Molecular Science

AIMS Molecular Science, 10(4): 295–310.
DOI: 10.3934/molsci.2023017
Received: 27 September 2023
Revised: 16 November 2023
Accepted: 21 November 2023
Published: 27 November 2023

http://www.aimspress.com/journal/Molecular

Mini review

Distribution, biosynthetic regulation, and bioactivities of mycosporine-2-glycine, a rare UV-protective mycosporine-like amino acid

Hakuto Kageyama[1,2,*] and Rungaroon Waditee-Sirisattha[3,*]

[1] Graduate School of Environmental and Human Sciences, Meijo University, 1-501 Shiogamaguchi, Tempaku-ku, Nagoya 468-8502, Aichi, Japan
[2] Department of Chemistry, Faculty of Science and Technology, Meijo University, 1-501 Shiogamaguchi, Tempaku-ku, Nagoya 468-8502, Aichi, Japan
[3] Department of Microbiology, Faculty of Science, Chulalongkorn University, Phayathai Road, Pathumwan, Bangkok 10330, Thailand

* **Correspondence:** Email: kageyama@meijo-u.ac.jp; Rungaroon.W@chula.ac.th; Tel: +81-52-838-2609; +66-2-2185091; Fax: +81-52-832-1179; +66-2-2527576.

Abstract: Mycosporine-like amino acids (MAAs) are ultraviolet (UV)-absorbing substances biosynthesized by specific algae and cyanobacteria. MAAs are thought to contribute to protection against UV radiation in the cells of MAA producers. In addition, it has been reported that MAAs exhibit distinct physiological activities including antioxidant activity, suggesting that they are multifunctional substances. Due to their useful activities, MAAs are also expected to have industrial applications such as skin care, cosmetics and pharmaceuticals. We have focused on mycosporine-2-glycine (M2G), a sole MAA biosynthesized by the halotolerant cyanobacterium *Halothece* sp. PCC7418 (hereafter referred to as *Halothece*). In cyanobacteria, M2G is a rare MAA that has been detected only in halotolerant strains. We have elucidated the biosynthetic pathway of M2G in *Halothece* and partially revealed its intracellular dynamics. In addition, we have reported several important bioactivities of M2G from the viewpoints of skin care and antiaging. This review systematically summarizes the distribution, biosynthetic regulation, and bioactivities of M2G.

Keywords: mycosporine-like amino acid; mycosporine-2-glycine; halotolerant cyanobacteria; osmoprotectant; antioxidant; antiinflammation; antiglycation

Abbreviations:
MAA: mycosporine-like amino acids;
M2G: mycosporine-2-glycine;
4-DG: 4-deoxygadusol;
NRPS: nonribosomal peptide synthetase;
DDG synthase: demethyl 4-deoxygadusol synthase;
HPLC: high performance liquid chromatography;
SOD: superoxide dismutase;
CAT: catalase;
DPPH: 2,2-diphenyl-1-pycrylhydrazyl;
ABTS: azinobis(3-ethyl-2,3-dihydrobenzothiazole-6-sulfonic acid);
IC_{50}: a half maximal (50%) inhibitory concentration;
NF-κB: nuclear factor-κB;
iNOS: inducible nitrogen monoxide synthase;
NO: nitrogen monoxide;
COX-2: cyclooxygenase-2;
PGE_2: prostaglandin E_2;
TNF-α: tumor necrosis factor-α;
IL: interleukin.

1. Introduction

In the biosphere, UV light is perhaps the most influential abiotic factor [1]. UV rays are classified into UV-A (315–400 nm), UV-B (280–315 nm) and UV-C (100–280 nm) [2]. UV-C, which has the highest energy and is highly destructive to living organisms, is completely absorbed by ozone and oxygen molecules in the stratosphere, so it does not reach the Earth's surface. Most UV-B rays are also absorbed by the ozone layer and the atmosphere, so only a small amount reaches the Earth's surface. As a result, the UV radiation that reaches the Earth's surface consists of 95% UV-A and 5% UV-B [3]. Although the amount of radiation that reaches the Earth's surface is small, UV-B is more harmful to living organisms than UV-A due to its higher energy [4]. Both UV-A and UV-B are known to induce photochemical damage to biomolecules such as DNA and proteins [5,6]. Therefore, protecting oneself from UV irradiation is one of the most important survival strategies for living organisms on Earth.

Certain organisms protect themselves from UV radiation by synthesizing UV-absorbing substances. M2G, a UV-absorbing substance, is the topic of this review. M2G belongs to a family of mycosporine-like amino acids (MAAs) which are biosynthesized by various organisms, such as algae, cyanobacteria, and fungi [7]. MAAs are water-soluble low-molecular-weight compounds with a structure in which amino acids are substituted for the core structure of cyclohexanone or cyclohexenimine [8]. Figure 1 shows the chemical structures of typical MAAs including mycosporine-glycine, which has a cyclohexenone structure, and M2G, shinorine, and porphyra-334, which have a cyclohexenimine structure. MAAs are characterized by absorption maxima from 310–362 nm depending on the chemical structures with large molar extinction coefficients (ε = 28, 100–50,000/(M·cm)) [9,10]. MAA's biosynthetic pathways have been elucidated especially in cyanobacteria [11–24]. For a detailed explanation of these biosynthetic pathways, please refer to other reports [25]. Briefly, MAAs are

formed by the binding of amino acids to 4-deoxygadusol (4-DG), a common precursor of MAAs produced from intermediates in the shikimate or pentose phosphate pathways. Generally, the ATP-grasp enzyme first attaches glycine to 4-DG to form mycosporine-glycine. D-Ala-D-Ala ligase or nonribosomal peptide synthetase (NRPS) then attaches another amino acid to mycosporine-glycine to form disubstituted MAAs (Figure 1). Differences in the substrate specificities of D-Ala-D-Ala ligase and NRPS lead to the binding of different amino acids to mycosporine-glycine, which contributes to the diversity of MAAs.

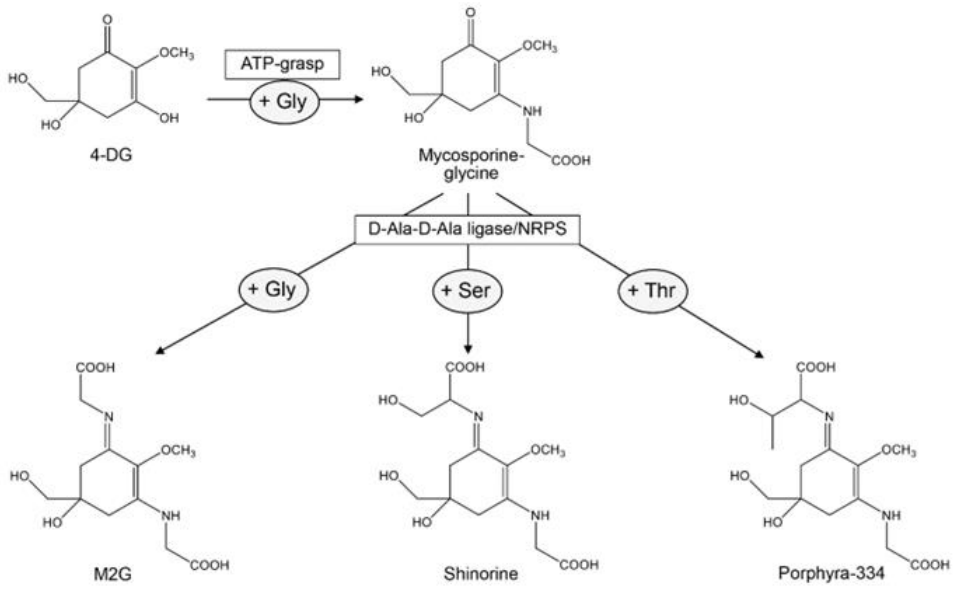

Figure 1. Biosynthetic pathways of MAAs from 4-deoxygadusol (4-DG).

The basic chemical structure of MAAs were revealed for the first time in the 1970s, and subsequently at least 60 kinds of MAA compounds have been discovered thus far [25]. Due to their strong UV absorbability, MAAs have been extensively studied as ingredients for sunscreen agents, and various physiological activities of MAAs have been reported. In such a background, we have developed research focusing on M2G accumulated in the halotolerant cyanobacterium *Halothece*. The purpose of this review is to summarize the findings about M2G that we have uncovered so far. We first characterize the distribution of M2G. Next, we describe the regulation of M2G biosynthesis in response to environmental stresses in *Halothece* cells. Lastly, we will explain the useful physiological activities of M2G that are important from an applied point of view.

2. Distribution of M2G

Among the known MAAs, M2G has a basic chemical structure in which two glycines are attached to a cyclohexenone ring. To date, only a limited number of species have been described that accumulate M2G and these species are listed in Table 1. The existence of M2G was first suggested in the sea anemone *Anthopleura elegantissima* [26].Analysis of zooxanthellate (including zooxanthellae) and apozooxanthellate (lacking zooxanthellae) specimens revealed similar concentrations of M2G-containing MAAs in these specimens, indicating that these compounds do not require symbiosis with

algae for their presence in sea anemones [26]. It was also shown that the accumulation of MAAs in this sea anemone was not controlled by UV irradiation [26]. In other sea anemones, M2G was detected in *Aulactinia marplatensis* and *Oulactis muscosa*, but was not detected in *Anthothoe chilensis* [27]. In corals, M2G has been detected in several species [28]. In the coral *Fungia scutaria*, the M2G levels were significantly higher than other MAAs [28]. It was reported that M2G was also found in the dinoflagellate *Symbiodinium* sp., whose host is the rose coral *Manicina areolata* [29]. A trace amount of M2G was also detected in *Maristentor dinoferus*, a ciliate that hosts *Symbiodinium* sp. [30]. *Symbiodinium* species have been known to produce mycosporine-glycine, shinorine, porphyra-334, and palythine in addition to M2G, and their production ability is thought to be limited to these five MAAs [29]. M2G has also been detected in sea hares and sea urchins. Several MAAs including M2G were detected in the eggs of the sea hare *Aplysia dactylomela* [31]. Among them, mycosporine-glycine was the most abundant. Feeding MAA-rich red algae tended to increase the amount of MAAs in eggs, but it did not increase the M2G content [31]. Ovaries of the sea urchin *Strongylocentrotus droebachiensis* fed the red alga *Chondrus crispus*, which is rich in MAAs, contained shinorine, porphyra-334, M2G, and trace quantities of palythine and asterina-330 [32]. Among diatoms, the accumulation of MAAs has been confirmed in *Thalassiosira* sp. and *Corethron criophilum*, and trace amounts of M2G were detected in *C. criophilum* [33].

Table 1. List of species that accumulate M2G.

Phylum	Species	Reference
Cnidaria (sea anemone)	*Anthopleura elegantissima*	[26]
	Aulactinia marplatensis	[27]
	Oulactis muscosa	[27]
Cnidaria (coral)	*Lobophyllia corymbosa*	[28]
	L. hemprichii	[28]
	Favia pallida	[28]
	F. stelligera	[28]
	Fungia scutaria	[28]
	F. repanda	[28]
	Acropora gemmifera	[28]
	A. formosa	[28]
	A. danai	[28]
	A. paniculata	[28]
Mollusca (sea hare)	*Aplysia dactylomela*	[31]
Echinodermata (sea urchin)	*Strongylocentrotus droebachiensis*	[32]
Myzozoa (dinoflagellate)	*Symbiodinium* sp.	[29]
Ciliophora (algal-bearing ciliate)	*Maristentor dinoferus*	[30]
Gyrista (diatom)	*Corethron criophilum*	[33]
Cyanobacteria	*Halothece* sp. PCC7418	[16]
	Euhalothece sp.	[34]
Bacillota (Gram-positive bacteria)	*Deinococcus radiodurans* R1	[40]

It should be noted that the chemical structure of M2G had not been determined by nuclear magnetic resonance (NMR) analysis in the reports above. In [26], the chemical structure of predicted

M2G, which showed absorption max at 331 nm, was based on the fact that only glycine was detected by alkaline hydrolysis (approximately twice the amount detected from mycosporine-glycine) and confirmation of the protonated mass [MH^+ = 303] by electrospray mass spectrometry analysis. In the case of [30], in addition to the protonated mass, absorption max value (331 nm) was used to identify M2G. In the other reports [27–29,31–33], M2G was identified by comparison of retention time of high-performance liquid chromatography (HPLC) analysis using standard samples. In prokaryotes, M2G has been detected in cyanobacteria and Gram-positive bacteria. In cyanobacteria, although many strains have been reported to biosynthesize and accumulate MAAs, only the halotolerant strains, *Halothece* and *Euhalothece* sp., were found to biosynthesize M2G [16,34]. The chemical structure of M2G was determined using NMR analysis for the first time on the sample produced by *Euhalothece* sp. [34]. After that, our research group found the accumulation of M2G in *Halothece* [16], and later conducted NMR analysis using M2G purified from *Halohtece* [35]. The NMR data we obtained, together with the NMR spectra, were published in the corresponding reference paper [35]. It also showed the protonation mass of M2G ([MH^+ = 303.1187) obtained by high-resolution LC/MS (ESI-TOF^+) analysis and absorption spectrum data of M2G [35]. The genes involved in M2G biosynthesis have been identified in *Halothece*, and several reports have been published on their molecular regulation [16,36–39]. It has also been reported that MAAs including M2G were induced by UV irradiation in an extreme radio-resistant and non-pathogenic Gram-positive bacterium, *Deinococcus radiodurans* R1 [40].

3. Regulation of M2G biosynthesis and environmental stress response in *Halothece* cells

3.1. Discovery of M2G biosynthetic genes in Halothece

In 2010, four MAA synthesis genes (*Ava_3855* to *Ava_3858*) from the cyanobacterium *Anabaena variabilis* ATCC 29413 were reported [12,13]. These genes were closely located in the genome (Figure 2). *Ava_3858* and *Ava_3857* encoded demethyl 4-deoxygadusol (DDG) synthase and *O*-methyltransferase, respectively, and were involved in the production of 4-DG. *Ava_3856* and *Ava_3855* encoded the above-mentioned ATP-grasp enzyme and NRPS, respectively, and produced shinorine. We investigated whether there are genes in the genome of *Halothece* that are homologous to these cyanobacterial MAA synthetic genes [16]. We found three *Halothece* genes, *H1078*, *H1077*, and *H1076*, which corresponded to the *A. variabilis* genes *Ava_3857*, *Ava_3856*, and *Ava_3855*, respectively. These three *Halothece* genes were adjacent to each other in the genome (Figure 2). On the other hand, the *Halothece H1590* gene (encoding the DDG synthase), which corresponded to the *A. variabilis Ava_3858* gene was present at a distant position in the *Halothece* genome (Figure 2). In addition, an extra sequence of unknown function was attached to the N-terminus of the *Halothece* H1590 protein (Figure 2). M2G biosynthesis was achieved by introducing these genes into *Escherichia coli* cells, confirming that these genes are responsible for M2G biosynthesis [16]. As for the MAA biosynthetic gene cluster structure, *A. variabilis* ATCC 29413 was the earliest example reported, so this structure tends to be recognized as a basic type, but in fact there are many exceptions such as *Halothece*. See other references for details [25,41].

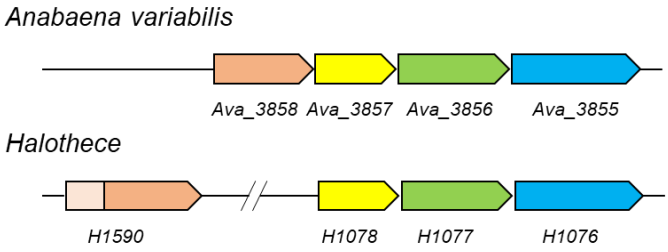

Figure 2. MAA biosynthetic genes in *Anabaena variabilis* ATCC 29413 and *Halothece*.

3.2. Environmental factors involved in M2G accumulation in Halothece

It has been previously reported that various cyanobacterial strains, such as *A. variabilis*, *A. doliolum*, *Nostoc commune*, and *Arthrospira* sp., increase the accumulation of MAAs after UV irradiation [42–45]. In general, UV-B appears to be more effective at inducing MAA biosynthesis than UV-A [7]. Similar to these cases, the accumulation of M2G in *Halothece* strains was also found to be significantly induced by UV-B irradiation [16].

In addition to UV-B irradiation, it was revealed that several environmental factors affected the accumulation of M2G in *Halothece*. Among them, the most significant inducer of M2G accumulation was salt stress. Under a low salinity condition (0.5 M NaCl), the amount of M2G accumulated in *Halothece* was small, but after shifting to a high salinity condition (2.5 M NaCl), the amount of M2G accumulation significantly increased [16]. The expression of all of the *Halothece* M2G biosynthetic genes *H1590* and *H1078-H1076* were induced when exposed to high salinity stress, suggesting that high expression of these genes is directly linked to the induction of M2G biosynthesis [36]. Sucrose-mediated osmotic stress also significantly induced M2G, although not as much as NaCl stress [38]. In addition, temperature has been shown to be involved in inducing M2G accumulation. A high temperature shock from 30°C to 37°C did not significantly affect M2G accumulation, whereas a cold shock from 30 ℃ to 23 ℃ significantly increased M2G accumulation [37]. On the other hand, M2G biosynthesis in *Halothece* was suppressed under sulfur-, nitrogen-, or phosphorus-deficient stress [38]. Conversely, an excessive supply of nitrate and addition of an appropriate amount of glycine or serine increased the accumulation of M2G in *Halothece* [36].

3.3. Putative physiological roles of M2G in Halothece cells

Intracellularly accumulated M2G is thought to perform multiple physiological functions in *Halothece* cells. First, as mentioned above, M2G was induced by UV-B irradiation [16], suggesting that it contributes to UV protection. Furthermore, it was recently found that M2G accumulation in *Halothece* circadianly oscillates. Intracellular accumulation of M2G increased during subjective daytime and decreased during subjective nighttime [39]. It is conceivable that M2G accumulates during the daytime UV exposure stress under natural environmental conditions to protect against UV irradiation. However, it should be noted that circadian oscillation of intracellular M2G accumulation was observed only under low salt conditions, and that the oscillation disappeared under high salinity conditions [39]. This is probably due to overexpression of M2G biosynthetic genes under high salinity conditions, which masked the circadian expression rhythm.

In addition to the UV protection role, M2G is thought to act as a compatible solute to regulate osmotic pressure in *Halothece* since M2G was significantly induced by salt stress and osmotic stress [16,38]. The introduction of M2G biosynthetic genes into *E. coli* cells conferred salt stress resistance of the transformed cells [46], supporting this hypothesis. It should be noted that M2G might not be the primary compatible solute in salt-stressed *Halothece* because glycine betaine, a major compatible solute, was accumulated to much greater levels than M2G in salt-stressed *Halothece* [36,47]. Since the biosynthesis of M2G responded more quickly to salt stress than that of glycine betaine [36], M2G may function early in the process of adaptation to a high salinity environment as an auxiliary compatible solute.

M2G may also be involved in the oxidative stress resistance mechanism that accompanies UV irradiation stress and salt stress. We reported that M2G exhibited antioxidant activity (details will be described later). We also found that the model cyanobacterium *Synechococcus elongatus* PCC7942 that was engineered to accumulate M2G by introduction of *Halothece* M2G biosynthetic genes exhibited resistance to oxidative stress induced by hydrogen peroxide. In this transformant strain, the upregulation of antioxidant defense-related genes for superoxide dismutase (*sodB*), catalase (*cat*), and 2-Cys peroxiredoxin (*tpxA*) was observed under oxidative stress conditions [48]. This result suggested that M2G can regulate the expression of genes involved in antioxidant defense in cyanobacteria.

4. Bioactivities of M2G from an application perspective

4.1. Antioxidative activity

Many MAA molecules have been reported to exhibit antioxidant activity [49]. Although the relationship between the chemical structure of MAA molecules and the degree of antioxidant activity has not yet been clarified, different types of MAAs have shown different degrees of activity. M2G exhibited radical scavenging activities using 2,2-diphenyl-1-pycrylhydrazyl (DPPH) and azinobis(3-ethyl-2,3-dihydrobenzothiazole-6-sulfonic acid) (ABTS) radicals. Cheewinthamrongrod et al. reported a half maximal (50%) inhibitory concentration (IC_{50}) value of 22 μM for the DPPH radical scavenging activity of M2G [50]. This value was lower than the IC_{50} value of 43 μM for mycosporine-glycine, which has been reported to have high antioxidant activity, and is comparable to the IC_{50} value of the well-known antioxidant ascorbic acid (2.8 μM) [50]. On the other hand, the IC_{50} value for porphyra-334 was 3.4 mM, which was much higher than that for M2G, and palythine showed no activity [51]. Thus, the DPPH assay demonstrated the high antioxidant capacity of M2G. Similarly, the ABTS assay also detected excellent radical scavenging activity of M2G. We reported that the IC_{50} values for ABTS radical scavenging by M2G, porphyra-334, and shinorine were 40, 133, and 94 μM, respectively, using highly purified compounds [35]. Trolox, a potent antioxidant used as a control in this experiment, had an IC_{50} value of 10 μM [35]. Table 2 shows the IC_{50} values for other MAAs using similar assay systems. Although a simple comparison cannot be made due to distinct experimental environments from different research groups, the relatively low IC_{50} value of M2G suggests that M2G is a good antioxidant. It would be interesting to uncover the antioxidant mechanism of action of MAAs including M2G in detail. These future studies may include not only the radical scavenging assays described above but also analysis using other antioxidant activity assays, such as scavenging singlet oxygen molecules and inhibiting lipid peroxide formation.

Table 2. The radical scavenging activities (IC_{50} values) of selected MAAs

Assay	MAAs	IC_{50} (μM)	Reference
DPPH	Mycosporine-glycine	4.2	[52]
		43	[50]
	Mycosporine-alanine	7600	[19]
	Shinorine	-	[52]
		399	[53]
	Porphyra-334	-	[52]
		3400	[50]
		185	[53]
	M2G	22	[50]
	Palythine	21	[53]
	7-O-(β-arabinopyranosyl)-porphyra-334	-	[54]
	Mycosporine-2-(4-deoxygadusol-ornithine)-β-xylopyranosyl-β-galactopyranoside	809	[54]
ABTS	Mycosporine-glycine	20 (pH6.0), 4 (pH7.5), 3 (pH8.5)	[51]
	Mycosporine-GABA	600	[55]
	Shinorine	- (pH6.0), - (pH7.5), 100 (pH8.5)	[51]
		94	[35]
	Porphyra-334	1000 (pH6.0), 400 (pH7.5), 80 (pH8.5)	[51]
		133	[35]
		>72 (pH5.8), >72 (pH6.6), 28 (pH7.4), 21 (pH8.0)	[56]
	M2G	40	[35]
	Asterina-330	1000 (pH6.0), 60 (pH7.5), 10 (pH8.5)	[51]
	Palythine	>72 (pH5.8), >72 (pH6.6), 23 (pH7.4), 12 (pH8.0)	[56]
	7-O-(β-arabinopyranosyl)-porphyra-334	9500	[55]
	Hexose-bound porphyra-334	58000	[55]
	Two hexose-bound palythine-threonine derivatives	16000	[55]
	Nostoc-756	515	[57]
	{Mycosporine-ornithine: 4-deoxygadusol ornithine}-β-xylopyranosyl-β-galactopyranoside	510	[55]
	Mycosporine-2-(4-deoxygadusol-ornithine)-β-xylopyranosyl-β-galactopyranoside	1040	[55]
		144	[57]
	13-O-(β-galactosyl)-porphyra-334	17000	[58]

Recently, it was found that application of M2G to the skin of mice affected the expression of genes involved in the antioxidant system in skin tissue. The reduction in SOD protein and CAT protein due to UV irradiation was inhibited by application of an emulsion containing M2G [59]. This result indicated that the application of M2G alleviates the UV irradiation-mediated decrease in reactive oxygen species scavenging in the skin tissue. In addition, when cultured human skin cells were subjected to oxidative stress using hydrogen peroxide, the addition of M2G to the medium restored the survival rate and alleviated DNA damage [50]. Thus, M2G is considered to be useful as a sunscreen agent and it also has an antioxidant effect. The molecular mechanism by which M2G regulates the expression of these antioxidant genes remains unknown. It is possible that the molecular activities of M2G, such as its antioxidant activity, may be related to regulation of the expression of antioxidant genes. This is one of the interesting research topics for future studies.

4.2. Anti-inflammatory activity

Inflammation is a physiological defense system against molecular and cellular damage induced by various stresses. Stress factors associated with inflammation include UV irradiation stress, oxidative stress, infection, and exposure to bacterial endotoxic lipopolysaccharides (LPS) [60]. The molecular responses induced by inflammatory stimuli are mediated by nuclear factor-κB (NF-κB)-regulated proteins, including inducible nitrogen monoxide synthase (iNOS), nitrogen monoxide (NO), cyclooxygenase-2 (COX-2), prostaglandin E_2 (PGE_2), tumor necrosis factor-α (TNF-α), and cytokines, such as interleukin-1 (IL-1) and IL-6 [61]. For example, it has been reported that UV-B irradiation induced the expression of *COX-2* and concomitantly stimulates the production of PGE_2, which can induce inflammation and cancer [62]. Thus, compounds exhibiting anti-inflammatory effects are not only important for skin care but are also useful for treating various diseases.

Several MAAs are known to exhibit anti-inflammatory effects. Tarasuntisuk et al. reported that M2G markedly inhibited NO production in RAW 264.7 macrophages treated with LPS [63]. In the same report, mycosporine-glycine, porphyra-334, and palythine did not show significant inhibitory effects against NO production [63]. In addition, M2G showed an inhibitory effect on the expression of *iNOS* and *COX-2* genes [63]. It was also reported that M2G inhibited the hydrogen peroxide-mediated induction of NF-κB protein in cultured human skin cells [50]. Among other MAAs, porphyra-334, shinorine, and mycosporine-glycine showed anti-inflammatory effects. Becker et al. reported that in THP-1-Blue cells, the addition of porphyra-334 to the medium inhibited the LPS-mediated induction of NF-κB activity [64]. Ying et al. also showed that application of an aqueous solution containing a mixture of shinorine and porphyra-334 to the dorsal skin of mice inhibited the UV irradiation-induced *NF-κB, IL-1β,* and *IL-6* gene expression [65]. Moreover, Suh et al. reported that addition of shinorine or mycosporine-glycine to the medium of HaCaT cells inhibited the upregulation of the *COX-2* gene induced by UV irradiation [52]. Thus, MAAs, including M2G, have potential applications in the pharmaceutical field as compounds with anti-inflammatory effects.

4.3. Anti-glycative activity

Glycation, also known as the Maillard reaction, is a series of chemical reactions in which sugar molecules are nonenzymatically attached to free amino and hydroxyl groups of biological compounds such as proteins and lipids [66]. The final products of glycation reactions, which are formed when free

amino groups of proteins react with reducing sugars such as glucose, are called advanced glycation end products (AGEs) [67]. Accumulation of AGEs impairs the structure and function of intracellular proteins, reduces enzymatic activity, and affects biological phenomena such as tissue homeostasis and regulation of gene expression, leading to various diseases [68–70]. It is also known that the accumulation of AGEs increases with aging [71].

We reported for the first time that MAAs exhibited antiglycation activity. The first report by Tarasuntisuk et al. demonstrated the ability of M2G to inhibit glycation-dependent lysozyme cross-linking. The IC_{50} values for M2G and porphyra-334 against cross-linking lysozyme dimer formation were 1.6 and 4.7 mM, respectively [72]. Considering that the IC_{50} value of aminoguanidine, a well-known glycation inhibitor, was 4.7 mM, it was suggested that M2G has excellent antiglycation activity [72]. Recently, we examined the inhibitory effects of purified M2G, shinorine, and porphyra-334 on the glyceraldehyde-dependent glycation reaction of collagen, elastin, and bovine serum albumin (BSA) *in vitro* [59]. We confirmed that porphyra-334 inhibited the glycation of elastin, but M2G did not show significant activity [59]. The mechanism by which the degree of inhibitory activity changes depending on the type of MAA and the type of target protein is not well understood. Besides the results above, we reported that putative pentose-bound shinorine and arabinose-bound porphyra-334 inhibited glycation-dependent lysozyme cross-linking [73]. In addition, Hartmann's research group as well reported the inhibitory effect of 10 MAAs on BSA glycation [9].

4.4. Inhibitory activity against collagenase

In vertebrates, collagen, a fibrous protein that constitutes various tissues such as skin and bones, accounts for 30% of the total human protein content [74]. Collagenase inhibitors are useful for antiaging because the reduction or degeneration of collagen causes tissue aging. MAAs are known to exhibit collagenase inhibitory activity. Hartmann et al. was the first to reveal that shinorine, palythine, and porphyra-334 inhibit bacterial collagenase activity [75]. Subsequently, we analyzed 10 additional MAAs and reported that asteria-330 showed the highest collagenase inhibitory effect (IC_{50} = 58.4 μM) [9]. We also performed experiments with M2G and porphyra-334 and reported IC_{50} values for inhibition of bacterial collagenase activity of 0.47 and >10 mM, respectively. Thus, our results indicated a greater collagenase inhibitory effect of M2G compared to porphyra-334. Since collagenase is a metalloprotease, it is speculated that the high metal chelating activity of M2G may be involved in the inhibition of collagenase activity [72,76].

5. Conclusions and future perspective

MAAs are natural compounds that have been utilized as active pharmaceutical ingredients for cosmetics and they are attracting attention for other industrial purposes. In this review, we focused on M2G and introduced potential applications for this multi-functional MAA. These activities of M2G are important from the viewpoint of skin care and are expected to support the development of various applications of MAAs including M2G. However, since the mechanism of action of these activities has not been clarified, further detailed investigation is essential. In order to widely develop MAAs for industrial use, strategies for MAA production are also important. At present, chemical synthesis of MAAs is difficult, and the establishment of new basic technologies such as production process technology using microorganisms is desired. For example, recently, it has been reported that MAAs,

including M2G, could be efficiently bioproduced by the introduction of cyanobacterial MAA synthetic genes into yeast [23].

Use of AI tools declaration

The authors declare they have not used Artificial Intelligence (AI) tools in the creation of this article.

Acknowledgments

This work was supported in part by the research support fund of the Research Institute of Meijo University.

Conflict of interest

The authors declare no conflict of interest.

References

1. Banaszak AT, Lesser MP (2009) Effects of solar ultraviolet radiation on coral reef organisms. *Photochem Photobiol Sci* 8: 1276–1294. https://doi.org/10.1039/b902763g
2. Gao Q, Garcia-Pichel F (2011) Microbial ultraviolet sunscreens. *Nat Rev Microbiol* 9: 791–802. https://doi.org/10.1038/nrmicro2649
3. Jallad KN (2017) Chemical characterization of sunscreens composition and its related potential adverse health effects. *J Cosmet Dermatol* 16: 353–357. https://doi.org/10.1111/jocd.12282
4. Gruber F, Peharda V, Kastelan M, et al. (2007) Occupational skin diseases caused by UV radiation. *Acta Dermatovenerol Croat* 15: 191–198.
5. Ikehata H (2018) Mechanistic considerations on the wavelength-dependent variations of UVR genotoxicity and mutagenesis in skin: The discrimination of UVA-signature from UV-signature mutation. *Photochem Photobiol Sci* 17: 1861–1871. https://doi.org/10.1039/c7pp00360a
6. Brown N, Donovan F, Murray P, et al. (2014) Cyanobacteria as bio-factories for production of UV-screening compounds. *OA Biotechnol* 3: 6.
7. Kageyama H, Waditee-Sirisattha R (2018) Mycosporine-like amino acids as multifunctional secondary metabolites in cyanobacteria: From biochemical to application aspects. In: *Studies in natural products chemistry*. Amsterdam, Netherlands: Elsevier. 153–194. https://doi.org/10.1016/B978-0-444-64179-3.00005-0
8. Wada N, Sakamoto T, Matsugo S (2015) Mycosporine-like amino acids and their derivatives as natural antioxidants. *Antioxidants (Basel)* 4: 603–646. https://doi.org/10.3390/antiox4030603
9. Orfanoudaki M, Hartmann A, Alilou M, et al. (2020) Absolute configuration of mycosporine-like amino acids, their wound healing properties and in vitro anti-aging effects. *Mar Drugs* 18: 35. https://doi.org/10.3390/md18010035
10. Pangestuti R, Shin KH, Kim SK (2021) Anti-photoaging and potential skin health benefits of seaweeds. *Mar Drugs* 19: 172. https://doi.org/10.3390/md19030172

11. Favre-Bonvin J, Bernillon J, Salin N, et al. (1987) Biosynthesis of mycosporines: Mycosporine glutaminol in *Trichothecium roseum*. *Phytochemistry* 26: 2509–2514. https://doi.org/10.1016/S0031-9422(00)83866-2
12. Singh SP, Klisch M, Sinha RP, et al. (2010) Genome mining of mycosporine-like amino acid (MAA) synthesizing and non-synthesizing cyanobacteria: A bioinformatics study. *Genomics* 95: 120–128. https://doi.org/10.1016/j.ygeno.2009.10.002
13. Balskus EP, Walsh CT (2010) The genetic and molecular basis for sunscreen biosynthesis in cyanobacteria. *Science* 329: 1653–1656. https://doi.org/10.1126/science.1193637
14. Spence E, Dunlap WC, Shick JM, et al. (2012) Redundant pathways of sunscreen biosynthesis in a cyanobacterium. *Chembiochem* 13: 531–533. https://doi.org/10.1002/cbic.201100737
15. Pope MA, Spence E, Seralvo V, et al. (2015) *O*-Methyltransferase is shared between the pentose phosphate and shikimate pathways and is essential for mycosporine-like amino acid biosynthesis in *Anabaena variabilis* ATCC 29413. *Chembiochem* 16: 320–327. https://doi.org/10.1002/cbic.201402516
16. Waditee-Sirisattha R, Kageyama H, Sopun W, et al. (2014) Identification and upregulation of biosynthetic genes required for accumulation of Mycosporine-2-glycine under salt stress conditions in the halotolerant cyanobacterium *Aphanothece halophytica*. *Appl Environ Microbiol* 80: 1763–1769. https://doi.org/10.1128/AEM.03729-13
17. Katoch M, Mazmouz R, Chau R, et al. (2016) Heterologous production of cyanobacterial mycosporine-like amino acids mycosporine-ornithine and mycosporine-lysine in *Escherichia coli*. *Appl Environ Microbiol* 82: 6167–6173. https://doi.org/10.1128/AEM.01632-16
18. Zhang ZC, Wang K, Hao FH, et al. (2021) New types of ATP-grasp ligase are associated with the novel pathway for complicated mycosporine-like amino acid production in desiccation-tolerant cyanobacteria. *Environ Microbiol* 23: 6420–6432. https://doi.org/10.1111/1462-2920.15732
19. Saha S, Sen A, Mandal S, et al. (2021) Mycosporine-alanine, an oxo-mycosporine, protect *Hassallia byssoidea* from high UV and solar irradiation on the stone monument of Konark. *J Photochem Photobiol B:* 224: 112302. https://doi.org/10.1016/j.jphotobiol.2021.112302
20. Chen M, Rubin GM, Jiang G, et al. (2021) Biosynthesis and heterologous production of mycosporine-like amino acid palythines. *J Org Chem* 86: 11160–11168. https://doi.org/10.1021/acs.joc.1c00368
21. D'Agostino PM, Javalkote VS, Mazmouz R, et al. (2016) Comparative profiling and discovery of novel glycosylated mycosporine-like amino acids in two strains of the cyanobacterium *Scytonema* cf. *crispum*. *Appl Environm Microbiol* 82: 5951–5959. https://doi.org/10.1128/AEM.01633-16
22. Shang JL, Zhang ZC, Yin XY, et al. (2018) UV-B induced biosynthesis of a novel sunscreen compound in solar radiation and desiccation tolerant cyanobacteria. *Environm Microbiol* 20: 200–213. https://doi.org/10.1111/1462-2920.13972
23. Kim S, Park BG, Jin H, et al. (2023) Efficient production of natural sunscreens shinorine, porphyra-334, and mycosporine-2-glycine in *Saccharomyces cerevisiae*. *Metab Eng* 78: 137–147. https://doi.org/10.1016/j.ymben.2023.05.009
24. Kageyama H, Waditee-Sirisattha R (2022) Mycosporine-like amino acids and scytonemin: Regulations, roles for adaptation of cyanobacteria to the environment, and potential applications. In: *Cyanobacterial physiology: From fundamentals to biotechnology*. SanDiego, CA, USA: Academic Press. 101–111. https://doi.org/10.1016/B978-0-323-96106-6.00016-2

25. Kageyama H (2023) *An introduction to mycosporine-like amino acids*. Singapore: Bentham Science Publishers. https://doi.org/10.2174/9789815136081123010l
26. Stochaj WR, Dunlap WC, Shick JM (1994) Two new UV-absorbing mycosporine-like amino acids from the sea anemone *Anthopleura elegantissima* and the effects of zooxanthellae and spectral irradiance on chemical composition and content. *Mar Biol* 118: 149–156. https://doi.org/10.1007/BF00699229
27. Arbeloa EM, Carignan MO, Acuña FH, et al. (2010) Mycosporine-like amino acid content in the sea anemones *Aulactinia marplatensis*, *Oulactis muscosa* and *Anthothoe chilensis*. *Comp Biochem Physiol B Biochem Mol Biol* 156: 216–221. https://doi.org/10.1016/j.cbpb.2010.03.011
28. Teai T, Drollet JH, Bianchini J-P, et al. (1997) Widespread occurrence of mycosporine-like amino acid compounds in scleractinians from French Polynesia. *Coral Reefs* 16: 169–176. https://doi.org/10.1007/s003380050071
29. Banaszak AT, Santos MGB, LaJeunesse TC, et al. (2006) The distribution of mycosporine-like amino acids (MAAs) and the phylogenetic identity of symbiotic dinoflagellates in cnidarian hosts from the Mexican Caribbean. *J Exp Mar Biol Ecol* 337: 131–146. https://doi.org/10.1016/j.jembe.2006.06.014
30. Sommaruga R, Whitehead K, Shick JM, et al. (2006) Mycosporine-like amino acids in the zooxanthella-ciliate symbiosis *Maristentor dinoferus*. *Protist* 157: 185–191. https://doi.org/10.1016/j.protis.2006.01.002
31. Carefoot TH, Harris M, Taylor BE, et al. (1998) Mycosporine-like amino acids: Possible UV protection in eggs of the sea hare *Aplysia dactylomela*. *Mar Biol* 130: 389–396. https://doi.org/10.1007/s002270050259
32. Adams NL, Shick JM, Dunlap WC (2001) Selective accumulation of mycosporine-like amino acids in ovaries of the green sea urchin Strongylocentrotus droebachiensis is not affected by ultraviolet radiation. *Mar Biol* 138: 281–294. https://doi.org/10.1007/s002270000464
33. Helbling EW, Chalker BE, Dunlap WC, et al. (1996) Photoacclimation of antarctic marine diatoms to solar ultraviolet radiation. *J Exp Mar Biol Ecol* 204: 85–101. https://doi.org/10.1016/0022-0981(96)02591-9
34. Kedar L, Kashman Y, Oren A (2002) Mycosporine-2-glycine is the major mycosporine-like amino acid in a unicellular cyanobacterium (*Euhalothece* sp.) isolated from a gypsum crust in a hypersaline saltern pond. *FEMS Microbiol Lett* 208: 233–237. https://doi.org/10.1111/j.1574-6968.2002.tb11087.x
35. Ngoennet S, Nishikawa Y, Hibino T, et al. (2018) A method for the isolation and characterization of mycosporine-like amino acids from cyanobacteria. *Methods Protoc* 1: 46. https://doi.org/10.3390/mps1040046
36. Waditee-Sirisattha R, Kageyama H, Fukaya M, et al. (2015) Nitrate and amino acid availability affects glycine betaine and mycosporine-2-glycine in response to changes of salinity in a halotolerant cyanobacterium *Aphanothece halophytica*. *FEMS Microbiol Lett* 362: fnv198. https://doi.org/10.1093/femsle/fnv198
37. Patipong T, Hibino T, Waditee-Sirisattha R, et al. (2019) Induction of antioxidative activity and antioxidant molecules in the halotolerant cyanobacterium *Halothece* sp. PCC7418 by temperature shift. *Nat Prod Commun* 14: 1–6. https://doi.org/10.1177/1934578X19865680

38. Waditee-Sirisattha R, Kageyama H (2022) Global transcriptome analyses and regulatory mechanisms in *Halothece* sp. PCC 7418 exposed to abiotic stresses. *Appl Microbiol Biotechnol* 106: 6641–6655. https://doi.org/10.1007/s00253-022-12163-y
39. Waditee-Sirisattha R, Ito H, Kageyama H (2022) Global transcriptional and circadian regulation in a halotolerant cyanobacterium *Halothece* sp. PCC7418. *Sci Rep* 12: 13190. https://doi.org/10.1038/s41598-022-17406-6
40. Huwaidi A, Ahmad KA, Magdy M, et al. (2020) Identification of mycosporine-like amino acids and expression of 3-dehydroquinate synthase gene in UV radiations-induced *Deinococcus radiodurans* R1. *Malays Soc Biochem Mol Biol* 23: 19–29.
41. Kageyama H, Waditee-Sirisattha R, Tanaka Y, et al. (2017) Osmoprotectant and sunscreen molecules from halophilic algae and cyanobacteria. In: *Algal green chemistry*. Amsterdam, Netherlands: Elsevier. https://doi.org/10.1016/B978-0-444-63784-0.00001-1
42. Sinha RP, Klisch M, Helbling EW, et al. (2001) Induction of mycosporine-like amino acids (MAAs) in cyanobacteria by solar ultraviolet-B radiation. *J Photochem Photobiol B* 60: 129–135. https://doi.org/10.1016/s1011-1344(01)00137-3
43. Singh SP, Sinha RP, Klisch M, et al. (2008) Mycosporine-like amino acids (MAAs) profile of a rice-field cyanobacterium *Anabaena doliolum* as influenced by PAR and UVR. *Planta* 229: 225–233. https://doi.org/10.1007/s00425-008-0822-1
44. Singh SP, Klisch M, Sinha RP, et al. (2008) Effects of abiotic stressors on synthesis of the mycosporine-like amino acid shinorine in the cyanobacterium *Anabaena variabilis* PCC 7937. *Photochem Photobiol* 84: 1500–1505. https://doi.org/10.1111/j.1751-1097.2008.00376.x
45. Rastogi RP, Incharoensakdi A (2014) Analysis of UV-absorbing photoprotectant mycosporine-like amino acid (MAA) in the cyanobacterium *Arthrospira* sp. CU2556. *Photochem Photobiol Sci* 13: 1016–1024. https://doi.org/10.1039/c4pp00013g
46. Patipong T, Hibino T, Waditee-Sirisattha R, et al. (2017) Efficient bioproduction of mycosporine-2-glycine, which functions as potential osmoprotectant, using *Escherichia coli* cells. *Nat Prod Commun* 12: 1593–1594. https://doi.org/10.1177/1934578X1701201017
47. Waditee-Sirisattha R, Kageyama H (2023) Halotolerance, stress mechanisms, and circadian clock of salt-tolerant cyanobacteria. *Appl Microbiol Biotechnol* 107: 1129–1141. https://doi.org/10.1007/s00253-023-12390-x
48. Pingkhanont P, Tarasuntisuk S, Hibino T, et al. (2019) Expression of a stress-responsive gene cluster for mycosporine-2-glycine confers oxidative stress tolerance in *Synechococcus elongatus* PCC7942. *FEMS Microbiol Lett* 366: fnz115. https://doi.org/10.1093/femsle/fnz115
49. Waditee-Sirisattha R, Kageyama H, Takabe T (2016) Halophilic microorganism resources and their applications in industrial and environmental biotechnology. *AIMS Microbiol* 2: 42–54. https://doi.org/10.3934/microbiol.2016.1.42
50. Cheewinthamrongrod V, Kageyama H, Palaga T, et al. (2016) DNA damage protecting and free radical scavenging properties of mycosporine-2-glycine from the Dead Sea cyanobacterium in A375 human melanoma cell lines. *J Photochem Photobiol B* 164: 289–295. https://doi.org/10.1016/j.jphotobiol.2016.09.037
51. de la Coba F, Aguilera J, Figueroa FL, et al. (2009) Antioxidant activity of mycosporine-like amino acids isolated from three red macroalgae and one marine lichen. *J Appl Phycol* 21: 161–169. https://doi.org/10.1007/s10811-008-9345-1

52. Suh SS, Hwang J, Park M, et al. (2014) Anti-inflammation activities of mycosporine-like amino acids (MAAs) in response to UV radiation suggest potential anti-skin aging activity. *Mar Drugs* 12: 5174-5187. https://doi.org/10.3390/md12105174
53. Gacesa R, Lawrence KP, Georgakopoulos ND, et al. (2018) The mycosporine-like amino acids porphyra-334 and shinorine are antioxidants and direct antagonists of Keap1-Nrf2 binding. *Biochimie* 154: 35–44. https://doi.org/10.1016/j.biochi.2018.07.020
54. Matsui K, Nazifi E, Kunita S, et al. (2011) Novel glycosylated mycosporine-like amino acids with radical scavenging activity from the cyanobacterium *Nostoc commune*. *J Photochem Photobiol B* 105: 81–89. https://doi.org/10.1016/j.jphotobiol.2011.07.003
55. Nazifi E, Wada N, Asano T, et al. (2015) Characterization of the chemical diversity of glycosylated mycosporine-like amino acids in the terrestrial cyanobacterium *Nostoc commune*. *J Photochem Photobiol B* 142: 154–168. https://doi.org/10.1016/j.jphotobiol.2014.12.008
56. Nishida Y, Kumagai Y, Michiba S, et al. (2020) Efficient extraction and antioxidant capacity of mycosporine-like amino acids from red alga dulse *Palmaria palmata* in Japan. *Mar Drugs* 18: 502. https://doi.org/10.3390/md18100502
57. Sakamoto T, Hashimoto A, Yamaba M, et al. (2019) Four chemotypes of the terrestrial cyanobacterium Nostoc commune characterized by differences in the mycosporine-like amino acids. *Phycol Res* 67: 3–11. https://doi.org/10.1111/pre.12333
58. Ishihara K, Watanabe R, Uchida H, et al. (2017) Novel glycosylated mycosporine-like amino acid, 13-O-(beta-galactosyl)-porphyra-334, from the edible cyanobacterium *Nostoc sphaericum*-protective activity on human keratinocytes from UV light. *Journal of Photochemistry and Photobiology B: Biology* 172: 102–108. https://doi.org/10.1016/j.jphotobiol.2017.05.019
59. Waditee-Sirisattha R, Kageyama H (2021) Protective effects of mycosporine-like amino acid-containing emulsions on UV-treated mouse ear tissue from the viewpoints of antioxidation and antiglycation. *J Photochem Photobiol B* 223: 112296. https://doi.org/10.1016/j.jphotobiol.2021.112296
60. Newton K, Dixit VM (2012) Signaling in innate immunity and inflammation. *Cold Spring Harbor Perspect Biol* 4: a006049. https://doi.org/10.1101/cshperspect.a006049
61. Radhiga T, Agilan B, Muzaffer U, et al. (2016) Phytochemicals as modulators of ultraviolet-b radiation induced cellular and molecular events: A review. *J Radiat Cancer Res* 7: 2–12. https://doi.org/10.4103/0973-0168.184607
62. Rundhaug JE, Fischer SM (2008) Cyclo-oxygenase-2 plays a critical role in UV-induced skin carcinogenesis. *Photochem Photobiol* 84: 322-329. 10.1111/j.1751-1097.2007.00261.x
63. Tarasuntisuk S, Palaga T, Kageyama H, et al. (2019) Mycosporine-2-glycine exerts anti-inflammatory and antioxidant effects in lipopolysaccharide (LPS)-stimulated RAW 264.7 macrophages. *Arch Biochem Biophys* 662: 33-39. https://doi.org/10.1016/j.abb.2018.11.026
64. Becker K, Hartmann A, Ganzera M, et al. (2016) Immunomodulatory effects of the mycosporine-like amino acids shinorine and porphyra-334. *Mar Drugs* 14: 119. https://doi.org/10.3390/md14060119
65. Ying R, Zhang Z, Zhu H, et al. (2019) The protective effect of mycosporine-like amino acids (MAAs) from *Porphyra yezoensis* in a mouse model of UV irradiation-induced photoaging. *Mar Drugs* 17: 470. https://doi.org/10.3390/md17080470

66. Fournet M, Bonte F, Desmouliere A (2018) Glycation damage: A possible hub for major pathophysiological disorders and aging. *Aging Dis* 9: 880–900. https://doi.org/10.14336/AD.2017.1121
67. Freund MA, Chen B, Decker EA (2018) The inhibition of advanced glycation end products by carnosine and other natural dipeptides to reduce diabetic and age-related complications. *Compr Rev Food Sci Food Saf* 17: 1367–1378. https://doi.org/10.1111/1541-4337.12376
68. Uribarri J, Cai W, Peppa M, et al. (2007) Circulating glycotoxins and dietary advanced glycation endproducts: two links to inflammatory response, oxidative stress, and aging. *J Gerontol A Biol Sci Med Sci* 62: 427–433. https://doi.org/10.1093/gerona/62.4.427
69. Matsuura N, Aradate T, Kurosaka C, et al. (2014) Potent protein glycation inhibition of plantagoside in Plantago major seeds. *Biomed Res Int* 2014: 208539. https://doi.org/10.1155/2014/208539
70. Münch G, Thome J, Foley P, et al. (1997) Advanced glycation endproducts in ageing and Alzheimer's disease. *Brain Res Brain Res Rev* 23: 134–143. https://doi.org/10.1016/s0165-0173(96)00016-1
71. Peng X, Ma J, Chen F, et al. (2011) Naturally occurring inhibitors against the formation of advanced glycation end-products. *Food Funct* 2: 289–301. https://doi.org/10.1039/c1fo10034c
72. Tarasuntisuk S, Patipong T, Hibino T, et al. (2018) Inhibitory effects of mycosporine-2-glycine isolated from a halotolerant cyanobacterium on protein glycation and collagenase activity. *Lett Appl Microbiol* 67: 314–320. https://doi.org/10.1111/lam.13041
73. Korteerakul C, Honda M, Ngoennet S, et al. (2020) Antioxidative and antiglycative properties of mycosporine-like amino acids-containing aqueous extracts derived from edible terrestrial cyanobacteria. *J Nutr Sci Vitaminol* 66: 339–346. https://doi.org/10.3177/jnsv.66.339
74. Yu CH, Khare E, Narayan OP, et al. (2022) ColGen: An end-to-end deep learning model to predict thermal stability of de novo collagen sequences. *J Mech Behav Biomed Mater* 125: 104921. https://doi.org/10.1016/j.jmbbm.2021.104921
75. Hartmann A, Gostner J, Fuchs JE, et al. (2015) Inhibition of collagenase by mycosporine-like amino acids from marine sources. *Planta Med* 81: 813–820. https://doi.org/10.1055/s-0035-1546105
76. Varnali T, Bozoflu M, Şengönül H, et al. (2022) Potential metal chelating ability of mycosporine-like amino acids: Acomputational research. *Chem Pap* 76: 2279–2291. https://doi.org/10.1007/s11696-021-02014-x

AIMS Press