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Review Article

Effects of UV radiation on human skin and its microbiota: a review on microbial UV sunscreens

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Abstract

Solar ultraviolet (UV) radiation is the culprit for molecular and genetic changes that occur to the skin. This effect can be direct or indirect through the generation of reactive oxygen species and free radicals. So, it is important to find potential molecules that can reduce these effects. In this review, we explored the contributions of microbial-originated UV sunscreens, particularly mycosporines and mycosporines-like amino acids (MAAs). These natural molecules are excellent ultraviolet rays (UVR) absorbers and antioxidant health protectors because they are eco-friendly, nontoxic and have strong photostability. Numerous microorganisms manufacture mycosporines as a defence against solar radiation, particularly those living in habitats with a high concentration of sunlight. Microbial mycosporines can be produced through fermentation processes in a time and space-efficient manner, and process modification and optimization can be done very easily due to their high consistency. It is also cost-effective as it has a simple growth culture and useful genetic manipulation. Thus, the knowledge regarding the synthesis pathway and therapeutic advantages of mycosporines of microbial origin is essential to be improved. Currently, only mycosporines production of marine life have been investigated, the remaining are unclear. We aimed to search more into the impacts of UV radiation on human skin and its microbiota and the microbial-based approaches to counter UV-induced damages.

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INTRODUCTION

Gradual thinning of the ozone layer increases the reach of natural UV radiation on the earth. This raises concern about the deleterious effect that might occur on living organisms, even with a small exposure range. The total disease burden of specific diseases or injuries is measured in disability-adjusted life years (DALYs) by the WHO's global burden disease studies. UV radiation exposure has a contribution to the world's global burden, where the value comes up to 0.1% of the total global disease burden with an estimated annual loss of 1.6 million DALYs *(1)*. The common issues related to UV-induced damages are unavoidable and need more attention.

UV radiation can be detrimental in different aspects depending on the affected areas. For example, exposure at the molecular level induces DNA damage that alters the gene structure causing mutations. UV-induced damage differs depending on its wavelength. The shorter the wavelength, the more harmful the UV radiation. The concerned rays are ultraviolet-A (UVA) and ultraviolet-B (UVB), with a wavelength of 320 to 400nm and 280-320nm, respectively *(2)*. UVA is oxidative,

which affects cellular stability with the formation of oxidative stress and inflammatory responses. UVB contains rays that can damage the DNA of skin cells and cause sunburn directly. Ultraviolet-C (UVC) has the highest energy content, and it is the most harmful ray to life. However, it reacts with the ozone layers and is constrained from reaching the ground *(3)*.

UV-induced damage is usually associated with overexposure to solar radiation without proper protection against it, such as sunscreen and clothing. UV radiation can cause direct DNA damage by inducing the formation of DNA photoproducts like pyrimidine photoproducts and purine photoproducts. These are mostly the result of the misincorporation of bases during the DNA replication process *(4)*. Besides that, the direct interaction of ionizing radiation towards DNA molecules leads to oxidizing damage that is implicated in several human diseases *(5)*. UV radiation also leads to the formation of free radicals and alkylating agents, which causes modified bases. Moreover, a high concentration of reactive oxygen species (ROS) induces damage to cell structure, lipids, proteins as well as DNA.

Long-term exposure to UV radiation ages the skin and causes a variety of problems, including sunburn, fine and coarse wrinkles, and the risk of skin cancer *(6)*. As a result, using sunscreen to limit the detrimental effects of UV radiation on the skin has attracted a lot of attention. This contributes to the production of synthetic sunscreens that have been formulated with UV radiation filters. Unfortunately, these synthetic products mostly show side effects on human health and the ecological system. The ideal properties of a good sunscreen are to cover a broad range of UV spectrum, have no chemical breakdown, and should not cause irritation or toxicity on the skin. This leads to the study of microbial resources that produce mycosporines and mycosporines-like amino acids (MAAs), which help to give protection from UV exposure. This review focuses on exploring the potential use of microbial-based agents against the detrimental effects of UV radiation.

IMPACTS OF UV RADIATION ON SKIN AND ITS MICROBIOTA

Sunlight, specifically UV radiation, exerts constant and immense environmental stress on the skin. UVA causes damaging effects on the skin after long-term exposure, whereas UVB is more frequently associated with acute exposure damage like erythema *(7)*. Meanwhile, the UV radiation with the shortest wavelength of 100-280nm is UVC which is effectively filtered by the stratospheric ozone, hence greatly reduces its interaction with our body. Apart from the penetrability of UV radiations, duration and site of exposure, skin pigmentation, and individual photosensitivity may alter responses to exposure. Many studies reported the health benefits brought by UV exposure (vitamin D-mediated or non-vitamin D-mediated) on blood pressure, osteoporosis and mental well-being *(8)*. However, it is widely understood that UV-induced health effects are proportional to the intensity of exposure. Generally, medical phototherapy with low-dose UV radiation is undoubtedly a mainstay of treatment to induce remissions for various skin conditions *(9)*. The detrimental impacts are substantially related to high-dose exposures. For example, higher-dose UV exposure provokes a deleterious skin injury that might aggravate existing psoriatic plaques *(7)*. Comparably, a similar mechanism leads to a poor adaptation of vitiligo melanocytes to the oxidative damages caused by the radiation, ebbing away from the skin pigmentation. Another study showed that short-term UV exposures may result in the deterioration of acute dermatitis and increased visits to hospitals *(10)*. In other skin-involving systemic disorders like systemic lupus erythematosus, extensive UV-induced apoptosis of keratinocytes might be the key factor to infuriating skin lesions, systemic flares, and auto-immunity *(11)*.

Skin ageing is also associated with UV exposure. Increased wrinkles, laxity, elastosis, and telangiectasia are the signs of UV-accelerated skin ageing. A study showed that enrichment of Staphylococcus, Cutibacterium, and Lactobacillus improves some indicators of skin health (e.g., UV spots, red areas), increasing the skin barrier integrity and therefore slowing down the photoaging process *(12)*. On the other hand, a loss of balance between the different *C. acnes* phylotypes cause cutaneous inflammation and hasten the ageing process *(13)*. Extensive studies reported that UV-induced DNA damage triggers the signalling of melanogenesis *(14)*. Interestingly, certain strains of bacteria and fungi produce melanin as a protection against UV radiation to increase survivability, precipitating the idea of whether the skin microbiome can acquire such melanin-producing capacity. Analogously, *Malassezia furfur*, a species of yeast that is naturally found on the skin surfaces of humans, secreted pityriacitrin, a broad-spectrum UV filter, to protect the fungi from UV radiation *(15)*. Responses and reactions to UV radiation vary widely among microorganisms. Findings lead to the quantitative understanding of Gram-positive bacteria adapted better to UV stress owing to the presence of their cell wall *(16)*. A phylum of Gram-negative bacteria, cyanobacteria, is equipped with another UV-adaptation machinery attributed to their evolutionary pattern during their early life on Earth. Meanwhile, Burns et al. (2019) found that UV exposures led to a decreased population of skin Lactobacillaceae *(17)*. *E. coli*, a facultative aerobe, was able to survive UV exposure and even acquired mutation accumulation. Others, especially obligate anaerobes like *P. aeruginosa*, could not survive the inhibition of respiration by reactive oxygen species accumulation *(18)*.

CONVENTIONAL SUNSCREENS AND THEIR ADVERSE EFFECTS

The skin acts as a natural protective barrier against UV rays with its pigmentation, antioxidants, DNA repair and

programmed cell death *(19)*. The most basic mean of photoprotection is by wearing clothes made of fabric that provides anti-UV characteristics. Besides, sunscreen is applied to directly block or reflect UV radiation. In addition, products like antioxidants, osmolytes and DNA repair enzymes were also used as a secondary measure to minimize skin damage inflicted by UV radiation. Classical sunscreens can be categorized into organic and inorganic sunscreens. Organic sunscreens contain chemicals (e.g. oxybenzone) as UV absorbers, whereas inorganic ones are made of metal oxides (e.g. zinc oxide) that serve as UV reflecters *(20)*. Sunscreen products may incorporate other ingredients to provide additional protective effects, such as inhibiting UV-induced oxidative stress or promoting the host's defensive capabilities, like endogenous photoprotection and reparation systems. Traditional inorganic sunscreens are thicker and whiter, owing to their formulation, resulting in the consumer looking aesthetically unflattering. A study showed that people applied only about 65% of the number of inorganic sunscreens compared with organic sunscreens, hindering the effectiveness of inorganic sunscreens in sun protection *(21)*. Since then, with the technology of micronization, inorganic sunscreens become much less visible on the skin.

There has been a lot of attention from the public gathered around the potential adverse effects of sunscreens or sunscreen-containing cosmetic products. The United States Food and Drug Administration (FDA) made amendments to improve the quality and safety of sunscreen products and proposed that titanium dioxide and zinc oxide are the only "generally recognized as safe and effective (GRASE)" ingredients used in sunscreen products. To another extent, aminobenzoic acid (PABA) and trolamine salicylate are not considered GRASE for use in sunscreens because of safety concerns *(22)*. As mentioned earlier, the transformation of sunscreen particles via micronization or, more recently, into nanoparticulate has fueled immense aspiration in the cosmetics industry. However, public fear of these unknown tiny objects impedes the progress of nano-modified chemical sunscreens. Until more concrete and detailed proven reports on the safety of nano-sunscreen, reservations remained.

Concerns over the endocrine-disrupting behaviours of chemical sunscreen have been raised over the last few decades. Ingredients used in chemical sunscreen have been associated with allergy or photoallergic contact dermatitis where recent studies demonstrated that sunscreen containing oxybenzone or benzophenone-3 causes photoallergic reactions *(23)*. The development of photo contact allergy from octocrylene-containing consumer products is most likely due to the presence of non-negligible concentrations of oxybenzone residues. It was found that exposure to oxybenzone-containing sunscreen significantly increases the risk of polycystic ovary syndrome in obese and overweight women *(24)*. Noteworthily, the distribution of oxybenzone across the placental barrier is associated with neonates with Hirschsprung's Disease, a congenital colonic disorder characterized by difficulty in defecation. Concerns have also been raised over the impacts of sunscreens on the environment. A ban on oxybenzone and oxynoxate had gone into effect in certain countries as it was believed that these ingredients caused direct or indirect bleaching of coral reefs *(25)*. Even though the concentration of these sunscreen constituents has not reached a toxic level for most aquatic life at this moment, considering they are not easily removed by conventional wastewater treatment methods, their persistence and bioaccumulation in the ecosystem are dangerously perturbing.

MICROBIAL-BASED AGENTS TO COUNTER UV-INDUCED DAMAGES

Given the above-mentioned potential harmful adverse effects of inorganic and chemical sunscreens, current research has geared toward the development of nature-inspired active ingredients for sunscreen products *(26)*. Melanin is a natural pigment that exists across many biological groups. Bacteria produce mostly eumelanin and allomelanins, whereas fungi synthesize allomelanins *(27)*. Melanins have been isolated from bacteria like *E. coli* and fungi such as *Candida albicans*. It has been found in Antarctic extremophiles like the black fungus, *Cryomyces antarcticus* and its roles against high UV radiation, desiccation, salinity and oxidation were proven *(28)*. *Streptomyces kathirae* was found to be a potential candidate for the industrial-scale production of melanins due to its high yields *(29)*. It is also known for its strong UV-absorbing properties and free radical-scavenging activity. Scytonemin, a brown pigment produced by cyanobacteria, has been shown to prevent up to 90% of solar UV radiation from entering a biological cell *(30)*. A genus of bacteria, Serratia, produces a red pigment known as prodigiosin which provides additional sunscreen protection when added to commercial sunscreen *(31)*. Violacein, another UV-absorbing pigment isolated mainly from *Janthinobacterium lividum*, Pseudoalteromonas sp. and Chromobacterium, has also been well-studied for its photo-protective activities *(28)*. Mycosporines and MAAs were produced by microorganisms, and the richest diversity of MAAs was found in *Stylophora pistillata* thus far *(32)*. These secondary metabolites have multiple biological functions focusing on photoprotection and antioxidant capacity.

MOLECULAR STRUCTURE AND BIOSYNTHESIS PATHWAY OF MYCOSPORINES AND MYCOSPORINES-LIKE AMINO ACIDS

Mycosporines and MAAs are a huge family of naturally occurring UV-absorbing sunscreen molecules. These molecules have evolved to give protection from severe exposure to UV radiation in various organisms. Mycosporine is a common name used to describe a collective group of water-soluble nitrogenous metabolites associated

with light-stimulated sporulation in terrestrial fungi. Mycosporine derivatives, grouped as mycosporine-like amino acids, have been identified in a wide range of organisms, such as cyanobacteria, microalgae, fungi, lichens and most marine animals. Mycosporines are known as mycosporines-like amino acids because of their conjugation with an amino residue or imino alcohol (Figure 1). They are made up of cyclohexanone or cyclohexenimine rings as their core chromophore structure, and they share the same chemical structure but differ in the substituents and/or presence of amino acids (Figure 2) *(33)*. MAAs are molecules of low molecular weight (<400 Da), colourless, uncharged and water-soluble. The absorption range of MAAs varies from 310nm to 362nm, and their spectra were determined by the structural differences that various MAAs possess.

They are a group of intracellular chemicals produced by the shikimate pathway, which is responsible for the production of aromatic amino acids. According to old assumptions, the biosynthetic pathway of MAAs begins with 3-dehydroquinate (DHQ), a six-membered carbon ring common to all MAAs, in the main route of the shikimate pathway and will be transformed to 4-deoxygadusol (4-DG) using the putative biosynthetic route *(34)*. It is now presumed to occur during the first part of the shikimate pathway, with the strong antioxidant 4-deoxygadusol (4-DG) as the direct precursor (Figure 3). In the third step, 4-DG incorporates the first nitrogen using an ATG grasp ligase to produce mycosporine-glycine, which

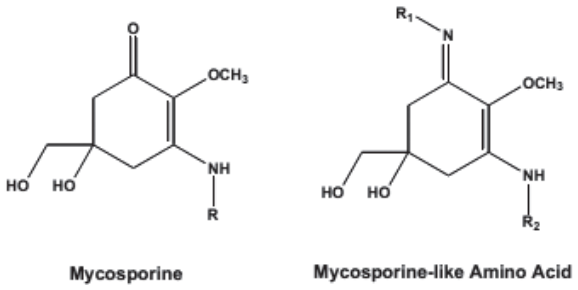

Figure 1. *The general structures of mycosporines and MAA*

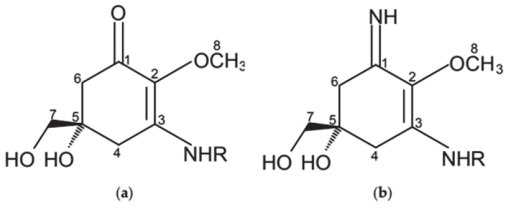

Figure 2. *(a) Aminocyclohexenone. (b) Aminocyclohexeniminone*

is the branch point for all other MAAs. The synthesis develops with the formation of primary MAA (mycosporine-glycine) followed by the synthesis of several secondary MAAs. However, contrasting evidence suggests that 4-DG is also derived from the conversion of pentose phosphate pathway intermediates, sedoheptulose-7-phosphate (SH-7P). Unfortunately, the inhibitors of the shikimate

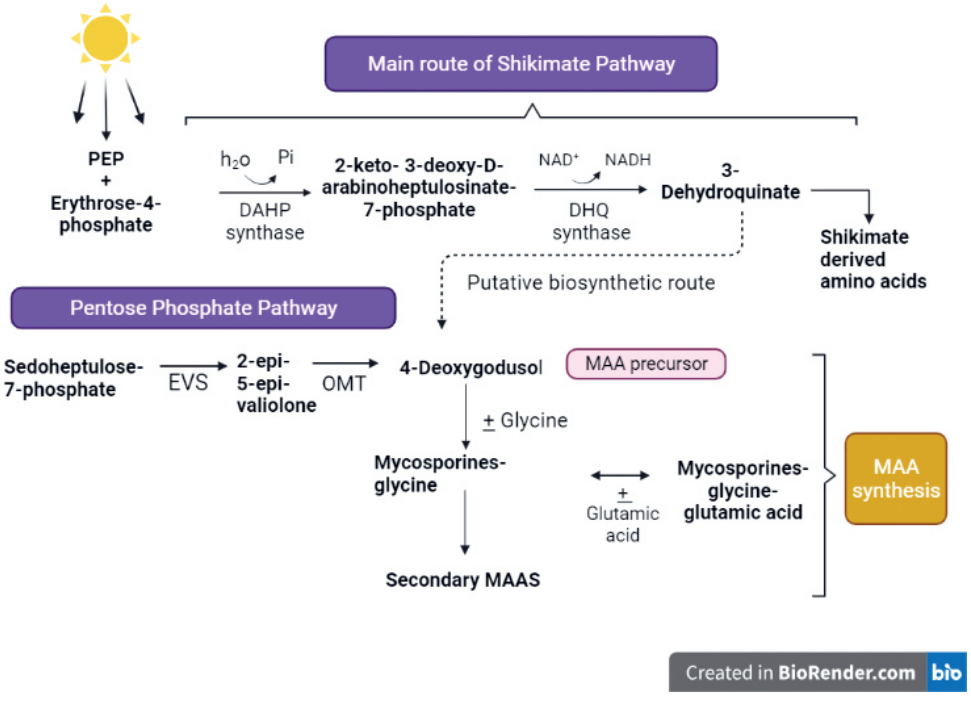

Figure 3. *Proposed biosynthesis pathways of mycosporine-like-amino acids. DAHP: 3-deoxy-D-arabino-heptulosonate phosphate, EVS: cyclase-2-epi-5-epi-valiolone synthase, OMT: O-methyltransferase, PEP: phosphoenolpyruvate, DHQ: 3-Dehydroquinate, MAA: mycosporine-like amino acid, Pi: inorganic phosphate.*

route, glyphosate and tyrosine, showed their ability to destroy the MAA biosynthesis in most cyanobacteria *(34)* and corals *(33)*. This data suggests that the shikimate pathway is predominant in producing a sufficient amount of MAAs for photoprotection, and the quantities of MAAs produced by the pentose phosphate pathway should have other biological functions. However, there are clear connections between the pentose phosphate and shikimate processes, where 4-DG is the parent core structure of MAAs in both pathways, and the addition of glycine yields mycosporine-glycine. This simple monosubstituted cyclohexenone-type MAA is a typical intermediary in the manufacture of di-substituted (aminocyclohexenimine-type) MAAs by adding a single amino acid residue (serine, threonine, etc.), giving MAAs like porphyra-334 and shinorine. Modifications to the connected side groups and nitrogen substituents (e.g., esterification, amidation, dehydration, decarboxylation, hydroxylation, sulfonation and glycosylation) are used to make other MAAs. The difference in the absorption spectra of MAAs is due to variations in amino acid side chains.

CHARACTERISTICS AND DIVERSE FUNCTIONS OF MYCOSPORINES AND MAAS

The diverse functions of mycosporines and MAAs are being studied vastly. Mycosporines come with a central cyclohexenone or cyclohexenimine ring, which absorbs UV light and dissipates energy as heat without generating reactive oxygen species, thus contributing to the suppression of UV-induced stress and serving as a viable alternative natural UV-absorbing chemical *(35)*. Apart from being a strong UV absorbent, their high molar extinction coefficients and resistance to several abiotic stressors like heat render them the advantage of being effective UV protectors *(36)*. A novel glycosylated MAA, 13-O-galactosyl-PR, extracted from the cyanobacterium *Nostoc sphaericum*, showed high protective activity on High sensitivity of human epidermal keratinocytes (HaCaT) culture treated with UVB and UVA and 8-methoxy psoralen *(37)*. Another study suggested that gels infused with MAAs and gadusol protected the human skin against the stress caused by high levels of UV exposure *(38)*. There were also many studies revolving around the use of MAAs as anti-photoaging agents. MAAs extracted from *Porphyra tenera,* containing porphyra-334 and shinorine, were reported to prevent skin photoaging induced by UV irradiation and reduce the damage to collagen and elastin *(39)*. It was found that these MAA-mediated anti-photoaging activities are associated with a reduction in the expression of interstitial collagenase (MMP-1), matrix metalloproteinases (MMP-3) and tumour necrosis factor-α (TNF-α) and a reduction in the content of tissue matrix metalloproteinase (MMPs). Palythine, a photostable model MAA, also exerts its photoprotective effects via modulation of genes encoding inflammatory cytokines, the oxidative stress response enzyme heme oxygenase 1 (HMOX1), and the matrix remodelling enzyme MMP-3 *(40)*.

Even though the research done on MAAs focused very much on photoprotection, their photoprotective capacity has no doubt, at least partially, been associated with their antioxidant activities against the photooxidative stress caused by ROS production. Several *in-vitro* studies have proven the role of MAAs as an antioxidant in scavenging ROS and suppressing singlet-oxygen damage *(41)*. However, large differences between MAAs have been noticed regarding their antioxidative strength. For example, imino-MAAs such as shinorine and porphyra-334 are weak antioxidants, while the dominant MAA, mycosporine-glycine, exhibits high antioxidative capacity. The highest antioxidant activity of mycosporines-glycine isolated from marine lichen *Lichina pygmaea* was reported to be eight-fold higher than ascorbic acid. Furthermore, the 2,2-diphenyl-1-picrylhydrazyl assay (DPPH) assay and oxygen radical absorption capacity (ORAC) assay upon mycosporine-glycine of the marine green alga also demonstrated better antioxidant capacity compared to shinorine and porphyra-334 *(42)*. It was also proposed that MAAs, like mycosporine-glycine and mycosporine-taurine, exhibit strong antioxidant activity by quenching the reactive oxygen species. Research also demonstrated that porphyra-334 and shinorine, isolated from seaweeds, provide both a direct antioxidant defence and stimulate enhanced cytoprotection by activating the molecular Keap1-Nrf2-ARE pathway *(42)*. The application of MAA-containing emulsions was shown to stimulate the expression of antioxidant-associated proteins like superoxide dismutase and catalase. In addition to the antioxidant properties, MAAs also exhibited inhibitory effects on glycation-dependent protein cross-linking, signifying their role in the anti-ageing aspect *(43)*.

On the other hand, ROS development and accumulation of free radicals due to UV damage will act in changing gene expression. Eventually, protein peroxidation occurs, leading to the activation of immune responses and different cellular pathways of inflammatory processes. The anti-inflammatory properties of MAAs, shinorine and porphyra-334, were tested in human myelomonocytic cells. The results showed that shinorine increased the activity of transcription factor NF-κB in a dose-dependent manner, while porphyra-334 reduced the activity of NF-κB and demonstrated anti-inflammatory action *(44)*. The immune-modulatory activities of MAAs were further confirmed as MAAs were found to modulate the biosynthesis of TNF-α and IL-6 as well *(45)*. Meanwhile, MAAs such as mycosporine-glycine, shinorine and porphyra-334 protected the human lung fibroblasts from UV-induced apoptosis dose-dependently. Studies revealed that porphyra-334 inhibits UV-induced apoptosis in HaCaT cells through attenuation of the caspase pathway and modulates miRNAs involved in the apoptosis-associated Wnt/Notch pathways *(39)*.

MAAs are also proposed to serve as intracellular nitrogen reservoirs. The MAA concentration of the red algae *Porphyra columbina* was reported to have increased after being exposed to ammonium treatment under UV radiation. It shows that nitrogen acts as a photoprotective barrier upon UV damage. Other functions of these compounds include the act of it as a metabolite in the regulation of sporulation and germination, especially among the classes *Ascomycetes*, *Basidiomycetes*, *Deuteromycetes* and *Zygomycetes*. Mycosporines and MAAs are also considered metabolites that aid the reproduction of marine invertebrates *(46)*. Besides that, a few hypotheses also concluded that this compound acts as an accessory pigment of photosynthesis *(34)*. Assumptions were made that they absorb the UV rays and convert them to light that is utilized for the photosynthesis process, increasing the respiration efficiency of mycosporines and MAA-rich plants eventually.

FUTURE DIRECTION: PRODUCTION, PURIFICATION & ENVIRONMENTAL IMPACTS

The optimization of mycosporines and MAAs yield for commercial production is essential to enable the use of these photoprotective compounds as therapeutic or aesthetic agents. It is of utmost importance that efforts and resources are allocated to increase their production concentration in microorganism models and alternatives such as a heterologous expression or organic synthesis of the analogues should be further explored. Biosynthetic gene clusters (BGCs) are locally clustered groups of two or more genes that together encode a biosynthetic pathway. Very recent work on the heterologous expression of multiple refactored MAA BGCs in *E. coli* and direct conversion of disubstituted MAAs into palythines by the Fe/2OG enzyme 2-oxoglutarate-dependent oxygenase (MysH) demonstrated new opportunities for the development of next-generation sunscreens. The isolation and purification methods of mycosporines and MAAs are other aspects that demand attention, considering a smooth mass production should entail such processes. Finally, taking into account all the potential therapeutic and commercial values that mycosporines and MAAs could have, their impacts on the environment and ecosystem should also be taken into consideration.

CONCLUSIONS

Mycosporines and MAAs are natural compounds that marine and terrestrial organisms utilize to protect themselves from the detrimental effects of UV radiation. Apart from their photoprotective ability, these compounds possess various benefits that aid the quality of human life. Taking into consideration the need for UV protective compounds that are toxic-free and environmentally friendly, mycosporines and MAAs stand as reliable alternatives for the development of sunscreens. More molecular regulations of these pathways remain understudied. Hence, researching the potential usage of mycosporines and MAAs can highlight the new functions of these compounds or confirm the current findings in detail. The more knowledge we obtain in uncovering the enormous potential of these compounds, the closer their industrial production will be to human protection without compromising our environment.

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