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Microalgal bioactive metabolites as promising implements in nutraceuticals and pharmaceuticals: inspiring therapy for health benefits

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Abstract The rapid increase in global population and shrinkage of agricultural land necessitates the use of cost-effective renewable sources as alternative to excessive resource-demanding agricultural crops. Microalgae seem to be a potential substitute as it rapidly produces large biomass that can serve as a good source of various functional ingredients that are not produced/synthesized inside the human body and high-value nonessential bioactive compounds. Microalgae-derived bioactive metabolites possess various bioactivities including antioxidant, anti-inflammatory, antimicrobial, anti-carcinogenic, anti-hypertensive, anti-lipidemic, and anti-diabetic activities, thereof rapidly elevating their demand as interesting option in pharmaceuticals, nutraceuticals and functional foods industries for developing new products. However, their utilization in these sectors has been limited. This demands more research to explore the functionality of microalgae derived functional ingredients. Therefore, in this review, we intended to furnish up-to-date knowledge on prospects of bioactive metabolites from microalgae, their bioactivities related to health, the process of microalgae cultivation and harvesting, extraction and purification of bioactive metabolites, role as dietary supplements or functional food, their commercial applications in nutritional and pharmaceutical industries and the challenges in this area of research.

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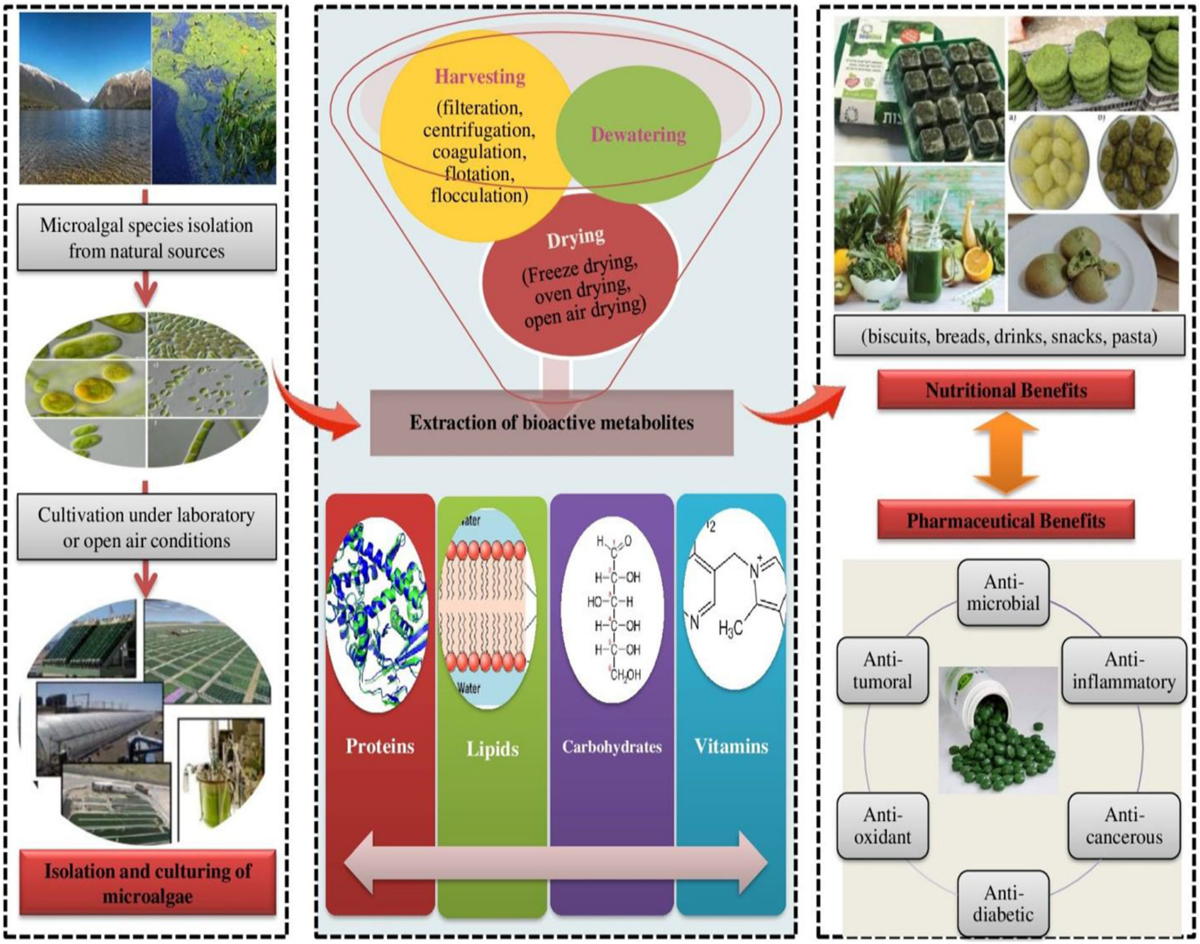
Graphical abstract



Keywords Bioactive metabolites · Bioactivities · Functional food · Microalgae · Nutraceutical · Pharmaceutical

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Introduction

The global population is rapidly growing and is predictable to reach 9.5 billion by 2050 leading to pressing concerns about issues like food security and malnutrition. To meet the global necessities, food production requires to be increased by two-fold (UNDES 2017; Kiran and Mohan 2021). More than 10.8% of the total world population does not have enough food to sustain them (FAO 2020). As food security is a major concern in the present era due to the exponential population spurt. This will put pressure on the agriculture system and will demand the escalation of agricultural area, rotation of crops and technologies to increase the yield. All these practices will further escalate the already existing problems like the degradation of soil, deforestation, and biodiversity loss (Sreeharsha and Mohan 2021). In this perspective, an alternate source is required which is easily producible, cost-effective and can provide quick and bulk production of valuable bioactive metabolites of nutrients, especially for low-income populations. However, microalgae seem to be one such potential/feasible alternative source as mankind uses them for ages (Sudhaker et al. 2019; Wang et al. 2021).

Microalgae are amazing organisms as they can grow in any place where humidity and light are available and can often survive in extreme environments (Srimongkol et al. 2022). The unique photosynthetic capability of microalgae allows them to efficiently produce high-value compounds because of the more efficient sunlight's utilization in comparison to higher plants (Bhuvana et al. 2019). The protein content produced by microalgae is greater than traditional sources of protein like meat (43% DW protein), yeast (39% DW protein), soy (37% DW protein), dried skimmed milk (36% DW protein) and peanuts (26%) (Soto-Sierra et al. 2018; Janssen et al. 2022) and extraction of microalgae derived proteins requires 100 times less water than the extraction of animal proteins (Koyande et al. 2019). Microalgae proteins have additional benefits such as low allergenicity and high protein quality compared to other plant proteins. Microalgae can also be grown to produce valuable bioactive compounds making them a good alternative to chemical synthesis. Furthermore, microalgae can be cultured in various physicochemical and environmental conditions like brackish or marine water and non-arable land hence, do not compete with the resources required for additional agricultural production of food crops (Paliwal et al. 2017; Mutanda et al. 2020). Apart from this, microalgae together with bacteria supply energy at all trophic stages and produce approximately 50% of oxygen, thus acting as the backbone of the food web. Moreover, the microalgal bioactive compounds are useful for humans as these are not produced/synthesized inside the human body.

Bioactive nutrients (bioproducts) are physiologically active substances with functional properties that can potentially improve health. These include enzymes, vitamins, sterols, pigments, fatty acids, proteins and alkaloids (Pai et al. 2022). The growth of microalgae in extreme environmental and phototrophic conditions has made it develop a protective system in the form of bioactive compounds like antioxidants, chlorophylls, carotenes and phycobiliproteins (Martínez-Ruiz et al. 2022). Bioactive compounds of microalgae origin like β-carotene, phycocyanin, linolenic acid, oleic acid, vitamin E, cobalamin (vitamin B12), cyanovirin, lutein, and zeaxanthin have exhibited antimicrobial, antienzymatic, antibiotic actions, anticarcinogenic, anti-inflammatory, photoprotective, anti-ageing, antioxidant and hypocholesterolemic properties (Sathasivam et al. 2019; Coulombier et al. 2021) and thus the potential to reduce and prevent diseases. They could serve as starting material for both micro- and macronutrients for the food, feed, pharmaceutical, medical and cosmetic industry.

The global production of algae' dry biomass is assessed to be 7 million tons having a market value of approximately 3.8–5.5 billion USD per annum (Brasil et al. 2017). The compound annual growth rate (CAGR) of *Spirulina* market is calculated to reach 9.4% by 2025 with a present market value of 0.63 billion USD (Koyande et al. 2019). Utilization of microalgal biomass for producing nutraceuticals, pharmaceuticals, and functional foods is quickly elevating as microalgae-derived bioactive compounds are interesting options for the nutraceutical, food and pharmaceutical industries in developing new products. However, selecting the potential microalgal isolate for a particular function like nutraceuticals and pharmaceuticals is extremely important as there is a huge number of microalgal species in nature. Equally important is the production/cultivation system of microalgae. The intervention of advanced technologies both at the operational and technological levels, are to be adopted to either modify the already existing manufacturing systems or to formulate some new robust systems. This will enhance the microalgae production and the bioactive compounds thereof. Further research is to be carried out with these bioactive compounds and also with already available ones to ascertain and verify their beneficial effects for humans/animals, biological potential in disease prevention/treatment and their fate in the environment. Also, there is a need to search for more new metabolites which are novel and potential candidates for the nutraceutical and pharmaceutical industries.

An attempt has been made in this communication to unravel the potential therapeutic and biological activities of microalgae bioactive compounds. It summarises the process of cultivation (including species differences, and growing conditions) and harvesting as these are the vital steps for production of microalgal-derived bioactive metabolites. Further, it focuses on the extraction and purification of bioactive metabolites. Lastly, this review emphasises the application of microalgal bioactive compounds as food and nutrient supplements. The studies reported here will enhance the current knowledge on microalgae and microalgae-derived bioactive metabolites having the ability to be used as nutraceuticals and pharmaceuticals. Moreover, this will pave the way for using the microalgal biomass for different purposes using the biorefinery concept, thus enhancing the dimensions of microalgal biotechnology.

Microalgal bioactive compounds and their potential biological activities and roles

Microalgae are the source of several valuable bioactive compounds which can be clustered into carbohydrates, proteins, pigments, sterols, polyunsaturated fatty acids (PUFAs), vitamins, minerals alkaloids and some other compounds that are not comprised in these classes. The biochemical composition of various microalgae species is shown in Table 1 and stepwise illustration for production of microalgae-derived valuable bioactive metabolites is shown in Fig. 1.

Microalgae are usually considered as a valuable protein source as many species possess protein upto 70% dry weight and are nutritionally similar to proteins like egg and soybean (Amorim et al. 2020) due to better digestibility and occurrence of essential amino acids. Species of *Spirulina* and *Chlorella* have approximately 60–70% protein (DW basis) with a good balance of essential amino acids required for human nutrition (Bleakley and Hayes 2017; Masten Rutar et al. 2022). The free amino acid profile of *Arthrospira* sp., *Haematococcus pluvialis, Acutodesmus acuminatus, Skeletonema costatum,* and *Botryococcus braunii* were examined using reverse phase HPLC and it was found that *Arthrospira* sp. contained the most free amino acids (316.1 ± 0.11 mg AA/100 g DW) while *Haematococcus pluvialis* contained the least amount of free amino acids (38.8 ± 0.15 mg AA/100 g DW) (Araya et al. 2021). Whole-cell protein is the utmost microalgae-based bioproduct utilized for human consumption as it possesses a high amount of protein per dry weight (Barka and Blecker 2016). In comparison to the extracted protein, cell wall and membranes shield the whole-cell protein making it slightly prone to severe pH changes, reducing functionality due to denaturation and aggregation. The production and evaluation of protein concentrates have been reported from numerous microalgal species, including *Arthrospira* sp. (Bleakley and Hayes 2017), *Chlorella* sp. (Alavijeh et al. 2020), *Scendenemus* sp. (Akaberi et al. 2019) and *Nannochloropsis* sp. (Gong et al. 2020). Protein hydrolysates obtained after enzymatic hydrolysis of extracted protein showed better biological value and certain bioactivities including antioxidative (Barkia et al. 2020). Protein hydrolysates of C*hlorella sorokiniana* were produced enzymatically using pepsin, thermolysin, and bromelain, and the peptide fraction (< 5 kDa) generated by pepsin depicted maximum angiotensin-converting enzyme (ACE)-inhibitory activity (34.29% ± 3.45%) and DPPH radical scavenging activity (48.86% ± 1.95%), while peptide fraction (< 10 kDa) generated by thermolysin showed high reducing power as measured by Tejano et al. (2019). Bioactive peptides produced from C*hlorella vulgaris* and *Spirulina* are classified as multifunctional peptides as they display more than one biological activity such as anti-inflammatory, antioxidant and anti-hyperlipidemic and can well modify specific biochemical or physiological process by affecting diverse targets (Li et al. 2019). Several microalgae-derived peptides are commercialized as functional foods, mainly in Japan (Andrade et al. 2018). A soluble fraction of functional proteins for food applications were produced from *Tetraselmis suecica* (50.4% DW) by using a single controlled beadmilling extraction method and the resulting protein extract had with superior surface activities and surface behavior (Garcia et al. 2018). Bertsch et al (2021) reported that emulsions formed from microalgae-derived proteins has low isoelectric pH, superior resistance and less pH dependency, subsequentl more interfacially stable in comparison to plants or animals derived.

Microalgae produce fatty acids and exotic acyl lipids which do not occur usually in terrestrial plants. Initially, the key goal of microalgal lipids research was biodiesel production but these lipids can also be used as alternative nutritional sources or as nutraceuticals (Udayan et al. 2022). The lipids'concentration in some

Table 1 Composition of dry biomass of different microalgae species

Microalgae species	Composition (%dry matter)			References
	Proteins	Lipids	Carbohydrates	
Anabena cylindrica	43–56	4–7	25–30	Becker (2004)
Aphanizomenon flos-aquae	62	3	23	Christaki et al. (2011)
Botryococcus braunii	39–40	25–34	19–31	Tibbetts et al. (2015)
Chaetoceros calcitrans	40	23	37	Velasco et al. (2016)
Chaetoceros gracilis	12	7.2	4.7	Brown (1991)
Chaetoceros muelleri	59	31	10	Velasco et al. (2016)
Chlamydomonas rheinhardii	48	21	17	Spolaore et al. (2006)
Chlamydomonas reinhardtii	48	21	17	Becker (2007)
Chlorella vulgaris	51–58	14–22	12–17	Mata et al. (2010)
Chlorella pyrenoidosa	57	2	26	Chisti (2007)
Dunaliella primolecta	12	–	–	Slocombe et al. (2013)
Dunaliela salina	57	6	32	Sousa et al. (2008)
Dunaliella sp.	34.17	14.36	14.57	Kent et al. (2015)
Dunaliella tertiolecta	11	–	–	Barbarino et al. (2005)
Euglena gracilis	39–61	22–38	14–18	Sousa et al. (2008)
Isochrysis galbana	50–56	12–14	10–17	da Silva and Aranda (2013)
Nannochloropsis sp.	30	22	10	Kent et al. (2015)
Nannochloropsis granulata	18–34	24–28	27–36	Tibbetts et al. (2015)
Nitzschia closterium	26	13	9.8	Brown (1991)
Phaeodactylum tricornutum	34.8	16.1	16.8	Tibbetts et al. (2015)
Pavlova sp.	24–29	9–14	6–9	Becker (2007)
Porphyridium cruentum	28–39	9–14	40–57	Becker (2007)
Prymnesium parvum	28–45	22–38	25–33	Ricketts (1966)
Scenedesmus obliquus	50–56	12–14	10–17	Cai et al. (2013)
Scenedesmus dimorphus	8–18	16–40	21–52	Kent et al. (2015)
Scenedesmus quadricauda	47	1.9	21–52	Bruton (2009)
Schizochytrium sp.	–	50–77	–	Chisti (2007)
Skeletonema costatum	25	10	4.6	Brown (1991)
Spirogyra sp.	6–20	11–21	33–64	Bruton (2009)
Spirulina maxima	60–71	6–7	13–16	Becker (2007)
Spirulina platensis	46–63	4–9	8–14	Sousa et al. (2008)
Synechococcus sp.	63	11	15	Becker (2007)
Tetraselmis chuii	31–46	25	12	Tibbetts et al. (2015)
Tetraselmis maculata	52	3	15	Schwenzfeier et al. (2011)
Thalassiosira pseudonana	34	19	8.8	Brown (1991)

microalgae species can range from 20 to 70% of the dried biomass (Chowdhury and Loganathan 2019). However, lipids production is dependent on microalgal species or types, cultivation conditions, and availability of nutrients, temperature, light, salinity, and pH (Morales et al. 2021). Microalgal-lipids are mainly composed of polar lipids (phospholipids and galactolipids) and neutral lipids (acylglycerols, free fatty acids, and carotenoids). During the exponential growth phase, microalgae are mostly rich in polar lipids, while triacylglycerols are accumulated under stress conditions when nutrients are restricted which is characteristically in the stationary phase. Neutral lipids are the major lipid components constituting

20–80% of dry weight in several marine microalgal species such as *Pavlova lutheri*, *Crypthecodinium cohnii*, *Nannochloropsis* sp., *Scenedesmus* sp. (Ratledge et al. 2001; Guedes et al. 2010; Ma et al. 2016; Chen et al. 2018). These lipids are rich in essential fatty acid and high-value long-chain polyunsaturated fatty acids (PUFAs) such α-linolenic acid, docosahexaenoic acid, eicosapentaenoic acid and arachidonic acid (Kothri et al. 2020). Oxylipins, oxygenated derivatives of PUFAs such as 11-hydroxyhexadeca-4,7,9,13-tetraenoic acid, 8-hydroxyhexadeca-4,6,10,13-tetraenoic acid, 13-hydroxyoctadeca-5,9,11,15-tetraenoic acid and polyunsaturated hydroxy acids were also isolated from some species of microalgae such as *Chlamydomonas debaryana* and *Nannochloropsis gaditana*. Sterols are a commercial product produced from microalgae *Chlorella* sp., *Dunaliella* sp., *Nannochloropsis salina* and *Nostoc carneum* (Fernandes and Cordeiro 2021). It has been estimated that microalgae could yield 678–6035 kg $ha^{-1}y^{-1}$ of phytosterol which is higher than the amount produced from rapeseed plants (Randhir et al. 2020).

Microalgae are rich in carbohydrates comprising a combination of mono-, oligo- and polysaccharides. Generally, carbohydrates and starch constitute nearly 20% and 10% (DW) of microalgal biomass, respectively. In contrast, content varies from species to species like *Porphyridium cruentum* (40–57%) and *Spirogyra* (33–64%) are higher in carbohydrates than most other microalge (Priyadarshani and Rath 2012). Carbohydrates can be glucose, starch, attached to lipids or proteins as glycolipids and glycoproteins, and a variety of complex polysaccharides depending upon the type of microalgal species. Water-soluble polysaccharides isolated from *Nannochloropsis oculata* were rich in (β1 → 3, β1 → 4)-glucans, (α1 → 3, α1 → 4)-mannans, and anionic sulphated heterorhamnans, and possess immuno-stimulatory properties (Pandeirada et al. 2019). A polysaccharide extracted from *Chlorella pyrenoidosa* showed amelioration in disorders related to lipid metabolism in hyperlipidemia rats (Wan et al. 2019). Three polysaccharide fractions of non-sulphated heteropolysaccharides obtained from a hot water extract of *Parachlorella kessleri* HY1 biomass and possess immunoactive properties on normal and melanoma immune cells in vitro conditions (Sushytskyi et al. 2020). From a nutritional perspective, microalgae also contain dietary fibers ranging from 36 to 60% of dry weight and are good for health (Peñalver et al. 2020). Recently, Guo et al. (2021) verified that high molecular weight polysaccharides obtained from *Chlorella pyrenoidosa* (CPS) and *Spirulina platensis* (SPS) decreased obesity in high fat induced obese mice (C57BL/6) by altering lipolysis or lipogenesis in liver and protects from imbalance of energy, systemic inflammation, fat accumulation in liver and dyslipidemia. CPS and SPS are heteropolysaccharides consisting of two segments of average molecular massese of (0.68×10^3 kDa and 2.98×10^3 kDa) and (0.58×10^3 kDa and 6.98×10^3 kDa), respectively.

Several micro-nutrients such as vitamins and minerals are also found in microroalgae (Sandgruber et al. 2021). Vitamins are vital biological micronutrients, which cannot be synthesized by organisms in appropriate amounts and thus must be acquired from the diet. *Dunaliella tertiolecta, Tetraselmis suecica, Chlorella* and *Spirulina* are able to synthesize vitamin B complex, E, and C (Del Mondo et al. 2020). Edelmann et al. (2019) examine the riboflavin, B12, folate, and niacin content in whole extract powders of microalgae and reported that vitamin B2 and B3 content ranged from 21 to 41 µg/g and 0.13–0.28 mg/g, respectively, in *Chlorella* sp., *Spirulina* and *Nannochloropsis gaditana*.

In recent years, several researchers have demonstrated in literature that bioactive compounds isolated from various microalgae species possess several pharmaceutical applications like anti-inflammatory, antimicrobial, and antioxidant activities and have the capability to improve health and lessen the risk of degenerative diseases (Sigamani et al. 2016; Bule et al. 2018; Kusmayadi et al. 2021). A detailed description of therapeutic roles possessed by microalgae-derived bioactive metabolites has been elaborated below. The health beneficial role and mode of action of various bioactive compounds have been explained in Table 2, and Fig. 2 illustrated the biochemical aspects of their health benefits.

Antioxidant activity

In usual physiological and environmental conditions, homeostasis is maintained between producing and degrading reactive oxygen species (ROS) through an antioxidant defense system comprising various antioxidants and antioxidative enzymes. However,

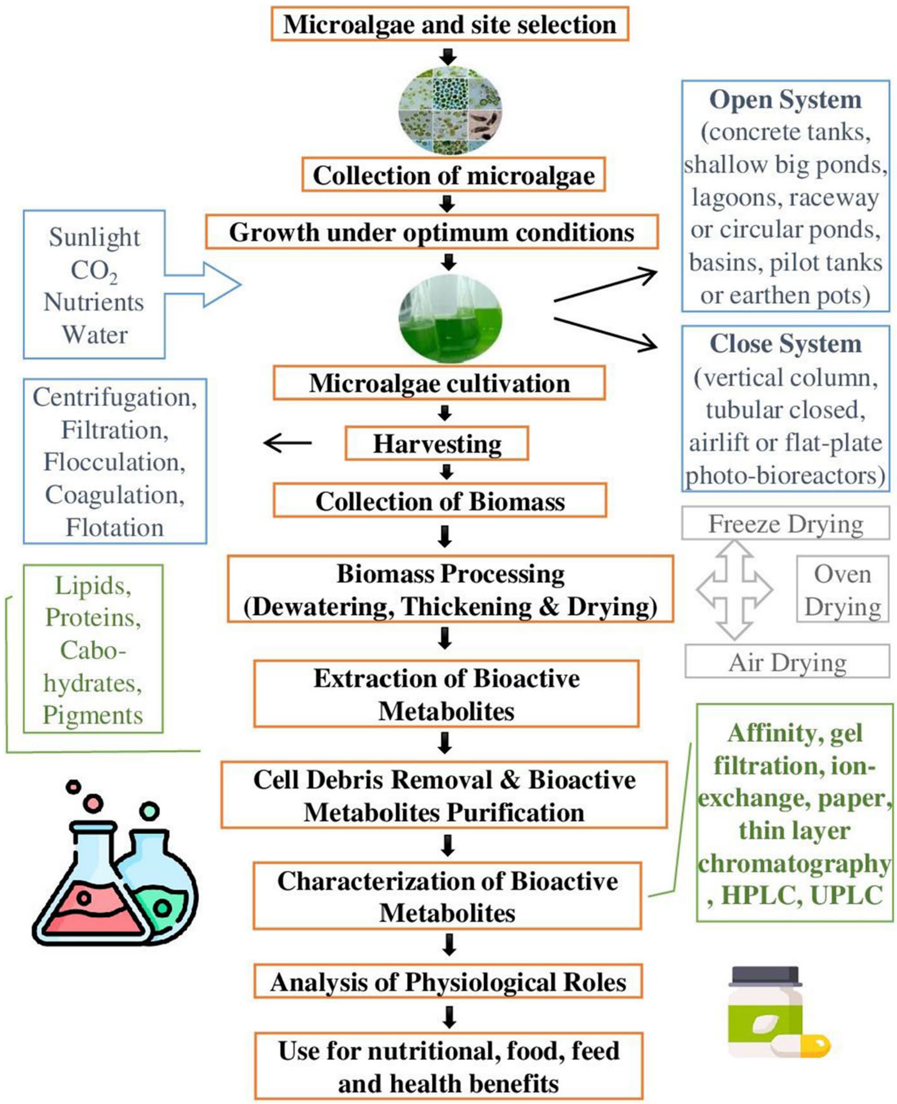

Fig. 1 The stepwise illustration for production of microalgae-derived valuable bioactive metabolites

disturbances in the favorable circumstances or by factors such as exposure to X-rays, gamma rays or UV rays can overwhelm the antioxidant defense system resulting in an imbalance that generates oxidative stress. Uncertainty in ROS homeostasis can lead to the activation of free radicals' chain reactions ultimately disturbing or damaging cell membranes, cells, tissues, organelles and generating potentially toxic compounds that cause various diseases initiation such as cancer, kidney failure, arthritis, Alzheimer's, hastened aging and Parkinson's (García-Sánchez et al. 2020). Microalgae produce a variety of antioxidant secondary metabolites that could have potential health benefits. For example, *Wilmottia murravi* and *Neochloris oleobundans* showed the high content of phenolic acids (> 20 mg gallic acid eq. g^{-1}), *Phormidium* sp. has a high amount of ascorbic acid content (12–14 µmol eq. g^{-1}), and *Anisancylus obliquus* has highest content of lipid-soluble compounds (Almendinger et al. 2021). Bioactive compounds having antioxidant activities, such as dimethylsulfoniopropionate isolated from *Prymnesium simplex* (Thariath et al. 2019) and mycosporine amino acids isolated from *Porphyra* (Figueroa 2021) are effective biochemical agents to block UV radiations. *Porphyra haitanensis*, *Chlorella vulgaris* and *Scenedesmus*

Table 2 The health benefits and mode of action of various microalgae derived bioactive metabolites

Health beneficial application	Microalgae	Bioactive compound	Target/mode of action	References
Antioxidant activity	*Chlorella vulgaris*	Phenolics and flavanoids	Radicle scavenging activity	Mtaki et al. (2020)
	Dunaliella salina	β-carotene	Inhibits ROS production	Fujitani et al. (2001)
	Haematococcus pluvialis	Astaxanthin	Antioxidant activity	Ciccone et al. (2013)
	Scenedesmus sp.	Lutein	Maintain homeostasis	Sánchez et al. (2008)
	Porphyridium sp.	Sulfated polysaccharides	Inhibits ROS formation	Huheihel et al. (2001)
	Chlorella vulgaris	Phenolics	Maintain homeostasis	Goiris et al. (2012)
	Nannochloropsis oculata	Peptides	Antioxidant activity	Samarakoon et al. (2013)
	Spirulina maxima	Phenolic compounds	Radicle scavenging activity	El-Baky et al. (2009)
	Nannochloropsis sp.	Phenolics	Radicle scavenging activity	Abd El-Baky et al. (2010)
	Gymnodinium mikimotoi	Monogalactosyl diacylglycerol	Inhibits ROS production	Meirless et al. (2003)
	Stephanodiscus sp.	Digalactosyl diacylglycerol	Enhanced cell differentiation	Hossain et al. (2005); Maeda et al. (2009)
	Scytosiphon lomentaria	Protein extract	Inhibits ROS production	Ahn et al. (2004)
Anti-inflammatory activity	*Spirulina platensis*	Phycocyanin	Suppresses IL-6, 8 and increases TGF-β1 production, inhibits COX-2 expression	Hao et al. (2018); Yoshimoto et al. (2019)
	Chlorella vulgaris	Protein hydrolysates	Modulates cytokines	Morris et al. (2007)
	Chlorella vulgaris	Sterols	Anti-inflammatory activity	Lopes et al. (2013)
	Anabaena cylindrical	Vitamin K	Prevent from toxic agents/pollutants	Tarento et al. (2018)
	Chlorococcum sp., & *Scenedesmus obliquus*	Linolenic acid	Anti-inflammatory activities and reduces acne	Day et al. (2009)
	Chlorella vulgaris & *Chlorococcum* sp.	Canthaxanthin	Anti-inflammatory actions	Charles et al. (2019)
	Chlorella zofigiensis & *Dunaliella salina*	Astaxanthin	Anti-inflammatory properties	Borowitzka (2013)
	Chlorella sp., *Scenedesmus* sp., & *Spirulina* sp.	Phycobiliproteins, hormone-like bioactive peptides	Inhibits inflammation	Gong et al. (2011)
	Nannochloropsis oculata	Docosapentaenoic acid (DPA)	Inhibits pro-inflammatory prostaglandin E2, NO, TNF-a, IL-6	Nauroth et al. (2010)
	Chlorella stigmatophora	Sulfated polysaccharide	Immunosuppressive activity	Matsui et al. (2003)

Table 2 continued

Health beneficial application	Microalgae	Bioactive compound	Target/mode of action	References
Antibacterial activity	*Skeletonema costatum*	Unsaturated, saturated long chain fatty acids	Acts on *Vibrio* sp.	Naviner et al. (1999)
	Euglena viridis	Organic extracts	Acts on *Pseudomonas*, *Aeromonas*, *Edwardsiella*, *Vibrio*, and *Escherchia coli*	Das et al. (2005)
	Dictyosphaerium pulchellum	Methanolic extracts	–	Bhadury and Wright (2004)
	Chlorococcum sp.	Aqueous extracts	–	Bhadury and Wright (2004)
	Chlorella vulgaris	Methanolic and hexanolic extracts	Acts on *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Bacillus subtilis*, *Escherchia coli*, and *Salmonella typhi*	Ghasemi et al. (2007)
	Chlorella pyrenoidosa	Saturated and unsaturated fatty acids	Acts on *Propionibacterium acnes*	Sibi (2015)
	Chlorella humicola	Pigments (carotenoid, chlorophyll)	Acts on *Bacillus subtilis*, *Staphylococcus aureus*, *Escherchia coli*, *Pseudomonas aeruginosa*, *Salmonella typhimurium*, *Klebsiella pneumonia*, and *Vibrio cholera*	Bhagavathy et al. (2011)
	Scenedesmus obliquus	Long chain fatty acids	Acts on *Staphylococcus aureus*, *Escherchia coli*, *Pseudomonas aeruginosa*, and *Salmonella* sp.	Catarina Guedes et al. (2011)
	Rhodella reticulate	Extracellular sulfated polysaccharides	Acts on *Staphylococcus aureus*, *Streptococcus pyogenes*, *Bacillus cereus*, and *Salmonella typhimurium*	Najdenski et al. (2013)
Antiviral activity	*Navicula directa*	Polysaccharide	Inhibits hyaluronidase	Lee et al. (2006)
	Chlorella autotrophica	Sulfated polysaccharides	Inhibits replication	Fábregas et al. (1999)
	Cochlodinium polykrikoide	Extracellular sulfated polysaccharides	Inhibition of cytopathic effect	Hasui et al. (1995)
	Porphyridium cruentum	Highly sulfated polysaccharide	HSV-1, HSV-2 & Vaccina	Huang et al. (2001); Raposo et al. (2013)
	Navicula directa	Sulfated polysaccharide	HSV-1, HSV-2 & Influenza-A	Lee et al. (2006); Ahmadi et al. (2015)
	Gyrodinium impudicum	p-KG03 exopolysaccharide	Inhibition of cytopathic effect	Yim et al. (2004)
Antifungal activity	*Chlamydomonas reinhardtii*	Methanolic extracts	Acts on *Candida kefir*, *Aspergillus niger*, and *Aspergillus fumigatus*	Ghasemi et al. (2007)
	Amphidinium sp.	Karatungiols	Acts on *Aspergillus niger*, and *Trichomonas foetus*	Washida et al. (2006)
	Prorocentrum lima	Polyether compounds	–	Bhadury and Wright (2004)
	Haematococcus pluvialis	Butanoic acid and methyl lactate	Acts on *Candida albicans*	Santoyo et al. (2009)

Table 2 continued

Health beneficial application	Microalgae	Bioactive compound	Target/mode of action	References
Anti-cancerous activity	*Botryococcus braunii* & *Microcystis aeruginosa*	Lipids	Cytotoxic activity against prostate, SHSY-5Y neuroblastoma and AGS gastric adenocarcinoma cell line	Inan et al. (2021)
	Chlorella pyrenoidosa	Polypeptide CPAP	Induces apoptosis	Wang et al. (2013)
	Chlorella vulgaris	Polypeptide	Antiproliferative activity and arrests cell cycle at G1 phase	Sheih et al. (2010)
		Sterols	Stabilizes phospholipid bilayers	Luo et al. (2015)
	Pavlova lutheria	Phytosterols	Inhibits colon cancer development	Ahmed et al. (2015)
	Chaetoceros calcitrans & *Dunaliella tertiolecta*	Vitamin D	Inhibits prostrate cell cancer growth	Giammanco et al. (2015)
	Chlorella pyrenoidosa	Mycosporinelike amino acid (MAA)	Inhibits cancerous cell growth	Kim and Kang (2011)
	Chlorella stigmatophora	Polysaccharides	Tumoricidal activity	De Morais et al. (2015)
	Chlorella sp.	Chlorophyll	Cytotoxic activity towards tumoral cells	Mishra et al. (2011); Khanra et al. (2018)
	Spirulina limacinum, Spirulina bacillaris & *Chlorella cohnii*	Phenolics	Cytotoxic special effects against human hepatocellular liver carcinoma cells	Gürlek et al. (2019)
	Scenedesmus sp., *Chlorella pyrenoidosa* & *Chlorococcum* sp.	Exopolysaccharides	Inhibits human colon cancer cell lines proliferation	Zhang et al. (2019)
	Dunaliella tertiolecta	Violaxanthin	Antineoplastic effects	Abida et al. (2013)
	Isochrysis galbana	(1 → 3, 1 → 6)-β-D-glucan sulfated exopolysaccharide	Cytotoxic against lymphoma cells	Sadovskaya et al. (2014)
	Arthrospira platensis	Extracellular polysaccharide	Cytotoxic against kidney and colon cancer cell line	Challouf et al. (2011)
Anti-hypertensive & anti-hyperlipidemic activity	*Nannochloropsis oculata*	Protein extract	Inhibits angiotensin I-converting enzyme	Samarakoon et al. (2013)
	Chlorella vulgaris	Polypeptide	Inhibits angiotensin I-converting enzyme	Sheih et al. (2009)
	Nanochloropsis sp.	Sterols	Reduces blood cholesterol levels in hyper and normocholesterolemic	Lopes et al. (2013)
	Chlorella, Spirulina & *Pavlova*	Vitamin B	Reduces cholesterol	Becker et al. (2004)
	Chlorella sp. & *Dunaliella* sp.	Glycoprotein	Inhibits angiotensin I activities and reduces LDL-cholesterol	Caporgno and Mathys (2018)

Table 2 continued

Health beneficial application	Microalgae	Bioactive compound	Target/mode of action	References
	Chlorococcum sp., *Dunaliella primolecta* & *Spirulina* sp.	γ-linoleic acid	Reduces blood pressure and prevents from heart diseases	Long et al. (2018); Koller et al. (2014)
	Chlorella vulgaris & *Nannochloropsis* sp.	Eicosapentaenoic acid	Regulates blood pressure, reduces blood clotting and prevents from heart diseases	Chiranjeevi and Venkata Mohan (2016)
	Chlorella sorokiniana & *Chlorococcum* sp.	β-carotene	Declines low-density lipoprotein	Galasso et al. (2019)
	Spirulina platensis & *Chlorella vulgaris*	Protein extracts and hydrolysates	Inhibits activity of angiotensin I-converting enzyme and acetylcholinesterase	Alzahrani (2018)
Anti-diabetic activity	*Porphyridium* sp.	Liquid extract	Inhibits α-glucosidase	Priatni et al. (2021)
	Nannochloropsis sp. & *Pavlova salina*	Polyunsaturated fatty acids	Anti-hyperglycemic, reduces blood glucose	Rohit et al. (2018)
	Dunaliella salina & *Isochrysis* sp.	Fucoxanthin and Zeaxanthin	Suppresses hyperglycaemia, prevents from diabetic diseases	Gong et al. (2016)
	Chlorococcum sp. & *Chlorella fusca*	Lutein	Prevents from diabetic retinopathy	Rasmussen and Johnson (2013); Liu et al. (2017)
	Chlorella vulgaris & *Haematococcus pluvialis*	Astaxanthin	Reduces diabetes	Capelli et al. (2013)
	Cosmospora sp. SF-5060	Aquastatin A	Hypogluycaemic activity	Seo et al. (2009)
	Phaeodactylum tricornutum	Fucoxanthin	Suppresses hyperglycaemia	Peng et al. (2011)

quadricauda derived antioxidant polysaccharides especially sulphated polysaccharides signify a group of valuable compounds with uses in food, medicine, and stabilizers and their therapeutic action mechanism is the activation and alteration of macrophages (Raposo et al. 2013; Khan et al. 2020). The antioxidant capacity of *Auxenochlorella pyrenoidosa*, *Chlorella vulgaris, Messastrum gracile, Desmodesmus subspicatus* and *Parachlorella kessleri* revealed that they contain high ferric reducing antioxidant power. *Auxenochlorella pyrenoidosa* showed highest phenol and flavonoid content, and the remaining four species induced Hsp 70 expression and promote the synthesis of the 70-kDa stress protein in brine shrimp *Artemia* (Tiong et al. 2020).

Anti-inflammatory activity

Inflammation is one of the most vital innate defense mechanisms whose long lasting effect can cause dysfunctions and abnormalities in metabolic pathways leading to various types of renal, cardiovascular, neurodegenerative, cancerous and skin diseases. Microalgae based bioactive metabolites such as pigments, modified polysaccharides, lipids, unsaturated fatty acids, vitamins, phenolic compounds and terpenoids can have anti-inflammatory properties when used as dietary supplements (Montero-Lobato et al. 2018; Choo et al. 2020). Phycocyanin when supplied to rats suffering from autoimmune disease encephalomyelitis caused downregulation of IFN-γ and IL-6 expressions (Cervantes-Llanos et al. 2018) and many cyanobacterias and microalgal species including *Spirulina platensis* are enriched with

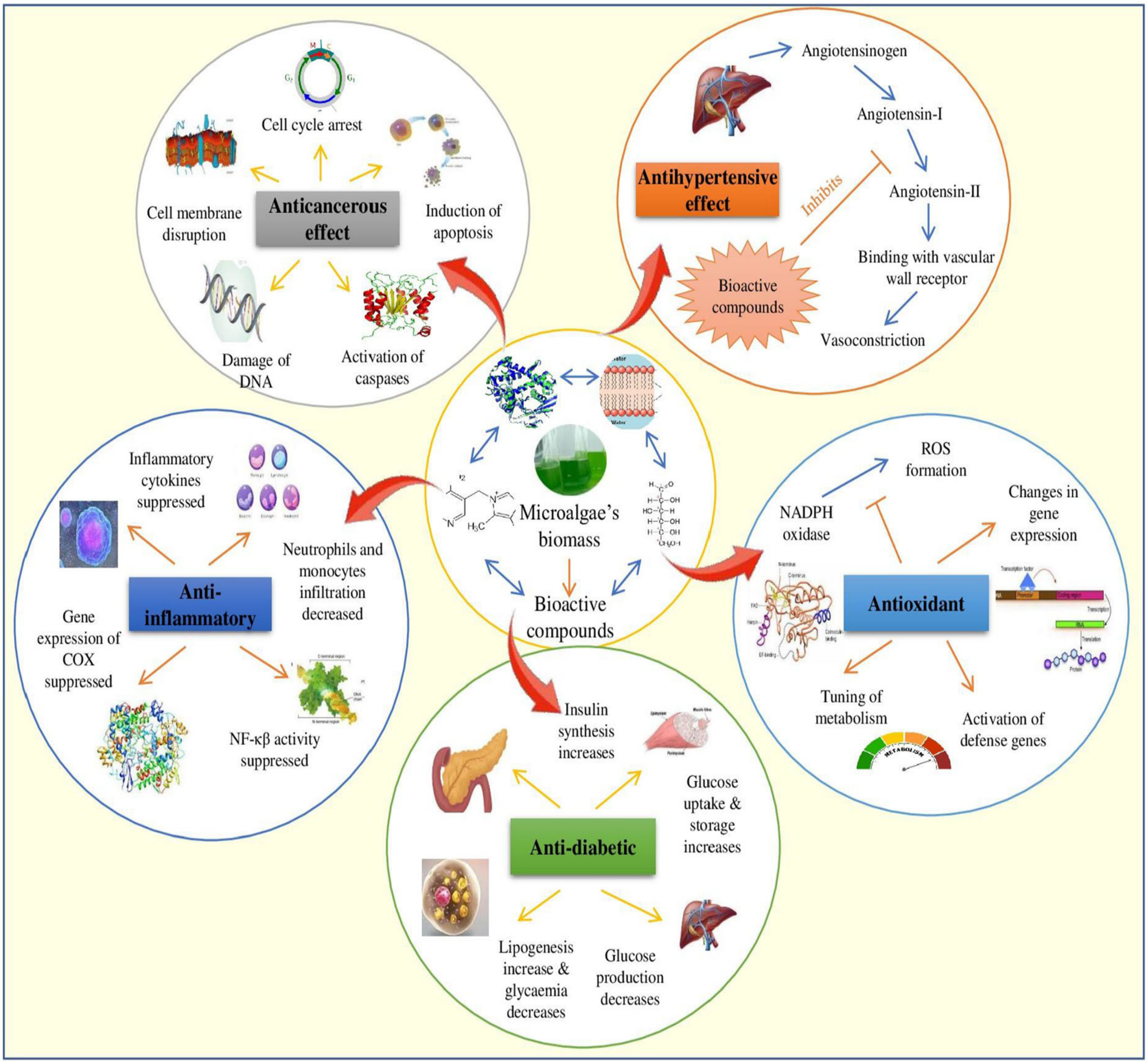

Fig. 2 Health benefits of microalgae based bioactive compounds

phyacocyanin (Pinto et al. 2022). Astaxanthin produced from *Haematococcus* inhibited production of nitrous oxide and prostaglandin E2, decreased the levels of proinflammatory cytokines (TNF-α, IL-1β, and IL-6), improved phagocytes function, diminished lipids and proteins' oxidative damage and reduced NF-κB expression (Speranza et al. 2012; Mularczyk et al. 2020; Wang and Qi 2022). When given in dosage of 100 mg/kg and 10 mg/kg it inhibited the lipopolysaccharides' induced inflammation and effect was comparable to prednisolone (anti-inflammatory drug) as reported by Ohgami et al. (2003). Likewise, polysaccharides extracted from *Chlorella stigmatophora* and *Phaeodactylum tricornutum* showed immunosuppressive and immunostimulatory effects, respectively both in vivo and vitro (Guzmán et al. 2003; Yang et al. 2019) The microalgae-based bioactive metabolites can inhibit the inflammation by either downregulating the expression of pro-inflammatory genes, hindering the production of cytokines and eicosanoids, fluctuating the cellular activities, altering the activities of enzymes such as phospholipase A2, cyclooxygenase-2 (COX2), nitric oxide synthase (NOS), or interrupting two or more signaling pathways especially NF-κB and MAPK's pathways which are the mediators of pro-inflammatory molecules formation (Tabarzad et al. 2020).

Antimicrobial activity

In humans, resistance developed against persistent uses of antibiotics led the necessity to find out innovative antimicrobial compounds. It has been reported in the literature that various bioactive compounds synthesized in microalgae such as carbohydrates, lipids, fatty acids, sulfur-containing heterocyclic compounds, terpenoids, phenolic acids and sterols possess antibacterial, antiviral and antifungal properties. Therefore, microalgae can be an inventive basis for antimicrobial compounds production. The first *antibacterial compound* isolated from microalgae is chlorellin in 1940's (Pratt et al. 1944). Short chain fatty acids present in the liquid ethanolic extract of *Haematococcus pluvialis* showed antimicrobial activity against *Escherichia coli* and *Staphylococcus aureus* (Santoyo et al. 2009). Likewise, phenolics present in methanolic extracts of *Chlorella vulgaris* showed antibacterial activity against *E. coli*, *Bacillus* sp., *Klebsiella* sp., and *Pseudomonas* sp. (Syed et al. 2015) and methanolic extracts of *Dunaliella tertiolecta* showed inhibitory activity against *Staphylococcus aureus* and *Porphyridium aeruginosa* (Pane et al. 2015). The extract of Nannochloropsis oceanica, Isochrysis sp. and Thalassiosira weissflogii showed antibacterial effect against *Vibrio harveyi* at 1.0×10^5, 10^6 and 10^7 CFU mL^{-1} concentrations where *N. Oceanica* exhibited largest zone of inhibition (Jusidin et al. 2022). Methanolic extract of *Chlorella* sp. UKM8 showed antibacterial activitiy against Gram-positive and Gram-negative bacteria at 0.312 to 6.25 mg/mL due to the presence of antimicrobial bioactive compounds phenol (18.5%), hexadecanoic acid (18.25%), phytol (14.43%), 9,12- and octadecadienoic acid (13.69%) reported by GC–MS analysis (Shaima et al. 2022). The bioactive compounds showed different mechanisms through which they inhibit bacterial growth including disruption of stability and permeability of phospholipid bilayer, leakage of internal substances, lessening nutrients absorption or inhibition of cellular respiration (Benfield and Henriques 2020).

Antiviral activity is possessed by numerous microalgal species such liquid extracts of *Haematococcus pluvialis* and *Dunaliella salina* showed antiherpetic activity (Santoyo et al. 2012), methanolic liquid extract of *Spirulina* revealed antiviral activity on HSV-1 (Chirasuwan et al. 2009) and α- & β-ionone, neophytadiene, β-cyclocitral and phytol extracted from microalgae have antimicrobial activity (Amaro et al. 2011). *Spirulina* enriched diet showed antiviral effect against HIV, augments sensitivity to insulin, regularize IL-6 and lipoprotein lipase activity. Immulina, a *Spirulina* extract activate improves immunological functions due to presence of Braun-type lipoproteins which trigger, and the immunity system by activating toll-like receptors (Kefayat et al. 2020). The inhibitory effect of microalgae-based bioactive metabolites is due to their interaction with a positive charge present on virus' cell surface, preventing its penetration into the host cell, or they can inhibit viral genome transcription finally obstruct the formation of new virus particles (Reynolds et al. 2021; Pradhan et al. 2022). *Hematococcus pluvialis* is enriched with astaxanthin which can reduce ALI and ARDS, therefore could have probable actions against cytokine storm caused by SARS-CoV-2 either by increase in lymphocytes and subsequently dimininshing alveolus oxidative damage or decreasing cytokine (IL-6) activity (Talukdar et al. 2020; Carbone et al. 2021). To this end, microalgae could be vital agents as the foundation for new vaccines types including SARS-CoV-2.

Despite having antibacterial and antiviral activities, antimicrobials are of great concern contrary to fungi which are pathogenic in nature. The literature has reported that amongst contagious diseases, fungal diseaeses are most deadly and 1.5 million deaths are caused by them annually (Rayens and Norris 2022). Black fungus or mucormycosis being the latest and most dreaded fungal infection highlighting the news these days (Shevade 2021). Microalgae are amongst the efficient challengers of *antifungal agents* due to the high synthesis of bioactive metabolites. Several strains of microalgae procured from freshwater lakes in Turkey showed antifungal role against *Saccharomyces cerevisiae*, *Candida albicans*, *Candida tropicalis*, *Chlorococcus* sp. and *Oscillatoria* sp. (Katircioglu et al. 2006). Liquid extracts of *Chlorella vulgaris* and *Chlorella ellipsoidea* showed antifungal activity against *Aspergillus niger* and *Aspergillus fumigatus* (Ghasemi et al. 2007), methyl lactate and butanoic acid from ethanolic extracts of *Haematococcus pluvialis* had antifungal activity against *Aspergillus niger*

(Santoyo et al. 2009), liquid extract of *Chlorococcum humicola* and supercritical CO_2 extracts from *Dunaliella salina* showed antifungal activity against *Aspergillus niger* and *Candida albicans* (Bhagavathy et al. 2011) and liquid extract of *Heterochlorella luteoviridis* and *Porphyridium purpureum* showed antifungal activity against *Candida albicans* (Mudimu et al. 2014). The aqueous extracts from microalgal species *Spirulina*, *Chlorella*, *Nannochloropsis*, *Scenedesmus* and *Phaeodactylum tricornutum* showed antagonistic activity against fungal pathogens *Alternaria* alternata, *Sclerotium rolfsii*, and *Rhizoctonia solani* in vitro and *S. obliquus* showed maximum inhibition against *S. rolfsii* (32.01 ± 4.82%), *Nannochloropsis* sp. (13.96 ± 5.26%), and *P. tricornutum* suppressed growth of *S. rolfsii* and *R. solani* up to 18.35 ± 3.45% (Schmid et al. 2022). In this view, microalgal species possessing antifungal activities may well substitute various chemical or artificial agents in recent and sustainable production of agricultural and food products.

Anticarcinogenic activity

The abnormal and uncontrolled growth of the cells with their ability to invade or expand in other body parts is known as cancer and it is a persistently growing threat to human health. Cancer is the second major cause of deaths occurred worldwide and it has been reported by International Agency for Research on Cancer (IARC) that 10 million deaths are caused by cancer and the number of new cases is expected to be increased in the upcoming years (Sung et al. 2021). Radiotherapy and chemotherapy are the main approaches to fight cancers, regardless of their life-threatening side effects and development of resistance. In the drug discovery research area, treatment of several diseases through plant-derived or natural products is a pioneering approach. Being a proficient source of valuable bioactive metabolites of therapeutic uses, microalgae are simply cultured and represent an eco-friendly methodology to drug discovery (Fayyad et al. 2019; Bratchkova and Kroumov 2020; Senousy et al. 2020). The various types of carotenoids such as lutein, β-carotene, astaxanthin and violaxanthin showed anticarcinogenic activities and microalgae are the rich sources of carotenoids (Ferdous and Yusof 2021). β-carotene showed antagonistic effect to cancer growth by suppressing polarization of M2 macrophages which are primarily involved in metastasis and progession of tumors, and reducing HCT116 (colon cancer cells) migration and incursion and when supplied twice/week at (5 and 15 mg/kg) for 11 weeks in vitro to the mice infected with colon cancer reduces growth of tumor (Lee et al 2020). C-phycocyanin extracted from *Spirulina platensis* showed anticancerous activity in HeLa and MCF7 cell lines by DNA fragmentation, apoptosis induction by upregulating Fas and caspases activation (Medina et al. 2008). Talero et al. (2015) revealed that β-carotene reduced growth, migration and invasion by inhibiting metalloproteinase in LoVo colon carcinoma cells. It has been demonstrated that *Chaetomorpha* sp. are the persuasive antitumor chemical representatives which can act as encouraging anticancerous agent (Haq et al. 2019). Moreover, cryptophycin 1 and borophycin isolated from *Nostoc* indicated anti-tumorigenic activity against human tumor cells, and KB and LoVo cell lines, respectively (Singh and Krishna 2019). Recently, it has been reported that methanolic extract (T1) of *H. pulvialis* showed anticancerous activity by suppressing invasion of breast cancer cells (MDA-MB-231) and promoting apoptosis through biochemical pathway involving p53/Bax/Bcl2 (Alateyah et al. 2022). The phytochemicals showed anticarcinogenic activities by interfering cancer initiation, growth, development or progression through variation of several mechanisms such as cells proliferation, growth and differentiation, apoptosis and metastasis.

Antihypertensive and antihyperlipidemic activity

Hypertension is a wide-reaching health issue due to its pervasiveness and association with other diseases. It is amongst the furthermost menace for untimely cardiac diseases, as compared to hyperlipidaemia and diabetes (Fobian et al. 2018). Hypertension remains the prominent reason for deaths worldwide, accounting for approximately 10.4 million deaths per year (Unger et al. 2020). Microalgal derived bioactive compounds with antihypertensive effects have been reported in the literature (Kim and Wijesekara 2010; Zhao et al. 2015; Barkia et al. 2019; Ramos-Romero et al. 2021). Firstly, Suetsuna and Chen (2001) revealed that the bioactive peptides extracted from *Chlorella vulgaris* and *Spirulina platensis* showed significant antihypertensive effects. A peptide (Val-Glu-Cys-Tyr-Gly-Pro-Asn-Arg-Pro-Gln-Phe) isolated from the protein hydrolysates of *Chlorella vulgaris* showed antihypertensive effect by inhibiting angiotensin I-converting enzyme (ACE) through a noncompetitive binding mode (Sheih et al. 2009) which is a chief enzyme involved in blood pressure regulation as it converts angiotensin I to angiotensin II (vasoconstrictor), and deactivates the bradykinin (vasodialator) (Lee et al. 2010). Many bioactive peptides isolated from protein hydrolysates of *Chlorella*, *Nannochloropsis*, *Spirulina* and *Isochrysis* showed ACE inhibitory activity with similar role to conventional blood pressure controlling drugs (Samarakoon and Jeon 2012; Samarakoon et al. 2013; Heo et al. 2017; Chen et al. 2020).

Hyperlipidaemia is one of the major causes of cardiovascular diseases due to eliciting atherosclerosis. Cholesterol is a very important structural and functional component of the cell membrane and associate with lipoproteins in the form of very low-density lipoproteins (VLDL), low-density lipoproteins (LDL) and high-density lipoproteins (HDL). Amongst them HDL is good for health and a rise in VLDL and/or LDL levels lead to cardiovascular distortions (Al-Fartusie et al. 2019). High levels of cholesterol led to high blood pressure ultimately disturbing the functions of various organs especially heart, kidney, liver and lungs, and altering an array of biochemical pathways. The liquid extract of *Spirulina* showed hypolipidaemic effects by declining triacyglycerols, maintaining cholesterol levels and preventing fatty liver production. It has been reported that *Spirulina* supplementation reduced the lipids (cholesterol, triacylglycerols and LDL) level in patients suffering from hyperlipidaemic nephrotic syndrome (Samuels et al. 2002). Similarly, supplementation with *Chlorella vulgaris* significantly lowered the levels of total lipids including triacylglycerols and cholesterol by altering the metabolism of lipids, reducing their absorption in the intestine and enhancing lipids excretion (Ryu et al. 2014). Furthermore, 10% incorporation of *Chlorella vulgaris* to broiler diets for 21 days improved the proportion of beneficial fatty acids (Alfaia et al. 2021). Carotenoids isolated from *Dunaliella* inhibit atherogenesis, abridged cholesterol present in plasma through inactivataing b-hydroxy-b-methylglutaryl CoA, enhancing activity of receptors and declining biosynthesis of cholesterol, thus prevent from heart diseases (Talebi et al. 2021).

Antidiabetic activity

Diabetes is continually interrelated with increased exposure of high blood pressure, cardiovascular diseases, neural and kidney failure. The number of diabetic patients is expected to rise from 463 million (9.3%) in 2019 to approximately 578 million by 2030 (10.2%) and 700 million (10.9%) by 2045 (Saeedi et al. 2019). The hypoglycaemic effects of various microalga species such as *Chlorella sorokiniana* (Chou et al. 2008), *Chlorella pyrenoidosa* (Senthilkumar and Ashokkumar 2012) and *Chlorella vulgaris* (Noguchi et al. 2013) has been reported in the literature. In streptozotocin-induced mice, liquid extract of *Chlorella vulgaris* showed the increased hypoglycaemic function of exogenously supplied insulin (Jong-Yuh et al. 2005) and likewise effect was reported in diabetic rats when supplemented with the water-soluble extract of *Spirulina* (Layam and Reddy 2006). It has been studied that *Nannochlorpsis gaditana* has antioxidant and antidiabetic activities which helps in preventing oxidative stress and alterations of metabolic pathways linked to diabetes (Nacer et al. 2019). Likewise, *Spirulina* (produced in Turkey), showed anti-hyperglycaemic and anti-hyperlipidaemia effect when supplied to diabetic rats by decreasing glucose, triglyceride and cholesterol levels by 20, 31, and 22% respectively (Guldas et al. 2020).

Extraction of microalgal bioactive metabolites

The key step for microalgal-derived bioactive metabolites production is the process of cultivation and harvesting. Being versatile in nature, microalgae are capable to grow under varied conditions like phototrophic, mixotrophic or heterotrophic cultures. Commercial production can be in outdoors, in concrete tanks shallow ponds, lagoons, raceway, basins, pilot tanks or earthen pots, and indoor cultivation can be in vertical column, tubular closed, airlift or flat-plate photobioreactors (Narala et al. 2016; Yin et al. 2020; Wilson et al. 2020). Raceway ponds are important for microalgae production at large scale. To augment or stimulate the bioactive metabolites production (proteins, carbohydrates, lipids, pigments, or minerals), microalgae are cultivated under a two-step system in which initial conditions are enriched in nutrients for obtaining the highest biomass yield and followed by limited growth nutrients to stimulate different biosynthetic pathways (Chiranjeevi and Venkata Mohan 2017; Ranadheer et al. 2019). *Chlorella vulgaris* and *Haematococcus plulvalis* have the highest production of triacylglycerols, fatty acids and carotenoids achieved when cultivated in nitrogen-enriched, or enhanced environmental conditions (Shah et al. 2016; Saha and Murray 2018).

Harvesting of microalgae involves an array of biological, chemical, electrical, and mechanical solid–liquid dissolution methods. Depending on quality and quantity of biomass, time of processing, type of species, and cost, different methods such as filtration (ultrafiltration, membrane filtration), floatation (dissolved air, dispersed air, electroflotation, ozonation-dispersed), coagulation, centrifugation, and flocculation (autoflocculation, electrolytic, bio-flocculation, chemical or microalgae mediated) or in combination are employed for dewatering microalgae (Singh and Patidar 2018). It has been proposed that a combination of separating techniques is more efficient as no universal method is known for harvesting microalgae irrespective of species. To increase cost-effectiveness, flocculation can be followed by sedimentation, centrifugation or filtration. Sedimentation and flocculation are superior and economical for de-watering microalgae. Recently, the potential mechanism and harvesting performance of four natural flocculants (Chitosan, Tanfloc, Cationic starch and *Moringa oleifera*) were studied and revealed that they improved the microalgae harvesting by electrostatic binding, bridging and better dewatering functionality. Tanfloc displayed more than 98% harvesting efficiency at low dosages (30 mg L^{-1} for *Chlorella vulgaris* and 20 mg L^{-1} for *Scenedesmus obliquus*) (Yang et al. 2021).

Several extraction and purification techniques are employed to recover targeted bioactive metabolites from microalgae' biomass. They are broadly divided into conventional and non conventional techniques.

Conventional techniques

Conventional extraction methods include Soxhlet, hydrodistillation and maceration. The Soxhlet method is simple, most popular and effective method for extraction of metabolites from solid sample technique involves a small amount of dry sample since its discovery in 1879. The dry sample is placed on Soxhlet apparatus where the solvent passes multiple times until the extraction has been completed (López-Bascón and Castro 2020). A large number of solvents such as hexane, chloroform, acetone, petroleum ether, dichloromethane, alone or either mixed with hexane or acetone, or their combinations with different ratios are used for Soxhlet extraction. But the usuage of nonpolar solvents is generally not suggested. Maceration involves the grinding of sample into minor particles or more homogenized form in order to upsurge the surface area for making a better solvent-sample mixture by increasing diffusion and this method has been used widely since a long time for extraction of essential oils (Zhang et al. 2018). Hydrodistillation method is basically used for the extraction of volatile compounds or fraction from food or another sample and involves three steps hydrodiffusion, hydrolysis, and decomposition by heat. It does not use organic solvents and involves distilled water for extraction. It's a complete process to physically separate and extract volatile conmpounds from non volatiles in one step through stripping by azeotropic distillation but this process is time consuming and uses high levels of energy (Hasbay and Galanakis 2018). Athough conventional techniques have been used commonly for extrcation of bioactive compounds, but these techniques require a large volume of organic solvents, high amounts of labor-skilled operators, and have low reproducibility (Amaro et al. 2015). However, productivity of conventional techniques rest on solvent's choice, compounds' polarity, type of extract, temperature and extraction time.

Non conventional or forward-looking techniques

Non conventional techniques for extraction of bioactive compounds are fully automated, use fewer organic solvents, and are more efficient, selective, and environmentally-friendly. They include supercritical fluid extraction, enzyme-assisted extraction, microwave-assisted extraction, ultrasound-assisted extraction, and pressurized-solvent extraction methods. Microwave assisted binary phase solvent extraction for lutein isolation from *Scenedesmus* sp., reduced extraction time by 3-folds and enhanced recovery by 130% as 11.92 mg/g of lutein (Low et al. 2020). Total lipid extraction by automated accelerated solvent extraction method in three microalgae species, *Scenedesmus* sp. LRB-AS 0401, *Chlorella zofingiensis* LRB-AZ 1201,

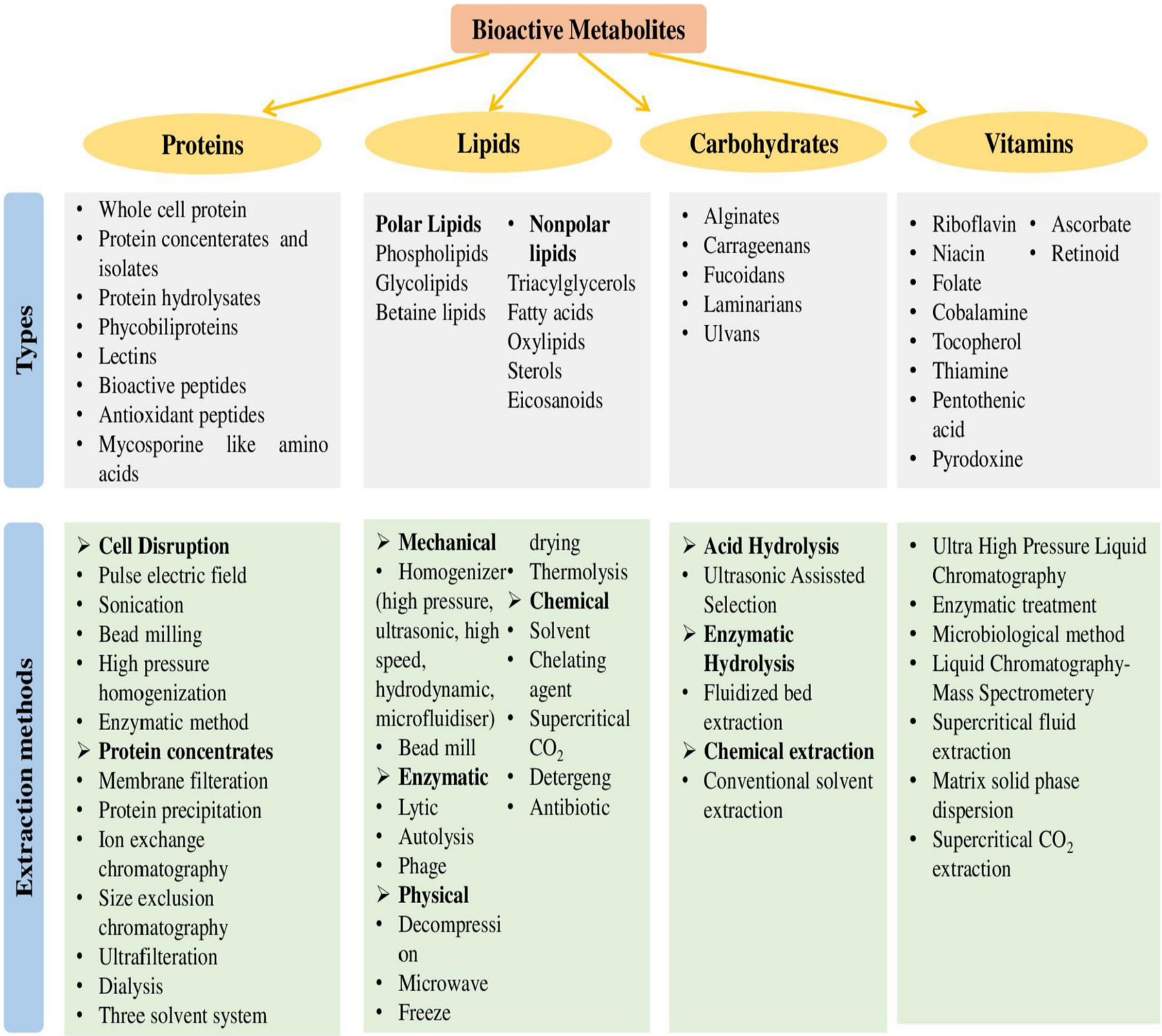

Fig. 3 The various types of bioactive metabolites comprised in microalgae's biomass and their extraction methods

and *Isochrysis galbana* LRB-CB 3100 were much higher than conventional methods (Chen et al. 2020).

The various extraction methods for targeted bioactive metabolites have been illustrated in Fig. 3 and for more particulars, see the review by Ventura et al. (2017). Following extraction of bioactive metabolites, purification steps are commonly needed to remove contaminating substances. Purification procedures usually comprise of various solvents like methanol/chloroform/water (4:2:1; v/v/v) mixture and physical methodologies, e.g., ion-exchange, affinity, molecular sieve, and membrane separation methods (Lim et al. 2014).

Microalgal derived bioactives as food and nutrient supplements

To cope up with the increasing food demand, cropping intensity has been increased, the area of cultivation has been expanded and yield enhancing techniques have led to environmental problems such as deforestation, biodiversity loss, habitat disturbance and land degradation. In this view, easily grown, and cost-effective production of nutrients is needed. Due to the presence of valuable essential nutrients, microalgae have been used as dietary complement or source of food in several portions of the world such as China, Mexico, Japan and Korea for hundreds of years. About 2000 years ago, microalga (*Nostoc*) was first consumed in China and far along *Spirulina* and *Chlorella* were consumed in Mexico, Taiwan and Japan (Sathasivam et al. 2019). Microalgae cultivation for biomass production at commercial level started approximately 60 years ago with the mass production of *Chlorella vulgaris* in Japan and Taiwan, and the cultivation of *Dunaliella salina, Spirulina* and *Haematococcus pluvialis* was established in Thailand, China, Israel, United States and Australia in 1980's (Hur et al. 2015). It has been demonstrated in a specific questionnaire study that Spanish microalgae consumers considered it nutritious, healthy, safe, sustainable and environmentally friendly food product (Lafarga et al. 2021).

Arthrospira (*Spirulina*) is attaining popularity throughout the world due to the presence of protein, phycocyanin, phenolics, pigments (carotenoids, xanthophyll's), polyunsaturated fatty acids such as linolenic acid and vitamins (A, B1, B2, B12). *Spirulina* has been marketed as a nutritional supplement "superfood" in the form of capsules, dried powder or flakes (Lafarga 2019; Lafarga et al. 2020). *Spirulina* constitute 30% of the total biomass production of microalgae worldwide. It was first harvested and marketed in Mexico in the sixteenth century from Texcoco Lake and was acknowledged as an upcoming food source by IAAM (International Association of Applied Microbiology) (Costa et al. 2019). *Spirulina* products are Generally Recognized as Safe (GRAS) by US Food & Drug Administration and are also commercialized in the European Union as novel foods. In Yangon (Myanmar), Myanmar-*Spirulina*-factory creates liquid extracts, chips, pasta and tablets and Cyanotech (Hawaii, USA) distributes dried powder known as "*Spirulina pacifica*" (Spolaore et al. 2006). *Spirulina* is recommended to be considered in the diet of astronauts in space by WHO because of excellent and compact food for travel (Matufi and Choopani 2020).

Chlorella, like *Spirulina* is also used as natural foods or can be incorporated into sweets, beans, pasta and snacks because it is rich in proteins, polysaccharides, ascorbic acid, vitamins, minerals and pigments (Cha et al. 2010; Priyadarshani and Rath 2012; da Silva Vaz et al. 2016). Additionally, *Chlorella* has been sold as a dietary supplement for vegetarians as it is high in B12 (Watanabe et al. 2014). *Chlorella* has turn out to be a rich source of bioactive metabolites or can be useful as a functional food and promotes sustainable health benefits (Silva et al. 2019). Because of the growing interest of nutritional and healthy balanced diets, production and worldwide sale of *Chlorella* raised and its worldwide market is predicted to touch 164 million US dollars in 2021 (Koyande et al. 2019). Over 70 corporations are producing *Chlorella* globally, Taiwan *Chlorella* Manufacturing and Co. (Taipei, Taiwan) being the leading producer by generating 400 tons of biomass (dried) per year. Silva et al. (2019) reported that *Chlorella* can be a rich source of high value bioactive metabolites with promising nutritional and health benefits. Recently, Bito et al. (2020) found that *Chlorella* contains high amounts of folate and iron compared to plant-derived foods and for supplementation. A meta-analysis revealed that *Chlorella* decreases total cholesterol levels, high blood pressure, and improves blood glucose levels.

Due to its high lipid and vitamin content, *Dunaliella salina* is also cultivated as food supplement. It is high in beta-carotene and thus could be utilized as natural food pigment (Pourkarimi et al. 2020). It has been recognized as a food supplement by US-FDA with GRAS status. *Dunaliella's* dried biomass constitutes upto 80% proteins (Becker 2007) and its essential amino acids content is sufficient to meet human requirements as set by FAO. *Dunaliella* derived β-carotene production started in 1980's in Australia, Israel and USA in the form of dried biomass or liquid extract (Borowitzka 2013). Due to high protein and mineral content, *Dunaliella* dried biomass can be included in several food items such as bread and pasta (El-Baz et al. 2017). In comparison to soybean and most commercialized microalgae, e.g., *Spirulina* and *Chlorella*, *Dunaliella* demonstrated improved quality and quantity of proteins (Sui and Vlaeminck 2020).

Scenedesmus is also recognized as a dietary source of nutrients but their production at a commercial scale is restricted. Their liquid extracts or dried biomass can be integrated into several food items such as pastas, snacks, soups, desserts and noodles (Sathasivam et al. 2019). Recently, da Silva et al. (2020) studied that diets containing *Scenedesmus obliquus* in male Wistar rats were well tolerated, with efficient protein digestibility, declined triglycerides (approximately 70%), atherogenic index (80%), and serum glucose

(42%) in comparison to standard diet suggesting that it could be a good, safe and sustainable source of food.

Haematococcus appears to be the most capable source of astaxanthin for industrial production in comparison to traditional chemical synthesis (Shah et al. 2016). At the present it is commercially cultivated and its market is predicted to increase of 13.2% from 2020 to 2027 to reach $148.1 million by 2027 (Jannel et al. 2020). Astaxanthin, a secondary metabolite possesses antioxidant, photoprotective and anti-inflammatory properties (Davinelli et al. 2018). In 2014, the cost of astaxanthin was estimated at USD 447 million globally, it surpassed USD 600 million in 2018 and it has been predictable that it will undoubtedly reach USD 880 million by 2026 (Panis et al. 2016; Ahuja et al. 2020) The nutritional benefits and implementation of several microalgae species into different food products has been illustrated in Table 3.

Limits and challenges in their production

The usage of microalgal-biomass as a basis of valuable bioproducts is not yet easy on the pocket at commercial scale due to limited concerns and challenges irrespective of an array of efforts and research struggles towards microalgae. Amongst the most prevalent challenge is the processing of microalgae which regulate the step-wise formation of bioactive compounds. The digestibility of microalgae-based nutraceuticals doesn't vary exclusively with genetic traits but also with the downstreaming high-tech process which is involved in biomass production. During the process of bioactive compounds formation, the maintenance of taste, color, consistency, odor and texture is a relevant issue (Camacho et al. 2019). Instead of several types of photobioreactors (tubulars, flat plates, plastic bags, columns or stirred tank), an advancement of the most economical, effective, less time consuming, less laborious and producible closed system which is proficient of working under delimited conditions with minimal contamination risks at large scale is a clampdown. However, a new development in the lightening and controlling conditions of closed system, and scale-up technologies to make it competent is also a restraint. Moreover, the isolation, harvesting, extraction and purification involved in downstream process are multifaceted and extravagant. The produced bioactive metabolites might be less sufficient, fragile, destroy or unusually reformed in the course of extraction process, thus raising the difficulty in their analysis and commercial scale-up. In this view, it is a noteworthy challenge to identify and characterize single bioactive compounds from microalgae biomass. Additionally, the enhancement of microalgae growth for sufficient biomass production annually under a sterile environment and an ideal way of microalgae culture testing for high-throughput screening are also one of the most central challenges. On the other hand, food safety is a pertinent facet to be examined during the microalgae technology and advancement. Therefore, the regulations on the production, exploitation and consumption of microalgae based bioactive compounds must be taken as a vital concern (Tang et al. 2020). The another limiting factor of utilizing microalgae at a commercial scale for human intake is the presence of high nucleic acids content which break down in to uric acid and may outcome in threatening health issues like gout.

Conclusion and future prospects

Microalgae undoubtedly illustrate their potential to come across ever growing population's needs for supplementary ecological food options. This review explored the prospective of microalgae for several renewable and sustainable bioactive metabolites with valuable properties which can be exploited in several nutraceutical, food and pharmaceutical industries by acting as efficient antimicrobial, anti-inflammatory, anti-cancerous, anti-hypertensive, antihyperlipidemic and antidiabetic agents. Concluding these products at a commercial scale, microalgae look like the redeemer of our future by representing a good alternative to chemical synthesis. Nonetheless, to commercialize microalgae-based valuable bioproducts, many hurdles are required to be overwhelmed. Once these challenges are overcome, implementing microalgae-derived bioactive metabolites into food products could lead to possible health benefits to humans and improvement of sustainability issues related to increasing population. The microalgae, hardly micrometers in size could be utilized multi-purposely and, hence, aid in decreasing the burden on non-renewable assets.

One significant area for further research is attention towards the advances of omics technologies and

Table 3 The nutritional benefits and implementation of various microalgae species into food products

Microalgae	Part or compound used	Amount used	Food product	Nutritional benefits	References
Nannochloropsis sp. & *Tetraselmis* sp.	Powdered biomass	0.5–3.0% flour substitution	Wheat tortillas	Increased protein and fat content, improved phenolic and carotenoid content, and enhanced antixodant activity	Hernandez-Lopez et al. (2021)
Tetraselmis chuii	Ethanol treated cells	0, 4, 8, 12 and 16% wheat flour substitution	Wheat bread	Improved dough rheology such as dough-stability-time, resistance to extension and elastic-recovery-compliance, bread quality such as at 12% substitution level specific volume increased from 2.1 to 2.69 mL/g, crumb firmness decreased from 1358 to 297 g and slice brightness increased from 25.2 to 49.0	Qazi et al. (2021)
Nannochloropsis gaditana L2 & *Chlamydomonas* sp. EL5	Biomass	1.0 and 3.0 g/ 100 g of flour	Gluten-free bread	Increase in levels of proteins, lipids, ash, and linolenic acid, 3% incorporation showed 100% increase in iron and calcium contents, influence textural properties significantly, and improved sensory and nutritional properties of gluten-free breads	Khemiri et al. (2020)
Chlorella minutissima, *Isochrysis galbana* & *Picochlorum* sp.	Biomass	0.5, 1, and 1.5% w/v	Canned fish burgers	Improved swelling ability, oil and water holding capacity, antioxidant capacity, better texture and sensory properties	Atitallah et al. (2019)
Chlorella & *Spirulina*	Biomass	–	Pork sausages	Enhanced amino acids content, ratio of essential/non-essential amino acids, nutritionally favourable profiles, can be considered as alternative soy protein	Marti-Quijal et al. (2019)
Chlorella vulgaris	Dry biomass powder	1.5% w/v	Breadsticks	Increased mineral content (iron and selenium), improved color and texture stability	Uribe-Wandurraga et al. (2019)
Arthrospira platensis, *Chlorella* sp. & *Tetraselmis* sp.	Dry biomass powder	0.5–2.0% w/v	Broccoli soup	Increase in levels of polyphenols and improved antioxidant capacity	Lafarga et al. (2020)
Arthrospira platensis	Dry biomass powder	2.6% w/v	Extruded snacks	Improved nutritional content, Increased protein, lipids and minerals	Lucas et al. (2018)
Chlorella vulgaris	Dry biomass powder	2, 4, 6% w/w	Cheese	Nutrional enhancement, increased levels of potassium, magnesium, zinc, and iron, and improved antioxidant potential	Tohamy et al. (2018)
Arthrospira platensis		15% w/w	Dehydrated soup	Nutritional enrichment, improved antioxidant capacity, and increased protein, fibre, ash and lipid content	Los et al. (2018)
Arthrospira platensis F&M-C256, *Chlorella vulgaris* Allma	Biomass	2% (w/w) and 6% (w/w)	Cookies	Improved content of protein and phenolics, improved antioxidant capacity and good sensory score	Batista et al. (2017)
Haematococcus pluvialis	Astaxanthin powder	5, 10, 15%	Cookies	Increased total phenolics, and antioxidant capacity	Hossain et al. (2017)

Table 3 continued

Microalgae	Part or compound used	Amount used	Food product	Nutritional benefits	References
Dunaliella salina	Dried biomass powder	1–3% w/w	Pasta	Nutrional enhancement, increased levels of potassium, magnesium, calcium, iron, unsaturated fatty acids and phytochemicals	El-Baz et al. (2017)
Arthrospira platensis	Dried biomass powder	750 mg per 100 g of product	Powered food	Better source of energy, protein, carbohydrates, dietary bioactive compounds, essential fatty acids, and vitamins	Santos et al. (2016)
Scenedesmus almeriensis	Carotenoids rich extract	0.1 and 0.21 mg mL-1	Virgin olive oil	Nutrional enhancement, increased levels of beta-carotene and lutein, enhanced oxidative stability and soil quality and declined peroxidation	Limon et al. (2015)
Nannochloropsis oculata	Dried biomass powder	1% (w/w)	Cookies and pasta	Improved nutritional profile, increased omega-3 levels (eicosapentaenoic and docosahexaenoic acids)	Babuskin et al. (2014)
Arthrospira platensis	Dried biomass powder	2 or 5% (w/w)	Cookies	Nutrional enhancement, increased levels of protein, fibre, ash and phenolics, and improved antioxidant potential	Bolanho et al. (2014)

synthetic biology to completely sequence the genome of microalgae keenly producing bioactive metabolites possessing nutraceutical and pharmaceutical applications. Around 60 algal strains have been sequenced and the information of their genome is accessible at "Phytozome" (phytozome.jgi.doe.gov) and "The Greenhouse" (greenhouse.lanl.gov) (Kumar et al. 2020). Through molecular genetics, genome editing tools, and omics data updating could be beneficial to recognize and describe the various biochemical pathways convoluted in the nutraceuticals' production and the monitoring mechanisms which elicit these metabolites' out. Plentiful research efforts are still needed to manipulate microalgal strains to augment targeted bioactive metabolites through mutagenesis, genetic engineering or synthetic biology. Biotechnological improvements in the construction and designing of large photo-bioreactor to make the microalgae cultivation, harvesting, dewatering and extraction a cost effective, less energy demanding, easily producible and efficient way at commercial scale. Co-extraction or subsequent extraction of various bioactive compounds with greater yields, less energy consumption, and environmentally friendly convenient way needs to be highlighted. As to achieve the pharmacological properties of microalgae-based bioactive compounds, several advances in in vivo clinical research studies are also needed. Through bioinformatics, an improved knowledge of structure and activity could enable the development of bioactive compounds with superior bioactivity and less non-desirable effects. Improvements in genetically modified techniques for cultivating microalgae in various wastewater sources could exploit their potential to favor bio-based process. Furthermore, progress in bioengineering related research is required towards green technology for microalgae-bioactive compounds production to accomplish the necessities complemented to plants.

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Declarations

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