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Cyanobacterial metabolites as a source of sunscreens and moisturizers: a comparison with current synthetic compounds

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ABSTRACT

The recognition that ultraviolet radiation has harmful effects on the skin has led to the commercial development of inorganic and synthetic organic UV filters that can reduce the negative effects of exposure to sunlight. In addition, moisturizing chemicals are extensively used in personal care products to improve the ability of skin to retain water. Whilst current UV filter and moisturizing chemicals have clear beneficial qualities, they may also have adverse effects such as contact sensitivity, oestrogenicity and even tumorigenic effects on human skin. Furthermore, the accumulation of these chemicals in the aquatic environment could be potentially harmful. Consequently, there is interest in exploiting safer alternatives derived from biological sources, especially from photosynthetic organisms such as cyanobacteria which have developed mechanisms for coping with high UV irradiation and desiccation. In order to overcome the detrimental effects of UV radiation, these microorganisms produce UV screening compounds such as mycosporine-like amino acids and scytonemin, which are good candidates as alternatives to current synthetic UV filters. In addition, extracellular substances produced by some extremophilic species living in hyper-arid habitats have a high water retention capacity and could be used in cosmetic products as moisturizers. In this review, we present an overview of the literature describing the potential of cyanobacterial metabolites as an alternative source for sunscreens and moisturizers.

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Introduction

The cosmetic and skin care products industry is a huge and rapidly expanding worldwide business (Kligman, 2000). In the USA, where there are more than 2000 companies related to manufacturing and distributing cosmetics, these products are integral to daily grooming. American adults, on average, use at least seven different skin care products each day (Wolf *et al.*, 2001). In 2014, the cosmetics market in Germany, France and the UK was 13.01, 10.6 and 10.4 billion Euros, respectively (<http://www.statista.com/statistics/382100/european-cosmetics-market-volume-by-country/>). Cosmetics, however, may contain products with possible undesirable consequences. A study in the UK revealed that over the course of a year, 23% of women and 13.8% of men experience some kind of adverse reactions to personal care products (Orton & Wilkinson, 2004). Cosmetics may have side effects such as contact sensitivity, oestrogenicity and even tumorigenic effects on human skin (Ichihashi *et al.*, 2003; Lu *et al.*, 2009). In addition, widespread use of cosmetics has led to a ubiquitous presence of some ingredients in the aquatic environment which can cause hormonal effects on aquatic organisms and insects (Christen *et al.*, 2011; Ozáez *et al.*, 2013).

Given the possible negative consequences of using such ingredients, cosmetic scientists have begun to investigate natural compounds that offer safer alternatives. In addition, the ability of organisms to self-renew and reproduce ensures that supplies are potentially sustainable. This is especially true for photosynthetic organisms using simply light energy, carbon dioxide and basic nutrients (Witcover *et al.*, 2013). Indeed, the use of plants as a source of new cosmetic ingredients is an option favoured by many companies (Kole *et al.*, 2005). For example, various natural substances extracted from aquatic or land plants can be used in sunscreens owing to both their UV screening properties and antioxidant activities. Carotenoids and phenols in angiosperms (e.g. Mahajan & Wasule, 2008), phlorotannins in brown seaweeds and mycosporine-like amino acids in red seaweeds and microalgae are among the well-known antioxidants and UV-absorbing compounds produced by plants (Hupel *et al.*, 2011). However, there are economic obstacles to the commercial exploitation of plants, including slow growth rates, seasonal growth, challenges in the cultivation of some species, the need for arable land and hence competition with food production and low levels of the active ingredients, all of which impact on the cost of production.

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An alternative approach involves the exploitation of photosynthetic cyanobacteria as a biological source of cosmetic ingredients. Cyanobacteria are genetically tractable prokaryotes which typically have higher photosynthetic and growth rates than higher plants. These microorganisms have basic nutritional requirements and can be grown using closed cultivation systems that do not compete with agriculture (Quintana *et al.*, 2011). Importantly, several species of cyanobacteria live in hyper-arid deserts and produce metabolites that give them the ability to cope with both high UV radiation and severe desiccation (Fleming & Castenholz, 2007). These extremophilic microorganisms therefore have great potential as a source of cosmetic products to be used in sunscreens and moisturizers.

In this review, we consider sunscreen and moisturizing personal care products (PCPs), highlighting the possible adverse effects related to some chemicals used in these products, and discuss the potential of cyanobacteria as an alternative source of novel metabolites for cosmetics production.

Sunscreens

Ultraviolet (UV: 280–400 nm) radiation induces short-term effects (sunburn) and chronic reactions (premature skin ageing and skin cancer) in human skin. Chronic repeated exposure to sunlight has been shown to be the main cause of benign and malignant skin tumours such as malignant melanoma (Lisby *et al.*, 2005). UV-B (280–320 nm), a minor component of the sunlight reaching the earth's surface, is the most cytotoxic and mutagenic region of the solar spectrum. UV-B is known to suppress immune reactions and upregulate gene expression through intracellular signal transduction pathways. It can also promote the formation of cyclobutane pyrimidine dimers and photoproducts that induce mutation in epidermal cells, and can lead to abnormal cell growth and increased risk of skin cancer (Budden & Bowden, 2013). The strong cytotoxic effects of UV-B occur in the upper epidermis as UV-B does not penetrate through to the dermis. In contrast, UV-A (320–400 nm) can reach the dermis where it is responsible for ageing changes such as wrinkling, dryness and pigment abnormalities. In addition, exposure to UV-A generates excess reactive oxygen species that indirectly damage DNA (Daniel *et al.*, 2004). The phototoxic effect of UV-B is greater than UV-A, but UV-B exposure is highly dependent on the season, time of day, cloud cover and latitude. In contrast, UV-A is relatively constant with a much higher intensity and is present all year round in harmful doses. Also, unlike UV-B, which cannot penetrate window glass, about 40% of the outdoor UV-A radiation dose can still be received indoors. Therefore, the main

requirement of PCPs including sunscreens, facial makeup and lip care products is UV-A protection (Daniel *et al.*, 2004).

Although skin cells have various mechanisms and strategies to minimize UV damage (such as antioxidants, DNA repair enzymes and stress signalling), excessive UV exposure can cause mutations and genetic instability. Over the past few decades, sun protection measures have been improved in order to reduce radiation exposure and the harmful effects of UV-A and UV-B. One of the most important protection measures against skin damage is the use of UV filters, which are incorporated in a wide range of PCPs including sunscreens, facial make-up and lip care products (Stiefel & Schwack, 2013). In order to better protect against UV radiation, consumers demand PCPs with a high sun protection factor (SPF), and therefore are exposed to significantly larger amounts and also a wider variety of UV filters (Manová *et al.*, 2013). The estimated worldwide production of UV filters is about 10 000 metric tonnes per year requiring high production volumes (Manová *et al.*, 2015). The most important aspect of the development of a new UV filter is safety: a sunscreen must be heat- and photo-stable, non-irritant, non-sensitizing and non-phototoxic. While the ingredients in many sunscreens can be effective in protecting human skin against UV radiation, they can also have adverse effects such as contact sensitivity and oestrogenicity (Ichihashi *et al.*, 2003). In addition, sunscreen ingredients potentially can have an adverse effect on the natural environment, especially when introduced into aquatic systems.

Sunscreen ingredients are generally divided into inorganic (physical blockers) and organic agents (chemical absorbers). Here we explain organic and inorganic UV filters separately and highlight the reported effects related to each group.

Inorganic UV filters

Inorganic UV filters consist of mineral particles that reflect or scatter sunlight. They are extensively used in sunscreen lotions as broadband sunscreens that reflect both UV-A and UV-B (Hexsel *et al.*, 2008). The inorganic UV filters used most frequently in cosmetic products are metal oxides such as titanium dioxide (TiO₂) and zinc oxide (ZnO). It has been argued that inorganic UV filters are safer than organic ones. However, there are concerns associated with the penetration and systemic effects of inorganic agents. Notably photoactivation of metal oxides by UV light can lead to the generation of reactive oxygen species such as H₂O₂ and singlet oxygen which are known to be cytotoxic and genotoxic (Serpone *et al.*, 2007). Also, to reduce the opacity associated with inorganic filters, TiO₂ and ZnO microparticles have

been replaced by TiO₂ and ZnO nanoparticles. This can have adverse effects as TiO₂ nanoparticles can pass through cell membranes and impair function of human dermal fibroblast cultures with decreases in cell area, proliferation, mobility and ability to form collagen (Pan *et al.*, 2009). Exposure to TiO₂ micro- and nanoparticles can also induce cell death in human neural cells and fibroblasts (Lai *et al.*, 2008). Nano-sized zinc oxide particles can also induce neural stem cell apoptosis, although this toxic effect is related to chemistry, rather than particle size (Deng *et al.*, 2008; Nohynek *et al.*, 2008). In addition, the impact of nanoparticle release into the natural environment is now a major concern (Baker *et al.*, 2014; Cross *et al.*, 2015; Schaumann *et al.*, 2015).

Synthetic organic UV filters

In contrast to physical blockers, organic UV filters are a group of compounds designed to absorb UV radiation rather than reflect it. The most frequently used organic UV filters in sunscreens and other PCPs are butyl methoxydibenzoylmethane (BM-DBM), ethylhexylmethoxycinnamate (EHMC) and octocrylene (OCR) (Fig. 1). These are photostable chemicals effective in the protection of human skin against UV damage (Manová *et al.*, 2013). However, in recent years, concerns have been raised about possible side effects of these synthetic filters.

OCR is a worldwide-approved UV filter which is increasingly used in PCPs offering protection against UV-B wavebands (Karlsson *et al.*, 2011). However, this UV filter can be a strong allergen and can lead to contact dermatitis in children and adults (Avenel-Audran *et al.*, 2010). Avenel-Audran *et al.* (2010) indicated that children and adults with a history of photoallergy from sunscreen products had positive patch and photopatch test reactions to OCR. In addition, Karlsson *et al.* (2011) reported 23 cases of positive patch and photopatch test reactions in patients with a history of reaction to the anti-inflammatory drug ketoprofen. A study in Switzerland by Schlumpf *et al.* (2010) showed that exposure to UV filters through PCP use was correlated with the presence

of chemicals in breast milk and they found that OCR and 4-methylbenzylidene camphor were present in 85.2% of the milk samples.

Methoxydibenzoylmethane (BM-DBM), also known as avobenzone, is another approved organic UV filter with absorption in the UV-A wavelength that has been linked with photoallergic contact dermatitis (Kerr *et al.*, 2012). A multicentre photopatch test study on 1031 patients across 12 European countries indicated that this oil-soluble UV filter, along with OCR and benzophenone-3, was the most frequent sunscreen absorber that led to photoallergic contact dermatitis (Kerr *et al.*, 2012). The reactive nature of BM-DBM has been reported by several groups, with Paris *et al.* (2009) finding that UV irradiation of BM-DBM results in an increase in the keto isomer and reactivity with key biomolecules such as nucleosides, tryptophan and tyrosine. Similarly, Stiefel & Schwack (2013) showed that the carbonyl group of BM-DBM and other related UV filters have a high tendency to form adducts with free amino acids or peptides, and suggest that such reactions can occur within the skin layer.

Ethylhexylmethoxycinnamate (EHMC) is a lipophilic UV filter with an absorption spectrum in UV-B that is used extensively in PCPs. EHMC has been the subject of significant debate regarding its accumulation in human tissue, and possible risks associated with potential endocrine-disrupting effects (Manová *et al.*, 2015). Investigations on rats into the effects of exposure to high concentrations of EHMC showed a marked decrease in the levels of thyroid hormones, which could affect both reproductive and neurological development (Axelstad *et al.*, 2011; Klammer *et al.*, 2007). In addition to possible adverse effects of EHMC on human health, its widespread use in cosmetics has led to a ubiquitous presence in the aquatic environment. Although EHMC levels are typically low in treated water (0.01–0.1 µg l⁻¹), they can be higher in lakes, rivers and coastal waters, and can be close to potentially harmful levels in untreated municipal water (up to 19 µg l⁻¹) (Christen *et al.*, 2011). An effect on the expression of genes involved in hormonal pathways in fish was observed at EHMC concentrations above 37.5 µg l⁻¹, and histological changes were seen at 394 µg l⁻¹ (Christen *et al.*, 2011). Furthermore, EHMC at these higher concentrations may also have a harmful effect on insects, with > 100 µg l⁻¹ affecting the invertebrate hormonal system by upregulating the ecdysone receptor, a key transcription factor (Ozáez *et al.*, 2013).

Given the possible adverse effects of the different organic and inorganic UV filters currently used in sunscreen cosmetics, there is a clear need for new UV filters without undesirable effects.

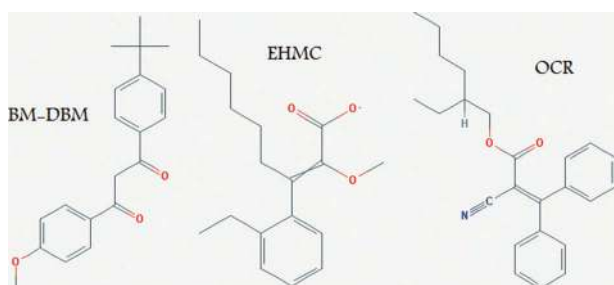


Fig. 1. Structure of butyl methoxydibenzoylmethane, ethylhexylmethoxycinnamate and octocrylene.

Moisturizers

Water is absolutely critical for the flexibility, normal functioning, maturation and desquamation of the skin, especially its outer layers. Because of the proximity of the outer layers to the environment, this barrier is always under major desiccation stress. Dryness of the skin can lead to undesirable results such as itchiness with visible characteristics such as redness, flaky appearance, cracks and even fissures which reduce the elasticity of the skin (Choi *et al.*, 2013). The ability of the skin to hold water is related to the stratum corneum (SC), which acts as a barrier against water loss. The water content of the SC ideally should be 20–35% – at a water content of less than 10% the skin has a rough and flaky appearance (Flynn *et al.*, 2001). Given that a critical level of hydration is required to allow the SC to maintain its flexibility and normal functioning, cosmetic scientists have investigated chemical moisturizers that are able to improve the SC's ability to retain water (Harding *et al.*, 2000). Moisturizers are complex mixtures of chemical agents specially designed to make the external layers of skin hydrated and more pliable by attracting water and reducing water evaporation. These cosmetic products are therefore formulated to prevent transepidermal water loss and retain or increase the content of water in the SC (Rawlings *et al.*, 2004).

Although the functional mechanism of this active cosmetic category is complicated, there are three basic properties which are consistent across all moisturizers: humectancy, occlusivity and/or emolliency. Humectants are moisturizer ingredients that attract and hold water in the outer layers of skin and act in two directions:

- (1) Attracting water from the dermis layer to the epidermis or SC (inside out).
- (2) Attracting moisture from the external environment to the skin (outside in).

One major drawback of humectants is that they increase transepidermal water loss by intensification of water absorption into the outer layers of skin where it can then be lost into the environment. To address this problem, humectants are always combined with an occlusive agent – ingredients such as petrolatum, mineral oil and vegetable waxes that form a film on the skin and prevent water loss (Kraft & Lynde, 2005).

Moisturizers can be considered as safe products in comparison to most traditional drugs which are used by dermatologists. However, inconvenient and undesirable skin reactions may be encountered through long-term usage of these products. It has been demonstrated that long-term treatment with moisturizers on

normal skin increases skin susceptibility to irritants and also influences the barrier function of normal skin (Held *et al.*, 1999; Buraczewska *et al.*, 2007). In addition, it has been indicated that moisturizers are able to change the mRNA expression of certain epidermal genes (Buraczewska *et al.*, 2009). Commonly used humectants in cosmetic moisturizers are glycerin, propylene glycol, sodium pyrrolidone carboxylic acid (sodium PCA) and urea (Rawlings *et al.*, 2004). Whilst these are generally regarded as weak contact sensitizers and therefore safe to use in moisturizers, there is evidence that at high concentrations, or when used by people with dermatitis, these compounds can trigger adverse skin reactions (Zesch, 1982; Andersen, 1999; Lodén *et al.*, 2002; Lessmann *et al.*, 2005). There is therefore a demand for new moisturizers which use alternative, non-irritant ingredients (Lodén, 2003).

Potential of Cyanobacterial Metabolites as Sunscreens

Cyanobacteria represent a diverse group of photosynthetic bacteria – from tiny single cells to large filamentous forms, and have great potential for biotechnological applications in agriculture, mariculture, biomedical, food and fuel (Singh *et al.*, 2016). One of the most interesting properties of cyanobacteria, especially extremophilic species, is their ability to overcome the detrimental effects of UV radiation, and they have a number of avoidance, protection and repair mechanisms (Fig. 2). A key mechanism is the production of UV-absorbing/screening compounds such as mycosporine-like amino acids (MAAs) and scytonemin which serve as natural photo-protectants (Richa *et al.*, 2011). In this section we summarize the biotechnological potential of MAAs and scytonemin synthesized by cyanobacteria.

Mycosporine-like amino acids (MAAs)

MAAs are a group of more than 20 water soluble, UV-absorbing metabolites providing screening protection against highly energetic photons in the UV-A wavelengths (Schmid *et al.*, 2003). Strong protection is due to MAAs having extremely high molar extinction coefficients (ϵ) ($\epsilon = 28100\text{--}50000 \text{ l mol}^{-1} \text{ cm}^{-1}$) (Wada *et al.*, 2013). MAAs are found in the cytoplasm and outer sheath of cyanobacteria and other algae such as dinoflagellates, where they act as filters to prevent UV-induced damage (Llewellyn & Ains, 2010; Carreto & Carignan, 2011; Wada *et al.*, 2015). MAAs are low molecular weight (< 400 Da) colourless molecules with absorption maxima typically of 310–362 nm. All MAA molecules contain a central cyclohexanone or cyclohexenimine ring that is responsible for UV absorption. Their biosynthesis in cyanobacteria occurs via specific pathways such as the

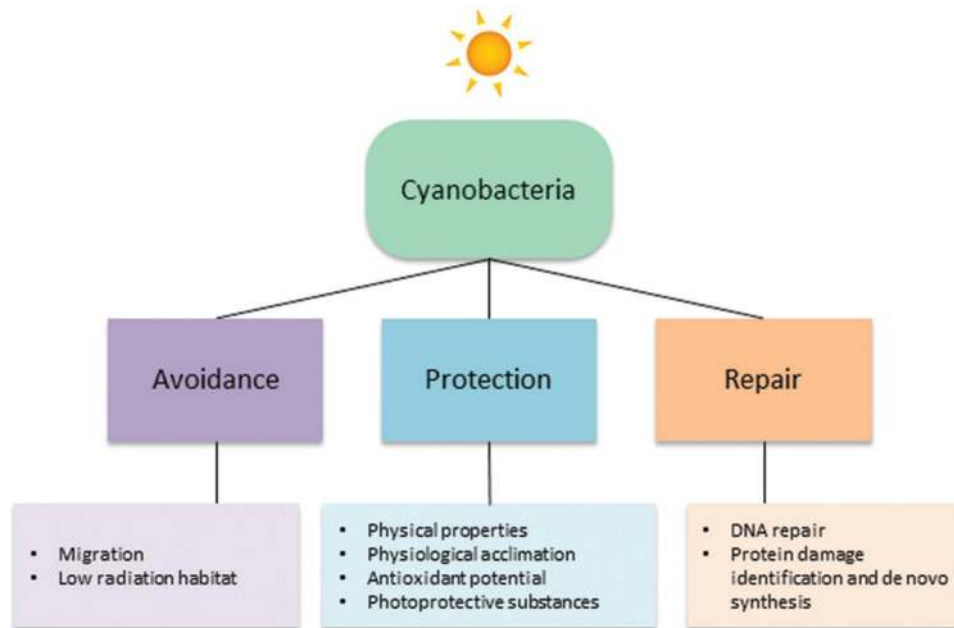


Fig. 2. Strategies used by cyanobacteria to counteract damaging UV from the sun.

shikimate pathway and pentose phosphate pathway. The structure and absorption spectra of MAAs are due to variation in nitrogen substituents and attached side groups (Table 1; Singh, 2009).

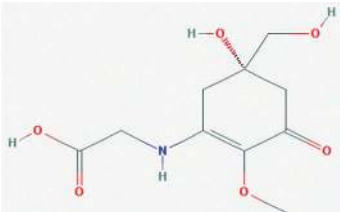
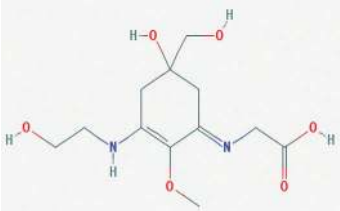
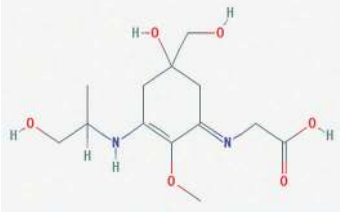
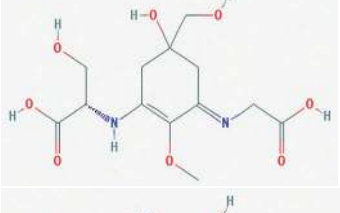

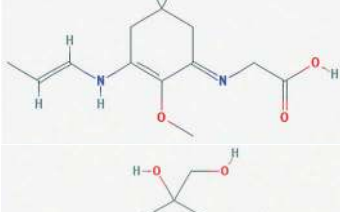
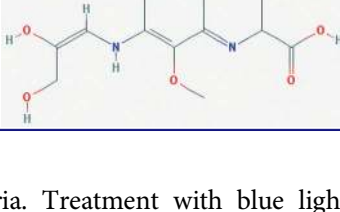
Different kinds of MAAs have been found in cyanobacterial species in a variety of habitats such as the marine environment (Liu *et al.*, 2004), hypersaline ponds (Kedar *et al.*, 2002), rice fields (Sinha *et al.*, 2003) and deserts (Bowker *et al.*, 2002), and further investigations in diverse habitats might reveal new MAAs. Recently, glycosylated MAAs have been isolated from the terrestrial cyanobacterium *Nostoc commune* (Matsui *et al.*, 2011; Nazifi *et al.*, 2013, 2015). One of these MAAs (absorption maximum 334 nm) was identified as a hexose-bound porphyrin-334 derivative with a molecular mass of 508 Da, another (absorption maximum 322 nm) as a two hexose-bound palythine-threonine derivative with a molecular mass of 612 Da. It was suggested that these purified glycosylated MAAs could have multifunctional roles as sunscreens and antioxidants. Mycosporines extracted from the red alga *Porphyra umbilicalis* are employed in the sunscreen products Helioguard 365TM (Mibelle AG Biochemistry, Switzerland) and HelionoriTM (Biosil Technologies, France). In Helioguard 365TM, mycosporines encapsulated into liposomes reduce lipid peroxidation on human skin and improve skin firmness and smoothness, supporting its ability to protect against premature skin ageing (Soule & Garcia-Pichel, 2014). Also, MAAs used in HelionoriTM (mycosporine-palythine, porphyrin-334 and shinorine) were shown to be photostable and heat-stable, with the ability to reduce sunburn and preserve membrane lipids when used

at concentrations of 1–4% (Soule & Garcia-Pichel, 2014).

MAAs have great biotechnological potential as natural UV sunscreen products. Misonou *et al.* (2003) studied the protective effects of MAAs against DNA damage and found that they were able to effectively block thymine dimer formation by UV radiation. Oyamada *et al.* (2008) examined the protective effects of three different kinds of MAAs (shinorine, porphyrin-334 and mycosporine-glycine) on human fibroblast cells and found that all three protected the cells from UV-induced cell death, with mycosporine-glycine having the strongest effect. They also found a promotional effect of MAAs on the proliferation of human skin fibroblast cells, and concluded that these secondary metabolites have potential application in cosmetics and toiletries.

In addition to their strong photo-protective capabilities, MAAs are also multifunctional secondary metabolites with various cellular functions. In extremophilic cyanobacteria, MAAs act as compatible solutes, able to boost cellular tolerance to desiccation, salt and heat stress (Singh, 2009). Furthermore, these metabolites are effective antioxidant molecules and are able to stabilize free radicals within their ring structure. For example, mycosporine-glycine is able to quench singlet oxygen and hydroxyl radicals before oxidative stress response genes and antioxidant enzymes are induced (Suh *et al.*, 2003). Photo-ageing of the skin is often caused by free radicals which are produced upon exposure to UV radiation. Treatment of skin with MAAs counteracts the process of free radical production: application of a cream containing 0.005% Porphyrin-334 encapsulated in liposomes significantly improved both firmness and smoothness of the skin after 4 weeks by 10% and 12%, respectively,

Table 1. Molecular structure, maximum absorption wavelength and molar extinction coefficient of MAAs from cyanobacteria.

MAAs	λ_{\max} (nm)	ϵ (l mol ⁻¹ cm ⁻¹)	Molecular structure
Mycosporine-glycine	310	28800	
Asterina-330	330	43800	
Palythanol	332	43500	
Mycosporine-2-glycine	334	43800	
Shinorine	334	44668	
Porphyra-334	334	42300	
Palythene	360	50000	
Euhalothece-362	362	43800	

comparable to creams containing synthetic UV filters (Daniel *et al.*, 2004).

Studies have sought to understand the optimal cultivation conditions to maximize the production of

MAAs in cyanobacteria. Treatment with blue light, UV-A and UV-B radiation has been shown to increase the induction of MAA synthesis (Riegger & Robinson, 1997). Furthermore a pterin UV-B specific

photoreceptor has been proposed to mediate the photosensory induction of MAAs (Portwich & Garcia-Pichel, 2000). In addition to UV radiation, other factors such as nutrient availability, salinity and temperature are known to affect accumulation of MAAs in the cell (Oren & Gunde-Cimerman, 2007). Surprisingly, Singh (2009) indicated that MAA synthesis under photo-heterotrophic growth is higher than under photo-autotrophic growth because under photo-autotrophic conditions, light and CO₂ can act as limiting factors. It was also shown that sulphur is essential for the synthesis of shinorine in *Anabaena variabilis*, with ammonium enhancing shinorine production and the absence of magnesium decreasing the synthesis of this MAA. The results of these studies show that the optimization of growth conditions can significantly increase the production of these biotechnologically important compounds in cyanobacteria. With such improvements and the development of industrial-scale cultivation technologies, these natural metabolites have the potential to supplement or replace commercially available sunscreens (Llewellyn & Aird, 2010; White *et al.*, 2011).

The biosynthesis of MAAs has also been investigated and appears to occur via two routes. In the cyanobacterium *Anabaena variabilis*, five enzymes are involved in the synthesis of the MAA shinorine, through the shikimate pathway: a deoxy-D-arabinoheptulosonate phosphate synthase (DAHP synthase); a dehydroquinase synthase homologue (DHQS); an O-methyl-transferase (O-MT); an ATP grasp ligase and an NRPS-like enzyme (Fig. 3). The shinorine biosynthesis starts with the formation of arabinoheptulosonate-7-phosphate, which is then transformed into the intermediate 4-deoxygadusol. In the next step, the combination of 4-deoxygadusol with a

glycine molecule gives mycosporine-glycine and finally an NRPS-like enzyme condenses mycosporine-glycine and serine to shinorine (Wada *et al.*, 2013; Mandal & Rath, 2014). However, Balskus & Walsh (2010) reported a different MAA biosynthetic pathway in cyanobacteria. They found that biosynthesis of shinorine in *Anabaena variabilis* and *Nostoc punctiforme* via 4-deoxygadusol proceeds from sedoheptulose 7-phosphate (precursor of the pentose phosphate pathway), rather than deoxy-D-arabinoheptulosonate phosphate (Fig. 3). Biosynthesis of MAA through the pentose phosphate pathway was evidenced by cloning the EVS (2-*epi*-5-*epi*-valiolone synthase) biosynthetic gene cluster of *A. variabilis* into a heterologous host for functional identification of MAA biosynthetic enzymes (Balskus & Walsh, 2010). Spence *et al.* (2012) examined the effect of deleting the EVS gene on MAA biosynthesis in *A. variabilis* and indicated that the EVS mutant of *A. variabilis* retained its ability to produce MAA on exposure to UV-A radiation. The authors proposed that functionally duplicate yet distinct convergent pathways exist for the biosynthesis of MAAs in cyanobacteria involving both the pentose phosphate pathway and the shikimate pathway to produce MAA via the convergent intermediate 4-deoxygadusol (Fig. 3).

Scytonemin

Scytonemin has a maximum absorption at 380 nm, and is found in the extracellular polysaccharide sheath of cyanobacterial mats, crusts or colonies where it serves as a protectant against short wavelength solar UV radiation. This lipid-soluble pigment is a small dimeric molecule (544 Da) that is unique among natural products and is

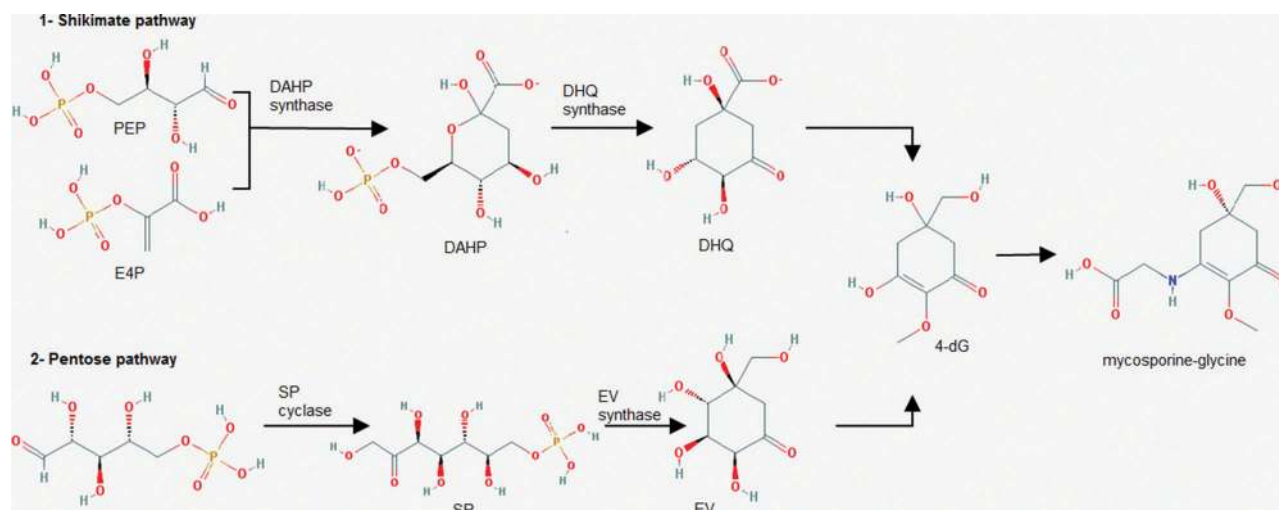


Fig. 3. Two possible pathways for the biosynthesis of mycosporine-glycine in the cyanobacterium *Anabaena variabilis*. 4-deoxygadusol can be produced through either the shikimate pathway or the pentose pathway, and is then combined with a glycine molecule to produce mycosporine-glycine. PEP: phosphoenolpyruvate; E4P: erythrose-4-phosphate; DAHP: 2-keto-3-deoxy-D-arabinoheptulosonate-7-phosphate; DHQ: 3-dehydroquinate; 4-dG: 4-deoxygadusol; SP: sedoheptulose-7-phosphate; EV: 2-*epi*-5-*epi*-valiolone (re-drawn from Wada *et al.*, 2013).

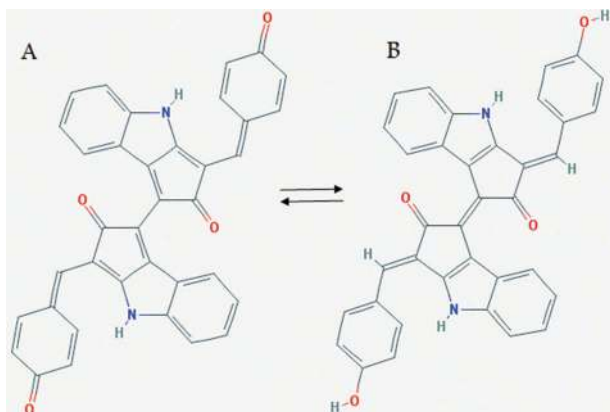


Fig. 4. Chemical structure of oxidized (A) and reduced (B) scytonemin.

composed of indolic and phenolic subunits linked by an olefinic carbon atom (Fig. 4). Due to its large extinction coefficient ($\epsilon = 250 \text{ l g}^{-1} \text{ cm}^{-1}$ at 384 nm), scytonemin is considered as an efficient photo-protective compound (Wada *et al.*, 2013). There are two forms of scytonemin based on the redox and acid-base conditions during the extraction process: an oxidized form (green) named fuscochlorin and a reduced form (red) known as fuscorhodin (Fig. 4).

Scytonemin is synthesized from metabolites of aromatic amino acid (tryptophan and tyrosine) biosynthesis (Fig. 5). UV-A treatment efficiently induces synthesis of scytonemin, whereas blue, green or red light has no significant effect (Garcia-Pichel & Castenholz, 1991). Other stress factors can also affect the synthesis of this alkaloid pigment in cyanobacteria. Dillon *et al.* (2002) examined the effect of heat, osmotic and oxidative stress on the synthesis of scytonemin in *Chroococcidiopsis* sp. and found that an increase in both temperature and photo-oxidative

conditions in conjunction with UV-A causes a synergic increase in the rate of production, whereas increased salt concentration inhibited synthesis. In contrast, Rath *et al.* (2012) showed that salinity induced the production of scytonemin in *Lyngbya aestuarii*. Fleming & Castenholz (2008) studied the effects of nitrogen source (N_2 , NO_3^- or NH_4^+) on scytonemin synthesis in *Nostoc punctiforme*, showing that this cyanobacterial species synthesized three to seven times more scytonemin while fixing nitrogen than when utilizing nitrate or ammonium. The exact mechanisms of scytonemin induction are unclear but multiple environmental signals may act to determine the level of this pigment in different species of cyanobacteria (Rastogi *et al.*, 2015).

A study on *Nostoc punctiforme* by Soule *et al.* (2007) revealed that an 18-gene cluster (ORFs: NpR1276–NpR1259) is associated with scytonemin production and NpR1273 was directly involved in the biosynthesis process. Also four putative genes, NpR1271 to NpR1274, were found to be responsible for the assembly of the scytonemin molecule. The transcription levels of all 18 genes were increased after 48 hours of UV-A exposure and all were co-transcribed as part of a single transcriptional unit (Soule *et al.*, 2009). Recently, Malla & Sommer (2014) generated the monomer moiety of scytonemin from tryptophan and tyrosine in *Escherichia coli* and discovered that only three enzymes are required for its *in vivo* production. The precise mechanism of scytonemin biosynthesis is still ambiguous, however, recent studies indicated that biosynthesis of this pigment in cyanobacteria is a highly conserved process (Rastogi *et al.*, 2015). Wada *et al.* (2013) proposed a pathway for scytonemin synthesis in cyanobacteria in which enzymes ScyA, B and C are assumed to

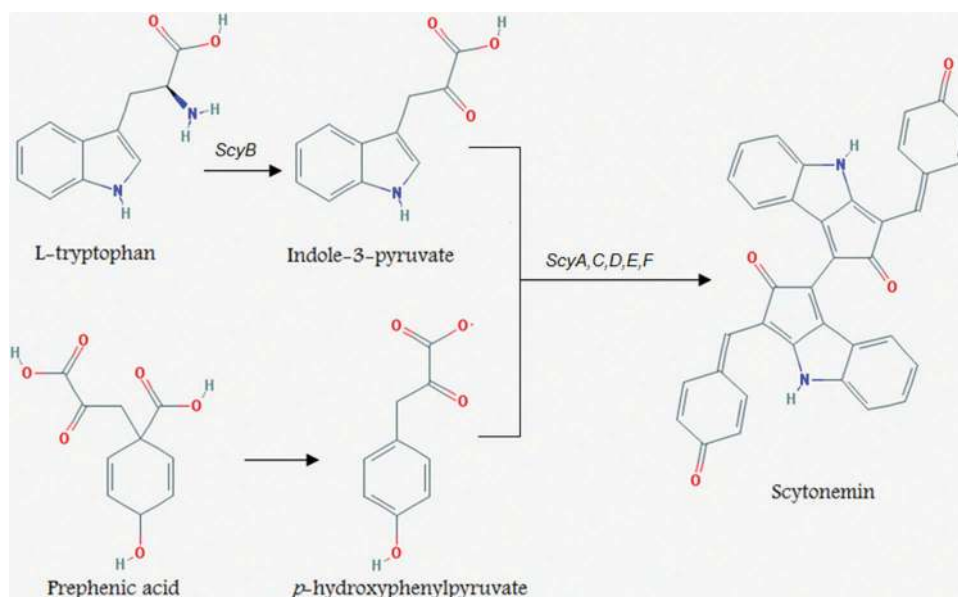


Fig. 5. Proposed biosynthesis pathway of scytonemin (Wada *et al.*, 2013).

catalyse the synthesis of scytonemin monomers, while ScyC, D and F are assumed to catalyse the dimerization of the subunits (Fig. 5).

Scytonemin is highly stable under different abiotic stressors and performs UV screening activity without any additional metabolic investment (Singh *et al.*, 2010). A photo-protective role of scytonemin has been shown (Garcia-Pichel *et al.*, 1992; Dillon & Castenholz, 1999; Gao & Garcia-Pichel, 2011) and Garcia-Pichel & Castenholz (1991) reported that scytonemin prevents up to 90% of solar UV radiation from entering the cell. In addition, scytonemin has antioxidant activity and functions as a radical scavenger to prevent cellular damage resulting from reactive oxygen species produced upon UV-radiation exposure (Matsui *et al.*, 2012; Rastogi *et al.*, 2015). Scytonemin also represses proliferation of T-cell leukaemia Jurkat cells ($IC_{50} = 7.8 \mu\text{M}$) in humans (Singh *et al.*, 2010). Given the potential of scytonemin in UV screening and free radical scavenging, together with its non-toxic properties, this highly stable pigment offers biotechnological opportunities for exploitation by the cosmetics industry (Stevenson *et al.*, 2002; Rastogi & Sinha, 2009).

Potential of Cyanobacterial Metabolites as Moisturizers

Extremophilic species of cyanobacteria have protective mechanisms which enable them to survive inhospitable habitats such as hyper-arid deserts and salt environments. One of these mechanisms is the production of copious external polysaccharide layers in the form of protective sheaths, slimes or capsules. Cyanobacteria such as *Chroococcidiopsis* and *Nostoc* species are able to survive with minimal water by synthesizing both internal and external polysaccharides (Warren-Rhodes *et al.*, 2013; Smith *et al.*, 2014). Tamaru *et al.* (2005) indicated that the desiccation tolerance of *Nostoc commune* is strongly associated with extracellular polymeric substances (EPS). They removed the EPS from *N. commune* cells by homogenizing colonies with a blender and filtering through a coarse filter paper, and showed that cells depleted in EPS were highly sensitive to desiccation. The hydrophilic/hydrophobic characteristics of EPS enable it to trap and accumulate water, and retard water loss during periods of desiccation (Tamaru *et al.*, 2005). Li *et al.* (2011) showed that *Nostoc commune* EPS has strong moisture-absorption and retention capacities compared with chitosan (a hygroscopic agent) and urea (a humectant). They found that after exposure to 43% relative humidity for 24 hours, the moisture absorption rate of EPS (10.1%) was much higher than that of chitosan (6.3%) and urea (5.8%).

Conventional humectant materials used in moisturizing creams, such as urea, glycerin and propylene

glycol, have reasonable moisture absorption abilities but their moisture retention capacity is poor (Zhao *et al.*, 2013). This leads to an increase in transepidermal water loss mitigated by occlusive agents that can have limitations such as undesirable odour, a greasy texture and potential allergenicity (Kraft & Lynde, 2005). A study by Li *et al.* (2011) found that the moisture retention value of cyanobacterial EPS (28%) was much greater than that of urea (15.9%) and chitosan (7.3%) indicating that cyanobacterial EPS have great potential to be used as humectants in cosmetic moisturizers without the need to be combined with an occlusive agent. The moisture retention capacity of sacran, a giant polysaccharide extracted from the cyanobacterium *Aphanothece sacrum*, is 10-fold higher than hyaluronic acid. This jelly-like anionic polysaccharide consists of 11 types of monosaccharides with about 11% sulphate groups and 12% carboxyl groups per sugar chain (Okajima *et al.*, 2008, 2009). It has been suggested that the strong moisture retention capacity of cyanobacterial EPS is due to strong interactions between water molecules and the hydrophilic -OH groups of the polysaccharides (Zhao *et al.*, 2013).

Another characteristic which makes cyanobacterial EPS suitable for cosmetic application is its antioxidant activity. EPS is capable of scavenging both superoxide anions and hydroxyl radicals *in vitro* (Li *et al.*, 2011). These compounds also can increase antioxidant enzyme activity, decrease lipid peroxidation and reduce oxidative damage induced by paraquat (Li *et al.*, 2011). In addition, several reports have indicated that cyanobacterial polysaccharides may have antiviral activity. For instance, nostoflan, an acidic polysaccharide isolated from *Nostoc flagelliforme*, has been indicated to have antiviral activity against pathogenic viruses such as HSV-1, HSV-2, human cytomegalovirus and influenza A virus (Kanekiyo *et al.*, 2005) through preventing the virus binding to the host cells (Kanekiyo *et al.*, 2007, 2008).

Cyanobacterial species synthesize and secrete EPS that consist of hydrated molecules of high molecular mass. These are composed of an array of uronic acid (glucuronic and galacturonic acid) and neutral sugar (glucose, galactose, mannose, fructose, ribose, xylose, arabinose, fucose and rhamnose) residues (De Philippis & Vincenzini, 1998), as well as non-carbohydrate constituents such as phosphate, lactate, acetate and glycerol (Chakraborty & Pal, 2014). Furthermore, cyanobacterial EPS contain sulphate groups, a feature unique among bacteria (Whitton, 2012). Surprisingly, many cyanobacterial EPS are characterized by a significant level of hydrophobicity because of the presence of some hydrophobic groups such as ester-linked acetyl groups, peptidic moieties and deoxyhexoses (Chakraborty & Pal, 2014). The composition of EPS in some species is labile and can be affected by

environmental changes. For instance, Caiola *et al.* (1996) reported that *Chroococidiopsis* cells have the ability to modify their envelope composition in response to water stress. They showed that desiccated cultures of these species have a complex envelope formed of sporopollenin-like compounds, acid sulphated and beta-linked polysaccharides, lipids and proteins which all are part of a very elaborate structure that allows the cyanobacterium to lose water slowly and in a controlled way.

The genetics of EPS biosynthesis in cyanobacteria have not been thoroughly examined but Pereira *et al.* (2009) proposed that genes related to EPS synthesis can be divided into three classes: (1) those encoding the enzymes involved in the biosynthetic pathways of nucleotide sugars or other components (*rfb ABCD* genes); (2) those coding for the glycosyl transferases which have not been thoroughly characterized; and (3) those required for the oligosaccharide or polysaccharide processing (*wz* genes).

Several environmental factors influence the expression of genes related to EPS production. In many species of cyanobacteria, nutrient deficiency (nitrogen and phosphorus) enhances EPS production rates as a consequence of an excess of photo-assimilated carbon, and excretion acts as an overflow mechanism to avoid damage to the photosynthetic apparatus (Chakraborty & Pal, 2014). EPS production rates in cyanobacterial species can be affected by other factors such as salt stress, irradiance, light cycle, temperature and culture age (De Philippis & Vincenzini, 1998). Culture age can also affect sugar composition, both qualitatively and quantitatively (Gloaguen *et al.*, 1995). Therefore, the production rate of EPS in cyanobacterial species could be increased either through genetic manipulation, or through the selective use of physiological conditions.

Conclusions and Future Perspectives

The biotechnological exploitation of cyanobacteria as a source of bioactive compounds for the cosmetic industry represents a promising area of research. This group of microorganisms produce UV absorbing/screening compounds such as MAAs and scytonemin that serve as natural photoprotectants and can be suitable alternatives to currently used synthetic UV filters. Also, some extremophilic species of cyanobacteria living in hyper-arid environments produce copious amount of external polysaccharide layers that act as water/moisture absorbers and are potent candidates to be used as moisturizers in skin products. However, whilst cyanobacterial compounds have attractive properties for the cosmetic industry, the key bottleneck is the economic and sustainable production of these bio-compounds at the large scales required by the industry. On-going research into the intensive cultivation of photosynthetic microorganisms in photobioreactors such as



Fig. 6. A bioence photobioreactor used for the cultivation of photosynthetic microorganisms at the Centre for Sustainable Aquatic Research, Swansea University.

the tubular system shown in Fig. 6, is bringing new understanding in terms of design, operation and scale-up (Fernandes *et al.*, 2015), and will steadily improve both the economics and feasibility of industrial production of cyanobacteria. Furthermore, the discovery and characterization of superior cyanobacterial strains from the environment, together with their domestication and metabolic improvement using modern genetic engineering approaches (Lai & Lan, 2015), have the potential to bring significant improvements in productivity. Such technical improvements coupled to market demand should see the increasing application of cyanobacterial metabolites in the cosmetics sector.

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Author contributions

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