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MARINE AND FRESHWATER MICROALGAE AS A SUSTAINABLE SOURCE OF COSMECEUTICALS*

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A prominent feature of stress-tolerant microalgae is their versatile metabolism, allowing them to synthesize a broad spectrum of molecules. In microalgae, they increase stress resilience of these organisms. In human body, they exhibit anti-aging, anti-inflammatory, and sunscreen activities. This is not surprising, given that many of the stress-induced deleterious processes in human body and in photosynthetic cell are mediated by the same mechanisms: 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 reactive oxygen species elimination systems including, *inter alia*, potent low-molecular antioxidants. Therefore, photosynthetic organisms are a rich source of bioactive substances with a great potential for curbing the negative effects of stresses, acting on human skin cells on a day-to-day basis. In many cases these compounds appear to be less toxic, less allergenic, and, in general, more "biocompatible" than most of their synthetic counterparts. The same algal metabolites are recognized as promising ingredients for innovative cosmetics and cosmeceutical formulations. Ever increasing efforts are being put 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 foods, nutraceuticals, pharmaceuticals, and cosmetology, associated with the global transition to a "greener" lifestyle. 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, a large-scale biotechnological production of microalgal biomass, enriched with the cosmeceutical compounds, is more technically feasible and economically viable than that of macrophyte biomass. The autotrophic cultivation of microalgae is generally simpler and often cheaper than that of heterotrophic microorganisms. Cultivation in bioreactors makes it possible to obtain more standardized raw biomass, quality of which is less dependent on seasonal factors. Microalgae biotechnology opens many possibilities to the "green" cosmeceutical production. However, a significant part of microalgae chemo- and biodiversity remains so far untapped. Consequently, bioprospecting and biochemical characterization of new algal species and strains, especially those isolated from habitats with harsh environmental conditions, is a major avenue for further research and development. Equally important is the development of approaches to cost-effective microalgae cultivation, as well as induction, extraction, and purification of cosmeceutical metabolites. World scientific community is rapidly accumulating extensive information on the chemistry and diverse effects of microalgae substances and metabolites; many substances of microalgal origin are extensively used in the cosmetic industry. However, the list of extracts and individual chemicals, isolated from them

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and thoroughly tested for safety and effectiveness, is not yet very large. Although excellent reviews of individual microalgal cosmeceutical groups exist, here we covered all the most important classes of such compounds of cosmeceutical relevance, linking the patterns of their composition and accumulation with the relevant aspects of microalgae biology.

Keywords: carotenoids, chlorophylls, lipids, mycosporine-like amino acids, antioxidants, UV screens

Microalgae are a large and diverse group of unicellular, prokaryotic, and eukaryotic microorganisms. They can grow in freshwater or seawater and play a key role in aquatic ecosystems as the primary producers (Masojídek et al., 2013). 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 (Algal Green Chemistry…, 2017 ; Marine Cosmeceuticals…, 2011 ; Thomas & Kim, 2013). Since the second half of the XX century, ever increasing efforts are being put 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 foods, pharmaceuticals, and cosmetology, associated with the global transition to a "greener" lifestyle (Algal Green Chemistry…, 2017 ; García et al., 2017 ; Marine Cosmeceuticals…, 2011).

As commercial demand increases, microalgae are cultivated at a large scale under different conditions (Borowitzka & Vonshak, 2017). 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 and climatic fluctuations / seasonality, in case of outdoor biomass production, must be taken into account in the process of biomass development for cosmetic lines (Carlsson et al., 2007 ; Marine Cosmeceuticals…, 2011).

Microalgae are a rich source of various compounds of commercial interest (Kijjoa & Sawangwong, 2004), especially those needed for cosmetics (Table 1): pigments, polysaccharides, and fatty acids (Borowitzka, 2013 ; Thomas & Kim, 2013). Most of the commercially promising active substances of microalgae are secondary metabolites, that accumulate in cells under unfavorable culture conditions for growth (Mulders et al., 2014 ; Solovchenko, 2013). Some of the metabolites have a chemical structure, which 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, which have formed during evolution (Solovchenko, 2010).

Table 1. Microalgal ingredients for the cosmetic industry and its main suppliers (Couteau & Coiffard, 2018)

Таблица 1. Ингредиенты из микроводорослей для косметической промышленности и их основные поставщики (Couteau & Coiffard, 2018)

Microalgae	Ingredients	Suppliers
Phaeodactylum tricornutum	Megassane	Soliance (merged with Givaudan Active Beauty)
	Depollutine	
Skeletonema costatum	Costalane	
Pyrocystis noctiluca		Microphyt
Chlorella	Dermochlorella D	CODIF Technologie Naturelle
	Dermochlorella DP	
	Agility chlorella	Roquette
		SetAlg
Odontella		Innov'Alg

The autotrophic cultivation of microalgae is generally simpler and often cheaper than that of heterotrophic microorganisms. It can be even economically efficient since microalgae can grow autotrophically (Algal Green Chemistry…, 2017 ; Masojídek et al., 2013). Cultivation in bioreactors makes it possible to obtain more standardized raw biomass, quality of which is less dependent on seasonal factors (Borowitzka, 1999 ; Zittelli et al., 2013). World scientific community has rapidly accumulated extensive information on the chemistry and diverse effects of substances and metabolites of microalgae (Coates et al., 2013 ; García et al., 2017 ; Levine, 2018). Many substances of microalgal origin have found extensive use in the cosmetic industry. However, the list of extracts and individual chemicals, isolated from them and thoroughly tested for safety and effectiveness, is not yet very large (Scott, 2015). Although excellent reviews of individual microalgal cosmeceutical groups exist (Fox & Zimba, 2018 ; Gong & Bassi, 2016 ; Julius, 2018 ; Mimouni et al., 2018 ; Morançais et al., 2018 ; Novoveská et al., 2019), here we covered all the most important classes of such compounds of cosmeceutical relevance (Eom & Kim, 2013), linking the patterns of their composition and accumulation with the relevant aspects of microalgae biology.

Structural and reverse polysaccharides

The bulk of the carbohydrates that make up algae are polysaccharides: up to 55 % of the dry matter (Algal Green Chemistry…, 2017 ; Morançais et al., 2018). 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 β-glucose molecules, linked by β-1,4 glycosidic bonds. 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) (Julius, 2018). α-glucans, such as α-1,4-glucans, are found in green, charophyte, glaucophyte, dinophyte, cryptomonad, and 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 (Julius, 2018). 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 chlorophytes contains both amylose and amylopectin (Algal Green Chemistry…, 2017). 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-glucans are used (Kijjoa & Sawangwong, 2004). β-1,3-glucans, *e. g.* paramylon, are synthesized by euglenophytes and Pavlovaceae from haptophytes. 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 (Julius, 2018). Microalgae also contain more exotic chemically modified, *e. g.* sulfated, polysaccharide species with unique physical and chemical properties, valued in the cosmetic industry (Arad & van Moppes, 2013 ; Silva et al., 2012).

Lipids

Microalgae represent an important “green” source of lipids, enriched with biologically active long-chain polyunsaturated fatty acids (hereinafter PUFA), such as γ-linolenic, arachidonic, and eicosapentaenoic (hereinafter EPA), docosahexaenoic acid (hereinafter DHA), and stearidonic acid – fatty acids, exerting vitamin F activity (Cohen & Khozin-Goldberg, 2010 ; Lee et al., 2013 ; Marine Macro- and Microalgae…, 2018 ; Mimouni et al., 2018 ; Ward & Singh, 2005). The lipids are divided into neutral and polar. Neutral lipids are mainly triacylglycerides, which are primarily accumulated in chloroplast or cytosolic lipid bodies, normally accumulated by microalgae in response to stresses (Solovchenko, 2012). Under those conditions, lipid content in oleaginous microalgae cells, such as *Schizochytrium* sp., *Pavlova lutheri*, *Isochrysis*, and *Nannochloropsis*, can reach 50–70 % of the cell dry weight. *Lobosphaera incisa* is capable of accumulating arachidonic acid up to 60 %

of the total fatty acids (Solovchenko et al., 2008). Certain microalgae species are known to accumulate EPA and DHA up to 3–5 % of the cell dry weight (Khozin-Goldberg et al., 2011). The genus *Schizochytrium* is a rich source of DHA (up to 37.7 % of the total fatty acids) (Cohen & Khozin-Goldberg, 2010 ; Mimouni et al., 2018). Microalgae, such as *Rhodomonas salina*, *Tetraselmis suecica*, *Thalassiosira pseudonana*, *Phaeodactylum tricornutum*, *Porphyridium cruentum*, *Nannochloropsis oculata*, and *Nannochloropsis gaditana*, are also intensively studied as potential sources of PUFA (Borowitzka, 2013 ; Solovchenko et al., 2008). A high EPA content was found in red microalgae, where it can reach 50 % of the total fatty acids (Cohen, 1999).

Accumulation of PUFA can be enhanced through the exposure of microalgae to various abiotic stresses, such as extreme salinities, temperatures, and shortage of N and P in the medium. Low-temperature stress for algae is one of the effective strategies for increasing PUFA. As a part of the adaptation to low temperature, microalgae increase PUFA production to maintain membrane fluidity. Cultivation of microalgae in bioreactors under controlled conditions allows to better standardize PUFA profiles of the algal lipid extracts.

Microalgae *Pavlova lutheri* and *Phaeodactylum tricornutum* show an increase in EPA content by about 20–30 % with a decrease in the cultivation temperature to +15 and +10 °C, respectively. On the other hand, high PUFA levels are observed within cell lipids when microalgae are grown under favorable conditions (Solovchenko et al., 2014). The production of “algal oil” by biotechnological methods for the purposes of the food and cosmetic industry has been proved for certain species: *Porphyridium cruentum* and *Crypthecodinium cohnii* (USA), *Schizochytrium* sp. (USA), and *Ulkenia* sp. (Germany) (Dufossé et al., 2005 ; Pulz & Gross, 2004 ; Spolaore et al., 2006). DHA 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 (Borowitzka, 2013 ; Cohen & Khozin-Goldberg, 2010 ; García et al., 2017 ; Kijjoa & Sawangwong, 2004).

In the cosmetic industry, “algal oil”, a concentrate of the essential ω-3 and ω-6 PUFA, is becoming more widespread. For infant formulations, “algal oil” from the dinoflagellate *Crypthecodinium cohnii* is used (30 % PUFA of the cell dry weight with DHA comprising approximately 50 % of the total PUFA). The technology for DHA obtaining from *Crypthecodinium* by Martek 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 Nutrinova produces DHA from *Ulkenia* sp. (branded “DHA Active”) (Pulz & Gross, 2004). Food supplements, containing microalgal DHA, are used for the prevention and treatment of diseases, associated with impaired brain activity, heart attack, and age-related visual impairment (Ward & Singh, 2005). EPA from *Porphyridium cruentum*, *Phaeodactylum tricornutum*, *Isochrysis galbana*, *Nannochloropsis* sp., and *Nitzschia laevis* is in demand for the prevention and treatment of lipid metabolism disorders. In cosmetics, this product is an important ingredient for restoring the water-lipid mantle of the skin (Dufossé et al., 2005 ; Spolaore et al., 2006).

Sterols perform a variety of functions in marine organisms, *inter alia* chemical defenses against attack by other organisms. Bioactive molecules, as steroid hormones, bile acids, and various biotoxins including steroid and triterpene saponins, can be considered as products of biotransformation of sterols. 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, *e. g.* in *Isochrysis galbana* and *Pavlova lutheri*. The main sterols of these microalgae include clionasterol, 4α-methyl poriferast-22-enol, poriferasterol, methylpavlovol, and epicampesterol. Thus, *Pavlova lutheri* can produce significant amounts of sterols (*ca.* 100 $mg \cdot g^{-1}$ total cell lipids), which can be further increased by ultraviolet (hereinafter UV) exposure of the microalga (Mimouni et al., 2018).

Algal sterols are promising precursors for vitamin D synthesis or as a part of emulsion bases in the production of soft dosage forms; they 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 (Marine Macro- and Microalgae…, 2018).

Pigments

Chlorophylls 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 chlorophylls depends on the algal group (Barbosa & Roque, 2019).

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 and skin with acne, as well as for care products for oily scalp (Freitas et al., 2019 ; Mu et al., 2019). 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. The experimental data suggests that these compounds are promising for development of nutraceuticals with a lipid-control activity or a cosmetic ingredient with lipolytic activity (Freitas et al., 2019). 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, and 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 chlorophyll preparation from higher plants.

Carotenoids are natural pigments that convey yellow, orange, or red hue to organisms, containing them. Chemically, they are a class of tetraterpenoids with a C_{40} backbone ubiquitously present in the photosynthetic apparatus of plants, microalgae, and cyanobacteria (Gong & Bassi, 2016 ; Sun et al., 2018). Carotenoids are divided into carotenes, the hydrocarbons devoid of oxygen, and xanthophylls, which contain oxygen (Gong & Bassi, 2016 ; Morançais et al., 2018 ; Novoveská et al., 2019 ; Sun et al., 2018). Around 750 natural carotenoids were isolated from various biological sources, of which about 200 were found in algae; nearly 30 of them were involved in photosynthesis of microalgae (Gong & Bassi, 2016). These are among the most diverse and widespread pigments in nature.

Carotenoids also found extensive use in the foods, nutraceuticals, pharmaceuticals, medicines, and cosmetic industry due to their antioxidant, antibacterial, antiviral, antifungal, anti-inflammatory, and antitumor properties (Black et al., 2020 ; Mulders et al., 2014 ; Novoveská et al., 2019). The antioxidant activity of carotenoids determines their application as functional food and cosmetics ingredients, as well as safe colorants (Boer, 2014). Currently, carotenoids, derived from microalgae, dominate certain segments of the natural pigment market (Novoveská et al., 2019). Overall, microalgal carotenoid production is considered as an important business opportunity for the healthcare and cosmetic industry of the future. The main carotenoids, currently commercially used in the world, are β-carotene, astaxanthin, lutein, canthaxanthin, zeaxanthin, and fucoxanthin (Gong & Bassi, 2016 ; Morançais et al., 2018). Lycopene and canthaxanthin are also biotechnologically important carotenoids. Natural carotenoids occur in microalgae as a mixture of *cis-trans* and optical isomers, whereas synthetic carotenoids are mostly in the free form. Natural carotenoids are preferred in cosmetic applications over their synthetic counterpart due to safety and higher bioavailability.

β-carotene is a yellow-orange strongly polar carotenoid. It is synthesized by photosynthetic organisms; it participates in light harvesting and photoprotection of chlorophyll and in prevention of damage to DNA by active oxygen forms (Davidi et al., 2015 ; Telfer, 2002). In nature, β-carotene is the most common precursor of vitamin A and a powerful antioxidant (Black et al., 2020). β-carotene is used as a food coloring agent, as well as in medicines, nutraceuticals, cosmetics, and feed (Novoveská et al., 2019). Commercial production of microalgal β-carotene employs diverse technologies from shallow ponds to advanced photobioreactors. β-carotene from *Dunaliella salina* (Fig. 1) was the first product, commercially obtained from microalgae (Lamers et al., 2010 ; Ye et al., 2009). The content of β-carotene in *Dunaliella salina* biomass reaches 10–14 % under stress conditions. Commercial companies, producing β-carotene from microalgae, include Aqua Carotene (USA), Nature Beta Technologies (Israel), Cognis Nutrition & Health (Australia), Cyanotech (USA), and Parry Nutraceuticals (India).

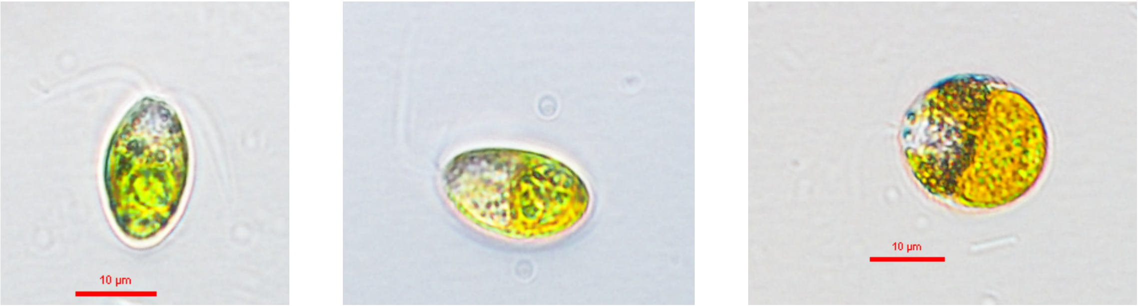


Fig. 1. Changes in *Dunaliella salina* cell morphology (left to right) in the course of high light and salinity stress-induced accumulation of β-carotene. Courtesy of Dr. Elena Seliwanova

Рис. 1. Изменение морфологии клеток микроводоросли *Dunaliella salina* (слева направо) в ходе накопления β-каротина под действием высокой солёности и света высокой интенсивности. Фото любезно предоставлены Е. А. Селивановой

Astaxanthin (3,3-dihydroxy-β-carotene-4,4-dione) is an oxygenated derivative of β-carotene. It is biosynthesized by some species of microalgae, fungi, and plants; this carotenoid gives salmon, shrimp, and lobsters, as well as their consumers, *e. g.* birds, their distinctive coloration (Novoveská et al., 2019). The high stress resilience of the astaxanthin-producing microalgae is a good marketing legend for the cosmetic industry, where extracts from these microalgae are offered as skin care products (Solovchenko, 2012). The natural pigment, represented mainly by the *3S,3′S* isomer, in antioxidant activity also exceeds its synthetic counterpart, which is a racemate comprised by all possible optical isomers (Han et al., 2013).

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 astaxanthin structure 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 across the lipid bilayer of the membrane, protecting it from the attacks of charged and uncharged reactive oxygen species (Hussein et al., 2006 ; Naguib, 2000). Astaxanthin protects microalgal cells from exposure to high light intensity and from harmful UV radiation, decreasing the formation of reactive oxygen species. This is also the basis for the use of *Haematococcus* extracts in protective skin care products (Cornish & Garbary, 2010 ; Tanaka et al., 2012).

Unlike β-carotene, astaxanthin is not a precursor of vitamin A, so it can be taken up safely without the risk of side effects, associated with vitamin A overdose. Astaxanthin has 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 central nervous system diseases (Goiris et al., 2012 ; Tanaka et al., 2012). For commercial cosmeceutical needs, astaxanthin is used in various forms: pills, capsules, syrups, oils, soft gels, creams, biomass dry powder, and granular powder (Cornish & Garbary, 2010 ; Thomas & Kim, 2013).

Haematococcus pluvialis (Fig. 2) is the most widely used as a producer of natural astaxanthin, although other microalgae, including *Chlorococcum* sp., *Chlorella zofingiensis*, *Botryococcus braunii*, *Chlamydomonas nivalis*, *Scotiellopsis oocystiformis*, and *Chloromonas nivalis*, are capable of synthesizing astaxanthin (Chubchikova et al., 2011). In *Haematococcus*, astaxanthin is predominantly esterified by fatty acids [$C_{16:0}$, $C_{18:2}$, and $C_{18:1}$ (Zhekisheva et al., 2005)]. Under stress conditions (nitrogen depletion, as well as high light intensity or salinity), *Haematococcus pluvialis* can accumulate astaxanthin up to 5–6 % of the cell dry weight during stress-induced transition of green vegetative cells into astaxanthin-rich resting haematocysts (Boussiba, 2000 ; Chekanov et al., 2016).

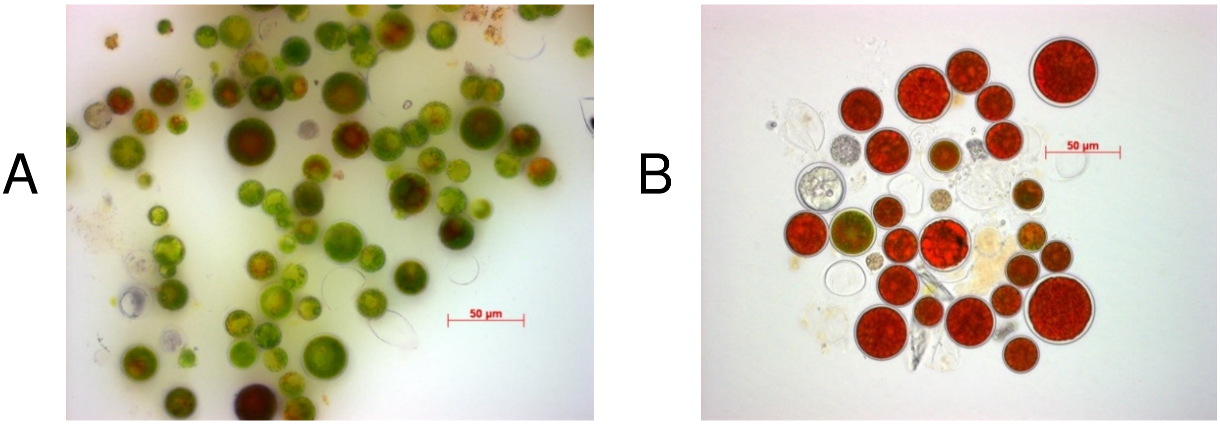


Fig. 2. Accumulation of astaxanthin in *Haematococcus pluvialis*: A – green vegetative cells, where accumulation has just begun; B – astaxanthin-rich haematocysts

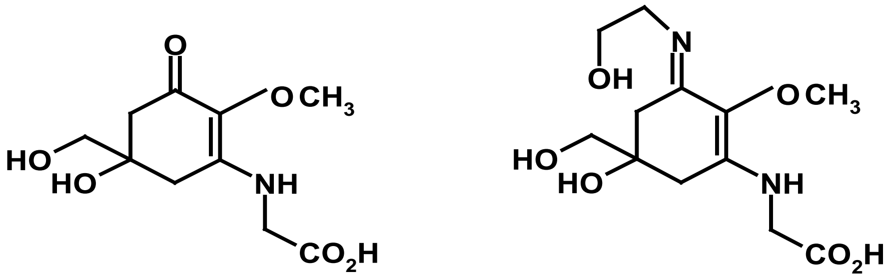
Рис. 2. Накопление астаксантина в клетках *Haematococcus pluvialis*: A — зелёные вегетативные клетки в начале накопления астаксантина; B — обогащённые астаксантином гематоцисты

Astaxanthin patents are related to food, feed, and nutraceutical, which are currently the main market driver for the pigment. Algatech (Israel), Nutrex Hawaii (USA), Cyanotech (USA), Jingzhou Natural Astaxanthin Inc. (China), Algaetech International (Malaysia), and Parry Nutraceuticals (India) are the main suppliers of microalgal astaxanthin on the market (Cornish & Garbary, 2010 ; Kijjoa & Sawangwong, 2004). Currently, astaxanthin from *Haematococcus* accounts for several percent of the global carotenoid market (Li et al., 2011) as a food coloring agent and a cosmetics ingredient.

Fucoxanthin is an accessory pigment in chloroplast of brown algae, phytoplankton, brown seaweed, and diatoms, giving them a brownish or olive-green color. 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 strong antioxidant activity. Fucoxanthin beneficial effects include antioxidant, antitumor, antidiabetic, and other activities (Kijjoa & Sawangwong, 2004 ; Novoveská et al., 2019). In cosmetics, it is used to whiten and improve skin condition, as well as a natural antioxidant and lipolytic agent.

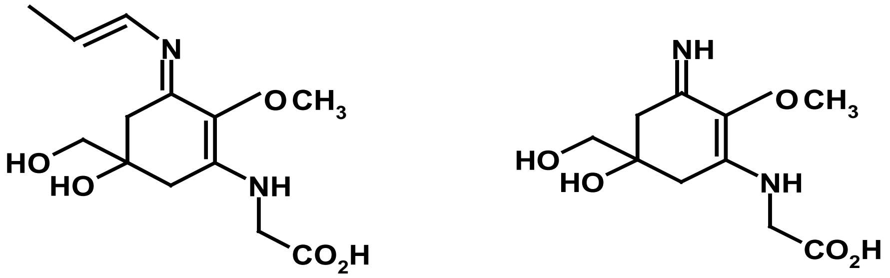
Mycosporine-like amino acids

Mycosporine-like amino acids (hereinafter 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 (Gröniger et al., 2000 ; Shick & Dunlap, 2002). 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 investigated in this regard. MAA are low-molecular mass, colorless, uncharged, and 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 (Shick & Dunlap, 2002) [Fig. 3 and (Wada et al., 2015)].



Mycosporyne-glycin (λ_{max} = 330 nm)

Shinorine (λ_{max} = 334 nm)



Palythene (λ_{max} = 360 nm)

Palythine (λ_{max} = 320 nm)

Fig. 3. Typical mycosporine-like amino acids and their absorption maxima

Рис. 3. Типичные представители микоспорин-подобных аминокислот с указанием длины волны максимума поглощения

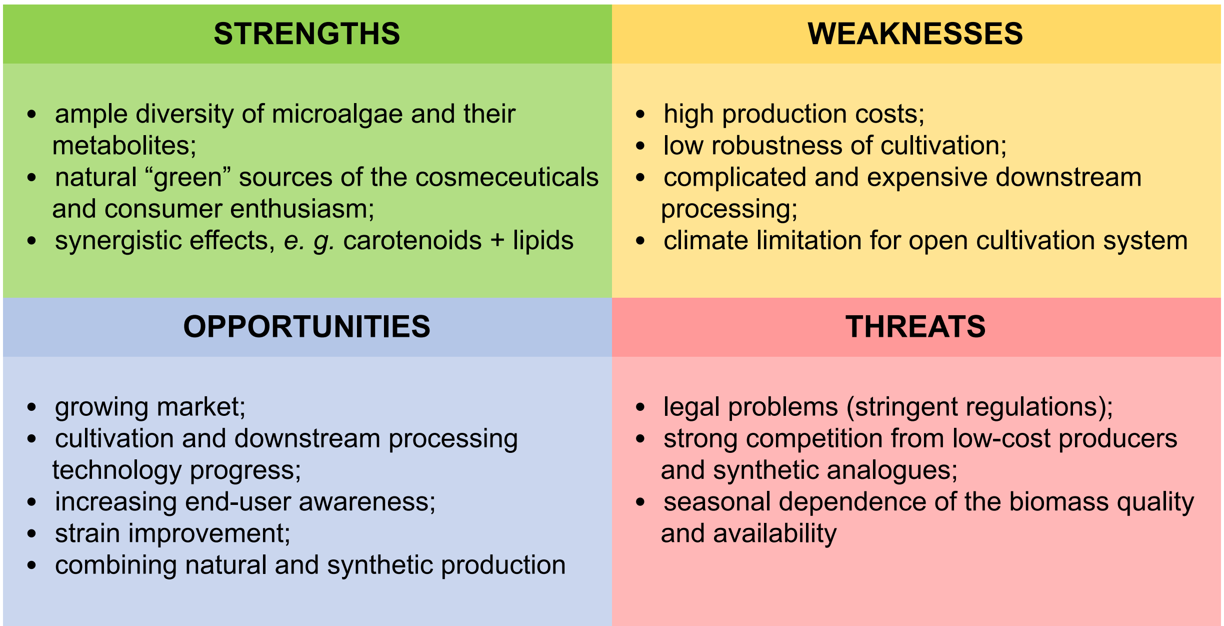
Prolonged exposure to UV radiation causes skin photoaging and several other disorders, *inter alia* fine and coarse wrinkling, and increases the risk of skin cancer. The most noticeable disorders include erythema, edema, blisters, sunburn cell formation, phototoxic reactions, photo-allergy, photo-sensitivity, and acute photo-immunosuppression (Brenner & Hearing, 2008). Sunscreens are commonly applied to reduce the harmful effects of UV on the skin. MAA are promising alternative UV-absorbing compounds of natural origin, which are highly soluble in water and do not generate reactive oxygen species upon absorption of UV radiation. More than 30 MAA from various organisms have been characterized (Gröniger et al., 2000 ; Torres et al., 2006). In addition to photoprotective properties, there is substantial evidence that MAA protect skin from aging and can exert antioxidant and anti-inflammatory activity; MAA can also inhibit protein glycation and collagenase activity. MMA anti-photoaging activity is thought to be related with reduction lipid peroxidation, a determinant of the aging process (de la Coba et al., 2009). Application of 0.005 % MAA in lecithin liposomes on the inner side of the forearm inhibited UVA-stimulated lipid peroxidation by 37 %; four-week treatments improved the skin elasticity and smoothness by 10 % and 12 %, respectively (Schmid et al., 2006). The tested MAA formulation was as effective as the standard cream, containing 1 % synthetic UV filters, Parsol® 1789 and 4 % UVB filters, Neo Heliopan® AV (Schmid et al., 2006). 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 UVA irradiated cells (Ryu et al., 2014). 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 (Suh et al., 2014).

A promising alternative to existing chemical and physical sunscreen filters is the use of multifunctional MAA, which are also suitable for cosmetics formulations (Godlewska et al., 2017 ; Suh et al., 2014). Experiments with cell culture models demonstrated UV-protective effects in HaCaT human keratinocyte cell line (Ishihara et al., 2017). Application of MAA prevented the UV-induced reduction of trans-urocanic acid and UV-stimulated histidine build-up. A crude methanol extract of cyanobacterium *Aphanizomenon flos-aquae*, enriched in MAA, showed a level of UVA protection as compared to a commercial skin care product with a sun protection factor SPF = 4 and a UVA/UVB protection ratio of 0.95 (Torres et al., 2006).

Conclusion 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 processes 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 reactive oxygen species elimination systems including potent low-molecular antioxidants.

Therefore, photosynthetic organisms are a rich source of bioactive substances with a great potential for curbing the negative effects of stresses on human skin cells from day to day. In many cases these compounds appear to be less toxic, less 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 microalgal biomass, enriched with the cosmeceutical compounds, is more technically feasible and economically viable than that of macrophyte biomass (Fig. 4).



STRENGTHS	WEAKNESSES
• ample diversity of microalgae and their metabolites; • natural “green” sources of the cosmeceuticals and consumer enthusiasm; • synergistic effects, *e. g.* carotenoids + lipids	• high production costs; • low robustness of cultivation; • complicated and expensive downstream processing; • 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

Fig. 4. SWOT analysis of production of cosmeceuticals from microalgal sources [modified from (Novoveská et al., 2019)]

Рис. 4. SWOT-анализ производства космецевтических субстанций из микроводорослей [по: (Novoveská et al., 2019), с изменениями]

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 algal 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 cosmeceutical metabolites.

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МОРСКИЕ И ПРЕСНОВОДНЫЕ МИКРОВОДОРОСЛИ КАК ВОЗОБНОВЛЯЕМЫЙ ИСТОЧНИК СОЕДИНЕНИЙ С КОСМЕЦЕВТИЧЕСКОЙ АКТИВНОСТЬЮ*

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Важная особенность экстремофильных и стресс-толерантных микроводорослей — их универсальный метаболизм, позволяющий им синтезировать широкий спектр биомолекул. Данные соединения повышают устойчивость клеток микроводорослей к неблагоприятным факторам. В организме человека биологически активные вещества способны замедлять старение и оказывать противовоспалительное и фотопротекторное действие. Это неудивительно, если учесть, что многие повреждения, вызываемые стрессами в организме человека и в фотоавтотрофных клетках, опосредуются одними и теми же механизмами, такими как атаки свободных радикалов и перекисное окисление липидов. Фотосинтетический аппарат клеток микроводорослей всегда подвержен риску окислительного повреждения, поскольку в процессе его функционирования постоянно генерируются высокие окислительно-восстановительные потенциалы и реакционноспособные молекулы. Этим факторам риска противостоят эффективные системы элиминации активных форм кислорода, включающие, среди прочих компонентов, мощные низкомолекулярные антиоксиданты. Как следствие, фототрофные организмы являются богатым источником биологически активных веществ с большим потенциалом для сдерживания негативных последствий стрессов, действующих на клетки кожи человека изо дня в день. Во многих случаях эти соединения оказываются менее токсичными, менее аллергенными и в целом более «биосовместимыми», чем большинство их синтетических аналогов. Те же самые метаболиты водорослей признаны перспективными ингредиентами для инновационных косметических средств и космецевтических рецептур. Исследователи прилагают всё больше усилий для поиска новых природных биологически активных веществ из микроводорослей. Поддерживает эту тенденцию и растущий спрос на натуральное сырьё для пищевых продуктов, а также нутрицевтики, фармацевтики и косметологии, связанный с глобальным переходом на «зелёные» (возобновляемые) источники сырья. В водорослях-макрофитах было обнаружено поразительное разнообразие соединений с космецевтическими эффектами, но одноклеточные водоросли не уступают им и даже превосходят их в этом отношении. В то же время крупномасштабное биотехнологическое производство биомассы микроводорослей, обогащённой космецевтическими соединениями, проще технически и выгоднее, чем производство или сбор биомассы

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макрофитов. Культивирование автотрофных микроводорослей, как правило, проще и дешевле, чем культивирование гетеротрофных микроорганизмов. Выращивание в биореакторах позволяет получать более стандартизированную сырую биомассу, качество которой в меньшей степени зависит от сезонных факторов. Биотехнология открывает множество возможностей для производства возобновляемого косметевтического сырья, однако значительная часть биоразнообразия микроводорослей и добываемых из них компонентов остаётся неизученной. Следовательно, поиск и получение биохимической характеристики новых видов и штаммов водорослей, особенно выделенных из местообитаний с суровыми условиями окружающей среды, — это одно из наиболее актуальных направлений дальнейших исследований. Не менее важна разработка подходов к рентабельному культивированию микроводорослей, а также к индукции, экстракции и очистке косметевтически активных метаболитов. Мировое научное сообщество стремительно накапливает информацию о химии и разнообразном действии соединений и метаболитов из микроводорослей; многие экстрагируемые из них вещества уже нашли широкое применение в косметической промышленности. Между тем перечень экстрактов и отдельных химических веществ, выделенных из них и тщательно проверенных на безопасность и эффективность, пока не очень велик. В литературе имеются содержательные обзоры по отдельным классам косметевтических субстанций из микроводорослей, но работы, охватывающие все основные группы таких соединений, встречаются редко. В данной статье рассмотрены наиболее важные классы химических веществ из клеток микроводорослей, обладающих косметевтическим потенциалом. Освещены закономерности состава и накопления этих веществ в связи с аспектами биологии микроводорослей.

Ключевые слова: каротиноиды, хлорофиллы, липиды, микоспорин-подобные аминокислоты, антиоксиданты, УФ-защитные соединения