



Recent advances in the bio-application of microalgae-derived biochemical metabolites and development trends of photobioreactor-based culture systems

Seyedeh Farzaneh Khaligh¹ · Ahmad Asoodeh^{1,2}

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Abstract

Microalgae are microscopic algae in sizes ranging from a few micrometers to several hundred micrometers. On average, half of the oxygen in the atmosphere is produced by the photosynthetic process of microalgae, so the role of these microorganisms in the life cycle of the planet is very significant. Pharmaceutical products derived from microalgae and commercial developments of a variety of supplements extracted from them originate from a variety of their specific secondary metabolites. Many of these microalgae are a reservoir of unique biological compounds including carotenoids, antioxidants, fatty acids, polysaccharides, enzymes, polymers, peptides, pigments, toxins and sterols with antimicrobial, antiviral, antifungal, antiparasitic, anticoagulant, and anticancer properties. The present work begins with an introduction of the importance of microalgae in renewable fuels and biodiesel production, the development of healthy food industry, and the creation of optimal conditions for efficient biomass yield. This paper provides the latest research related to microalgae-derived substances in the field of improving drug delivery, immunomodulatory, and anticancer attributes. Also, the latest advances in algal biocompounds to combat the COVID-19 pandemic are presented. In the subject of cultivation and growth of microalgae, the characteristics of different types of photobioreactors, especially their latest forms, are fully discussed along with their advantages and obstacles. Finally, the potential of microalgae biomass in biotechnological applications, biofuel production, as well as various biomass harvesting methods are described.

Keywords Microalgae · Immunomodulatory · Cancer · Photobioreactor · COVID-19

Abbreviations

TAP	Textured algal proteins	DCs	Dendritic cells
EPA	Eicosapentaenoic acid	MHC	Major histocompatibility complex
DHA	Docosahexaenoic acid	APCs	Antigen-presenting cells
CWS	Cell wall skeleton	EPS	Epoxy polysaccharides
IFN- γ	Interferon-gamma	ECP	Extracellular polysaccharide
TLR	Toll-like receptor	TSP	<i>Tribonema</i> Sp. derived sulfated polysaccharide
AXT	Astaxanthin	FAPS	Fatty acid potassium salts
QC	Glutaminy cyclase	JNK	Jun N-terminal kinase
β -SQDG18	1,2- <i>O</i> -Distearoyl-3- <i>O</i> - β -D-sulfoquinovosylglycerol	MMP	Matrix metalloproteinases
		HGF-1	Gingival fibroblast cell line
		MCP-1	Monocyte chemoattractant protein-1
		MITF	Microphthalmia-associated transcription factor
		ROS	Reactive oxygen species
		SP@DOX	Biohybrid compound containing doxorubicin and spirulina microalgae
		ISCOMs	Immune-stimulatory complexes
		AMPS	<i>Amphora subtropica</i>
		AF	<i>Amphora frustules</i>

✉ Ahmad Asoodeh
Asoodeh@um.ac.ir

¹ Department of Chemistry, Faculty of Science, Ferdowsi University of Mashhad, Mashhad, Iran

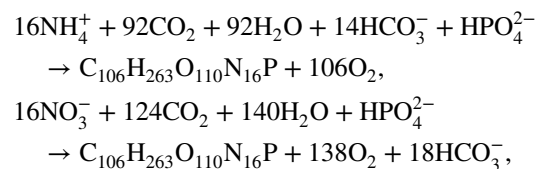
² Cellular and Molecular Research Group, Institute of Biotechnology, Ferdowsi University of Mashhad, Mashhad, Iran

DE-XER	Modified diatoms with silica xerogel
MNPs	Magnetic nanoparticles
GA	Gum arabic
AMs	Alginate microspheres
RBD	Recombinant receptor-binding domain
ARB	Angiotensin receptor blockers
CGN	Carrageenan
I-C	Iota-Carrageenan
HRV	Human rhinovirus
hCoV	Human coronavirus
GRFT	Griffithsin
ARDS	Acute respiratory distress syndrome
ALI	Acute lung damage
ASX	Astaxanthin
PBRs	Photobioreactors
ORC	Open raceway bioreactor
ExPS	Extracellular polymeric substances
PSBRs	Porous substrate photobioreactors
OMEGA	Offshore membrane enclosures for growing algae
TGF	Third-generation feedstock
NREL	National Renewable Energy Laboratory

Introduction

Microalgae are a very diverse group of aquatic plants that have found a wide range of applications in biotechnology today. These unicellular species can be classified into two categories: prokaryotic microalgae, such as cyanobacteria, and eukaryotic microorganisms like green algae and diatoms. These microscopic photosynthesizers, despite their effective role in producing oxygen on Earth, are found in almost all water on Earth due to their high dispersion and frequency (Li et al. 2019). High nutritional value as well as the potential of these microorganisms in the production of bioactive compounds with various pharmaceutical and food applications, using them as a raw material for the extraction of environmentally friendly biofuels as well as its applications in monitoring and purifying environmental pollutants, has attracted the attention of many researchers around the world (Majidian et al. 2018; Sigamani et al. 2016). Given the potential of microalgae to satisfy many global demands, many countries are looking to create production units for these microorganisms. In general, the difference between macro and microalgae is as follows: macroalgae are multicellular organisms that can be seen without the help of a microscope. Its general shape is similar to a plant and includes stems and leaves having the potential to grow tens of meters. Of the 4000 different seaweeds, only a few have been used for human consumption. Microalgae are unicellular photosynthetic organisms that help trap the sun's energy due to the presence of chlorophyll pigments. Therefore,

they undergo photosynthesis ten times more than terrestrial plants. *Spirulina*, *Chlorella* or blue-green algae (also called cyanobacteria) are also well known in this variety. Due to high efficient biomass production, their application of carbon dioxide capture, production of biofuels, and biotechnological programs, a great focus has been placed on these microorganisms. France and Spain have been considered for the production of macroalgae, while the focus of Germany, Spain, and Italy is on microalgae (Araújo et al. 2021). In recent years, China has emerged as an important hub for the production of microalgae, especially commercially important ones such as *Spirulina* (*Arthrospira*), *Chlorella*, *Dunaliella*, and *Haematococcus*. It is estimated that about two-thirds of microalgal biomass is produced in China, about 90% of which is spent on human consumption (Chen et al. 2020a, b, c). Biomass produced in algae as a result of photosynthesis depends on inorganic compounds such as CO₂, solar energy, and various nutrient availability in the water body. As a result of the production of biomass, algae have become biological purifiers in wastewater treatment. According to the following equations, the chemical formula C₁₀₆H₂₆₃O₁₁₀N₁₆ indicates algal biomass (ammonium and nitrate are the nitrogen sources, respectively; Dalrymple et al. 2013):



In recent years, to overcome the lack of fossil fuels, there has been a lot of focus on microalgae as sustainable renewable energy. Using the oil content of most microalgae (about 20–80%), different types of fuel can be extracted, for example, kerosene and biodiesel (Randrianarison and Ashraf 2017). Although algal biofuels have become a promising technology, there are several barriers such as high optimal cultivation conditions, the low solar energy conversion efficiency of photosynthesis, and economic costs related to the cultivation and processing of biomass (Radakovits et al. 2010). Therefore, to achieve the maximum amount of algal biomass, modern methods such as hydrothermal liquefaction and direct secretion of products through genetic engineering are used (Daroch et al. 2013; Ghasemi et al. 2012; Radakovits et al. 2010).

Chemical synthesis of algal bioactive compounds is difficult. Research shows that microalgae can produce a wide range of bioactive substances with antimicrobial, antiviral, antiproliferative, antioxidant, and antibiotic activities (Talero et al. 2015). Many of these metabolites are secreted within the cell to promote the defense mechanism against harsh environmental factors (Bhadury

and Wright 2004). Today, a high-calorie diet, along with the modern human lifestyle, has led to health challenges such as obesity, heart disease, and diabetes. Therefore, the food industry is trying to enrich human diet by focusing on improving the health of consumers with the addition of vitamins and dietary supplements (Sigamani et al. 2016). Microalgae are rich natural sources of carbohydrates, protein, fiber, and enzymes and have significant amounts of B and A vitamins, omega 3 fatty acids, as well as numerous minerals such as iodine, potassium, iron, magnesium, and calcium. On the other hand, they are very low in calories and can be used as dietary supplements in various diets (Laamanen et al. 2021). Among microalgae, the species *Chlorella vulgaris*, *Haematococcus pluvialis*, *Spirulina platensis*, *Dunaliella salina*, and *Aphanizomenon* are now widely used around the world to make food supplements for humans and as a nutrient additive to animal feed (Hemantkumar and Rahimbhai 2019; Nicoletti 2016). One of the current challenges is to provide quality food for humans in such a way that this production has the least risk to the environment. The meat analog industry has provided benefits, including reduced ecological and environmental adverse effects, and providing healthy meals for vegetarian and vegan customers, animals, and welfare. Microalgae's biomass incorporation into meat concentrates creates fibrillary textured extrudates due to the highly resistant microalgal cell wall and elevated fat content. Given that the reduction of moisture is important in the formation of the fibrous structure; mechanical texture analysis has shown that extrudates with favorable characteristics could be obtained with 30% microalgae incorporation at a moisture level of 60% (Caporgno et al. 2020). In recent years, the production of textured algal proteins (TAP) has improved the use of algae in the food industry. It is fibrous and very similar in structure to meat (MišurCoVá et al. 2010). There are a variety of saturated and unsaturated fatty acids (FAs) in microalgae, including saturated FAs ($n = 19$), monounsaturated FAs ($n = 26$), and polyunsaturated fatty acids (PUFAs; $n = 68$; Maltsev and Maltseva 2021). The source of long-chain unsaturated fatty acids such as eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) and arachidonic acid, which are abundant in fish oil, are microalgae that feed on fish. Therefore, the use of microalgae genes to produce DHA acid and arachidonic acid in transgenic plants such as soybeans, flaxseeds, and tobacco has been considered (Robert et al. 2005).

To achieve successful production of algae-derived compounds in various fields, it is necessary to create high amounts of biomass. Different conditions and methods can affect the growth of microalgae, factors such as (1) suitable light sources, (2) creating efficient operating procedures, (3) minimizing contamination rate, and (4) reducing consumption costs (Konur 2021). Cultivation of microalgae on a large

scale is usually done in open ponds and various types of photobioreactors. However, in open ponds, there is a possibility of pollution and a lack of control of optimal conditions, which make it possible for only certain types of microalgae to grow (Parmar et al. 2011).

Properties of microalgae biocompounds

Algae are a diverse group of autotrophic organisms that range from unicellular to multicellular forms. Using light energy and inorganic nutrients, these microorganisms produce a wide variety of biochemical compounds in their biomass, including lipids, carbohydrates, polysaccharides, proteins, pigments, etc. The relation between the biotechnological world of microalgae and biomedical applications due to their bioactive compounds has attracted much attention. (Fu et al. 2019). In addition to the application of microalgae in the food industry, biofuels, wastewater treatment, their use in pharmaceutical and biomedical fields as antioxidant, antibacterial, antiviral, anticancer, anti-inflammatory, immunomodulatory agents, and many other valuable properties have become a strong point for human life's survival. Microalgae-derived bioactive compounds have shown satisfactory results in treating a variety of disorders including diabetes, HIV/AIDS, malaria, and obesity (Mutanda et al. 2020). To extract and utilize biologically valuable algal compounds, cell walls are lysed by various methods, including mechanical/physical homogenization, ultrasonication and pulsed electric field, microwave, chemical, and biological (enzymes) methods (Balasubramaniam et al. 2021). Recent advances in biomedicine and biotechnology using microalgae and their biomaterials will be discussed below.

Immunomodulatory properties of various bio compounds of microalgae

Due to the presence of abundant immune-boosting compounds, the market for increasing the production of microalgae in various forms of capsules, powders, and tablets is very profitable and discussed below. Chuang et al. (2014) examined the antileukemia properties of *Dunaliella salina* in leukemia-implanted BALB/c mice. The results of oral administration of *D. salina* (184.5, 369, and 922.5 mg/kg) in the mice are as follows: spleen metastasis inhibition and increased survival in mice increased the population of T and B cell accumulations, but reduced the amounts of monocyte and macrophage levels in the blood, enhancing the proliferation of T and B cells, raising the cytotoxicity properties of NK cells, and improving the phagocytic activity of macrophages. In another study, the molecular mechanism of the improvement of the human immune system was assessed by analyzing the blood cells of the volunteers before and

after oral administration of spirulina hot water extract. The results indicated that extracts of *Spirulina platensis* can target NK cells and monocytes. NK cells function is enhanced by interferon-gamma (IFN- γ) through an interleukin (IL) 12/IL-18-dependent fashion production and cytolysis in > 50% of subjects. The maturation of monocytes/macrophages in volunteers receiving the extract was demonstrated by increasing in vitro stimulation of blood cells with BCG cell wall skeleton (CWS) as a ligand for toll-like receptor (TLR) 2 and 4 (Hirahashi et al. 2002). In addition, other *Spirulina* immunomodulatory activities include: enhancing the phagocytic activity of macrophages and the increasing production of cytokines and antibodies (Ghaeni and Roomiani 2016). In the following, we discuss the influence of various bioactive compounds derived from microalgae, including astaxanthin (AXT), sulfolipids, and polysaccharides, on immunoenhancing applications. AXT is a reddish pigment that belongs to the carotenoids. In addition to microalgae, other organisms such as bacteria, fungi, and yeast are the sources of supply. Commercial supplements of this compound (approved by the FDA), which are mainly extracted from *Haematococcus pluvialis*, are important in the global field so that its market value has been over US\$100 million in 2018 (Brendler and Williamson 2019). The effects of AXT on oxidative stress and immunosenescence in D-galactose-induced aging in rats were determined by Chen et al. (2020a, b, c). The results showed a decrease in malondialdehyde levels and an increase in AXT-induced antioxidant activity. The ability to improve histopathological liver damage as a result of inhibiting oxidative stress was also observed. In addition to the role of AXT in age delaying through activating the Nrf2/Keap1 pathway and suppressing the NF- κ B pathway, its effect was significant in reducing IL-1 β and IL-6 and enhancing the levels of IL-2, immunoglobulin G, and secretion immunoglobulin M. Moreover, AXT extracted from shrimp cephalothorax was applied to investigate the cytokine release of splenocytes in *Helicobacter pylori*-infected mice. 60 rats (divided into three groups of 20) were treated with a daily oral dose of 10 or 40 mg of AXT for 6 weeks. The results of this study indicate the effect of AXT on the alteration of the secretion patterns of cytokines during *H. pylori* ($50 \mu\text{g mL}^{-1}$) infection so that the levels of the IL-10, IL-2, and IFN- γ increased in a dose-dependent manner (15–2000 pg/mL, $P < 0.05$). In general, changes in AXT-induced cytokine secretion patterns were observed during *Helicobacter pylori* infection (Davinelli et al. 2019). Sulfolipids are involved in the formation of thylakoids in algal chloroplasts (Frentzen 2004). There are reports of its advantages in biomedical programs and the prevention of several diseases. For example, these can act as an inhibitor of glutamyl cyclase (QC) in Alzheimer's disease. QC inhibitory metabolites in various microalgae species can be screened using the new “reverse metabolic” technique. The

compounds in the methanolic extract of *Sc. Accuminatus* showed a QC inhibition of 81% and 76% at concentrations of 0.25 mg/mL and 0.025 mg/mL, respectively. Among the structural properties of glutamyl cyclase inhibitors are core structure, metal binding group, and flexible linker with short length. In this regard, the various sections of sulfonamides, including the negatively charged sulfonate group at the 6-hydroxyl glucose position, the ether sequence, and the glucose unit, act as the metal bonding group, the linker, and the scaffold structure, respectively (Hielscher-Michael et al. 2016). Furthermore, the role of sulfolipids in improving the immune system as an immune adjuvant response is mentioned below. Manzo et al. (2017) fabricated a chimeric sulfoglycolipid (called β -SQDG18) as a vaccine adjuvant by using *Thalassiosira weissflogii*. β -SQDG18 can trigger human dendritic cells (DCs) by a TLR2/TLR4-independent mechanism to promote an improvement in the immune response against B16 mouse melanoma cells. Other immunomodulatory properties of this analog include induction of CD83 and CD86-positive DCs with upregulation of major histocompatibility complex (MHC) II molecules as well as elevated levels of IL-12 and INF- γ . In addition, the levels of IL-1 α , IL-1 β , IL-18, and IL-27 expression increased after 24 h. To further explore DC-based vaccines against tumors, subcutaneous injection of β -SQDG18 (at a dose of 25 mg) was applied against B16 mouse melanoma cells. As a result, a reduction in tumor growth and spread of both memory lymphocytes and antigen-presenting cells (APCs) was observed. Among the various types of bioactive compounds derived from microalgae, polysaccharides and particularly extracellular polysaccharides (ECP) or epoxy polysaccharides (EPS) are more important due to their biological and rheological properties (Khora and Navya 2020), which we will discuss in more detail below. The immunoenhancing activity of microalgal EPS derived from *Thraustochytridae* sp. mutant GA strain was checked out by measuring its impact on the growth of T and B lymphocytes as well as cytokine production of T cells. The microalgal EPS causes B cell proliferation with about 30% respect to the control group even at the lowest dilution (10^{-11}), thus improving humoral immunity by enhancing antibody production (No effect on T cells). In addition, a decrease in IL-6 and INF- γ secretion (at 10^{-3} dilution) and no effect on tumor necrosis factor α (TNF- α) level were evident (Park et al. 2017). *Tribonema* sp. is a filamentous microalga rich in lipid and polysaccharides with low protein content, so the application of this microorganism in the biodiesel and bioethanol industry has been developed (Wang et al. 2014). In the study conducted by Chen et al. (2019) after extracting sulfated polysaccharide from *Tribonema* sp. (TSP) with a yield of 1.5%, first, its composition and chemical structure were determined and then immunostimulation activities on RAW264.7 macrophage cells were performed. The results of this study indicate that TSP

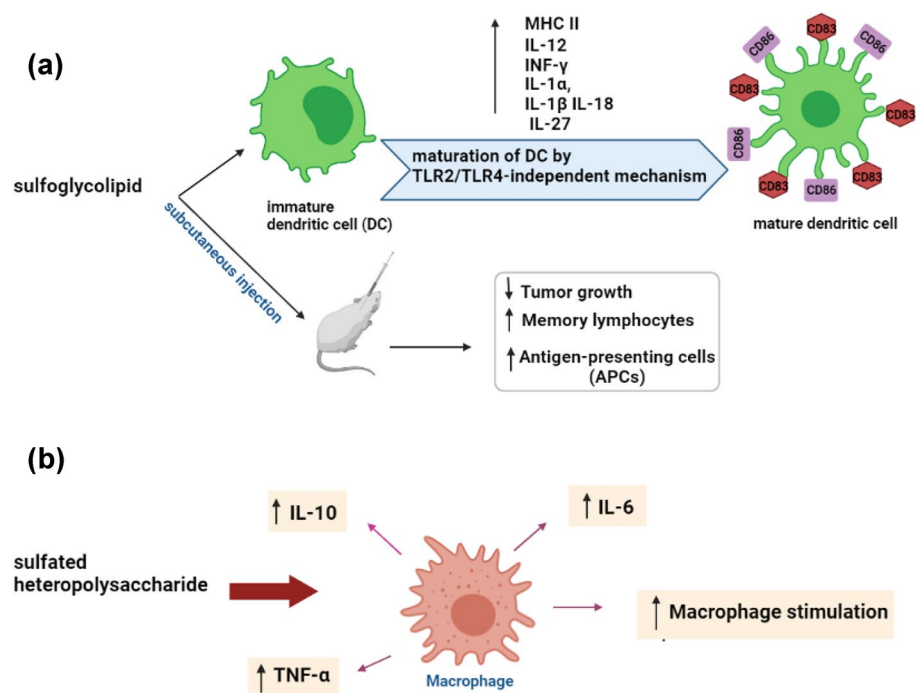
as a heteropolysaccharide is mainly composed of galactose and can also strongly stimulate the RAW264.7 cells and upregulation of cytokines including IL-6, IL-10, and TNF- α (Fig. 1). Also, the results of the effect of different concentrations of TSP on the viability of RAW264.7 macrophages displayed that treatment with 25 $\mu\text{g}/\text{mL}$ TSP significantly increased cell viability compared to the control. Cell viability at 200 $\mu\text{g}/\text{mL}$ of TSP was close to control. Mainly, TSP could be a potent stimulus for RAW264.7 cells.

Anticancer properties of microalgae-derived biocompounds

Malignancies can rise anywhere in the body due to the non-programmed growth of cells in a multi-stage process. In general, there are more than 200 types of cancer that can be affected by a variety of factors, including genetic alterations, ionizing radiation, chemical/toxic compounds, and various pathogens. The biopsy is an ideal screening option for cancer diagnosis, which clarifies the type and extent of cancer. Tissue biopsy is the ideal screening option for cancer diagnosis, which clarifies the type and stage of cancer. Depending on the progression of the disease, various treatment approaches will be suggested by health-care providers, which include chemotherapy, radiation therapy, surgery, hormone therapy, immunotherapy, stem cell transplant treatments, targeted therapy, and nanotechnology-based therapies (Miller et al. 2019). Over 60% of anticancer medicines are derived from natural sources. Therefore, marine organisms, especially microalgae, play an important role in the

prevention and improvement of cancer due to their richness in bioactive compounds (Dyshlovoy and Honecker 2015). However, *in silico* techniques and the use of ISE algorithms are invaluable in creating a robust model to help identify new candidates for natural-based anticancer drugs. Unlike traditional methods, using these approaches saves time and costs (Rayan et al. 2017). Wide health benefits of omega-3 and omega-6 fatty acids such as cancer prevention and cardioprotective effects have attracted the attention of human society. Microalgae can be a proper alternative to fish oil, due to having large quantities of EPA and DHA (Lupette and Benning 2020). Gas chromatographic–mass spectrometry analysis of the fatty acid content of *Chlorella* sp. S14 showed a value of 52.87% PUFAs, which contained 12.37% n-3 PUFAs determined by total PUFAs, along with 2.16% α -linolenic acid and 2.16% cis-11, 14, 17-eicosatrienoic acid. The growth inhibitory effect of the PUFA-rich extract exhibited that the MCF-7 cells were more sensitive than the A549 cells, so that at the highest concentration, (150 $\mu\text{g}/\text{mL}$), the percentage cell viability was equal to 31.5% and 62.56% in the breast and lung cancerous cells, respectively (Vilakazi et al. 2021). Sayegh et al. (2016) characterized the PUFAs constituent in the fungus *Thamnidium elegans* (cultivated on raw glycerol) and the microalga *Nannochloropsis salina* in a laboratory-scale homemade glass photobioreactor. After lipid extraction, gas chromatography estimated the lipid content of algae, mainly fish oil composed of EPA, containing glycolipids plus sphingolipids (52.7%), neutral lipids (28.5%), and phospholipids (18.8%). *In vitro*, antiproliferative studies against MCF-7 cells were performed by

Fig. 1 Immunomodulation of microalgal-derived sulfated biocompounds. **a** Favorable effects of chimeric sulfoglycolipid purified from *Thalassiosira weissflogii* on dendritic cell activation as well as increase in the expression of various cytokines. Subcutaneous injection of sulfoglycolipid showed positive impacts against B16 mouse melanoma cells. **b** RAW264.7 macrophage cells stimulation and related cytokines by sulfated heteropolysaccharide extracted from *Tribonema* sp. (Chen et al. 2019)



water-soluble forms of PUFAs, i.e., fatty acid potassium salts (FAPS), which indicate a dose-dependent lethal effect ($IC_{50}=0.45 \mu\text{g/mL}$). It has also been reported that the antitumor properties of DHA are induced through prolongation of the cell cycle between the G2-to-M transition phase and increased expression of caspase-3, procaspase-8, and Bcl-2 genes (Kang et al. 2010). Studies of growth inhibitory and apoptosis properties of DHA belonging to *Cryptocodinium cohnii* showed that this fatty acid (40–160 μM) inhibits the growth of MCF-7 cells in a dose-dependent manner by 16.0 to 59.0% of the control after 72 h. According to flow cytometric studies, induction of G1 sub-cells was equivalent to 64.4–171.3% of control levels after incubation with 80 mM fatty acid for three incubation times of 24, 48, and 72. In addition, western blot analysis showed an increase in Bax/Bcl-2 ratio of 303.4% and 386.5% after 48 and 72 h, respectively (Chiu et al. 2004). In n-3 PUFA-treated cancerous cells, increased ROS production and increased lipid peroxidation play a significant role in inducing antitumor properties (Kang et al. 2010). The impact of n-3 PUFAs on plasma membrane composition and their transduction pathways has been considered in several cancer cells. Lipid raft structures are mostly made up of saturated fatty acids, especially cholesterol. Placement of PUFAs in these structures, due to their less favorable interaction with cholesterol, makes PUFAs-rich/cholesterol-poor non-raft domains which disrupt the development of cancer cells (Ulmann et al. 2013). In a study by Altenburg and Siddiqui (Altenburg and Siddiqui 2009), n-3 PUFAs-treated MDA-MB-231 breast cancer cells showed a significant reduction in chemokine receptor CXCR4 levels because successful CXCR4-mediated signaling requires the lipid rafts. Extensive studies have studied the antitumor properties of algae-derived polysaccharides and identified them as promising therapeutic agents. Umemura et al. (2003) revealed that D-galactan sulfate is associated with L-(+)-lactic acid (GA3P) extracted from toxic *Gymnodinium* sp. A3 is a potent catalytic inhibitor of both DNA topoisomerase (topo) I and topo II. Unlike topo poisons such as camptothecin or teniposide, GA3P does not cause the accumulation of DNA–topo I/II cleavable complexes and even diminishes their amount (induces inversion of the reaction). This observation indicated a high affinity of the GA3P for the enzymes relative to the topo poisons. Furthermore, GA3P showed moderate toxicity (0.67–11 mg/mL) in different cell lines. Xie et al. (2018) extracted a novel polysaccharide (100 $\mu\text{g/mL}$) from *sargassum* (family *Sargassaceae*) and studied its anticancer mechanism. The result demonstrated that although most processes in cancers are carried out through the Jun N-terminal kinase (JNK), p38 mitogen-activated protein kinase (p38 MAPK) signaling and the downstream matrix metalloproteinases-(MMP) 9/MMP-2, this polysaccharide inhibited MCF-7 cell proliferation by activating the JNK signal pathway involving p53, caspase-3,

and caspase-9. Therefore, this type of polysaccharide can be a promising prospect for cancer treatment. Due to the association of JNK activity with ROS production, MCF-7 cells were treated with 5 μM SP600125 as a JNK inhibitor for 1 h before exposure to polysaccharides. Flow cytometry results showed a significant increase of ROS in MCF-7 cells within 48 h ($p < 0.01$). Parra-Riofrío et al. (2020) used two autotrophic and heterotrophic conditions to evaluate the yield of EPS derived from *Tetraselmis suecica*. Heterotrophic culture of *T. suecica* has benefits relative to autotrophic, such as improving the EPS content and its antioxidant properties, further increase in algal biomass, and enhancement of lipids, proteins, and carbohydrate accumulation. Extraction EPS under autotrophic and heterotrophic conditions showed cytotoxic effects against the gingival fibroblast cell line (HGF-1) with IC_{50} equivalent to 165 $\mu\text{g/mL}$ and 61 $\mu\text{g/mL}$, respectively. Therefore, their use for biological activities is not recommended. Recently, a great deal of focus has been placed on microalgae as a source of new proteins and peptides with anticancer, antioxidant, and other biomedical properties. The unique features of these biological peptides are mainly due to their unusual amino acid, which is mainly produced as a result of enzymatic digestion (Kang and Kim 2013). One of these attractive features is the ability of peptides extracted from *chlorella* to inhibit the UVB-induced MMP-1 level (MMP-1 leads to premature aging under UV irradiation). The mechanism of this inhibitory process is proved by suppressing the expression of transcription factor AP-1 and cysteine-rich 61, and also by enhancing the generation of monocyte chemoattractant protein-1 (MCP-1) in human skin fibroblasts (Chen et al. 2011). Therefore, the use of microalgae-derived peptides in the cosmetics industry, especially in the skincare line, is very developed (Apone et al. 2019). Also, Oh et al. (2015) purified a special peptide with a molecular mass of 526 Da and Met-Gly-Arg-Tyr sequence from the fermented microalga, *Pavlova lutheri* by yeast *Hansenula polymorpha* and examined its anti-melanogenesis and antioxidant activities (scavenging of DPPH, hydroxyl and hydrogen peroxide radicals with IC_{50} was reported as IC_{50} 0.285, 0.068 and 0.988 mM, respectively). In addition to reducing the production of intracellular ROS, the results showed the ability of the polypeptide to inhibit melanin synthesis by suppressing microphthalmia-associated transcription factor (MITF) and tyrosinase protein expression by the activation of the ERK pathway in α -MSH-stimulated B16F10 melanoma cells. Hence, *P. lutheri*-derived polypeptides can be considered in cosmetic products. Wang and Zhang (2016) isolated 15 polypeptides from *Spirulina platensis* using hydrolysis and gel filtration chromatography which exhibited cytotoxic effects against five cancer cells including HepG-2, MCF-7, SGC-7901, A549 and HT-29 with the IC_{50} values between 31.25 and 336.57 $\mu\text{g/mL}^{-1}$. Among them, a new peptide,

YGFVMPRSGLWFR, was determined by papain-digested hydrolysates which showed potent antiproliferative properties on A549 cancer cells (Its IC_{50} value was $104.05 \mu\text{g}/\text{mL}^{-1}$). These spirulina-derived peptides can be used as an effective tool in biomedical activities by inducing toxic effects on cancer cells without adversely affecting normal cells. Salem and Ismail (2021) studied the protective mechanism of *Spirulina platensis* in γ -irradiation and/or thioacetamide-treated rats. Induced nephrotoxicity was associated with changes in antioxidant enzymes, kidney function markers, inflammatory markers, and markers associated with oxidative stress. *Spirulina* extract exerts a protective effect by regulating the expression of miR-1 and miR-146a genes (by adenosine monophosphate-activated protein kinase/mammalian target of rapamycin signaling route), inhibiting the release of reactive oxygen species (ROS), inflammatory factors, and autophagy (via AMPK/mTOR pathway).

Targeted drug delivery to cancer cells without damage to healthy cells has become a promising strategy in cancer treatment. The use of diatom microalga for the synthesis of an innovative hybrid multifunctional drug delivery system has recently been studied in targeted cancer therapies (Hussein and Abdullah 2020). The outer layer of these structures is composed of functionalized microalga with vitamin B12 linked with photoactivatable elements, which cause specific identification of colon cancer cells. Rhenium (I) tricarbonyl as a chemotherapeutic agent is released slowly at a specific site, thus reducing the need for a lower dose and its adverse effects. Furthermore, at least a twofold toxicity effect of this structure on HCT-116 was observed upon light irradiation (Delasoie et al. 2020). A summary of the anticancer action of biochemical compounds derived from different algal species is given in Table 1. One of the main goals of proteomic research is to provide information on the direction of early

Table 1 Types of biocompounds derived from different microalgae and their *biological activity*

Bioactive compounds	Microalgae	Target cell	Mechanism of action	References
n-3 PUFAs	<i>Chlorella</i> sp. S14	MCF-7 breast cancer cell/ A549 human lung epithelial cells	Growth inhibitory effect of tumor cells	Vilakazi et al. (2021)
EPA	<i>Nannochloropsis salina</i>	MCF-7 breast cancer cell	Dose-dependent lethal effect	Sayegh et al. (2016)
DHA	<i>Cryptocodinium cohnii</i>	MCF-7 breast cancer cell	Induction of sub-G1 cells/ down-regulation of Bcl-2 gene expression	Chiu et al. (2004)
GA3P (D-galactan sulfate associated with L-(+)-lactic acid)	<i>Gymnodinium</i> sp. A3	Human myeloid leukemia K562 cells	Induction of apoptosis	Umemura et al. (2003)
Polysaccharide	Phaeophyceae (Sargassum)	MCF-7 breast cancer cell	Cell growth inhibition by activating the JNK signal pathway	Xie et al. (2018)
Exopolysaccharide	<i>Tetraselmis suecica</i> (Kyllin)	HL-60 myeloid leukemia cells, MCF-7 breast cancer cell and NCI-H460 lung cancer cell line	Antiproliferative effects	Parra-Riofrío et al. (2020)
Peptide	<i>Chlorella</i>	Human skin fibroblasts	Suppressing expression of transcription factor AP-1 and cysteine-rich 61/MCP-1 production	Chen et al. (2011)
Peptide (Met-Gly-Arg-Tyr)	<i>Pavlova lutheri</i>	B16F10 melanoma cells	Suppressing microphthalmia-associated transcription factor (MITF) and tyrosinase (TYR) protein expressions	Oh et al. (2015)
Peptide (YGFVMPRSGL-WFR)	<i>Spirulina platensis</i>	A549 cancer cells	Antiproliferative action	Wang and Zhang. (2016)
Carotenoids	<i>Chlorella ellipsoidea</i>	Colon carcinoma (HCT-116)	Dose-dependent cytotoxic activity	Cha et al. (2008)
C-Phycocyanin	<i>Spirulina platensis</i>	MDA-MB-231 cells	Antiproliferative effect through the MAPK signaling pathway	Jiang et al. (2018)
Fucoidan (polysaccharide)	<i>Fucus vesiculosus</i>	Lewis lung carcinoma (LLC) cell line	Triggers of TNF production and phagocytic activities	Alekseyenko et al. (2007)

diagnosis and effective treatment of diseases with a better understanding of their physiology and pathology. Furthermore, recent advances in bioinformatics have led to rapid growth in analysis, and the collection of a lot of biological data. The Reinado research team has analyzed the *Nannochloropsis gaditana* proteome based on applied proteomics (comparative analysis of obtained protein information with the existing patents database). They identified 488 proteins with potential industrial applications, among which the UCA01 protein (related to the prohibition family) was selected for validation studies, so that, the recombinant form of this protein exhibited antiproliferative activity against colon adenocarcinoma (Caco2) and hepatocellular carcinoma (HepG-2). Generally, the study of the bioalgorithm of proteins identified in the proteome of model microorganisms can promise the emergence of new tools for cancer treatment (Carrasco-Reinado et al. 2021).

Influence of microalgae in pharmaceutical fields

Today, modern drug delivery systems can be a viable alternative to conventional drugs with major barriers (e.g., high toxicity and low solubility). Recently, microalgae have been noticed for utilizing biodegradable microencapsulated delivery systems. The existence of junctional pores of about 14–16 nm in diameter is considered a pathway for the transfer of small and larger biomolecules (Barsanti and Gualtieri 2014). To increase drug delivery efficiency in gastrointestinal diseases, the use of engineered spirulina with a magnetic coating to make micro-swimmers has been reported. By controlling the dehydration and rehydration

processes of spirulina, the loading of cargo is possible through continuous water channels and junctional pores on the cell membrane. These swimmers can move and navigate the intestinal tract through an external magnetic actuation. The release of drug cargo from the swimmer is released by two mechanisms: induced biodegradation by the host and/or concentration gradient-driven diffusion. Bioactive protection of guest TGF- β 1 as a cargo inserted in swimmers was confirmed by human mesenchymal stem cell differentiation (Fig. 2; Yan et al. 2019). *Spirulina platensis* has been used as a natural carrier to fabricate a novel biohybrid system containing doxorubicin (SP@DOX) for targeted delivery and fluorescence imaging-guided chemotherapy (Zhong et al. 2020). The drug-loading process was performed through an electrostatic force between the positively charged doxorubicin and the negatively charged *spirulina*. Studies on the release kinetics of SP@DOX in the pH range of 5.5 to 9.0 showed that DOX released more than 58% in response to low pH, especially pH 5.5. Therefore, the use of biohybrid systems can be promisingly effective in tumor tissues. On comparing the results of the MTT assay of DOX and SP@DOX within 72 h, less toxicity was observed in the biohybrid compound due to its time-dependent release characteristic. Among the advantages of making this biodegradable compound are: (1) high accumulation in the target tissue followed by increased therapeutic effect, (2) great fluorescence imaging capacity for noninvasive in vivo exploration as a result of high chlorophyll, (3) sustained-release pH-responsive drug (Chen et al. 2022). A variety of drug carriers are commonly used micelles, inorganic nanoparticles, virus-like particles, virosomes, liposomes, silicon oxide

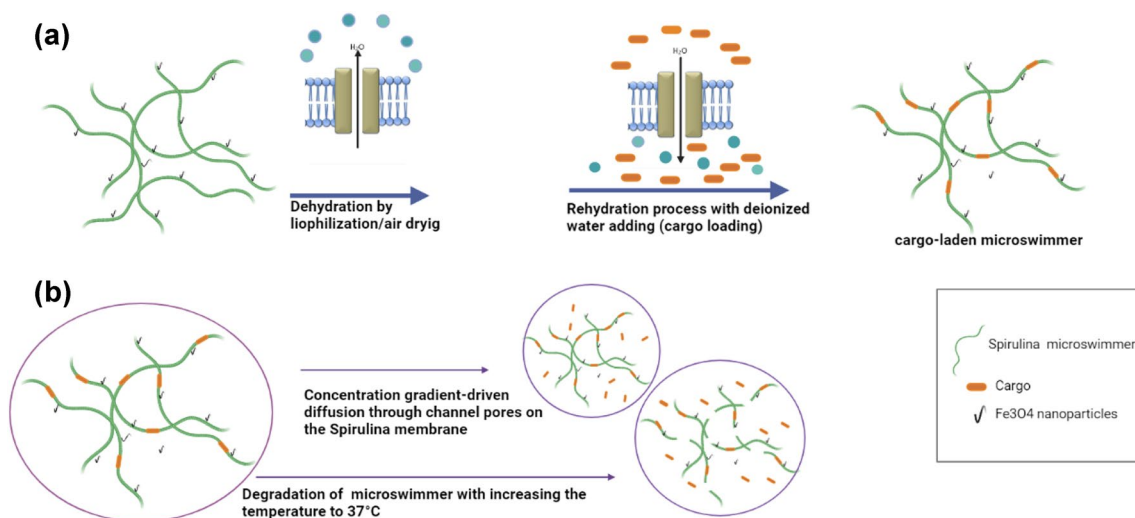


Fig. 2 Improving drug delivery efficiency using *spirulina* as micro-swimmers. **a** The dehydration and rehydration processes of *Spirulina* cells allow the loading cargo through continuous aqueous channels and extra junctional pores on the membrane. Magnetic actuations

navigate cargo-laden micro-swimmers inside a sinuous microfluidic channel filled with mouse intestinal fluids. **b** The cargo release mechanism is done in two ways, host degradation, and/or concentration gradient-driven diffusion (Yan et al. 2019)

nanoparticles, nanoemulsions, polymeric nanoparticles, and immune-stimulatory complexes (ISCOMs; Trucillo 2021). Although silica nanoparticles have become a promising tool in nanomedicine due to their convenient properties such as small size and allowing surface modification, and ease of synthesis, the existence of toxic materials and the requirement for high cost and energy cannot be ignored. Biosilica derived from diatoms as a single cell eukaryotic microalga is a good alternative to synthetic silica, and various studies have examined its impact on drug efficacy (Khavari et al. 2021). Sasirekha et al. (2019) used natural silica from the *Amphora subtropica* (AMPS) species for drug delivery applications. After extracting the *Amphora frustules* (AF) exoskeleton from the AMPS cultures, functionalization was performed by chitosan (Chi@AF) for doxorubicin loading (Chi@AF-DOX). The encapsulation efficiency of the DOX was 89%. The anticancer behavior of DOX and Chi@AF-DOX in A549 cells by MTT assay showed dose-dependent toxicity in both compounds. The IC_{50} value of free DOX and Chi@AF-DOX was reported at $6.15 \pm 0.005 \mu\text{g/mL}$ and $65 \pm 0.005 \mu\text{g/mL}$ respectively. The use of Chi@AF-DOX causes higher stability and lower toxicity effects of free DOX, efficient drug loading, and strong luminescence. The low cytotoxicity of Chi@AF-DOX could make it an alternative to synthetic nanomaterial used in drug delivery applications. Uthappa et al. (2018) designed a hybrid compound containing modified diatoms (DE) with silica xerogel (DE-XER) through a facile sol–gel method which acts as a pH-sensitive micro drug carrier for diclofenac sodium drug. The pore volume of the bare DE was $0.021 \text{ cm}^3/\text{g}$ and after surface modification increased to $0.199 \text{ cm}^3/\text{g}$. The presence of n xerogel skeleton on the surface of the diatom causes an increase in the surface area and pore volume so that, according to the FESEM results, the pores of the diatom were measured around 200–300 nm. This material improves the obstacles related to diclofenac sodium, including its short half-life and rapid metabolism in the liver. According to the study by Zamani et al. (2019), oral administration of *Dunaliella salina* extract was successfully conducted using magnetic nanoparticles (MNPs) grafted with gum arabic (GA) as a biocompatible scaffold. The physicochemical investigation of GA-coated MNPs exhibited the favoring of encapsulation, uniform shape, hydrodynamic size $> 200 \text{ nm}$, and 6.8% content of GA. According to the in vitro release study, the final relative release values of 72.41% in the first 8 h in the logarithmic phase were reported. The antioxidant and cytotoxic investigation of microalgal extract-loaded GA-MNPs on both MCF-7 and HeLa cells showed strong antioxidant and anticancer impact in a time- and dose-dependent manner. Alginates are polysaccharides found in brown seaweed and most abundant among marine biopolymers and, after cellulose, the most abundant among biopolymers in the world. The process of extracting alginate from brown

seaweed is a simple method and it can be extracted from dried brown algae by using dilute mineral acid and sodium carbonate (Uyen et al. 2020). Alginate microspheres (AMs) have received a lot of attention as a novel drug delivery system. The AMs act as a transient cover to support the various encapsulated drugs (e.g., indomethacin (Bose et al. 2016), metformin hydrochloride (Nayak et al. 2016), diloxanide furoate (Shukla et al. 2014), and metoprolol tartrate (Rajinikanth et al. 2003)). Three techniques have been considered for fabricating microspheres, i.e., extrusion, spray drying, and the emulsification/gelation method. According to the encapsulation route, microspheres can be divided into two groups: microcapsules and micromatrices. In microcapsules, the drug nucleus is covered by a polymeric material, while in micromatrices the drug is uniformly distributed in the polymer matrix (Solanki 2018).

Can algae contribute to the war with COVID-19?

From the end of 2019 until today, a new virus from the coronavirus family threatens human society and other animals. Concerns about the new Corona or COVID-19 virus are that for the third time in less than two decades, the world is facing a deadly coronavirus epidemic (Andreadakis et al. 2020). Common diagnostic tests for SARS-CoV-2 are separated based on a reverse transcription-polymerase chain reaction (RT-PCR) assay and serological tests. However, the hasty production of many of these kits has caused uncertainty in the interpretation of the test and its effectiveness (Lerner et al. 2020). Nowadays, the possibility of using synthesized products from microalgae in the production of serological test kits based on the immunoassay method has been investigated. Mainly, SARS-CoV-2 recombinant receptor-binding domain (RBD) has been considered in serological tests. Microalgae have become a significant promising platform for the production of viral protein antigens (Chia et al. 2021). For example, Berndt et al. (2021) reported the production of the SARS-CoV-2 spike protein RBD by using the green algae *Chlamydomonas reinhardtii*. They described three versions of the RBD by appending different intracellular localization motifs to the transgene including (a) a chloroplast-directed design with the *psaE* chloroplast sequence presented in the N-terminus. (b) a secreted type with peripherin 2 (PHC2) signal peptide localized in the N-terminus (c) an ER-Golgi retained type by the addition of a C-terminal KDEL target motif to the C-terminus of the RBD fusion protein containing the PHC2 secretion peptide. The results showed that among these three variants, the version targeted for ER–Golgi has applicable size, folding, and amino acid sequence as well as has the potential to bind the angiotensin-converting enzyme-2 (ACE2) receptor (the main target of SARS-CoV-2; Fig. 3). So, algae could be recognized

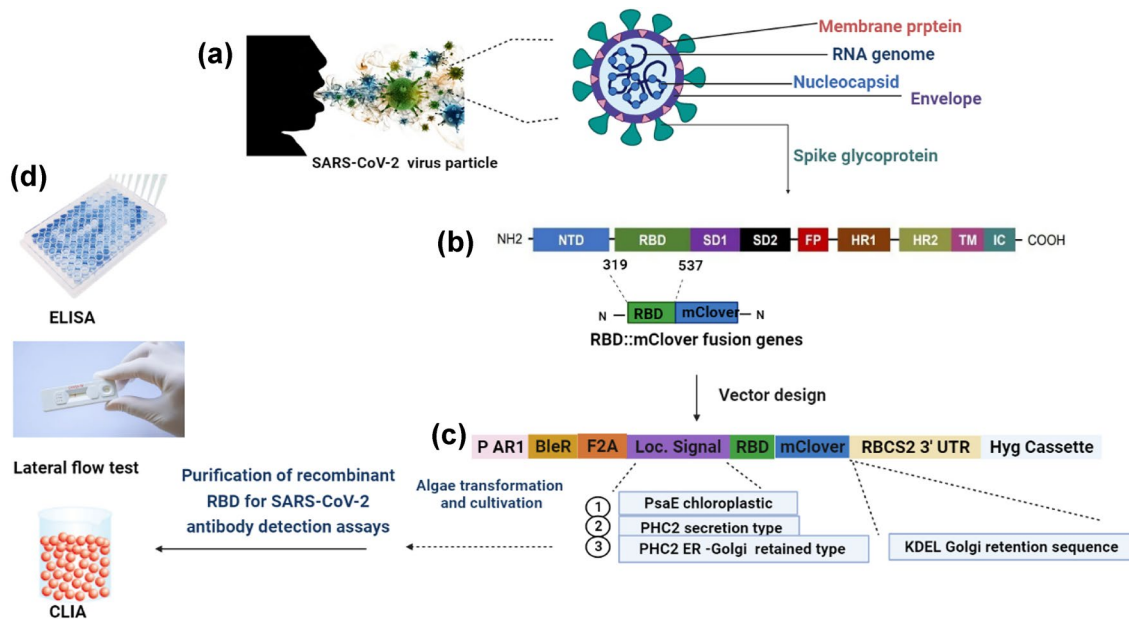


Fig. 3 Potential of *Chlamydomonas reinhardtii* microalgae in the production of SARS-CoV-2 antigens and its application in serological tests. **a** Schematic illustration of SARS-CoV-2 structure. **b** SARS-CoV-2 spike protein structure. NTD, N-terminal domain; RBD, receptor binding domain; FP, fusion peptide; HR1 and HR2, homology region 1 and 2; TM, transmembrane anchor; IC, intracellular tail. Amino acids 319–537 of the SARS-CoV-2 spike protein was selected to generation of recombinant RBD. Green fluorescent protein derivative mClover was used for high-throughput screening. **c** Vector construction. Generation of three versions of the RBD by different intra-

cellular localization motifs in the *C. reinhardtii* transgene. The vector comprises the AR1 promoter (PAR1), bleomycin resistance gene (BleR), FMDV foot-and-mouth disease virus 2A (F2A) ribosomal-skip motif, mClover green fluorescent protein tag, and hygromycin resistance cassette (Hyg cassette). **d** Recombinant RBD can be applied to produce vaccine antigens or reagents to recognize antibodies in patient serum via various assays including *ELISA* (enzyme-linked immunosorbent assay), *CLIA* (chemiluminescence immunoassay), and lateral flow tests (Berndt et al. 2021)

as a novel approach to vaccine antigen development and reagents to identify antibodies in patient's serum, rapidly and cost-effectively. Also, innovative advances in gene editing technologies increase the potential for algae to participate in the production of proteins needed to identify or amplify SARS-CoV 2 proteins to resolve health concerns caused by COVID-19. The production of injectable vaccines should not overlook recent advances in the development of oral vaccines (Gunasekaran and Gothandam 2020). The Biotech Company, TransAlgae, has developed an edible vaccine using genetically engineered *Chlamydomonas reinhardtii* for SARS-CoV-2. It was reported that it is possible to produce up to 1 mg of the recombinant antigen per gram of dried algal biomass (if contamination is ignored). Finally, lyophilized algae can be encapsulated to produce an “edible vaccine” for oral administration. The resistant wall of algae transports active antigens in a protected manner from acidic, protease-rich surroundings in the stomach to the intestine, which in turn induces immune and hemorrhagic events (Sami et al. 2021). A variety of therapeutic approaches against COVID-19 to date have been proposed, such as remdesivir, chloroquine, and angiotensin receptor blockers (ARB). Although many of these available therapeutic options present obstacles such as the need for FDA

approval, drug resistance, and cardiovascular toxicity, they have to some extent been able to improve COVID-19 patients. Unique antiviral and immune-boosting properties of several species of algae can provide reliable pharmaceutical tools (Hans et al. 2020). Polysaccharides extracted from marine microorganisms have been identified as antiviral agents for many years. Seaweed polysaccharides can disrupt various stages of the SARS-CoV-2 life cycle by inhibiting adhesion, reverse transcriptase activity, and protease activity (Iravani and Varma 2021). Chen et al. (2020a, b, c) have come up with an interesting idea for the treatment of COVID-19 based on nanotechnology. They proposed that loading S or N protein of coronavirus onto carrageenan (CGN) oligosaccharides capped AuNPs would produce an immunological vaccine adjuvant and stimulate antibody secretion. Carrageenan belongs to the family of sulfated polysaccharides found in certain red algae species. The basic structure of these compounds consists of alternating repetitive disaccharide units including 3-linked β -D-galactopyranose (G-units) and 4-linked α -galactopyranose (D-units) or 3, 6-anhydro- α -galactopyranose (AnGal-units; Jiang et al. 2021). The successful observation of inhibition of coronavirus by lambda-CGN has been published. Cell culture studies have shown that this compound not only inhibits

influenza A and B viruses (range of EC_{50} values from 0.3 to 1.4 $\mu\text{g/mL}$), but also inhibits SARS-CoV-2 (EC_{50} value of $0.9 \pm 1.1 \mu\text{g/mL}$). In addition, intranasal administration of this compound into mice resulted in 60% survival of mice infected with influenza A without weight loss. The antiviral mechanism of λ -CGN inhibits the binding of the virus to receptors on the surface of the host cell, which prevents the virus from penetrating (Jang et al. 2021). The development of CGN in nasal decongestant sprays and lozenges in the treatment of throat infections has received much attention. Recently, the effectiveness of nasal spray comprising Iota-Carrageenan (I-C) in preventing SARS-Cov-2 has been evaluated by hospital health care workers who are associated with COVID-19-infected patients. After receiving four daily doses of I-C spray or placebo for 21 days by 394 volunteers, the findings showed that the prevalence of COVID-19 in the I-C receiving group was significantly lower than in placebo (1.0% vs. 5.0%). In addition, no difference was observed between the two groups in terms of the occurrence of adverse effects (17.3% in the I-C group and 15.2% in the placebo group; Figueroa et al. 2021). Also, Morokutti-Kurz et al. (2017) developed carrageenan-containing lozenges as a therapeutic agent against viral infections human rhinovirus (HRV) 1a, HRV8, influenza virus A H1N1n, coxsackievirus A10, and human coronavirus (hCoV) OC43 of the throat. Lozenges containing 10 mg of I-C cause structural changes in viral glycoproteins by maintaining low pH inside the mouth. They observed during the residence time of the lozenge in the mouth, the viral titer is reduced by 85% and 91% for influenza A virus and hCoV-OC43, respectively.

Red alga-derived griffithsin (GRFT), which is a carbohydrate-binding protein, is effective in reducing the spread of multiple viral infections, including the hCoV-OC43, hCoV-229E, and hCoV-NL63 in vitro and SARS-CoV in vivo. GRFT is prevented from spreading viral infection by binding to spike glycoproteins (Zumla et al. 2016). Therefore, it seems that GRFT can be efficient in inhibiting SARS-CoV-2 cellular entry and various enzymatic activities. The structure of the GRFT is in the form of a homodimer where each of its subunits is composed of three carbohydrate-binding domains of 121 amino acids. These domains can bind to the mannose, glucose, and *N*-acetyl glucosamine monosaccharides in enveloped viruses. Such a unique structure can also induce broad-spectrum antiviral properties against HIV (human immunodeficiency virus), hepatitis C virus (HCV), Japanese encephalitis virus (JEV), herpes simplex virus 2 (HSV-2), and porcine epidemic diarrhea virus (PEDV; Lee 2019; Alsaidi et al. 2021). In severe COVID-19 patients, activation of oxidative stress and severe pulmonary inflammatory responses induce a violent immune response cytokine storm, which in turn leads to the development of acute respiratory distress syndrome (ARDS). ARDS is associated with elevated levels of

proinflammatory cytokines including TNF- α , IL-6, IL-1, and chemokines (CCL3, CCL2, CXCL9, CXCL10), leading to severe immune system activity and acute lung damage (ALI; Tang et al. 2020). Microalgae-derived astaxanthin (ASX) is a reddish pigment that belongs to a group of chemicals such as terpenes. In addition to its antioxidant and oxidative stress-reducing properties, its anti-inflammatory action in cytokine release syndrome is very significant. Therefore, applying the ASX in lungs infected by SARS-CoV-2 may suppress the excessive secretion of inflammatory factors such as IL-1B, IL-2, IL-6, IL-8, IL-10, INF- γ , TNF- α , and VEGF as well as modulate oxidative stress by inhibiting the production of oxidative enzymes and ROS (Talukdar et al. 2020). *Spirulina* is a green-blue alga in the form of a spiral that contains 70% protein and is rich in phenolic acids, essential fatty acids, amino acids, sulfated polysaccharides, and vitamin B12. Therefore, the use of *spirulina* as a popular supplement has long been considered. Numerous studies have reported the antiviral properties of *spirulina*. Induction of interferon-gamma production and activation of immune cells by *spirulina* play a significant role in activating the immune system against viruses (Daoud and Soliman 2015). Calcium *spirulina* is a novel sulfated polysaccharide isolated from *spirulina* that contains several units of monosaccharides such as ribose, rhamnose, mannose, galactose, xylose, fructose, glucose, galacturonic acid, glucuronic acid, sulfate, and calcium. This polysaccharide has been shown to inhibit the replication of several enveloped viruses including human cytomegalovirus, mumps virus, herpes simplex virus type 1, measles virus, HIV-1, and influenza A virus (Hayashi et al. 1996). *Spirulina*-derived phycocyanin is also known as an NADPH oxidase inhibitor with anti-inflammatory activity. According to reports, *spirulina* may be an effective candidate for adjuvant therapy for COVID-19 patients (Singh et al. 2020). Numerous biotechnological studies have demonstrated the potential of algae in the pharmaceutical field to have a great potential to help fight COVID-19. In addition, using an algae supplement in powder or capsule form can strengthen the immune system and prevent the spread of severe viral infections.

Microalgae harvesting techniques by various types of photobioreactors

To exploit and commercialize microalgae as a valuable natural resource for biomedical programs, their production in a large area has become a challenge. Recently, the construction of photobioreactors with new and innovative designs for algae cultivation on a large scale has attracted attention. Among the most important features of these systems is the control of culture conditions including light, gas transfer, temperature, acidity level, and protection from the entry of

pollutants and foreign particles (Vasumathi et al. 2012). In general, photobioreactors (PBRs) can be divided into two categories: open and closed types. Among the open types, first introduced by Ostwald in the 1960s, the open raceway bioreactor (ORC) was examined (Mehariya et al. 2021). ORC with an area of about 1000 and 5000 m² has low energy consumption (3.72 W/m³) and construction costs. The basic structure of ORC consists of two channels with linked curves with mixing devices for continuous circulation of culture medium and microalgae. The role of the light source and gas supply for biomass growth is also obvious (Raes et al. 2014). There are different configurations of open bioreactor systems, such as circular pond systems and inclined surface systems (Hosseini et al. 2015). The open system has several obstacles, including the possibility of contamination by protozoa and bacteria (excessive use of antibiotics to address this issue, in addition to creating antibiotic resistance, reduces the safety of biomass produced for human and animal feed production), the need for large non-arable land for real-world application, lack of light penetration into the deeper layers of the culture medium, nutrient shortages, and temperature fluctuations (Ryu et al. 2019). The closed photobioreactors family can be divided into a tubular bioreactor, a flat plate bioreactor, and a vertical column bioreactor. The limitations of open systems have been removed with the advent of closed types in various geometric configurations so that increasing the surface-to-volume ratio enhances efficiency and value-added microalgae biomass (Carvalho et al. 2011). A Tubular photobioreactor is one of the most suitable types of PBRs, which include plastic or glass tubes. They can be in different shapes, such as horizontal, spiral, vertical, near horizontal, fence-like, conical, and sloping and the culture is rotated employing pumps or air pressure systems inside the tubes (Tan et al. 2018). The turbulence process of the culture medium is applied by an air pump to prevent the deposition of algal cells. In these systems, dissolved oxygen accumulation is usually high, which causes light respiration. Other limitations of this system are the accumulation, precipitation, and, adhesion of algae to the walls of the tubes (Singh and Sharma 2012). The general structure of tubular PBRs is divided into two parts: the tubular part (where algal biomass grows) and the degasser unit (which prevents light oxidation). Microalgae are circulated from the degasser unit to the reactor part and returned to the degasser unit on an ongoing route. Another disadvantage of this system is the problem of temperature regulation as well as the aeration inefficiency that is done in the degasser section. At the beginning of the tube, the concentration of carbon dioxide is high and oxygen is low, and its temperature is adjusted, but near the end of the tube, these values are reversed and the desired temperature changes (Huang et al. 2017; Converti et al. 2006). Generally, a flat-panel photobioreactor like closed PBRs consists of two transparent flat plates

(polycarbonate, plexiglass, or plastic bags) that are connected in a rectangular cube to form a small-diameter aquarium. The flat-panel photobioreactor has received a lot of attention due to its high level of light absorption. However, due to the self-shading of microalgae cells between the flat plates, LED lamps are used (Xu et al. 2009). Vertical column PBRs are composed of transparent cylindrical columns to facilitate good light penetration. Several factors have made vertical column reactors important, including the homogeneous distribution of photosynthetic organisms, increasing the illumination exposure time, and increasing residence time of CO₂ due to the longer contact time between gas and liquid (Pawar 2016). The presence of a gas sparger at the bottom of the reactor causes conversion of the influent sparged gas into tiny bubbles which improves the mixing process and removes the O₂ generated in photosynthesis. Depending on the flowing manner, vertical column PBRs are divided into two groups: bubble column and airlift reactors (Ugwu et al. 2008). Bubble column PBRs have satisfactory properties such as desirable heat and mass transfer rates, decreased shear stress on microorganisms, enhanced light scattering and penetration due to the bubbles, and improved scalability. The salient limitations of this model are the random flow pattern and sedimentation process. Photosynthetic efficiency and biomass yield greatly depend upon the gas flow rate. The significant limitation of this model is the random flow pattern which affects biomass yield efficiency (Wong et al. 2017). Airlift reactors are developed from a cylindrical vessel containing several interconnecting zones which is composed of an inner tube (called a riser), where the gas mixture flows upward from the sparger and an outer part (called downcomer) which circulates the medium from downward into the riser (Yen et al. 2019). Airlift reactors have been widely used in biotechnological processes in recent decades, including aerobic fermentation to produce a variety of food products, wastewater operations, and other similar operations. These types of reactors are suitable for processes in which uniform and rapid distribution of reactive components is necessary, as well as for multiphase systems (liquid–gas–solid) that require high mass and heat transfer (Fuchs et al. 2021; Yen et al. 2019). Although all the mentioned PBRs have been considered and used for many years, the obstacles related to cultivation conditions, harvesting and equipment as well as low algal cell density have made them unpopular. Algal biofilm-based systems have become a promising technology in that the algal biomass is immobilized on a substrate and is separated from the aquatic culture medium (Gross et al. 2015). To manufacture these systems, there are several pivotal steps: firstly, there are various carrier materials such as a film for microalgae attachment. Proper attachment of microalgae to the support surface requires a gel-like matrix of extracellular polymeric substances (ExPS) that is secreted by a variety of

microorganisms, such as bacteria. ExPS is made up of various biomolecules, including nucleic acids, proteins, polysaccharides, and lipids produced by different types of microorganisms which play an important role in the creation of an adsorbent, diffuse, and heterogeneous scaffold for the growth and cell interactions of microalgae (Fig. 4). The higher diversity of bacteria causes more microalgal binding and provides more carbon sources for them (Choudhary et al. 2017). Next, the binding potential of microalgae to the film surface should also be considered. For example, *Chlorella* sp. and *Scenedesmus* sp. as well as cyanobacteria and heterotrophic bacteria have been studied for this purpose (Ahn et al. 2013). Finally, optimizing environmental conditions from an engineering perspective should also be considered. The flow velocity of the cultivation environment and temperature are two influential factors in the distribution of algal species and the efficiency of biofilm composition. Generally, lower flow rates are desirable for the placement of filamentous microalgae and higher flow rates induce colonization of green microalgae. Furthermore, higher temperatures, despite their positive effect on the growth and colonization

of bacteria, increase their enzymatic activity in the decomposition of organic matter, which in turn improves the proliferation and photosynthesis process of microalgae (Liu et al. 2016; Villanueva et al. 2011; Gross and Wen 2014). Usually, algal biofilm PBRs fall into two categories: submerged systems and porous substrate photobioreactors (PSBRs). In submerged-biofilm PBRs, the biofilms are usually attached to impermeable surfaces, which are either constantly or intermittently soaked in the culture medium. In the case of PSBRs, a biofilm containing a fine-microporous substrate is used, which separates the biofilm from the aquatic medium. The smaller size of the substrate pores than the algal cells causes the biomass to separate from the medium and accumulate on one side of the substrate (Fig. 5; Li et al. 2017). Conventional PBRs require large amounts of energy resources to overcome air resistance. Therefore, the construction of cost-effective alternative devices has been considered. Recently, pressure-driven bioreactors as novel devices are equipped with a vacuum pump that raises the culture medium flow to the container at the top of the device. In these systems, energy consumption is reduced by about

Fig. 4 Schematic illustration of algal biofilm formation

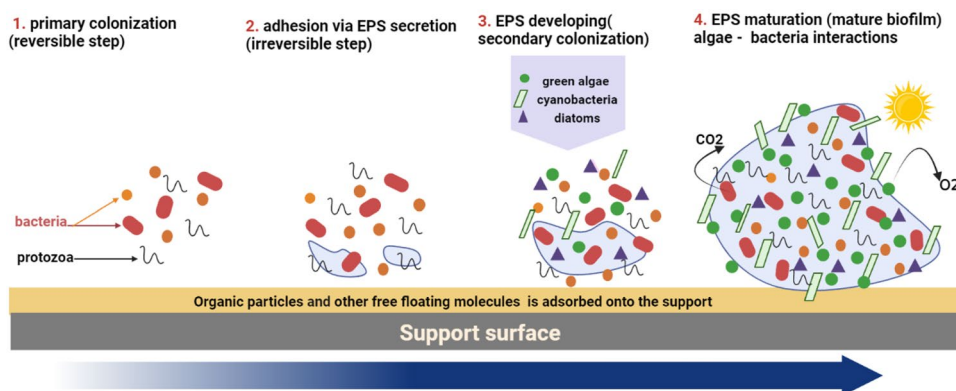
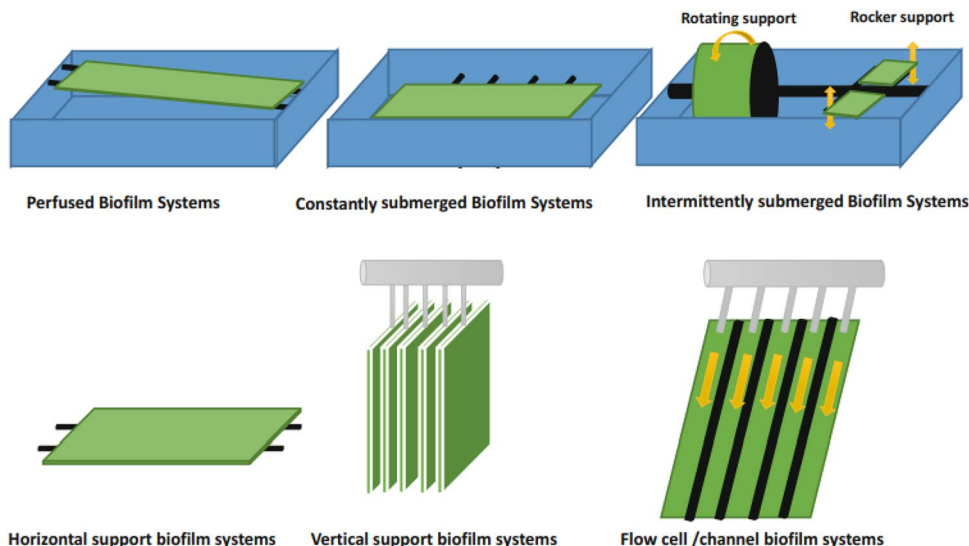


Fig. 5 The schematic illustrations of important classes of biofilm systems. According to the relative motion of cultivation medium and biofilm support, these systems are divided into three categories: perfused biofilm systems, constantly and intermittently submerged biofilm systems (top row). Besides, due to the position of the biofilm support, these arrangements can be classified into horizontal, vertical, and flow cell (bottom row; Li et al. 2017)



99.3% (Zhong et al. 2020). In the years 2000–2012, the National Aeronautics and Space Administration (NASA) of the USA introduced the Offshore Membrane Enclosures for Growing Algae (OMEGA) method. NASA's OMEGA system is an innovative method to grow algae, wastewater treatment, and CO₂ catch and ultimately produce aviation biofuels. OMEGA photobioreactors consist of large flexible plastic tubes floating in seawater and the mixing process is done by force driving by waves (minimizing energy consumption). The advantages of these systems are very significant, including: addressing concerns about the cost of structural mechanical equipment and commercial culture media as well as algae cultivation on the offshore eliminates competition with agricultural land and costs associated with land resources (Ullman and Grimm 2021). The different types of photobioreactors for algal growth are shown in Fig. 6).

Microalgae biomass

Microalgae biomass has become an inspiring source of energy with multifaceted applications in the production of sustainable nutrients, biofuels, and dietary supplements. Therefore, mass cultivation of these natural biofactories has been considered in the last few decades. High efficiency, high content of lipids and other bioactive components, ability to grow in wastewater, and no need for large farms are the advantages of algal biomass production compared to traditional crops (Orejuela-Escobar et al. 2021). To use microalgae as a source of renewable energy (biofuels) and environmental applications, large-scale industrial production of algae has been proposed. However, it is possible to use traditional small-scale cultivation for human consumption. The first sure step in the commercialization process of microalgae production is the selection of suitable species and strains for cultivation. Selected strains must be able to withstand a wide range of environmental conditions of temperature, salinity, light, and pH. To produce biomass on an industrial scale, green microalgae belonging to the *Chlorophyceae*

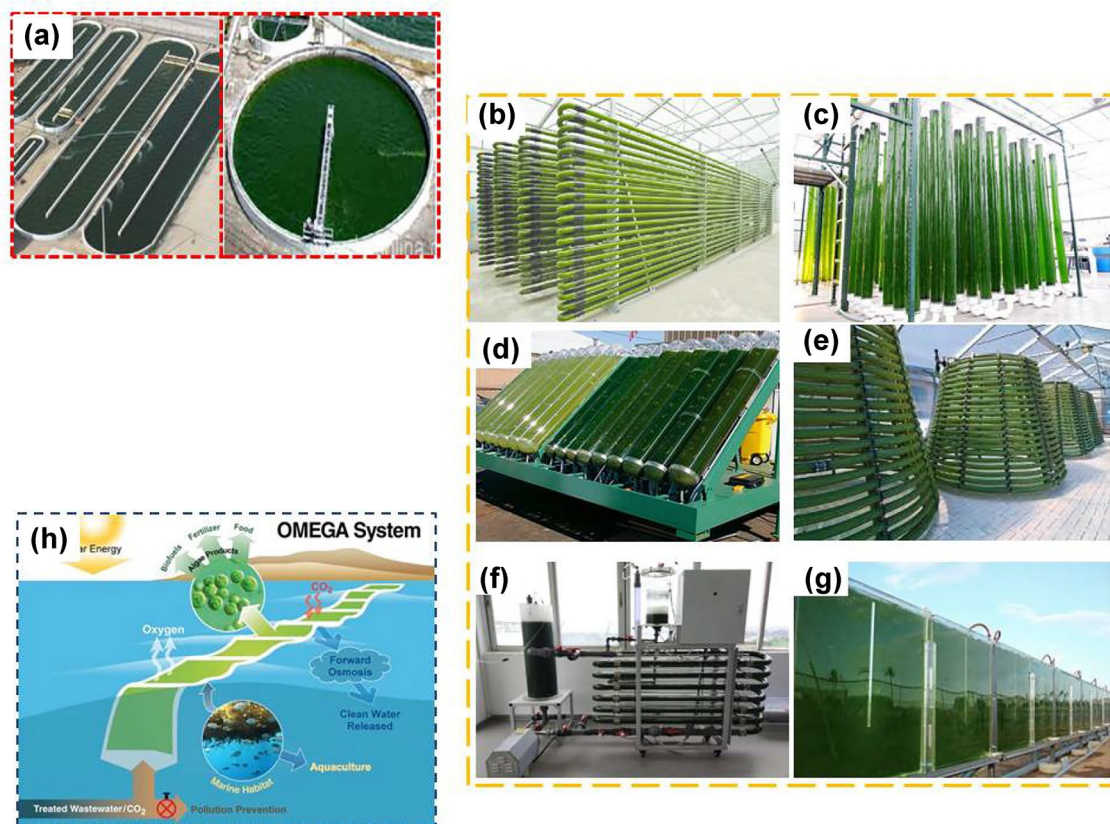


Fig. 6 Various models of algal photobioreactors. **a** Open ponds cultivation systems (circular and raceway designs), **b** horizontal tubular type (Brányiková and Lucáková 2021), **c** vertical tubular type (Alaswad et al. 2015), **d** inclined tubular type (Brányiková and Lucáková

2021), **e** conical type (Koller 2015), **f** pressure-driven type (Zhang et al. 2020), **g** flat plate type, and **h** Offshore Membrane Enclosures for Growing Algae (OMEGA; Ullman and Grimm 2021)

class, including species such as *Chlorella*, *Hematococcus*, and *Donatella*, are commonly used (Benedetti et al. 2018). The largest units producing *D. salina* were built in Australia in wide and shallow ponds (each pond up to 400 ha and a total area of more than 700 ha). The production of this algae for its valuable product, beta-carotene, attracted a lot of attention (Borowitzka and Moheimani 2013). Genetic modification has the potential to revolutionize the microalgae-based industry. Transfer of genes isolated from other species such as resistance genes to light, excessive heat stress, pH alteration, and pathogens have been welcomed to produce strains with favorable commercial characteristics. Genome sequencing, advances in metagenomes, and genetic manipulation all make important contributions to studies on microalgae (Fajardo et al. 2020). Following the growth of microalgae in different types of cultivation systems, biomass harvesting and drying is an important step in terms of cost and energy intensity. Using various physical and chemical techniques, such as flotation, centrifugation, filtration, coagulation and flocculation, and algal biomass can be isolated (Roy and Mohanty 2019). It should be noted that the use of the mentioned methods requires investment and high operating costs. Biological methods including auto-flocculation as a result of increasing pH or using high concentrations of Ca^{2+} ions and biological flocculation using microbes and biopolymers have also been considered (Wrede et al. 2014). The energy crisis, pollution, and the devastating environmental effects of using fossil fuels have led to the use of renewable energy. Therefore, microalgae have received a great deal of attention as a renewable and environmentally friendly biofuel in response to global warming, climate change, energy crisis, and the decrease in natural resources. Numerous experiments have been performed on microalgae as a rich source of oil for the production of biofuels. By extracting oil and also using these algae directly, third-generation feedstock (TGF) has been produced. TGF has several advantages including less production time, high photosynthetic efficiency, high growth rate, low-cost nutrients for growth, and a process toward sustainable and cost-effective fuel production (Mathimani and Pugazhendhi 2019). The purpose of the National Renewable Energy Laboratory (NREL) project was to evaluate the mechanism of lipid synthesis in high-lipid-producing microalgae and to use genetic engineering to improve microalgae strains (Milledge 2010).

Conclusion

A study of technology and economic aspects of algae production shows that they can be used in various fields of material production in the pharmaceutical, nutraceutical, and cosmetic industries. Substitution of fossil fuels with green fuels has always been a dream of environmentalists.

The use of microalgae due to their potential in the production of combustible oils up to 60% in some species for the production of biofuels has yielded valuable results and has turned them into a renewable energy source. In one of the sections of this paper, the focus is on the cultivation of algae in photobioreactors, so that the function of these systems is described and their advantages and drawbacks are reported. Cultivation of microalgae in photobioreactors can be considered a promising approach for the integration of wastewater treatment and CO_2 capturing, which have become universal challenges. In the field of nanomedicine, the use of microalgae as a safe and innovative carrier for targeted drug delivery improves drug-loading efficiency and reduces toxicity effects. According to the major articles reviewed, usually, immunoenhancing properties of various bio compounds of microalgae are induced mainly through the activation of various types of cytokines, NK cells, and several immunoglobulin classes. Furthermore, In addition to examining the anticancer properties of various compounds extracted from microalgae, the latest achievements in controlling the COVID-19 pandemic were reported.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

References

- Ahn CH, Song HM, Lee S, Oh JH, Ahn H, Park JR et al (2013) Effects of water velocity and specific surface area on filamentous periphyton biomass in an artificial stream mesocosm. *Water* 5(4):1723–1740
- Alaswad A, Dassisti M, Prescott T, Olabi AG (2015) Technologies and developments of third generation biofuel production. *Renew Sustain Energy Rev* 51:1446–1460
- Alekseyenko T, Zhanayeva SY, Venediktova A, Zvyagintseva T, Kuznetsova T, Besednova N et al (2007) Antitumor and antimetastatic activity of fucoidan, a sulfated polysaccharide isolated from the Okhotsk Sea *Fucus evanescens* brown alga. *Bull Exp Biol Med* 143(6):730–732
- Alsaïdi S, Cornejal N, Mahoney O, Melo C, Verma N, Bonnaire T et al (2021) Griffithsin and carrageenan combination results in antiviral synergy against SARS-CoV-1 and 2 in a pseudoviral model. *Mar Drugs* 19(8):418
- Altenburg JD, Siddiqui RA (2009) Omega-3 polyunsaturated fatty acids down-modulate CXCR4 expression and function in MDA-MB-231 breast cancer cells. *Mol Cancer Res* 7(7):1013–1020
- Andreadakis Z, Kumar A, Román RG, Tollefsen S, Saviile M, Mayhew S (2020) The COVID-19 vaccine development landscape. *Nat Rev Drug Discov* 19(5):305–306
- Apone F, Barbulova A, Colucci MG (2019) Plant and microalgae derived peptides are advantageously employed as bioactive compounds in cosmetics. *Front Plant Sci* 10:756

- Araújo R, Vázquez Calderón F, Sánchez López J, Azevedo IC, Bruhn A, Fluch S et al (2021) Current status of the algae production industry in Europe: an emerging sector of the Blue Bioeconomy. *Front Mar Sci* 7:1247
- Balasubramaniam V, Gunasegavan RD, Mustar S, Lee JC, Mohd Noh MF (2021) Isolation of industrial important bioactive compounds from microalgae. *Molecules* 26(4):943
- Barsanti L, Gualtieri P (2014) *Algae: anatomy, biochemistry, and biotechnology*. CRC Press, Boca Raton
- Benedetti M, Vecchi V, Barera S, Dall'Osto L (2018) Biomass from microalgae: the potential of domestication towards sustainable biofactories. *Microb Cell Fact* 17(1):1–8
- Berndt A, Smalley T, Ren B, Badary A, Sproles A, Fields F et al (2021) Recombinant production of a functional SARS-CoV-2 spike receptor binding domain in the green algae *Chlamydomonas reinhardtii*. *bioRxiv*
- Bhadury P, Wright PC (2004) Exploitation of marine algae: biogenic compounds for potential antifouling applications. *Planta* 219(4):561–578
- Borowitzka MA, Moheimani NR (2013) Sustainable biofuels from algae. *Mitig Adapt Strat Glob Change* 18(1):13–25
- Bose P, Nagaraju R, Saritha D, Padmasri B, Reddy PS (2016) Preparation and evaluation of indomethacin loaded alginate microspheres. *Ceska a Slov Farm* 65(3):104–110
- Brányiková I, Lucáková S (2021) Technical and physiological aspects of microalgae cultivation and productivity—*spirulina* as a promising and feasible choice. *Org Agric* 11(2):269–276
- Brendler T, Williamson EM (2019) Astaxanthin: how much is too much? A safety review. *Phytother Res* 33(12):3090–3111
- Caporgno MP, Böcker L, Müssner C, Stirnemann E, Haberkorn I, Adelman H et al (2020) Extruded meat analogues based on yellow, heterotrophically cultivated *Auxenochlorella protothecoides* microalgae. *Innov Food Sci Emerg Technol* 59:102275
- Carrasco-Reinado R, Escobar-Niño A, Fajardo C, Morano IM, Amil-Ruiz F, Martínez-Rodríguez G et al (2021) Development of new antiproliferative compound against human tumor cells from the marine microalgae *Nannochloropsis gaditana* by applied proteomics. *Int J Mol Sci* 22(1):96
- Carvalho AP, Silva SO, Baptista JM, Malcata FX (2011) Light requirements in microalgal photobioreactors: an overview of biophotonic aspects. *Appl Microbiol Biotechnol* 89(5):1275–1288
- Cha KH, Koo SY, Lee DU (2008) Antiproliferative effects of carotenoids extracted from *Chlorella ellipsoidea* and *Chlorella vulgaris* on human colon cancer cells. *J Agric Food Chem* 56(22):10521–10526
- Chen CL, Liou SF, Chen SJ, Shih MF (2011) Protective effects of Chlorella-derived peptide on UVB-induced production of MMP-1 and degradation of procollagen genes in human skin fibroblasts. *Regul Toxicol Pharmacol* 60(1):112–119
- Chen X, Song L, Wang H, Liu S, Yu H, Wang X et al (2019) Partial characterization, the immune modulation and anticancer activities of sulfated polysaccharides from filamentous microalgae *Tribonema* sp. *Molecules* 24(2):322
- Chen H, Wang X, Wang Q (2020a) Microalgal biofuels in China: the past, progress and prospects. *GCB Bioenergy* 12(12):1044–1065
- Chen X, Han W, Wang G, Zhao X (2020b) Application prospect of polysaccharides in the development of anti-novel coronavirus drugs and vaccines. *Int J Biol Macromol* 164:331–343
- Chen Z, Xiao J, Liu H, Yao K, Hou X, Cao Y et al (2020c) Astaxanthin attenuates oxidative stress and immune impairment in d-galactose-induced aging in rats by activating the Nrf2/Keap1 pathway and suppressing the NF- κ B pathway. *Food Funct* 11(9):8099–8111
- Chen T, Zhao H, Zheng Y, Cai Y, Ren B, Dong R (2022) Bifunctional biohybrid magnetically propelled microswimmer. *Chem Eng J* 439:135490
- Chia WY, Kok H, Chew KW, Low SS, Show PL (2021) Can algae contribute to the war with COVID-19? *Bioengineered* 12(1):1226–1237
- Chiu LCM, Wong EYL, Ooi VE (2004) Docosahexaenoic acid from a cultured microalga inhibits cell growth and induces apoptosis by upregulating Bax/Bcl-2 ratio in human breast carcinoma MCF-7 cells. *Ann N Y Acad Sci* 1030(1):361–368
- Choudhary P, Malik A, Pant KK (2017) *Algal biofilm systems: an answer to algal biofuel dilemma* Algal Biofuels. Springer, Berlin, pp 77–96
- Chuang WC, Ho YC, Liao JW, Lu FJ (2014) *Dunaliella salina* exhibits an antileukemic immunity in a mouse model of WEHI-3 leukemia cells. *J Agric Food Chem* 62(47):11479–11487
- Converti A, Lodi A, Del Borghi A, Solisio C (2006) Cultivation of *Spirulina platensis* in a combined airlift-tubular reactor system. *Biochem Eng J* 32(1):13–18
- Dalrymple OK, Halfhide T, Udom I, Gilles B, Wolan J, Zhang Q et al (2013) Wastewater use in algae production for generation of renewable resources: a review and preliminary results. *Aquatic Biosyst* 9(1):1–11
- Daoud HM, Soliman EM (2015) Evaluation of *Spirulina platensis* extract as natural antiviral against foot and mouth disease virus strains (A, O, SAT2). *Vet World* 8(10):1260
- Daroch M, Geng S, Wang G (2013) Recent advances in liquid biofuel production from algal feedstocks. *Appl Energy* 102:1371–1381
- Davinelli S, Melvang HM, Andersen LP, Scapagnini G, Nielsen ME (2019) Astaxanthin from shrimp cephalothorax stimulates the immune response by enhancing IFN- γ , IL-10, and IL-2 secretion in splenocytes of *Helicobacter pylori*-infected mice. *Mar Drugs* 17(7):382
- Delasoie J, Schiel P, Vojnovic S, Nikodinovic-Runic J, Zobi F (2020) Photoactivatable surface-functionalized diatom microalgae for colorectal cancer targeted delivery and enhanced cytotoxicity of anticancer complexes. *Pharmaceutics* 12(5):480
- Dyshlovoy SA, Honecker F (2015) Marine compounds and cancer: where do we stand? *Mar Drugs* 13(9):5657–5665
- Fajardo C, De Donato M, Carrasco R, Martínez-Rodríguez G, Mancera JM, Fernández-Acero FJ (2020) Advances and challenges in genetic engineering of microalgae. *Rev Aquac* 12(1):365–381
- Figuerola JM, Lombardo M, Dogliotti A, Flynn L, Giugliano RP, Simonelli G et al (2021) Efficacy of a nasal spray containing Iota-Carrageenan in the prophylaxis of COVID-19 in hospital personnel dedicated to patients care with COVID-19 disease. *Int J Gen Med* 14:6277–6286
- Frentzen M (2004) Phosphatidylglycerol and sulfoquinovosyldiacylglycerol: anionic membrane lipids and phosphate regulation. *Curr Opin Plant Biol* 7(3):270–276
- Fu W, Nelson DR, Mystikou A, Daakour S, Salehi-Ashtiani K (2019) Advances in microalgal research and engineering development. *Curr Opin Biotechnol* 59:157–164
- Fuchs T, Arnold ND, Garbe D, Deimel S, Lorenzen J, Masri M et al (2021) A newly designed automatically controlled, sterilizable flat panel photobioreactor for axenic algae culture. *Front Bioeng Biotechnol* 9:566
- Ghaeni M, Roomiani L (2016) Review for application and medicine effects of *Spirulina*, microalgae. *J Adv Agric Technol* 3(2):114–117
- Ghasemi Y, Rasoul-Amini S, Naseri A, Montazeri-Najafabady N, Mobasher M, Dabbagh F (2012) Microalgae biofuel potentials. *Appl Biochem Microbiol* 48(2):126–144
- Gross M, Wen Z (2014) Yearlong evaluation of performance and durability of a pilot-scale revolving algal biofilm (RAB) cultivation system. *Biores Technol* 171:50–58
- Gross M, Jarboe D, Wen Z (2015) Biofilm-based algal cultivation systems. *Appl Microbiol Biotechnol* 99(14):5781–5789

- Gunasekaran B, Gothandam K (2020) A review on edible vaccines and their prospects. *Braz J Med Biol Res* 53(2):1–10
- Hans N, Malik A, Naik S (2020) Antiviral activity of sulfated polysaccharides from marine algae and its application in combating COVID-19: mini review. *Bioresour Technol Rep* 13:100623
- Hayashi T, Hayashi K, Maeda M, Kojima I (1996) Calcium spirulan, an inhibitor of enveloped virus replication, from a blue-green alga *Spirulina platensis*. *J Nat Prod* 59(1):83–87
- Hemantkumar JN, Rahimbhai MI (2019) Microalgae and its use in nutraceuticals and food supplements. *Microalgae—from Physiology to Application*, p 10
- Hielscher-Michael S, Griehl C, Buchholz M, Demuth HU, Arnold N, Wessjohann LA (2016) Natural products from microalgae with potential against Alzheimer's disease: sulfolipids are potent glutaminyl cyclase inhibitors. *Mar Drugs* 14(11):203
- Hirahashi T, Matsumoto M, Hazeki K, Saeki Y, Ui M, Seya T (2002) Activation of the human innate immune system by *Spirulina*: augmentation of interferon production and NK cytotoxicity by oral administration of hot water extract of *Spirulina platensis*. *Int Immunopharmacol* 2(4):423–434
- Hosseini NS, Shang H, Ross GM, Scott JA (2015) Microalgae cultivation in a novel top-lit gas-lift open bioreactor. *Biores Technol* 192:432–440
- Huang Q, Jiang F, Wang L, Yang C (2017) Design of photobioreactors for mass cultivation of photosynthetic organisms. *Engineering* 3(3):318–329
- Hussein HA, Abdullah MA (2020) Anticancer compounds derived from marine diatoms. *Mar Drugs* 18(7):356
- Iravani S, Varma RS (2021) Important roles of oligo- and polysaccharides against SARS-CoV-2: recent advances. *Appl Sci* 11(8):3512
- Jang YJ, Shin H, Lee MK, Kwon OS, Shin JS, Kim Y et al (2021) Antiviral activity of lambda-carrageenan against influenza viruses in mice and severe acute respiratory syndrome coronavirus 2 in vitro. *Sci Rep* 11:821
- Jiang L, Wang Y, Liu G, Liu H, Zhu F, Ji H et al (2018) C-Phycocyanin exerts anti-cancer effects via the MAPK signaling pathway in MDA-MB-231 cells. *Cancer Cell Int* 18(1):1–14
- Jiang JL, Zhang WZ, Ni WX, Shao JW (2021) Insight on structure-property relationships of carrageenan and its chemically modified derivatives: a review. *Carbohydr Polym* 257:117642
- Kang KH, Kim SK (2013) Beneficial effect of peptides from microalgae on anticancer. *Curr Protein Pept Sci* 14(3):212–217
- Kang KS, Wang P, Yamabe N, Fukui M, Jay T, Zhu BT (2010) Docosahexaenoic acid induces apoptosis in MCF-7 cells in vitro and in vivo via reactive oxygen species formation and caspase 8 activation. *PLoS ONE* 5(4):e10296
- Khavari F, Saidijam M, Taheri M, Nouri F (2021) Microalgae: therapeutic potentials and applications. *Mol Biol Rep* 48:4757–4765
- Khora SS, Navya P (2020) Bioactive polysaccharides from marine macroalgae. *Encycl Mar Biotechnol* 1:121–145
- Koller M (2015) Design of closed photobioreactors for algal cultivation. In: *Algal biorefineries*, pp 133–186
- Konur O (2021) Algal biomass production for biodiesel production: a review of the research. In: *Biodiesel fuels based on edible and nonedible feedstocks, wastes, and algae*, pp 695–717
- Laamanen C, Desjardins S, Senhorinho G, Scott J (2021) Harvesting microalgae for health beneficial dietary supplements. *Algal Res* 54:102189
- Lee C (2019) Griffithsin, a highly potent broad-spectrum antiviral lectin from red algae: from discovery to clinical application. *Mar Drugs* 17(10):567
- Lerner AM, Eisinger RW, Lowy DR, Petersen LR, Humes R, Hepburn M et al (2020) The COVID-19 serology studies workshop: recommendations and challenges. *Immunity* 53(1):1–5
- Li T, Strous M, Melkonian M (2017) Biofilm-based photobioreactors: their design and improving productivity through efficient supply of dissolved inorganic carbon. *FEMS Microbiol Lett* 364(24):fnx218
- Li K, Liu Q, Fang F, Luo R, Lu Q, Zhou W et al (2019) Microalgae-based wastewater treatment for nutrients recovery: a review. *Biores Technol* 291:121934
- Liu J, Danneels B, Vanormelingen P, Vyverman W (2016) Nutrient removal from horticultural wastewater by benthic filamentous algae *Klebsormidium* sp., *Stigeoclonium* spp. and their communities: from laboratory flask to outdoor Algal Turf Scrubber (ATS). *Water Res* 92:61–68
- Lupette J, Benning C (2020) Human health benefits of very-long-chain polyunsaturated fatty acids from microalgae. *Biochimie* 178:15–25
- Majidian P, Tabatabaei M, Zeinolabedini M, Naghshbandi MP, Chisti Y (2018) Metabolic engineering of microorganisms for biofuel production. *Renew Sustain Energy Rev* 82:3863–3885
- Maltsev Y, Maltseva K (2021) Fatty acids of microalgae: diversity and applications. *Rev Environ Sci Biotechnol* 20:515–547
- Manzo E, Cutignano A, Pagano D, Gallo C, Barra G, Nuzzo G et al (2017) A new marine-derived sulfoglycolipid triggers dendritic cell activation and immune adjuvant response. *Sci Rep* 7(1):1–10
- Mathimani T, Pugazhendhi A (2019) Utilization of algae for biofuel, bio-products and bio-remediation. *Biocatal Agric Biotechnol* 17:326–330
- Mehariya S, Goswami RK, Verma P, Lavecchia R, Zuurro A (2021) Integrated approach for wastewater treatment and biofuel production in microalgae biorefineries. *Energies* 14(8):2282
- Milledge J (2010) The potential yield of microalgae oil. *Biofuels Int* 4(1):44–45
- Miller KD, Nogueira L, Mariotto AB, Rowland JH, Yabroff KR, Alfano CM et al (2019) Cancer treatment and survivorship statistics, 2019. *CA Cancer J Clin* 69(5):363–385
- MišurCoVá L, KráčMar S, KLeJduS B, VaCeK J (2010) Nitrogen content, dietary fiber, and digestibility in algal food products. *Czech J Food Sci* 28(1):27–35
- Morokutti-Kurz M, Graf C, Prieschl-Grassauer E (2017) Amylmetacresol/2, 4-dichlorobenzyl alcohol, hexylresorcinol, or carrageenan lozenges as active treatments for sore throat. *Int J Gen Med* 10:53
- Mutanda T, Naidoo D, Bwapwa JK, Anandraj A (2020) Biotechnological applications of microalgal oleaginous compounds: current trends on microalgal bioprocessing of products. *Front Energy Res* 8:598803
- Nayak AK, Pal D, Santra K (2016) Swelling and drug release behavior of metformin HCl-loaded tamarind seed polysaccharide-alginate beads. *Int J Biol Macromol* 82:1023–1027
- Nicoletti M (2016) Microalgae nutraceuticals. *Foods* 5(3):54
- Oh GW, Ko SC, Heo SY, Nguyen VT, Kim G, Jang CH et al (2015) A novel peptide purified from the fermented microalga *Pavlova lutheri* attenuates oxidative stress and melanogenesis in B16F10 melanoma cells. *Process Biochem* 50(8):1318–1326
- Orejuela-Escobar L, Gualle A, Ochoa-Herrera V, Philippidis GP (2021) Prospects of microalgae for biomaterial production and environmental applications at biorefineries. *Sustainability* 13(6):3063
- Park GT, Go RE, Lee HM, Lee GA, Kim CW, Seo JW et al (2017) Potential anti-proliferative and immunomodulatory effects of marine microalgal exopolysaccharide on various human cancer cells and lymphocytes in vitro. *Mar Biotechnol* 19(2):136
- Parmar A, Singh NK, Pandey A, Gnansounou E, Madamwar D (2011) Cyanobacteria and microalgae: a positive prospect for biofuels. *Biores Technol* 102(22):10163–10172
- Parra-Riofrío G, García-Márquez J, Casas-Arrojo V, Uribe-Tapia E, Abdala-Díaz RT (2020) Antioxidant and cytotoxic effects on tumor cells of exopolysaccharides from *Tetraselmis suecica*

- (Kyllin) Butcher grown under autotrophic and heterotrophic conditions. *Mar Drugs* 18(11):534
- Pawar SB (2016) Process engineering aspects of vertical column photobioreactors for mass production of microalgae. *ChemBioEng Rev* 3(3):101–115
- Radakovits R, Jinkerson RE, Darzins A, Posewitz MC (2010) Genetic engineering of algae for enhanced biofuel production. *Eukaryot Cell* 9(4):486–501
- Raes E, Isdepsky A, Muylaert K, Borowitzka M, Moheimani N (2014) Comparison of growth of *Tetraselmis* in a tubular photobioreactor (Biocoil) and a raceway pond. *J Appl Phycol* 26(1):247–255
- Rajinikanth P, Sankar C, Mishra B (2003) Sodium alginate microspheres of metoprolol tartrate for intranasal systemic delivery: development and evaluation. *Drug Deliv* 10(1):21–28
- Randrianarison G, Ashraf MA (2017) Microalgae: a potential plant for energy production. *Geol Ecol Landsc* 1(2):104–120
- Rayan A, Raiyn J, Falah M (2017) Nature is the best source of anticancer drugs: Indexing natural products for their anticancer bioactivity. *PLoS ONE* 12(11):e0187925
- Robert SS, Singh SP, Zhou XR, Petrie JR, Blackburn SI, Mansour PM et al (2005) Metabolic engineering of *Arabidopsis* to produce nutritionally important DHA in seed oil. *Funct Plant Biol* 32(6):473–479
- Roy M, Mohanty K (2019) a comprehensive review on microalgal harvesting strategies: current status and future prospects. *Algal Res* 44:101683
- Ryu KH, Lee JY, Heo S, Lee JH (2019) Improved microalgae production by using a heat supplied open raceway pond. *Ind Eng Chem Res* 58(21):9099–9108
- Salem AA, Ismail AF (2021) Protective impact of *Spirulina platensis* against γ -irradiation and thioacetamide-induced nephrotoxicity in rats mediated by regulation of micro-RNA 1 and micro-RNA 146a. *Toxicol Res* 10(3):453–466
- Sami N, Ahmad R, Fatma T (2021) Exploring algae and cyanobacteria as a promising natural source of antiviral drug against SARS-CoV-2. *Biomed J* 44(1):54–62
- Sasirekha R, Sheena TS, Deepika MS, Santhanam P, Townley HE, Jeganathan K et al (2019) Surface engineered *Amphora* subtropicala frustules using chitosan as a drug delivery platform for anticancer therapy. *Mater Sci Eng C* 94:56–64
- Sayegh F, Elazzazy A, Bellou S, Moustogianni A, Elkady AI, Baeshen MN et al (2016) Production of polyunsaturated single cell oils possessing antimicrobial and anticancer properties. *Ann Microbiol* 66(3):937–948
- Shukla S, Jain D, Verma K (2014) Formulation and in vitro characterization of alginate microspheres loaded with diloxanide furoate for colon-specific drug delivery. *Asian J Pharm (AJP)* 4(4):199–204
- Sigamani S, Ramamurthy D, Natarajan H (2016) A review on potential biotechnological applications of microalgae. *J Appl Pharm Sci* 6:179–184
- Singh R, Sharma S (2012) Development of suitable photobioreactor for algae production—a review. *Renew Sustain Energy Rev* 16(4):2347–2353
- Singh S, Dwivedi V, Sanyal D, Dasgupta S (2020) Therapeutic and nutritional potential of *Spirulina* in combating COVID-19 infection. *AJIR Prints* 49(1):1–8
- Solanki N (2018) Microspheres an innovative approach in drug delivery system. *MOJ Bioequiv Availab* 5(1):56–58
- Talero E, García-Mauriño S, Ávila-Román J, Rodríguez-Luna A, Alcaide A, Motilva V (2015) Bioactive compounds isolated from microalgae in chronic inflammation and cancer. *Mar Drugs* 13(10):6152–6209
- Talukdar J, Dasgupta S, Nagle V, Bhadra B (2020) COVID-19: Potential of microalgae derived natural astaxanthin as adjunctive supplement in alleviating cytokine storm. Available at SSRN 1–17
- Tan XB, Lam MK, Uemura Y, Lim JW, Wong CY, Lee KT (2018) Cultivation of microalgae for biodiesel production: a review on upstream and downstream processing. *Chin J Chem Eng* 26(1):17–30
- Tang Y, Liu J, Zhang D, Xu Z, Ji J, Wen C (2020) Cytokine storm in COVID-19: the current evidence and treatment strategies. *Front Immunol* 11:1708
- Trucillo P (2021) Drug carriers: classification, administration, release profiles, and industrial approach. *Processes* 9(3):470
- Ugwu C, Aoyagi H, Uchiyama H (2008) Photobioreactors for mass cultivation of algae. *Biores Technol* 99(10):4021–4028
- Ullmann J, Grimm D (2021) Algae and their potential for a future bioeconomy, landless food production, and the socio-economic impact of an algae industry. *Org Agric* 11(2):261–267
- Ulmann L, Mimouni V, Blanckaert V, Pasquet V, Schoefs B, Chénais B (2013) The polyunsaturated fatty acids from microalgae as potential sources for health and disease. Nova Science Publishers, New York
- Umemura K, Yanase K, Suzuki M, Okutani K, Yamori T, Andoh T (2003) Inhibition of DNA topoisomerases I and II, and growth inhibition of human cancer cell lines by a marine microalgal polysaccharide. *Biochem Pharmacol* 66(3):481–487
- Uthappa U, Sriram G, Brahmkhatri V, Kigga M, Jung HY, Altalhi T et al (2018) Xerogel modified diatomaceous earth micro-particles for controlled drug release studies. *New J Chem* 42(14):11964–11971
- Uyen NTT, Hamid ZAA, Tram NXT, Ahmad N (2020) Fabrication of alginate microspheres for drug delivery: a review. *Int J Biol Macromol* 153:1035–1046
- Vasumathi KK, Premalatha M, Subramanian P (2012) Parameters influencing the design of photobioreactor for the growth of microalgae. *Renew Sustain Energy Rev* 16(7):5443–5450
- Vilakazi H, Olasehinde TA, Olaniran AO (2021) Chemical characterization, antiproliferative and antioxidant activities of polyunsaturated fatty acid-rich extracts from *Chlorella* sp. S14. *Molecules* 26(14):4109
- Villanueva VD, Font J, Schwartz T, Romani AM (2011) Biofilm formation at warming temperature: acceleration of microbial colonization and microbial interactive effects. *Biofouling* 27(1):59–71
- Wang Z, Zhang X (2016) Inhibitory effects of small molecular peptides from *Spirulina* (*Arthrospira*) *platensis* on cancer cell growth. *Food Funct* 7(2):781–788
- Wang H, Ji C, Bi S, Zhou P, Chen L, Liu T (2014) Joint production of biodiesel and bioethanol from filamentous oleaginous microalgae *Tribonema* sp. *Biores Technol* 172:169–173
- Wong JWC, Rajeshwar D, Tyagi A (2017) Current developments in biotechnology and bioengineering. Elsevier, Amsterdam, pp 693–717
- Wrede D, Taha M, Miranda AF, Kadali K, Stevenson T, Ball AS, Mouradov A (2014) Co-cultivation of fungal and microalgal cells as an efficient system for harvesting microalgal cells, lipid production and wastewater treatment. *PLoS ONE* 9(11):e113497
- Xie P, Horio F, Fujii I, Zhao J, Shinohara M, Matsukura M (2018) A novel polysaccharide derived from algae extract inhibits cancer progression via JNK, not via the p38 MAPK signaling pathway. *Int J Oncol* 52(5):1380–1390
- Xu L, Weathers PJ, Xiong XR, Liu CZ (2009) Microalgal bioreactors: challenges and opportunities. *Eng Life Sci* 9(3):178–189
- Yan X, Xu J, Zhou Q, Jin D, Vong CI, Feng Q et al (2019) Molecular cargo delivery using multicellular magnetic microswimmers. *Appl Mater Today* 15:242–251

- Yen HW, Hu IC, Chen CY, Nagarajan D, Chang JS (2019) Design of photobioreactors for algal cultivation biofuels from algae. Elsevier, Amsterdam, pp 225–256
- Zamani H, Rastegari B, Varamini M (2019) Antioxidant and anti-cancer activity of *Dunaliella salina* extract and oral drug delivery potential via nano-based formulations of gum Arabic coated magnetite nanoparticles. *J Drug Deliv Sci Technol* 54:101278
- Zhong D, Zhang D, Xie T, Zhou M (2020) Biodegradable microalgae-based carriers for targeted delivery and imaging-guided therapy toward lung metastasis of breast cancer. *Small* 16(20):2000819
- Zumla A, Chan JF, Azhar EI, Hui DS, Yuen KY (2016) Coronaviruses—drug discovery and therapeutic options. *Nat Rev Drug Discov* 15(5):327–347

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