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Review Article

PHARMACEUTICALLY VALUABLE BIOACTIVE COMPOUNDS OF ALGAE

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ABSTRACT

Pharmaceutically valuable products from microalgae and its industrial commercialization today is still in its infancy and can be seen as a gateway to a multibillion dollar industry. Microalgae generally grow autotrophically and are ubiquitous in nature. They represent a major untapped resource of genetic potential for valuable bioactive agents and fine biochemical. This proven ability of microalgae to produce these compounds places these microorganisms in the biotechnological spotlight for applications and commercialization as in the pharmaceutical industry. The production of microalgal metabolites, which stimulate defense mechanisms in the human body, has spurred intense study of the application of microalgal biomass and products thereof in various food preparations, pharmacological and medical products. There is, therefore, a huge scope for further study of the identified algal compounds and their activities in the treatment and prevention of various diseases, in addition to an ongoing search for other, as yet undetected, metabolites.

Keywords: Algae, Pharmaceuticals, Bioactive compounds.

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INTRODUCTION

The markets for both pharmaceuticals and nutraceuticals are growing quickly worldwide, and it is this global scope that particularly attracts consumers. A growing proportion of today's promising pharmaceutical research focuses on the production of potent bioactive compounds from algae. Thus, the untapped potential of algae in the field of pharmaceuticals has to be still explored to grow and capitalize on tremendous global marketing opportunities.

Algae are emerging as one of the most promising sources of sustainable crops with potential health benefits including protein, Omega 3, and antioxidants. The pharmaceutical potential of the large variety of algae species is just starting to be explored. A lot of research aims to enhance particular pigments and products within certain algae species that have nutritional, nutraceutical, or pharmaceutical value.

While the pharmaceutical content in the common baseline algae strains is small, current market values for these products are extremely high. The major products currently being commercialized or under consideration for commercial extraction include carotenoids, phycobilins, fatty acids, polysaccharides, vitamins, sterols, and biologically active molecules for use in human and animal health. There is a range of pharmaceutical products derived from algae. Some of them include: Antimicrobials, antivirals and antifungals, neuroprotective products, therapeutic proteins, and drugs.

WHAT ARE BIOACTIVE COMPOUNDS?

Bioactive compounds are physiologically active substances with functional properties in the human body. There is, therefore, great enthusiasm for the development and manufacture of various biocompounds that can potentially be used as functional ingredients such as carotenoids, phycocyanins (PC), polyphenols, fatty acids, and polyunsaturated compounds [1]. An interest in the production of bioactive compounds from natural sources has recently emerged, driven by a growing number of scientific studies that demonstrate the beneficial effects of these compounds on health benefits [2]. These natural products are important in the search for new pharmacologically active compounds and play an important role in new drug discovery for the treatment of human diseases [3]. Many clinically viable and commercially available drugs with antitumor and anti-infective activity originated as natural products.

MICROALGAE AS A SOURCE OF BIOACTIVE COMPOUNDS

Algae, in general, are found all over the globe and in every ecological niche conceivable. They, therefore, have unique properties to help them survive even in adverse conditions they encounter in the ecosystem. These unique attributes are brought about by changes in their macro- and micro-molecular constituents in the cell which are formed under the stressed situations the algae faces. These unique metabolites often have special properties and can be considered as bioactive compounds in addition to the macromolecules the algae generally have. There are thousands and thousands of algal species and only 25-30% of them have been identified and collected. Hence, there is a huge unexplored resource available to be exploited in the pharmaceutical industry. Microalgae are known to produce various therapeutically effective biocompounds that can be obtained from the biomass or released extracellularly into the medium [4]. These microorganisms contain many bioactive compounds such as proteins, polysaccharides, lipids, vitamins, enzymes, sterols, and other high-value compounds with pharmaceutical and nutritional importance that can be employed for commercial use [5].

TYPES OF BIOACTIVE COMPOUNDS

Bioactive compounds from microalgae can be obtained directly from primary metabolisms, such as proteins, fatty acids, vitamins, and pigments, or can be synthesized from secondary metabolism. Such compounds can present antifungal, antiviral, antialgal, antienzymatic, or antibiotic actions [6]. Many of these compounds (cyanovirin, oleic acid, linolenic acid, palmitoleic acid, vitamin E, B12, β-carotene, PC, lutein, and zeaxanthin) have antimicrobial, antioxidant, and anti-inflammatory properties, with the potential for the reduction and prevention of diseases [7-10]. In most microalgae, the bioactive compounds are accumulated in the biomass; however, in some cases, these metabolites are excreted into the medium; these are known as exometabolites.

RESEARCH RESULTS ON WELL-STUDIED ALGAL STRAINS

A huge volume of research on bioactive compounds from well-studied algal forms such as *Arthrospira* (*Spirulina*), *Botryococcus braunii, Chlorella vulgaris, Dunaliella salina, Haematococcus pluvialis,* and *Nostoc* has led to the identification of antimicrobial, antiviral, anticoagulant antienzymatic, antioxidant, antifungal, anti-inflammatory, and

anticancer activity [1,5,11,12,14]. These studies have been based on the extraction of bioactive compounds from these microalgae [15-17]. The prokaryotic blue-green algae or cyanobacteria are known to produce intracellular and extracellular metabolites with potential biological activities, such as antibacterial, antifungal, antiviral, antitumor, anti-human immunodeficiency virus (HIV), anti-inflammatory, antioxidant, antimalarial, herbicidal, and immunosuppressant effects [18,19]. The therapeutic importance of *Spirulina,* one of the most extensively studied blue-green algae, has been reported in several studies. These include its use in the treatment of hyperlipidemia, cancer, HIV, diabetes, obesity, and hypertension, the improvement of the immune response in renal protection against heavy metals and drugs, and the reduction in serum levels of glucose and lipids, among others [20-23].

Nostoc, another blue-green alga, biomass has been used in the medical field and as a dietary supplement because of its protein, vitamin, and fatty acid content. The medical value of this microalga was established by its use in the treatment of fistula and for some forms of cancer [24]. Historically, the biomass of *Nostoc* is described as anti-inflammatory, and it is also found to aid in digestion, blood pressure control, and immune boosting. Cyanovirin, a potential protein molecule produced by a *Nostoc* species, showed a positive effect in the treatment of HIV and influenza A (H1N1) [25,7]. *Nostoc* species also contains a spectrum of polyunsaturated fatty acids (PUFAs) that include essential fatty acids such as linoleic, α-linolenic, γ-linolenic, octadecatetraenoic, and eicosapentaenoic acid [26]. Essential fatty acids are precursors of prostaglandins, attracting significant interest from the pharmaceutical industry.

Several other studies suggest that *Nostoc* produces compounds with antimicrobial, antiviral, and anticancer activity. These results have encouraged its cultivation on a large scale, and it has great economic potential due to its nutritional and pharmaceutical importance and the pharmaceutical industry [27].

Chlorella, a very common green alga was discovered by the Japanese, traditional consumers of algae, who usually eat and enjoy it as a food supplement. *Chlorella* is rich in chlorophyll, proteins, polysaccharides, vitamins, minerals, and essential amino acids with molecular constituents of 53% (w/w) protein, 23% (w/w) carbohydrate, 9% (w/w) lipids, and 5% (w/w) minerals and oligo elements [28]. These nutrient concentrations can be varied by manipulation of the culture conditions, in which they are grown. The biomass of *Chlorella* is also rich in vitamin B complex, especially B12, which are vital in the formation and regeneration of blood cells. Like *Spirulina*, *Chlorella* has a GRAS certificate issued by the FDA and can thus be used as food without risk to human health when grown in a suitable environment with proper hygiene and good manufacturing practices [28,29].

The pharmaceutical importance of *Chlorella* is attributed to its medicinal properties. There is ample experimental evidence of its antitumor, anticoagulant, antibacterial, antioxidant, and antihyperlipidemia effects in addition to a hepatoprotective property and the immune-stimulatory activity of enzymatic protein hydrolyzate [30-34]. Many antioxidant compounds are thought to be responsible for *Chlorella* functional activities. Antioxidants such as lutein, α-carotene, β-carotene, ascorbic acid, and α-tocopherol, which are active against free radicals, have been identified. Some of these compounds not only are important as natural colorants or additives but also may be useful in reducing the incidence of cancer and in the prevention of macular degeneration [30,35].

By far one of the most important bioactive compounds in *Chlorella* is β-1,3 glucan, an active immune stimulator that reduces free radicals and blood cholesterol. The efficacy of this compound against gastric ulcers, sores, and constipation has been reported. It also has been demonstrated to have preventive action against atherosclerosis and hypercholesterolemia, as well as antitumor activity [36]. *Chlorella* is produced by more than 70 companies. Taiwan *Chlorella* Manufacturing Co. (Taipei, Taiwan) is the world's largest producer of *Chlorella*, with over 400,000 tons of biomass produced per year. The significant production also occurs in Klötze (Germany) (80–100 t year^{-1} of dry biomass) [37].

Dunaliella is also a green unicellular halotolerant microalga that has been extensively studied for its pharmaceutically active compounds. This microalga is popularly studied as an extremophile, unique physiology, and therefore, many biotechnological applications. *Dunaliella* is a source of carotenoids, glycerol, lipids, and other bioactive compounds such as enzymes and vitamins. This microalga is a major source of natural β-carotene, able to produce up to 14% of its dry weight under conditions of high salinity, light, and temperature as well as nutrient limitation [38]. In addition to β-carotene, this microalga is rich in protein and essential fatty acids, which can be consumed safely, as evidenced by GRAS recognition [28]. Compounds in the *Dunaliella* biomass have various biological activities such as antioxidant, antihypertensive, bronchodilatory, analgesic, muscle relaxant, hepatoprotective, and antiedemal properties. The microalgal biomass can also be used directly in food and pharmaceutical formulations [39].

Chang *et al*. [40] showed that *Dunaliella* cells contained antibiotic substances. According to these authors, the crude extract of this microalga strongly inhibited the growth of *Staphylococcus aureus, Bacillus cereus, Bacillus subtilis*, *and Enterobacter aerogenes*. In another study, *Dunaliella* showed antibacterial activity against other microorganisms of importance to the food industry, which includes *Escherichia coli, Candida albicans,* and *Aspergillus niger* [41,42]. Under ideal growing conditions, *Dunaliella* can be stimulated to produce approximately 400 mg of β-carotene per square meter of growing area.

The cultivation of *Dunaliella*for, the production of β-carotene, has been conducted in several countries, including Australia, India, Israel, the USA, and China [43-45]. An ingredient of *Dunaliella* with a strong ability to stimulate cell proliferation and improve the energy metabolism of the skin was released by Pentapharm (Basel, Switzerland) [46]. New pilot plants are under development in India, Chile, Mexico, Cuba, Iran, Taiwan, Japan, Spain, and Kuwait [38].

ALGAL MACROMOLECULES AS BIOACTIVE COMPOUNDS AND THEIR PHYSIOLOGICAL EFFECTS

Oxidative damage caused by reactive oxygen species (ROS) to lipids, proteins, and nucleic acids can cause many chronic diseases such as heart disease, atherosclerosis, cancer, and aging. In general, microalgal strains are considered a rich source of antioxidants, with potential applications in pharmaceuticals, food, and cosmetics [47]. Antioxidant compounds, such as dimethylsulfoniopropionate and mycosporine amino acids, were isolated from microalgae and are potent chemical blockers of UV radiation [48]. In addition to these compounds, pigments, lipids, and polysaccharides with antioxidant activity can also be found in microalgae.

Good examples of such compounds are the C-PC is a blue photosynthetic pigment that belongs to the group of phycobiliproteins found in large quantities in the cyanobacteria, Rhodophyta, and Cryptophyte [49]. PC has applications as a nutrient and natural food colorants and cosmetics. In addition, it has application in medical diagnostics and pharmacology in the detection of cancer, and therefore, of great pharmaceutical importance. It is usually extracted from the biomass of *Spirulina* [50], *Porphyridium cruentum* [51] and *Synechococcus* [49]. Among the carotenoid compounds, β-carotene and astaxanthin are prominent. These compounds have application in the food and pharmaceutical industries because of their antioxidant properties and pigmentation ability.

Polysaccharides represent a class of high value-added components with applications in pharmaceuticals, food, cosmetics, fabrics, stabilizers and emulsifiers [52]. Microalgal polysaccharides contain sulfate esters, are referred to as sulfated polysaccharides, and possess unique medical

applications. The basic mechanism of therapeutic action is based on the stimulation of macrophages and modulation. The biological activity of sulfur polysaccharides is linked to their sugar composition, position, and degree of sulfation [53]. Some studies have reported that sulfated polysaccharides derived from microalgae inhibit viral infection, such as encephalomyocarditis virus, Herpes simplex virus types 1 and 2 (HSV1, HSV2), HIV, hemorrhagic septicemia in salmonid virus, swine fever virus, and varicella virus [54,55].

Carrageenan is a sulfated polysaccharide that can directly bind to human papillomavirus to inhibit not only the viral adsorption process but also the input and the subsequent process of the uncoating of the virus [56]. The importance of polysaccharides in the pharmaceutical industry lies in the fact that the extraction of this compound is relatively easy from microalgae.

The lipid compositions of microalgae are found to be responsible for its antimicrobial activity. This antimicrobial property of microalgae is because of their potential to produce compounds such as α- and β-ionone, β-cyclocitral, neophyte diene, and phytol 55. Antimicrobial activity against human pathogens, such as *E. coli*, *Pseudomonas aeruginosa, S. aureus,* and *Staphylococcus epidermidis*, has been attributed to γ-linolenic acid, eicosapentaenoic acid, hexadecatrienoic acid, docosahexaenoic acid, palmitoleic acid, lauric acid, oleic acid, lactic acid, and arachidonic acid [57].

Microalgae produce several anti-inflammatory compounds in their biomass that may exert a protective function in the body when consumed as food or used as pharmaceuticals and cosmetics. Because of their anti-inflammatory properties, microalgal biomass is being considered for applications in tissue engineering for the development of scaffolds, for use in the reconstitution of organs and tissues [58,59]. This is an important application for humans, especially in patients with burns in which the skin was completely lost [60]. Microalgal compounds with such properties are the long-chain PUFAs [61,62], sulfurized polysaccharides [63], and pigments [64]. Many microalgal polysaccharides possess the ability to modulate the immune system through the activation of macrophage functions and the induction of ROS, nitric oxide, and various other types of cytokines/chemokines [65]. Macrophages are able to regulate several innate responses and secrete cytokines and chemo-cytokines that serve as signals for immune and inflammatory molecular reactions [66]. Sulfated polysaccharides with anti-inflammatory activity can be applied in skin treatments inhibiting the migration and adhesion of polymorphonuclear leukocytes [63].

In humans, the oxidation reactions driven by ROS can lead to irreversible damage to cellular components, including lipids, proteins, and DNA degradation and/or mutation. Consequently, this damage can lead to several syndromes such as cardiovascular disease, some cancers, and the degenerative diseases of aging [67]. Pigments derived from microalgae have neuroprotective properties, being valuable sources as functional ingredients in pharmaceutical products that show efficient action in the treatment and/or prevention of neurodegenerative diseases. Vitamin E derived from algae has preventive effects for many diseases, such as atherosclerosis and heart disease, as well as neurodegenerative diseases, such as multiple sclerosis [68].

Carotenoids have great potential benefits to human health, including the treatment of degenerative diseases, such as macular degeneration and cataract development. These compounds act as antioxidants, reducing oxidative damage by ROS. Studies indicated that increased intake of phenols decreased the occurrence of degenerative diseases. Phenolic compounds from microalgae with the potential to fight free radicals have been reported [69].

Scientific findings indicate astaxanthin for multimodal intervention for many forms of degenerative diseases, including cardiovascular diseases, cancer, metabolic syndrome, cognitive impairment, age-related immune dysfunction, stomach and ocular diseases (macular degeneration, cataract, glaucoma, diabetic retinopathy, and retinitis pigmentosa), and skin damage [70]. High levels of lycopene from algae in plasma and tissues were inversely related to coronary heart disease, myocardial infarction, and the risk of atherosclerosis [70].

CONCLUSION

Bioactive metabolites of microalgal origin are of special interest in the development of new products for pharmaceutical, cosmetic, and food industries. Further research should be conducted with these bioactive compounds to verify their beneficial effects for humans, their degradability when released into the environment, and their effects when used in animals. Pharmaceutically valuable products and its industrial commercialization today are still in its infancy and can be seen as a gateway to a multibillion dollar industry. Scientists have just started to tap the enormous biological resource and physiological potential of microalgal species growing in all ecological niches. In recent years, innovative processes and products have been introduced in both macro- and microalgal biotechnology. One can expect that future trends in the involvement of microalgal utilization in the pharmaceutical industry will lead to a diversity of technical solutions for the use of PBR for cultivating microalgae. These will be adapted to the autecological demands of strains and to application aims for biomass, valuable substances, and ecology. An exhaustive inventory of species in all regions accompanied by proper taxonomic handling and strain collection could be a basis for future success. While the use of microalgae in functional foods and animal feed could soon reach the level of mass products, their use in pharmaceutical applications appears to be developing very rapidly.

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