrospira*
Arachidonic acid (AA)	Infant formulas for full-term/preterm infants Nutritional supplements	*Porphyridium*
Eicosapentaenoic acid (EPA)	Nutritional supplements, Aquaculture	*Nannochloropsis, Phaeodactylum, Nitzschia*
Docosahexaenoic acid (DHA)	Infant formulas for full-term/preterm infants, Nutritional supplements, Aquaculture	*Crypthecodinium, Schizochytrium*

Bioactive Compounds from Cyanobacteria: Microalgae contain numerous bioactive compounds that can be harnessed for commercial use. They have emerged as important sources of proteins and value added compounds with pharmaceutical and nutritional importance. Initially considered as laboratory curiosities or nuisances agents in water bodies, but now cyanobacteria or blue green algae form an important component of integrated nutrient management in agriculture and are exploited in commercial biotechnological ventures [15,16] as a source of pigments, vitamins, phycocolloids, immuno-diagnostic agents and therapeutics and for biofuel production [17, 18].

Several bioactive metabolites produced by cyanobacteria and algae have been discovered by screening programs, employing target organisms quite un-related to those for which the metabolites evolved [19]. Many of these chemicals have diverse range of biological activities and chemical structures, which affect many biochemical processes within the cells (mainly directed against photosynthetic process). Such chemicals are presumably related to the regulation and succession of algal and bacterial populations and can be involved as natural herbicide or bio-control agents [20].

The existence of algicidal and bactericidal properties of cyanobacteria is to be expected in the light of the co-occurrence of these organisms in aquatic natural communities, where an inhibitory interaction occurred between producers and competitors within the same ecosystem. A pronounced reduction of gram positive bacteria in lakes during the occurrence of cyanobacterial water blooms was reported by Chrost [21] and the production of antibacterial substances may be one reason for this phenomenon. Cyanobacterial bioactive allelo-chemicals that have been characterized as algicides are directed against photosynthesis (photosystem II) and therefore are termed natural herbicides. Light-dependent processes are unique to both prokaryotic cyanobacteria and eukaryotic algae and are therefore logical targets for a bioactive producer organism in competing with other such organisms (the targets) in the same habitat.

Many cyanobacteria produce compounds are generally considered to be secondary metabolites, that is, compounds that are not essential for general metabolism or growth of the organism and are present in restricted taxonomic groups. Cyanobacteria such as *Microcystis,Anabaena,Nostoc* and *Oscillatoria* produce a great variety of secondary metabolites. A number of important marine cyanobacterial molecules, including dolastatin 10, cryptophycins and curacin A, have been discovered and these were either in preclinical or clinical testing as anticancer agents [22].

Many secondary metabolites are potent toxins, causing health problems for animals and humans when the producer organisms occur in masses in water bodies. Cyanobacterial lipopeptides include different compounds like cytotoxic (41%), antitumor (13%), antiviral (4%), antibiotics (12%) and the remaining 18% activities include antimalarial, antimycotics, multi-drug resistance reversers, antifeedant, herbicides and immunosuppressive agents [23] ; besides the immune effect, blue green algae improves metabolism (**Fig. 1**).

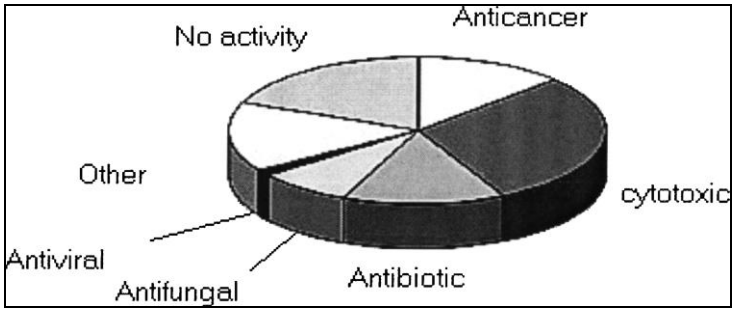

FIGURE 1: BIOLOGICAL ACTIVITIES OF MARINE CYANOBACTERIAL COMPOUNDS [23]

Cyanobacteria are a prolific source of nearly 800 diverse bioactive secondary metabolites, originating mainly from nonribosomal peptide synthetase (NRPS) or mixed polyketide synthase (PKS)–NRPS biosynthesis [24, 25]. Their role as antiviral, anti-tumour, antibacterial, anti-HIV and a food additive have been well established. Cyanobacteria are a simple, but primitive and diverse group of microorganisms, with characteristics in common to both bacteria and algae. Their success as a group in a wide range of habitats has been attributed to their unique physiological characters and high adaptive ability under a wide range of environmental conditions.

The potential of cyanobacteria as a source of a variety of compounds such as polysaccharides, lipids, proteins, vitamins, sterols, enzymes, pharmaceuticals and other fine chemicals is well recognized, and their demand is now on an increasing trend (**Table 2**). This compilation reviews the salient advances in the discovery of bioactive compounds from cyanobacteria and their significance in agriculture and industry. The cyanobacterium *Spirulina platensis* is rich in nutrients, such as proteins, vitamins, minerals, carbohydrates, and γ-linolenic acid. It is gaining more and more attention, not only for the foods aspects but also for the development of potential pharmaceuticals [26].

TABLE 2: BIOTECHNOLOGICAL APPLICATIONS OF BIOACTIVE COMPOUNDS FROM MICROALGAE AND CYANOBACTERIA [39, 40]

Species	Group	Product	Application	Culture system
Spirulina platensis	Cyanobacteria	Phycocyanins, biomass	Health food, cosmetics	Open ponds, natural lakes
Chlorella vulgaris	Chlorophyta	Biomass, Ascorbic acid	Health food, food supplement, food surrogate	Open ponds, basins, glass tube PBR
Dunaliella salina	Chlorophyta	Carotenoid, β carotene	Health food, food supplement, feed	Open pond, lagoons
Haematococcus pluvialis	Chlorophyta	Carotenoids, astaxanthin	Health food, pharmaceuticals, additives	Open ponds, PBR
Odontella aurita	Bacillariophyta	Fatty acids	Pharmaceuticals, cosmetics, baby food	Open food
Porphyridium cruentum	Rhodophyta	Polysaccharides	Pharmaceuticals, cosmetics, nutrition	Tubular PBR
Isochrysis galbana	Chlorophyta	Fatty acids	Animal Nutrition	Open ponds
Phaedactylum tricornutum	Bacillariophyta	Lipids, Fatty acids	Nutrition, fuel production	Open ponds, Basins
Lyngbya mujuscule	Cyanobacteria	Immune modulators	Pharmaceuticals, nutrition	Open ponds

In contrast to higher plant, hydroperoxy-unsaturated fatty acids, especially hydroperoxy-linoleic acid or linolenic acid in algae have been found to be the intermediate compound of physiological bioactive that involved in chemical defense or wound etc., such as jasmonic acid, *n*-hexanal, 2(*E*)- and 3(*Z*)- nonenal, 2(*E*) and 3(*Z*)-hexenal [27]. *Anabaena spp* produce a number of bioactive compounds, mostly lipopeptidases that have antibiotic, antialgal, anticancer, anti-inflammatory, cytotoxic and enzyme-inhibiting effects [23, 28].

Oscillatoria spp. can produce fatty acids, tetraamine, spermine and piperazine derivatives which show antimicrobial activity [29]. Thillairajasekar *et al*., [30] showed the presence of fatty acids from hexane and ethyl acetate extract of *Trichodesmium erythraeum* showed antimicrobial activity. Phycocyanin and Phycoerythrin are produced by cyanobacteria (Spirulina) and recently have been used as fluroscent labelling agent. They are proteinaceous in structure and exhibit a high extinction coefficient. One future commercial application of microalgae could be in the production of special lipids.

The Omega-3-fatty acids found in the oils of certain cold-water marine fish are considered to be responsible to reduce incidence of coronary heart disease. These fatty acids are likely to originate from the plankton in food chain. Several leptosins were isolated from the marine alga *Leptosphaeria sp.* and their biological activity evaluated, Of these leptosin M exhibited significant cytotoxicity against human cancer cell lines.The sulphated polysaccharide of the red microalga *Porphyridium sp.* showed high order of antiviral activity against herpes simplex virus (HSV-1 and 2) both *in vitro* and *in vivo* [31].

The cyanobacterium *Phormidium sp.* has been reported to inhibit growth of different Gram positive and Gram-negative bacterial strains, yeasts, and fungi [32]. Similarly *Lyngbya majuscula* [23] that produces numerous chemicals including nitrogen-containing compounds, polyketides, lipopeptides, cyclic peptides and many others [33].

The biological activity of these compounds is also diverse and includes protein kinase C activators and tumour promoters, inhibitors of microtubulin assembly, antimicrobial and antifungal compounds and sodium-channel blockers.

The number of bioactive compounds isolated or produced from *Nostoc* species is increasing continuously. Cryptophycins are anticancer agents isolated from terrestrial *Nostoc* strains [34, 35]. Recently, it has also been found that the carbolinium alkaloid, nostocarboline (**Fig. 2**) isolated from *Nostoc* acts as cholinesterase inhibitor, an enzyme targeted in the treatment of Alzheimer'disease [36].

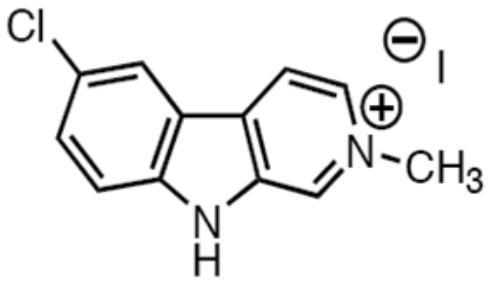

FIGURE 2: NOSTOCARBOLINE

Recently, an interesting compound, norharmane (**Fig. 3**) from *Nodularia harveyana* exhibited anticyano-bacterial activity against both filamentous and unicellular cyanobacteria and may be used for the control of toxic algal blooms [37].

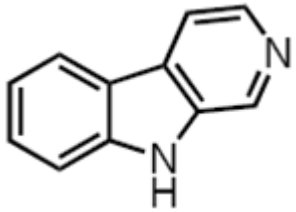

FIGURE 3: NORHARMANE

Borophycin (**Fig. 4**) is a complex boron containing polyketide isolated from marine strains of *Nostoc linckia* and *Nostoc spongiaeforme var. tenue* [38].

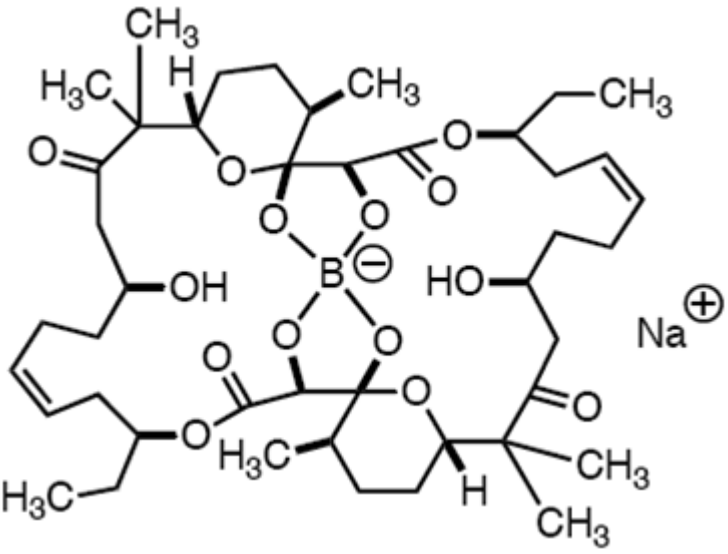

FIGURE 4: BOROPHYCIN

CONCLUSION: The potential of cyanobacteria as a source of a variety of compounds such as polysaccharides, lipids, proteins, vitamins, sterols, enzymes, pharmaceuticals and other fine chemicals is well recognized, and their demand is now on an increasing trend. Likewise the diverse end uses of microalgale includes Carbon neutral Biofuel production and Bioenergy generation; Capture and bioconversion of carbon dioxide (CO_2) from industrial processes; Ingredients for human health and wellbeing products, including essential omega 3 oils, antioxidants and pigments; Ingredients for aquaculture and agriculture feeds; Bioremediation and valorisation of agricultural and industrial effluents.

Microalgal biotechnology is similar to conventional agriculture, but has received quite a lot of attention over the last decades, because they can reach substantially higher productivities than traditional crops and can be extended into areas and climates unsuitable for agricultural purposes (e.g. desert and seashore lands).

Microalgae production is an important natural mechanism to reduce the excess of atmospheric CO_2 by biofixation and recycling of fixed C in products, ensuring a lower greenhouse effect, reducing the global environmental heating and climate changes. Microalgae cultivation also presents less or no seasonality, are important as feed to aquaculture and life-support systems, and can effectively remove nutrients (or pollutants) (e.g nitrogen and phosphorus) from water. Microalgal systems for sunlight driven environmental and production applications can clearly contribute to sustainable development and improved management of natural resources.

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