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Microalgae: A valuable bio-resource for pharmaceuticals and nutraceuticals

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ABSTRACT

Microalgae are diverse microorganisms known for producing a range of biologically active compounds. As primary photosynthetic autotrophs, they convert about 60% of their biomass into carbohydrates, offering a renewable alternative to fossil fuels. Rich in antioxidants, microalgae are also considered a future "superfood" and used as nutritional supplements, especially in combating malnutrition. When cultivated under controlled conditions, microalgae offer an eco-friendly and cost-effective source of valuable compounds. Key commercial species include *Spirulina*, *Chlorella vulgaris*, *Haematococcus pluvialis*, *Dunaliella salina*, and *Aphanizomenon flos-aquae*. Due to their rapid growth and minimal resource needs, they are cultivated on a large scale to help meet global food demands. Microalgae produce a wide array of compounds such as fatty acids, carotenoids, polysaccharides, and bioactive substances with anti-inflammatory, antimicrobial, and antioxidant properties. This review explores microalgae cultivation, harvesting, and their bioactive applications in health-related industries.

1. INTRODUCTION

The world population is going to touch about 9.7 billion at the end of 2050 that imposes a great challenge to the sustainable development and availability of natural resources on Earth [1]. As a result, the food demand will increase drastically with the growing population [2]. In particular, the global food crisis is attracting unprecedented attention due to concerns regarding its safety and sustainability. Therefore, it is urgent to search for renewable and alternative sources for both traditional food and energy [3]. Microalgae are single celled prokaryotic (cyanobacteria) and eukaryotic (higher algal species) photoautotrophs that can produce up to 60% of their biomass in form of carbohydrate or oil [4]. These photoautotrophs grow in diverse habitats including lakes, pounds, rivers, oceans, and even wastewater. There are around 72,500 algal species, names for 44,000 of which have probably been published, and 33,248 names have been processed by AlgaeBase [5]. Beside the primary producer of aquatic ecosystem, the biomass of microalga is potent source of carbon compounds which can be utilized as biofuels, health supplements, and cosmetics [6]. Microalgae produce a wide range of bioactive products, including polysaccharides (PS), lipids, pigments, proteins, and vitamins [7]. On the other hand, microalgae also involve in waste water treatment by removing toxic substances by chelating/adsorbing with the help of exopolysaccharides [8,9]. A new emphasis in bio-refinery has been spurred by the interest in microalgae as a sustainable and renewable feedstock for the production of biofuels. They also help to preserve agricultural soil fertility and boost crop productivity and acts as bio-fertilizers [10]. Hence, to full-fill the demand of over-growing populations, there is a need of commercializing the algal bioproducts by mass culturing of microalgal species. While on the similar note, during stress condition microalgae have the capability to mitigate the stress condition and evolve itself in significant manner in such situations through their defensive mechanism [Figure 1]. Despite considerable variability in the literature and lack of long-term full-scale

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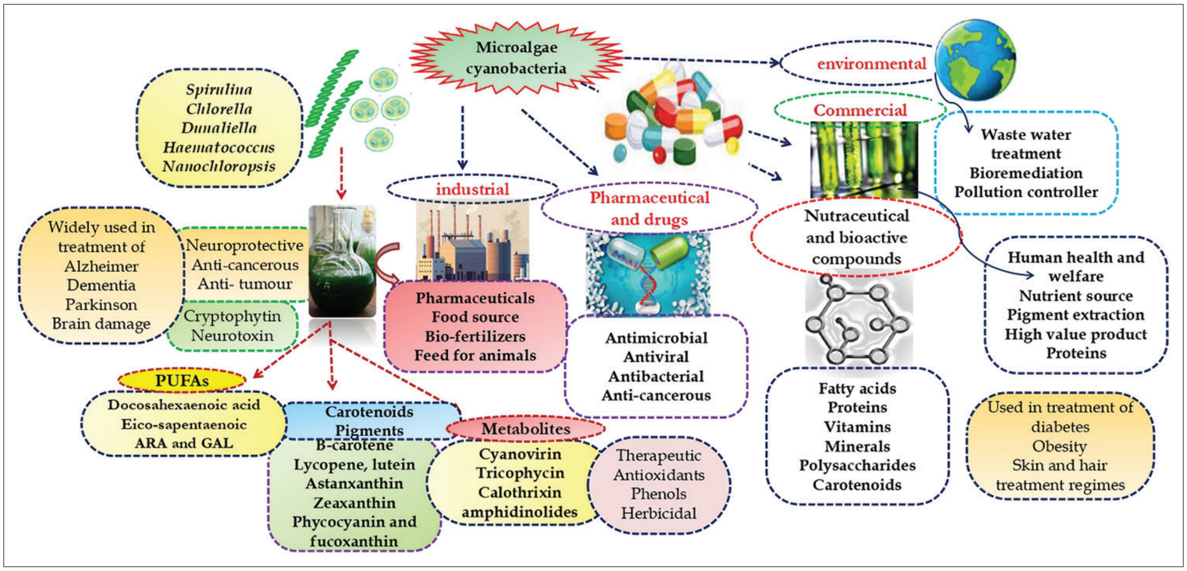

Figure 1: Diagram showing potential applications of microalgae.

data, microalgae cultivation for food production generally appears to be more sustainable than terrestrial crop farming. Furthermore, compared to other crops, the cultivation of microalgae does not require fertile land, herbicides, or pesticides, so there will be no competition for these resources. Microalgae can be cultured and cultivated in ponds, shallow water, and artificial tanks with little pressure and their biomass is used in producing valuable bioproducts. Even wastewater from home sewage systems and palm oil milling effluents can be used to cultivate microalgae, which can help in wastewater treatment [11,12]. Beside many advantages in microalgae farming, there are still a number of challenges. For instance, the small size of the cells, negative charge on the cell surface, low cell density, and low biomass production of microalgae make the harvesting process extremely expensive [13]. Hence, to develop microalgae as a sustainable bio-resource, there is a need of cost-effective techniques for microalgae harvesting to achieve large-scale commercial production.

In addition, microalgae are also potent source of valuable non-enzymatic antioxidants such as cysteine, proline, non-protein thiols, and glutathione under normal and stress conditions [14]. Common microalgal species which are used in nutraceutical and biotechnological based applications are *Spirulina platensis/ maxima (Arthrospira)*, *Chlorella vulgaris, Dunaliella salina, and Haematococcus pluvialis* [15]. They grow in large scale with regard to high protein content molecule which is commonly known as "single cell protein (SCP)." On the other hand, there are some red algae such as *Porphyridium*, *Rhodella*, and *Galdieria,* which also contain the water soluble phycobiliproteins having anti-inflammatory, hepatoprotective, and neuroprotective activity [16]. The derivatives of polyunsaturated fatty acids (PUFAs) such as linoleic acid and arachidonic acid (AA) are extracted from the microalgae that show the cognitive property [17]. Further, in present condition, the extensive application of microalgae in pharmaceuticals and nutraceuticals industries is not economically feasible due to their high cost. In large-scale industrial applications of microalgae, the energy-intensive harvesting process occupies up to 30% of the total cost [18]. Microalgal bioactive metabolites are therefore of particular interest in the medical, pharmaceutical, cosmetic, and food industries [19]. Hence, further investigation regarding the potential benefits of microalgal-based metabolites to humans is necessary [20]. In light of this, this review investigates the bioactive metabolites and high-value compounds produced by microalgae and their possible applications in the life sciences, particularly in pharmaceutical, nutraceutical, and healthcare.

2. CULTIVATION AND HARVESTING OF MICROALGAE

Microalgae, being an aquatic photosynthetic organism, exhibit rapid growth rates compared to terrestrial plants and do not present a competitive threat to crops or lands [21]. Contrary to plants, they require less attention, low space, and minimum time for growth. They have inherent capability to accumulate valuable bioproducts within their cells that make them a suitable candidate for serving as raw material for industrial purpose [22]. In addition, the cultivation of microalgae does not require herbicides and pesticides, in contrast to other crops. As a result, microalgae cultivation does not engage in resource competition [23]. Despite the advantages of cultivating microalgae, the progress in its development is hindered by various challenges; one such issues are low biomass production and the small size of cells [23]. Addressing the limitations, over the years, various technologies have in consideration to increase the mass production of microalgae in highly controlled laboratory conditions [23]. For better microalgal growth, there is ample light, efficient gas exchange, easy operation, low contamination risk, and it is cost-effective [24]. Culturing and cultivation systems of microalgae can be categorized into two categories: (1) Open pond (further sub-categorized into deep ponds, shallow ponds, and artificial ponds) and (2) culturing in photobioreactor [25]. Open pond cultivation stands as one of the earliest and simplest methods for large-scale cultivation of microalgae and it requires lesser investment and man power. Cultivation typically occurs in open systems, including natural water bodies (ponds and lakes) and artificial setups such as raceway ponds, circular ponds, and tanks [26]. Due to its vast economic potential, abundance of bioactive compounds, low cost, and easy availability, it is well-suited for large-scale industrial use. For example, *Spirulina* and *Dunaliella* cultivated and harvested in open lakes in Texcoco and in Hutt Lagoon Australia, respectively, for production of the β-carotene [27,28]. While on the similar note, artificial open pond system mainly is recently implemented by some countries such as Japan and Taiwan to cultivate

C. *vulgaris* as food supplement. The pond cultivation is the most frequent used approach for the cultivation of microalgae [29]. Beside this, various designs of closed photobioreactors have been developed to achieve better growth control and operating parameters. The three most common types for larger-scale cultivation systems are horizontal tubular reactors, bubble column vertical tubular reactors, and flat plate or panel (FP) type photobioreactors [30]. Improved growth rates and increased biomass yields are the outcome of photo-bioreactors, which reduce external contamination and enable precise control of light, temperature, pH, and nutrients [31]. Closed photo-bioreactor is a technological advancement for sustainable uses of microalgae in industries such as pharmaceuticals, nutraceuticals, bio-stimulants, biofuels, and aquaculture systems [25]. Flat plate photobioreactors are recommended for mass production of microalgae in both indoor and outdoor culture systems due to their high irradiation of plate surface. For example, closed photobioreactor is used for mass cultivation of *H. pluvialis* and *C. vulgaris* [32,33]. Harvesting of microalgae is considered as an important step of the processing of microalgae which makes it about 25–30% of the total cost production on the basis of high-energy demand and cost ratio. The grown biomass was harvested by gravitational settling and then centrifuged to obtain thick algal slurry. This algal slurry is further increased by cultivating the algal species beyond 12 days associated with increase in biomass production [34]. The supernatant was discarded, and the thickened microalgae were centrifuged and the thickened algal slurry was further used for metabolite extraction. There are major four types of the harvesting techniques by which we harvest the microalga (i) filtration, (ii) centrifugation, (iii) flocculation, and (iv) flotation; each step is discussed briefly.

2.1. Filtration

Harvesting of microalgae using a semi-permeable membrane, which permits the separation of culture medium while retaining algal biomass, is referred to as filtration. This method is generally employed to harvest such species of microalgae that are principally at risk to prone as well as delicate in nature and through adopting this method that the dense culture is obtained [35]. There are various other methods of filtration which is as follows, (i) cross flow filtration, (ii) tilted membrane panel filtration, (iii) axial vibration membrane filtration, (iv) ultra-filtration, and (v) polyacrylonitrile-based membrane filtration. The microalgal sp. such as C. *vulgaris* is harvested through the cross-flow filtration as well as axial vibration membrane filtration method for the large-scale production [36].

2.2. Centrifugation

Based on the difference in density between the particle and the surrounding medium, centrifugation is a physical dewatering technique that accelerates particle movement and separation by creating a centrifugal force. This technique can quickly lead to a high harvest efficiency and a higher biomass concentration [37]. The efficiency of the centrifugation depends on the settling characteristics of the cells and the retention time of the slurry in the centrifuge [38]. There are two main advantages of this process; firstly, centrifugation can be used effectively to recover microalgal biomass with 80%–90% of biomass recovery within 2–5 min, and secondly, there is no chemical additives are required. On comparing with sedimentation and magnetic separation, the centrifugation has the highest efficiency. The major disadvantage of this technique is that there is destruction of the cell structure of algae due to high gravitational force and shear stresses algae [39]. However, certain species (*Tetraselmis suecica*, *Isochrysis galbana,* and *Skeletonema costatum*) exhibited tolerance to shear stress as observed by Michiels *et al*. [40]. The main centrifugal devices that possess the potential to be utilized in biomass harvesting are (i) disk stack centrifuges, (ii) multi chamber centrifuges, (ii) tubular centrifuges, (iv) decanters centrifuge, and (v) hydro-cyclones [41]. Among these, the disc-stack centrifuge is the most common centrifuge used for separating algae biomass for various applications. Using extremely high centrifugal forces in a single continuous process, a disc-stack centrifuge has been successfully used to separate liquids from one another as well as solids from liquids [42].

2.3. Flocculation

The scattered free floating microalgal cells accumulate and form larger particle known as floc which on charge separation and with the help of flocculating agent in the presence of higher sedimentation rate facilitate the harvesting [43]. Based on the nature of flocculating agent, flocculation is mainly divided into two groups; one is chemical flocculants and second is bio-flocculants. Chemical flocculants are iron and aluminium salts which remove 90–95% of the biomass production of microalgae at normal situation [44]. In earlier study, it has been demonstrated that the cultures of *Chlorella* spp. are harvested by chemical flocculation method. However, this approach is not considered as eco-friendly regarding to the environment as well as for human welfare due to their toxic chemical effects [44]. Further, bio-flocculating method of harvesting is eco-friendly in nature due to their existence in nature. For example, chitosan biomolecule found in nature but it produces in artificial manner that helps to recover 90–95% of the cell in culture media. Some microalgae like *Desmodesmus brasiliensis, Chlorella vulgaris* and Scenedesmus are harvested by using the bio-flocculating method. [45].

2.4. Flotation

Flotation is the manifested technique of harvesting in which small particle as form of bubble can access the floating of microalgal cells that attach on the surface of the culture media [46]. This phenomenon shows the higher production efficiency of cells at low-cost ratio with easy availability. *Scenedesmus* spp., *C. vulgaris, I. galbana,* and *T. suecica* harvested through the flotation method [47,48].

The different farming and harvesting sequences are shown in Figure 2. Besides, reviewing the process of cultivation and harvesting the question ascends that what is the need for the production of the microalgae on such a large scale. The answer to this infers that the microalgae are the diverse group of microorganisms that are bestowed with the antioxidants, vitamins, minerals, and other potent bioactive molecules that are remarkably use for the human and animal welfare, as a food supplement, nutritional requirement, and also against various diseases. That is the reason the microalgae are exploited on large scale for the commercial purpose to meet the human need for food as well as for nutritional scarcity. The various nutraceutical and pharmaceutical product extracted from microalgae has been discussed briefly in below section.

3. ALGAL METABOLITES

Being the first photosynthetic organisms, the microalgal species play important role in aquatic ecosystems and covers up around 40% of global photosynthesis [49]. Due to their habitats, the microalgal species are in direct contact with the changing environmental conditions that positively or negatively alter the physiological and

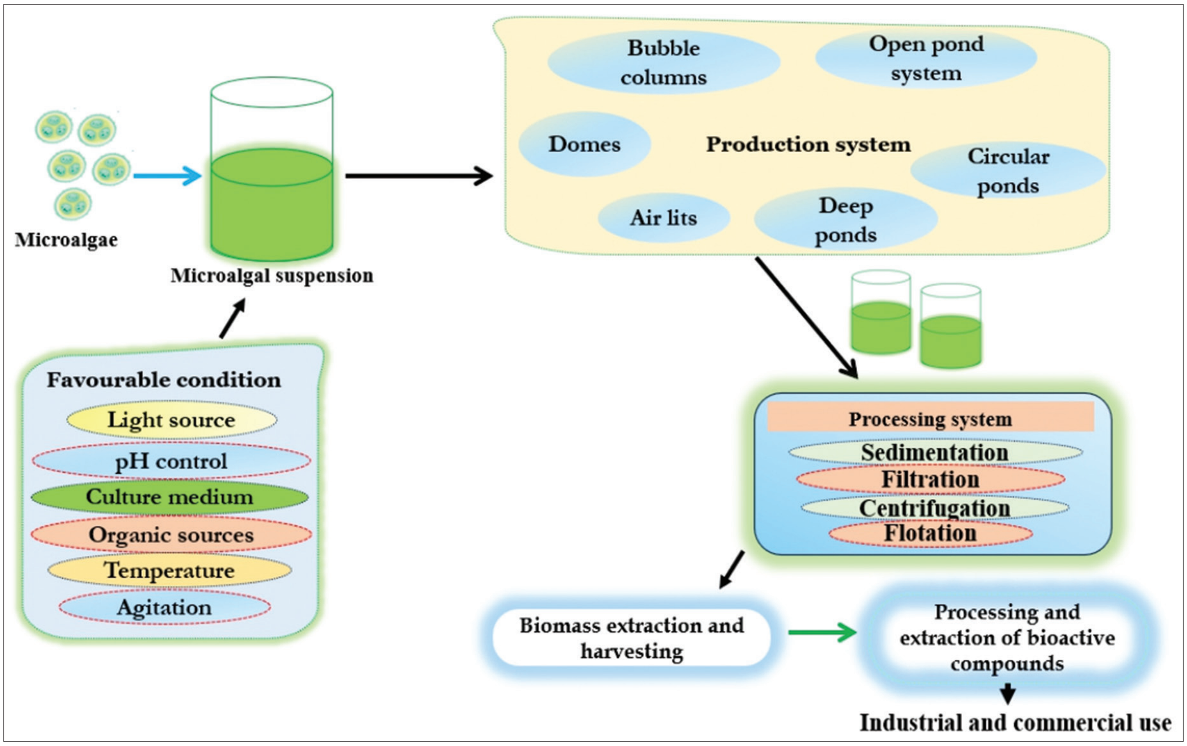

Figure 2: Various steps involved in cultivation and culturing of microalgae.

biochemical activities of cell. Several studies have been conducted and results are much more interesting that these microalgal species have immense potential to synthesize important metabolites in response to adverse environmental conditions with possible applications to humans in different fields of interest. Microalgae have been described as rich sources of various bio-compounds of commercial interest [50]. Microalgal origin bioactive compounds are categorized either from primary metabolites (proteins, lipids, carbohydrates, and nucleic acids) or from secondary metabolites. These bio-active compounds have antifungal, antiviral, anti-cancer, and antibiotic properties. Bioactive metabolites of microalgal origin are of special interest in the development of new products for medical, pharmaceutical, cosmetic, and food industries because from microalgae have been used as food by humans for thousands of years [51]. There are around 110 commercial producers of microalgae present in the Asia-Pacific region, with capacities ranging from 3 to 500 tons/year and around nine-tenths of algal cultivation is located in Asia. Major countries of commercial microalgae producers are located in China, Taiwan and India. Despite of high number of microalgal genus, only few have commercially importance such as *Spirulina*, *Chlorella*, *Haematococcus*, *Dunaliella*, *Botryococcus*, *Phaeodactylum*, *Porphyridium*, *Crypthecodinium*, *Nannochloris*, *Schizochytrium*, *Tetraselmis,* and *Skeletonema* [52]. Microalgae are a highly promising group of microorganisms for the development of new products and applications due to their vast biodiversity and the recent advancements in genetic engineering [53]. According to recent research, microalgae are capable of producing a wide range of chemical compounds having antimicrobial, antiviral, anticoagulant, antifungal, anti-inflammatory, and anticancer activity [54-56]. In this context, the further sections are firstly focused on role of micro-algae as bio-stimulants, bio-fertilizers and bio-pesticides and secondly use of bioactive compounds as pharmaceuticals and nutraceuticals.

4. MICROALGAE AS BIO-STIMULANTS, BIO-FERTILIZERS, AND BIO-PESTICIDES

Microalgae generally enhance plant growth through three main mechanisms: Functioning as bio-fertilizers, acting as bio-stimulants, and serving as bio-pesticides [25,57]. The most widespread use of microalgae biomass is as bio-fertilizers, making it the predominant method of application [57,58]. According to Swarnalakshmi *et al*. [59], applying a biofilm containing the cyanobacterium *Anabaena torulosa* to a wheat crop significantly increased the amount of available nitrogen in soil. Dineshkumar *et al*. [60] evaluated the impact of different concentrations of *C. vulgaris* and *S. platensis* on rice growth and yield to assess their potential as biofertilizers. Both microalgae species positively influenced key growth parameters, including plant height, leaf number, leaf area, and both fresh and dry biomass. Their application enabled a reduction of up to 50–75% in the recommended nitrogen fertilizer dosage without compromising plant performance. The use of *S. platensis* biomass as a biofertilizer for various leafy vegetables, including *Brassica rapa*, *Eruca sativa, B. rapa, Amaranthus gangeticus, Brassica oleracea,* and *B. rapa*. The results demonstrated that *Spirulina*-based biofertilizers significantly promoted plant growth by improving key biometric parameters such as leaf count, plant height, root length, and overall biomass, along with enhancing seed germination rates [61].

Microalgae, especially cyanobacteria, play a key role in managing soil-borne diseases and pathogenic fungi in plants through the production of biologically active compounds [62]. The green alga C. *vulgaris* produces chlorellin, a bioactive compound known to inhibit the growth of both Gram-negative and Gram-positive bacteria. This marked the first documented instance of an algal-derived substance exhibiting biopesticidal activity [63,64]. Methanolic extract of the brown seaweed *Sargassum wightii* was found to be effective against *Xanthomonas oryzae*, the bacterial pathogen responsible for rice blight

[65]. A study by Kumar *et al*. [66] demonstrated that inoculating spice crop seeds with the cyanobacteria *Anabaena laxa* and *Calothrix elenkinii* enhanced the activity of the enzyme β-1,3-endoglucanase in both shoots and roots, which is known to degrade components of pathogen cell walls. In addition, the treatment led to increased fungicidal activity, along with improvements in plant dry weight, and shoots and root length. Microalgae consist of sesquiterpenes, alkaloids, and amines that have insecticidal properties [67]. Eremophilone, a sesquiterpene found in microalgae *Calothrix* spp., has insecticidal properties and can effectively control pests in *Oryza sativa* [68]. The cyanobacterium *Nostoc* spp. ATCC 53789 produced cryptophycin 1, an active depsipeptide. This chemical exhibits antiproliferative and antimitotic properties, primarily inhibiting the cell cycle during the metaphase of mitosis in yeasts of the *Cryptococcus* genus [69].

5. MICROALGAL NUTRACEUTICALS

Cyanobacteria and other microalgal species have inimitable property to perform photosynthesis and convert the solar energy into chemical energy in form of ATP which is further used in production of bioactive compounds [56]. The word "nutraceutical" in general is categorized as the combination of "nutrition" and "pharmaceutical," that is, compounds that having properties of being used as food supplements and in prevention of chronic diseases. Nutraceutical compounds are mainly dietary derivatives extracted initially from plants but now shifted toward algae with easy cultivation and culturing and beneficial effects [70]. In China around 2000 years, the first use of algae (*Nostoc*) by humans is observed to survive during famine and after that a much research on algal derivatives nutraceutical compounds are still performed to feed over growing population [71]. Since the past 20 years, nutraceutical application of microalgae has focused specifically on four major microalgae: *Spirulina* (*Arthrospira*), *Chlorella, Dunaliella*, and *Haematococcus*. Beside this, *Nostoc, Aulosira, Phormidium,* and *Anabaena* are also potent source of bioactive compounds as well as secondary metabolites including fibers [9,14]. On the other hand, due to presence of minerals, vitamins (A, C, B1, B2, B6, and niacin) and micro/macro-nutrients make microalgae a valuable food supplements in Asian countries where population is not under control and also throughout the world [9,56].

Among different genera of blue-green algae, *Spirulina* is grown worldwide and used as a food supplement due to having highest protein content and thus also called as SCP [72]. Along with protein, *Spirulina* is also a rich source of PUFAs [73], pigments [74,75], and vitamins and phenolics [76]. There are two species of *Spirulina* having different geographical distributions, that is, *S. platensis* diversified in Africa, Asia, and South America while *S. maxima* is confined to Central America. Commercialization of *Spirulina* is common in India, Taiwan, China, Bangladesh, Pakistan, Burma (Myanmar), and USA. The species of *Spirulina* is commonly used as a protein supplement because having low purine concentration hence risk associated with high uric acid accumulation is very low in human beings [77] and it also lowers the cardiovascular diseases by reducing the cholesterol level [78]. Further, *Spirulina* also has good source of PUFA hence high oil content (7%) in form of α-linolenic acid, ϒ-linoleic acid (GLA), stearidonicacid, eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and AA. In study of [79], the nutraceutical property of *Spirulina* is further improved by fermenting it with the lactic acid bacterium *Lactobacillus plantarum*. The GLA, AA, EPA, and DHA are mainly extracted from *Spirulina, Porphyridium, Nanochloropsis, Crypthecodinium,* and *Schizochytrium* that extensively used as nutritional supplements for infants [80]. Besides, this major compound that is extracted from cyanobacteria is phycocyanin (a blue photosynthetic water-soluble pigment) and carotenoids (functions as photo-protection) that extensively used as food supplements and in cosmetic industries. Number of workers has reported high phycocyanin content in different species of cyanobacteria such as *Nostoc, Anabaena, Spirulina,* and *Phormidium* [81,82]. Cyanobacteria are also good source of PS having different glycosidic bonds that is used as an important food supplements. Cyanobacteria *Aphanothece halophytica* are good source of galactose and mannose [83] while immulina and immurella were isolated from *S. platensis* [84].

Another important microalga having nutraceutical property is the green algae *Chlorella*. The name *Chlorella* was derived from the Greek word "chloros" and the Latin "ella" that mean green and small, respectively. *Chlorella* is originated on earth during pre-Cambrian period about 2.5 billion years ago and in current situation Japan is the world leader in *Chlorella* microalgae consumption [85,86] and the dried biomass contains about 45–55% protein, 20% fat, 20% carbohydrate, 5% fiber, 9–18% dietary fiber, 10% minerals and vitamins, and other important bioactive compounds [87]. Being a green algae *Chlorella* contains both chlorophyll-a and chlorophyll-b as light harvesting pigment and considered as the richest source of chlorophyll available. Core of various species discovered–*C. vulgaris* is the most researched until now. Consumption of protein in human diet is very essential for building block of muscles because proteins are the ultimate source of protein and essential amino acids. As compared to protein present in beef meat, the proteins in *Chlorella* are 3 times more and easily digested due to low-molecular-weight and thus play an important preventive role on cellular damage [88]. Further, *Chlorella* is also a potential source of fatty acids in form of oleic, palmitic, and linolenic acid. Other species such as *Chlorella emersonii*, *Dunaliella*, *Nannochloris*, and *Phaeodactylum tricornutum* reported to contain more than 50% lipid content [89,90]. Ferreira *et al*. [91] compared to the fatty acid profile in form of production of long chain (LC) PUFAs in *Chlorella homosphaera, Chlorella* spp. and *Chlorella minutissima* grown in BG 11 or basal media led to the foundation that lipids in dry mass of these strains are 22.4% w/w, 21% w/w, and 21.5% w/w, respectively. This study mainly describes the role of *Chlorella* in production of PUFAs, particularly the essential fatty acids that can be applied in the food production. *Chlorella* also produces PS and major PS is the β-1,3-glucan that is used as an antioxidant, immune-stimulator, and effectively reduces the blood lipid levels [71]. Monosaccharide (glucose) along with galactose, mannose, rhamnose, N-acetylglucosamide, and N-acetylgalactosamine is some major PS excessively synthesized by *Chlorella pyrenoidosa*, and *Chlorella ellipsoidea* that is used as food supplement [92,93]. *Chlorella* is an important source of vitamins and minerals and it can be easily consumed as food supplement by both adults and children for the fulfillment of their daily dietary intake of vitamins. Vitamins that present in *Chlorella* spp. are Vitamin B1, B2, B3, B5, B6, E, K, α-carotene, and β-carotene. Beside this, trace amount of folic acid (Vitamin B9) is also present in *Chlorella* that plays an important role in regulation of basal metabolism of cells and also protects the skin and mucous membranes as well as strengths the bones and teeth [94].

Next to *Chlorella*, another important unicellular green alga is *Dunaliella* mainly *D. salina* that is a potent source of important nutraceutical compounds such as β-carotene, glycerol, and protein that can easily be dig out through its thin cell wall. Being a marine green algae culturing of *Dunaliella* is done in brackish water, marine water, and highly saline water and the annual production is around 1200 tons dry weight per year [95]. *Dunaliella* is mainly cultured for extraction of β-carotene and Israel, China, USA, and Australia are the leading contributors around the world. In recent time, more advance techniques are used for production of Betatene by AquaCarotene Ltd. Cyanotech Corp, Nature Beta Technologies, and Western Biotechnology [96]. Apart of β-carotene, *Dunaliella* also used in the production of trace amount of lutein and lycopene [97] and yields around 400 mg β-carotene/m^2 of cultivation area under optimum environmental condition [98]. Beside consumptions as food supplements, carotenoids from *Dunaliella* are a good free radical scavenger which results in decrease membrane damage, enzyme inactivation, and thereby increased the production. Beta-carotene is used as an orange dye and as a Vitamin C supplement. Protein, fat, and carbohydrate content in the 100 mg dry mass of *Dunaliella* is around 7.4, 7.0, and 29.7 mg, respectively. *Dunaliella* also serve as potent source of nutrients such as magnesium (Mg) and some vitamins such as Vitamin B1 (thiamin), Vitamin B2 (riboflavin), Vitamin B3 (niacin), Vitamin B5 (pantothenic acid), Vitamin B6 (pyridoxine), Vitamin B9 (folic acid), and Vitamin B12 (cobalamine).

Another important unicellular biflagellate freshwater green microalga is *H. pluvialis* cultivated mainly for extraction of strong antioxidant astaxanthin (up to 2–3% on dry weight) under favorable or unfavorable conditions [99,100]. Consumption of astaxanthin is proved to be a good nutritional supplement and also act as an anti-inflammatory and anticancer agent for cardiovascular diseases. Due to this property, dry biomass of *H. pluvialis* has widely used in production of capsules, creams, granulated powders, oils, soft gels, syrups, and tablets [101]. Photoautotrophic culture of *H. pluvialis* is mainly carried out in open raceway ponds or closed photobioreactors. The cellular composition of *H. pluvialis* varies notably between its "green" and "red" stages of cultivation [102]. *H. pluvialis* can accumulate approximately 5% DW of astaxanthin which is considered as a natural source of this high-value carotenoid protein. Beside this, *H. pluvialis* is also potent source of proteins, lipids (phospholipids and glycolipids), carbohydrates, carotenoids, neoxanthin, violaxanthin, β-carotene, lutein, zeaxanthin, adonixanthin, adonirubin, canthaxanthin, echinenone, and chlorophylls [98]. The sources and impact of various bioactive compound of nutraceutical importance is listed in Table 1 [103-114] and their detail application is described in Figure 1.

6. MICROALGAL PHARMACEUTICAL

Microalgae are potent sources of various bioactive compounds (carbohydrates, lipids, PUFA, proteins, vitamins, and enzymes) having pharmaceutical properties and thus extensively used in pharmaceutical industry [115]. Further, fluctuating environmental condition such as deprivation of minerals and nutrient, light (high and low), temperature (heat and cold), and pH significantly enhance the synthesis of microalgae-based secondary metabolites [116]. Microalgae-based nutraceutical compound is β-carotene, omega-3 fatty acids, and algal oil, and due to this, microalgae are tremendous choice [56]. Thus, rising call for these compounds overlays the approach for sustainable microalgal technology [117]. The secondary metabolites were primarily extracted from plants but due to lesser production and seasonal dependency, the attention is engrossed toward the microalgae. The enormous kind of pharmaceutical products from microalgae is discussed below:

The extracts obtained from microalgal species possess defensive properties such as antimicrobial, antiviral, and antifungal properties, for example, certain species such as *Chlorella* and *Spirulina* are abundantly used in dermatology, as a constituent to the skin care product as well as also vastly used in sun protection regime and hair care treatments [118,119]. However, certain species along with pharmaceutical products also produce other toxic substances such as *Ochromonas* spp. The antibacterial activity to the microalgae is attributed due to presence of highly volatile compounds such as phenols and fatty acid [119]. Further, several current researches have geared toward the production of neuroprotective compounds to treat Alzheimers syndrome, memory loss, cognitive impairment, neural death, dementia, and brain damage [120]. The Neuroprotective products decelerate the progress of disease related to the nervous system by reducing the reactive oxygen species damage that causes to the brain in neurodegenerative diseases. The microalgal species are well-known to produce such compounds that are beneficial against the nerve persistence. For example, *Spirulina* spp. is seen to encompass 14.18% of phycocyanin (having neuroprotective properties) that providing protection and reducing cognitive impairment such as Alzheimer's Disease or Parkinson's Syndrome [121,122]. In recent years, microalgae have proven to be an ideal model for safer, efficient, and economic means of therapeutic production. Therapeutic proteins from microalgae are a cost-effective process which reduces the increasing burden on the treatment of cancer and other diseases that involve expensive treatments [123]. The green algae *Chlamydomonas reinhardtii* has been testified for large-scale production of certain protein such as vascular endothelial growth factor, high mobility group protein 1, Domain 14 human fibronectin, and Domain 10 of human fibronectin. Furthermore, certain studies specify that human proinsulin has also been produced by microalgae [124].

Cosmetological products such as eyeliners, lipsticks, eye shadows, moisturizers, facial cleansers, and beauty masks actively use compounds extracted from *Chlorella* and *Spirulina* [125]. Beside this, *Chondrus crispus* (Irish moss) is well known for the persuasive source of carrageenan (PS) which basically used in dermatological product primarily in skin and hair regime formulations. Similarly, non-toxic nature of cyano-phycocyanin is used as a potential substance for the topical treatment of various skin diseases in place of conventional medicine due to less side effects [126].

It has also been reported that algal extracts also used in manufacturing of drugs which are sustainable and cost-effective. For example, anti-cancer drugs such as cryptophycin 1, apratoxins, dolastatins, saxitoxin (local anesthetics), and brevetoxins (polyketide toxins) are typically isolated from blue-green algae (cyanobacteria) [127]. The various pharmaceutical compounds from microalgae are shown in Table 1. Several genera of algal species, such as *Spirulina, Botryococcus, Chlorella, Dunaliella, Hematococcus,* and *Nostoc* spp., have been reported to yield valuable bioactive compounds having pharmaceutical properties [128-130]. Cyanobacteria (blue green algae) are well recognized to yield metabolites (both intracellularly and extracellularly) with impending biological actions [131,132]. Further, *Arthospira* are widely used in the cure of diabetes, obesity, and hypertension along with cancer [133,134]. Similarly, *Nostoc* is widely used in the medical field as a dietary supplement as it is rich source of protein, vitamin, and fatty acid [132]. These essential fatty acids are precursors of prostaglandins, which is gaining noteworthy recognition in pharmaceutical industry. Parallel it is also used in the treatment of fistula and cancer. The *Nostoc* also contains protein called cyanovirin which is used in treatment of HIV and influenza [135]. Thus, these necessitate the cultivation of microalga and cyanobacteria on large scale to accomplish human welfare [136,137]. On a similar note, *Chlorella,* which falls under green alga was earlier being used in food as it is an edible alga, and is now well-known food supplement of high nutra-efficiency. It contains high proportion of chlorophyll, vitamins

Table 1: Bioactive compounds from microalgae and cyanobacteria and their potential role.

Class of compounds	Bioactive from microalgae	Microalgae	Potential use	References
Polyunsaturated hydrocarbons	β-carotene Lutein	• *Botryococcus braunii* • *Chlamydocapsa* spp. • *Chlorella sorokiniana* • *Chlorococcum* spp. • *Dunaliella*	Used as cosmetics additives as natural food coloring agents and as health food, Possess properties like Anti-aging, help in curing coronary disease prevention, cancer, immune control, retinal and sensory disability enhancement and low-density lipoprotein	[103-105]
Lipids fatty acids	Arachidonic acid, Eicosapentaenoic acid, Docosahexaenoic acid	• *Spirulina* • *Porphyridium* spp. • *Scenedesmus* • *Lobosphaera incisa* • *Crypthecodinium cohnii*, *Nannochloropsis* spp. • *Schizochytrium* spp. • *Ulkenia* spp. • *Phaeodactylum tricornutum*	Enhancing cardiovascular health, fostering mental growth, and support, offering anti-inflammatory properties guarding against atherosclerosis, boosting nervous system and cognitive function, promoting infants' growth, functional advancement, and vision improvement.	[106]
Phenolic	Chlorogenic acids and caffeic acids	• *Isochrysis* spp. • *Chlorella vulgaris* • *Nannochloropsis* spp.	Exhibiting anti-cancer effects, blocking HIV-1 integrase activity, reducing the mutagenicity of carcinogenic compounds, and containing antioxidant and antispasmodic properties.	[107]
Phenolic	Astaxanthin, Canthaxanthin, Violaxanthin	• *Haematococcus* spp. • *Chlamydomonas nivalis* • *Chlorococcum braunii* • *Chlorella vulgaris* • *Chondria striolata* • *Monoraphidium* spp. • *Tetradesmus obliquus* • *Chlamydocapsa* spp. • *Chlorococcum* spp.	Enhancing skin protection, promoting eye health, boosting muscle strength and endurance, shielding against oxidative damage, serving as additives in aquaculture feeds and nutraceuticals, defending against cancer, inflammation, metabolic syndrome, diabetes, neurodegenerative and ocular diseases, as well as lung injury, restraining alveolar wall swelling and myeloperoxidase activity. Additionally, it exhibits anti-proliferative activity, increases Vitamin E levels, and possesses antioxidative, anti-inflammatory, and neuroprotective properties.	[104,108]
Phycobili protein	Phycocyanin Phycoerythrin Porphyridium chlorophyll a Proteins	• *Anabaena. flos-aquae* • *Caulerpa racemosa* • *Ulva lactuca* • *Caulerpa racemosa and Spirulina* • *Porphyridium* • *Scenedesmus* • *Chlorella* spp. • *Microcystis aeruginosa*	Improves light utilization efficiency, food coloring agents, food antioxidants, humans and plants Functional foods, animal feed supplements, bioplastics production, antioxidant properties, immune activators, prevent atherosclerosis, cancer, and coronary diseases, and also used in photo-ageing protective formulations, cytotoxicity toward tumoral cells	[103,109]
Vitamins	Vitamins D and K B_{12}, B_9, B_6 A, C, D, E	• *Spirulina* spp. • *Chlamydomonas* spp. • *Chlorella* spp. • *Scenedesmus* spp. • *Dunaliella tertiolecta* • *Nannochloropsis oculata* • *Chaetoceros calcitrans*	Antioxidants serve as food supplements and sources of essential vitamins, contributing to the reduction of breast cancer risks, promoting DNA repair and histone methylation, and exhibiting chemo-preventive activities. They are also utilized in nutraceuticals and cosmetics.	[110,111]
Polysaccharides	Starch, cellulose, hemicellulose, pectin Sulfated	• *Chlorella vulgaris* • *Fucus vesiculosis* • *Margalefidinium polykrikoides* • *Porphyridium* spp., • *Turbinaria conoides* • *Sargassum wightii* • *Porphyra* spp.	Nanocellulose finds applications in biofilters, biofuels, cosmeceuticals, bioplastics, and more. Extracts from *Laminaria* spp. offer preventive and therapeutic benefits across various stages of viral infections, including inhibiting reverse transcriptase in HIV infections and blocking cytopathic effects and cell adhesions during viral infections. Certain molecules derived from algae can be utilized in vaccines and antibody production for preventing and treating COVID-19. Additionally, these extracts demonstrate antioxidative, immunomodulatory, and anti-inflammatory properties.	[111,112]
Polysaccharides	Carrageenan naviculan, fucoidans, lectin, agar, laminaran, alginate, glycosaminoglycan			[113,114]

(B_{12}) and minerals, proteins, and amino acids, PS [137]. *Chlorella* also possesses medicinal properties which are widely applied in pharmaceutical industry. Several reports suggest that *Chlorella* is endowed with antitumor, anticoagulant, antioxidant, antiviral property, as well as hepato-protective property [71,138]. The most important bioactive compound obtained from *Chlorella* is β-1, 3 glucan, which is an active immune stimulator that diminishes oxidative stress as well as maintains the blood cholesterol. Another important green alga is *D. salina* which is a halo-tolerant microalga that has been widely premeditated for its pharmaceutically active compounds. It is a potent source of glycerol, carotenoids, lipids, and other bioactive compounds. Due to high β-carotene content, it is consumed since early. The bioactive compounds extracted from *Dunaliella* possess, antihypertensive, broncho-dilatory, and anti-edemal properties [139]. It also displays antibacterial activity against various microorganisms, hence, an important agent for food industry. An important ingredient from *Dunaliella* possesses a strong ability to stimulate cell proliferation and improve the energy metabolism of the skin. Therefore, culturing and harvesting of microalgae to fulfill the food demand along with rectifying health issues which considered as a new tool in field of pharmaceutical and nutraceutical industries. The sources and activity of various pharmaceutical compounds extracted from cyanobacteria and microalgae are listed in Table 1 and Figure 1.

6.1. Emerging Biotechnology and Omics for Microalgal Metabolites

Microalgae have an incredible ability to synthesize a variety of metabolites during their growth, including pigments, LC-PUFAs, starch, proteins, bio-hydrogen, and other valuable compounds [140,141]. Various approaches such as omics, clustered regularly interspaced short palindromic repeats–CRISPR-associated protein (CSIPR/Cas), and genetic engineering (transcription activator-like effector nucleases [TALENs] and zinc-finger nucleases [ZFNs]) are commonly used to increase the production efficiency of these high-value metabolites [142-144]. Genome sequences are critical in reconstructing metabolic pathways. In contrast to genomics, metagenomics focuses on complete microbial populations, offering additional information from DNA data extracted directly from environmental samples [145]. An omics-based technology employs a systematic, stepwise strategy to engineer organisms for the efficient biosynthesis of targeted products [146]. A study was conducted to assess intracellular responses to the synthesis of 3-hydroxypropionate (3-HP), a valuable compound synthesized by *Synechocystis* spp. PCC 6803 using proteome and metabolomic methods. The study concluded that cellular processes were differentially controlled, and overexpressing particular transporter genes boosted 3-HP synthesis [147,148].

Recent progress in molecular technologies has provided the foundation for precise genome editing. The principal strategies developed for this purpose include ZFNs, TALENs, and the CRISPR-Cas [149,150]. Song *et al*. [151] employed RNP-mediated CRISPR/Cas9 technology to produce highly purified zeaxanthin by preventing lutein synthesis through knocking ZEP gene and α-branch of lycopene epsilon cyclase gene, resulting in 60% greater zeaxanthin yield than the parental strain in Chlamydomonas reinhardtii. Lin *et al*. [152] employed the CRISPRa/i system to regulate gene expression in *Chlorella sorokiniana* UTEX 1602. They found that gene regulation by dCas9-VP64 (CRISPRa) boosted protein content by about 60% (w/w), but gene regulation through dCas9-KRAB (CRISPRi) raised protein content to 65%, with lipid accumulation ranging from 150 to 250 mg/L (WT: 150 mg/L). Hao *et al*. [153] conducted a functional characterization of long-chain acyl-CoA synthetase (LACS) isozymes by generating CRISPR/Cas9-mediated knockouts of the ptACSL1–5 genes. Their study demonstrated the feasibility of producing gene knockout mutants through large-fragment deletions using multiplexed CRISPR/Cas9 and provided valuable insights into the functional roles of LACS isozymes in regulating lipid metabolism in oleaginous microalgae. A study by Daboussi *et al*. [154] reported that TALEN-mediated silencing of UDP-glucose pyrophosphorylase, a carbohydrate storage pathway gene, resulted in a 45-fold increase in triacylglycerol accumulation in *P. tricornutum*. Overexpression of FAX1**,** FAX2**,** and ABCA2 genes led to a 1.8-fold increase in starch accumulation under nitrogen-deprived conditions and a 53% increase under nutrient-replete conditions in *Chlamydomonas reinhardtii* [155]. Advances in genetic engineering technologies and metabolic engineering have enormous potential for the development of sustainable microalgal cell factories.

7. FUTURE PROSPECTS

Microalgae are a potent source of valuable bio-resource for pharmaceuticals and nutraceuticals due to their rich biochemical composition. However, several bottlenecks exist in the utilization of microalgae for these purposes, and future research directions aim to address these challenges and enhance their viability. Future research may involve genetic engineering, biotechnological approaches, and selective breeding to enhance traits such as growth, primary and secondary bio-active compounds. These modern technologies will optimize productivity, reduce costs, and minimize environmental risk. Moreover, recent cultivation systems such as photobioreactors, open ponds, and hybrid systems are under practice to enhance sustainability. Future research directions may include exploring novel extraction techniques such as supercritical fluid extraction, ultrasound-assisted extraction, and enzyme-assisted extraction to improve yields and purity. Research on the development of innovative microalgae-derived products and formulations tailored for pharmaceutical and nutraceutical applications is essential. This includes encapsulation techniques to improve stability and bioavailability, as well as formulation optimization to enhance sensory attributes and consumer acceptability. Addressing regulatory requirements and market demands is crucial for the commercialization of microalgae-based products. This will include conducting safety assessments, establish quality standards, and explore market trends to ensure compliance and competitiveness in the pharmaceutical and nutraceutical industries. Microalgae show promise as bio-resources for pharmaceuticals and nutraceuticals, but key research and bottleneck challenges must be addressed to unlock their full potential and enable mainstream adoption.

8. CONCLUSION

Microalgae are a diverse group of unicellular photosynthetic prokaryotic and eukaryotic organisms that are ubiquitous in nature ranging from usual to extreme habitats. Their economic importance worldwide is associated with a wide range of applications of microalgae, from the food industry to medicine, from immunostimulants to biofuels, from cosmetology to agriculture. In near future these microalgal species are uses as super food due to having valuable bioactive ingredients such as proteins, lipids, and carbohydrates as well as various phytochemicals such as carotenoids, PUFAs, sterols and phenolics. These bioactive compounds can exhibit considerable health promoting effects, such as antioxidant, anti-inflammatory, anti-cancer, and antimicrobial effects [Figure 1]. Microalgae biomass is a promising source of both nutritional and functional additives. The microalgal species behaves as commanding asset for renewable and highly quantitative production because they require minimum resources, land, and also easily cultivated under adverse environmental conditions. Furthermore, with the advancement in recombinant DNA technology, these microalgae can be easily manipulated genetically, thus enhancing their interest for production of valuable bioactive compounds. Thus, the large-scale production of microalgae may lead to fulfillment of human need for food and nutrition as well as various bioactive compounds.

9. AUTHORS' CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agreed to be accountable for all aspects of the work. All the authors are eligible to be an author as per the International Committee of Medical Journal Editors (ICMJE) requirements/guidelines.

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This study does not involve experiments on animals or human subjects.

13. DATA AVAILABILITY

All the data is available with the authors and shall be provided upon request.

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15. USE OF ARTIFICIAL INTELLIGENCE (AI)-ASSISTED TECHNOLOGY

The authors declares that they have not used artificial intelligence (AI)-tools for writing and editing of the manuscript, and no images were manipulated using AI.

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