Review

Microalgae as a sustainable source of cosmeceuticals

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Simple Summary: Photosynthetic organisms such as microalgae are a rich source of substances curbing negative effects of stresses acting of human skin cells. In many cases these compounds appear to be less toxic, allergenic, and generally more "biocompatible" than most of their synthetic counterparts. The large-scale biotechnological production of the microalgal biomass enriched with the cosmeceutical compounds is more technically feasible and economically viable than that of macrophyte biomass. Therefore, increasing effort is invested by the scientific community to isolation and characterization of potential cosmeceutical substances from microalgae. In line with this trend, we review here the state-of-the-art for the key group of cosmeceutical substances and the microalgae producing them, their biological significance, and the beneficial effects for human health and, particularly, skin health.

Abstract: A prominent feature of stress-tolerant microalgae is their versatile metabolism allowing then to synthesize a broad spectrum of molecules with beneficial effects on many aspects of human body functioning. This is in line with the current understanding that many stress-induced deleterious processes in the human body and in photosynthetic cell are mediated by the same mechanisms such as free-radical attacks and lipid peroxidation. These related risks are kept at bay by optical screening of harmful UV, enzymatic ROS elimination systems, and potent low-molecular antioxidants. Microalgae synthesize a broad spectrum of compounds exerting antioxidant and/or UV-absorbing properties. In microalgae, they increase stress-resilience of these organisms. In human body, they exhibit photoprotective, antiaging, and sunscreen activities. Therefore, these algal metabolites were recognized as promising ingredients for innovative cosmetics and cosmeceutical formulations. Ever increasing effort is being invested into the search for new natural biologically active substances from microalgae. This trend is also fueled by the growing demand for natural raw materials for food, pharmaceuticals and cosmetology associated with the global transition to a "greener" lifestyle. Here, we review the currently accumulated knowledge about the main groups of cosmeceutical compounds from microalgae.

Keywords: microalgae, carotenoids, chlorophylls, lipids, mycosporin-like amino acids, antioxidants, UV-screen

1. Introduction

Microalgae are a large and diverse group of unicellular, prokaryotic and eukaryotic microorganisms. They can grow in fresh water or seawater and play a key role in aquatic ecosystems as the primary producers responsible for around a half of photosynthesis on Earth [1,2]. Microalgae are characterized by the presence of versatile metabolic pathways capable of producing a broad spectrum of molecules. Many of these metabolites exert a plethora of beneficial effects on human health, particularly on skin condition and functioning [3-5]. Biologically active compounds from microalgae have antiviral, antifungal, or antibiotic effects [2,3,6,7]. Starting from the second half of the last century, ever increasing effort is being invested into the search for new natural biologically active substances from microalgae. This trend is also fueled by the growing demand for natural raw materials for food, pharmaceuticals, and cosmetology associated with the global transition to a "greener" lifestyle [3,5,8].

Peculiar composition of pigments is among the main discriminants of the major algal taxa such as green, brown, and red alga, there are also significant differences in other aspects of chemical composition between these as well as lower-level taxa [9]. As commercial demand increases, microalgae begin to be cultivated at a large scale under different conditions [10]. This gives rise to differences in chemical composition of raw materials from microalgal biomass and hence to problems in the process of mass production of cosmetic extracts from the point of view of standardization. Therefore, growing conditions, climatic fluctuations, seasonality must be taken into account in the process of developing cosmetic lines [5,11,12].

The biodiversity of microalgae is enormous, with more than 50,000 different microalgae species, and only a modest portion of these species have been more or less studied [1,9,13]. Such diversity implies a large application potential that has yet to be exploited. Microalgae are a rich source of various compounds of commercial interest [14], especially for cosmetics (Table 1), the production of purified pigments, polysaccharides, fatty acids and bulk biomass [4,15]. Some of the interesting molecules or compounds, such as pigments, vitamins, fatty acids, and proteins, are of a primary nature, while others are secondary metabolites. Most of the commercially promising active substances of microalgae are secondary metabolites that accumulate in cells under unfavorable environmental conditions for growth [16,17]. Some of the metabolites have a chemical structure that is not found in terrestrial organisms and has a function that is not yet understood. The high potential of microalgae as raw materials for the pharmaceutical and cosmetic industries is associated with the presence of substances serving for environmental stress acclimation that have formed during evolution [18].

Table 1. Raw materials from microalgae and their suppliers [19].

Microalgae	Raw Materials	Suppliers
Phaeodactylum tricornutum	Megassane Depollutine	Soliance
Skeletonema costatum	Costalane	Soliance
Pyrocystis noctiluca		Microphyt
Chlorella	Dermochlorella D Dermochlorella DP Agility chlorella	Codif Codif Roquette Setalg
Odontella		Innov'alg

The cultivation of microalgae is generally simpler and often cheaper than that of heterotrophic microorganisms. It can be economically efficient, since microalgae can grow autotrophically [2,3]. Cultivation in bioreactors makes it possible to obtain more standardized raw biomass whose quality is less dependent on seasonal factors [20-22].

World scientific community has rapidly accumulated extensive information on the chemistry and diverse effects of substances and metabolites of microalgae (see [7,8,23] and references therein). Many substances of microalgal origin found extensive use in the cosmetic industry, the list of extracts and individual chemicals isolated from them thoroughly tested for safety and effectiveness is not yet very large [24]. Although excellent reviews of individual microalgal cosmeceutical groups exist (see e.g. [25-30]), here we covered all most important classes of such compounds of cosmeceutical relevance [31] linking the patterns of their composition and accumulation with the relevant aspects of the biology of microalgae.

2. Inorganic substances

Mineral substances are accumulated by cells of microalgae and in the extracellular matrices in the form of ions, insoluble salts and, in part, in the form of organometallic compounds. In general, 75 to 85% of the mineral substances are water-soluble salts and 15-25% are salts insoluble under physiological conditions. Inorganic substances, primarily iodine and zinc, are the constituents of enzymes, vitamins, pigments, and regulatory molecules orchestrating vital functions of algal cells [26]. Some trace elements in algae are ubiquitous: iodine, zinc, chromium, nickel, aluminum, boron, potassium, sodium [26]. Their biological role has not yet been fully studied and their pertinence to certain cellular structures is not always clear. Algae can bioconcentrate and bioaccumulate, concentrating and accumulating mineral substances in the layers in bioavailable form. the concentration of some mineral substances in tissues is tens (calcium), hundreds (bromine, chromium) and thousands (zinc, barium, iodine) times higher than their content in seawater. Microalgae live in a wide variety of biocenoses, so their mineral composition is closely related to that of their habitat [26].

3. Structural and reserve polysaccharides

The bulk of the carbohydrates that make up algae are polysaccharides—up to 55% of the dry matter [3,27]. Their high content is explained by the importance of their functions in microalgal cell: structural support and storing of carbon reserves. A widespread structural polysaccharide, cellulose is a major component of cell wall of many algal species (3–18% of the cell dry weight). It is a linear homopolymer of 300-10000 β-glucose molecules linked by β-1-4 glucoside bonds. The cellulose filaments are hold together by hydrogen bonds, which gives the cellulose greater mechanical strength and elasticity. It does not break down when heated to 200° C, it is insoluble in water and weak acids [27]. Other frequently encountered polysaccharides of microalgae are divided into two groups according to the type of sugar bonds in their polymer chains. These are α-1,4-glucans (starch and floridean starch) and β-1,3-glucans (chrysolaminarin and paramylon) [27]. α-glucans such as α-1,4-glucans are found in green, char, glaucophyte, dinophyte, cryptomonad, red microalgae as well as in cyanobacteria. The latter are characterized by a high degree of branching resembling in this regard glycogen, the evolutionary oldest reserve glucan [27]. Cryptomonad starch, as in red algae, contains more amylopectin (branched molecules with α-1,4 and α-1,6 bonds) than amylose (linear chains with α-1,4 bonds). Starch of green and char algae contains both amylose and amylopectin [3]. It differs from the starch of higher plants by a lower molecular weight of amylose and amylopectin and a smaller size of granules. In cosmetics, mostly α-1,4- and α-1,6-glucan are used [14].

β-1,3-glucans e.g. paramylon are synthesized by euglenophytes and *Pavlova* from haptophytes. Thus, representatives of the genera *Astasia* and *Euglena* accumulate paramylon to more than 50 % of the cell dry weight. Chrysolaminarin is a water-soluble glucan, a reserve product of golden, yellow-green, and diatom microalgae. This is a colorless substance similar to laminarin of kelps [27]. Microalgae also contain more exotic chemically modified (e.g. sulfated) polysaccharide species with unique physical and chemical properties valued in the cosmetic industry [32,33]. Although many of these polysaccharides are scarcely characterized from the chemical point of view, they are vigorously used as cosmeceutical ingredients [27].

4. Microalgal lipids

4.1. Long-chain polyunsaturated fatty acids

Microalgae represent an important "green" source of lipids enriched in biologically active long-chain polyunsaturated fatty acids (PUFA) such as γ-linolenic (GLA), arachidonic (ARA), and eicosapentaenoic (EPA), docosahexaenoic acid (DHA), and stearidonic acid (SDA) fatty acids exerting vitamin F activity [28,34-37]. The lipids are divided into neutral and polar species. Neutral lipids are mainly triacylglycerides, which are mainly accumulated in chloroplast or cytosolic lipid bodies, frequently accumulated by microalgae in response to stresses [38,39]. Under those conditions, lipid content in oleaginous microalgae such as *Schizochytrium* sp., *Pavlova lutheri*, *Isochrisis* and *Nannochloropsis* microalgal cells can reach 50-70% of cell dry weight. *Lobosphaera incisa* is capable of accumulating ARA up to 60% of total fatty acids [40,41], see also Figure 1. Certain microalgae species are known to accumulate EPA and DHA (EFA) up to several percent of the dry cell mass [42]. Microalgae commercialized for their essential PUFA include representatives of the genera *Crypthecodinium*, a traustochytrid *Schizochytrium*, and an ameboid *Ulkenia* (strictly speaking, the latter two species are not microalgae but they remain the important organisms within the framework of microalgal biotechnology). Thus, the genus *Schizochytrium* is a rich source of DHA (up to 37.7% of the total fatty acids) tested for safety [28,35]. Microalgae such as *Rhodomonas salina*, *Tetraselmis suecica*, *Thalassiosira pseudonana*, *Phaeodactylum tricornutum*, *Porphyridium cruentum*, *N. oculata*, *N. gaditana* are also intensively studied as potential sources of PUFA [10,41]. Thus, a high content of EPA was found in red microalgae where eicosapentaenoic acid can reach 50% of the total fatty acids [43,44].

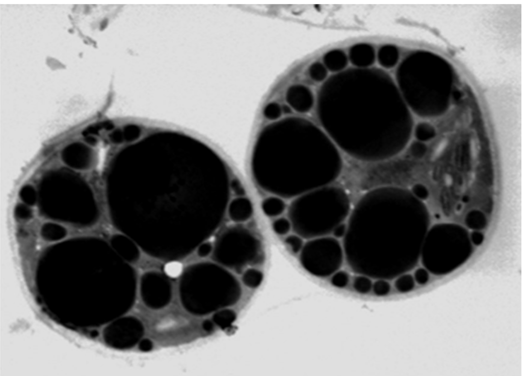


Figure 1. Accumulation of lipids enriched with arachidonic acid in nitrogen-deprived *Lobosphaera incisa*. The electron micrograph of *L. incisa* cells filled with oil bodies (electron-dense round-shaped structures).

Accumulation of PUFA can be enhanced through the exposure of microalgae to various abiotic stresses, such as extreme salinities, temperatures, shortage of N and P in the medium. Low-temperature stress for algae is one of the effective strategies for increasing PUFA. As part of the adaptation to low temperature, microalgae increase the production of PUFA to maintain membrane fluidity. The microalgae *P. lutheri* and *P. tricornutum* show an increase in EPA content by about 20–30% with a decrease in the cultivation temperature to 15°C and 10°C, respectively. On the other hand, high PUFA levels are observed when microalgae harboring them are grown under favorable conditions if these PUFA are incorporated into structural lipids [45]. *Crypthecodinium cohnii* ATCC 30556 when grown in a medium with 0.9 % NaCl gives the highest DHA yield of 131.55 mg L^{-1}. Collectively, the microalgal oils featuring a high content PUFA is a feasible alternative to fish oil (ca. 100 mg g^{-1} DHA, ca. 180 mg g^{-1} EPA). Many more exotic microalgal species including those from *Dinoflagellata*, *Bacillariophyceae*, and *Prymnesiophyceae* accumulate lipids harboring GLA, ARA, EPA and DHA in biotechnologically significant amounts [28]. The production of "algal oil" by biotechnological methods for the purposes of the food and cosmetic industry is approved for certain microalgal species: *Porphyridium cruentum*, *Cryptecodinium cohnii* (USA), *Schizochitrium* sp. (USA), *Ulkenia* sp. (Germany) [46-48]. Cultivation of the microalgae in bioreactors under controlled conditions provides the lipid extracts which are more uniform in their PUFA profiles.

Docosahexaenoic acid is essential for humans as a major PUFA of brain cell membrane lipids, retina, heart muscle, and sperm; it is also important for the development of young children [8,14,15,35]. Consumption of lipids enriched in polyunsaturated fatty acids such as DHA and EPA diminishes risk of cardiovascular and inflammatory diseases [36].

In the cosmetic industry, the "algae oil," a concentrate of the essential ω-3 and ω-6 PUFA is becoming more widespread. For the production of infant formulae, "algae oil" from the dinoflagellate *Cryptecodinium cohnii* is used (30% PUFA of cell dry weight with DHA comprising ca. 50% of the total PUFA). The technology for obtaining DHA from *Cryptecodinium* by Marthek company (USA) is based on aseptic heterotrophic cultivation of the proprietary algal strain. OmegaTech (USA) produces a cheaper "algal oil" from *Schizochytrium* sp. (branded "DHA Gold"), which is approved for the production of nutraceuticals and food products and is used in skin care products, especially natural cosmetics. German company Nutriniva processes produces DHA from *Ulkenia* sp. (branded "DHA Active") [48]. Food supplements containing microalgal DHA used for the prevention and treatment of diseases associated with impaired brain activity, heart attack, age-related visual impairment and are in high demand [37,46]. EPA from *P. cruentum*, *Ph. tricornutum*, *I. galbana*, *Nannochloropsis* sp., and *Nitzshia laevis* is sought after for the prevention and treatment of lipid metabolism disorders. In cosmetics, the product is an important ingredient for restoring the water-lipid mantle of the skin [22,46,47].

4.2. Microalgal phytosterols

Sterols perform a variety of functions in marine organisms, including chemical defenses against attack by other organisms. Such bioactive molecules as steroid hormones, bile acids, various biotoxins including steroid and triterpene saponins, can be considered as products of biotransformation of sterols. The content of sterols in algae follows a seasonal trend. The structural closeness of algal sterols to the sterols commonly used in cosmetic chemistry allows to use them as emulsion bases and raw materials for obtaining, for example, vitamin D and creating new medical preparations and cosmetics on their basis.

Microalgal sterols can be components of the cell wall, for example, in *I. galbana* and *P. lutheri*. The main sterols of these microalgae include lionasterol, 4-α-metilporiferast-22-enol, porifrasterol, methylpavlovol and epicampisterol. Thus *P. lutheri* can produce significant amounts of sterols (ca. 100 mg g^{-1} total cell lipids) which can be further increased by UV exposure of the microalga [28,49].

Algal sterols are promising precursors for synthesis of other sterols which are in high demand, for example active forms of vitamin D, or as part of emulsion bases in the production of soft dosage forms and are potential agents for the treatment of atherosclerosis and have antitumor and anti-inflammatory effects. Thus, desmosterol of microalgae is a versatile precursor giving rise to many biologically active steroids [3,34].

5. Pigments

5.1. Chlorophylls

Chlorophylls (Mg-porphyrin-polyisoprenoids) are pigments that absorb light in the blue and red regions of the visible spectrum. They are central to photochemical conversion of light energy in photosynthesis. Within photosynthetic cells, chlorophylls are always bound to proteins. Chlorophylls *a*, *b*, *d*, and *f* have a long apolar phytol chain lacking in chlorophylls *c*. All microalgal taxa contain chlorophyll *a* whereas the composition of accessory chlorophylls depends on the algal group [9,50].

The antimicrobial, anti-inflammatory effect of chlorophyll-based drugs, their ability to stimulate not only hematopoiesis, but also the healing of wounds and ulcers, has long been known. As an antiseptic additive, chlorophyll is popular in cosmetics for oily skin, skin with acne, and care products for oily scalp [3,6,51]. The chlorophyll derivatives 13-hydroxy-phaeophytin and 13-hydroxy-phaeopharnesin isolated from the cyanobacterium *Spirulina* and green microalga *Chlorella* demonstrated a significant lipid-reducing activity in the model of differentiated adipocytes 3T3-L1. Experimental data suggest that these compounds are promising for development as a nutraceutical with a lipid-control activity or a cosmetic ingredient with lipolytic activity [51].

The pronounced deodorizing properties of chlorophyll derivatives were the basis for their widespread use as an active component of hygiene products used for oral care, deodorants in natural cosmetics. In the cosmetics of the natural direction of skin care, chlorophyll is also used as a pigment. Production of chlorophyll-based cosmeceutical additives is a very promising direction for substituting the chlorophyll preparation from higher plants.

5.2. Carotenoids

Carotenoids—natural pigments that convey yellow, orange, or red hue to the organisms containing them. Chemically, they are a class of tetraterpenoids with a C40 backbone ubiquitously present in the photosynthetic apparatus of plants and microalgae [25,52]. Carotenoids are divided into carotenes, the hydrocarbons devoid of oxygen, and xanthophylls, which contain oxygen [25,29,30,52]. Around 750 natural carotenoids were isolated from various biological sources, of which about 200 are found in algae; nearly 30 of them are involved in photosynthesis of microalgae [25,53]. These are among the most diverse and widespread pigments in nature (Table 2).

Table 2. Distribution of carotenoids in microalgae (modified from [53]).

Division	Carotene		Xanthophyll										
Class	β[1]	α	Ze	Vi	Ne	Da	Dd	Fx	Va	Lu	Lo	Sx	Other xanthophyll(s)
Cyanophyta	H	L	H										No, L; Ec, H; My, H
Glaucophyta	H		H										
Rhodophyta	H		H										
Cryptophyta		H	L										Al, L; Cr, L; Mo, L
Heterokontophyta													
Chrysophyceae	H		L			L	L	H	L				
Raphidophyceae	H		H	L		L	L	L					
Bacillariophyceae	H		L			L	L	H					
Xanthophyceae	H		L			H	H						Va-FA, L
Eustigmatophyceae	H			H					L				
Haptophyta	H		L			L	H	H					Fx-FA, L
Dinophyta	L		L			L	H	L					Pe, H
Euglenophyta	H		L		L	L	H				L	L	
Chlorarachniophyta	H		L	L	L					L	L		Lo-FA, L
Chlorophyta													
Prasinophyceae	H	L	L	H	H					L	L	H	Pr, L; Lo-FA, L; Sx-FA, H
Chlorophyceae	H	H	L	H	H					H	L	L	Sx-FA, L
Trebouxiophyceae	H		L	H	H					H			
Charophyceae	H		L	H	H					H			

[1] H, Major carotenoid in most species of the class; L, Low content in most species or major carotenoid in some species. α, α-carotene; β, β-carotene; Al, alloxanthin; Cr, crocoxanthin; Da, diatoxanthin; Dd, diadinoxanthin; Ec, echinenone; -FA, fatty acid ester; Fx, fucoxanthin; Lo, loroxanthin; Lu, lutein; Mo, monadoxanthin; My, myxol glycosides and oscillol glycosides; Ne, neoxanthin; No, nostoxanthin; Pe, peridinin; Pr, prasinoxanthin; Sx, siphonaxanthin; Va, vaucheriaxanthin; Vi, violaxanthin; Ze, zeaxanthin.

Carotenoids are biologically active compounds whose main functions in photosynthetic organisms are light harvesting for photosynthesis and photoprotection [25,52]. In addition, they have antioxidant, antibacterial, antiviral, antifungal, anti-inflammatory, and antitumor properties [30,54]. Carotenoid also found extensive use in the food, medicines, and cosmetics industry due to their beneficial effects on human health [3,6,30]. The antioxidant activity of carotenoids determines it application as functional food and cosmetics ingredients and safe colorants [55]. The bioavailability of carotenoids is enhanced when they are combined with dietary lipids. Currently, carotenoids derived from microalgae dominate certain segments of the natural pigment market [30]. Overall, microalgal carotenoid production is considered as an important business opportunity for the healthcare and cosmetics industry of the future. The main carotenoids that are currently commercially used in the world are β-carotene, astaxanthin, lutein, canthaxanthin, zeaxanthin, and fucoxanthin [25,29]. In addition, lycopene and cantaxanthin are also biotechnologically important carotenoid species.

Natural carotenoids occur in microalgae as a mixture of cis-trans and optical isomers whereas synthetic carotenoids are mostly or exclusively represented by the trans isomers. Natural carotenoids are preferred in cosmetic applications over their synthetic counterpart due to safety and bioavailability problems of the latter.

5.2.1. β-Carotene

β-Carotene is a yellow-orange strongly apolar carotenoid. It is synthesized by photosynthetic organisms, participates in the photoprotection of chlorophyll and the prevention of damage to cell DNA by active oxygen forms [56,57]. Microalgae normally accumulate the carotenoids as photosynthetic pigments to 0.1–2% of cell dry weight. By contrast, secondary carotenoids including β-carotene are accumulated in the lipid globules of the chloroplast and cytoplasmic oil bodies facilitating the photoprotection of the cell [56,58,59]. In nature, β-carotene is the most common precursor of vitamin A and a powerful antioxidant (but prone to exert a prooxidant activity under certain circumstances) [54]. β-Carotene is used as a food coloring agent, in medicine, nutraceuticals, cosmetics and feed [30].

Commercial production of microalgal β-carotene employs diverse technologies from the relatively primitive cultivation of algae in shallow ponds to the intensive cultivation of in advanced bioreactors. β-Carotene from *Dunaliella salina* (Figure 2) was the first product commercially obtained from microalgae [60,61]. The content of β-carotene in the biomass of *D. salina* reaches 10-14% under stressful conditions. Approximately a half of the natural pigment is represented by its 9-cis-isomer, which has a higher antioxidant activity. Commercial companies producing β-carotene from microalgae include Aqua Carotene (USA), Cognis Nutrition & Health (Australia), Cyanotech (Hawaii, USA) and Parry Nutraceuticals (India).

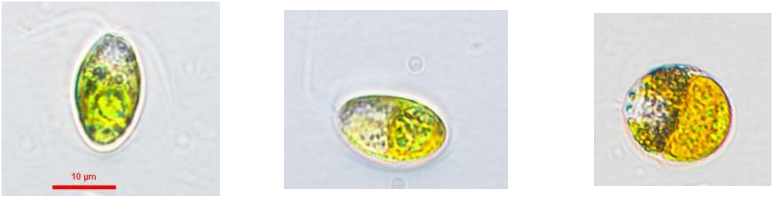


Figure 2. Changes in the cell morphology of *Dunaliella salina* (from left to right) in the course of high-light and salinity stress induced accumulation of β-carotene. Courtesy of Dr. Elena Seliwanova.

5.2.2. Astaxanthin

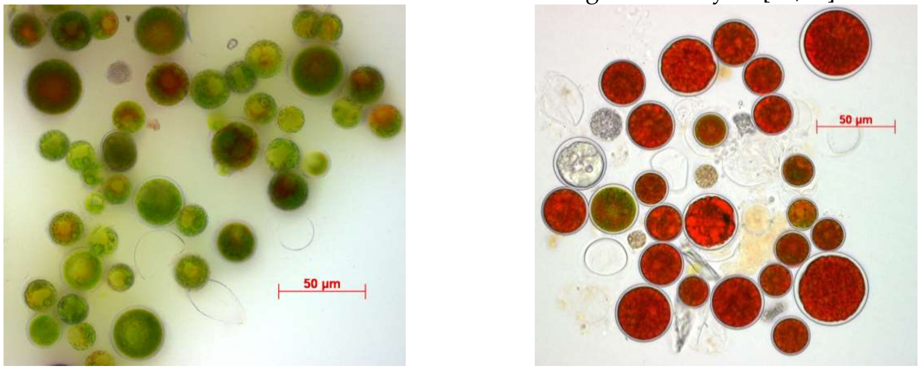
Astaxanthin (3,3-dihydroxy-β-carotene-4,4-dione) is an oxygenated derivative of β-carotene. It is found naturally in a wide variety of living organisms, including microalgae, fungi, plants, seafood, and some birds such as flamingos and quails; this carotenoid gives salmon, shrimp, and lobsters their distinctive coloration [30,62]. Astaxanthin is associated with a unique natural phenomenon—red snow, observed high in the mountains and in the circumpolar regions of the Earth. The unusual reddish or pink color of snow is due to the mass reproduction of one of the species of *Chlamydomonas* (*Chlamydomonas nivalis*). In addition to the green pigment chlorophyll, the cells of this algae contain astaxanthin. Unlike many species of freshwater algae, *Chlamydomonas nivalis* prefers cold environmental conditions and thrives at temperatures below freezing. The extremophilicity and hence a high stress resilience of the microalgae is a good marketing legend for the cosmetics industry, where *Chlamydomonas nivalis* extracts are offered for skin care products [32].

Two oxygen-containing groups (keto- and hydroxyl groups) are present on each terminal rings in astaxanthin molecule increase its antioxidant efficiency and gives it a characteristic absorption spectrum and hence the deep red color. The natural pigment represented mainly by the *3S,3´S* isomer, also exceeds in antioxidant activity its synthetic counterpart which is a racemate comprised by all possible optical isomers [63].

Antioxidant activity of astaxanthin exceeds considerably that of other carotenoids such as β-carotene, protecting the lipid structures of the cell, especially cell membrane phospholipids. The unique structure of astaxanthin facilitates its accumulation in cell membranes. Unlike other antioxidants, which are located either inside or outside the lipid bilayer of the membrane, astaxanthin molecules have a unique ability to be located both inside and outside the membrane protecting it from charged and uncharged reactive oxygen species (ROS) [64-66]. Astaxanthin protects microalgal cells from exposure to high light intensity and from harmful UV radiation decreasing the formation of ROS. This is also the basis for the use of *Hematococcus* extracts in protective skin care products [67,68]

Unlike β-carotene, astaxanthin is not a precursor of vitamin A, so 20 mg d^{-1} it can be taken up safely without the risk of side effects associated with vitamin A overdose. Astaxanthin has a pronounced anti-inflammatory and antitumor effects and a rare ability to penetrate the blood-brain barrier. The latter characteristic determines its efficiency in prevention and treatment of diseases of the central nervous system [68,69]. For commercial cosmeceutical use, astaxanthin is used in various forms, such as pills, capsules, syrups, oils, soft gels, creams, biomass, and granular powder [14,67,70].

Microalga *Haematococcus pluvialis* (Figure 3) is the most widely used as a producer of natural astaxanthin although other microalgal species including *Botryococcus braunii*, *Chlamydomonas nivalis*, *Neochloris wimmeri*, *Protosiphon botryoides*, *Scotiellopsis oocystiformis*, *Chloromonas nivalis*, and are capable of synthesizing astaxanthin [71]. Astaxanthin is synthetized via the isoprenoid pathway. In *Haematococcus*, astaxanthin is predominantly esterified by fatty acids (C16:0, C18:2, and C18:1 [72,73]). Under stressful conditions such as nitrogen depletion, high light intensity or salinity *H. pluvialis* can accumulate astaxanthin up to 5-6% of the cell dry weight. The stresses promote the transition of the green vegetative cells into the astaxanthin-rich resting haematocysts [74,75].



(**a**) (**b**)

Figure 3. Accumulation of astaxanthin in *Haematococcus pluvialis*. (**a**) Green vegetative cells where accumulation has just begun. (**b**) Astaxanthin-rich haematocysts.

Astaxanthin patents are related to food, feed, and nutraceuticals, which are currently the main market driver for the pigment. Alga Technologies (Israel), Cyanotech (Israel), Jingzhou Natural Astaxanthin Inc (China), Algaetech International (Malaysia) and Parry Nutraceuticals (India) are the main suppliers of microalgal astaxanthin on the market [14,67]. In 1999, astaxanthin was approved by the US FDA as an effective dietary supplement with powerful antioxidant properties. Currently, astaxanthin derived from *Haematococcus* accounts for several % of the carotenoid market [76,77]. The current market price of natural astaxanthin varies widely depending on its purity and constitutes, on an average, several thousand US $ per kilogram. Synthetic astaxanthin is predominantly used now as a feed additive in aquaculture, mainly consumed by the salmon feed industry, due to cost considerations. Natural astaxanthin is of commercial importance as a food coloring agent and a cosmetics ingredient.

5.2.3. Lutein and zeaxanthin

Lutein (β,ε-carotene-3,3-diol) is a yellow pigment from the xanthophyll family. It is synthesized only by plants (leafy vegetables) and microalgae. Lutein is an accessory pigment associated with light-harvesting antenna, it also protects cells from photo-oxidative damage [6,78]. Lutein and a structurally close to it zeaxanthin [5,6,78] help to maintain normal vision and are the only carotenoids found in the retina and lens of the eye. Their depletion is associated with age-related macular degeneration [3,73]. Green microalgae such as *Muriellopsis* sp., *Scenedesmus almeriensis*, *Coccomyxa acidophila*, and *Chlorella protothecoides* produce significant amounts of lutein. The highest yield of lutein in microalgae is observed under favorable conditions or slight limitation by light conductive for the development of the light harvesting antenna. Microalgae is a sustainable and effective alternative source of the xanthophyll, as it yields three to six times more lutein than its common source—*Calendula* or *Tagetes* petals. However, production of lutein from microalgae on an industrial scale is still in its infancy.

5.2.4. Fucoxanthin

Fucoxanthin is one of the most abundant carotenoids constituting more than 10% of the total carotenoids in marine environment. It is an accessory pigment in chloroplasts of brown algae, phytoplankton, brown seaweed, and diatoms giving them a brownish or olive-green color. The microalgae *Phaeodactylum tricornutum* and *Isochrysis galbana* are the main commercially significant producers of fucoxanthin. Structural peculiarity of this pigment includes the presence of an unusual double allyl carbon and two hydroxyl groups, which are thought to increase its high energy transfer efficiency (80%) and a strong antioxidant activity. Fucoxanthin beneficial effects include antioxidant, antitumor, antidiabetic, and other activities [14,30,79]. In cosmetics, it is used to whiten and improve the condition of the skin, as well as a natural antioxidant and lipolytic agent.

6. Mycosporin-like amino acids (MAA)

6.1. Structure and functions of MAA

Mycosporin-like amino acids (MAA) are secondary metabolites found in marine organisms of any climate zone including microalgae, especially affected by high fluxes of solar radiation or hypersaline conditions [80-83]. In the course of evolution, cyanobacteria acquired UV-protective mechanisms, one of which is based on UV blocking by MAA. Over the past 30 years, cyanobacteria from the orders Synechococcales, Chroococcales, Oscillatoriales, and Nostocales have been studied for the presence of new MAA, while the orders Gloeobacterales, Spirulinales, Pleurocapsales, and Chroococcidiopsidales remain scarcely studied in this regard. The genera *Nostoc* and *Anabaena* are currently the most studied cyanobacterial taxa—sources of MAA. Currently, there are 20 different types of MAA of cyanobacterial origin.

MAA are low molecular (normally < 400 Da), colorless, uncharged, water-soluble molecules. MAA possess a similar backbone but differ in functional groups, they include cyclohexenone or cyclohexenimine ring conjugated with an amino alcohol group or a nitrogen subgroup of an amino acid [82]. Amino cyclohexenone derivatives contain cyclohexenone conjugated with an amino acid, examples include mycosporin-glycine (Myc-Gly), mycosporin-taurine (Myc-Tau). Derivatives of amino cyclohexeneimine include shinorin (SH), porfira-334 (PR), usujiene (Usu), asterina-330 (AS), palitin (PI), mycosporine-2-glycine (Myc-2-Gly) and many other molecular species (see Figure 4 and [84]).

Mycosporyne-glycin
(λ_{max} = 330 нм)

Shinorine
(λ_{max} = 334 нм)

Palythene
(λ_{max} = 360 нм)

Palythine
(λ_{max} = 320 нм)

Figure 4. Typical mycosporin-like amino acids and their absorption maxima.

Prolonged exposure to ultraviolet (UV) radiation causes photo-aging of the skin and a number of other disorders, including sunburn, fine and coarse wrinkles, and increases the risk of skin cancer. Sunscreens are commonly applied to reduce the harmful effects of UV on the skin. Recently, there has been a growing demand for replacing chemical sunscreens with natural UV-absorbing compounds. MAA are promising alternative UV-absorbing compounds of natural origin which are highly soluble in water and do not generate ROS upon absorption of UV radiation. More than 30 MAA from various organisms have been characterized [81]. In addition to photoprotective properties, there is substantial evidence that MAA protect against skin aging, can exert antioxidant, anti-inflammatory activity; MAA can also inhibit protein glycation and collagenase activity. They are considered to be anti-aging components [85]. One of the most potent compounds in terms of anti-aging activity is mycosporin-2-glycine (M2G).

The exact role of MAA in living organisms is still being debated. They are characterized by high biological activity, but most studies on MAAs focus on their photoprotective ability [18]. Their alternative functions include osmotic regulation, reproduction control, nitrogen storage in the cell, and ROS elimination. It is assumed that MAA exhibit strong antioxidant activity by interacting with ROS, originating also from endogenous photosensitizers [86]. Its high antioxidant efficiency is probably associated with a lower reduction potential and a greater ability to release electrons to stabilize and inactivate free radicals [85].

6.2. MAA as sunscreens

Exposure to sunlight might be harmful depending on the amount of absorbed radiation and the depth of its penetration to skin. Shorter UV-B waves are absorbed mainly by keratinocytes of the *stratum corneum* (SC) of the skin to a depth of 160-180 mμ, and longer UV-A waves penetrate deeper to about 1 mm, thus reaching the dermis layer. UV overexposure leads to diverse skin damages. The most noticeable include sunburn, erythema, edema, blisters, sunburn cell formation (SBC), phototoxic reactions, photoallergy, photosensitivity, and acute photoimmunosuppression [87].

A promising alternative to existing chemical and physical sunscreen filters is the use of multifunctional MAA, which are also suitable for cosmetics formulations [88]. Experiments with cell culture models demonstrated beneficial effect on fibroblast growth in 3T3 mice exposed to UV-A radiation and UV-protective effects in HaCaT cell line [89]. Application of MAA prevented the UV-induced reduction of trans-urocanoic acid and UV-stimulated histidine build-up. A crude methanol extract of cyanobacterium Aphanizomenon flos-aquae enriched in MAA showed a level of UV-A protection as compared to a commercial skin care product with a sun protection factor SPF = 4 and a UV-A/UV-B protection ratio of 0.95 [90].

6.3. MAA for prevention of photoaging

The anti-photoaging activity of MAA is thought to be related with reduction lipid peroxidation, a determinant of the aging process [91]. Application of 0.005% MAA in lecithin liposomes on the inner side of the forearm inhibited UV-A-stimulated lipid peroxidation by 37%, four-week treatments improved the skin elasticity and smoothness by 10% and 12%, respectively [92]. The tested MAA formulation was as effective as the standard cream containing 1% synthetic UV filters, Parsol® 1789 and 4% UV-B filters, Neo Heliopan® AV [92]. MAA also inhibited the UV-enhanced activity of elastase, which leads to the decomposition of elastin and the formation of wrinkles by 82.5% as compared to unprotected UV-A irradiated cells [93]. In addition, MAA can protect the skin from photoaging by regulating the expression level of genes associated with inflammation, such as COX-2. Treatment of the model cells with Myc-Gly caused a two-fold decline in COX-2 mRNA levels [85].

7. Conclusions and outlook

Microalgae are naturally equipped in terms of metabolic plasticity to cope with diverse stresses. They synthesize a broad spectrum of molecules exerting potent beneficial effects on many aspects of human body functioning. This is scarcely surprising given that many of the stress-induced deleterious process in the human body and in a photosynthetic cell are mediated by the same mechanisms such as free-radical attacks and lipid peroxidation. It is also worth noting that the photosynthetic machinery of microalgae is always at risk of oxidative damage since high redox potentials and reactive molecules are constantly generated during its functioning. These risks are kept at bay by efficient ROS elimination systems including potent low-molecular antioxidants.

Therefore, photosynthetic organisms are a rich source of substances with a great potential for curbing the negative effects of stresses acting of human skin cells on a day-to-day basis. In many cases these compounds appear to be less toxic, allergenic and, in general, more "biocompatible" than most of their synthetic counterparts. Although a dramatic diversity of cosmeceuticals was discovered in macrophyte algae, single-celled algae are on the same level or even surpass them in this regard. At the same time, the large-scale biotechnological production of the microalgal biomass enriched with the cosmeceutical compounds is more technically feasible and economically viable than that of macrophyte biomass, although with certain reservations (Figure 5).

STRENGTH	WEAKNESSES
• Ample diversity of microalgae and their metabolites	• High production costs • Low robustness of cultivation • Complicated and expensive downstream processing

• Natural "green" sources of the cosmeceuticals and consumer enthusiasm • Synergistic effects (e.g. carotenoids + lipids)	• Climate limitation for open cultivation system
OPPORTUNITIES	THREATS
• Growing market • Cultivation and downstream processing technology progress • Increasing end-user awareness • Strain improvement • Combining natural and synthetic production	• Legal problems (stringent regulations) • Strong competition from low-cost producers and synthetic analogues • Seasonal dependence of the biomass quality and availability

Figure 5. SWOT analysis of production of cosmeceuticals from microalgal sources (modified from [30]).

Even such a brief review makes obvious the advantages and the potential of microalgal biotechnology for the "green" cosmeceutical production. However, a significant part of the chemo- and biodiversity of microalgae remains so far untapped. Consequently, bioprospecting and biochemical characterization of new species and strains, especially those isolated from habitats with harsh environmental conditions is a major avenue for further research and development. As important is the development of efficient approaches to cost-effective cultivation of microalgae as well as induction, extraction, and purification of the cosmeceutical metabolites.

Author Contributions: Conceptualization, T.P. and S.Kh.; writing—original draft preparation, A.S.; writing—review and editing, all authors; supervision, A.S.; project administration, A.L. All authors have read and agreed to the published version of the manuscript."

Funding: This research was funded by the Ministry of Science and Higher Education of the Russia Federation, grant number RFMEFI60419X0213.

Institutional Review Board Statement: Not applicable.

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

References

1. Richmond, A. *Handbook of microalgal culture: biotechnology and applied phycology*; Wiley-Blackwell: 2008.
2. Masojídek, J.; Torzillo, G.; Koblízek, M. Photosynthesis in Microalgae. In *Handbook of Microalgal Culture: Applied Phycology and Biotechnology*, 2 ed.; Richmond, A., Hu, Q., Eds. John Wiley & Sons, Ltd.: Chichester, UK, 2013; pp. 21-35.
3. Rastogi, R.P.; Madamwar, D.; Pandey, A. *Algal green chemistry: recent progress in biotechnology*; Elsevier: 2017.
4. Thomas, N.V.; Kim, S.-K. Beneficial effects of marine algal compounds in cosmeceuticals. *Marine drugs* **2013**, *11*, 146-164.
5. Kim, S.-K. *Marine cosmeceuticals: trends and prospects*; CRC Press: 2011.
6. MU, N.; Mehar, J.G.; Mudliar, S.N.; Shekh, A.Y. Recent advances in microalgal bioactives for food, feed, and healthcare products: commercial potential, market space, and sustainability. *Comprehensive Reviews in Food Science and Food Safety* **2019**, *18*, 1882-1897.
7. Coates, R.C.; Trentacoste, E.; Gerwick, W.H. Bioactive and novel chemicals from microalgae. *Handbook of Microalgal Culture* **2013**, 504-531.
8. García, J.L.; de Vicente, M.; Galán, B. Microalgae, old sustainable food and fashion nutraceuticals. *Microbial Biotechnology* **2017**, *10*, 1017-1024.
9. Barbosa, A.J.; Roque, A.C. Free Marine natural products databases for biotechnology and bioengineering. *Biotechnology journal* **2019**, *14*, 1800607.

10. Borowitzka, M.A.; Vonshak, A. Scaling up microalgal cultures to commercial scale. *European Journal of Phycology* **2017**, *52*, 407-418, doi:10.1080/09670262.2017.1365177.
11. Carlsson, A.; Van Beilen, J.; Möller, R.; Clayton, D.; Bowles, D. Micro-and Macro-Algae: Utility for Industrial Applications, outputs from the EPOBIO project, CNAP, University of York. CPL Press, UK, available at www. epobio. net/pdfs/0709AquaticReport. pdf …: 2008.
12. Paul, N.A.; Tseng, C.; Borowitzka, M. Seaweed and microalgae. *Aquaculture: farming aquatic animals and plants* **2013**, 268-293.
13. Guiry, M. AlgaeBase.org. 2020; Vol. 2014, pp AlgaeBase is a database of information on algae that includes terrestrial, marine and freshwater organisms.
14. Kijjoa, A.; Sawangwong, P. Drugs and cosmetics from the sea. *Marine Drugs* **2004**, *2*, 73-82.
15. Borowitzka, M.A. High-value products from microalgae—their development and commercialisation. *Journal of applied phycology* **2013**, *25*, 743-756.
16. Mulders, K.J.M.; Lamers, P.P.; Martens, D.E.; Wijffels, R.H. Phototrophic pigment production with microalgae: biological constraints and opportunities. *Journal of Phycology* **2014**, *50*, 229-242, doi:10.1111/jpy.12173.
17. Solovchenko, A.E. Physiology and adaptive significance of secondary carotenogenesis in green microalgae. *Russian Journal of Plant Physiology* **2013**, *60*, 1-13, doi:10.1134/s1021443713010081.
18. Solovchenko, A. Photoprotection in Plants: Optical Screening-based Mechanisms. 1 ed.; Springer: Heidelberg, New York, 2010; p 167.
19. Couteau, C.; Coiffard, L. Chapter 15 - Microalgal Application in Cosmetics. In *Microalgae in Health and Disease Prevention*, Levine, I.A., Fleurence, J., Eds. Academic Press: 2018; https://doi.org/10.1016/B978-0-12-811405-6.00015-3pp. 317-323.
20. Borowitzka, M.A. Commercial production of microalgae: ponds, tanks, and fermenters. In *Progress in industrial microbiology*, Elsevier: 1999; Vol. 35, pp. 313-321.
21. Gupta, P.L.; Lee, S.M.; Choi, H.J. A mini review: photobioreactors for large scale algal cultivation. *World J Microbiol Biotechnol* **2015**, *31*, 1409-1417, doi:10.1007/s11274-015-1892-4.
22. Zittelli, G.; Biondi, N.; Rodolfi, L.; Tredici, M. Photobioreactors for Mass Production of Microalgae. In *Handbook of Microalgal Culture: Applied Phycology and Biotechnology*, 2 ed.; Richmond, A., Hu, Q., Eds. Blackwell: 2013; pp. 225-266.
23. Levine, I.A. Chapter 1 - Algae: A Way of Life and Health. In *Microalgae in Health and Disease Prevention*, Levine, I.A., Fleurence, J., Eds. Academic Press: 2018; https://doi.org/10.1016/B978-0-12-811405-6.00001-3pp. 1-10.
24. Scott, R. Marine ingredients: latest actives from the deep. *Personal Care* **2015**, *4*, 43-44.
25. Gong, M.; Bassi, A. Carotenoids from microalgae: A review of recent developments. *Biotechnol Adv* **2016**, 10.1016/j.biotechadv.2016.10.005, doi:10.1016/j.biotechadv.2016.10.005.
26. Fox, J.M.; Zimba, P.V. Chapter 8 - Minerals and Trace Elements in Microalgae. In *Microalgae in Health and Disease Prevention*, Levine, I.A., Fleurence, J., Eds. Academic Press: 2018; https://doi.org/10.1016/B978-0-12-811405-6.00008-6pp. 177-193.
27. Julius, M.L. Chapter 6 - Carbohydrate Diversity in Microalgae: A Phylogenetically Arranged Presentation. In *Microalgae in Health and Disease Prevention*, Levine, I.A., Fleurence, J., Eds. Academic Press: 2018; https://doi.org/10.1016/B978-0-12-811405-6.00006-2pp. 133-144.
28. Mimouni, V.; Couzinet-Mossion, A.; Ulmann, L.; Wielgosz-Collin, G. Chapter 5 - Lipids From Microalgae. In *Microalgae in Health and Disease Prevention*, Levine, I.A., Fleurence, J., Eds. Academic Press: 2018; https://doi.org/10.1016/B978-0-12-811405-6.00005-0pp. 109-131.
29. Morançais, M.; Mouget, J.-L.; Dumay, J. Chapter 7 - Proteins and Pigments. In *Microalgae in Health and Disease Prevention*, Levine, I.A., Fleurence, J., Eds. Academic Press: 2018; https://doi.org/10.1016/B978-0-12-811405-6.00007-4pp. 145-175.
30. Novoveska, L.; Ross, M.E.; Stanley, M.S.; Pradelles, R.; Wasiolek, V.; Sassi, J.F. Microalgal Carotenoids: A Review of Production, Current Markets, Regulations, and Future Direction. *Mar Drugs* **2019**, *17*, doi:10.3390/md17110640.

31. Eom, S.-H.; Kim, S.-K. Cosmeceutical applications from marine organisms. *Cosmeceuticals and Cosmetic Practice; Farris, PK, Ed.; John Wiley Sons, Ltd.: Chichester, UK* **2013**, 200-208.
32. Arad, S.; van Moppes, D. Novel sulfated polysaccharides of red microalgae: basics and applications. In *Handbook of Microalgal Culture: Applied Phycology and Biotechnology*, Wiley Online Library: 2013; pp. 406-416.
33. Silva, T.H.; Alves, A.; Popa, E.G.; Reys, L.L.; Gomes, M.E.; Sousa, R.A.; Silva, S.S.; Mano, J.F.; Reis, R.L. Marine algae sulfated polysaccharides for tissue engineering and drug delivery approaches. *Biomatter* **2012**, *2*, 278-289.
34. Malcata, F.X.; Pinto, I.S.; Guedes, A.C. *Marine Macro-and Microalgae: An Overview*; CRC Press: 2018.
35. Cohen, Z.; Khozin-Goldberg, I. Searching for PUFA-rich microalgae. In *Single Cell Oils*, 2 ed.; Cohen, Z., Ratledge, C., Eds. American Oil Chemists' Society: Champaign IL, 2010; pp. 201-224.
36. Lee, J.-C.; Hou, M.-F.; Huang, H.-W.; Chang, F.-R.; Yeh, C.-C.; Tang, J.-Y.; Chang, H.-W. Marine algal natural products with anti-oxidative, anti-inflammatory, and anti-cancer properties. *Cancer Cell International* **2013**, *13*, 1-7.
37. Ward, O.P.; Singh, A. Omega-3/6 fatty acids: alternative sources of production. *Process biochemistry* **2005**, *40*, 3627-3652.
38. Solovchenko, A.; Merzlyak, M.; Khozin-Goldberg, I.; Cohen, Z.; Boussiba, S. Coordinated carotenoid and lipid syntheses induced in *Parietochloris incisa* (Chlorophyta, Trebouxiophyceae) mutant deficient in Δ5 desaturase by nitrogen starvation and high light. *Journal of Phycology* **2010**, *46*, 763-772, doi:10.1111/j.1529-8817.2010.00849.x.
39. Solovchenko, A. Physiological role of neutral lipid accumulation in eukaryotic microalgae under stresses. *Russian Journal of Plant Physiology* **2012**, *59*, 167-176.
40. Khozin-Goldberg, I.; Shrestha, P.; Cohen, Z. Mobilization of arachidonyl moieties from triacylglycerols into chloroplastic lipids following recovery from nitrogen starvation of the microalga *Parietochloris incisa*. *BBA-Molecular and Cell Biology of Lipids* **2005**, *1738*, 63-71.
41. Solovchenko, A.; Khozin-Goldberg, I.; Didi-Cohen, S.; Cohen, Z.; Merzlyak, M. Effects of light intensity and nitrogen starvation on growth, total fatty acids and arachidonic acid in the green microalga *Parietochloris incisa*. *Journal of Applied Phycology* **2008**, *20*, 245-251.
42. Khozin-Goldberg, I.; Iskandarov, U.; Cohen, Z. LC-PUFA from photosynthetic microalgae: occurrence, biosynthesis, and prospects in biotechnology. *Applied microbiology and biotechnology* **2011**, 10.1007/s00253-011-3441-x, 1-11, doi:10.1007/s00253-011-3441-x.
43. Khozin, I.; Adlerstein, D.; Bigongo, C.; Heimer, Y.M.; Cohen, Z. Elucidation of the Biosynthesis of Eicosapentaenoic Acid in the Microalga Porphyridium cruentum (II. Studies with Radiolabeled Precursors). *Plant Physiology* **1997**, *114*, 223-230.
44. Cohen, Z. Production of polyunsaturated fatty acids by the microalga *Porphyridium cruentum*. In *Production of Chemicals by Microalgae*, Cohen, Z., Ed. Taylor and Francis: London, 1999; pp. 1-24.
45. Solovchenko, A.; Lukyanov, A.; Solovchenko, O.; Didi-Cohen, S.; Boussiba, S.; Khozin-Goldberg, I. Interactive effects of salinity, high light, and nitrogen starvation on fatty acid and carotenoid profiles in Nannochloropsis oceanica CCALA 804. *European Journal of Lipid Science and Technology* **2014**, *116*, 635-644.
46. Dufossé, L.; Galaup, P.; Yaron, A.; Arad, S.M.; Blanc, P.; Murthy, K.N.C.; Ravishankar, G.A. Microorganisms and microalgae as sources of pigments for food use: a scientific oddity or an industrial reality? *Trends in Food Science & Technology* **2005**, *16*, 389-406.
47. Spolaore, P.; Joannis-Cassan, C.; Duran, E.; Isambert, A. Commercial applications of microalgae. *Journal of bioscience and bioengineering* **2006**, *101*, 87-96.
48. Pulz, O.; Gross, W. Valuable products from biotechnology of microalgae. *Applied microbiology and biotechnology* **2004**, *65*, 635-648.
49. M, U.N.; Mehar, J.G.; Mudliar, S.N.; Shekh, A.Y. Recent Advances in Microalgal Bioactives for Food, Feed, and Healthcare Products: Commercial Potential, Market Space, and Sustainability. *Compr Rev Food Sci Food Saf* **2019**, *18*, 1882-1897, doi:10.1111/1541-4337.12500.

50. Scheer, H. An overview of chlorophylls and bacteriochlorophylls: biochemistry, biophysics, functions and applications. In *Advances in photosynthesis and respiration*, Grimm, B., Porra, R., Scheer, H., Eds. Springer: Dordrecht, 2006; Vol. 25, pp. 1-26.
51. Freitas, S.; Silva, N.G.; Sousa, M.L.; Ribeiro, T.; Rosa, F.; Leão, P.N.; Vasconcelos, V.; Reis, M.A.; Urbatzka, R. Chlorophyll derivatives from marine cyanobacteria with lipid-reducing activities. *Marine drugs* **2019**, *17*, 229.
52. Sun, T.; Yuan, H.; Cao, H.; Yazdani, M.; Tadmor, Y.; Li, L. Carotenoid Metabolism in Plants: The Role of Plastids. *Mol Plant* **2018**, *11*, 58-74, doi:10.1016/j.molp.2017.09.010.
53. Takaichi, S. Carotenoids in Algae: Distributions, Biosyntheses and Functions. *Marine Drugs* **2011**, *9*, 1101-1118.
54. Black, H.S.; Boehm, F.; Edge, R.; Truscott, T.G. The Benefits and Risks of Certain Dietary Carotenoids that Exhibit both Anti- and Pro-Oxidative Mechanisms-A Comprehensive Review. *Antioxidants (Basel)* **2020**, *9*, doi:10.3390/antiox9030264.
55. Boer, L. Biotechnological Production of Colorants. Springer Berlin Heidelberg: 2013; 10.1007/10_2013_241pp. 1-39.
56. Davidi, L.; Levin, Y.; Ben-Dor, S.; Pick, U. Proteome analysis of cytoplasmatic and of plastidic β-carotene lipid droplets in *Dunaliella bardawil*. *Plant Physiology* **2015**, *167*, 60-79, doi:10.1104/pp.114.248450.
57. Telfer, A. What is b-carotene doing in the photosystem II reaction centre? *Philosophical Transactions of the Royal Society-Ser B-Biological Sciences* **2002**, *357*, 1431-1440.
58. Davidi, L.; Shimoni, E.; Khozin-Goldberg, I.; Zamir, A.; Pick, U. Origin of β-carotene-rich plastoglobuli in *Dunaliella bardawil*. *Plant Physiology* **2014**, *164*, 2139-2156, doi:10.1104/pp.113.235119.
59. Solovchenko, A.; Neverov, K. Carotenogenic response in photosynthetic organisms: a colorful story. *Photosynthesis research* **2017**, 10.1007/s11120-017-0358-y, doi:10.1007/s11120-017-0358-y.
60. Lamers, P.P.; van de Laak, C.C.W.; Kaasenbrood, P.S.; Lorier, J.; Janssen, M.; De Vos, R.C.H.; Bino, R.J.; Wijffels, R.H. Carotenoid and fatty acid metabolism in light-stressed *Dunaliella salina*. *Biotechnology and Bioengineering* **2010**, *106*, 638-648, doi:Doi 10.1002/Bit.22725.
61. Ye, Z.-W.; Jiang, J.-G.; Wu, G.-H. Biosynthesis and regulation of carotenoids in *Dunaliella*: progresses and prospects. *Biotechnology Advances* **2009**, *26*, 352-360.
62. Lim, K.C.; Yusoff, F.M.; Shariff, M.; Kamarudin, M.S. Astaxanthin as feed supplement in aquatic animals. *Reviews in Aquaculture* **2017**, 10.1111/raq.12200, doi:10.1111/raq.12200.
63. Han, D.; Li, Y.; Hu, Q. Astaxanthin in microalgae: pathways, functions and biotechnological implications. *Algae* **2013**, *28*, 131-147.
64. Dhankhar, J.; Kadian, S.S.; Sharma, A. Astaxanthin: a potential carotenoid. *International Journal of Pharmaceutical Sciences and Research* **2012**, *3*, 1246-1259.
65. Hussein, G.; Sankawa, U.; Goto, H.; Matsumoto, K.; Watanabe, H. Astaxanthin, a carotenoid with potential in human health and nutrition. *Journal of natural products* **2006**, *69*, 443-449.
66. Naguib, Y. Antioxidant Activities of Astaxanthin and Related Carotenoids. *J Agric Food Chem* **2000**, *48*, 1150–1154.
67. Cornish, M.L.; Garbary, D.J. Antioxidants from macroalgae: potential applications in human health and nutrition. *Algae* **2010**, *25*, 155-171.
68. Tanaka, T.; Shnimizu, M.; Moriwaki, H. Cancer chemoprevention by carotenoids. *Molecules* **2012**, *17*, 3202-3242, doi:10.3390/molecules17033202.
69. Goiris, K.; Muylaert, K.; Fraeye, I.; Foubert, I.; De Brabanter, J.; De Cooman, L. Antioxidant potential of microalgae in relation to their phenolic and carotenoid content. *Journal of applied phycology* **2012**, *24*, 1477-1486.
70. Rodriguez-Garcia, I.; Guil-Guerrero, J.L. Evaluation of the antioxidant activity of three microalgal species for use as dietary supplements and in the preservation of foods. *Food chemistry* **2008**, *108*, 1023-1026.
71. Chubchikova, I.; Drobetskaya, I.; Minyuk, G.; Dantsyuk, N.; Chelebieva, E. Screening of green microalgae as potential source of nature ketocarotenoids. 2. Features of growth and secondary carotenogenesis in the representatives of the genus Bracteacoccus (Chlorophyceae). *Marine Ecological Journal* **2011**.

---

72. Zhekisheva, M.; Boussiba, S.; Khozin-Goldberg, I.; Zarka, A.; Cohen, Z. Accumulation of oleic acid in *Haematococcus pluvialis* (Chlorophyceae) under nitrogen starvation or high light is correlated with that of astaxanthin esters. *Journal of Phycology* **2002**, *38*, 325-331, doi:10.1046/j.1529-8817.2002.01107.x.
73. Zhekisheva, M.; Zarka, A.; Khozin-Goldberg, I.; Cohen, Z.; Boussiba, S. Inhibition of astaxanthin synthesis under high irradiance does not abolish triacylglycerol accumulation in the green alga *Haematococcus pluvialis* (Chlorophyceae). *Journal of Phycology* **2005**, *41*, 819-826, doi:10.1111/j.0022-3646.2005.05015.x.
74. Chekanov, K.; Lukyanov, A.; Boussiba, S.; Aflalo, C.; Solovchenko, A. Modulation of photosynthetic activity and photoprotection in Haematococcus pluvialis cells during their conversion into haematocysts and back. *Photosynthesis research* **2016**, *128*, 313-323.
75. Boussiba, S. Carotenogenesis in the green alga *Haematococcus pluvialis*: cellular physiology and stress response. *Physiologia Plantarum* **2000**, *108*, 111-117, doi:10.1034/j.1399-3054.2000.108002111.x.
76. Domınguez-Bocanegra, A.; Legarreta, I.G.; Jeronimo, F.M.; Campocosio, A.T. Influence of environmental and nutritional factors in the production of astaxanthin from Haematococcus pluvialis. *Bioresource technology* **2004**, *92*, 209-214.
77. Li, J.; Zhu, D.; Niu, J.; Shen, S.; Wang, G. An economic assessment of astaxanthin production by large scale cultivation of *Haematococcus pluvialis*. *Biotechnology Advances* **2011**, *29*, 568-574, doi:http://dx.doi.org/10.1016/j.biotechadv.2011.04.001.
78. Prasanna, R.; Sood, A.; Suresh, A.; Nayak, S.; Kaushik, B. Potentials and applications of algal pigments in biology and industry. *Acta Botanica Hungarica* **2007**, *49*, 131-156.
79. Petrushkina, M.; Gusev, E.; Sorokin, B.; Zotko, N.; Mamaeva, A.; Filimonova, A.; Kulikovskiy, M.; Maltsev, Y.; Yampolsky, I.; Guglya, E. Fucoxanthin production by heterokont microalgae. *Algal Research* **2017**, *24*, 387-393.
80. Řezanka, T.; Temina, M.; Tolstikov, A.; Dembitsky, V. Natural microbial UV radiation filters—Mycosporine-like amino acids. *Folia Microbiol* **2004**, *49*, 339-352.
81. Gröniger, A.; Sinha, R.; Klisch, M.; Häder, D. Photoprotective compounds in cyanobacteria, phytoplankton and macroalgae—a database. *Journal of Photochemistry & Photobiology, B: Biology* **2000**, *58*, 115-122.
82. Shick, J.; Dunlap, W. Mycosporine-like amino acids and related gadusols: biosynthesis, accumulation, and UV-protective functions in aquatic organisms. *Annual Review of Physiology* **2002**, *64*, 223-262.
83. Sinha, R.; Singh, S.; Häder, D. Database on mycosporines and mycosporine-like amino acids (MAAs) in fungi, cyanobacteria, macroalgae, phytoplankton and animals. *Journal of Photochemistry & Photobiology, B: Biology* **2007**, *89*, 29-35.
84. Wada, N.; Sakamoto, T.; Matsugo, S. Mycosporine-like amino acids and their derivatives as natural antioxidants. *Antioxidants* **2015**, *4*, 603-646.
85. Suh, S.-S.; Hwang, J.; Park, M.; Seo, H.H.; Kim, H.-S.; Lee, J.H.; Moh, S.H.; Lee, T.-K. Anti-inflammation activities of mycosporine-like amino acids (MAAs) in response to UV radiation suggest potential anti-skin aging activity. *Marine drugs* **2014**, *12*, 5174-5187.
86. Ehling-Schulz, M.; Bilger, W.; Scherer, S. UV-B-induced synthesis of photoprotective pigments and extracellular polysaccharides in the terrestrial cyanobacterium Nostoc commune. *Journal of Bacteriology* **1997**, *179*, 1940-1945.
87. Brenner, M.; Hearing, V.J. The protective role of melanin against UV damage in human skin. *Photochemistry and photobiology* **2008**, *84*, 539-549.
88. Domínguez, H. Algae as a source of biologically active ingredients for the formulation of functional foods and nutraceuticals. In *Functional ingredients from algae for foods and nutraceuticals*, Elsevier: 2013; pp. 1-19.
89. Ishihara, K.; Watanabe, R.; Uchida, H.; Suzuki, T.; Yamashita, M.; Takenaka, H.; Nazifi, E.; Matsugo, S.; Yamaba, M.; Sakamoto, T. Novel glycosylated mycosporine-like amino acid, 13-O-(β-galactosyl)-porphyra-334, from the edible cyanobacterium Nostoc sphaericum-protective activity on human keratinocytes from UV light. *Journal of Photochemistry and Photobiology B: Biology* **2017**, *172*, 102-108.

90. Torres, A.; Enk, C.D.; Hochberg, M.; Srebnik, M. Porphyra-334, a potential natural source for UVA protective sunscreens. *Photochemical & Photobiological Sciences* **2006**, *5*, 432-435.

91. De la Coba, F.; Aguilera, J.; De Galvez, M.; Alvarez, M.; Gallego, E.; Figueroa, F.; Herrera, E. Prevention of the ultraviolet effects on clinical and histopathological changes, as well as the heat shock protein-70 expression in mouse skin by topical application of algal UV-absorbing compounds. *Journal of dermatological science* **2009**, *55*, 161-169.

92. Schmid, D.; Schürch, C.; Zülli, F. Mycosporine-like amino acids from red algae protect against premature skin-aging. *Euro Cosmetics* **2006**, *9*, 1-4.

93. Ryu, J.; Park, S.-J.; Kim, I.-H.; Choi, Y.H.; Nam, T.-J. Protective effect of porphyra-334 on UVA-induced photoaging in human skin fibroblasts. *International journal of molecular medicine* **2014**, *34*, 796-803.