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Microalgae: Sustainable Cell Factories for Functional Foods and Ingredients

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Abstract

Microalgae are unicellular photosynthetic organisms that offer a sustainable solution for producing bioactive compounds essential for human health. Due to their biochemical versatility and minimal resource requirements, they serve as an efficient cell factory for synthesizing functional ingredients like proteins, omega-3 fatty acids, carbohydrates, vitamins, and antioxidants. This review highlights recent advancements in microalgal biotechnology, emphasizing their potential to meet the rising demand for diverse and nutritionally enriched foods. The adaptability and capacity of microalgae for genetic and metabolic engineering enable the production of targeted compounds, paving the way for tailored functional food and ingredient development. To achieve full-scale industrial implementation, it is imperative to address challenges including scaling up cultivation processes, optimizing metabolic pathways, and maintaining stable gene expression. The integration of systems biology with bioprocess engineering principles offers significant potential for improving productivity, advancing sustainability, and enhancing economic feasibility. As global dietary preferences evolve towards plant-based options, microalgae emerge as key players in reshaping the food and ingredient industries towards more environmentally conscious practices.

Keywords: Cell Factory, Functional Foods and Ingredients, Microalgae

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1. Introduction

Microalgae, a diverse group of unicellular photosynthetic organisms, have emerged as a promising frontier in the realm of sustainable biotechnology. Their microscopic size and ability to harness solar energy through photosynthesis make them efficient producers of a wide range of bioactive compounds essential for human health [1-2]. Microalgae are classified into various species such as *Chlamydomonas* sp., *Chlorella* sp., *Arthrospira (Spirulina)* sp., *Haematococcus* sp., etc., which are light-driven cell factories that synthesize bioactive compounds from primary metabolites such as lipids, proteins, and carbohydrates and secondary metabolites such as pigments, carotenoids, vitamins, and minerals at various their growth stages [3-4]. This biochemical versatility endows microalgae with considerable utility as valuable reservoirs for sustainably synthesizing functional ingredients, offering an environmentally conscientious alternative to conventional sources with a substantially diminished ecological footprint [5].

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The global population, set to reach 9.7 billion by 2050 according to the United Nations, propels a correlated surge in food demand [6-7]. Transformative shifts in dietary patterns, notably in emerging economies, manifest an inclination toward diverse, economically valuable foods. This trend aligns with a preference for nutritionally enriched diets and the growing popularity of functional foods, offering health benefits beyond basic nutrition [8]. The increasing consumer awareness of health and wellness has led to a notable shift in behavior, fostering a demand for food products that offer more than basic nutritional value. This demographic transformation substantively fuels the market for a variety of food products. The intricate interplay between demographic shifts, dietary preferences, and the demand for innovative food products underscores the multifaceted evolution of global food [6].

As consumers increasingly lean towards natural, plant-based options, microalgae offer a promising way to produce functional ingredients like omega-3 fatty acids, antioxidants, and protein-rich biomass or plant-based protein [4-5, 8]. This inherent versatility positions microalgae as dynamic cellular entities with the capacity to adapt to and address the evolving requirements of the food and nutraceutical sectors [6-8]. The latent potential of microalgae, as sustainable and adaptable cell factories, stands as a pivotal force capable of reshaping the paradigm of food and ingredient production. In contrast to conventional crops, microalgae necessitate minimal land and water resources, presenting an environmentally friendly alternative [5]. Notably, microalgae possess a distinctive capability to sequester carbon dioxide through photosynthesis [2-6]. Leveraging this trait, microalgae cultivation can be seamlessly integrated into carbon capture strategies, thereby mitigating greenhouse gas emissions [9]. Furthermore, microalgae contribute significantly to environmental remediation by extracting nutrients from wastewater. This dual functionality aligns seamlessly with the tenets of a circular economy and sustainable resource management. Consequently, these efficiencies culminate in a more sustainable production process characterized by diminished inputs and a mitigated environmental impact [10-11].

This review aimed to present the recent advancements in microalgal biotechnology, emphasizing their potential as cell factories for the production of bioactive compounds, which are utilized as functional food and ingredients essential for human health.

2. Biochemical Composition of Microalgae

The biochemical composition of microalgae is a harmonious blend of proteins, lipids, carbohydrates, pigments, vitamins, minerals, antioxidants, and other bioactive compounds. The diversity in nutritional content among different microalgae species presents a vast array of options for developing functional foods and ingredients [12].

2.1. Proteins

Microalgae contain a protein content that varies from 30-80 mass percent, and their protein production can exceed that of conventional land crops by more than 10 times [13]. Microalgal proteins possess a well-balanced amino acid profile, meeting the nutritional guidelines established by the WHO, FAO, and UNU for human and animal dietary requirements. Their capacity to provide essential amino acids in ample quantities designates these proteins as high-quality sources [14]. Certain microalgae as listed in Table 1, including *Haematococcus* sp. [14], *Chlorella* sp., *Dunaliela* sp. [15], *Nannochloropsis* sp. [16], and *Spirulina* sp. [17] are recognized as valuable protein sources due to their favorable amino acid composition such as alanine, arginine, glutamic acid, isoleucine, leucine, lysine, phenylalanine, threonine, and valine.

Table 1 The composition of amino acids in proteins present in different types of microalgae species

Amino acid	Amino acid content (g/100g protein)				
	H. pluvialis	*C. vulgaris*	*D. salina*	*N. oceanica*	*S. platensis*
Alanine	11.14 ± 1.44	10.82 ± 0.32	10.99 ± 0.32	2.95 ± 0.12	6.07 ± 0.20
Arginine	5.63 ± 0.37	7.33 ± 0.21	8.16 ± 0.24	2.60 ± 0.01	4.85 ± 0.12
Aspartic acid	1.42 ± 0.04	8.54 ± 0.25	9.56 ± 0.28	4.93 ± 0.02	7.24 ± 0.11
Cysteine	0.44 ± 0.02	1.47 ± 0.04	1.63 ± 0.04	0.26 ± 0.05	1.12 ± 0.02
Glutamic acid	8.96 ± 0.88	10.28 ± 0.30	12.41 ± 0.37	4.78 ± 0.03	9.04 ± 0.01
Glycine	9.60 ± 0.67	7.14 ± 0.21	8.71 ± 0.26	2.65 ± 0.01	3.94 ± 0.27
Histidine	1.85 ± 0.06	1.52 ± 0.04	1.73 ± 0.05	0.77 ± 0.01	8.06 ± 0.37
Isoleucine	1.85 ± 0.03	3.36 ± 0.10	4.09 ± 0.12	1.88 ± 0.03	4.66 ± 0.41
Leucine	8.13 ± 0.37	8.41 ± 0.25	9.58 ± 0.28	3.20 ± 0.04	6.13 ± 0.23
Lysine	8.70 ± 0.36	5.35 ± 0.16	5.99 ± 0.17	2.67 ± 0.01	6.84 ± 0.19
Methionine	1.79 ± 0.06	2.52 ± 0.07	2.79 ± 0.08	0.98 ± 0.01	1.91 ± 0.37
Phenylalanine	5.44 ± 0.26	6.17 ± 0.18	6.98 ± 0.20	2.27 ± 0.23	5.34 ± 0.30
Proline	5.50 ± 0.24	5.08 ± 0.15	5.23 ± 0.15	2.21 ± 0.02	1.65 ± 0.31
Serine	6.85 ± 0.56	4.34 ± 0.13	4.81 ± 0.14	1.60 ± 0.01	3.32 ± 0.62
Threonine	5.18 ± 0.47	5.46 ± 0.16	5.16 ± 0.15	2.23 ± 0.01	3.44 ± 0.23
Tryptophan	0.64 ± 0.03	0.21 ± 0.01	0.18 ± 0.01	n.d.	n.d.
Tyrosine	2.75 ± 0.14	4.34 ± 0.13	4.86 ± 0.14	1.32 ± 0.03	4.18 ± 0.11
Valine	2.94 ± 0.15	6.89 ± 0.20	7.23 ± 0.21	2.50 ± 0.01	6.41 ± 0.14
Ref.	[14]	[15]	[15]	[16]	[17]

2.2. Lipids and Fatty Acids

The capability of microalgae to convert carbon into valuable compounds makes them attractive for sustainable lipid production. The predominant components of most lipids derived from microalgae are glycerol and polyunsaturated fatty acids (PUFAs), featuring chains containing twelve or more carbon atoms. Microalgae contain various types of omega-3 fatty acids, primarily comprising long-chain fatty acids (LCFAs) and very long-chain fatty acids (VLCFAs) with carbon atom counts ranging from 16 to 22. Among these, α-linolenic acid (ALA, C18:3), eicosapentaenoic acid (EPA, C20:5), and docosahexaenoic acid (DHA, C22:6) exhibit the highest omega-3 fatty acid levels, collectively constituting over 13% of the total fatty acid [18-20]. Table 2 provides information on microalgae species along with their omega-3 fatty acid contents. Interestingly, the current cost-effectiveness of producing algal PUFAs has outpaced that of biofuel production. As a result, a significant number of producers have redirected their attention to PUFA production for food, nutraceutical, and commodity oils [21].

Table 2 Lipid and free omega-3 fatty acid contents found in different microalgae.

Microalgae species	Lipid content (%w/w)	Omega-3 contents (% total fatty acid)			Ref
		ALA (C18:3)	EPA (C20:5)	DHA (C22:6)	
Chlorella sp.	28.00-53.00	13.20	1.30	n.d.	[22]
Dunaliella salina	6.00-25.00	38.4	0.05	5.12	[22]
Botryococcus braunii	9.55-26.00	11.20	2.23	3.88	[23]
Isochrysis sp.	22.00-34.10	6.30	0.90	15.00	[24]
Rhodomonas sp.	9.50-20.50	22.00	12.60	4.70	[24]
Nanochloropsis sp.	21.30-37.80	n.d.	30.80	n.d.	[24]

2.3. Carbohydrates

An essential group of macronutrient substances presented in the hydrophilic portion of microalgae biomass includes different categories of carbohydrates, with a particular focus on polysaccharides [12]. Microalgal cells contain a substantial proportion of polysaccharides, which can be categorized into three groups: structural cell wall polysaccharides (CWPS), reserve polysaccharides (RPS; such as α- and β-glucans), and extracellular polysaccharides (EPS). The diversity in microalgal cell wall structures leads to variations in the composition and configuration of CWPS, encompassing β-glucans, β-mannans, α-rhamnans, β-galactofuranans, and various heteropolysaccharides. Fibrillar components like cellulose or chitin contribute to microalgal cell wall formation. Branched starches and β-glucans are the prevailing RPS [25]. Specific genera of eukaryotic green and red microalgae, such as *Chlorella* sp., *Porphyridium* sp., *Rhodella* sp., *Botryococcus* sp., and *Dunaliellas* sp., alongside prokaryotic microalgae like *Nostoc* sp. and *Spirulina* sp., are recognized for producing substantial amounts of polysaccharides. Extracellularly released EPS forms protective layers to endure adverse environmental conditions, exhibiting cohesion and adhesion. Notably, these microalgal polysaccharides demonstrate diverse biological activities, including immunomodulation, antitumor, antibacterial, and antioxidant effects. Additionally, researchers have been examining microalgae polysaccharides and their derivatives, such as dietary fibers, as a promising prebiotic source for the development of functional foods and being utilized in medicinal applications [26].

Overview of microalgae species, their carbohydrate types, and applications in functional foods based on findings from various research studies were listed in the table 3. Microalgae carbohydrates are primarily composed of polysaccharides, starch, glycogen-like compounds, and exopolysaccharides. For instance, *Chlorella vulgaris* contains polysaccharides and dietary fibers, which are beneficial for digestive health and act as prebiotics, promoting the growth of beneficial gut bacteria [27]. On the other hand, *Spirulina platensis* is rich in glycogen-like polysaccharides, which are particularly valuable in developing low-glycemic foods, such as gluten-free baked goods, for individuals with dietary restrictions [28]. Furthermore, *Porphyridium cruentum* produces sulfated polysaccharides, known for their potent antioxidant and immune-boosting properties, making them suitable for functional beverages designed to enhance immune health [29]. The starch and exopolysaccharides from *Dunaliella salina* serve as natural thickeners and gelling agents in food applications such as sauces, soups, and functional food gels [30]. Similarly, *Nannochloropsis gaditana* provides fiber-enriched ingredients for snacks and nutritional bars that promote digestive health [31]. In addition, the complex carbohydrates and astaxanthin-linked polysaccharides in *Haematococcus pluvialis* are of interest for antioxidant-rich dietary supplements and energy drinks [32]. Meanwhile, *Tetraselmis suecica* contributes mannans and galactans, which are used as stabilizers and emulsifiers in plant-based dairy alternatives, such as vegan yogurts [33].

Table 3 Microalgae-derived carbohydrates and their applications in functional foods.

Microalgae Species	Type of Carbohydrates	Applications in Functional Foods	Ref
Chlorella vulgaris	Polysaccharides, dietary fiber	Prebiotic supplements for gut health; low-calorie food additives	[27]
Spirulina platensis	Glycogen-like polysaccharides	Low-glycemic index ingredients; gluten-free baked goods	[28]
Porphyridium cruentum	Sulfated polysaccharides	Antioxidant-rich functional beverages; immune-boosting supplements	[29]
Dunaliella salina	Starch, exopolysaccharides	Natural thickeners in sauces and soups; functional food gels	[30]
Nannochloropsis gaditana	Cell wall polysaccharides	Fiber-enriched snacks; nutritional bars targeting digestive health	[31]
Haematococcus pluvialis	Complex carbohydrates, astaxanthin-linked polysaccharides	Antioxidant-rich dietary supplements; energy drinks	[32]
Tetraselmis suecica	Mannans, galactans	Stabilizers in dairy alternatives; emulsifiers in plant-based yogurts	[33]

2.4. Pigments, Vitamins, Minerals and Antioxidants

Microalgae exhibit a vibrant spectrum of pigments, including chlorophylls, carotenoids, and phycobiliproteins. Chlorophyll imparting the green color associated with various microalgae species such as *Chlorella* sp., *Chlamydomonas* sp. and *Nannochloropsis* sp. are frequently employed in commercial production [3]. Carotenoids, such as astaxanthin found in *Haematococcus* sp. and β-carotene found in *Dunaliella* sp., contribute to red, orange, and yellow hues. These pigments not only serve as natural colorants in food but also possess antioxidant properties, enhancing the stability of functional products. Microalgae are rich sources of vitamins, including B-complex vitamins (B1, B2, B3, B6, B12) and vitamin E [12]. *Spirulina* sp., for example, is recognized for its high vitamin B12 content, making it a valuable option for plant-based diets that may lack this crucial nutrient. *Chlorella* sp. is another microalga rich in vitamins, particularly vitamin C and vitamin K, as well as minerals such as magnesium and zinc. Additionally, *Dunaliella salina* stands out for its beta-carotene content, contributing to its role as a potent antioxidant [3]. *H. pluvialis* is rich in astaxanthin, comprising 4–5% of its dry weight exhibiting various health benefits including antioxidative,anticancer, antidiabetic, and anti-inflammatory effects [4-5].

3. Advancements in Microalgal Cell Factory

Microalgae boast a remarkable metabolic complexity allowing for the production of an array of unique algae-specific compounds. Consequently, they have become heralded as versatile multiproduct cell factories. Generally, microalgae thrive on minimal resources such as light, CO_2, water, and minerals, essential for their growth through photosynthesis. However, they can also utilize additional nutrients to expedite their growth as demonstrated in Figure 1. Notably, their biochemical composition is highly adjustable through manipulating cultivation conditions, offering significant control over their output [34]. Traditionally, microalgae were cultivated in basic open ponds; however, recent advancements in research and technology have resulted in a wide range of efficient bioreactor designs optimized for high productivity [1]. In studies focusing on photobioreactors, researchers have investigated the cultivation of microalgae such as *Chlorella vulgaris* and *Nannochloropsis* sp [35]. These species are suitable for cultivation in controlled environments provided by photobioreactors, where factors such as light intensity, temperature, and nutrient availability can be precisely regulated. By fine-tuning these parameters, researchers have achieved higher biomass yields and enhanced production of functional ingredients such as omega-3 fatty acids and antioxidants [23].

Microalgae possess diverse metabolites that can be harnessed to create various compounds. Application of genetic and metabolic engineering methodologies becomes feasible to augment the synthesis of targeted compounds, modify extant biochemical products, or even introduce entirely novel metabolic pathways [34]. Genetic engineering holds promise for high-productivity strains, targeting fermentable carbohydrates or fatty acids. Strategies involve enhancing photosynthesis, modifying enzymes for lipid production, and identifying limiting steps [2]. Research in this area has yielded encouraging results across different enzymes and microalgae species, identifying potential target genes and organisms for further investigation [9]. Recent advancements in transformation methods have facilitated genetic manipulation in

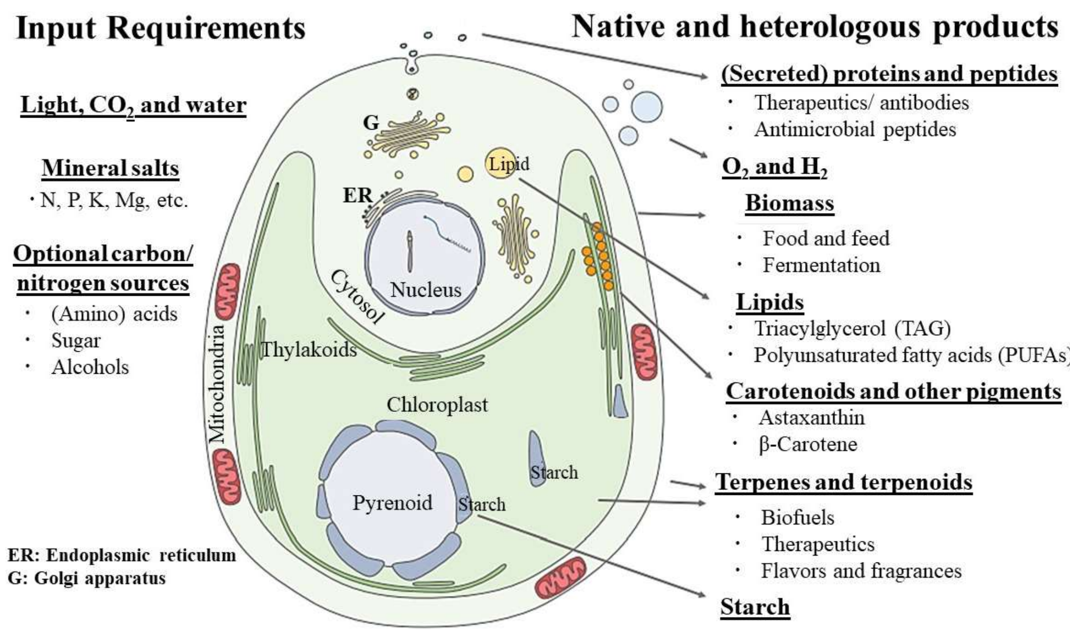

Figure 1 The cell structure of microalgae and diversity of microalgal cell factory products (Adapted from Einhaus, Baier & Kruse [34]).

various microalgal species, including lipid-producing ones like *C. reinhardtii*, *P. tricornutum*, and *Nannochloropsis* sp. Various techniques such as nanoparticle bombardment, glass bead agitation, bacterial conjugation, agrobacterium transformation, and electroporation enable the introduction of genetic material into the cell nucleus, primarily to manipulate gene expression [18]. Another promising approach is manipulating transcription factors, which can regulate multiple metabolic pathways simultaneously, offering the potential for comprehensive intervention. By redesigning enzymes in the carotenoid pathway and systematically screening for bottlenecks of *C. reinhardtii*, significant advancements have been made in enhancing astaxanthin production. A combined strategy involving the expression of β-carotene ketolase, phytoene synthase, and β-carotene hydroxylase, astaxanthin production levels have been substantially increased, offering promising prospects for industrial biotechnology [36]. Redirecting metabolic flux through the manipulation of enzyme activities and substrate availability in metabolic pathways leads to the production of target compounds. The development of the genome-scale model integrates 837 genes, 887 reactions, and 801 metabolites (iMS837) for *Synechococcus elongatus* PCC7942, representing a significant advancement in understanding and utilizing this cyanobacterium as a microbial cell factory. The iMS837 enhances comprehension of vital metabolic pathways such as fatty acid biosynthesis, oxidative phosphorylation, photosynthesis, and transport. Computational analysis with the iMS837 model identified novel targets like *fab*F enzyme overexpression, augmenting omega-3 fatty acid production [37].

4. Challenges and Future Directions

While the potential of microalgae as cell factories for functional foods and ingredients is promising, several challenges must be addressed to realize their full commercial and industrial potential. Scaling up microalgal cultivation to industrial levels while maintaining high productivity and purity remains a significant challenge. Optimization of culture conditions is crucial for maximizing biomass and metabolite production [24]. Altering metabolic pathways to enhance the production of desired compounds poses challenges in balancing target compound synthesis with cellular growth and viability. Additionally, ensuring stable gene expression and minimizing metabolic burden is critical for successful metabolic engineering efforts [36]. Continued efforts in strain selection and genetic manipulation are needed to develop high-yielding microalgal strains with enhanced productivity and adaptability [2]. Advanced bioreactor designs and process control strategies should be developed to optimize cultivation while minimizing resource consumption and environmental impact [35]. Integration of systems biology and/or synthetic biology approaches with bioprocess and metabolic engineering can provide insights into microalgal metabolism and facilitate optimized strain and cultivation process design [1, 9]. Implementation of biorefinery concepts for integrated production of multiple value-added products can enhance overall process economics and sustainability.

5. Conclusion

Microalgae represent a promising frontier in sustainable biotechnology, offering diverse bioactive compounds crucial for human health. Their adaptability, coupled with genetic and metabolic engineering capabilities, positions them as versatile cell factories addressing evolving industry demands. Microalgae provide functional ingredients like proteins, omega-3 fatty acids, carbohydrates, vitamins, and antioxidants, enhancing nutrition and product stability. Advancements in cultivation, genetic manipulation, and metabolic engineering have bolstered their productivity and specificity. By optimizing conditions and leveraging their metabolic complexity, microalgae can revolutionize functional food and ingredient production sustainably.

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