

Review

The Prospects of Algae-Derived Vitamins and Their Precursors for Sustainable Cosmeceuticals

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Abstract: Aquatic algae are a rich source of a wide range of bioproducts intended to compete for a sizable global market share. Thanks to the gradual shift towards the use of natural products, microalgae-derived bioactive compounds offer an ecofriendly and vegan option to the cosmeceutical sector, whose products aim to improve skin health but currently consist of mostly synthetic chemicals. In particular, algae-derived vitamins and their precursors are being explored and widely used in the cosmeceuticals industry as compounds that contain biologically active ingredients with therapeutic benefits. The present review highlights the current strategies for industrial production of an array of vitamins from algae for cosmeceutical applications. When compared to traditional plant sources, algae have been found to accumulate vitamins, such as A, B1, B2, B6, B12, C and E, in high concentrations. The purpose of this review is to provide context for the development of a green and sustainable algae-derived bioeconomy by summarizing and comparing the current market for vitamins and precursors derived from algae, as well as presenting novel strategies and key findings from the most recent research in this area. Emphasis is placed on novel biotechnological interventions that encompass genetic modifications, genetic engineering, and media development to enhance vitamin biosynthesis.

Keywords: algae; vitamins; skin treatment; bioactive compounds

Citation: Arora, N.; Philippidis, G.P. The Prospects of Algae-Derived Vitamins and Their Precursors for Sustainable Cosmeceuticals. *Processes* **2023**, *11*, 587. <https://doi.org/10.3390/pr11020587>

Academic Editors: Marijana Zovko Končić and Sylwia Zielińska

Received: 27 January 2023

Revised: 10 February 2023

Accepted: 14 February 2023

Published: 15 February 2023



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1. Introduction

Algae, as one of the oldest life forms, with centuries of evolution and adaptation, have undergone a variety of metabolic adaptations that allowed them to withstand harsh environmental conditions, making them a top candidate for several industrial and consumer applications [1]. Algae biomass has been used to produce energy (bioethanol, biodiesel, biogas, biohydrogen, and bio-oil) and a variety of bioproducts such as pigments, bioplastics, fatty acids, proteins, biofertilizers, biochar, vitamins, polyphenols, and phytosterols [2]. To achieve cost-competitive commercialization of algal-based biofuels and bioproducts, industry has invested in the biorefinery concept, which is based on valorization of the entire biomass (lipids, carbohydrates, proteins, and other micro-components) to marketable products [3]. In 2017, the global market for algae-based bioproducts was estimated to be USD 33 billion with a projected increase to USD 53 billion by 2026 [4]. Carotenoids (β -carotene and astaxanthin) and omega-3 polyunsaturated fatty acids (PUFA), such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are currently market leaders for high-value products [1] (Figure 1). Expanding the repertoire, algae-derived vitamins and provitamins are gaining traction as value-added products due to their high market demand and applications in the food, feed, cosmetic, chemical, and pharmaceutical industries.

Vitamins and related products, such as provitamins, biopigments, and antioxidants, are critical for overall health and immunity. More than 20 of the 30 known types of vitamins (including water-soluble and fat-soluble ones) are essential for humans and animals and must be obtained through diet or supplementation [5]. The commercial

production of vitamins occurs via chemical synthesis, extraction from natural sources, or microbial biotechnology (fermentation and biocatalysis) [6]. However, chemical synthesis uses nonrenewable chemicals, resulting in toxic waste streams, whereas extracts derived from plants and animals tend to be expensive with low yields and quality variations, urging the transition to microbe-based vitamin production, which is not only more sustainable, but also safer and more suitable for internal and external applications [7]. Moreover, owing to their renewable nature, ability to synthesize simple and complex vitamins in desirable chiral conformations, and economic viability, microbes have recently become the industry's first choice [7].

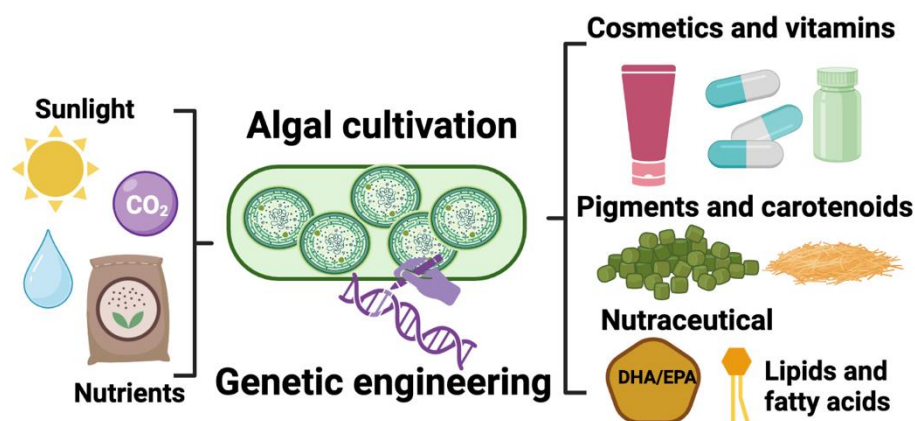


Figure 1. Synthesis of value-added products using algal strains.

Given the growing market interest and consumer awareness of natural and sustainable products, industry has begun to replace synthetic molecules with natural equivalents that are safer, renewable, and environmentally friendly. In particular, the cosmetics sector, which in 2020 had a global market size of USD 278 billion and was predicted to grow at a compounded annual growth rate (CAGR) of 5% from 2021 to 2028 [8], has demonstrated a significant shift towards products made from plants and microbes. Within the wider cosmetics sector, the use of vitamins has increased considerably owing to the hybrid nature of cosmeceuticals that straddles the line between cosmetics and pharmaceuticals. The complete list of vitamins and their market demand and CAGR is listed in Table 1. As recently reviewed elsewhere, several bacteria, yeast, and fungi species have been genetically engineered to increase intracellular vitamin production, including vitamins A, B, C, D, E, and K. [5,6].

Moreover, in addition to vitamins, algae can be exploited for several other metabolites used in the cosmeceutical industry, including mycosporine-like amino acids (such as mycosporine-2-glycine), fucosterol, scytonemin, polyphenols, squalene, carotenoids, chlorophyll, 2/3-hydroxy acids, and fatty acids (reviewed elsewhere) [9–11]. Unlike previous reviews, the current paper focuses on the potential of algae as cell factories for vitamin production in the cosmeceutical industry. The usage and role of vitamins in cosmeceuticals is summarized first, followed by a comprehensive overview of vitamin production research to date. The review also summarizes the key strategies employed to boost vitamin biosynthesis in a variety of algal strains.

Table 1. Vitamin generic and chemical names, market size and compounded annual growth rate (CAGR), and natural sources.

Vitamin (Generic Name)	Vitamin Chemical Name(s)/Class	Market Size (USD Billion)	CAGR	Natural Sources	Reference
A/provitamin A	Retinol, retinal, α -carotene, β -carotene, γ -carotene, xanthophylls, β -cryptoxanthin	0.52/0.47	4.81/6.9	Leafy vegetables, spinach, carrots	[12,13]
B1	Thiamine, thiamine pyrophosphate	0.17	13.9	Potatoes, vegetables	[14]
B2	Riboflavin, flavin mononucleotide, flavin adenine dinucleotide	1.3	6.1	Vegetables, fruits	[15]
B3	Niacin (nicotinic acid), niacinamide	0.37	2.5	Yeast, nuts	[16]
B5	Pantothenic acid, panthenol, pantetheine	0.46	6.2	Pulses, grains	[17]
B7	Biotin	1.9	5.11	Nuts	[18]
C	Ascorbic acid, dehydroascorbic acid, calcium ascorbate, sodium ascorbate	1.3	6.1	Citrus fruits, cabbage, paprika	[19]
D	Calcitriol, ergocalciferol (D2), cholecalciferol (D3)	1.3	7.1	Yeast, wheat germ oil, cabbage, citrus fruits	[20]
E	Tocopherols (α , β , γ , Δ), tocotrienols (α , β , γ , Δ)	0.67	7.54	Nuts, seeds, grains	[21]
K	Phylloquinone (K1), menaquinones (K2) and menadiones (K3)	0.79	6.89	Green leafy vegetables	[22]

2. Vitamins Used in the Cosmeceutical Industry

The cosmeceutical industry has gained a lot of interest in the last three decades as an integration of cosmetics and pharmaceuticals [23]. The term “cosmeceutical” refers to active substances that can improve skin health and prevent and treat various dermatologic conditions [24]. Vitamins, phytochemicals, antioxidants, enzymes, and essential oils are some of the key active ingredients found in lotions, creams, ointments, and other skincare products [24]. Vitamins and their derivatives (including provitamins) are widely used in the cosmetics and cosmeceutical industries due to their reported beneficial effects on the skin, including protection against dehydration, skin aging, and sun damage. Vitamins A, C, E, and B3 are the most commonly used vitamins in the skincare industry [25]. Topical application of lipophilic vitamin E (d- α -tocopherol), an antioxidant molecule, is known to treat skin conditions caused by oxidative stress, such as UV-induced erythema, edema, sunburns, and lipid peroxidation [26–28]. It also acts as a stabilizer agent in skincare formulations. Furthermore, vitamin E is used in antiaging and moisturizing formulations and is known to reduce wrinkles, lines, and sagging [29]. Due to vitamin E’s photosensitivity, it is usually used in its most stable derivative form, tocopheryl acetate, which is converted to vitamin E after skin penetration [30].

Similarly, vitamin A (retinol) is an active ingredient in acne, hyperpigmentation, psoriasis, and antiaging products [31]. It reportedly stimulates new skin cell and collagen production, thus reducing wrinkles, scars, burns, and stretch marks [32]. However, because of the potential for teratogenicity in pregnant women, the use of retinol in cosmetics is prohibited in Europe [33]. Similarly, because of safety concerns, the concentration of vitamin A derivatives in body lotions is limited to 0.05% and 0.3% retinol equivalent in hand, face,

and other rinse-off formulations [33]. As a result, vitamin A derivatives, such as retinyl palmitate, retinal, 3-dehydroretinol (vitamin A2), and provitamin A (9-cis β -carotene), that are enzymatically hydrolyzed in the skin, are preferred by the cosmetics industry [26].

Water-soluble vitamin C (L-ascorbic acid) is commonly used in a variety of topical formulations. It is well known for its ability to increase collagen synthesis, has a high antioxidant capacity, reduces hyperpigmentation, provides UV-light protection, and elicits the production of several skin lipids [34,35]. Due to the instability and aqueous nature of vitamin C, its derivatives, such as magnesium ascorbyl phosphate and ascorbyl-6-palmitate inside carrier molecules, are used in cosmetics to increase skin absorption and metabolism to the active form of the vitamin [36].

Provitamin D2 (ergosterol) and provitamin D3 (7-dehydrocholesterol) are the main sources for fat-soluble vitamin D (calcitriol) [37]. Although vitamin D can be synthesized in the skin during UV-B exposure, the use of sunscreens with a sunscreen protection factor (SPF) of 30 can reduce UV-B radiation absorption by 30% and reduce the skin's vitamin D3 production capacity by 95–98% [38]. Furthermore, colder climates, air pollution, skin pigmentation, and aging all reduce vitamin D3 synthesis in the skin significantly [38,39]. As a result, over one billion people worldwide are vitamin D deficient [38]. Moreover, vitamin D and its analogues are used to treat acne and psoriasis, which are both hyperproliferative skin conditions [40,41]. However, because of the structural similarity of vitamin D2 and vitamin D3 to the hormone testosterone, they are banned from cosmetic products in Europe and provitamins are instead used in cosmetics products in the United States [39].

B vitamins are water-soluble compounds that are divided into eight subgroups: B1, B2, B3, B5, B6, B7, B9, and B12. Vitamins B1, B2, B3, B5, and B7 are among those that are used in several dermatologic formulations and, thus, have a high value in cosmeceuticals. For example, vitamin B2 (riboflavin) is used as a yellow coloring agent in cosmetics and hair dyes, whereas vitamin B1 (thiamin) is combined with other B vitamins for skin treatments [42]. Vitamin B3 (niacinamide) is a powerful antioxidant that reportedly promotes skin lipid composition modulation, reduces transepidermal water loss, improves skin elasticity, and reduces hyperpigmentation, wrinkles, and fine lines [35,36]. Vitamin B5 (pantothenic acid) is also used in skin formulations to improve hydration, reduce itching, and soothe skin inflammation, whereas vitamin B7 (biotin; vitamin H) is a key ingredient in many hair care products [43]. Vitamin K is a fat-soluble vitamin that occurs naturally in two forms: vitamin K1 (phylloquinone) and vitamin K2 (menaquinone) [44]. It is an essential component of blood coagulation factors. It has been reported that applying vitamin K topically helps to reduce the severity and clear up bruises after laser treatment [45]. Furthermore, it has been shown to reduce skin pigmentation and prevent vascular manifestations of aging [46].

3. Microalgae as Biofactories for Vitamin Production

Currently, large-scale vitamin production is accomplished through chemical synthesis or extraction from plant, animal, and microbial sources. Industrial microbial fermentation has only been established for vitamin K2 (using engineered strains of *Bacillus subtilis*), vitamin B12 (using *Pseudomonas denitrificans*, *Propionibacterium shermanii*, and *Sinorhizobium meliloti*), vitamin B2 (using *B. subtilis* and a filamentous fungus, *Ashbya gossypii*), and vitamin C (using *Gluconobacter oxydans*, *Bacillus megaterium*, and *Ketogulonicigenium vulgare*) [6,47–49]. Despite extensive research and data on augmenting vitamin yields in heterotrophic microbes, such as bacteria, yeast, and fungi, via media/fermentation engineering and genetic manipulations (classical mutagenesis and genetic engineering), the main disadvantage of using heterotrophic microbes is the high capital cost associated with organic media components that need to contain costly sugar and other essential nutrients [5]. In this regard, photosynthetic algae have a high potential to serve as the biological chassis for commercially viable and sustainable vitamin production (Figure 2). Algae can be grown outdoors at large scale in open raceway ponds in minimal media, photosynthetically converting inexpensive atmospheric CO₂ to biomass, thereby lowering manufacturing costs, when compared to microbes. Furthermore, using recent high-throughput technologies, several algae strains can be genetically engineered

to increase endogenous bioproduct synthesis and/or produce non-native compounds. As a result, several microalgal bioproducts derived from *Dunaliella*, *Haematococcus*, *Chlorella*, and *Parachlorella* species, including proteins, omega-3, -6 and -9 fatty acids, chlorophylls, antioxidants, carotenoids, and polysaccharides, can nowadays be found in a range of cosmetics [50,51].

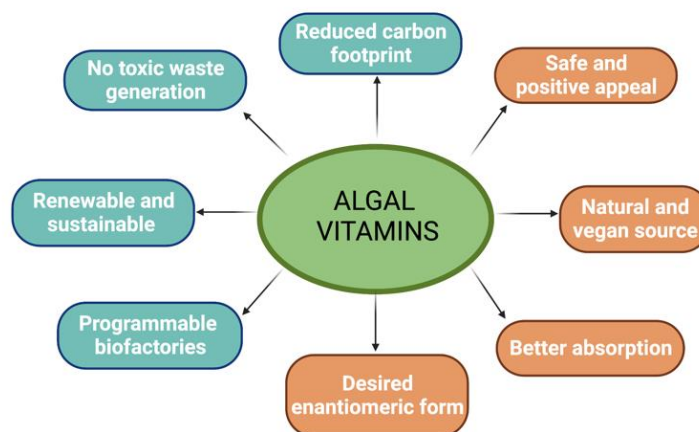


Figure 2. Advantages of algae and algal vitamins (and provitamins). Orange boxes outline advantages of algae-derived vitamins, whereas green boxes express advantages of using algae as vitamin sources.

3.1. Synthesis of Provitamin A (β -Carotene) by Algae

Both freshwater and marine algae are able to synthesize several vitamins and provitamins utilized in the cosmeceuticals industry. Indeed, the biosynthesis and yield of vitamins depends on the algal species, abiotic factors such as nutrition, light, temperature, pH, and trace elements, and photoperiod, growth phase, and harvesting conditions [1]. The first high-value commercial compound extracted from *Dunaliella salina* was provitamin A (β -carotene) [52,53]. In fact, depending on the cultivation conditions, this alga can accumulate 6–14% of ash-free dry cell weight (AFDCW) as β -carotene, leading to a yield of 100 g/Kg DCW [54]. Research is being conducted to improve the yield and lower the cost of β -carotene in *Dunaliella* and other algal strains. For example, one well-studied strategy is cultivation parameter optimization, in which physiological stress (nutrient deprivation/starvation, high salinity, temperature fluctuation, or high light intensity) has led to an increase in intracellular β -carotene accumulation, although this is generally associated with biomass loss, which reduces overall productivity. Increasing β -carotene productivity without compromising biomass has been accomplished by manipulating micronutrient concentration, such as iron and copper, addition of carbon sources (bicarbonate, acetate, wastewater, glucose), various light regimes, supplementation with phytohormones (kinetin, gibberellic acid, and indole-3-acetic acid), and two-stage cultivation that separately optimizes biomass production and β -carotene synthesis, as listed in Table 2 [55–61]. Notably, β -carotene levels are also influenced by cell growth stage, with higher accumulation reported in the stationary phase than the growth phase [62]. Bioprospecting of novel algal strains with high intracellular β -carotene biosynthesis is an active area of interest. *Tetrademus obliquus* SGM19, *T. obliquus* SGM09, *Dunaliella tertiolecta* DCCBC26, *D. salina* DF15, and *Chlamydomonas acidophila* have been reported to possess high carotene levels, ranging from 0.55 mg/g to 8.3 mg/L (Table 2).

Table 2. Production of β -carotene from algal species.

Algae	Conditions	Yield	References
<i>Dunaliella salina</i>	Media enriched with acetate (67.5 mM), FeSO ₄ (450 μ M)	70 pg/cell	[55]
	Sound frequency (200 Hz) and limited nitrate (0.25 g/L)	12.5 mg/g	[63]
	Molybdenum disulfide nanoparticles (50 μ g/L) and high light (600 μ mol photons/m ² s)	0.15 mg/mg	[64]
	Optimized glucose (15 g/L), nitrate (1.8 g/L), and phosphate (0.013 g/L)	8.12 mg/g	[58]
	8-h illumination with 400 μ mol photons/m ² s	7.24 %	[65]
	Optimized glucose (13.23 g/L), KNO ₃ (2.145 g/L), and NaCl (35.6 g/L)	6.07 mg/g	[66]
	Floating photobioreactor (PBR) using seawater desalination concentrate	14.4 g/m ³ of culture	[67]
	Stimulated diurnal irradiance in summer (14/10, light/dark and 2000 μ mol photons/m ² s maximum irradiance)	67.54 mg/L	[59]
	Flashing light (50 Hz)	16 mg/L	[68]
	Kinetin (1 μ M)	23.03 mg/L	[60]
	Indole-3-acetic acid (1 μ M)	23.03 mg/L	
	Two-stage cultivation in raceway ponds	15 mg/L	[69]
	Helix tube PBR, continuous cultivation	30 mg/L	[67]
	Modified Johnson's media with 10 mM NaHCO ₃ and high light intensity (1000 μ mol photons/m ² s)	5.9 pg/cell	[70]
	Hybrid PBR	4.85 mg/g	[71]
	Modified Johnson's media with nitrate (5 mM) and 20% NaCl	0.261 ng/cell	[72]
	UV-C mutants cultivated in 2.5 M NaCl under light intensity of 200 μ mol photons/m ² s	3.06 mg/g	[73]
	Light intensity (200 μ mol photons/m ² s) with 0.9 mM nitrate and 3.8 M NaCl	0.19 pg/cell	[74]
	Open raceway ponds	7.1 mg/L	[75]
	100 mM NaHCO ₃	0.18 mg/g	[61]
<i>Dunaliella tertiolecta</i> DCCB26	ALE, blue light adaptation in blue–red shifting wavelengths	33.94 μ M	[56]
	CRISPR-Cas9 (silencing of β -carotene hydroxylase)	1.4 mg/L	[76]
	Artificial sea water with 0.5 M NaCl	2.45 mg/g	[62]
<i>Dunaliella</i> FACHB-558	Two-stage cultivation, anaerobically digested poultry water (first stage) + BG-11 (second stage)	7.26 mg/L	[77]
<i>Dunaliella bardawil</i>	8.7 W/m ² of UV-A radiation with 250 W/m ² PAR and nitrogen deprivation	51.5 pg/cell	[78]
<i>Tetraselmis obliquus</i> SGM09	BG-11 minimal media	0.55 mg/g	[79]
		0.67 mg/g	
<i>Tetraselmis obliquus</i> SGM19	BG-11 with nitrate (1.5 g/L) and ultrasound (33 kHz and 1.4 bar at 10% duty cycle)	0.77 mg/g	[80]
<i>Tetraselmis striata</i> CTP4	Ethyl methyl sulphonate mutant	4.20 mg/g	[81]

Table 2. Cont.

Algae	Conditions	Yield	References
<i>Chlamydomonas reinhardtii</i>	Silencing of autophagy gene (ATG8) and nitrogen starvation	23.75 mg/g	[82]
	Overexpression of phytoene synthase (PSY) gene	1.2 mg/g	[83]
<i>Chlamydomonas acidophila</i>	Light intensity (240 $\mu\text{mol photons/m}^2\text{s}$)	8.3 mg/L	[57]
<i>Chromochloris zofingiensis</i>	Ethyl methylsulphonate mutant with addition of gibberellin acid-3 (10 mg/L) in two-stage cultivation (C/N = 180/1 and 200 mM NaCl)	0.52 g/L	[84]
<i>Scenedesmus</i> sp. CPC2	Overexpression of PSY gene	31.8 mg/g	[85]
<i>Phaeodactylum tricornutum</i>	Co-overexpression of 1-deoxy-D-xylulose 5-phosphate and lycopene cyclase	4.34 mg/g	[86]

BG-11: Blue green media; Hz: hertz; PAR: photosynthetic active radiation; UV, ultraviolet.

It has also been reported that exposure to UV-A radiation (320–400 nm) and photosynthetically active radiation (PAR; 400–700 nm) can be used to increase β -carotene accumulation in algae [57,78]. For example, combining 8.7 W/m² UV-A radiation with 250 W/m² PAR stimulated long-term growth of *Dunaliella bardawil* and doubled β -carotene concentration [78]. Similarly, ultrasound (33 kHz and 1.4 bar at 10% duty cycle) increased β -carotene levels in *T. obliquus* SGM19 by 31.5% when compared to a control [79]. A recent study found that combining audible sound vibrations (200 Hz) and nitrate deficiency increased β -carotene levels in *D. salina* by 37% when compared to a control (no sound vibrations and no nitrate deprivation) [63]. This increase in β -carotene levels was attributed to the beneficial effects of audible soundwaves through an increase in cell wall thickness and cell division, enhancing the alga's survival under suboptimal nutrient conditions [63]. Furthermore, the addition of molybdenum disulfide nanoparticles (MoS₂NPs) with high light irradiance (600 $\mu\text{mol photons/m}^2$) increased β -carotene accumulation in *D. salina* 1.47-fold over the control due to improved quenching of reactive oxidative species (ROS) [64].

Most of the commercial mass production of algae is carried out in open cultivation systems, including shallow big ponds, tanks, circular ponds, and raceway ponds [71]. Earlier studies have reported large-scale cultivation, operated with paddle wheels, of *Dunaliella* in oblong raceway ponds, reporting β -carotene productivity of 400 mg/m² day [53,87]. Recent studies are focused on increasing the yield by developing novel cultivation systems to decrease the media costs, reduce culture crashes, and increase ease of downstream processing. For instance, a bicarbonate-based carbon capture and algal production system in the ocean (BICCAPSO) was evaluated as a means of reducing the cost of algae cultivation [67]. The authors grew *D. salina* in an outdoor floating photobioreactor (PBR) using seawater desalination concentrate. Notably, algal growth was higher as compared to artificial seawater media, with 4.75% β -carotene accumulation at a cost of USD 42.80/kg biomass [67]. Pilot scale cultivation of a local strain, *D. bardawil*, in open raceway ponds in Eilat, Israel, for 300 days per year, exhibited an average biomass productivity of 4 g AFDCW/m² day [54]. Pilot scale cultivation of *D. salina* in open raceway ponds in Iran using two-stage cultivation achieved 7.1 mg/L β -carotene concentration [75]. Furthermore, application of closed cultivation systems using a 20 L hybrid helical-tubular PBR was designed to combine the benefits of an airlift PBR for effective mass transfer with those of an open pond system for high surface area to volume ratio, leading to a β -carotene yield of 4.85 mg/g DCW in *D. salina* [71].

Genetic manipulation and engineering efforts to increase β -carotene levels in algae have been successful. In a recent study, an ethyl methyl sulphonate (EMS) mutant of *Chromochloris zofingiensis* cultivated in a two-stage heterotrophic system with the addition of phytohormone, gibberellin acid-3 (GA-3, 10 mg/L), high carbon to nitrogen ration (C/N = 180/1), and NaCl (200 mM) resulted in 39.2% higher β -carotene accumulation than

the wild-type (WT) strain [84]. Similarly, an EMS mutant of *Tetraselmis striata* (ED 5) showed 2.3-fold higher β -carotene levels as compared to WT [81]. Another study utilized physical mutagenesis by irradiating *D. salina* cells with UV-C [73]. One of the mutants showed β -carotene accumulation at the stationary phase that was 8.5-fold higher than WT [73]. Moreover, adaptation of *D. salina* to blue light using adaptive laboratory evolution (ALE) enhanced the level of β -carotene by 19.7% compared to WT, when cultivated using a blue-red shifting light regime [56]. Furthermore, silencing of two autophagy-related genes, ATG1 and ATG8, in *Chlamydomonas reinhardtii*, using a miRNA-based gene silencing approach, revealed that under nitrogen starvation, algal mutants with ATG1 and ATG8 knockdowns showed 1.58- and 2.34-fold higher β -carotene levels compared to WT, respectively, without compromising growth [82]. The authors hypothesized that a decrease in autophagy activity triggered β -carotene biosynthesis in the alga, allowing it to quench the ROS produced by nitrogen deficiency. In another study, a synthetic phytoene synthase (psy) gene construct was expressed in *Scenedesmus* sp. CPC2, resulting in enhanced β -carotene yield of 31.8 mg/g and a productivity of 95.5 mg/L day, which are superior to most reported algae-based β -carotene production as a result of the PSY gene, which catalyzes the first step of carotenoid synthesis in algae, redirecting the carbon flux towards β -carotene formation [85]. Similar results have been reported for mutant strains of *C. reinhardtii* overexpressing the PSY gene [83]. In addition, overexpression of two key carotenogenic genes, namely, 1-deoxy-D-xylulose 5-phosphate (DXS) and lycopene cyclase (LCY), in the diatom *Phaeodactylum tricorutum*, resulted in a 0.7-fold increase of β -carotene levels compared to WT through the action of the gene DXS, which catalyzes the first step of carotenoid biosynthesis, and the gene LCY, responsible for cyclation of lycopene to β -carotene [86]. Lately, the use of advanced genetic engineering strategies, such as clustered regularly interspaced short palindromic repeat (CRISPR), has emerged as a versatile tool for genome editing in several organisms [76]. Using *D. salina*, β -carotene hydroxylase (catalyzing the conversion of β -carotene to zeaxanthin) was silenced, leading to increased β -carotene accumulation (1.4-fold) compared to WT [76].

3.2. Synthesis of Other Key Vitamins by Algae

Algal strains, such as *T. suecica*, *Isochrysis galbana*, *D. tertiolecta*, and *Chlorella stigmatophora*, have been found to synthesize vitamin A, group B vitamins, vitamin C, and vitamin E at levels higher than those derived from plant sources [88]. Among the tested algal strains, maximum vitamin A (493,750 IU; IU = 0.6 μ g of β -carotene), vitamin B1 (32.3 μ g/g), vitamin B6 (2.8 μ g/g), and vitamin C (191 μ g/g) were attained in *T. suecica*, while *C. stigmatophora* showed the highest vitamin E (669 μ g/g) and biotin (1.1 μ g/g) levels (Table 3). Other marine algal strains, such as *Tetraselmis* sp., *Pavlova pinguis*, *Stichococcus* sp., and *Nannochloropsis* sp., have also been reported to contain high levels of vitamins [89]. The content of vitamin B3 (niacin) in three macroalgal strains (*Fucus serratus*, *Laminaria hyperborea*, and *Rhodymenia palmata*) was found to be 23.0 g/g, 19.0 g/g, and 25.5 g/g, respectively [90]. Similarly, phytoplankton, such as *Skeletonema costatum*, *Stephanopyxis turris*, *Gonyaulax polyedra*, and *Coccolithus huxleyi*, have been shown to release vitamin B1 (thiamine), B7 (biotin), and B12 (cobalamin) into the culture medium [91]. The presence of vitamin B2 and vitamin B3 in commercial powders of *Nannochloropsis gaditana* and *Chlorella* sp. showed the latter alga to be richer in vitamin B2 (0.24 mg/g) and vitamin B3 (0.28 mg/g) as compared to the former one [92].

Table 3. Production of other key vitamins from algal strains.

Vitamin	Algae	Conditions	Yield	References
Vitamin B1	<i>T. suecica</i>	No stress	32.3 µg/g	[88]
	<i>Isochrysis galbana</i>		14 µg/g	
	<i>D. teriolecta</i>		29 µg/g	
	<i>Chlorella stigmatophora</i>		14.6 µg/g	
	<i>Tetraselmis</i> sp.		109 mg/g	
	<i>Nannochloropsis</i> sp.	Continuous light and harvesting in log phase	70 mg/g	[89]
Vitamin B2	<i>T. suecica</i>	No stress	19.1 µg/g	[88]
	<i>Isochrysis galbana</i>		30 µg/g	
	<i>D. teriolecta</i>		31.2 µg/g	
	<i>Chlorella stigmatophora</i>		19.6 µg/g	
	<i>Nannochloropsis</i> sp.		62 mg/g	
	<i>Nannochloropsis gaditana</i>	Continuous light and harvesting in log phase	22.1 µg/g	[89]
Vitamin B3	<i>Chlorella</i> sp.	Commercialized powder	20.7–33.6 µg/g	[92]
	<i>Nannochloropsis gaditana</i>		0.24 mg/g	
	<i>Chlorella</i> sp.		0.11 mg/g	
Vitamin B5	<i>T. suecica</i>	No stress	37.7 µg/g	[88]
	<i>Isochrysis galbana</i>		9.1 µg/g	
	<i>D. teriolecta</i>		13.2 µg/g	
	<i>Chlorella stigmatophora</i>		21.4 µg/g	
Vitamin B7	<i>T. suecica</i>	No stress	0.8 µg/g	[88]
	<i>Isochrysis galbana</i>		1.0 µg/g	
	<i>D. teriolecta</i>		0.9 µg/g	
	<i>Chlorella stigmatophora</i>		1.1 µg/g	
Vitamin C	<i>Chaetoceros calcitrans</i>	Harvesting at logarithmic phase	44 fg/cell	[93]
	<i>Chaetoceros gracilis</i>		510 fg/cell	
	<i>Chroomonas salina</i>		295 fg/cell	
	<i>Nannochloropsis oculata</i>		61 fg/cell	
	<i>T. suecica</i>		530 fg/cell	
	<i>Isochrysis</i> sp.		76 fg/cell	
	<i>Thalassiosira pseudonana</i>		46 fg/cell	
	<i>Nannochloris atomus</i>	No stress	90.5 fg/cell	[94]
	<i>Pavlova lutheri</i>		56 fg/cell	
	<i>Skeletonema costatum</i>		700 fg/cell	
			315 fg/cell	
	<i>D. teriolecta</i>	Nitrogen source (urea, 2 mg atom N/L)	2.31 mg/g	
	<i>Chlorella pyrenoidosa</i>	Heterotrophic cultivation with glucose (5 g/L) in fermenters	1 mg/g	[95]
		Mutant strain	1–2 mg/g	

Table 3. Cont.

Vitamin	Algae	Conditions	Yield	References
Vitamin E	<i>T. suecica</i>	No stress	191 µg/g	[88]
	<i>Isochrysis galbana</i>		119 µg/g	
	<i>D. teriolecta</i>		163 µg/g	
	<i>Chlorella stigmatophora</i>		100.2 µg/g	[89]
	<i>Tetraselmis</i> sp.		3 mg/g	
	<i>Stichococcus</i> sp.		2.5 mg/g	
	<i>Trentepohlia aurea</i>	Nitrogen source (NH ₄ Cl, 120 mg/L) and light intensity (43 to 143 µmol photons/m ² s, two stage)	0.3 mg/g	[96]
	<i>N. oculata</i> SAG 38.85	Nitrogen limitation and harvesting at stationary phase	1445.66 µg/g	[97]
	<i>Haematococcus pluvialis</i>		1179.91 µg/g	
	<i>Microchloropsis salina</i>		1094 µg/g	
	<i>Coccomyxa</i> sp.		1062 µg/g	
	<i>Chlorococcum novae-angliae</i>	No stress	785 µg/g	
	<i>Chlamydomonas nivalis</i>		719.73 µg/g	
	<i>N. oculata</i>	Nitrogen deficiency (441 µM/L)	2325 µg/g	[98]
	<i>T. suecica</i>	No stress	421.8 µg/g	[88]
	<i>Isochrysis galbana</i>		58.2 µg/g	
	<i>Chlorella stigmatophora</i>		669.0 µg/g	
			116.3 µg/g	
	<i>D. teriolecta</i>	Nitrate source (urea, 2 mg nitrogen/L)	1.81 mg/g	[94]
		Harvesting in logarithmic phase	0.37 mg/g	[99]
	<i>T. suecica</i>		0.39 mg/g	
	<i>I. galbana</i>	Harvesting in late stationary phase	55.4 µg/g	[100]
	<i>Trentepohlia aurea</i>	Nitrogen source (NH ₄ Cl, 120 mg/L) and light intensity (43 to 143 µmol photons/m ² s, two stage)	2.4 mg/g	[96]
	<i>Euglena gracilis</i>	Autotrophic	1.422 mg/g	[101]
	<i>Diacronema vlkianum</i>	Harvesting in late stationary phase	551.3 µg/g	[102]
Vitamin K1	<i>Anabaena cylindrica</i>	Optimization: light intensity (320 µmol photons/m ² s), NaNO ₃ (1700 mg/L), K ₂ HPO ₄ (34.6 mg/L)	22 µg/L day	[103]

Genome-wide analysis of biotin biosynthesis genes in 13 eukaryotic algae revealed the existence of 44 biotin biosynthesis-related enzymes, laying the groundwork for targeting key genes to improve biotin synthesis via genetic engineering approaches [104]. When the vitamin C (ascorbic acid) content of 11 microalgae was assessed, *Chaetoceros gracilis* (1.6% DCW) and *Nannochloropsis oculata* (0.75% DCW) exhibited the highest levels [93]. Another study found that vitamin C was successfully increased (twofold) in mutant (UV and chemical) strains of *Chlorella pyrenoidosa* grown in heterotrophic media with glucose as the carbon source [95]. The authors also analyzed the vitamin C content of 23 other microalgal strains and found that *Chlorella miniata* UTEX 24 (3.4 mg/g cells) and *Chlorocloster engadinensis* UTEX 307 (1.4 mg/g cells) had the highest intracellular levels. The effect of various nitrogen sources (nitrate, nitrite, ammonium, and urea) on synthesis of provitamin

A, vitamin C, and vitamin E by *D. tertiolecta* was determined in an effort to maximize vitamin biosynthesis in the alga [94]. The authors reported maximum provitamin A and vitamin C in urea-fed cultures and maximum vitamin E in nitrate-supplemented media. Indeed, using urea as a nitrogen source provides a more cost-effective option, particularly for large-scale cultivation.

The vitamin E (α -tocopherol) content of 130 microalgae and cyanobacterial strains was examined to determine how levels differed depending on algae class, species, and growth phase [97]. Only 20 of the tested algae strains had vitamin E content greater than 400 $\mu\text{g/g}$. Under nitrogen limitation at the stationary phase, *N. oculata* had the highest vitamin E content. Other strains of interest included *Microchloropsis salina*, *Coccomyxa* sp., *Haematococcus pluvialis*, *Chlorococcum novae-angliae*, and *Chlamydomonas nivalis* (Table 3). Overall, the study concluded that Chlorophyta and Heterokontophyta had the highest vitamin E levels, while Cyanobacteria and Rhodophyta had relatively low levels. When the effect of nitrogen depletion on vitamin E biosynthesis in *N. oculata* was studied, the alga was found to accumulate the most vitamin E when nitrate was limited in the late stationary phase, which was 4.6- and 1.37-fold higher than with no nitrogen deprivation in the early and late stationary phases, respectively [98]. Similarly, it has been reported that *I. galbana* accumulated high levels of vitamin E in the late stationary phase, which was 16 times higher than in exponential phase [100]. Another algal strain, *Euglena gracilis*, has been reported to accumulate high levels of vitamin E when cultivated in photoautotrophic mode [101]. To maximize the productivity of vitamin E, the authors of that study utilized a two-stage cultivation, whereby a mixotrophic mode was utilized in the first stage to increase biomass, followed by autotrophy in the second stage to induce vitamin E biosynthesis in the cells, thus achieving a sevenfold increase in vitamin E productivity.

The content of vitamin K1 in seven algae species indicated that the cyanobacterium *Anabaena cylindrica* was the richest source [103]. Interestingly, the vitamin K1 level (200 $\mu\text{g/g}$) obtained in cyanobacteria was sixfold higher than that reported for rich dietary sources such as spinach and parsley, confirming the promising industrial promise of algae as sources of vitamins. Since vitamin D3 is not used in cosmetics, it is only discussed here in brief. To date, only two studies have reported the presence of vitamin D3 in *Chlorella minutissima*, *Nannochloropsis oceanica*, *Nannochloropsis limnetica*, *Anthriscus maxima*, *Rhodomonas salina*, *D. salina*, and *T. suecica* [105,106]. In the first study, the authors reported maximum vitamin D3 yield of 0.48 $\mu\text{g/g}$ only in *N. oceanica* after UV-B exposure (22 kJ/m^2 day for 7 days). In the second study, the authors reported that exposure of *N. oceanica*, *N. limnetica*, and *D. salina* to UV-B (15 kJ/m^2 day for 3 days), in general, induced vitamin D3, with *D. salina* showing the maximum level (2.7 $\mu\text{g/g}$).

4. Conclusions and Outlook

Considering the growing interest in natural vitamins for cosmeceutical applications, there is growing industrial interest in converting photosynthetic algae into biological factories for natural and sustainable production of vitamins, provitamins, and derivatives. The current review provides an in-depth look at the potential of using a wide range of algal species, both marine and freshwater, for synthesis of both fat-soluble and water-soluble vitamins. Indeed, when compared to chemical-based vitamin synthesis, vitamin production from algae has several advantages, including yielding natural and desired enantiomeric forms of the compounds of interest, no toxic byproducts, safer for skin application, sustainable use of renewable sources, and a positive appeal to the consumer. To date, several algal species have been reported to synthesize vitamins at yields higher or comparable to those of their plant-based counterparts. However, algal vitamins have yet to compete with existing chemical synthesis production systems due to the underlying challenge of achieving cost-competitive scalability.

Future research should concentrate on increasing vitamin yields through media engineering, which includes (1) manipulating cultivation parameters, such as two-stage cultivation; (2) bioprospecting natural, high vitamin-producing strains; (3) using small

chemical modulators, such as phytohormones, signaling molecules, and amino acids, to aid with stress tolerance and high productivity, particularly in outdoor cultivation systems; (4) optimizing algal harvesting time; and (5) improving extraction and downstream processing (recovery and purification). With regard to the future application of genetic engineering, it will be essential to gain a solid understanding of the intricate regulatory mechanisms that govern the biosynthesis of vitamins in algae. This will allow researchers to identify potential bottlenecks and reroute carbon flux towards the desired vitamin pathway using high throughput “omics” technologies, such as transcriptomics and metabolomics. To further improve vitamin production in algae, it will be necessary to gain a better understanding of the storage, degradation, and interdependence of the vitamin production pathway with other metabolic pathways. Indeed, the application of cutting-edge techniques in genetic engineering, such as CRISPR-Cas9, can be of assistance in the process of tailoring algal strains for use as bioreactors for vitamins. Ultimately, in order to commercialize vitamins derived from algae, it will be necessary to develop highly productive large-scale outdoor cultivation systems that result in economies of scale for both biomass and vitamin yield.

Author Contributions: N.A. and G.P.P.: conceptualization. N.A.: writing—original draft and data curation. G.P.P.: review and editing. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: All data are fully available without restriction and are included in the manuscript file.

Acknowledgments: Figures 1 and 2 were made using [Biorender.com](https://biorender.com) (accessed on 11 February 2023).

Conflicts of Interest: The authors declare no conflict of interest.

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