Revealing the potential of cyanobacteria in cosmetics and cosmeceuticals — A new bioactive approach

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A B S T R A C T

The growing concern over appearance, health and aging has driven the exploration for cosmetics based on natural sources. Alongside with plants, algae and eukaryotic microalgae, cyanobacteria have been explored for the isolation of compounds with potential application in the cosmetic and cosmeceutical field. The long evolutionary history of cyanobacteria and exposure to environmental stress conditions seems to be the basis for the production of compounds with protective roles against external factors, such as desiccation, UV radiation and salinity. The production of exopolysaccharides, UV-protectors such as mycrosporine like amino acids and scytonemin, and antioxidant and anti-inflammatory compounds, by a wide range of cyanobacteria genera, coupled with a growing demand for natural origin products, places these organisms in the investigation line linked to cosmetics. The low nutritional requirements for large scale culture and the possibility to increase compounds production by manipulating culture conditions, also highlights the importance of these organisms as an alternative and a promising source for cosmetics based on nature. In this review, a general overview of the state of the art regarding the potential of cyanobacteria for the cosmetic and cosmeceutical industry is provided, emphasizing the main properties required in skin care formulations.

Keywords: Cyanobacteria Cosmetics Natural compounds Skin aging

1. General introduction

The skin major functions include the protection against desiccation, UV-radiation and the maintenance of the body homeostasis, in variables, such as temperature and osmolarity [1]. In addition, the skin is an organ of social communication, self-esteem and exteriorization of health. Although aesthetic appearance has always been a subject of great importance, the life expectancy and the concern over skin health and aging has undergone a considerable increase, resulting in a significant demand for skin care products.

The importance of a healthy skin drives the development of topical products designed to protect against exogenous and endogenous injurious agents. Most of these products are regulated as cosmetics [2,3] and cover a great variety of product categories, such as skin creams, UV-protectors, anti-aging and hypoallergenic products [4]. Currently, besides the cosmetic term, cosmeceutical terminology has also been introduced, which is referred to as a cosmetic product with active ingredients that exerts a pharmaceutical therapeutic benefit, such as anti-inflammatory [5]. Since cosmetic and cosmeceutical products are part of everyone's daily life, a variety of choice options and higher efficacy is always expected by the consumer [6]. Also, in the last decades a great concern for safer skin care products has been raised, not only due to human health concerns but also due to environmental issues. The detection of pharmaceuticals and personal care products (PPCPs), such as cosmetics, in environmental ecosystems has become a worldwide matter [7]. Studies have clearly shown that the elimination of PPCPs in municipal Sewage Treatment Plants (STP) is often incomplete [7] and several negative impacts were ascribed to ecosystems and organisms [8–10].

As a result of the harmful effects attributed to use of synthetic compounds, cosmetic research has increasingly focused investigation on natural compounds. Although cosmetics based on natural sources have always been used, in particular those based on plants [11], macroalgae and eukaryotic microalgae [12], the use of natural extracts in

cosmetics has of late been highlighted. In fact, researchers continue to corroborate that cosmetic formulations based on natural compounds play relevant and effective roles for skin benefit [13], induce less side effects [3,14] and are ecologically friendly [15]. In addition, the greater clarification, involvement and interest of citizens on the side effects of synthetic compounds has made the investment in natural compounds research more attractive [16].

Alongside with plants and algae, cyanobacteria have also come into focus as an alternative source of compounds for application in skin care. Allied with the production of metabolites with potential application as pharmaceuticals, nutraceuticals, cosmetics, food conservators and biosensor [17], cyanobacteria have the capacity to self-renew, which guarantee sustainable supplies [18], cultivation does not require arable land, and environmental impacts are minimal [19,20]. In fact, concerns with environmental sustainability have shown that cyanobacteria are multifunctional bio-agents for safe and eco-sustainable activities such as agriculture [21], production of biofuels [22,23] and production of bioactive compounds with application in human health [24,25]. Some compounds present in cyanobacteria have revealed photo-protective, moisturizing, antioxidant, anti-inflammatory and regenerative properties, making them interesting in the protection and homeostasis of the integumentary system and its derivatives, and in the application in health and wellness treatments such as thalassotherapy [26].

In recent years several reviews have been published within the theme of natural compounds derived from photosynthetic organisms, in skin protection. However, in addition to cyanobacteria, these reviews have focused on other sources, such as macroalgae, microalgae and plants, being the reference to cyanobacteria limited to a small number of cyanobacteria genera, namely *Spirulina*, *Arthrospira* and *Nostoc* [12,26,27]. Given the wide diversity of cyanobacteria genera and the arsenal of compounds produced by these organisms and with potential application in skin care products (see Table 1), we aim with this review to compile the research work that has been performed so far within this subject, in order to reinforce the role of cyanobacteria as a source of compounds with application in cosmetics and cosmeceuticals, and to broaden the range of cyanobacteria genera that might be interesting to explore for cosmetic purposes.

2. Cyanobacteria in cosmetics/cosmeceuticals

Cyanobacteria or blue-green algae are photosynthetic prokaryotes with a long evolutionary history [28], which resulted in a wide variety of species occupying different habitats [29]. In fact, cyanobacteria are ubiquitous in both terrestrial and aquatic environments, even in extremes, such as Antarctic dry valleys, thermophilic lakes, and lava caves [30–32]. In the course of their evolution, cyanobacteria have also strengthened unique symbioses with other organisms. [33]. Although invertebrates shelter an infinity of secondary metabolites with potent biological properties, the microbiota associated seems to be the true source of the compounds [34]. This is particularly interesting in the case of sea organisms, where the potential of sea invertebrates to provide beneficial secondary metabolites relies on its incredible microbiota, namely in cyanobacteria [35].

In recent years, cyanobacteria have been considered an alternative approach to natural compounds with applications in the cosmetics industry [18,36]. By presenting complex photosynthetic, adaptation and defense systems, cyanobacteria are capable of producing various metabolites, such as flavonoids, pigments (*e.g.* β-carotene, c-phycoerythrin, phycobiliproteins), phenols, saponins, steroids, tannins, terpenes and vitamins [37–39]. Many cyanobacteria species live in extreme environments, including high exposure to solar radiation and long periods of desiccation. In order to survive in such extreme conditions, cyanobacteria produce compounds that allow protection against ultraviolet (UV) radiation, and compounds capable of reducing extreme dehydration and oxidative stress [40,41]. Several cyanobacteria genera, such as *Spirulina*, were also found to be rich in nutrients, as proteins, essential fatty acids, vitamins, and minerals [42], which are important components in cosmetic formulations.

2.1. UV protection

Solar radiation is one of the environmental factors that most contribute to skin aging and carcinogenesis [43–45]. Skin pigmentation is an endogenous mechanism that protects against the damages caused by high exposure to sunlight [43], since melanin absorbs a broadband of UV-radiation and removes reactive oxygen species (ROS) [43], one of the major UV-induced cellular consequences [46]. Due to consumer demand for the presence of sunscreens in sunscreen lotions, moisturizers, facial makeup and lipsticks [47], tons of UV filters are produced globally each year [48].

The market offers sunscreens that contain inorganic and organic UV filters. Inorganic UV filters are physical blockers that exhibit mineral particles, such as titanium dioxide (TiO_2) and zinc oxide (ZnO) [49], that despite absorbing considerable UV-radiation, also produce highly oxidizing radicals [49]. Even when these particles are used as nanoparticles, it has been found that they induce toxicity in human dermal fibroblasts in culture, since they can pass through the cell membrane [50]. In alterative to inorganic filters, organic ones have been extensively used, being butyl methoxydibenzoylmethane (BM-DBM), ethylhexylmethoxycinnamate (EHMC), octocrylene (OCR) and benzophenone-4 (BP-4) the most used in PCPs and sunscreens [18]. However, several studies report side effects of these compounds, such as endocrine disruptor effects [51,52] and contact dermatitis in children [53]. UV filters such as BM-DBM, EHMC or OCR, were found to react with free peptides in human skin, supporting a direct correlation between the formation of protein adducts and contact dermatitis [54]. UV synthetic filter residues have also been detected in STP surface waters and river sediments [55,56], and several studies have reported toxicity to different organisms [10]. Therefore, despite its effectiveness against ultraviolet radiation, sunscreens and cosmetics containing synthetic UV filters can cause adverse effects to humans and ecosystems.

In cyanobacteria, the adaptation to environments with strong solar radiation was achieved through the production of compounds with photo protective effect, such as mycosporine-like amino acids (MAAs) and scytonemin (SCY) [45,57]. MAAs are metabolites, involved in the photo protective mechanisms of organisms, such as bacteria, lichens, fungi and cyanobacteria [58]. Concerning cyanobacteria, the MAAs shinorine and porphyra-334 were identified in three species of Nodularia (*Nodularia spumigena, Nodularia baltica* and *Nodularia harveyana*) [59] and two types of glycosylated MAAs were characterized from a *Nostoc commune* strain [60]. In this later study, a 1050-Da MAA in a cyanobacteria water extract was found to contribute to approximately 27% of the total radical scavenging activity, measured by the trolox equivalent antioxidant capacity (TEAC), which demonstrates a potent radical-scavenging activity *in vitro*. After that, several MAAs glycosylated from *Nostoc commune* have been identified [61,62]. In addition, some other common MAAs have already been found in cyanobacteria, such as mycosporine-tau, mycosporine-glycine, asterina-330, palythinol, mycosporine-2-glycine, palythene and euhalothece-362 [63,64].

Considering the potential effect of MAAs on the skin, a study involving 20 middle-age women demonstrated that a cream containing 0.005% MAAs extracted from a red algae can neutralize UV-A effects and improve skin smoothness [47]. Furthermore, the MAAs, shinorine and porfira-334 isolated from red algae, have already been marketed for use in sunscreens [63,64]. These two compounds, in addition to 13-β-Gal-P334, isolated from the cyanobacteria *Nostoc sphaericum* were reported to induce protective activity against the human keratinocyte HaCaT cell line exposed to UVA + 8-methoxypsoralen radiation [65]. The study revealed a cell photoprotective activity with an EC_{50} of 27 μM and 39 μM for the 13-β-Gal-P334 and porphyra-334 respectively, in comparison with an EC_{50} of 294 μM for the mycosporine-glycine,

Table 1
Interesting bioactive potential of cyanobacteria for cosmetics and cosmeceuticals.

Activity	Cyanobacteria	Compound/extract	Assay	Biological model	Reference
Anti-inflammatory	*Aphanothece sacrum*	Sacran	*In vivo* induced allergic dermatitis using TNCB[a]	Mice	[101]
Antioxidant	*Scytonema* sp.	SCY[b]	*In vivo* immunodotblot assay of ROS[c] scavenging activity and Thymine dimers formation	Cyanobacterial cells	[85]
	Nostoc commune	SCY[b]	ABTS[e]		[86]
		MAAs[d]			[60]
	Nostoc sphaericum	MAA (13-β-Gal-P334)[d]			[65]
	Nostoc commune	EPS[f]	*In vitro* superoxide anion and hydroxyl radical scavenging activity		[78]
			In vivo enzymatic assays (SOD, CAT, GPX, MDA)[g] and Paraquat assay[h]	*Caenorhabditis elegans*	
	Plectonema boryanum *Hapalosiphon intricatus* *Anabaena doliolum* *Oscillatoria acuta*	Methanolic extracts	DPPH[i]	–	[116]
	Oscillatoria sp. *Chroococcidiopsis thermalis* *Leptolyngbya* sp. *Calothrix* sp. *Nostoc* sp. *Phormidium* sp.	Phenolic extracts	ABTS[e] and DPPH[i]	–	[87]
	Synechocystis sp. *Leptolyngbya* sp. *Oscillatoria* sp.	Methanolic Extracts	DPPH[i]	–	[88]
	Nostoc sp. *Anabaena* sp. *Calothrix* sp. *Oscillatoria* sp. *Phormidium* sp.	Ethanolic extracts	DPPH[i] and FRAP[j]	–	[89]
	Cyanosarcina sp. *Phormidium* sp. *Scytonema* sp. *Leptolyngbya* sp.	Cell-free extracts	DPPH[i]	–	[92]
	Oscillatoria sp. *Lyngbya* sp. *Microcystis* sp. *Spirulina* sp.	Cell-free extracts	DPPH[i] and FRAP[j]	–	[93]
	Lyngbya sp.	MAAs[d] and SCY[b]	DPPH[i]	Cyanobacterial cells	[66]
	Spirulina platensis	Biomass containing carotenoids	Resonance Raman spectroscopy	Humans	[113]
Moisture-absorption Moisture-retention	*Nostoc commune*	EPS[f]	Moisture weight gain-and-loss assay[k]	–	[78]
			Moisture-retention function (ATR-FTIR spectral analysis)[l]	Mouse - male BALB	
Photo Protection	*Lyngbya* sp.	MAAs[d] and SCY[b]	Irradiation with photosynthetically active radiation and UV-A and UV-B radiation	Cyanobacterial cells	[66]
	Scytonema sp.	SCY[b]	Irradiation with photosynthetically active radiation and UV-A and UV-B radiation	Cyanobacterial cells	[85]
	Arthrospira platensis	Aqueous and organic extracts	Senescence-associated β-Galactosidase Activity assay Propidium Iodide Mediated Cell Cycle Analysis assay	nHDF[m]	[,112]
	Nostoc sphaericum	MAA (porphyra-334; shinorine; 13-β-Gal-P334)[d]	Cell proliferation assay	HaCat[n]	[65]
Whitening	*Oscillatoria agardhii*	Chloroform-methanol extract	Tyrosinase activity assay	–	[106]
	Spirulina	C-phycocyanin	Tyrosinase activity assay	B16F10[o]	[107]

[a] TNCB: 2,4,6 trinitrochlorobenzene was used to sensitize mice.
[b] SCY: Scytonemin.
[c] ROS: Reactive oxygen species.
[d] MAAs: Mycosporine-like amino acids.
[e] ABTS: 2,2′-azinobis (3-ethylbenzothiazoline- 6-sulfonic acid) as substrate in a colorimetry assay.
[f] EPS: Exopolysaccharide.
[g] SOD: Superoxide desmutase; CAT: Catalase; GPX: Glutathione peroxidase; MDA: Melondialdehyde.
[h] Paraquat: A highly toxic herbicide to animals and humans which induce oxidative stress.
[i] DPPH: 2,2-diphenyl-1-picrylhydrazyl free radical scavenging assay.
[j] FRAP: Ferric reducing antioxidant power assay.
[k] *Nostoc* polysaccharide, chitosan and urea were grounded into fine powder and oven-dried at 100 °C for 4 h to be compared.
[l] ATR-FTIR: Attenuated Total-Reflectance Fourier-Transform Infrared Spectroscopy.
[m] nHDF: Human fibroblasts cell line.
[n] HaCat: Keratinocytes cell line.
[o] B16F10: Murine melanoma cells.

which highlights its potential use in the skin photoprotection.

In contrast to MAAs, SCY is predominantly produced by cyanobacteria [66], being mostly found in the exopolysaccharide sheath [67]. SCY is a dimeric compound composed of indolic and phenolic subunits, and soluble in lipids [68]. It is known to be synthesized in response to UV-A radiation [69] and was found to reduce the penetration of UV-A

by 90% in cyanobacteria cells [70]. SCY has a maximum *in vivo* absorption of 370 nm while, purified it has an adsorption of 386 nm [118,57]. According to Proteau et al. [68], the biosynthesis of SCY is probably related to tyrosine and tryptophan derivatives. SCY exists in both oxidized and reduced forms [66,71] and four different derivatives of SCY have also been reported, dimethoxyscytonemin, tetramethoxyscytonemin, scytonin [119] and scytonemin-3a-imine [72]. Considering SCY effectiveness against UV radiation, Ferroni et al. [73] attributed the insensitivity of a *Nostoc flagelliforme* strain to UVA and UVB to the presence SCY, in addition to MAAs, emphasizing the role of these compounds in photoprotection. Given the potential of MAAs and SCY in photo-protection, these highly stable pigments offer opportunities for their use in sunscreens.

2.2. Moisturizing

Daily moisturizing routines are commonly used by all social classes and demonstrate the great concern for a healthy skin [3]. Moisturizers contain a range of combinations of chemical agents, such as emollients, occlusives and humectants, directed to attract, retain and increase the water content and reduce water evaporation [2,74] in order to prevent transepidermal water loss (TEWL) [18]. However, uncomfortable skin reactions from topical formulations may occur, such as sensory or subjective sensations with no signs of inflammation [74] and some subclinical injuries [14]. The occlusive agents for example, have limitations in terms of odors, allergic reactions and oily texture [2]. However, since humectants may enhance water absorption from the dermis into the epidermis where it can then be lost into the environment, they are almost always combined with an occlusive agent in order to form a hydrophobic barrier over the skin [2].

The potential use of cyanobacteria as moisturizing agents in cosmetics comes from the fact that these organisms have protective mechanisms against dehydration, namely through the production and excretion of exopolysaccharides (EPS). Cyanobacteria EPS are composed by various sugars and uronic acid that may account for more than 60% of the dry weight [41]. In cells, EPS can appear covalently linked or attached to the cell surface, forming sheaths, capsules and mucilage [75]. The tolerance of cyanobacteria to salinity in extreme saline environments seems to be due to a thick EPS layer surrounding the cells [76]. It was found that *Nostoc commune* EPS-depleted cells and *N. commune*, containing a small amount of EPS, were both sensitive to desiccation, suggesting that the amount of EPS has a crucial role in the desiccation tolerance in *N. commune* [76].

Since EPS are composed by molecules with water absorption and retention capacity, such as the uronic acid [77], they have been studied for this purpose in cosmetics in comparison with other ingredients. A higher water absorption capacity by EPS was demonstrated for a species of *Nostoc commune* (10.1%) compared to urea (5.8%) [78]. In the same study, a higher water retention capacity was also achieved with EPS (28%), when compared to urea (15.9%) and chitosan (7.3%), suggesting that the cyanobacterial EPS has a greater potential to be used as a natural humectant in the cosmeceutical industry with the benefit of not having to be combined with an occlusive agent. Okajima et al. [79] extracted the polysaccharide sacran from the cyanobacterium *Aphanothece sacrum* extracellular matrix and found it to be composed of sugar residues, such as uronic acid, muramic acid, and mannose [80]. In a comparison of moisture retention between sacran and hyaluronic acid, higher viscosity, higher water absorption efficiency, and a capability to absorb salines, containing multivalent metal ions, such as Ca^{2+} and Mg^{2+}, was found for sacran. These findings were particularly interesting since hyaluronic acid has a high cost and limited production, being however one of the most used ingredients in cosmetics products [81]. Sacran is, thus, a cyanobacteria gel that has the potential to be used as a high moisturizing agent.

2.3. Antioxidant

Through routine metabolic endogenous processes or under exogenous aggressions, skin cells produce reactive oxygen species (ROS) that are the basis of skin damage and aging. Although cells possesses their own endogenous antioxidant systems, excessive ROS production due to external injurious stimuli, such as UV-radiation and smoke, often triggers oxidative stress [44].

In cyanobacteria, both the EPS and the UV absorption compounds MAAs and SCY, mentioned above, were found to have antioxidant potential, which highlight their interest in cosmetics. In fact, aligned to their function in skin hydration, another feature that makes EPS possible and useful in cosmetic application is their antioxidant potential. For EPS extracted from a *Nostoc* strain, an *in vitro* dose-dependent antioxidant activity was registered [78]. Using as animal model the free-living nematode *Caenorhabditis elegans*, the authors revealed an increase in the activity of the antioxidant enzymes superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPX) and a decrease in the lipid peroxidation levels, to about 13.5%. The data obtained indicated an antioxidant efficacy comparable with that of the known antioxidant resveratrol, which is able to suppress *in vitro* as well as *in vivo* the peroxidation of lipids and other macromolecules, being extensively used in cosmetics [82]. EPS from cyanobacteria have, thus, been described as being able to sequester superoxide anions and hydroxyl radicals, increase the activity of enzymes involved in the mechanism of oxidative stress reduction and reduce lipid peroxidation.

Concerning MAAs and SCY, in addition to their photo protection function, they have also been singled out as promising antioxidants. Several studies point to the performance of MAAs and SCY in the sequestration of free radicals [60–62,83,36,71,84]. Rastogi & Incharoensakdi [66] reported that the MAAs as well as SCY from *Lyngbya* sp. CU2555 presented a dose-dependent antioxidant activity, with antioxidant rates of 14.5%, 53.0% and 68.9%, at MAAs concentrations of 0.115, 0.230 and 0.460 mg mL^{-1} respectively, and 12%, 33% and 57% at SCY concentrations of 0.5, 1.0 and 2.0 mg mL^{-1} respectively, thus making them able to prevent ROS. An efficacy of the SCY pigment from *Scytonema* sp. R77DM in reducing the production of intracellular ROS and thymine dimers (CPD) lesions induced by UV-radiation *in vivo* was also reported [85]. In this study, significant inhibitory effects on ROS production were observed in cyanobacterial cells treated with SCY (20.83%), ascorbic acid (45.75%), and SCY and ascorbic acid combined (58.65%), after exposure of UVA + UVB + PAR (photosynthetically active radiation). In addition, under similar conditions, the percentage of CPD inhibition (16.3%, 30.7% and 41.91%, respectively) was directly proportional to the decrease of ROS. In previous studies, it was already described that SCY significantly reduced the formation of ROS as well as the harmful effects of UV radiation and associated damages with SCY from the cyanobacterium *Nostoc commune* and *Rivularia* sp., supporting the use of SCY as an active antioxidant and photo protective ingredient in cosmeceuticals [86,83].

From a *Nostoc sphaericum* strain an IC50 of 17 mM of antioxidant activity was obtained with the MAA β-Gal-P334 [65], being this comparable to other glycosylated MAAs such as Hexose-bound-P334 (IC50 of 58 mM) and 7-O-(β-arabinopyranosyl)-P334 (IC50 of 9.5 mM) from *N. commune* [60–62].

Furthermore, polyphenols are a group of secondary metabolites that, in addition to antioxidant activity, participate in defense mechanisms against abiotic stresses [39]. In a study involving several cyanobacteria strains, the antioxidant activity determined by the 2,2′-azinobis (3-ethylbenzothiazoline- 6-sulfonic acid (ABTS) and the 2,2-diphenyl-1-picrylhydrazyl ($DPPH^{\bullet}$) antioxidant assays resulted in EC50 values of 63.45 and 67.49 μg mL^{-1}, respectively, for a *Leptolyngbya* strain, and 65.79 and 69.38 μg mL^{-1} for *Calothrix* sp. [87]. The authors found that the antioxidant potential was directly related to the amount and type of phenolic compounds extracted from the cyanobacteria biomass. Also IC50 values

between 54.59 μg mL^{-1} and 65.16 ± 1.4 μg mL^{-1} were registered in *Synechocystis* strains [88], and 30.72 μg mL^{-1} in *Calothrix* strains [89] with the $DPPH^{\bullet}$ antioxidant assay, which reveals a promising antioxidant potential for these cyanobacteria genera.

In addition to the studies mentioned above, several others point to a wide range of cyanobacteria genera, covering virtually all groups within the phylum, both coccoid and filamentous forms, from which antioxidant properties have been described. In these studies are included the genera *Synechocystis* [88], *Nostoc* [90,86], *Spirulina* [91], *Cyanosarcina*, *Phormidium*, *Scytonema* and *Leptolyngbya* [92] and *Microcystis, Lyngbya* and *Oscillatoria* [93]. This antioxidant potential seems to be related to the presence of phenolic compounds, flavonoids and pigments such as phycobiliproteins (PBPs), which are pigments involved in the uptake of light and also referred to as photo protectors [94]. The main PBPs present in the cyanobacteria are phycocyanin (PC-blue) and phycoerythrin (PE-red). Both PC and PE have been described as having antioxidant and anti-inflammatory activity [94,95]. Cell-free extracts from four thermotolerant strains, *Cyanosarcina* sp. SK40, *Phormidium* sp. PD40–1, *Scytonema* sp. TP40 and *Leptolyngbya* sp. KC45, revealed that both phenolic compounds and PBPs are responsible for high thermostability and antioxidant activities of the cyanobacteria extracts, with the strain *Leptolyngbya* sp. KC45 showing the highest antioxidant value of 7.44 ± 0.14 and 3.89 ± 0.08 mg gallic acid equivalent (GAE) g^{-1} dry weights, determined by DPPH and reducing power assay, respectively [92], suggesting that crude extracts may be used as thermostable antioxidative agents in cosmeceutical products. Also *Lyngbya* sp. and *Oscillatoria* sp. strains revealed a DPPH radical scavenging activity of 248.39 ± 11.97 mg ascorbic acid (AA) g^{-1} dry weights, and 465.31 ± 25.76 mg (AA) g^{-1} respectively, probably as a result of the total PBPs content, total phenolic content (TPC) and total flavonoid content (TFC) [93]. In this study, a *Lyngbya* sp. strain showed a total PBPs content of 127.01 mg g^{-1} (with 51.07 mg g^{-1} phycoerythrin and 41.29 mg g^{-1} phycocyanin), a TPC of 5.02 ± 0.20 mg g^{-1} and a TFC of 664.07 ± 19.76 mg g^{-1}, while the *Oscillatoria* sp. strain strain showed a TPC of 2.96 ± 0.14 mg g^{-1} and a TFC of 552.59 ± 46.27 mg g^{-1}, revealing the strains as good sources of antioxidant compounds.

Mice supplemented with *Spirulina platensis* and phycocyanobilin (PCB), which is the active form of the main compound C-phycocyanin (PC-C) in *S. platensis*, revealed a reduction in UVB-induced skin tumorigenesis, an affect that was attributed to an anti-inflammatory and antioxidant effect [96]. For PC-C a powerful antioxidant effect was described, such as the sequestration of peroxyl and hydroxyl radicals and inhibition of lipid peroxidation [97]. In addition to its antioxidant potential, this phycobiliprotein has been used as a natural colorant in the food industry and in cosmetics to replace synthetic dyes, due to the fact that it is non-toxic, non-carcinogenic and very blue in color [98].

2.4. Anti-inflammatory

Along with a protective physical barrier function, skin is actively involved in immune processes, such as allergic dermatitis and inflammatory responses [99]. Topical corticosteroids are the main compounds used in treatment for allergic dermatitis. Nevertheless, this treatment is limited by the induction of severe side effects, such as cutaneous atrophy, striae, and adrenal suppression [100]. A higher anti-inflammatory effect in induced allergic dermatitis in mice by the polysaccharide sacran from *Aphanothece sacrum*, when compared with hydrocortisone was reported [101]. Furthermore, sacran was also found to inhibit the release of cytokines and chemokines involved in skin allergy. The potent anti-inflammatory effects of sacran in rats were also reported, being ascribed to the inhibition of swelling and neutrophil infiltration in carrageenan-induced rat paw edema [102]. Moreover, sacran significantly suppressed 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced mouse ear edema, as well as pro-inflammatory cytokines. Besides sacran, SCY also demonstrated anti-inflammatory and anti-proliferative properties [103]. As described by these late authors SCY was found to inhibit the activity of the rhPKCβ1 inflammatory enzyme mediator with an IC50 of 3.4 ± 0.4 μM and to inhibit human fibroblasts proliferation with an IC50 of 5.4 ± 3.2 μM. Also, the anti-inflammatory potential of SCY was evaluated in an induced mouse ear edema, in which the topical application of SCY reduced the edema with an ED50 of 10.9 μg/ear ± 5.0. These results point to an anti-inflammatory effect comparable to other anti-inflammatory compounds, which highlight the potential of SCY as an anti-inflammatory agent.

2.5. Whitening

Whitening is one of the demands in cosmetic formulations directed to the treatment of pigmentation disorders such as melasma, freckles and lentigo senilis, that results from the abnormal accumulation of melanin [104].

Tyrosinase is an enzyme involved in melanin biosynthesis, being its inhibition a target for whitening compounds [105]. Although very few works have been performed in this area, cyanobacteria have shown some potential for the isolation of compounds with tyrosinase inhibitory activity and consequently in the treatment pigmentation disorders. An example is the compound osccillapeptin G isolated from *Oscillatoria agardhii* that was found to induce a tyrosinase inhibition effect to 55% of control [106]. Also, with PC from *Spirulina* sp., a significant reduction in tyrosinase activity by negatively regulated tyrosinase gene expression, was described, which resulted in a suppression of melanin synthesis [107].

2.6. Anti-aging

Skin aging, as aging in general, is rather difficult to define as it a result of mechanisms involving genetics and environmental factors [108]. Premature skin age or photoaging, in contrast to the chronological aging, is a result of the exposition to environmental stressors [13]. Specially in exposed skin, aging is accelerated by extrinsic factors, such as UV radiation, air pollution, smoking and weather conditions, namely wind and cold [109,110]. Clinical signs of photoaging include dryness, hype and hypo pigmentations, wrinkles, loss of firmness and elasticity, and leathery texture [13,44,111]. As already described, cyanobacteria produce compounds with potential use in skin moisture (*e.g.* EPS), UV protection (*e.g.* MAAs and SCY) and protection against ROS (*e.g.* EPS, MAAs, SCY, polyphenols, PBPs), being therefore interesting for application in skin anti-aging products. Considered skin firmness and elasticity, effects were also described for fibroblasts. In dermis, the fibroblasts are responsible for the production of extracellular matrix (ECM), which mostly comprehends collagen and elastin, providing firmness and elasticity [111]. Extracts from *Arthrospira platensis* were found to increase cell viability and decrease DNA damage due to inhibition of thymine dimers and matrix metalloproteinases (MMP), in normal human dermal fibroblasts (nHDFs) exposed to UV-B radiation [112]. Also, in a clinical trial involving 10 volunteers between 25 and 54 years, supplemented for 8 weeks with two daily doses of 0.7 g of powdered *Spirulina platensis*, a considerable increase in the concentrations of cutaneous carotenoids (22% on average) was verified, in addition with a slight increase in the collagen/elastin skin index [113].

Skin moisture, UV protection, stimulation of fibroblasts proliferation and increase in the antioxidant potential are mechanisms that led to the retardation of skin aging. As exposed in the above topics, cyanobacteria produce compounds that can interfere in all these processes, being thus interesting for cosmetics directed to skin-aging prevention.

3. Other advantages of cyanobacteria for cosmetics

Besides the production of compounds of interest, the natural sources must also be profitable in terms of biomass and compounds rates. In this aspect cyanobacteria also offer advantages, namely concerning to the

low demand for culture requirements both in terms of nutrition and space, and the possibility to increase the production of compounds by manipulating culture conditions. Effectively, cyanobacteria growth requires only basic nutrients, and cultivation is not dependent on arable land, which decreases environmental impacts and allows for wider cropping location points [19]. Also cyanobacteria can be cultured under continuous cultivation, which also ensures smaller cultivation areas and is considered the most feasible system for large scale production, both in terms biomass rates, product quality and costs associated with investments, such as for operation and harvesting (reviewed by [114]). The possibility to increase the compounds production is based on the evident influence of culture conditions, namely in variables such as UV radiation and salinity. For MAAs and SCY, it was found that the production of these photoprotectors is highly dependent on these same variables. In a *Lyngbya* sp. culture, an exposition for 72 h to 320 nm UVA and 295 nm UVB radiation, significantly increased the synthesis of MAAs and SCY [66]. Also, the growth of the filamentous strain *Scytonema* sp. R77DM under UV-radiation stress, resulted in a 2- to 3-fold increase in SCY biosynthesis [85]. Related to salinity, it has been reported that cyanobacteria inhabiting hypersaline environments accumulate large concentrations of MAAs, that are released from the cells when placed in medium with lower salinity [115]. For EPS, factors such as salt stress, irradiance, light cycle and temperature, were also found to influence production (reviwed by [75,114]). Under high salt concentrations of 500 mmol L^{-1} NaCl, for example, a significant increase in total carbohydrates and EPS content was described for a *Microcoleus vaginatus* cyanobacterium isolated from desert algal crusts [76] and cultured under laboratory conditions. This increase ranged 363% and 161% of unstressed cells respectively for total carbohydrates and EPS, and was followed by a decrease to original levels when the culture was transferred to non-saline medium, which suggests an involvement of EPS in the enhancing salt tolerance. For polyphenolics and flavonoids, the accumulation of the natural antioxidants gallic, caffeic, chlorogenic and ferulic acids and vanillic, rutin and quercetine, was also stimulated in several cyanobacteria species by exposure to salt stress conditions [116]. These later authors demonstrated also that the increase in total phenol, flavonoids and carotenoid content under different salt conditions was positively correlated with the antioxidant activity of the cyanobacteria extracts, emphasizing the role of salinity in the production and activity of the compounds. Low rates of UV-B radiation have been also considered an efficient technology for the production of photosynthetic pigments and polyphenolics. In a study involving *Nostoc muscorum*, *Phormidium foveolarum*, and *Arthrospira platensis* strains, an increase in biomass production, total phenolic content, photosynthetic pigments (*e.g.* chlorophyll *a*, carotenoids, and phycobiliproteins) and nonenzymatic antioxidants (*e.g.* proline, ascorbate, cysteine) was obtained at an UV-B rate of 0.045 $W{\cdot}m^{-2}$ when compared to an UV-B rate of 0.23, and 0.45 $W{\cdot}m^{-2}$ [117]. Also, in this study, an increase of 97.9%, 86.11% and 77.08% in the antioxidant activity of *A. platensis, P. foveolarum* and *N. muscorum*, respectively, was obtained at the lower UV- B rate, highlining the role of radiation in the production and activity of the compounds.

The evidences described above, although only based on laboratory scale studies, are suggestive of the potential that the manipulation of the culture conditions can bring to the increment of the production of compounds and, combined with the sustainable biomass production, reveal cyanobacteria as a strategy to efficiently produce natural compounds for natural skin care products.

4. Conclusion

The increased concern with skin health, particularly regarding appearance and aging is reflected in a higher demand for new cosmetic products, mainly of natural origin, with less side effects and environmentally friendly. The effective mechanisms of cyanobacteria against dissection, radiation and oxidative stress, through the production of specific compounds, makes this group of organisms promising in the cosmetic/cosmeceutical industry. In this sense cyanobacteria, may be used as an efficient biotechnology to produce natural ingredients, such as EPS, UV filters, and antioxidants for skin care products. Along with the potentialities required for cosmetic formulations, cyanobacteria offer facilities in terms of culture for biomass and compounds production, which can make the production more cost-effective. The studies presented in this review reflect the work that has been invested in the application of cyanobacteria in cosmetics and emphasize the biotechnological potential of these organisms as an economically and sustainable base for the cosmetic industry.

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Author contributions

Rosário Martins and Vitor Vasconcelos were involved in planning and supervising the work. Janaína Morone and Anna Alfeus were involved in collecting and organizing the data. All authors were involved in the analysis of the collected data and in the writing of the manuscript.

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