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Review Article

Different sources of mycosporine-like amino acids: Natural, heterologous expression, and chemical synthesis/ modifications

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Abstract

Background and aims: Due to the increasing incidence of skin cancer and other skin disorders caused by ultraviolet (UV) irradiation, development of more efficient sunscreens seems to be essential. Mycosporine-like amino acids (MAAs) are one group of the natural UV absorbent compounds with sunscreen characteristics that have been the focus of a number of researches. This article aims to introduce different sources of MAAs in order to discuss pros and cons in finding the best way for high-scale MAAs production.

Methods: Scientific databases and search engines including Science Direst and Google Scholar were investigated using "Mycosporine-like aminoacid" AND "Production" as main keywords.

Results: An increasing number of publications have been published regard to MAAs in recent 10 years. Publications showed that a wide range of organisms can produce these UV-absorbing compounds, especially under stressful and extreme conditions. Numerous studies has been performed to identify the pharmaceutical and cosmeceutical applications of MAAs. However, it is still challenging to choose the best source for the large-scale production of these compounds. Direct MAAs extraction from natural sources, heterologous production of MAAs using recombinant DNA technology or metabolic engineering, and a few studies of chemical synthesis of MAA derivatives have been reported, so far.

Conclusion: Among various reports, direct extraction from the natural source has got the main position, until now. However, there is an increasing interest on the recombinant production of MAAs in new hosts, with more appropriate features for large-scale production. Nevertheless, it also seems that the chemical synthesis of these compounds is not affordable.

Keywords: Mycosporine-like amino acids, Large-scale production, Sunscreen, UV protectants

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Introduction

The frequency of ultraviolet radiation (UVR) received by the Earth surface is anticipated to rise today, because of the decrease in aerosols and cloud coverage. Regard to this event, different organisms have developed biochemical and mechanical defense systems, such as DNA repair mechanisms, antioxidant processes, and the synthesis of UV-absorbing substances to avoid photo damage. A wide variety of UV-screening substances have been discovered, ranging from mycosporines and mycosporine-like amino acids (MAAs) in cyanobacteria, fungi, algae, and some animals, to melanin in mammals (1,2). The family of naturally occurring, thermally and photochemically stable UV protectants known as MAAs has been reported in many aquatic species, including marine and freshwater creatures, which subjected to high levels of harmful UV irradiation. Cyanobacteria, macroalgae, phytoplankton, fungi, microalgae, and animals with various characteristics from different ecosystems especially marine organisms are just a few examples of the MAAs sources. Along with other significant photoprotective chemicals such as carotenoid pigments in plants and numerous microbes, and scytonemin in cyanobacteria, MAAs have been evolutionarily conserved in marine life (1,3). Additionally, MAAs exhibit pharmacologically significant anti-oxidative, anti-aging, and anti-inflammatory traits. Furthermore, MAAs are necessary for cellular defense against drought and osmotic control (4).

MAAs potentials, such as their UV-absorption, antioxidant properties, and physicochemical characteristics, make them attractive preventative or therapeutic agents used in the treatment of disorders induced by free-radicals or harmful UV irradiation in humans (5).

However, they have been broadly studied, the biosynthetic pathways required to produce MAAs in an affordable industrial manner are not completely understood. The manufacturing process for these compounds is relatively difficult. For instance, there is a requirement to farm a huge amount of seaweed. A better understanding of the MAAs biosynthetic pathways would make large-scale commercial biosynthesis in an easier-to-cultivate heterologous bacterial host like *Escherichia coli* (6). On the other hand, due to their chiral centers, MAA molecules

are extremely challenging to chemically synthesize, and make their large-scale synthesis challenging and results in unreasonably high manufacturing costs (7).

Materials and Methods

This article discusses the different methods for MAAs production and their pros and cons, as a guide for choosing the best method to produce industrial quantities of these compounds. In this regard, scientific database and search engines including Science Direst and Google Scholar were searched using "Mycosporine-like aminoacid" AND "Production" as main keywords. About 1000 publications were reported by Science Direct that were relevant to the main keywords. They were surveyed and the most relevant ones that were published in more recent years, were assessed in details. More than 7000 related publications archived in Google Scholar were assessed and reduced the number of publications by focusing on the recent publications after 2010, and the most relevant ones were assessed in details.

Result and Discussion

Mycosporine-like amino acids structure

Once exposed to high light levels, a number of organisms from different categories, such as microalgae, macroalgae, lichens, corals, and fungi, can produce a group of secondary metabolites identified as MAAs, also referred to as microbial sunscreen. MAAs are extremely stable molecules in their environment and their molecular weights range from 188 Da to 1050 Da (8).

They exhibited a distinctive absorption spectrum with a single, narrow band that has a maximum absorption between 309 and 362 nm and the extinction coefficients of up to 50 000 $M^{-1}.cm^{-1}$. The differences in functional groups and nitrogen substituents can cause changes in the absorption spectra of MAAs. These colorless, water-soluble compounds consist of nitrogen-substituted aminocyclohexanone or aminocyclohexenimine rings. Aminocyclohexanone derivatives, including mycosporine-glycine and mycosporine-taurine, are composed of cyclohexenone conjugated with an amino acid. The first carbon atom attaches to an amino acid, amino alcohol, or an enaminone chromophore, and the third carbon atom binds to a cyclohexenimine conjugated with glycine or methylamine (1,9). At the first carbon, L-Gly (e.g., mycosporine-2-Gly), L-Thr (e.g., porphyrin-334), L-Ser (e.g., shinorine), and L-Ala are frequently presented as foundations (6). The cyanobacterium *Euhalothece* sp. was reported to produce a rare and unique MAA, made up of the amino acid alanine (10).

Different derivatives of MAAs have been reported. There have been several reports of glycosylated MAAs; for instance, Nazifi et al found two unique glycosylated MAAs in the cyanobacterium *Nostoc commune* of land (11). In another work, Kenji Ishihara et al isolated and characterized a new glycosylated MAA (13-O-β-galactosyl-porphyra-334) as a UV-absorbing molecule from the comestible cyanobacterium *Nostoc sphaericum*, also called "ge xian mi" or "cushuro" in China and Peru (12). Moreover, some coral-isolated MAAs contain sulfate esters (13). Notably, the complete configuration of the bulk of MAAs, particularly the fifth carbon, has not been thoroughly explained, except for a few analogs such as mycosporine-glycine, porphyra-334, palythene, and palythine (14).

Mycosporine-like amino acid biosynthesis pathway

The shikimate pathway was the initial putative pathway in MAAs biosynthesis. Through this pathway, 3-dehydroquinate is a precursor to 4-deoxygadusol, a primary precursor of MAAs, resulting in the formation of primary and secondary MAAs. The synthesis of MAAs and fungal mycosporines is thought to start with 3-dehydroquinate and go through gadusols. Mycosporine-glycine and fungal mycosporine-serinol were synthesized from natural D-(-)-quinate as a starting point (15).

The second pathway, proposed by Balskus and Walsh, suggests that MAAs are produced from the intermediate sedoheptulose 7-phosphate via the pentose phosphate pathway and from there, via the four-enzyme shinorine synthesis. These enzymes are encoded by a gene cluster containing 3-dehydroquinate synthase, O-methyltransferase, adenosine triphosphate (ATP) grasp, and a nonribosomal peptide synthetase homolog. It has been postulated that each of these enzymes has a particular function during shinorine synthesis. For example, 3-dehydroquinate synthase and O-methyltransferase are required to produce 4-deoxygadusol, while ATP grasp and a nonribosomal peptide synthetase homolog are responsible for joining glycine and serine to 4-deoxygadusol, respectively (1,16). The importance of this process in the production of primary MAA shinorine in the cyanobacterium *Anabaena variabilis* ATCC 29413 was validated by cloning and heterologous expression of the full gene cluster in *E. coli* (1).

Even though experimental evidence supports the pentose phosphate pathway, shikimate pathway blockers, including tyrosine and glyphosate, have been shown to suppress MAA synthesis in cyanobacteria and corals. In addition, the cyanobacterium *Anabaena variabilis* ATCC 29413 made shinorine even though its cyclase-2-epi-5-epi-valiolone synthase gene had been deleted. These findings indicate that the effective method for MAA synthesis to provide photoprotection is the shikimate pathway, and the MAAs synthesized via the pentose phosphate pathway in adequate concentrations should serve other biological purposes. Nevertheless, the pentose phosphate and shikimate pathways connect. In both processes, mycosporine-glycine is produced by adding glycine to 4-deoxygadusol, which serves as the primary core structure of MAAs. Through the attachment of a single amino acid residue such as serine or threonine, this straightforward mono-substituted cyclohexenone-type MAA is frequently used as an intermediate in creating di-substituted MAAs,

giving rise to some common MAAs, such as shinorine and porphyra-334. In this phase, the DNA codes for a protein similar to non-ribosomal peptide synthetase (NRPS) or a D-alanyl-D-alanine ligase. A potential MAA biosynthetic route is shown in Figure 1. By modifying the connected side groups and nitrogen substituents, more MAAs are created. Some modifications include esterification, amidation, dehydration, decarboxylation, hydroxylation, sulfonation, and glycosylation (2,17).

Mycosporine-like amino acid bioactivity

The protection against UVR is the most prominent feature of MAAs. The main factors influencing these properties are spectral properties and molar extinction coefficients. They commonly cover a significant portion of the UVR spectrum that penetrates the Earth's surface with a maximum absorption wavelength between 300 and 400 nm (7,15). In recent years, porphyra-334, shinorine, and mycosporine-glycine have been the most extensively studied MAAs. In these molecules, photo-excited states calm down by moving from the singlet excited state to the triplet excited state, followed by non-radiative decay, which leads to a controlled loss of energy as heat without producing reactive oxygen species (18). The intensity of UVR exposure that organisms receive, influenced by latitude, altitude, seasonality, and water depth, is directly correlated with the number of MAAs in those species. They selectively gather in tissues that are exposed to the most UVR. The location of MAAs within the cell affects how well they can defend against light. Three out of every 10 photons are prevented from reaching sensitive biological targets by these substances, which have been discovered mainly in the cytoplasm of various cyanobacterial species. Meanwhile, MAAs build up extracellularly in *Nostoc commune*, providing a more vigorous defense against ultraviolet light. The fact that MAAs are found in fossils shows that they helped organisms to protect from the harmful effects of UVR in the past (2,17,19).

Besides their actions as photo-protectants, MAAs also function as anti-oxidants, inhibiting singlet oxygen-induced damage by scavenging free radicals and other reactive oxygen species (20,21). In a recent study, the antioxidative and antiglycative properties of comestible *N. commune* extract were evaluated. The researchers also studied the effects of the environment on the magnitude of antioxidative or antiglycative impact. Both antioxidative and antiglycative activities were greater in colonies isolated from the field than in those from the laboratory. This enhanced field extract activity may result from significant bioactive substances having these qualities, such as MAAs, phycobiliproteins, and polyphenols. Because of this, the environment in which *N. commune*

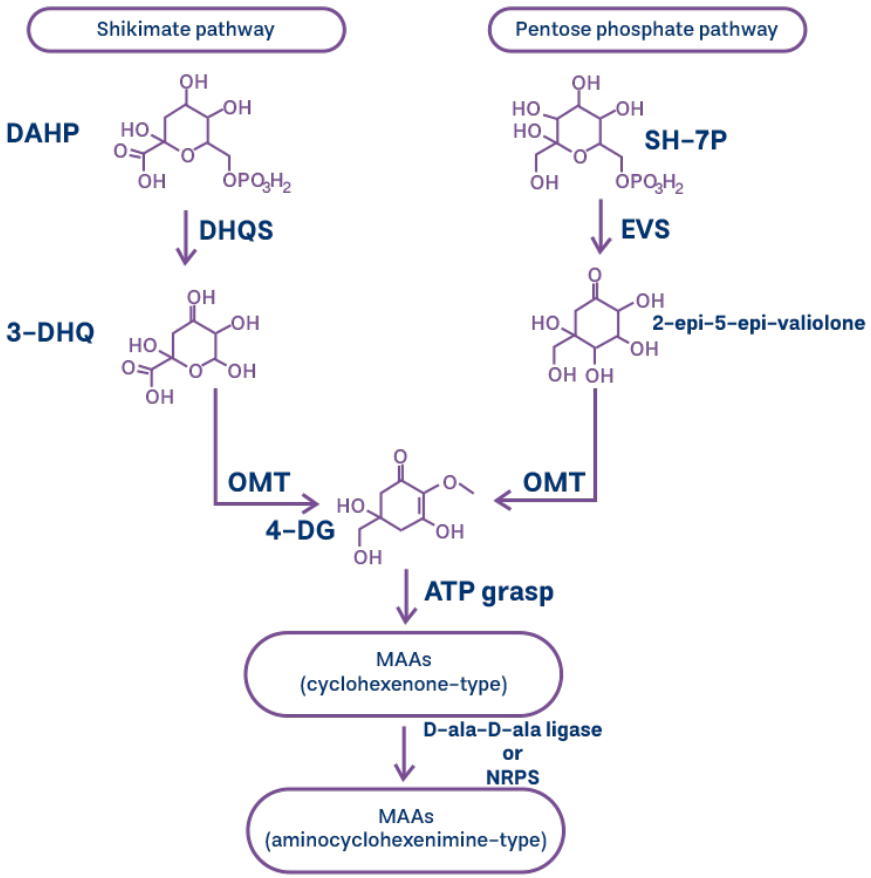

Figure 1. Schematic diagram of the pathway of MAAs synthesis. Abbreviations: SH-7P: sedoheptulose-7-phosphate; DAHP: 3-deoxy-D-arabino-heptulosonate; 3-DHQ: 3-dehydroquinate; OMT: O-methyltransferase; 4-DG: 4-deoxygadusol; ATP grasp: adenosine triphosphate grasp; DHQS: 3 dehydroquinate synthase; EVS: cyclase-2-epi-5-epi-valiolone synthase; D-ala-D-ala ligase: D-alanyl-D-alanine ligase; NRPS: nonribosomal peptide synthase; MAAS: mycosporine-like amino acids.

cells are grown may greatly affect how many beneficial chemicals they have (22).

Utilizing a variety of analytical methods, *in vitro* investigations of MAA antioxidative activities revealed that external factors, such as acidity or temperature might boost their antioxidant power. Shinorine and porphyra-334 were shown to have little antioxidative activity, whereas porphyra-334's antioxidative properties increased in response to environmental changes, such as heat stress. On the other hand, 4-deoxygadusol and mycosporine-glycine, the main MAA that is highly expressed, were both strong antioxidants (23).

DNA protection from oxidative stress brought on by reactive oxygen species (ROS) is another function attributed to MAAs. In one study, the human melanoma cell line A375 was employed as a model to examine the genesis of skin cancer. Mycosporine-2-glycine protected DNA from H_2O_2-related damage. As shown by this comet assay, mycosporine-2-glycine displayed a moderately strong genoprotective effect, comparable to ascorbic acid. Thus, the results of this direct *in vivo* assay suggested that mycosporine-2-glycine may have a protective function against DNA damage brought on by oxidative stress imposed on by H_2O_2 (24).

The osmotic stress is a variable that MAAs may be able to counteract. Cyanobacteria typically exhibit considerable quantities of MAAs in hypersaline conditions, indicating that these substances may have an osmotic role that helps the cells adapt to the high salinity. Oxidative stress can develop in these conditions as a result of cell dehydration and the formation of reactive oxygen species. Osmotic equilibrium can be recovered by producing MAAs. The ability of MAAs to increase cellular tolerance to abiotic stress factors such as temperature, desiccation, and salinity has been reported. MAAs, also known as "osmotic solutes" are common in high-salt environments. A gypsum crust-dwelling, halotolerant cyanobacterium produces a very high concentration of MAA, which accounts for around three percent of the wet weight of the cells. It was noted that a quick evacuation of MAAs occurred in conjunction with a decrease in the salinity levels of their environment. Furthermore, it has thought that MAAs, which have been found in cold aquatic habitats, can function as osmoprotectants in subfreezing temperatures. Therefore, MAAs may play a role in how sea ice algae adjust to osmotic changes. MAAs are stored by many microorganisms in the area inside their cells. In a hypertonic environment, this creates an osmotic pressure inside the cell, which lowers salt stress However, the amounts of these chemicals in freshwater creatures tend to be much lower. MAAs also help organisms grow more resilient to environments when water becomes a scarce resource. There have been reports of significant levels of glycosylated MAAs in the extracellular matrix or membrane that surrounds microorganisms. Only those compounds, however, do not offer enough defense against the effects of drought stress. MAAs can be incredibly beneficial in the fight against the negative consequences of high temperatures (2,19,25).

When necessary, the nitrogen atoms in MAAs, which are nitrogenous compounds with a minimum of one atom per molecule, could be released. MAAs could therefore be used to store nitrogen inside of cells. Ammonium ions and UVR were found to work together synergistically, increasing the content of MAA. If MAAs are developed as intracellular nitrogen storage molecules, nitrogen mobilization should occur in the absence of alternative acceptable forms of nitrogen. The idea that MAAs might be nitrogen storage molecules, on the other hand, is not backed up by any evidence about how MAAs break down inside cells and release nitrogen atoms (26).

Another intriguing characteristic of MAAs that has been observed is their anti-inflammatory function. In a study, Suh et al investigated the microalga MAA extracts' *in vitro* anti-inflammatory capacity. The immortal human keratinocytes known as HaCAT cells were treated with an elevated dose of MAAs and subjected to UV light. Porphyra-334 showed no impact on cyclooxygenase-2 gene expression, whereas mycosporine-glycine and shinorine had an inhibitory influence on the expression of genes linked to inflammation. Different MAAs have also demonstrated varying anti-inflammatory characteristics (27). The effects of MAAs on regulatory and defensive mechanisms that are involved in inflammatory conditions were the main topic of study for Becker and colleagues (28). They used shinorine and porphyra-334 of the red alga *Porphyra* sp. The human myelomonocytic THP-1 and THP-1-Blue cells were exposed to MAAs in the presence or absence of lipopolysaccharide (LPS), and the effects of MAAs on key signaling cascades, including transcription factor nuclear factor kappa-B (NF-κB) activation and tryptophan metabolism, were subsequently examined. In unstimulated THP-1-Blue cells, both MAAs boosted NF-κB activity; the enhancement was dose-dependent and became more significant with shinorine administration. In LPS-stimulated cells, shinorine modestly induced NF-κB, but porphyra-334 decreased NF-κB activity in this inflammatory condition. In motivated cells treated with porphyra-334 and with the minimum treatment dose of both MAAs, tryptophan metabolism was slightly and suppressively altered. Despite having identical structures, MAAs have varied effects on how inflammation occurs (28).

Protein glycation produces advanced glycation end-products (AGEs), which are connected to the development of aging and age-related illnesses. Interestingly, it was discovered that MAAs could suppress protein glycation. One study examined the effects of adding mycosporine-2-glycine or a combination of porphyra-334 and shinorine on the glycation-dependent cross-linking of hen egg white lysozyme, a structural homologue of human lysozyme. Inhibitory action was present in both samples with additional MAAs, with mycosporine-2-glycine isolated from *Aphanothece halophytica* displaying more efficacy than the combination of porphyra-334 and shinorine.

Based on these results, it seems that mycosporine-2-glycine, in particular, and MAAs, in general, may be able to help stop the production of AGEs (29,30). Results from a different investigation revealed that all of the MAAs put to the test could inhibit collagenase in a dose-dependent way. Therefore, MAAs might have an impact on several stages of the healing process for wounds as well as aging (31).

Different sources of mycosporine-like amino acids

For the first time, Wittenberg et al. discovered chemicals with strong UV absorbance from *Physalia physalis,* a siphonophore. Mycosporines were found in sporulating mycelia of fungi in 1965 (32). Some years later, MAAs were identified in cyanobacteria and corals from the Great Barrier Reef. After that, a wide range of organisms, including heterotrophic bacteria, fungi, cyanobacteria, microalgae, macroalgae, lichens, invertebrates such as sponges, dinoflagellates, corals, crustaceans, and sea urchins**,** and vertebrates, as with fishes, have been found to contain MAAs. According to a number of studies, animals can consume MAAs or obtain them through symbiosis to accumulate them. MAAs are absent from advanced plants, whose flavonoids provide UVR protection, as well as larger vertebrates, in which melanin plays the protective role. Particularly in creatures that reside in habitats with high UVR levels, MAAs are ubiquitous (2).

Given that MAAs have garnered considerable interest in the pharmaceutical and cosmetics industries, it is essential to determine their origins. These multifunctional compounds are three common sources: natural sources, bacterial expression, and chemical synthesis.

Natural sources of mycosporine-like amino acids

Numerous studies evaluating the content and composition of MAA have been conducted on species from diverse settings across the globe, ranging from tropical to arctic regions. Natural resource screenings, like those that have been done in the past few years, are necessary to find new compounds in nature that can protect against the sun (5,33,34).

Macroalgae are one of many organisms that may be employed for biomolecule applications. Among the biocompounds in this class, MAAs stand out because they are photoprotective, have antioxidant properties, and are highly photo- and thermo-stable. These are all desirable characteristics for cosmeceutical product development. In a recent study, six new MAAs were isolated from the red algae *Bostrychia scorpioides* (33). Of the 17 red algae species of native Antarctica studied, *Bangia atropurpurea, Curdiea racowitzae*, and *Porphyra endiviifolium* displayed the greatest MAA concentrations. While, on the European coast, the highest concentrations of MAAs were detected in *Gymnogongrus devoniensis*. After that, *Ceramium nodulosum, Bangia atropurpurea*, and *Gelidium pusillum* had the highest levels of MAAs [35]. Red macroalgae such *as Gelidium amansii, Gracilaria confervoides*, and *Bangia fusco-purpurea* have been studied as potential sources of MAAs. In that study, *B. fusco-purpurea* had the greatest possible MAA content of any red macroalgae species (36).

Cyanobacteria are gram-negative prokaryotic organisms that use photosynthesis to transform CO_2 and solar energy into compounds. Cyanobacteria have drawn much interest as a prospective group of species capable of creating industrially significant chemicals due to their photoautotrophic characteristics, faster growth rate, and ease of handling genetically. According to several recent studies, cyanobacteria are potential species with useful secondary metabolites, such as MAAs (37). In a study, Brazilian researchers analyzed 69 cyanobacteria. According to their findings, the UHPLC-DAD/QTOFMS technique proved a practical, trustworthy, and effective approach for identifying and screening MAAs in cyanobacterial strains. They thoroughly screened cyanobacterial strains for MAA production, and the results showed that distinct cyanobacterial genera isolated from various Brazilian biomes and habitats were important producers of different kinds of MAAs. MAA production was not linked to different biomes or environments in the cyanobacterial strains that were looked at (38).

Additionally, microalgae are an environmentally benign source of biomolecules like MAAs because they are simple to produce and have a quick reproduction rate. It was discovered that various circumstances and characteristics significantly influenced the expression of MAAs in particular microalgal species. When exposed to sunlight, it has been discovered that some species, including the diatom *Guinardia striata, Alexandrium excavatum*, and *Phaeocystis pouchetii,* significantly increase their MAAs concentration. In some other species, the special radiations of light were found to be associated with MAA production (39). It was shown that roughly 152 species of marine microalgae create MAAs, with the bloom-forming algal groups such as prymnesiophytes, raphidophytes, cryptomonads and, dinoflagellates showing the largest ratio of these substances. But the expression of MAAs molecules in these marine creatures sometimes depends exclusively on their exposure to UV and bright light, no matter how they are classified taxonomically (26). On the other hand, certain microalgae only produce MAAs under stressful conditions. According to a recent study, *Desmodesmus* sp. could produce MAAs under high salinity conditions, while these compounds were not produced under normal growth conditions (40).

Numerous yeast varieties are also described as a possible source of such molecules for commercial manufacturing since they can synthesize mycosporine and carotenoid chemicals. Mycosporine biosynthesis is something that has been shown to be unique to certain taxonomic groups. Following photostimulation, some species could manufacture mycosporine while others were unable to. The idea that mycosporine production is a plesiomorphic trait of fungi seems more likely than the idea that the same substance would be made by a similar metabolic process in many different types of fungi with different phylogenetic

histories. Substantial quantities of mycosporine have been found in ascomycetous yeasts and dimorphic fungi from the orders Dothideales and Capnodiales as well as the order Taphrinales. Nevertheless, it looks to be absent from the subphylum Saccharomycotina. Mycosporines are found in numerous families of basidiomycetous yeast. Except for the Naohideales, mycosporine-producing species have been identified in the classes Cystobasidiomycetes, Agaricostilbomycetes, the monotypic class Mixiomycetes, and Septobasidiales, the only known mycosporine-producing group within the class Pucciniomycetes. Mycosporine species from the order Tremellales have been reported in the subphylum Agaricomycotina. Mycosporines were not produced by organisms of the order Cystofilobasidiales, with the exception of *Phaffia rhodozyma* and the genus Udeniomyces (41).

According to the present theory, animals cannot synthesize MAAs and must get them through nutrition or—as has recently been proposed—symbiotic bacteria in the gut. According to studies published, the MAA precursor termed gadusol, can be produced by several animals, including some fish, reptiles, amphibians and birds. In addition, genes involved in MAAs production have been discovered in sea anemones, indicating that certain organisms may be able to create MAAs. However, this has not been demonstrated in zooplanktons, which most likely obtain MAAs through their diet or symbiotic relationship (42).

Heterologous expression of mycosporine-like amino acids

The high cost of extracting MAAs from natural sources, as well as the small amounts of MAAs that can be made from them, makes it hard for the pharmaceutical and cosmetics industries to use them. Culturing certain organisms like microalgae is one solution to deal with the constrained bioavailability of natural resources. These photosynthesis-capable microorganisms are simple to grow in a lab setting, and cyanobacterial farming can be used to produce large amounts of needed chemicals and energy while cutting CO_2 emissions. *Escherichia coli* cultures *in vitro* are still used in biotechnological operations as heterologous expression vehicles for producing many bioactive molecules and recombinant proteins. Incorporating foreign biosynthetic gene clusters into the host genome of *E. coli*, yeast, or other appropriate organisms is applied for heterologous expression of desired compounds in recombinant biotechnology. Various species, such as bacteria, yeast, and other heterologous expression systems, can be used in this regard. *Anabaena variabilis* ATCC 29413's biosynthetic gene cluster, which is required to manufacture UV-absorbing MAAs, was also effectively extracted and expressed in bacteria (4,43).

In particular, the *in vitro* synthesis of the major MAA, shinorine, was effectively carried out in *E. coli* after introducing the cyanobacterial 4-gene *mys* cluster. The MAAs were also heterologously expressed in *E. coli* utilizing *mylA–E* (a 5-gene cluster) derived from the cyanobacterium *Cylindrospermum stagnale*, synthesizing both mycosporine-lysine and the newly discovered MAA mycosporine-ornithine. An MAA gene cluster found in *Nostoc linckia* led to the creation of an MAA precursor called 4-deoxygadusol, followed by four different MAAs, including Porphyra-334, shinorine, mycosporine-glycine, palythine and mycosporine-glycine-alanine (4,6,44).

While few findings have reported the production of MAAs and the genes associated with their biosynthesis by gram-positive bacteria, genome mining of the gram-positive bacterial database uncovered two bacteria affiliated to the order Actinomycetales, *Actinosynnema mirum* DSM 43827 and *Pseudocardia* sp. strain P1, which contain a gene cluster homologous to biosynthetic gene clusters recognized in cyanobacteria. Heterologous expression of these biosynthetic gene clusters in *Streptomyces avermitilis* SUKA22 resulted in accumulating shinorine and Porphyra-334 as well as a novel MAA by *S. avermitilis* SUKA22 transformants carrying the biosynthetic gene cluster for MAA of *A. mirum*. In comparison, *A. mirum* did not produce MAAs under normal cultural conditions (45).

Chemical synthesis/modifications of mycosporine-like amino acids

The attempt at chemical synthesis is driven by the low extraction efficiency from natural sources, the requirement for mass production, and the necessity for reference molecules for chemical analysis. In the initial attempts at the chemical synthesis of mycosporines, D-(-)-quinic acid was utilized as an alluring chemical for the synthesis of mycosporine asymmetrically. It was not feasible to employ this process for large-scale production, however, due to the excessive number of synthesis stages, limited efficiency, and usage of hazardous, combustible components (46). Nevertheless, efforts to chemically produce macosporins and MAAs have been continued. For example, Andreguetti et al provided a description of an effective and environmentally sustainable method for preparing MAA analogs using ultrasound and microwave technology. The MAAs analogs were prepared through a green chemistry method that substitute one oxygen of m-cyclohexanedione by the nitrogen of different amino acids (47). MAAs structures were used for the rational design of efficient sun-protective agents. Result of a study showed that the designed compounds were stable at high temperature, and their solubility in water or organic solvents can be balanced. They have relative similar structure with MAA and can be considered as a good candidate for sunscreen development (48). Researchers have recently made a number of promising UV sunscreens using simple chemical processes. This gives them a source that is good enough to use in cosmetics (2).

Conclusion

MAAs as natural sun-protective agents have been gained great attentions in recent years. Marine derived

bioactive compounds have been applied in a wide range of pharmaceutical and cosmeceutical products with high value market. Focus on MAAs as potential valuable bioactive compounds have been growing day to day. Rather than natural source and direct extraction, heterologous expression of these compounds in more simple and more known biotechnological organisms, such as bacteria and yeast, can be a respectable alternative way for large scale production of MAAs in industrial field. Complete chemical synthesis of these compounds has not yet been approved as a good substituent for natural compound extraction. However, chemical modifications of those be naturally synthesized in high amount can lead to the novel MAAs derivatives with more potent or newly developed potentials for pharmaceutical and cosmeceutical applications.

Authors' contributions

All authors equally contributed to data collection and manuscript writing. All authors read and confirmed the final manuscript.

Conflict of Interest Disclosures

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