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UV Sunscreens of Microbial Origin: Mycosporines and Mycosporine-like Aminoacids

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Abstract: Exposure to ultraviolet radiation (UVR) is harmful to living organisms, causing damage to macromolecules such as DNA, RNA, proteins and lipids. Depending on the wavelength, the injury could be direct or indirect through reactive oxygen intermediates, so it is desirable to find compounds that can reduce both. Many organic chemicals used in commercial sunscreen possess estrogenic activity *in vivo*. In this report we analyzed recent patents related to UV sunscreens of microbial origin, in particular mycosporines (MYC) and mycosporine-like aminoacids (MAA). Both are promising natural alternatives for both direct (UV-absorption) and indirect (antioxidant) protection, given they show strong photostability and absence of cytotoxicity. It becomes clear that although the search for natural photoprotective molecules is relatively recent, efforts have been invested mainly in marine environments, remaining still many potential photoprotective molecules to find in other type of habitats. Furthermore, unicellular microorganisms have several advantages for the production of metabolites of interest, since they improve the production costs due to its simplicity of culture and easy genetic manipulation. The knowledge of the biosynthesis pathway of MYC and MAA is essential to improve rationally their expression levels. Currently, only the MAA pathway in bacteria has been reported, remaining the MYC pathway unclear. Future perspectives include the heterologous expression of MYC and/or MAA in industrially friendly microorganisms (bacteria and yeast) in order to co-produce different UV-protective molecules and thus cover a broader UV spectrum and simplify the production process.

Keywords: Algae, antioxidants, carotenoids, cyanobacteria, microorganism, mycosporine, mycosporine-like aminoacid, photoprotection, radiation protection, sunscreens, UV filters, UVB, yeast.

INTRODUCTION

The gradual increase of the natural UV radiation (principally UV-B) reaching the earth's surface as a result of the depletion of the stratospheric ozone layer, raises concern about the detrimental effects that may generate to living organisms and photosensible materials. Even slight changes in exposure to UV radiation (UVR) may have far reaching implications for life and it is known to significantly impact not only organisms but also more complex organizations levels, as communities and ecosystems [1]. On a molecular level, exposure to UVR is highly detrimental, given it induces DNA damage [2, 3]. UVR-induced damage is wavelength dependent; UV-A (320 to 400 nm) causes only indirect damage to DNA, proteins, and lipids through reactive oxygen intermediates, while UV-B (280 to 320 nm) causes both direct and indirect damage to DNA molecules. Although UV-C (200 to 280 nm) radiation is the most harmful to life, at present it does not reach the Earth surface (except high mountain locations) due to complete atmospheric absorption [4].

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UV-B direct damage involve mostly the absorption of UV-B photons by the bases and produces two major kinds of DNA lesions, cyclobutane pyrimidine dimers (CPD) and pyrimidine (6,4) pyrimidone dimers, with mutagenic and cytotoxic implications [5]. UV-B radiation has long been recognized as causing skin erythema (sunburn) and it is known that cumulative exposure results in DNA damage, eye damage and immunosuppression, eventually leading to skin cancer [3, 6, 7].

Living organisms have developed several strategies to address the damaging effects of UV radiation. For the direct injuries of UVR some organisms synthesize cellular metabolites that absorb the radiation and avoid accumulation of damage in DNA, like melanin [8]. Indirect protection is also provided, for example by carotenoid pigments and other antioxidants that quench the reactive oxygen species (ROS) produced by the UVR [9, 10]. A group of cellular metabolites have been proposed as photoprotective compounds with both direct and indirect protection activity: mycosporines (MYC) and mycosporine-like amino acids (MAA) [11, 12].

UV radiation also affects photo-sensible materials, causing detrimental effects that impact in the maintenance of their quality and integrity. A current application of UV protectors is its incorporation in the manufacture of fabric used for clothing to reduce the fading of colors [13]; but UV protection can

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impact in a wide range of applications, including paints, cosmetics, pharmaceutical and environmental remediation.

In sunscreens, the antioxidants are used as UV-protective additives to combat potentially hazardous photogenerated free radicals. They are effective because of their singlet oxygen quenching ability and scavenging of peroxyl radicals [14, 15]. In particular, carotenoids pigments are also efficient for blue light (near UV-A) filtering in homogeneous solution [16].

Many organic chemicals that absorb UV radiation are used in commercial sunscreen products for skin protection and in other cosmetics for improve product stability and durability. Some of these chemicals possess estrogenic activity *in vivo* in the range of other known xenoestrogens [17-21]. Also they are highly lipophilic and therefore can be bioaccumulated in the environment and in lipids of organisms. Humans can be exposed to UV screens by dermal absorption or through the food chain, and their long-term exposure can lead to effects on reproduction and ontogeny [22-24]. In this scenario, the need to search for natural alternatives and environmentally innocuous agents for photoprotection becomes clear. A promising alternative is the use of MYC and MAA from microbial sources to provide both direct (UV-absorption) and indirect (antioxidant) protection.

MYCOSPORINES AND MYCOSPORINES-LIKE AMINO ACID

Mycosporines are water-soluble molecules formed by a cyclohexenone core linked with an amino acid or amino-alcohol that absorb UV radiation between wavelength 310 to 320 nm [11]. Mycosporines-like amino acid are imine derivate of mycosporines with UV absorption range between 310 and 360 nm.

The first mycosporine was detected in the 1960s in fungi and was initially associated with the induction of sporulation [25-27]. Currently, MYC and MAA are considered to be multipurpose metabolites with a variety of functions including antioxidant capacity, accessory pigments in photosynthesis, nitrogen storage, thermal protection and osmotic stress protection [28]. Fungi produce only MYC, while cyanobacteria, micro/macroalgae and marine organisms can synthesize both MYC and MAA [29]. Some marine organisms (eg. black sea cucumber *Holothuria atra* [30] and scallop *Patinopecten yessoensis* [31]) potentially are able to convert and bioaccumulate certain MAA into other types of mycosporines through the action of intestinal bacteria.

Mycosporines have a great potential as sunscreen active ingredients given their natural role as a photoprotective molecule, and since their prevent UV-B induced cell destruction. It was demonstrated that MYC can partially prevent pyrimidine dimer formation and completely prevent UV-B induced erythema when is applied to the skin prior to irradiation [32]. It has been demonstrated that MYC present high photochemical stability, high performance in UVB absorption and additional antioxidant capabilities, in addition to its absence of cytotoxicity [12, 33-35]. This shows that the potential application of MYC in cosmetics, pharmaceutical, materials, food, animal and human photoprotection is promising.

It has been reported *in vitro* photostability of MAA [36-38], its antioxidant properties and its cutaneous photoprotective ability *in vivo* on mouse skin [39, 40]. These properties have led to their current commercialization as active ingredient of skin care and cosmetic products. Examples of these are Helioguard 365®, a formulation containing MAA porphyra-334 and shinorine (λ max = 334 nm); and Helionori®, a composition containing the same two MAA plus palythine (λ max = 320 nm).

Recently a biosynthetic pathway for the production of the MAA Shinorine in cyanobacteria has been reported [29], which derived from the precursor of the pentose phosphate pathway sedoheptulose 7-phosphate. A cluster of four genes was found to be responsible for the conversion from that metabolite to the MAA shinorine. A dehydroquinate synthase (DHQS) homolog, 2-epi-5-epi-valiolone synthase, and an O-methyltransferase convert the sedoheptulose 7-phosphate into 4-deoxygadusol, after which an ATP-grasp homolog and a non-ribosomal peptide synthase attach glycine and serine to generate mycosporine-glycine and shinorine. A second study confirmed the genes involves in other cyanobacterial species for the synthesis of the MAA Mycosporine-2-Glycine [41]. While MYC biosynthesis has not been formally described yet, Balskus EP and Walsh CT [29] also describes the existence of homologous genes (putatively involved in MYC synthesis) for some fungi with genome sequences available, but it has not been yet experimentally confirmed.

ANALYSIS OF RECENT PATENTS ON MICROORGANISM AS SOURCE OF SUNSCREENS

A list of patents was obtained from web databases using the search keywords "Mycosporine" or "sunscreen" or "Mycosporine-like aminoacid" or "photoprotection". The databases used were: *World Intellectual Property Organization, WIPO* (http://www.wipo.int/patentscope/search/en/search.jsf), with a database of 2,164,174 patents; *European Patent Office* (http://www.epo.org/searching/free/espacenet.html), with a database of more than 70 million patent documents; and *United States Patents and Trademark Office* (http://www.uspto.gov/patents/process/search/index.jsp). The search yielded a total of 35 pertinent patents which are here reviewed (Table **1**). In this regard, we have not considered the patents based on extracts whose active molecules were not identified (such as US6669944, WO2004067780, US7063974, WO03041679) and mixes of peptides and proteins (like US20040131580 and EP1433463).

In this work we considered MYC-glycine and MYC-taurine as a MAA according to the patent authors and Bandaranayake WM [11], although we suggest a reclassification given that we consider its chemical structure more important than its isolation source.

Most patents analyzed were developed with organism from marine environments (Fig. **1**), comprising 76.2% of the reviewed developments. The search for natural photoprotective molecules is relatively recent (except for the first one, all patents are dated after the year 2000, Table **1**), hence it is very important to invest efforts in exploring different types of environments, especially extreme ones, to increase the diversity of sources available as alternative sunscreen producer with

Table 1. Recent patents involving microorganisms as source of sunscreens.

Ref. Authors	Year	Title	Patent No.	Country Area	Applicant
[42] Eiji N.; Jiyunichi K.; Reiko A.	1984	Mycosporine-like amino acid	JPS59137450	Japan	Mitsubishi Chem Ind
[43] Huner N.; Krol M.; Ivanov A.; Sarhan F.	2000	Solar radiation protection composition	WO0024369	World WIPO	Huner Norman; Krol Mariana; Ivanov Alexander; Sarhan Fathey
[44] Huner N.; Krol M.; Ivanov A.; Sarhan F.	2004	Solar radiation protection composition	US6787147	United States	Huner Norman; Krol Mariana; Ivanov Alexander; Sarhan Fathey
[45] Sirop J. C.; Pradines R. D.	2001	Topical cosmetic composition, useful for protecting skin and hair against sunlight, containings an extract from the red alga *polysiphonia lanosa*	FR2803200	France	Brevets Licences ET Commercialisations Laboratoires BLC Thalgo Cosmetic SA
[46] Andre G.; Pellegrini M.; Pellegrini L.	2001	Algal extracts containing amino acid analogs of mycosporin are useful as dermatological protecting agents against ultraviolet radiation	FR2803201	France	Gelyma SRL
[47] Llewellyn C. A.; Galley E.	2002	Personal care compositions	WO0239974	World WIPO	Natural Enviroment Research Council; Llewellyn Carol Anne; Galley Edward
[48] Llewellyn C. A.; Galley E.	2003	Personal care compositions	EP1341514	Europe EP	Plymouth Marine Lab
[49] Enk D. C.; Srebnik M.; Lev O.; Hochberg M.; Dor I.; Torres-Kerner A.; Dembitzky V.	2003	The utilization of natural pigments from Lichens, cyanobacteria, fungi and plants for sun protection	WO03020236	World WIPO	Hadasit Medical Research Service & Development Limited; Yissum Research Development Company of The Hebrew University of Jerusalem; Enk David Claes; Srebnik Morris; Lev Ovadia; Hochberg Malka; Dor Inka; Torres-Kerner Avital; Dembitzky Valerie
[50] Enk D. C.; Srebnik M.; Lev O.; Hochberg M.; Dor I.; Torres-Kerner A.; Dembitzky V.	2003	The utilization of natural pigments from lichens, cyanobacteria, fungi and plants for sun protection	AU2002329025	Australia	Hadasit Medical Research Service & Development Limited; Yissum Research Development Company of The Hebrew University of Jerusalem
[51] Enk D. C.; Srebnik M.; Lev O.; Hochberg M.; Dor I.; Torres-Kerner A.; Dembitzky V.	2005	The utilization of natural pigments from lichens, cyanobacteria, fungi and plants for sun protection	US20050129630	United States	Enk David Claes; Srebnik Morris; Lev Ovadia; Hochberg Malka; Dor Inka; Torres-Kerner Avital; Dembitzky Valerie
[52] Schmid D.; Schürch C.; Zülli F.	2004	Cosmetic skin care products and cosmetic agents for protecting skin against premature aging	EP1473028	Europe EP	Schmid Daniel; Schürch Cornelia; Zülli Fred.; Mibelle A. G.
[53] Ewart H. S.; Zhang J.; Barrow J. C.	2007	Compositions comprising porphyra and methods of making and using thereof	WO2007144779	World WIPO	Ocean Nutrition Canada Ltd; Ewart Harry Stephen; Zhang Junzeng; Barrow James Colin
[54] Kunshan G.; Ping L.; Juntian X.; Zhihui C.; Yuming Q.	2007	Cosmetic including natural substance having sun-screening function	CN101061995	China	Shantou University
[55] Scoglio S.; Canestrari F.; Benedetti S.; Zolla L.	2007	Extracts of *Aphanizomenon flos-aquae* and nutritional, cosmetic and pharmaceutical composition containing the same	US20100021493	United States	Nutratec SRL

(Table 1) Contd….

Ref. Authors	Year	Title	Patent No.	Country Area	Applicant
[56] Scoglio S.; Canestrari F.; Benedetti S.; Zolla L.	2007	Extracts of *Aphanizomenon flos-aquae* and nutritional, cosmetic and pharmaceutical composition containing the same	CN101489527	China	Nutratec SRL
[57]Scoglio S.; Canestrari F.; Benedetti S.; Zolla L.	2008	Extracts of *Aphanizomenon flos-aquae* and nutritional, cosmetic and pharmaceutical composition containing the same	WO2008000431	WIPO	Nutratec SRL; Scoglio Stefano; Canestrari Franco; Benedetti Serena; Zolla Lello
[58] Scoglio S.; Canestrari F.; Benedetti S.; Zolla L.	2008	Extracts of *Aphanizomenon flos-aquae* and nutritional, cosmetic and pharmaceutical composition containing the same	CA2656160	Canada	Nutratec SRL
[59] Scoglio S.; Canestrari F.; Benedetti S.; Zolla L.	2009	Extracts of *Aphanizomenon flos-aquae* and nutritional, cosmetic and pharmaceutical composition containing the same	MX2009000137	Mexico	Nutratec SRL
[60] Scoglio S.; Canestrari F.; Benedetti S.; Zolla L.	2009	Extracts of *Aphanizomenon flos-aquae* and nutritional, cosmetic and pharmaceutical composition containing the same	KR10200900483 99	Korea	Nutratec SRL
[61] Scoglio S.; Canestrari F.; Benedetti S.; Zolla L.	2009	Extracts of *Aphanizomenon flos-aquae* and nutritional, cosmetic and pharmaceutical composition containing the same	EP2032122	Europe EP	Nutratec SRL
[62] De La Coba Luque F.; Aguilera Arjona J.; López Figueroa F.	2007	Use of a mycosporin-tipe amino acid (porphyra 334) as an antioxidant	WO2007026035	World WIPO	Universidad De Málaga; De La Coba Luque Francisca; Aguilera Arjona José; López Figueroa Félix
[63] De La Coba Luque F.; Aguilera Arjona J.; López Figueroa F.	2007	Use of a mycosporin-type amino acid (M-gly) as an antioxidant	WO2007026036	World WIPO	Universidad De Málaga; De La Coba Luque Francisca; Aguilera Arjona José; López Figueroa Félix
[64] De La Coba Luque F.; Aguilera Arjona J.; López Figueroa F.	2007	Use of a mixture of mycosporin-type amino acids (asterin 330 + palythine) as an antioxidant	WO2007026037	World WIPO	Universidad De Málaga; De La Coba Luque Francisca; Aguilera Arjona José; López Figueroa Félix
[65] De La Coba Luque F.; Aguilera Arjona J.; López Figueroa F.	2007	Use of a mycosporin-type amino acid (shinorine) as an antioxidant	WO2007026038	World WIPO	Universidad De Málaga; De La Coba Luque Francisca; Aguilera Arjona José; López Figueroa Félix
[66] De La Coba Luque F.; Aguilera Arjona J.; López Figueroa F.	2008	Uso de aminoácido tipo micosporina (shinorine) en productos para prevención y tratamiento de eritema actínico, fotocarcinogénesis y fotoenvejecimiento	ES2301426	Spain	Universidad De Málaga
[67] De La Coba Luque F.; Aguilera Arjona J.; López Figueroa F.	2008	Uso de aminoácido tipo micosporina (porfira 334) en productos para prevención de procesos cancerígenos	ES2301293	Spain	Universidad De Málaga
[68] López Figueroa F.; Aguilera Arjona J.; De La Coba Luque F.; Korbee Peinado N.	2009	Composición para protección solar a base de extracto de algas y líquenes	ES2317741	Spain	Universidad De Málaga
[69] Wolf F.	2009	Cosmetic sunscreen composition	GB2472021	United Kindom	Jurlique R&D
[70] Sakakibara M.; Torii M.; Miyamoto M.	2009	Mycosporin-like amino acid derivative having glycosyl group and method for producing the same	JP2009120562	Japan	Dainippon Ink & Chemicals

(Table 1) Contd….

Ref. Authors	Year	Title	Patent No.	Country Area	Applicant
[71] Han T. J.; Park J. H.	2010	Method for manufacturing non-toxic extract for blocking uv from red algae	KR100969325	Republic of Korea	Incheon University Industry Academic Cooperation Foundation
[72] Han T. J.; Park J. H.	2011	Method for preparing uv screening nontoxic extract from red algae, and nontoxic sunscreen using same	WO2011096628	World WIPO	Incheon University Industry Academic Cooperation Foundation; Han Tae Jung; Park Jin Hee
[73] Han T. J.; Park J. H.	2012	Method for preparing uv screening nontoxic extract from red algae, and nontoxic sunscreen using same	CN102740869	China	Incheon University Industry Academic Cooperation Foundation
[74] O'Connor C.; Skill S. C.; Llewellyn C. A.	2011	Topical composition	WO2011158041	World WIPO	The Boots Company PLC; Plymouth Marine Laboratory; O'Connor Clare; Skill Stephen Charles; Llewellyn Carol Anne
[75] Zhenhong S.; Jing L.; Fang W.	2012	Beauty product containing desert algae radiation-proof ingredient and natural medical whitening ingredient and preparation method thereof	CN102764206	China	Su Zhenhong
[76] Zhahoui Z.; Xin G.; Zhiheng X.; Jiachao X.	2012	Preparation method for laver mycosporine-like amino acids porphyra-334	CN102659621	China	Ocean University of China

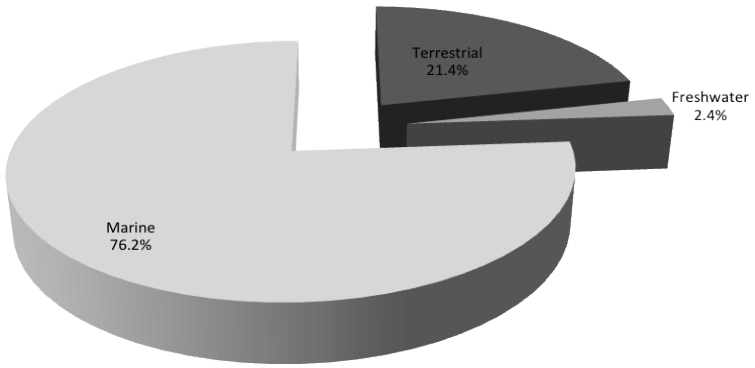


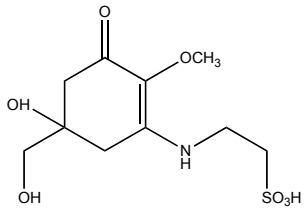
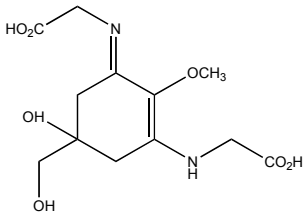
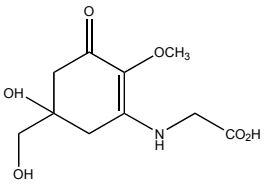
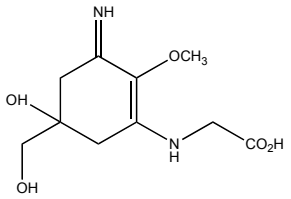
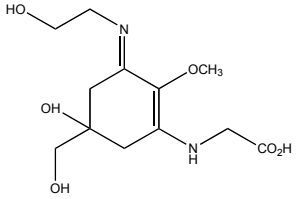
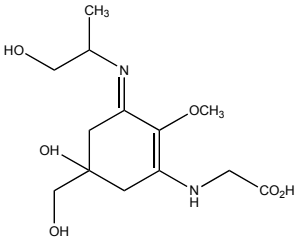
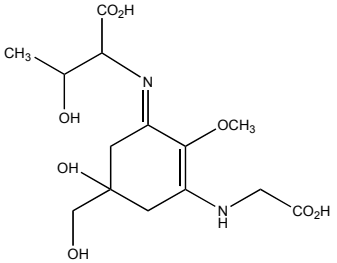
Fig. (1). Environmental source of microorganisms used for production of photoprotection compounds in the patents reviewed.

potential industrial application. Only about 21.4% of patents explored terrestrial environments, just 4.8% of these with exclusivity. This reflects that until today the terrestrial environment has been neglected in the search of new sources of natural sunscreens.

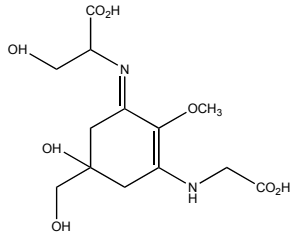
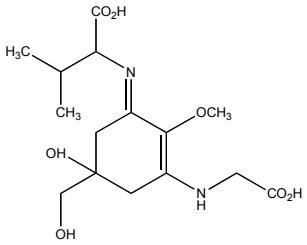
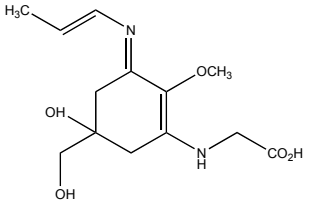
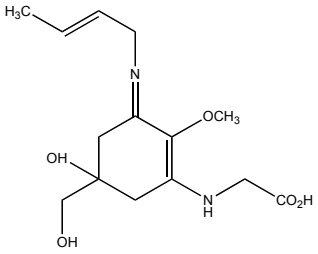
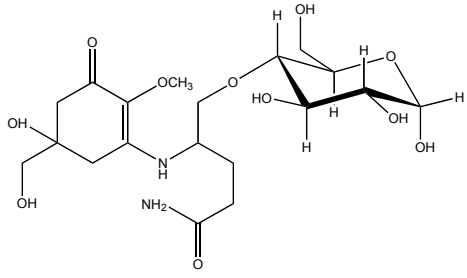
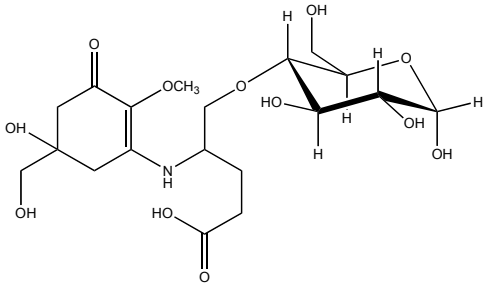
In the patents reviewed here a clear predominance (54.2%) of the *algae* taxon as source of natural sunscreens can be observed, followed by bacteria (18.8%), lichens and fungi (10.4%), plants (6.3%) and finally animals (2.0%) (Fig. **2**). This impacts in the main kind of molecules found, given that MAA are most frequent in algae, whereas MYC are most common among fungi. The main algae employed in the patents were multicellular and belonging to genera *Porphyra*, including the species *P. umbilicalis, P. leucosticta* and *P. tenera* (Table **2**). Unicellular organisms employed were mainly bacteria (prokaryotes) such as *Aphanizomenon flos-aquae* and *Nostoc commune*, but it have been employed the dinoflagellate (eukaryotes) *Gymnodinium catenatum*. Clearly, there is much work yet to be done on unicellular eukaryotes, of which yeasts, based on recent findings (see below), deserve particular attention. Unicellular microorganisms have several advantages to work with, such as the time and relative simplicity of culture which influences their cost of industrial scale production.

As expected, based on the main type of organisms studied, 81.4% of the UV-absorbing compounds reported are MAA (Fig. **3**) and there are no patents exclusively using MYC as sunscreens until date, except for Argentinian patent P090103845 [35]. This patent was based on the synthesis of Mycosporine-glutaminol-glucoside by yeasts, and the procedures for production, purification and use. While MYC and MAA grant both direct and indirect protection against solar radiation, the UV spectral properties of the latter might be more affected by temperature and pH than the former [77]. For that reason it would be desirable that sunscreen compositions would consist of a combination of both kind of molecules,

Table 2. Most commonly used species as source of sunscreens, compounds produced, chemical structure and maximum absorbance.

Type of organism	Species	Compound	λ max	Structure	Type of molecule
Algae	*Porphyra umbilicalis* [52, 53, 69, 76] *Porphyra leucosticta* [53, 62, 67, 68, 76] *Porphyra tenera* [46, 53, 71-73, 76] *Polysiphonia lanosa* [45, 46]	Mycosporine-taurine	296 nm		MAA
		Mycosporine-2-glycine	303 nm		
	Gymnogongrus devoniensis [65, 66]	Mycosporine-glycine	310 nm		
Cyanobacteria	*Aphanizomenon flos-aquae* [49-51, 55-61] *Nostoc commune* [43, 44, 70] *Plectonema boryanum* [43, 44]	Palythine	320 nm		
		Asterina-330	330 nm		
		Palytinol	332 nm		
Dinoflagellates	*Gymnodinium catenatum* [47, 48]	Porphyra-334	334 nm		

(Table 2) Contd….

Type of organism	Species	Compound	λ max	Structure	Type of molecule
		Shinorine	334 nm		
		Mycosporine-glycine-valine	335 nm		
Lichens	*Lichina pygmaea* [63]	Usujirene	354 nm		
		Palythene	360 nm		
Lichens	*Lichina pygmaea* [63]	Mycosporine-glutaminol-glucoside	310 nm		MYC
Filamentous fungi	*Collema* associated fungus [49-51]				
Yeasts	*Phaffia rhodozyma*, *Dioszegia* spp., *Rhodotorula minuta* and others [35]	Mycosporine-glutamicol-glucoside	310 nm		

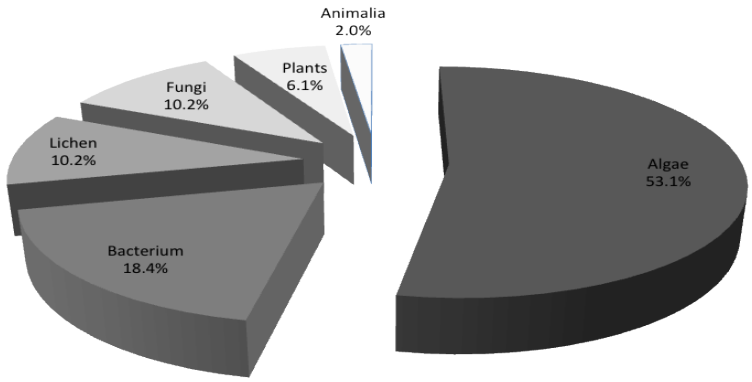


Fig. (2). Distribution of different types of organisms used as natural source of photoprotective compounds.

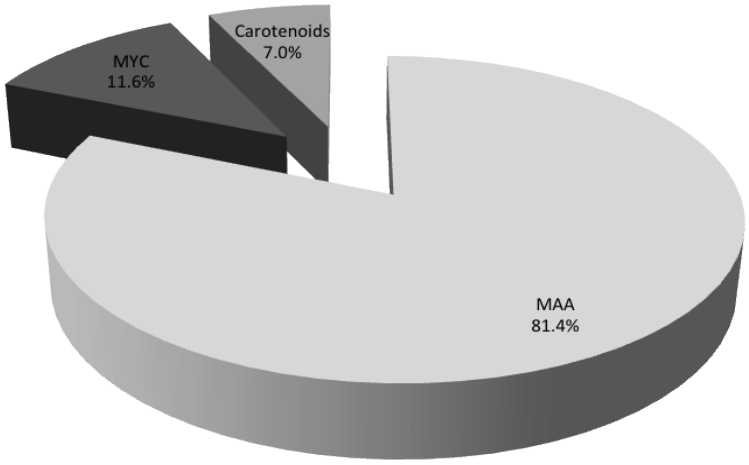


Fig. (3). Distribution of patents based on the type of photoprotective compound evaluated as natural sunscreen.

and even supplemented with other antioxidants compounds such as carotenoids. This strategy ensures a broad UV absorption spectrum and the maintenance of UV filter and antioxidant capabilities over a wide range of conditions.

YEASTS AS A NATURAL SOURCE OF MYC AND OTHER PHOTO-PROTECTIVE COMPOUNDS

Many types of yeast have the capability of producing both MYC and carotenoid compounds (Table **3**), and are presented as a promising source of such molecules for industrial production [78, 79]. Mycosporine production was shown to be a species-specific trait exclusive of certain taxonomic groups. Certain species were able to produce MYC after photostimulation, while others did not. The hypothesis that mycosporine synthesis is a plesiomorphic character in fungi seems more parsimonious than a hypothetical appearance of a similar biochemical pathway producing an identical compound in multiple phylogenetically diverse lineages [80, 81].

In ascomycetous yeasts and dimorphic fungi, significant concentrations of MYC were reported in species of the orders Dothideales and Capnodiales (subphylum Pezizomycotina) and in the order Taphrinales (subphylum Taphrinomycotina) [82-84]. However, it seems to be missing in the subphylum Saccharomycotina. In basidiomycetous yeast, MYC where detected in several groups. Within the subphylum Pucciniomycotina mycosporines producing species were reported in the class Cystobasidiomycetes (with the exception of the Naohideales), in the class Agaricostilbomycetes, in the monotypic class Mixiomycetes, (Mixia osmundae), and in Septobasidiales as the only known mycosporine producing group within the class Pucciniomycetes [81]. In the subphyllum Agaricomycotina, mycosporines species were reported in the order Tremellales. On the contrary, species of the order Cystofilobasidiales did not produce mycosporines [80] with the only exception of the species *Phaffia rhodozyma* (synonym of *Xanthophyllomyces dendrorhous*) and the genus *Udeniomyces* [85]. Table **3** depicts a list of interesting yeast species able to produce different photoprotective compounds including MYC and carotenoid pigments.

Since MYC was found in yeasts by Libkind *et al.* [86] only a single mycosporine with maximum absorption at 310 nm could be isolated among the basidiomycetes yeasts [81]. This mycosporine was identified as mycosporine-glutaminol-glucoside (MGG), which consist of a cyclohexenone core attached to a glutaminol and glucose molecule [87]. Some authors have described the presence of four different kinds of MYC in fungi [25, 26], all of them with an absorbance maximum at 310 nm, but it was questioned because it would be "artifacts" in the process of extraction instead of natural MYC [88]. However, Volkmann *et al.* [89]

Table 3. Interesting yeasts species as source of photoprotective and antioxidant compounds.

Specie	Taxonomy	Origin	Compounds Produced	References
Aureobasidium pullulans	Ascomycetous (Dothideales)	Hypersaline and oligotrophic waters	myc-gln-glu and myc-glc-glu	[83, 94, 99]
Taphrina sp.	Ascomycetous (Thaprinales)	Plant pathogen	β-carotene; γ-carotene; licopene; β-zeacarotene	[100]
Rhodotorula minuta	Basidiomycetous (Cystobasidiales)	Oligotrophic waters	Torulene; β-carotene; γ-carotene; myc-gln-glu; other unidentified pigments	[78, 81, 86, 101-103]
Cystofilobasidium spp.	Basidiomycetous (Cystofilobasidiales)	Oligotrophic waters and tree sap-flows	Torularhodinaldehyde; 16-hydroxytorulene; β-carotene; γ-carotene	[104, 105]
Phaffia rhodozyma / *Xanthophyllomyces dendrorhous*	Basidiomycetous (Cystofilobasidiales)	Oligotrophic waters and stromata of the fungi *Cytaria hariotii*	Astaxanthin; phoenicoxanthin; echinenone; torulene; β-carotene; γ-carotene; myc-gln-glu	[85, 97]
Dioszegia spp.	Basidiomycetous (Tremellales)	Cold environments (water, soil and *C. hariotti*)	β-carotene; γ-carotene; plectanixanthin, myc-gln-glu	[80, 106]

observed that the forms glutaminol and glutamicol are present in the fungal genera *Coniosporium* and *Sarcinomyces*, independently of the extraction or purification method. In this regard, two kinds of mycosporines with the forms glutaminol and glutamicol were reported among ascomycetes yeasts and dimorphic fungi [83].

The molecular weight of MGG is 464.5 g mol^{-1} and the molar extinction coefficient is 25,000 M^{-1} which is almost half the one reported for other MAA. Despite this relative low molar extinction coefficient, MGG content represents a large proportion of yeast cell dry mass reaching in certain cases up to ca. 50 mg g^{-1} dry biomass [80, 85], a concentration much larger than that observed in other MAA-producing microorganisms (< 9 mg g^{-1}) [90, 91]. The photostability of MAAs has been described by Conde *et al.* [36-38] for porphyra-334, shinorine and palythine, which supported the role of MAAs as potent and stable UV absorbers [92]. However, it was later demonstrated that MGG is photochemically more stable than other MAAs studied so far [12], and thus could act as a natural sunscreen in fungi. There are clear indications that MGG protects yeasts against the harmful effects of UVR avoiding the direct damage of DNA [12]. Yeast biodiversity studies in extreme habitats showed that MGG accumulating species are most frequent in highly UV exposed environments [34, 78, 93, 94]. It was also shown that MGG possess antioxidant activity [12], and that its ability to act as a quencher of singlet oxygen is comparable to that of Mycosporine-glycine [33].

Yeasts are also known by the ability of certain species to produce carotenoid pigments with high antioxidant activity including the biotechonologically relevant astaxanthin produced by *Phaffia rhodozyma* [95] as well as many others (torularhodin, torulene, β-carotene, and γ-carotene) [79, 96]. The consistent occurrence of mycosporines and carotenoids in some specific phylogenetic groups has potential applications in yeast systematics [80]. Moreover, it can be applied for the rapid identification of the cold-adapted yeast *Phaffia rhodozyma* over other pigmented species. *Phaffia* produces MGG and astaxanthin [85, 97] both compounds are released when ethanolic extraction at high temperatures is applied. The resulting characteristic UV-Visible spectrum allows the unequivocal identification of this species [98]. Yeasts producing both carotenoids and MGG have also been detected and represent interesting natural sources of UV-absorbing and antioxidant compounds [80, 85]. This was exploited in P090103845 patent [35], but still has enormous potential to improve sunscreens compositions.

CURRENT & FUTURE DEVELOPMENTS

At present, most of the inventions related with sunscreens are based on organic and/or inorganic compounds that may have adverse effects on health and the environment [17-21, 107]. The main disadvantages of common organic ingredients are their estrogenic activity and the potential for photo-irritant or photo-sensitizing reaction in susceptible individuals. On the other hand, a drawback of using inorganic components in sunscreens is their dispersion issues, which often require an additional material for coating. A promising approach is the use of natural molecules such as MAA, MYC and carotenoids, which have not only shown to absorb efficiently UV radiation and combat photogenerated free radical, but also have a strong photostability and absence of cytotoxicity.

To improve rationally the expression of MYC and MAA is essential to know the biosynthesis pathways of them and their molecular regulation. At present, only the biosynthesis of MAA in bacteria has been reported [29, 41], so the MYC biosynthesis remains unclear. The accumulating knowledge regarding the genetic and molecular basis of the biosynthesis of these compounds will foster future research seeking for the overexpression of these metabolites by genetic engineering. Recently, a new patent has been published in which the three known genes involved in the synthesis pathway of shinorine in *A. variabilis* are expressed in bacteria [108]. In this

way, it is also possible to generate an organism that co-expresses high amounts of different metabolites of interest, such as MYC, MAA and carotenes, simplifying the production processes and consequently, lowering costs.

UV radiation reaching the earth's surface is a major biological concern due to its gradual increase as a result of the depletion of the ozone layer and the impact of global warming. Hence, the need to find nonirritant natural alternatives and environmentally innocuous agents for photoprotection is inescapable. While searching for natural photoprotective molecules is relatively recent, the terrestrial environment is still largely unexplored, missing the opportunity to find valuable metabolites. Moreover, unicellular microorganisms give the possibility to reduce the production cost for its simplicity of culture and genetic manipulation.

Yeast appears as an interesting source or even bio-factory of MYC and Carotenoids, as well as possibly MAA through genetic engineering. A promising strategy to address the human and materials photoprotection issue would be a composition with a combination of both molecules, MYC and MAA, that will result in a broader UV absorption spectrum and a wider range of stability. Advances in molecular biology and biotechnology are invaluable tools that will be crucial to overcome the current technical limitations and improve industrial competitiveness, increasing production levels and decreasing growth requirements of cultures.

As presented in the current review, extensive research still has a major role to play in the uncovering of the enormous potential of natural photoprotective molecules of microbial source, and its use in pharmaceutical, cosmetics and materials industries.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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