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Review

Recent Advances in Marine Microalgae Production: Highlighting Human Health Products from Microalgae in View of the Coronavirus Pandemic (COVID-19)

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Abstract: Blue biotechnology can greatly help solve some of the most serious social problems due to its wide biodiversity, which includes marine environments. Microalgae are important resources for human needs as an alternative to terrestrial plants because of their rich biodiversity, rapid growth, and product contributions in many fields. The production scheme for microalgae biomass mainly consists of two processes: (I) the Build-Up process and (II) the Pull-Down process. The Build-Up process consists of (1) the super strain concept and (2) cultivation aspects. The Pull-Down process includes (1) harvesting and (2) drying algal biomass. In some cases, such as the manufacture of algal products, the (3) extraction of bioactive compounds is included. Microalgae have a wide range of commercial applications, such as in aquaculture, biofertilizer, bioenergy, pharmaceuticals, and functional foods, which have several industrial and academic applications around the world. The efficiency and success of biomedical products derived from microalgal biomass or its metabolites mainly depend on the technologies used in the cultivation, harvesting, drying, and extraction of microalgae bioactive molecules. The current review focuses on recent advanced technologies that enhance microalgae biomass within microalgae production schemes. Moreover, the current work highlights marine drugs and human health products derived from microalgae that can improve human immunity and reduce viral activities, especially COVID-19.

Keywords: build-up; pull-down; cultivation; harvesting; drying; extraction; antioxidants; anti-inflammatory; cytokine storm; anti-TNF-α therapy; immunity; lung damage; COVID-19

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1. Introduction

Recently, aquatic industries have been developed successfully [1,2], as well as aquatic products (aquatic plants and aquatic animals), which have great benefits for human health, immunity, and nutrition [3,4]. Aquatic plants (microalgae and seaweed) are photosynthetic organisms that consume carbon, nutrients, and solar energy and convert them into organic compounds, such as proteins, lipids, carbohydrates, and pigments [5], which may be transformed into several bioproducts. The production of aquatic plant biomass is an important branch of aquaculture activities.

Aquatic plant biomass has a wide range of organic materials of commercial interest, such as antioxidants, biopolymers, pigments, polysaccharides, and biopeptides [6]. Aquatic plant biomass has received attention at the commercial and academic levels due to its multiple applications in several fields, including food supplements [4,7,8], pharmaceuticals [3,9], cosmetics [7,10,11], aquaculture [2,12–17], biofuel [2,18,19], and biofertilizers [20–24]. Moreover, algae biomass can produce many bioenergy sources, such as biomethane, bioethanol, biodiesel, biohydrogen, and bio-oil [25–30]. However, concerning the environmental applications of algae biomass, a wide range of polluted wastewater types, including sewage, industrial, agriculture, and aquaculture effluents, can also be treated through the phytoremediation mechanism [31–38]. Furthermore, algae biomass can effectively reduce highly

toxic compounds to less biologically toxic compounds, producing a variety of high-value products [35–37,39,40].

According to the statistics report of the Food and Agriculture Organization (FAO) [41], in 2003, the biomass of *Arthrospira* (*Spirulina*) produced in China only was 16,483 tons (Ts). The global biomass production of microalgae was 93,756 Ts in 2010 and 87,000 Ts in 2018. In 2019, the total global production of microalgae biomass was 56,465 Ts, which was produced by the top ten producers in the world (China 97.16%, Chile 1.6%, France 0.37%, Greece 0.25%, Tunisia 0.25%, Burkina Faso 0.25%, Central African Republic 0.09%, Chad 0.04%, Bulgaria 0.005%, and Spain 0.003%). FAO statistics reported that because of their commercial attitude, they do not capture the true production of microalgae in some countries, including the United States of America, Australia, Czechia, Iceland, India, Italy, Japan, Malaysia, and Myanmar [42]. In 2019, FAO statistics also reported that commercial microalgae biomass contributes less than 0.2% of the global production of aquatic biomass (microalgae and seaweed). *Arthrospira* (*Spirulina*) comprises 96.56% of global microalgae biomass production, while the remaining (0.44%) comes from four species of green microalgae: *Haematococcus pluvialis* (242 Ts, 0.429%), *Chlorella vulgaris* (4.77 Ts, 0.008%), *Tetraselmis* sp. (1.45 Ts, 0.003%), and *Dunaliella salina* (0.22 Ts, 0.0004%) [41].

From laboratory scale to commercial production, biomass from *Arthrospira*, *Chlorella*, *Haematococcus*, and *Nannochloropsis* has been produced globally in many countries to serve several industries, including biofertilizers, animal feeds, aqua-feed, and human food supplements [43]. In terms of algae biomass volume, *Arthrospira*, followed by *Chlorella*, is the most productive species [44]. These two species are the most promising microalgae for energy production, including biogas, bioethanol, and biodiesel. Some species, such as *Tetraselmis* sp., *Isochrysis* sp., *Dunaliella* sp., *Phaeodactylum* sp., and *Scenedesmus* sp., also have high industrial importance, while some species, such as *Chaetoceros* sp., *Thalassiosira* sp., and *Acutodesmus* sp., are of low industrial importance [45,46].

The main advantages of marine microalgae are greater than the advantages of freshwater microalgae or terrestrial plants. There is no competition between marine microalgae and freshwater microalgae or terrestrial plants in the utilization of freshwater sources or arable land. However, freshwater, and marine microalgae are more efficient in carbon sequestration and growth rates than terrestrial plants [47,48].

Microalgae biomass production technologies have unique characteristics that make them more suitable for the production of certain species and for commercial purposes. Their land requirements, construction, operational expenses, technical development, and environmental parameter management vary according to the technological method used [49]. Although microalgae biomass has shown environmental benefits, it also has serious consequences related to rising energy, water supply, wastewater management, land use, and the risk of microbial contamination [50–52]. Microalgae biomass production techniques that are cost-effective, environmentally friendly, and practical are urgently needed on a large scale [53]. Despite the widespread applications of microalgae, there are many obstacles to the development and promotion of biomass production technologies [54]. The microalgae biomass production scheme mainly consists of two processes: (I) the Build-Up process and (II) the Pull-Down process. Generally, the Build-Up process consists of (1) the super strain concept and (2) cultivation, while the Pull-Down process consists of (1) harvesting, (2) drying, and (3) extraction [55].

Microalgae biomass production technologies have huge potential for innovation, by using low-cost techniques that expand and revolutionize algae industries, especially for human health products. Currently, the coronavirus epidemic (COVID-19) remains the most significant health concern in the world, and it is critical to discover effective drugs to stop this epidemic from killing hundreds of thousands of people [56]. To combat COVID-19, scientists, professionals, and global health organizations have been working together to develop and implement quick diagnoses, reliable vaccinations, and treatment approaches [57]. Some microalgae-derived bioactive compounds and metabolites can successfully treat many diseases, while others can improve human immunity and decrease

viral activities, especially COVID-19 [57–59]. The effectiveness of these suggested bioactive molecules obtained from microalgae biomass in combating viral diseases varies depending on the technology used for biomass production, which mainly consists of two stages: (I) the Build-Up process and (II) the Pull-Down process.

Here, the current review aimed to provide an overview of the recent advanced technologies that enhance the microalgae biomass within the microalgal biomass production scheme, starting with strain selection, genetic optimization, culture systems, growth conditions, nutrient limitations, and harvesting, drying, and extraction techniques. Moreover, the current work focuses on marine drugs and human health products from microalgae that can improve human immunity and reduce viral activities, including COVID-19.

2. Build-Up Process

2.1. Super-Strain Concept

The greatest challenge in the algae biomass industry is finding suitable strains for industrial applications. To achieve the "super strain concept", several steps should be performed, such as algal strain selection, morphological and molecular identification, optimum growth condition determination, growth curve determination, and high biomass yield production under different culture conditions [60].

2.1.1. Strain Selection

According to algaebase.org [61], there are more than 150,000 species of microalgae around the world; however, only a few species have been studied in terms of their beneficial applications [55,60,62]. There are more than 37 microalgae culture collections (collections, centers, and seeds banks) around the world, mostly in the USA and the EU. Microalgae species differ in their biochemical compositions; therefore, algae collections isolate and identify several strains for their purposes. To reduce the culture period of microalgae, cultured strains should be robust and resistant to unsuitable stress conditions (abiotic conditions), such as light, temperature, and salinity, as well as resistant to biotic stress conditions, such as herbivores and pathogens [63]. To select the best-performing microalgae strains, some standard criteria are required, including (1) high biomass production rates, (2) pathogen resistance, (3) optimization to growth media, (4) a high rate of CO_2 capture and exchange, (5) adaptation to several environmental culture conditions, and (6) enhancing performance characteristics through the applications of genetic engineering, breeding, and genome editing [60]. Recently, many studies have attempted to enhance the biomass yield of the required molecules, mainly lipids, carbohydrates, proteins, and other valuable bioactive compounds, under various stressful conditions at laboratory levels. However, it is important to develop a microalgae culture of effluent wastewater to produce high value-added products at mass production levels [55].

2.1.2. Strain Transformation

Microalgae are a viable option for genetic engineering because they are unicellular and have a simple genetic structure with quick reproduction capabilities [55]. Microalgae's bioactive compounds and metabolites can be enhanced by genetic engineering techniques to produce them more reliably, as well as by increasing their volume and concentration. These techniques are applied to increase bioactive compound and metabolite production for the transformation of the substrate into the target product, especially in the field of human health products [64].

Recently, genetic modification techniques have been successfully used in the microalgae industry due to their potential to improve microalgae biomass production [65]. Important results have been reported in microalgae genomics, including the development of efficient gene-transformation systems, engineering, and biomass optimization [60]. The microalgae cell wall is the key step in achieving the transformation process. As a result, protoplast or enzyme-treated cells are used in microalgae transformation methods [7]. In general, these techniques include biotic and abiotic stresses (Figure 1), such as transferring

genes isolated from one species to another to produce breeding strains with desirable commercial characteristics, such as excessive tolerance to light and heat stress, resistance to herbivores and pathogens, and the ability to compete against opportunistic organisms or express biosynthetic pathways toward more profitable strains [66].

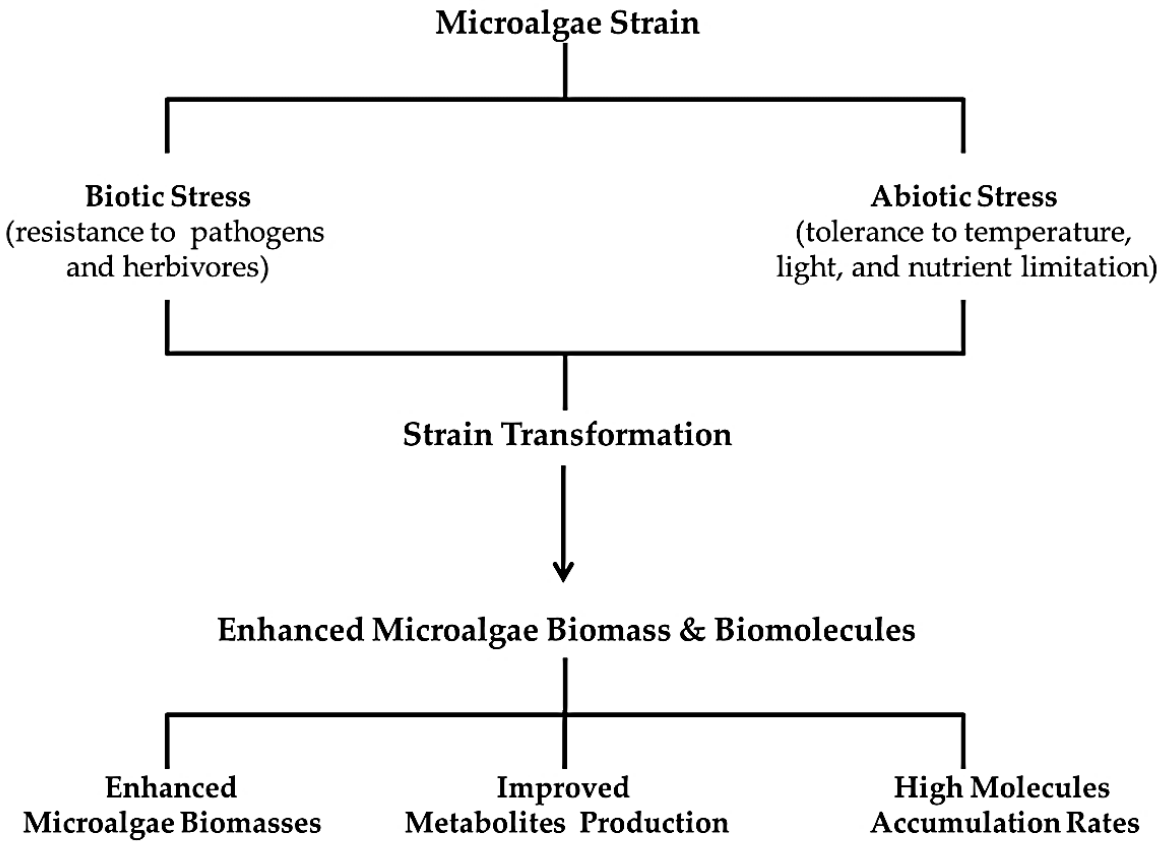

Figure 1. Schematic diagram illustrating the desired implementation of genetic modification traits toward higher production of microalgae biomass.

Chlamydomonas reinhardtii, a plant model organism, is the most extensively studied microalgae strain for genetic modification [67]. This species has been successfully utilized as a source of enzymes and feed additives [68,69], nutrient supplements, such as selenium [70], gut-active biologics [71], antibodies and immunotoxins [72], and vaccine subunits [73]. However, this species is not used in aquaculture. *A. platensis*, *C. calcitrans*, *C. vulgaris*, and *Nannochloropsis* sp. are the major microalgae species that have been extensively studied to produce genetically modified species as aquaculture feed, improving their nutritional value and increasing the market value of their products [74–78].

Prasad et al. [79] demonstrated stable *Agrobacterium*-mediated DNA transfer in the nuclear genomes of two strains of haptophytes (*I. galbana* and *Isochrysis* sp.). First, *Isochrysis* sp. and *I. galbana* were co-cultivated with the *A. tumefaciens* strain LBA 4404 carrying pCAMBIA 1380-pds-L504R to evaluate their resistance to the herbicide norflurazon and the antibiotic hygromycin. This work shows that, in the case of 200 M acetosyringone, *Isochrysis* sp. co-cultivated with *Agrobacterium* resulted in a huge number of norflurazon-resistant cells, whereas *I. galbana* did the same in the case of 100 M acetosyringone. Despite the lack of pre-treatment before co-cultivation with *Agrobacterium*, the vector could still enter *Isochrysis* and penetrate the cell membrane's calcium-rich barrier. Prasad [80] confirmed that the metabolic engineering of *Pavlova lutheri* was successively performed using the *Agrobacterium*-mediated nuclear transformation protocol.

Genetically modified microalgae can be used to produce other recombinant proteins. Kim et al. [81] reported that Flounder fry that fed on transformed *Chlorella ellipsoidea* had a

25% increase in growth after 30 days of feeding, demonstrating that the recombinant protein can be transferred up the food chain while maintaining function. Successful transgenic studies have been conducted in *Dunalella salina* and *Haematococcus pluvialis* to enhance carotenoid accumulation. Vaccines against white spot disease that affect a variety of crustaceans have been effectively developed by *Dunaliella salina* [73,82]. Fayyaz et al. [65] confirmed that microalgal pigment production is increased by transformed cartenogenic genes, such as *bkt*, *psy*, *chyB*, and *pds*, while microalgae lipid content may also increase by the overexpression of enzymes, such as LPAT, DGAT2, GPAT, and MAT.

Way-Rong et al. [83] demonstrated that in *Chlorella sorokiniana* and *Chlorella vulgaris*, the overexpression of the enzyme carbonic anhydrase is a potential method for effectively capturing excess CO_2. Transgenic microalgae species of *Chlorella sorokiniana* and *Chlorella vulgaris* with an exogenous MlCA gene showed an increased biomass, protein percentage, and lipid accumulation. The same findings were reported by Wei et al. [84], who concluded that the biomass productivity of *Nannochloropsis oceanica* was improved by the overexpression of a nuclear-encoded, cbbX-homologous, candidate RuBisCO activase (g1915 or 'nNoRca-like') that is transcriptionally stimulated at air-level CO_2. However, the microalgal transformation of either nuclear or chloroplast genomes is achievable (Figure 2) using several methods, including *Agrobacterium*-mediated methods, electroporation, enzyme-mediated methods, silicon carbide whiskers, glass beads, and microprojectile bombardment [55]. Table 1 details the history of the most commercially important microalgae strains that have been genetically transformed using the respective strategies.

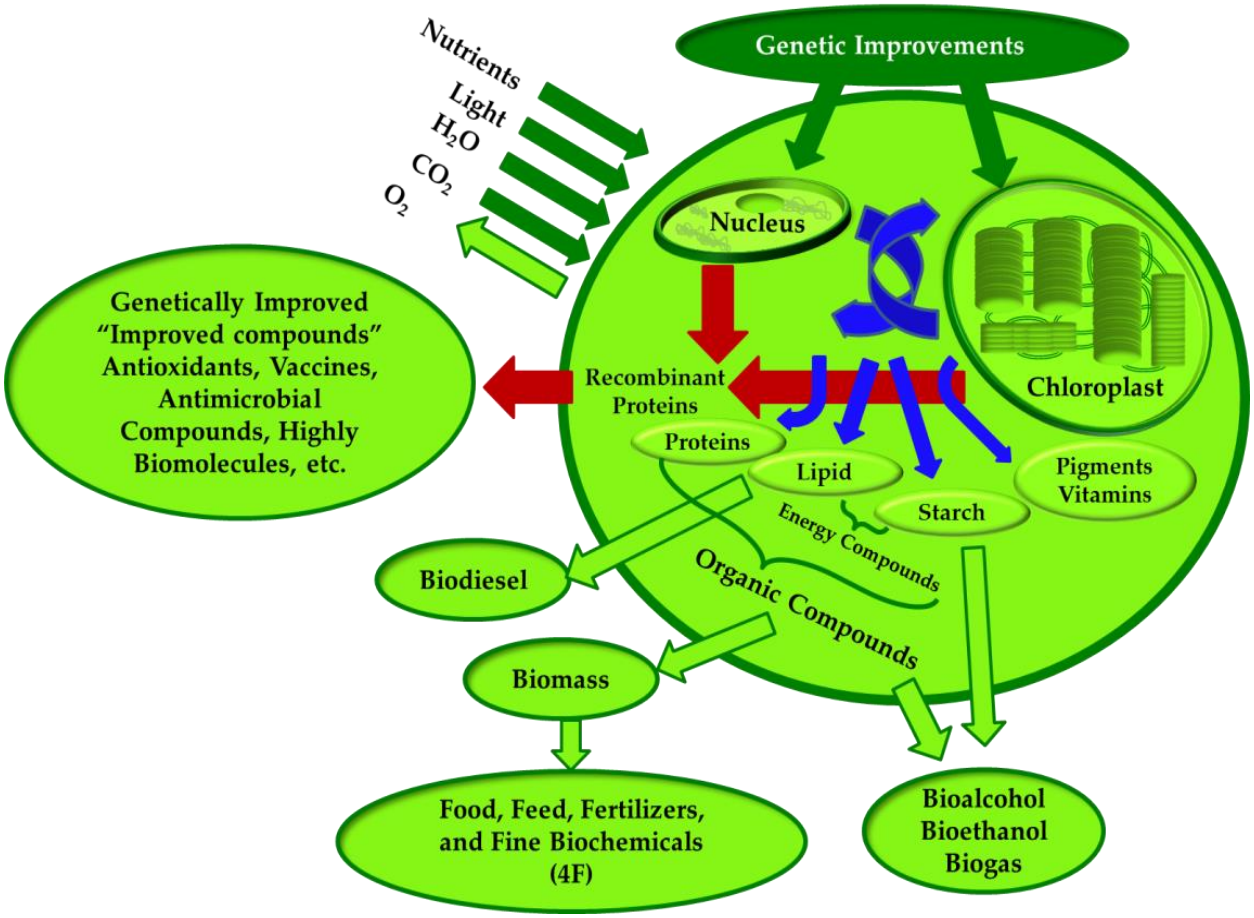

Figure 2. Scheme of the natural processes in microalgae genetic modifications.

Table 1. Transformations of some microalgae species.

Transformation Methods	Microalgae Species	Refs.
PEG mediated	*Pleurochrysis carterae*	[85]
	Dunaliella salina	[86]
Enzyme-Mediated	*Chlorella vulgaris*	[87]
Silicon carbide fibers	*Amphidinium* sp.	[88]
	Chlamydomonas reinhardtii	[89]
Electroporation	*Chlamydomonas reinhardtii*	[90]
	Chlorella sp.	[75]
	Nannochloropsis oculata	[78]
Glass beads	*Dunaliella salina*	[73]
	Chlamydomonas reinhardtii	[91]
	Platymonas subcordiformis	[92]
Agrobacterium-mediated	*Chlorella vulgaris*	[76]
	Haematococcus pluvialis	[93]
	Nannochloropsis sp.	[74]
Microprojectile bombardment	*Chlorella zofingiensis*	[77]
	Phaeodactylum tricornutum	[94]
	Chaetoceros sp.	[95]

2.2. Cultivation Aspects

Microalgae biomass is an attractive, renewable, and sustainable source for many bioproducts, such as drugs, pharmaceuticals, and food supplements [96]. The biochemical composition and biomass productivity of microalgae vary depending on many factors, including cultivation systems, environmental growth conditions, nutrient availability and limitations, the interaction of microalgae and bacteria, and the type of cultured species [97]. Any changes in cultivation aspects lead to a change in the biochemical composition of microalgae, which may significantly affect the productivity of microalgae biomass. Advances in the development of microalgae biomass require appropriate conditions. However, the percentages of microalgae biochemical compositions are positively or negatively affected by these parameters [98]. Carbohydrates contribute 15–40% of the biomass of microalgae, which is a direct result of CO_2 capture via the Calvin cycle. Carbohydrates exist in several forms, such as polysaccharides (found in cell walls), starch (found in plastids), glycogen, cellulose, and other similar substances [99]. Microalgae are a rich source of protein and contribute 30–70% of the algal biomass, having nutritional benefits higher than traditional protein sources, such as eggs, meat, milk, legumes, and soybeans [53]. During the exponential growth phase, microalgae tend to accumulate a lot of protein [100]. Lipids are the most important components of microalgae, providing about 5–65% of the algal biomass, and they have higher nutritional benefits than other traditional sources [55,60].

2.2.1. Cultivation Systems

The cultivation system is the most significant key that controls microalgae biomass productivity. Globally, two microalgae culture systems have been implemented: an open pond (OP) raceway and a closed pond (photobioreactors, PBR). These types are effective in producing high-value biomass from microalgae, and they also help reduce environmental stress by sequestering CO_2 [101].

Based on the literature, it is difficult to evaluate the performance of different outdoor systems due to their different locations and operating systems [102]. In the open pond culture system, microalgae utilize atmospheric CO_2 and sunlight. Circular ponds, inclined systems, and raceway ponds are the most popular open pond forms for microalgae cultivation [103]. Photobioreactors operate under controlled conditions. In terms of pH, medium agitation, and light intensity, the regulated growth environment of the PBR ensures consis-

tency. After a complicated chemical process, H_2O and CO_2 are converted into algal biomass rich in oil content in the PBR system [104].

However, some authors have indicated that the hybrid system is a third culture system that uses both OP and PPR [105,106]. In general, a PBR system is more cost-effective than an OP system in terms of its operation, maintenance, and energy consumption. However, in terms of pH, medium agitation, and light intensity, the PBR has a greater control over biomass production than the open pond method. As a result, the microalgae biomass productivity of PBR is much higher [105].

Carotenoids have increased demands and a variety of commercial applications, especially in pharmaceuticals, with great potential as antioxidants. Prieto et al. [107] studied the effect of the culture system (tubular PBR or OP) and feeding regime (batch and semi-continuous regime) on carotenoid productivity and β-carotene abundance of *Dunaliella salina*. The highest carotenoid productivity (10% DW) and β-carotene abundance (90% of the total carotenoids) were obtained using a PBR culture system, rather than OP. Because of its potential application in pharmaceuticals, drugs, and human nutrition sectors, astaxanthin has a high antiviral and antioxidant capacity that is widely employed in several industries. Table 2 shows a comparison between the two types of microalgae cultivation systems.

Table 2. Comparison of the two types of microalgae cultivation systems [108].

Properties	Open Pond Cultivation	Closed Pond Cultivation
Required space	High	Low
Water loss	Very high	Low
Biomass quality	Variable	Variable and able to increase
Biomass concentration (g L^{-1})	Low (0.1 and 0.5)	High (0.5 and 8)
Efficiency of light utilization	Low	Excellent
Temperature	Variable	Controlled
CO_2 loss	High (depend on pond depth)	Low (controlled)
Contamination	High	Low
Cleaning	None	Required
Process control	Limited	Possible
Weather dependence	High	Low
Start-up	1.5–2 Months	0.5–1 Month
Capital expenses	High	higher
Operating costs	Low	High
Efficiency of harvesting	Low	High

According to Li et al. [109], natural astaxanthin may be less expensive than synthetic astaxanthin, using recently developed low-cost PBR and OP methodologies. According to a comprehensive financial analysis, *Haematococcus* biomass and astaxanthin production have lower costs than USD 18 and 718 kg^{-1}, respectively. Regarding the economic and environmental aspects, the use of wastewater effluent as an alternative culture medium provides the nutrients needed for microalgae production, in addition to an increase in biomass and astaxanthin production [110,111].

2.2.2. Stress via Environmental Growth Conditions

Temperature is one of the main factors controlling microalgae biomass. If the temperature changes outside of the optimal range, it may cause the overgrowth, inhibition, or death of microalgae cells [105]. In many cases, higher temperatures enhance biomass production, especially carbohydrates, which may be related to the participation of the thermophilic

enzyme system in sucrose generation [112], while lower temperatures generally reduce carboxylase activities [113]. Most microalgae species can survive at an ideal temperature of 20–30 °C.

Covarrubias et al. [114] reported that thermophilic algae, such as *Anacystis nidulans* and *Chaetoceros*, can survive at temperatures of up to 40 °C [114]. In the culture of microalgae under uncontrolled conditions, such as their cultivation in an open pond, the surface temperature may be higher than 40 °C, and a loss of culture water will be obtained. This significant problem can be dealt with when using controlled culture conditions, such as indoor cultivation or PBR. If indoor cultivation and/or PBR are conducted in hot areas, an additional cooling unit must be provided. Therefore, it makes the culture expensive. As a result, the development of biomass production is limited [105].

Ferro et al. [115] observed that microalgae biomass tends to be higher in summer than winter, while the cold-stress tolerance of *Desmodesmus* sp. and *Scenedesmus* sp. was higher when grown in Nordic culture conditions [115]. Temperature has been used as a stress therapy to stimulate the production of beneficial metabolites. *C. vulgaris* cultivation at 25 °C produced higher carbohydrate and lipid levels than cultivation at 30 °C [116]. Most studies have focused on lipid accumulation under high temperatures, and there are few studies on the effect of temperature on carbohydrate and protein accumulation; thus, more studies on this topic are still needed [55].

Another important factor controlling microalgae biomass production is radiation, which is a primary energy source for photosynthesis and has a direct impact on the growth rate, cell composition, and CO_2 fixation rate [7]. Muhammad et al. [55] demonstrated a well-documented linear relationship between biomass productivity and carbohydrate content with increasing radiation intensity, although the effect of light intensity varies by species. Increasing radiation above the optimal level may affect photosynthesis, while biomass saturation reduces light penetration due to self-shading. Gifuni et al. [117] reported that a lower light intensity (less than 275 µmol m^2 s^{-1}) may result in decreased carbohydrate production over time. The key enzyme for carbohydrate production (called phosphoglucomutase) may be regulated by radiation.

De Farias Silva et. al. [118] found that under high light intensity (252–364 µmol m^{-2} s^{-1}) and high temperature (28 °C), the biomass of *Pseudoneochloris marina* (260 mg L^{-1} day^{-1}) improved. However, these conditions did not appear optimal for protein, lipids, and pigment production. In contrast, under low light intensity (140 µmol m^{-2} s^{-1}) and low temperature (20 °C), the maximum protein content (236 mg g^{-1}) was observed. To protect cells from stress, as well as in response to high light intensity, microalgae tend to synthesize high-energy compounds, such as carbohydrates and lipids [55].

Both the quality and quantity of radiation are important keys affecting the performance of the photosynthetic process [119]. García-Cubero et al. [120] demonstrated that, in the upper layer of a dense culture, while photoinhibition increased, cells in the lower layers may already be light-deprived when light penetrates the culture, resulting in a decreased biomass production. In the case of dense cultures, while photoinhibition may occur in the upper layer, cells in the lower layers may be light-deprived due to light attenuation as they penetrate the culture, resulting in a reduced biomass production [120]. As reported by El-Khouly et al. [121], LED light is an emerging and cost-effective technology in microalgae production due to its lower power consumption, longer life, lower heat dissipation, smaller mass and size, less heat generation when supplying light, longer life span, especially in comparison to fluorescent lamps, and higher conversion efficiency. Mohsenpour and Willoughby [122] observed that red light enhanced the biomass production of both *C. vulgaris* and *G. membranacea* (0.135 g L^{-1} day^{-1} and 0.184 g L^{-1} day^{-1}, respectively). An enhanced growth rate was observed in *N. salina* cultured in PBR using a white LED (400 to 780 nm) by achieving a maximum growth rate of 150 µmol photons m^{-2} s^{-1} at 0.521 day^{-1}. Using blue light, *Nannochloropsis* sp. had the highest specific growth rate, at 0.64 day^{-1} [123]. The effects of radiation on microalgae biomass productivity and carbohydrate content, as the most affected compound, have been extensively studied, as presented in Table 3.

Table 3. Effects of different radiations on microalgae biomass and carbohydrate production, with metabolite improvement percentages.

Irradiance Stress ($\mu mol\ m^{-2}\ s^{-1}$)	Microalgal Strain	Biomass Production ($mg\ L^{-1}$)	Carbohydrate Productivity ($mg\ L^{-1}\ Day^{-1}$)	Metabolite Improvement (%)	Refs.
890	*S. obtusiusculus*	978	280	31	[124]
300	*C. sorokiniana*	2800	170	-	[125]
650	*Tetradesmus obliquus*	1700	800	30	[126]
310	*Desmodesmus* sp.	2380	-	13.4	[127]
2000	*B. braunii*	1300	900	-	[128]

2.2.3. Stress via Nutrient Availability and/or Limitations

Nitrogen, potassium, and phosphorus (macronutrients) have a primary effect on the growth of microalgae; however, nutrient limitation or availability (starvation) is an applied strategy to enhance the metabolite composition and biomass production of microalgae [55]. During the Calvin cycle, nitrogen and phosphorus limitations can convert fixed carbon, directing it toward the production of non-nitrogenous compounds, such as lipids and carbohydrates, especially polysaccharides, starch, and glycogen. When *Chlorella* was grown under nitrogen conversion from sufficient conditions to nitrogen-starved conditions, carbohydrate content increased from 12 to 54%, while proteins decreased to 20% from 60% [129]. Similarly, when *Chlorella* sp. was cultured under phosphorus limitation conditions, the carbohydrate content increased from 10 to 60%, while the protein content decreased from 57% to 7% [130].

Microalgae culture medium should be cost-effective, develop and meet the requirements of microalgae cells, and be simple to produce. In marine hatcheries, the production cost of microalgae as livefeeds is about 30% of the total cost of larval production, which is a constraint to marine hatchery development. Therefore, forms of agricultural fertilizers should be used in medium preparation rather than laboratory-grade products. However, nutrient ratios (N/P ratios) are an important key that enhances the biochemical composition and biomass production of microalgae [131–133].

Ashour and Kamel [133] reported that the cost of cultured media prepared from agricultural fertilizers (commercial grade of nitric acid and/or ammonium sulfate with the same N/P ratio and concentration of F/2 standard medium) was about 1/37:1/39 times lower than F/2 culture medium, respectively, enhancing the lipid content and biomass productivity of *Nannochloropsis oceanica*. Another interesting point to discuss is the source and form of carbon. Carbon is important for maintaining the culture of microalgae. Sucrose (as a carbon source) is required for cell function, growth, and development, energy storage, and stress absorption. HCO_3^- and CO_2, inorganic carbon forms, are important for photosynthesis, CO_2 capture, and bioproduct accumulation [55]. Table 4 shows the effects of nutrient limitations (macro and micronutrients) on microalgae biomass production ($mg\ L^{-1}$), carbohydrate production ($mg\ L^{-1}$), and metabolite improvement (%) because of the application of a nutrient limitation strategy.

Table 4. Effect of nutrient limitations on microalgae biomass productivity and metabolite improvement.

Nutrient Limitation/Starvation	Microalgal Strain	Carbohydrate Productions (mg L^{-1})	Metabolite Improvements (%)	Biomass Productions (mg L^{-1})	Refs.
Nitrogen	*A. platensis*	4.3	9.36	192	[134]
Nitrogen	*M. aeruginosa*	-	20	2.25×10^7 cell mL^{-1}	[135]
Phosphorus	*A. platensis*	6.31	59.7	195	[134]
Sulfur	*C. reinhardtii*	5070	51	-	[136]
vitamins, N, P, and metal	*Tetraselmis* sp.	420 mg g^{-1}	130	5720	[137]
Calcium and magnesium	*C. sorokiniana*	450	50	-	[135]
Multiple nutrients	*Desmodesmus* sp.	400 mg g^{-1}	64	1950	[138]

The most popular carbon source is sodium bicarbonate, which increases the medium pH, improves the availability of dissolved inorganic carbon, and stimulates cell growth and the generation of energy-rich molecules. However, some algae are vulnerable to high shifts in pH, which negatively affect biomass productivity [139,140]. Table 5 shows the effect of different carbon sources on the biomass productivity of microalgae, as well as on the improvement of protein and carbohydrate percentages.

Table 5. Effect of different carbon sources on the biomass production and metabolite content of microalgae.

Stress Conditions	Microalgal Strain	Biomass Production (mg L^{-1})	Stress on Carbohydrate Content (%)		Stress on Protein Content (%)		Refs.
			Before	After	Before	After	
0.9 g L^{-1} $NaHCO_3$	*Scenedesmus* sp.	28.32	18.5	31	47	49.5	[140]
5% Pentose	*C. minutissima*	60	32.5	58.5	15.5	14	[129]
5% CO_2	*A. quadricellulare*	900 mg L^{-1}	31	71	20	14	[141]
5% CO_2	*C. sorokiniana*	960 mg L^{-1}	30.2	53	24	10	[141]

The application of microalgae in aquaculture wastewater treatment is valuable because this process is very cost-effective and enables nitrogen and phosphorus to be recycled and to produce biomass or utilize it as fertilizer. In addition, in many cases, it is not important to provide an external source of carbon to remove these elements [142]. Integrating aquaculture wastewater treatment with microalgae production in the recirculation aquaculture system (RAS) not only develops the environment but also increases economic benefits [143]. Microalgae biomass generated through this technology can be used in cosmetics, pharmaceuticals, animal feeds, and biofuels, including those derived from lipids collected throughout the process [144]. Under most conditions, the supernatant of aquaculture wastewater has a lower nutrient content than sludge from the bottom of the aquaculture system [145]. Table 6 shows the nutrient content of aquaculture wastewater produced from different cultured animals.

Table 6. Nutrient content of several aquaculture wastewaters *.

Animal Type	TN (mg L^{-1})	NH_3-N (mg L^{-1})	TP (mg L^{-1})	COD (mg L^{-1})	TS (g L^{-1})	Refs.
Shrimp	361	90	NA	1321	NA	[146]
Shrimp	>365	84	NA	1593	NA	[147]
Shrimp	>395	102	NA	1201	13	[148]
Rainbow trout	1.2	0.27	0.2	17.6	0.01	[149]
Crucian carp	6	1	>0.7	NA	NA	[150]
nd	111	0.07	NA	20	NA	[151]
nd	778	50	384	349	20	[150]

* TN: total nitrogen, NH_3-N: ammonia-nitrogen; TP: total phosphorus, COD: chemical oxygen demand, and TS: total solids. NA: not detected.

Environmentally, microalgae cells, especially those of *Scenedesmus abundans* and *Chlorella minutissima* [152], are a sustainable and environmentally friendly resource that can treat several types of industrial wastewater [145]. The aquaculture effluent contains many pollutants that may harm the environment. However, algal cells can utilize these chemicals and convert them into valuable biomass. Only 20–30% of the nitrogen in fish food is absorbed or consumed by fish, while the rest is returned to the water [153]. As a result, in addition to suspended particles, wastewater contains a considerable quantity of nitrogen and phosphorus, which can harm the ecosystem [154]. According to the literature, Table 7 shows the biomass productivity of several microalgal species cultured in wastewater.

Table 7. Biomass productivity of microalgal species cultured in wastewater.

Microalgae Species	Wastewater Type	Biomass Productivity (mg dw L^{-1} d^{-1})	Refs.
B. braunii	Municipal wastewater	345.6	[155,156]
S. obliquus	Municipal wastewater	26	[155,156]
P. carterae	Industrial wastewater	33	[155,156]
B. braunii	Industrial wastewater	34	[155,156]
C. pyrenoidosa	Industrial wastewater	8.114	[155,156]
C. saccharophila	Industrial wastewater	23	[155,156]
D. tertiolecta	Industrial wastewater	28	[155,156]
Chlorella sp.	Industrial wastewater	0.00005	[157]
C. vulgaris	Industrial wastewater	0.0019	[158]
Chlorella sp.	Agricultural wastewater	81.4	[155,156]
Neochloris sp.	Industrial wastewater	0.109	[159]
C. minutus	Synthetic wastewater	2.04	[160]
G. pleurocapsoides	Synthetic wastewater	3.34	[160]

2.2.4. Microalgae–Bacteria Interaction

Recently, controlling the interactions between microalgae and bacteria has received global attention, which may improve the efficiency of biomass production from microalgae and their related bioactive compounds. However, studies of the interaction between microalgae and bacteria have shown a significant influence of parasitic relationships on algal growth [161]. The evaluation of the effect of bacteria on algae biomass cannot be fully understood if taken individually. Traditionally, in algal cultures, bacteria are known to be

pollutants. Therefore, the development of the axenic biomass production of microalgae has always been a priority [1].

Interactions between microalgae and bacteria have the potential to increase algal biomass production with biomolecules relevant to commercial aquaculture interests, such as lipids and carbohydrates. In this context, all typical bacterial properties (motility, chemotaxis, type IV secretion systems, quorum sensing systems, and the production of growth promoters) may be relevant in interactions with microalgae and may affect their biomass [162].

Interactions between bacteria and microalgae are very complicated. Currently, there is little information about the chemical nature of a handful of common mediator molecules, such as nutrients, that control the relationship between microalgae and bacteria [163]. The main mediator molecules regulating the interaction between microalgae and bacteria were identified as amino acids and vitamins. Effective control of these chemical reactions has been recommended as a useful strategy to increase biomass yield and reduce microalgae production costs. Despite this, only a limited amount of information is provided at the molecular level [164].

With a better understanding of the molecular control of microalgae–bacteria interactions with sequenced organisms, particular algal–bacterial systems may be driven to achieve the desired results [1]. Table 8 shows examples of microalgae–bacteria interactions that promote algal growth and biomass production, reduce production costs, and improve the accumulation of valuable bioactive compounds, such as fatty acids, lipids, starch, and carbohydrates. These examples show bacteria's importance in improving carbon storage in microalgae, which is especially beneficial in algal biomass production [164].

Table 8. Microalgae enhancements as a result of co-cultivation with bacteria.

Microalgal Strain	Bacterium Strain	Interactions (Microalgae Enhancement)	Refs.
C. sorokiniana	*brasilense*	11% increase in cell density	[165]
A. protothecoides	*A. brasilense*	90% increase in cell density	[165]
I. galbana	*Alteromonas* sp.	52% increase in cell density	[166]
I. galbana	*Labrenzia* sp.	71% increase in cell density	[166]
P. tricornutum	*Stappia* sp.	72%, 144%, and 172% increase in growth, chlorophylls, and pigment, respectively	[166]
C. vulgaris	*S. smaltophilia*	18%, 20%, and 22% increase in productivity, growth rate, and biomass, respectively	[167]
T. striata	*P. bermudensis*	200% increase in biomass productivity	[168]
C. minutissima	*Escherichia coli*	700% increase in biomass productivity	[169]
T. pseudonana	*D. shibae*	35% increase in cell density	[170]
Ankistrodesmus sp.	*Rhizobium* sp.	29% increase in dry weight	[171]
Dunaliella sp.	*Muricauda* sp	7% increase in cell biovolume	[172]
C. sorokiniana	*brasilense*	40% and 35% increase in cell density and growth rate, respectively	[173]
C. vulgaris	*brasilense*	16% and 11% increase in cell density and growth rate, respectively	[173]
B. braunii	*Rhizobium* sp.	55% increase in optical density	[174]

3. Pull-Down Process

The Pull-Down process includes (1) harvesting and (2) drying algal biomass (wet weight). In the case of the manufacture of algal products, the (3) extraction of bioactive compounds is included [175].

3.1. Harvesting Technologies

Harvesting (dewatering) is the separation of algae biomass from the culture column using several harvesting techniques. The harvesting of microalgae is a significant challenge facing microalgae cultivation, which is attributed to the small cell size (5–20 µm), low biomass concentrations (0.2–1.0 g L^{-1} in OP and 2–9 g L^{-1} in PBR), their similar density to water (1.08–1.13 g mL^{-1}), and a negative charge on their cells. The cost of the harvesting process contributes to 20–30% of the total cost of biomass production.

Harvested biomass contains a lot of moisture, which reduces the quality of biomass within a few hours at room temperature. However, the selected harvesting technique impacts the quality of microalgae biomass [7]. As reported by Mathimani and Mallick [176], microalgae harvesting techniques are (1) physical techniques, which include centrifugation, filtration, gravity sedimentation, and flotation; (2) chemical techniques (flocculation methods), including inorganic and organic flocculants; (3) biological techniques, including autoflocculation and bioflocculation [177]. Harvesting techniques may be used alone or in combination with other techniques. However, there is no all-purpose harvesting approach that can handle all types of microalgae suspensions in terms of cost, energy consumption, and target products.

Among all the harvesting methods, centrifugation is considered the most widely and fastest-used harvesting technology [55]. A study by Levine and Fleurence [178] concluded that centrifugation technology works based on the density difference, which offers more advantages over other technologies, such as chemical-free biomass, biological-free biomass, no toxicity, 100% complete recovery efficiency, short duration, and high biomass quality. These advantages make the centrifugation technique the main technology used in the food products, cosmetics, and pharmaceutical industries. Although centrifugation has been reported as a very effective technique, it is highly energy consuming and expensive when applied on a commercial scale [179]. There are several types of centrifugation equipment, including the nozzle discharge centrifuge, continuous flow centrifuge, spiral plate centrifuge, self-cleaning disc stack centrifuge, and decanter bowl centrifuge [179].

Recently, harvesting edible fungi, either fungal spores or fungal pellets, has become the most recent sustainable, cost-effective, and highly efficient harvesting technique [177]. The co-cultivation of microalgae with fungal spores has been studied by Zhou et al. [180], who reported that using fungi pellets could harvest more than 95% of microalgae biomass in a short time (about 1.5 h), resulting in a great performance of the microalgae biomass [181]. In aquaculture, the selected fungi strain should have a high safety level and should not contain toxic components. Some fungi species, such as *Aspergillus* sp., *Penicillium* sp., and *Monascus* sp., which are classified as food-grade, have a safety level as a value-added compound, while the beneficial impacts of these fungi on aquatic animals have not yet received much attention from aquaculture scientists [177,181]. Interestingly, the Revolving Algal Biofilm technique (RAB technology), which was designed to grow microalgae on a film, was supposed to be a promising harvesting technology to simplify harvesting and wastewater treatment and increase land-use efficiency [182]. In this technology, when compared to traditional harvesting technologies, RAB technology is more efficient, cost-effective, and environmentally friendly for harvesting the biomass attached to films via a scraper [177,182–184].

3.2. Drying Technologies

After harvesting microalgae biomass, the harvested biomass contains a high water content that must be drained before further treatments of the biomass, depending on the type of process and the products that will be extracted in the next step. Neves et al. [185]

stated that the value of microalgal biomass may be lost depending on the drying technique applied. The drying process changes the characteristics of microalgae cells. In the food industry, the nutritional quality of dried microalgae may decrease due to the loss of pigments, proteins, carbohydrates, lipids, and other valuable components. In general, pigments are most affected by drying techniques and drying conditions, such as the temperature level, time exposed, and oxygen [185]. There are several drying methods, including solar, cross-flow air-drying, oven and microwave drying, and spray- and freeze-drying [7]. Solar drying is the most environmentally friendly drying technique, but it is time-consuming and requires a massive surface area [186]. Spray-drying is assumed to be an effective technique for high-value-added products. This technique can produce green or green dark microalgae powder due to the use of spray-drying at the correct temperature [187].

Interestingly, spray-dried microalgae biomass can also be used for pharmaceutical products and human food supplements. There are two different spray-drying techniques: spray-drying and drum-drying. The second method is recommended for pharmaceutical and human food consumption products due to its better digestibility, lower investment, and less energy [188]. Freeze-drying is a widely applied drying technique used in the pharmaceutical and food industries since the cell constituents are well protected without cell wall disruption using this technique [187].

Among all drying techniques concerning maximizing the productivity of microalgae biomass, spray-drying is the most promising technology used to extract high-value products. However, the spray-drying technique is costly and may damage the biomass pigment content [189]. In the future, more attention should be given to improving the spray drying-technique so that it can be applied to all microalgae products. As described by Ruiz-Dominguez et al. [190], *Muriellopsis* sp. contains low amounts of astaxanthin, zeaxanthin, and violaxanthin, while having a huge amount of lutein. However, these pigments have received global attention and extensively contribute to pharmacological, antiviral, food supplement, nutraceutical, and several biotechnological applications. Ruiz-Domínguez et al. [190] compared the effect of spray-drying and freeze-drying techniques on the biomass yield of *Muriellopsis* sp. and found that the freeze-drying technique increased the lutein content and recovery by 0.3–2.5-fold when compared to the spray-drying technique. They concluded that the freeze-drying technique is a promising technique for lutein production, particularly for pharmacological, antiviral, food supplement, and nutraceutical applications [190]. Similar findings were reported by Stramarkou et al. [191] on *Chlorella vulgaris*. The advantages and disadvantages of the most common drying techniques are shown in Table 9.

Table 9. Advantages and disadvantages of the most common microalgae biomass-drying technologies [55].

Method	Advantages	Disadvantages
Solar	Sustainable and no energy consumption	Dependence on the weather
Spray	Fast and economical method, suitable for algae production for human consumption	Degradation in the quality, operational cost
Freeze	Highly energy intensive	Applicable for small scale
Oven drying	Less energy intensive	Suitable for small scale
Crossflow air-drying	Economical and fast drying	Energy cost
Incinerator	Algal biomass burning can be avoided	High cost and complicated

3.3. Extraction Technologies

In recent years, high-value bioproducts derived from microalgae biomass, especially in the fields of pharmaceuticals and human food supplements, have received global interest. Therefore, choosing the correct extraction procedure is important to consider. The extraction of bioactive compounds from microalgae biomass is no less important than the harvesting or drying techniques. The extraction technique is one of the most important keys to determining the quality of the target product, especially in the fields of nutrition and medicine. While extracting the biomolecules from microalgae biomass, it is necessary to use a completely biocompatible technology that does not change or affect the bioactivity of the extracted molecule [192].

Based on the microalgae's target product and the nature of the bioactive compounds, the extraction method is determined. Several extraction procedures may be used to disrupt the cell wall [193]. Currently, traditional extraction procedures include organic solvents, such as methanol, acetone, chloroform, and diethyl ether, which have been used many times [194]. Onay et al. [195] reported that conventional organic solvent extraction procedures include Folch [196], Bligh and Dyer [197], and Soxhlet [198], while some assisted lipid extraction techniques include cell disruption, homogenization, microwave, ultrasonication, glass bead, and lyophilization-assisted methods [195].

Several published reports have demonstrated the efficiency of one-step or assisted extraction techniques for lipid extraction from microalgae. Koberg et al. [199] used a one-step biodiesel extraction process using a microwave and ultrasonication directly from *Nannochloropsis*. The direct transesterification of *Cryptococcus curvatus* was determined using the microwave irradiation technique of Cui et al. [200]. Cheng et al. [201] investigated the direct transesterification of *Chlorella pyrenoidosa* using a microwave-assisted lipid extraction method, compared to the two-step process of biodiesel extraction. They reported that for *Chlorella pyrenoidosa*, the one-step technique demonstrated a six-fold greater biomass than the two-step procedure [201]. Table 10 shows the most important microalgae extraction techniques, cell extraction, and cell rupture mechanisms [202].

Table 10. Techniques for microalgae cell extract and cell rupture mechanisms.

Category	Technique	Mechanism	Refs.
Mechanical	High-pressure homogenization	When cells are pushed to flow via a narrow valve under tremendous pressure, they break.	[203]
	Rotor–stator homogenization	Cells are disrupted by the shearing between a fixed outer stator and a rapid-spinning inner rotor when they are drawn into a long shaft	[204]
	Bead milling	Contact of cells with agitated beads crushes them.	[205]
	Grinding with mortar and pestle	Cells are crushed when they are cut between two hard surfaces, such as a stationary mortar and a rotating pestle. Before the grinding procedure, the sample is frozen by submerging it in liquid nitrogen.	[206]
	Ultrasonication	The cavitation, which is created by high-frequency sound waves, causes the cells to explode	[207]
	Hydrodynamic cavitation	Cells break down by the cavitation caused by a rapid shift in pressure	[208]
	Screw expeller pressing	When the dried cells are pressed through a barrel-like chamber, a large volume of them is crushed. Direct oil extraction is possible with this technique.	[209]

Table 10. *Cont.*

Category	Technique	Mechanism	Refs.
Physical	Repeated freeze-thaw	Production of intracellular ice crystals during the freezing process and cell expansion during the thawing process both cause cell disruption.	[210]
	Osmotic shock	When fluid comes into cells rapidly during a sudden osmotic transition, internal pressure builds up in the cells, causing the cells to burst.	[211]
	Explosive decompression	Gas bubbles escape out from the cells in point holes when pressure is released suddenly	[212]
	Pulsed electric field (PEF)	The effect of electroporation, caused by strong electric fields, causes cells to lysis	[177]
	Microwave	The intrusion of water vapor within the cells causes the cells to be disturbed. Microwaves create a fast fluctuating electric field that leads to the development of heat due to the frictional forces by inert-molecular movement.	[213]
	Thermolysis (autoclave)	When cells are heated to 121 °C for 30 min, they are lysed. Heat is transferred from the outside to the inside of the cells via the cell membrane.	[214]
Chemical	Alkalis or acids	The cell membrane is solubilized through saponification with an alkali or acid	[215]
	Detergent(surfactant)	Detergent chemicals cause cellular disruption by dissolving cell membrane proteins.	[216]
	Enzyme E	Through the process of enzymatic hydrolysis, the enzyme digests the cell wall.	[217]

New generations of green extraction technologies have been developed. These technologies do not require the involvement of toxic solvents. Global interest has been conducted in green extraction technologies that enhance the yield of extracted molecules while minimizing environmental impacts [218]. These environmentally friendly technologies require bioactive products to be obtained, thus reducing environmental impact, in agreement with various green chemistry principles. In addition, a minimization of extraction time and yield (productivity) has been obtained [40]. In recent years, the demand for safer, greener, and more natural bioproducts that do not require toxic solvents has increased. For *Botryococcus* sp., *Chlorella vulgaris*, and *Scenedesmus* sp., Lee et al. [219] reported that microwaves were the most effective technique used in oil extraction.

According to Lee et al. [202], green extraction techniques are divided into mechanical (such as high-pressure homogenization, rotor-stator homogenization, bead milling, grinding with mortar and pestle, ultrasonication, hydrodynamic cavitation, and screw expeller pressing), physical (such as repeated freeze–thaw, osmotic shock, explosive decompression, pulsed electric field, microwave, and autoclave), and chemical (such as the use of acids or alkalis, surfactant, and enzyme) techniques.

Alam et al. [7] demonstrated that, currently, many bioproducts are extracted from marine microalgae at a commercial scale, including for human nutrition, phycobilins, animal and aquatic feed, PUFA, sterols, β-carotene, vitamins, stable isotope biochemicals, polysaccharides, bioactive molecules of antimicrobials, antibacterial, antiviral, anti-inflammatory, and anticancer drugs. Most recently, microalgae extracts have been strongly recommended as an anti-pro-inflammatory agent, as well as a blocker, and inhibitor of cytokine storm and Tumor Necrosis Factor-α (TNF-α), suggesting that microalgae extracts are an attractive source against many diseases, including COVID-19 [220]. The most notable microalgae species rich in astaxanthin and carotenoids are *Haematococcus pluvialis* [221] and *Dunaliella salina* [222,223]. Species rich in omega-3, PUFA, and fatty acids include *Phaeodactylum tricor-*

nutum [224], *Porphyridium cruentum* [225], *Crypthecodinium cohnii* [226], and *Nannochloropsis* spp. [227].

Microalgal extracts, such as polysaccharides, are extensively used in food items as thickeners and stabilizers [228]. As reported by Rahman [229], in 2010, over 75% of the global market and manufacturing of microalgae were utilized in human health food (mainly EPA and DHA). In the USA, microalgae-derived DHA is found and marketed in more than 99% of all baby foods [230]. Taufiqurrahmi et al. [231] demonstrated that phycoerythrin and phycocyanin, red and blue pigment–protein complexes, respectively, extracted from *Arthrospira platensis*, were extensively used in the food industry as natural coloring agents [231]. Zanella and Alam [232] reported that some microalgae strains were significant suppliers of specific compounds that accumulate in huge quantities, particularly when grown under ideal environmental conditions.

4. Microalgae Derivatives against the COVID-19 Cytokine Storm

Several studies have suggested that a key factor in COVID-19 patients' deaths is Acute Respiratory Distress Syndrome (ARDS). Cytokine storm syndrome causes ARDS. ARDS is the main cause of death in COVID patients [233]. Intensive care units (ICUs) are necessary for ARDS patients if mechanical ventilation is needed [234]. Pro-inflammatory cytokines (IL-1, IL-6, and NFT-α), as well as chemokines (CCL2, CCL3, CXCL10, and CXCL9), are produced during a cytokine storm in great quantities, leading to an overactive immune system and Acute Lung Damage (ALI) in a short time [235,236]. The drugs considered for the treatment of COVID-19 may operate through one of two mechanisms: (1) slowing the rate of viral reproduction or (2) symptom suppression by anti-inflammatory therapy [237].

Patients with COVID-19 often suffer immune damage caused by a reactive cytokine storm as a result of hyperactive inflammatory responses that culminate in cytokine release syndrome [238,239]. Tzachor et al. [59] reported that as a part of the cytokine storm (CS), the overflow of TNF-α results in destabilized endothelial cell networks, which cause damage to the vascular barrier, capillary damage, diffuse alveolar damage (DAD), apoptotic cell death, and multi-organ failure [59]. Since the pandemic started, TNF-blockers have demonstrated promising results in the treatment and mitigation of severe sickness [240]. The increased production of TNF-α has a significant role in disrupting the lung endothelial and epithelial barriers, which may cause ARDS [241].

Interestingly, several studies reported that introducing microalgae derivatives to COVID-19 patients may reduce the cytokine storm and have anti-TNF-α effects, preventing ARDS and ALI [56,59,242–245], as shown in Figure 3.

Microalgae are of commercial importance due to their structural, functional, and nutritional importance, as well as their high yield of proteins, lipids, carbohydrates, and other bioactive compounds [97]. According to the literature, microalgae derivatives have many beneficial immunomodulatory effects on humans [246]. Microalgae are one of the richest sources of natural bioactive compounds that have antioxidant, anti-inflammatory, antimicrobial, and antiviral activities [247]. Therefore, microalgae can scavenge free radicals; thus, the damage caused by free radicals is reduced either in vitro or in vivo [248,249]. These natural free radical scavengers include carbohydrates (polysaccharide, monosaccharide, oligosaccharide, carrageenan, alginate, etc.), proteins (amino acids, peptides, DNA, and RNA), lipids (fatty acids, saturated fatty acids, unsaturated fatty acids, phospholipids, polyunsaturated fatty acids, omega-3, AA, EPA, DHA, etc.), pigments (phycobiliprotein, phycocyanin, phycoerythrin, β-carotenes, lutein, zeaxanthin, astaxanthin, chlorophyll, violaxanthin, etc.), vitamins, and minerals [250].

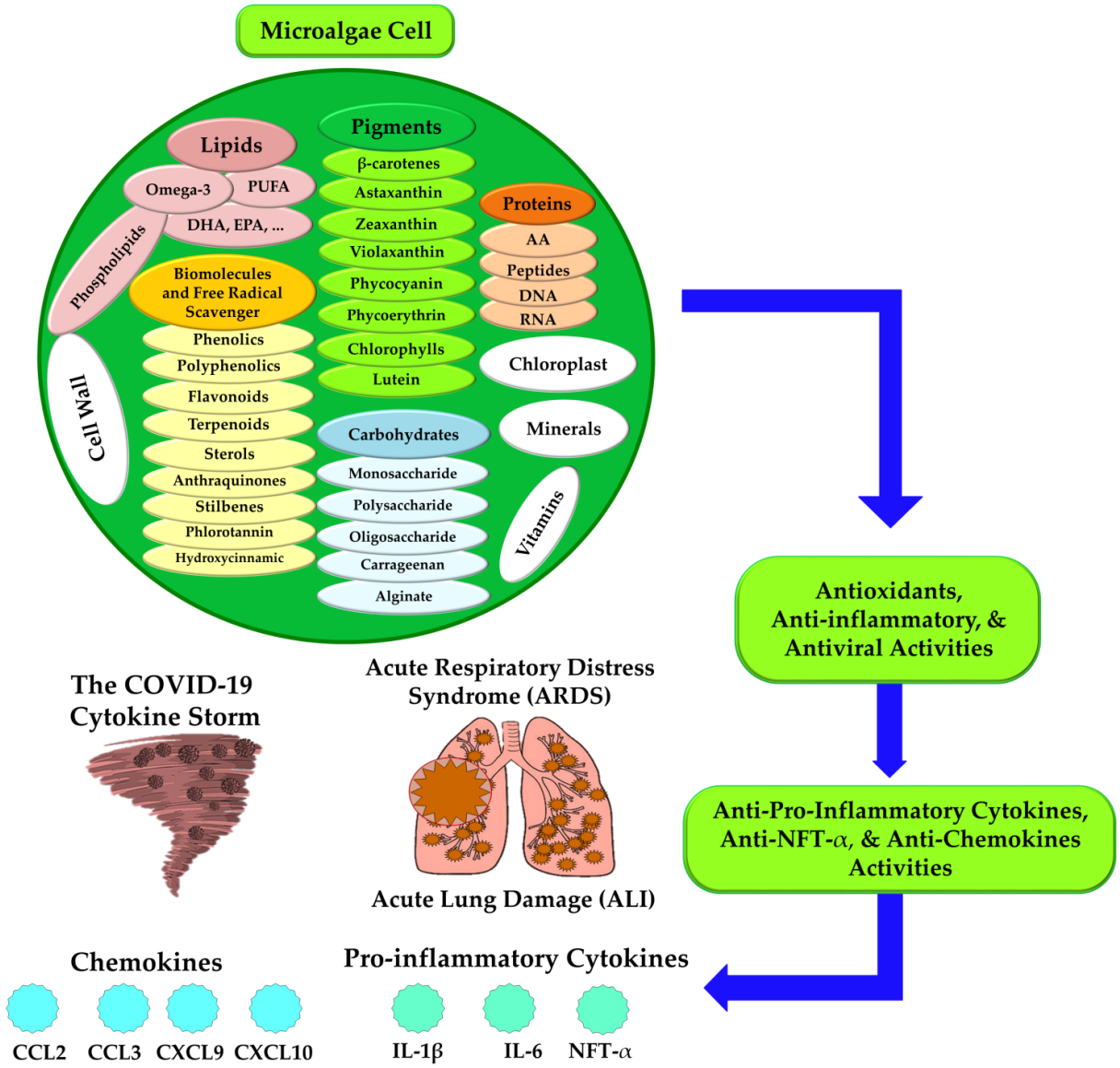

Figure 3. Impact of microalgae-derived products and the Coronavirus (COVID-19) pandemic.

However, many types of free radical scavengers are found in different origins of microalgae and are well known as antioxidant compounds, such as phenolics, polyphenolics, flavonoids, terpenoids, sterols, anthraquinones, stilbenes, phlorotannin, and hydroxycinnamic compounds [193]. For the biomedical applications of microalgae carotenoids, the biological activities of β-carotene, astaxanthin, and phycocyanin are widely recognized as being candidates for use as natural antioxidants, as well as antiviral and anti-inflammatory substrates [251]. The natural superfood supplement *Arthrospira* is well known as a powerful natural source of pigments, such as phycocyanin, phycobiliproteins, β-carotenes, lutein, and astaxanthin [16,252–254], amino acids and polysaccharides [255] that have a long history of several biomedical applications [256]. The success of any of the microalgae biomedical products depends on which technologies are applied in the cultivation, harvesting, drying, and extraction of the active biomolecules of these health products. In the context of combating COVID-19 using the extract of the blue–green algae *Arthrospira platensis*, Tzachor et al. [59] investigated the effect of several doses of *A. platensis* extracts, as a novel approach, as TNF-blockers and TNF-α inhibitors. *A. platensis* (strain UTEX 3086) was grown in flat panel airlift photobioreactors (PBR, 180 L) using Zarrouk medium [257], under a control temperature (31 ± 2 °C), pH (10.8 ± 0.2 °C), and filtered air conditions

(with a flow of 0.5 vvm). In this study, the only different cultural condition was cultural illumination, which was performed in two irradiations: (1) Solar *Spirulina*: full-range solar irradiation (750 µmol m^2 s^{-1}) and (2) LED *Spirulina*: red, blue, and UV at photosynthetic irradiation of 750 µmol m^2 s^{-1}. The two different cultures (Solar and LED) were physically extracted using water and freeze–thawing cellular disruption, as previously described by Chu et al. [220]. In this study, macrophages and monocytes, which were stimulated by pathogenic stimulator lipopolysaccharides (LPSs), were exposed to several doses of *A. platensis* extracts from both Solar and LED. Photosynthetically active *Arthrospira* (LED *Spirulina*) inhibited the secretion of TNF-α by 70% and 40% from LPS-activated macrophage and monocyte cells, respectively. The findings of this study suggest that the advanced technologies applied in the production of the bioactive compounds of *Arthrospira platensis*, in both their culture (including the PBR system with controlled conditions of temperature, pH, and filtered air using Zarrouk medium and LED photosynthetic illumination) and extraction (physically extracted using water and freeze–thawing cellular disruption), are strongly recommended, as these molecules may serve as blockers and inhibitors of TNF-α and act as anti-NFT-α, suggesting that the extracts of blue–green microalga *A. platensis* may be attractive for combating COVID-19 [220].

5. Conclusions and Future Perspectives

Microalgae have a wide range of commercial applications, such as aquaculture, biofertilizer, biofuel, cosmetics, functional foods, and pharmaceuticals, receiving more global attention both industrially and academically. The success of the biomedical products of microalgae biomass, as well as their derivatives or metabolites, mainly depends on the technologies used in the cultivation, harvesting, and drying processes, as well as the extraction of bioactive molecules. The extract of the blue–green microalgae *A. platensis* may be an attractive source for combating COVID-19, depending on the techniques used for culturing, harvesting, drying, and extracting its bioactive substrates. The production scheme for microalgae biomass mainly consists of two processes: (I) the Build-Up process and (II) the Pull-Down process. The Build-Up process consists of (1) the super strain concept and (2) cultivation aspects. The Pull-Down process includes (1) harvesting and (2) drying algal biomass (wet weight). In some cases, such as the manufacture of algal bioproducts, the (3) extraction of bioactive compounds is included. To achieve the "super strain concept", the selection of the microalgal strain must (1) have all primary requirements of the quality and quantity of bioactive molecules, especially concerning its lipid content and profile, (2) be able to be genetically engineered, and (3) be able to produce bioenergy and valuable co-products that enhance economic profitability. Economically, scientists are searching for microalgae strains that have been genetically engineered to increase growth rate, biomass yield, lipid content, and high-value co-products. Genetic improvement techniques have been widely applied to revolutionize the microalgae cultivation industry. Considering these observations, there is a need for innovations, solutions, and technologies that enhance and advance the commercial viability of algal biomass production and its technologies. Closed photobioreactor systems (PBR) are better than open pond systems (OP) in terms of their operation, maintenance, and biomass productivity, and they produce a greater control over biomass production than open pond systems. Temperature and light intensity must be adjusted to promote the accumulation of targeted bioactive compounds. Microalgae culture medium should be cost-effective, promote rapid development, meet the requirements of microalgae cells, and be easy to produce. LED light is a cost-effective technology for producing microalgae. Microalgal–bacteria interactions promote algal growth and biomass production, reduce production costs, and improve the accumulation of valuable bioactive compounds. The centrifugation harvesting technique is considered the most widely harvested technology. Recently, Revolving Algal Biofilm (RAB technology) has been proposed as a promising technology to simplify harvesting and wastewater treatment and increase land-use efficiency. Among all drying techniques concerning maximizing the productivity of microalgae biomass, spray-drying is the most promising technology

used to extract high-value products. In the future, more attention should be given to the improvement of spray-drying and the development of the devices and methods applied to all types of microalgae products. Globally, the most frequently extracted molecule from microalgae is oil. Green extracting technologies are being developed that do not require the involvement of toxic solvents.

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