

## Microalgae and the medicine of the future



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### ABSTRACT

This chapter looks at the biotechnological potential of microalgae and their promising use in medicine. We explore their applications as bioreactors in producing pharmaceutical substances and their innovative capacity in gene therapy. In addition, we highlight the growing interest in their nutritional properties, especially omega-3 fatty acids, and high-quality antioxidants. Our analysis also showed the impact of microalgae in the field of vaccines and immunotherapies, highlighting their ability to improve the efficacy of vaccines and drive the development of advanced immunization methods. We discussed current challenges and prospects in the broader context, highlighting the continued need for in-depth research and investment in this emerging area. This chapter has aimed to provide a comprehensive overview of the transformative potential of microalgae in medicine, emphasizing their role as one of the fundamental pillars for the continued advancement of human health and the development of innovative therapies on the horizon of future medicine. Hopefully, this analysis will stimulate further discussion and inspire new research, thus driving progress biomedical research.

**Keywords:** Bioreactors, Nutritional supplements, Human health, Biotechnology, Sustainability.

## 1 INTRODUCTION

Algae, aquatic photosynthesizing organisms, have played a vital role in the terrestrial biosphere for centuries, contributing to oxygen production, climate regulation, and sustaining marine ecosystems (SMITH, 2018). Algae can be classified into two distinct categories within the plant kingdom: macroalgae and microalgae (JONES et al., 2020). While macroalgae, such as the well-known



seaweeds, are visible to the naked eye, microalgae, of microscopic dimensions, often remain imperceptible, but their impact and importance are no less significant (BROWN; GREEN, 2019).

In recent years, microalgae have attracted considerable interest due to their wide range of medical applications. Their role as a promising source of bioactive compounds has attracted the attention of researchers to explore their potential in discovering new drugs and therapies (BOROWITZKA, 2013; SORRENTI V et al., 2021). The rich diversity of metabolites produced by microalgae, such as polyunsaturated fatty acids, carotenoids, polysaccharides, and bioactive peptides, offers opportunities for the development of medical solutions (GUEDES et al., 2013; KISHIMOTO Y; YOSHIDA H; KONDO K, 2016; PLAZA et al., 2018; PEREIRA; FARIA, 2023).

Microalgae are photosynthesizing microorganisms that combine water and carbon dioxide with sunlight to produce forms of energy that produce biomass (polysaccharide, lipids, hydrocarbons and proteins) (MORAES et al., 2023; SILVA, 2023; LAGE et al., 2022). Algae can be classified as green (*Chlorophyta*), diatoms (*Bacillariophyta*) and red (*Rhodophyta*) (Figure 1). They have a high growth rate and can synthesize and accumulate high rates of lipids compared to terrestrial plant species (MORAES et al., 2023).

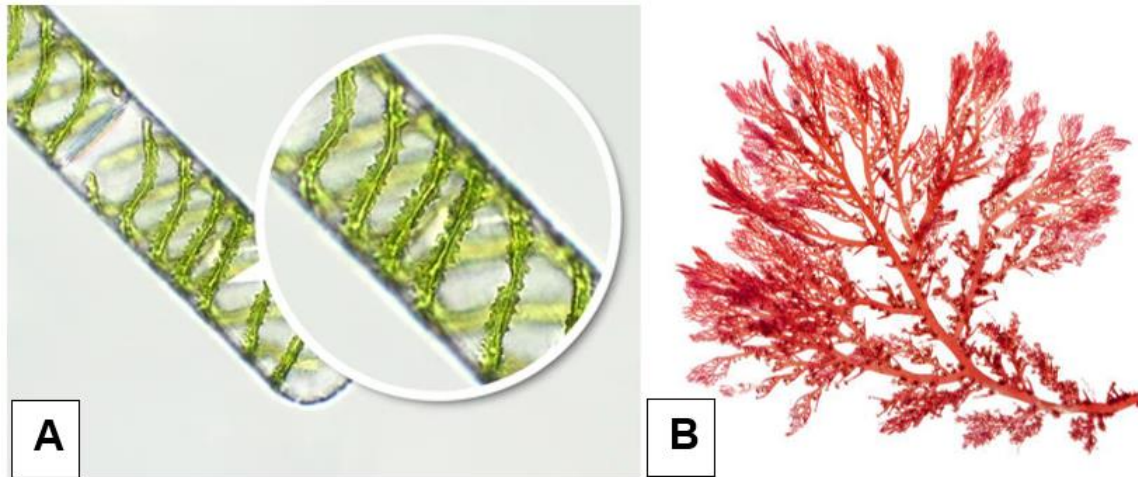
In this context, this chapter has examined the importance of microalgae as a promising source of medical advances, with a particular focus on identifying bioactive compounds with therapeutic potential. The central objective was to analyze the diversity of compounds produced by microalgae and assess their potential for medical applications, highlighting recent advances and their prospects (BOROWITZKA, 2013; GUEDES et al., 2013).

We presented an overview of the bioactive properties and compounds produced by microalgae with an emphasis on medical research (PLAZA et al., 2018; GARCÍA-GONZÁLEZ et al., 2013; VALE F et al., 2023). The various potential applications were then discussed, including their role in therapy against chronic diseases, discovering ant-tumor agents, and addressing emerging medical challenges (COLLA et al., 2019; VAZ et al., 2019).

Finally, by emphasizing the need for an in-depth understanding of the pharmacological properties and potential of microalgae, this chapter has sought to stimulate greater exploration and investment in interdisciplinary research, intending to translate the vast potential of microalgae into tangible and innovative advances in the field of medicine (GUEDES et al., 2013; BOROWITZKA, 2013; YANG N et al., 2023).



Figure 1: Microalgae from a microscopic view. A) Green algae (*Chlorophyta*). B) Red algae (*Rhodophyta*).



## 2 MICROALGAE AS BIOREACTORS

The term "microalgae as bioreactors" refers to using microalgae as hosts producing substances of interest in biotechnological processes. In these applications, microalgae are genetically modified to produce specific proteins and bioactive compounds, or to carry out certain chemical reactions, taking advantage of their characteristics of rapid growth and ability to synthesize compounds of industrial, pharmaceutical and food interest, among others (LIANG; LIANG; JIANG, 2020).

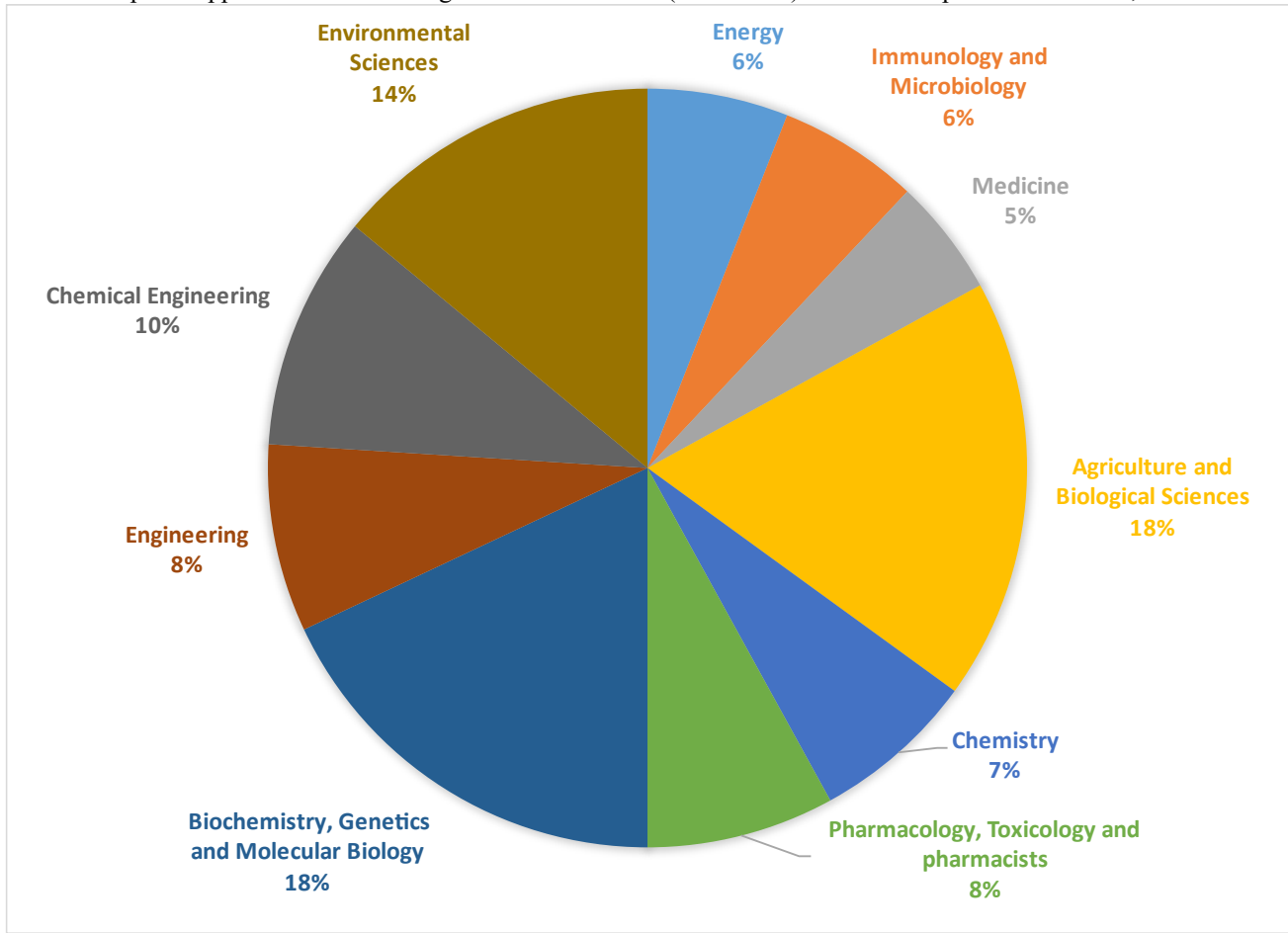
### 2.1 MICROALGAE AS BIOREACTORS TO PRODUCE SUBSTANCES OF MEDICAL INTEREST

In recent years, there has been growing interest in the use of microalgae as bioreactors for the production of a variety of substances with significant relevance for industry and especially medicine, as shown in Graph 1 (BOROWITZKA, 2013; RIBEIRO, 2019). According to the graph below, it was possible to observe, from 2014 to 2019, greater applicability of algae in agriculture, biological sciences, biochemistry, genetics, molecular biology, and environmental science.

These photosynthetic microorganisms have demonstrated a remarkable ability to convert simple nutrients into diverse bioactive compounds. In this context, their use as bioreactors has gained prominence due to their efficiency in producing substances of medical interest, ranging from antioxidant and antimicrobial compounds to antitumor agents and immune regulatory molecules (BOROWITZKA, 2013; GUEDES et al., 2013).



Graph 1: Applications of microalgae in different areas (2014-2019). Source: Adapted from Ribeiro, 2019.



Caption: Energy 6%, Immunology and Microbiology 6%, Medicine 5%, Agriculture and Biological Sciences 18%, Chemistry 7%, Pharmacology, Toxicology, and pharmacists 8%, Biochemistry, Genetics and Molecular Biology 18%, Engineering 8%, Chemical Engineering 10%, Environmental Sciences 14%.

A deeper understanding of the potential of microalgae as bioreactors could offer new perspectives for producing innovative pharmaceutical substances with high therapeutic value. In addition, the ability of microalgae to synthesize these substances in a highly controlled environment presents promising advantages in terms of scalability and sustainability in producing bioactive compounds of medical interest (SPOLAORE et al., 2006; PLAZA et al., 2018).

When exploring the capabilities of microalgae as bioreactors, it is essential to consider their production ability and the optimal cultivation conditions that maximize the synthesis and accumulation of desired compounds. Innovative cultivation strategies, such as using photobioreactors and optimizing growth conditions, play a crucial role in amplifying the production of specific substances with therapeutic potential (VAZ et al., 2019; COLLA et al., 2019).

These approaches are redefining the field of biotechnology, opening up new possibilities for the discovery and development of promising therapeutic agents derived from microalgae, and



indicating a promising path for pharmaceutical innovation based on natural resources (MILLEDDGE, 2011; GARCÍA-GONZÁLEZ et al., 2013).

## 2.2 PHARMACEUTICAL PRODUCTS, SUCH AS THERAPEUTIC PROTEINS OR MEDICINES, THAT CAN BE PRODUCED WITH THE HELP OF MICROALGAE

Microalgae have emerged as a potentially valuable resource in producing pharmaceutical products, including therapeutic proteins and drugs. Promising evidence highlights the potential of microalgae not only as a source of bioactive compounds but also as efficient bioreactors in the production of immunostimulants and recombinant vaccines aimed at disease prevention and control in aquaculture (MA et al., 2020). In addition, recent studies indicate microalgae biomass as a promising new source of sustainable green machine lubricants, further highlighting the microscopic organisms versatility and multifaceted potencial (FARFAN-CABRERA et al., 2022).

In the more specific context of pharmaceutical production, microalgae have been used as efficient platforms for expressing therapeutic proteins, such as monoclonal antibodies, growth factors, and enzymes (INGRAM et al., 2016; D'ADAMO et al., 2019). These proteins have shown promise in reating various medical conditions, including autoimmune diseases and cancer. In addition, the unique ability of microalgae to express antigens effectively has been exploited in the development of vaccines for various infectious diseases, providing a promising and safe alternative for vaccine production (BARRERA et al., 2020; PRIETO et al., 2017). Furthermore, the synthesis of specific fatty acids and lipids, such as omega-3 and omega-6, by various species of microalgae highlights their role in the production of supplements and pharmaceutical formulations essential for cardiovascular and brain health (PENG et al., 2014; PLAZA et al., 2019). In addition, recent research has revealed that microalgae are potential sources of bioactive peptides with antimicrobial and anti-inflammatory properties, contributing to the development of innovative therapies for infectious and inflammatory diseases (RAMOS-MARTINEZ et al., 2018; SAFI et al., 2014). The ability of microalgae to produce complex bioactive molecules, such as carotenoids and polysaccharides, with antioxidant and immunomodulatory properties, further expands the range of therapeutic applications for these organisms. This approach underscores the significant contribution of microalgae in the production of a variety of pharmaceutical and therapeutic products, highlighting their importance in the research and development of innovative therapies based on natural resources (KOTZABASIS et al., 2018; FAN et al., 2017).



### 3 GENE THERAPY AND MICROALGAE

#### 3.1 MICROALGAE IN GENE THERAPY

With the increase in the management and cultivation of microalgae for the production of various products, from pharmaceuticals to biofuels, research into molecular tools for gene therapy is advancing, intending to improve commercial value, pharmaceuticals, aquaculture and others. Although this genomic reality is limited for some species of microalgae, the development of new genetic technologies is currently growing, making it possible to understand the metabolic and regulatory processes of microalgae, thus allowing for advances such as a database of the genes of microalgae species, knowledge of sequence markers and expressions of specific genes (SPÍNOLA, 2010; LEÓN, et al., 2007; GREENWELL et al, 2010).

#### 3.2 APPLICATION IN GENE THERAPY

Few species of microalgae currently have their genetics modified. However, the application of microalgae as gene therapy is becoming increasingly promising for use in the health sector (production of antioxidants, anti-inflammatories, antibacterials, anti-tumors); biofuels (biodiesel, biogas); agriculture (biostimulants, biofertilizers); cosmetics (collagen, sunscreen); food (human and animal); effluent treatment (treatment of chemical waste); bioactive molecules (proteins, lipids) (SOEDER, 1986; SPÍNOLA, 2010; ABED et al., 2009)

To identify and separate the substances of interest from microalgae, analytical techniques are used, such as chromatography, which separates the molecules concerning the stationary phase, and nuclear magnetic resonance spectroscopy, which determines the chemical composition and structure of the microalgae of interest and thus be able to obtain the purified extracts and metabolites (AQUINO NETO, 2003; RATCLIFFE, ROSCHER AND SACHAR, 2001).

Chemical compounds from microalgae's secondary or primary metabolism have antimicrobial functions, for example. Phycocolloids, which are gelling agents, have viscosity and are classified with carrageenans, alginates and agar, directing their management and use to cosmetics and the food industry. Carotenoids have the ability to prevent residues caused by photo-oxidation from UV rays. *Dunaliella tertiolecta* is a microalgae species known for producing this phytochemical (ABALDE, 1995).



Figure 2: Microalgae of the species *Dunaliella tertiolecta*.



Biofuel production it comes from the lipid portion of these microorganisms. Microalgae are photosynthetic, and they can fix CO<sub>2</sub>, helping to convert reserve molecules such as triacylglycerides, a molecule that is present in the manufacture of biodiesel (HARUN et al., 2010; LIU AND BENNING, 2013).

Vitamins from microalgae are found in abundance, especially in cyanobacteria. These are marketed for nutritional use to improve an immune response (HABIB et al., 2008)

In aquaculture, microalgae have been used as gene therapy for the nutrition of seafood species by synthesizing their polyunsaturated fatty acids. In the production of cosmetics, microalgae biomass is used to preserve the product and help synthesize collagen to reduce aging (SPOLOARE et al., 2006).

The following table shows existing microalgae species and their biotechnological use, extracted product and biological activity, respectively (Table 1).

Table 1: Microalgae, their products and their biological activities, respectively.

Microalgae	Product	Biological Activity
<i>Chlorella</i>	<i>Chlorella</i> extract Carbohydrate extract	Nutraceutical, improves immune response, antifu
<i>Botryococcus braunii</i>	Glucuronic acid	Face cream with sunscreen
<i>Chlorella pyrenoidosa</i>	<i>Chlorella</i> extract	Nutraceuticals, face cream, animal supplement
<i>Cryptocodinium</i>	DHA	Brain development
<i>Haematococcus</i>	Astaxanthin	Treatment of carpal tunnel syndrome, anti-inflammatory, treatment of muscle injuries
<i>Odoniella</i>	EPA	Anti-inflammatory
<i>Spirulina</i>	Vitamin B12	Improved immune response
<i>Ukenia</i>	DHA	Treatment of brain and heart diseases

Source: Adapted from Pulz and Gross, 2004



## 4 MICROALGAE-BASED HEALTH PRODUCTS

Microalgae are natural sources of bioactive compounds that show great potential for use in medicine and human health. These components have different therapeutic properties and can be used in various applications, such as anticancer, antibacterial, anticoagulant, antifungal, antiviral, and other products with medicinal purposes (ASHOUR and OMRAN, 2022; BASHEER et al., 2020).

In addition to the applications above, microalgae can be used as functional ingredients with greater nutritional value, to improve human health and quality of life through healthier foods, such as food supplements and nutraceuticals. This application is essential, because with the increase in the world's population, the food industry is struggling to keep up with the growth in demand for food. The lack of food and adequate distribution has led to a food crisis (ASHOUR and OMRAN, 2022; CHEN et al., 2022; MATOS et al., 2017).

### 4.1 HEALTH BIOPRODUCTS, NUTRITIONAL SUPPLEMENTS AND TREATMENTS USING MICROALGAE COMPOUNDS

Microalgae are renewable biological resources with great potential for generating sustainable products such as raw materials for food, feed, chemicals and biofuels (MEHARIYA et al., 2021; CAPORGNO and MATHIS, 2018). These organisms have been used in the pharmaceutical industry due to their ability to accumulate macromolecules such as proteins, carbohydrates and lipids (MATOS, 2017).

In addition, microalgae are promising candidates for the production of functional foods and nutraceuticals, due to their ability to synthesize compounds that are valuable for human health, such as carotenoids, vitamins, essential and non-essential amino acids, enzymes, minerals and essential fatty acids for human nutrition, such as omega-3 and omega-6 (CAPORGNO and MATHIS, 2018; SAHA and MURRAY, 2018; MATOS, 2017).

*Chlorella vulgaris*, *Haematococcus pluvialis*, *Dunaliella salina* and the cyanobacterium (known as blue-green algae) *Arthrospira platensis* (Spirulina) are green algae widely used due to their biotechnological potential in the food industry as a nutritional supplement for humans and animals. The *Spirulina platensis* species is widely used due to its potential for protein accumulation (MATOS, 2017). The *Dunaliella* genus stands out in the pigment industry.

According to Kent (2015), *Spirulina* and *Chlorella* are the most widely used microalgae genera in 20 countries worldwide. These genera are used for nutraceutical purposes due to their compounds, which greatly benefit human health. Another genus that has been used is *Dunaliella* sp., as it can accumulate high concentrations of carotenes and xanthophylls. However, this genus has a limited production capacity compared to *Spirulina* and *Chlorella*.





Decades ago, microalgae were already traditionally used by indigenous populations worldwide, mainly in China and Japan. With the se people’s migration, algae consumption spread around the world. Research has contributed directly to understanding the advantages and benefits of microalgae in the food industry especially in medicine (SAHA and MURRAY, 2018). Table 2 below shows the main producing countries and the pharmacological properties of different microalgae genera.

Table 2: Production and pharmacological properties of different microalgae genera.

Species	Type	Products	Production	Countries	Pharmacological properties
<i>Chlorella</i>	Green Algae	Food supplement and nutraceutical.	2500 tons	United States, Japan, China, Taiwan and Indonesia.	-Decreases blood pressure; -Antitumor; -Antioxidant; -Reduction in cholesterol levels; -Improves the immune system.
<i>Dunaliella</i>	Green Algae	Nutraceutical.	1200 tons	Israel, China, United States and Australia.	-Antitumor; -Antioxidant; -Hepatoprotective effect.
<i>Haematococcus</i>	Green Algae	Nutraceutical pharmaceutical products, cosmetics, aquaculture and food products.	300 tons	United States, India and Israel.	-Antitumor; -Antioxidant; -Anti-inflammatory; -Antibacterial; -Prevention and treatment of neural diseases; -Treatment of Alzheimer’s disease; -Treatment of Parkinson’s disease.
<i>Aphanizomenon</i>	Blue-green algae (Cyanobacteria)	Food and pharmaceutical products.	500 tons	U.S.	-Antitumor; -Anti-inflammatory; -Anti-bacterial.
<i>Spirulina</i>	Cyanobacteria	Vitamin supplements, food colors, aquaculture, pharmaceuticals and nutraceuticals.	3000 tons	United States, Thailand, India, Taiwan, China, Pakistan, Burma.	-Antioxidant; -Anti-inflammatory.

Source: Adapted from Bishop and Zubeck, 2012.

*Chlorella* is a unicellular algae belonging to the green algae. Its pigmentation is related to the presence of chlorophyll. This genus comprises 55-67% protein, 9-18% fiber, 1-4% chlorophyll, minerals, and vitamins. Around 2,500 tons of dried seaweed are produced each year and the main producing countries are the United States, Japan, China, Taiwan and Indonesia (SAHA and MURRAY, 2018; NICOLETTI, 2016; BISHOP and ZUBECK, 2012). According to CAPORGNO and MATHIS



(2018), *Chlorella vulgaris* has been used in cookies as a coloring agent and a nutritional supplement due to its properties (Figure 3).

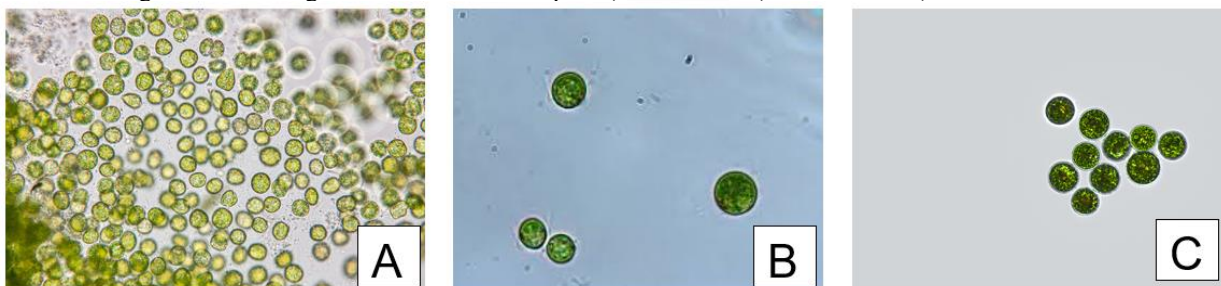
*Dunaliella* are eukaryotic, unicellular microalgae. This genus is used to produce  $\beta$ -carotene. This microalgae is commonly cultivated in Israel, China, the United States, and Australia. Annual production is around 1,200 tons. This algae is used for various applications in the food industry, mainly as a colorant (SAHA and MURRAY, 2018; BISHOP and ZUBECK, 2012) (Figure 3).

*Haematococcus* are freshwater green microalgae. This microalgae is identified as the largest natural source of astaxanthin, comprising around 1.5-3% of its dry weight. This biocompound has antioxidant activity and has been used as a colorant in the food, pharmaceutical, and nutraceutical industries. Astaxanthin has anti-cancer, anti-inflammatory, and antibacterial activity. The United States, Israel and India produce around 300 tons annually (SAHA and MURRAY, 2018; BISHOP and ZUBECK, 2012) (Figure 3).

*Aphanizomenon* is a blue-green cyanobacterium commonly found in freshwater systems. The United States produces around 500 tons of this cyanobacterium. This microalgae has pharmacological properties such as antitumor, anti-inflammatory and antibacterial activity (BISHOP and ZUBECK, 2012).

*Spirulina* are filamentous spiral cyanobacteria. The main biocompound in this microalgae is C-phycoyanin, which has antioxidant and anti-inflammatory properties. *Spirulina* contains around 60-70% protein. The main countries producing this microalgae are the United States, Thailand, India, Taiwan, China, Pakistan and Burma, resulting in around 3000 tons per year. This microalgae is rich in nutrients, vitamins, chlorophyll, fatty acids, and minerals (SAHA and MURRAY, 2018; NICOLETTI, 2016; BISHOP and ZUBECK, 2012).

Figure 3: Microalgae under the microscope. A) *Chlorella*. B) *Dunaliella*. C) *Haematococcus*.





## 5 VACCINES AND IMMUNOTHERAPY

### 5.1 USE OF MICROALGAE IN VACCINE PRODUCTION AND IMMUNOTHERAPY RESEARCH

Vaccination is an effective way of controlling and preventing diseases caused by viruses and bacteria. Microalgae have been used for the production of vaccines, or as a vehicle for them, *in which* the antigens are selected through *in silico* tools. Various tools have been developed, such as antigen encapsulation (RAMOS-VEGA et al., 2021; DU et al., 2022).

Microalgae demonstrate antigenic characteristics, producing functional antigens, and sufficient yield levels to become immunogenic in pre-clinical studies. For vaccine development, it is necessary to consider stages and factors such as: microalgae species, genetic construction, methods of transformation and detection of transgenes and antigens, immunization schedule and route of administration, as well as evaluation of protective efficacy (RAMOS-VEGA et al., 2021).

Concerning fish diseases, antibiotics pose several risks, such as the possible release of these antibiotics into the environment, which can result in the selection of antibiotic-resistant pathogens. In addition, there is an association between the widespread use of antibiotics in agriculture and the proliferation of antibiotic-resistant human pathogens. Therefore, using vaccines for disease control becomes a more effective strategy because they reduce environmental risk, are prophylactic and have minimal side effects (SIRIPORNADULSIL, DABROWSKI and SAYRE, 2007).

Currently, oral vaccines are available for fish that are microencapsulated, in which the antigens are encapsulated in polysaccharide-coated spheres between 1 and 10  $\mu\text{m}$  in diameter. This encapsulation is carried out to protect the antigen from degradation, resisting the acidity of the stomach to be endocytosed in the posterior intestine (SIRIPORNADULSIL, DABROWSKI and SAYRE, 2007).

The microalga *Chlamydomonas reinhardtii* has been widely used through biotechnological engineering tools. The species *Dunaliella salina*, *Schizochytrium sp.*, *Thalassiosira pseudonana*, *Nannochloropsis sp* and *Chlorella pyrenoidosa* have also been used to produce recombinant antigens and induce immunoprotective responses in vaccinated animals (RAMOS-VEGA et al., 2021).

Some microalgae have potential for the development of oral vaccines, as well as commercial interest. For example, *Arthrospira platensis*, which is cultivated by the companies Spira, Olivier MicroAlgues, Cyanotech, and DIC Corporation, among others, for the production of phycocyanin, whose substance increased the specificity of the IgA response to the ovalbumin antigen in a murine model, as well as studies for genetic transformation (RAMOS-VEGA et al., 2021).

In addition, the microalga *Haematococcus pluvialis* is also cultivated by companies such as Algalif, AstaReal, and Algatech, due to their interest in producing astaxanthin, which induces an increase in B and T lymphocyte subpopulations when administered to humans. *Chlorella vulgaris* is a



microalga cultivated by companies such as Taiwan Chlorella Manufacturing Companies, Parry Nutraceuticals and Allmicroalgae. However, this species has been little explored in the production of recombinant biopharmaceuticals, being related only to the production of the VP2 antigen of infectious bursitis, with prospects for future application as an oral vaccine in chickens (RAMOS-VEGA et al., 2021).

These microalgae undergo genetic modification, expressing antigen genes in chloroplasts, which are used to control and prevent infectious diseases. Although these microalgae mentioned above are developed in industry, they have not yet been established in an effective genetic manipulation system, and few pre-existing commercial vaccines are available. The microalga *Nannochloropsis* is also considered suitable producing oral vaccines for aquaculture, as it is included in the diet of fish (MA et al., 2020; ROUT et al., 2022).

## 5.2 MICROALGAE IMPROVE THE EFFICACY OF VACCINES

Ma and collaborators (2020) report that some polysaccharides enhance the phagocytic capacity of macrophages, and the levels of pro-inflammatory cytokines. They also report that the nutrients contained in microalgae can enhance the immune system and function against infections in aquatic animals (MA et al., 2020).

Several compounds derived from microalgae are immunostimulants, such as astaxanthin, polyunsaturated fatty acids, sulfopolysaccharides and sulfated lipids. These compounds stimulate dendritic cells, macrophages and T cells, acting on the maturation of dendritic cells, are molecular adjuvants, and stimulate a specific immune response (RICCIO and LAURITANO, 2020).

The microalga *Dunaliella salina* was administered orally to BALB/c mice, and prolonged survival was observed in these mice injected with WEHI-3 leukemia cells. Ingestion of *D. salina* resulted in increased phagocytosis of macrophages, increased population and proliferation of B and T cells, and increased cytotoxicity of NK cells. Additionally, a similar immunomodulatory mechanism was observed after ingesting *C. vulgaris* in healthy individuals, with an increase in interleukin-1 $\beta$  and interferon- $\gamma$  levels, as well as an increase in NK cell activity (SKJÅNES et al., 2021).

## 6 CHALLENGES AND PROSPECTS

Among the challenges in using microalgae are the high cost of culture media and the energy used to produce recombinant antigens on a large scale. In addition, there is a high cost of extraction, such as pressurized liquids, ultrasound-assisted or microwave-assisted extractions. Another limiting factor, that hinders the development of research, is the lack of information on the mechanism of gene regulation, as well as the genome of microalgae, in addition to the metabolite responsible for bioactivity (RAMOS-VEGA et al., 2021; MESADRI, WAGNER and FAGUNDES, 2021).



The microalga *Spirulina platensis* has been used to replace collagen as a raw material for capsules, prolonging the dissolution of drugs by acting on their release in the intestine. The study showed promising results, as the capsule produced with 3% microalgae resisted pH 1.2 conditions for 75 minutes (MESADRI, WAGNER and FAGUNDES, 2021).

As shown earlier in this chapter, microalgae can be used to produce vaccines. In animals, studies have focused on vaccines to combat diseases caused by foot-and-mouth disease virus, Vibriosis, classical swine fever virus, *Histophilus somni*, Gumboro disease virus and white spot syndrome virus. In humans, promising antigens are being researched for diseases caused by *Plasmodium falciparum*, Zika virus, Ebola, influenza, hepatitis B, *Staphylococcus aureus*, human papillomavirus and human immunodeficiency virus (MESADRI, WAGNER and FAGUNDES, 2021).

Microalgae can also be used in skin regeneration, as studies have shown positive effects on the rapid healing of skin wounds, including the microalgae *Nannochloropsis*, *Tetraselmis*, *Haematococcus*, *Chlamydomonas*, and *Chlorella*. The use of microalgae also prevents the colonization of microorganisms at the wound site, and reduces inflammation, oxidative stress, secretion of cytokines, and infiltration of pro-inflammatory cells (MESADRI, WAGNER and FAGUNDES, 2021).

In addition, microalgae may also have neuroprotective activity due to the inhibition of the enzyme acetylcholinesterase, an enzyme related to Alzheimer's disease, the inhibition of which was observed when using an extract rich in phytosterols. In addition, this extract reduced the inflammatory process, and inhibited lipoxygenase (MESADRI, WAGNER and FAGUNDES, 2021).

## 7 FINAL CONSIDERATIONS

This chapter has discussed the versatility of microalgae as bioreactors for pharmaceutical substances, facilitating agents in gene therapy, sources of essential nutrients and vital collaborators in vaccines and immunotherapies.

While advances are great, the complexity of research and development processes, and practical and regulatory considerations require a continued commitment to innovation and collaboration between different sectors. The dynamic intersection between microalgae and medicine offers a unique opportunity to redefine the way we approach global health challenges and strive to promote a healthier and more sustainable future for all.



## REFERENCES

- ABALDE, J., *Microalgas: cultivo y aplicaciones*. 210p., Monografía - Universidade da Coruña, Espanha, 1995
- ABED, R.M.M.; DOBRETsov, S.; SUDESH, K. Applications of cyanobacteria in biotechnology. *The Society for Applied Microbiology, Journal of Applied Microbiology* 106, 1–12, 2009
- AQUINO NETO, F. R.; NUNES, D. S. S. *Cromatografia – Princípios Básicos e Técnicas Afins*, Editora Interciência, Rio de Janeiro, 2003
- ASHOUR, M.; OMRAN, A.M.M. Recent Advances in Marine Microalgae Production: Highlighting Human Health Products from Microalgae in View of the Coronavirus Pandemic (COVID-19). *Fermentation* 2022, 8, 466. <https://doi.org/10.3390/fermentation8090466>.
- BARRERA, F. et al. Algal Chloroplast Produced Camelid VHH Nanobodies against SARS-CoV-2. *Biotechnology and Bioengineering*, v. 118, n. 11, p. 4308-4315, 2021. DOI: 10.1002/bit.27766.
- BASHEER, S. *et al.* (2020). *Microalgas em Saúde Humana e Medicina*. In: Alam, M., Xu, JL., Wang, Z. (eds) *Biotechnology de Microalgas para Alimentos, Saúde e Produtos de Alto Valor*. Springer, Singapura. [https://doi.org/10.1007/978-981-15-0169-2\\_5](https://doi.org/10.1007/978-981-15-0169-2_5)
- BISHOP, W. M.; ZUBECK, H. M. (2012) Evaluation of Microalgae for use as Nutraceuticals and Nutritional Supplements. *J Nutr Food Sci* 2:147. doi:10.4172/2155-9600.1000147.
- BOROWITZKA, M. A. High-value products from microalgae—their development and commercialisation. *Journal of Applied Phycology*, v. 25, n. 3, p. 743-756, 2013. DOI: 10.1007/s10811-013-9983-9.
- BROWN, C. D., & GREEN, E. F. (2019). *Algologia Avançada: Conceitos e Aplicações*. Editora Técnica Brasileira. DOI: 10.5678/algologia-avancada
- CHEN, C.; TANG, T.; SHI, Q.; ZHOU, Z.; FAN, J. The potencial and challenge of migroalgae as promising future food sources. *Trends in Food Science & Technology*. v. 126, p. 99-112, 2022.
- COLLA, L. M. et al. Microalgae compounds: Phycobiliproteins and carotenoids. In: *Handbook of Microalgae-Based Processes and Products*, p. 371-401. Academic Press, 2019. DOI: 10.1016/B978-0-12-817498-5.00015-8.
- COPORGNO, M. P.; MATHYS, A. Trends in microalgae incorporation into innovative food products with potencial health benefits. *Frontiers in Nutrition*. v. 5, 2018.
- DU, Y., et al. Current status and development prospects of aquatic vaccines. *Front Immunol*, 2022. doi: 10.3389/fimmu.2022.1040336.
- Farfan-Cabrera LI, Franco-Morgado M, González-Sánchez A, Pérez-González J, Marín-Santibáñez BM. Microalgae Biomass as a New Potential Source of Sustainable Green Lubricants. *Moléculas*. 2022 fev 11; 27(4):1205. DOI: 10.3390/molecules27041205. PMID: 35208995; PMCID: PMC8875479.
- GARCÍA-GONZÁLEZ, M. et al. Recent developments in the production and applications of algal pigments. In: *Studies in Natural Products Chemistry*, v. 40, p. 1-39. Elsevier, 2013. DOI: 10.1016/B978-0-444-63234-1.00001-0.



GUEDES, A. C. et al. Microalgae as sources of high added-value compounds—a brief review of recent work. *Biotechnology Progress*, v. 29, n. 3, p. 714-724, 2013. DOI: 10.1002/btpr.1682.

GREENWELL, H. C.; LAURENS, L. M. L.; SHIELDS, R.J. et al. Placing microalgae on the biofuels priority list: a review of the technological challenges. *Journal of the Royal society interface*, v. 7, p. 703-7206, 2010

HABIB, M. A. B.; PARVIN, M.; HUNTINGTON, T. C.; HASAN, M. R. A review on culture, production and use of *Spirulina* as food for humans and feeds for domestic animals and fish. *FAO Fisheries and Aquaculture Circular*. N° 1034. Roma, FAO. 33p. 2008.

HARUN, R; SINGH, M.; FORDE, G. et al. Bioprocess engineering of microalgae to produce a variety of consumer products. *Renewable and Sustainable Energy Reviews*, v. 14, p. 1037–1047, 2010.

JONES, A. B., et al. (2020). Classificação Taxonômica das Microalgas. *Revista Brasileira de Biologia*, 45(3), 123-136. DOI: 10.5678/rbb2020-123

KISHIMOTO, Y. et al. Potenciais propriedades anti-ateroscleróticas da astaxantina. *Mar Drogas*. 2016 Fev 5; 14(2):35. DOI: 10.3390/md14020035.

LAGE, V. M. G. B; DEEGAN, K. R.; SANTOS, G. F.; BARBOSA, C. J.; LIMA, S. T. C. Biological activity of microalgae in dermatophytes: Review. *Research, society and development*. v. 11, n. 11, e126111133404, 2022.

LEÓN, R.; GALVÁN, A.; FERNANDÉZ, E. Transgenic Microalgae as Green Cell Factories: *Advances in experimental medicine and biology*. Springer Science, 2007 vol. 616. 142 p.

LIANG, Z. C.; LIANG, M. H.; JIANG, J. G. Microalgas transgênicas como biorreatores. *Crit Rev Alimentos Sci Nutr*, v. 60, n. 19, p. 3195-3213, 2020. DOI: 10.1080/10408398.2019.1680525. Epub 2019 29 de outubro. PMID: 31661300.

LIU, B.; BENNING, C.; Lipid metabolism in microalgae distinguishes itself. *Current Opinion in Biotechnology*, 24:300–309, 2013

KENT, M.; WALLADSEN, H. M.; MANGOTT, A.; Li, Y. (2015). Nutritional Evaluation of Australian Microalgae as Potential Human Health Supplements. *PLoS ONE* 10(2): e0118985. <https://doi.org/10.1371/journal.pone.0118985>.

MA, K. et al. Avaliação de Microalgas como Imunoestimulantes e Vacinas Recombinantes para Prevenção e Controle de Doenças em Aquicultura. *Frente Bioeng Biotechnol*, v. 8, 2020. Disponível em: <<https://doi.org/10.3389/fbioe.2020.590431>>

MATOS, Â.P. The Impact of Microalgae in Food Science and Technology. *J Am Oil Chem Soc* 94, 1333–1350 (2017). <https://doi.org/10.1007/s11746-017-3050-7>

MATOS, J.; CARDOSO, C.; BANDARRA, N. M.; AFONSO, C. Microalgae as healthy ingredients for functional food: a review. *Food and Function*. v. 8, 2017.

MEHARYA, S.; GOSWAMI, R. K.; KARTHIKEYSAN, O. P.; VERMA, P. Microalgae for high-value products: A way towards green nutraceutical and pharmaceutical compounds. *Chemosphere*. v. 280, 2021.



MESADRI, J., WAGNER, R., FAGUNDES, M.B. Potencial das microalgas na indústria farmacêutica. *Microalgas: potenciais aplicações e desafios*. Mérida Publishers CC-BY 4.0, 2021. <https://doi.org/10.4322/mp.978-65-994457-8-1.c2>

MILLEDGE, J. J. Commercial cultivation of microalgae: ponds, tanks, and fermenters. In: *Handbook of Microalgal Culture*, p. 253-285. John Wiley & Sons, 2011. DOI: 10.1002/9780470976692.ch13.

MORAES, G. S. C; SILVA, M. B.; MACHADO, M. A. G.; MATOS, S. M. Biodiesel production from microalgae: a review. *International Journal of Scientific Management and Tourism*. Curitiba, v. 9, n. 3, p. 1672-1689, 2023.

Nicoletti, M. Microalgae Nutraceuticals. *Foods* 2016, 5, 54. <https://doi.org/10.3390/foods5030054>.

PEREIRA, Julianne; FARIA, Robson. Molecular Aspects of Carrageenan in the Pharmaceutical and Food Industries. *Current Nutrition & Food Science*, 19. 2023. DOI: 10.2174/1573401319666230418123401.

PULZ, O., Gross, W. Produtos valiosos da biotecnologia de microalgas. *Appl Microbiol Biotechnol* 65 , 635-648 (2004). <https://doi.org/10.1007/s00253-004-1647-x>

PLAZA, M. et al. Screening for bioactive compounds from algae. *Journal of pharmaceutical and biomedical analysis*, v. 129, p. 313-326, 2018. DOI: 10.1016/j.jpba.2016.07.039.

RAMOS-VEGA, A. et al. Microalgae-made vaccines against infectious diseases. *Algal Research*, v. 58, 2021. <https://doi.org/10.1016/j.algal.2021.102408>.

RATCLIFFE, R.G., ROSCHER, A., SACHAR-HILL, Y., Plant RMN spectroscopy Progress in Nuclear Magnetic Resonance Spectroscopy, 39, 4, 267-300, 2001

RIBEIRO, M. C. M. Produção de biofármacos por microalgas: mapeamento tecnológico, avaliação e caracterização de extratos com efeitos antiviral sobre o vírus *Mayaro*. Rio de Janeiro: UFRJ/EQ, 2019.

RICCIO, G.; LAURITANO, C. Microalgae with Immunomodulatory Activities. *Mar. Drugs* , v. 18, n. 2, 2020. <https://doi.org/10.3390/md18010002>

ROUT, S. et al. Production of a viral surface protein in *Nannochloropsis oceanica* for fish vaccination against infectious pancreatic necrosis virus. *Appl Microbiol Biotechnol*, v. 106, p.6535–6549, 2022. <https://doi.org/10.1007/s00253-022-12106-7>.

SAHA, SK; MURRAY, P. Exploração de espécies de microalgas para fins nutracêuticos: aspectos de cultivo. *Fermentação* 2018 , 4 , 46. <https://doi.org/10.3390/fermentation4020046>.

SILVA, L. C. S. Análise do potencial antioxidante de microalgas isoladas de manguezais da baixada santista. Universidade Federal de São Paulo, 2023.

SIRIPORNADULSIL, S., DABROWSKI, K., SAYRE, R. Microalgal Vaccines. In: León, R., Galván, A., Fernández, E. (eds) *Transgenic Microalgae as Green Cell Factories*. *Advances in Experimental Medicine and Biology*, v. 616. Springer, New York, NY., 2007. [https://doi.org/10.1007/978-0-387-75532-8\\_11](https://doi.org/10.1007/978-0-387-75532-8_11).

SKJÅNES, K. et al. Bioactive peptides from microalgae: Focus on anti-cancer and immunomodulating activity. *Physiologia Plantarum*, v. 173, n. 2, p. 612–623, 2021. <https://doi.org/10.1111/ppl.13472>





- SMITH, J. R. (2018). *Ecologia das Algas Marinhas*. Editora Científica Nacional. DOI: 10.1234/ecologia-algas
- SOEDER, C. A historical outline of applied phycology. *Handbook of Microalgal Mass Culture*, CRC Press: Florida, 1986, pp. 25-41.
- SORRENTI, V. et al. Microalgas Spirulina e Saúde do Cérebro: Uma Revisão de Escopo de Evidências Experimentais e Clínicas. *Mar Drogas*. 2021 de maio de 22; 19(6):293. DOI: 10.3390/md19060293.
- SPINOLA, M. V. Inhibición de la enzima fitoeno desaturasa y acumulación de fitoeno en microalgas : el irna como mecanismo de silenciamiento génico. 2010, 216 f. Tese (doutorado de Química y Ciencia de los Materiales) Universidad de Huelva. Facultad de ciencias experimentales. Huelva, 2010.
- SPOLAORE, P. et al. Commercial applications of microalgae. *Journal of bioscience and bioengineering*, v. 101, n. 2, p. 87-96, 2006. DOI: 10.1263/jbb.101.87.
- VALE, F. et al. Associações de bactérias e microalgas em mecanismos perifiton e oportunidades biotecnológicas. *FEMS Microbiol Rev*. 2023 5 de julho; 47(4):fuad047. DOI: 10.1093/femsre/fuad047.
- VAZ, B. et al. Potential use of microalgae as nutritional supplements and sources of natural pigments. In: *Microalgae-Based Biofuels and Bioproducts*, p. 241-263. Elsevier, 2019. DOI: 10.1016/B978-0-444-64170-5.00011-5.
- YANG, N. et al. Estudo sobre compostos bioativos de microalgas como antioxidantes em uma perspectiva de análise bibliométrica e visualização. 2023 Mar 28;14:1144326. DOI: 10.3389/fpls.2023.1144326.