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Natural Products – Review

Recent progress in unraveling the biosynthesis of natural sunscreens mycosporine-like amino acids

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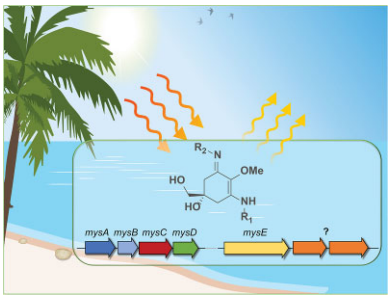
Abstract: Exposure to ultraviolet (UV) rays is a known risk factor for skin cancer, which can be notably mitigated through the application of sun care products. However, escalating concerns regarding the adverse health and environmental impacts of synthetic anti-UV chemicals underscore a pressing need for the development of biodegradable and eco-friendly sunscreen ingredients. Mycosporine-like amino acids (MAAs) represent a family of water-soluble anti-UV natural products synthesized by various organisms. These compounds can provide a two-pronged strategy for sun protection as they not only exhibit a superior UV absorption profile but also possess the potential to alleviate UV-induced oxidative stresses. Nevertheless, the widespread incorporation of MAAs in sun protection products is hindered by supply constraints. Delving into the biosynthetic pathways of MAAs can offer innovative strategies to overcome this limitation. Here, we review recent progress in MAA biosynthesis, with an emphasis on key biosynthetic enzymes, including the dehydroquinate synthase homolog MysA, the adenosine triphosphate (ATP)-grasp ligases MysC and MysD, and the nonribosomal peptide synthetase (NRPS)-like enzyme MysE. Additionally, we discuss recently discovered MAA tailoring enzymes. The enhanced understanding of the MAA biosynthesis paves the way for not only facilitating the supply of MAA analogs but also for exploring the evolution of this unique family of natural sunscreens.

One-Sentence Summary: This review discusses the role of mycosporine-like amino acids (MAAs) as potent natural sunscreens and delves into recent progress in their biosynthesis.

Keywords: Sunscreen, Mycosporine-like amino acids, Biosynthesis

Graphical abstract



Introduction

Skin cancers rank among the most common types of cancer in the United States. Approximately 1.4 million Americans are living with melanoma, while over 3 million experience nonmelanoma skin cancer, including basal cell carcinoma and squamous cell carcinoma (Rogers et al., 2015). Solar radiation, particularly ultraviolet (UV) radiation, is a risk factor for major skin cancer forms (Ahmed et al., 2020; Lopes et al., 2021). UV rays are classified into three subtypes according to their wavelengths, including UVA at 315–400 nm, UVB at 280–315 nm, and UVC at 100–280 nm. UVA constitutes over 95% of ground-level UV rays and mainly activates sensitizing molecules, which subsequently produce reactive oxygen species (ROS) and oxidize cellular components (Jagger, 1985). In contrast, short-wave UVB rays directly induce photodamage to biomolecules such as DNA and proteins independently of the formation of ROS (Gasparro, 2000; Jagger, 1985; Meador et al., 2002). Given that ozone absorption and atmospheric scattering block most of the most energetic UVC, UVB is considered the most important etiological factor for squamous cell carcinoma and basal cell carcinoma (D'Orazio et al., 2013). However, the recent depletion of the stratospheric ozone layer, increasing the level of UV reaching Earth, highlights the need for effective human protection against UV radiation (Häder et al., 2011; McKenzie et al., 2007).

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A variety of chemical and physical UV-absorbing materials have been developed for sun protection, including synthetic chemicals like oxybenzone and metal oxide particles like titanium dioxide and zinc oxide. Synthetic anti-UV compounds, usually utilizing aromatic ring systems, effectively absorb UV rays through ultrafast excited state intramolecular proton transfer as their energy dissipation mechanism and prevent further photochemical reactions (Ignasiak et al., 2015). For example, enol-oxybenzone undergoes ultrafast tautomerization into a keto tautomer after UVA irradiation (Baker et al., 2015), with the excited tautomer returning to the ground state by dissipating energy as heat. However, concerns surrounding the potential toxicity of synthetic sunscreens are escalating. Recent reports reveal the rapid skin penetration of organic sunscreens and emphasize potential health risks associated with human exposure and systemic accumulation of these chemicals (Matta et al., 2019). Indeed, several studies have detected sunscreen ingredients in women's breast milk and human urine samples (Schlumpf et al., 2010). Additionally, some commercial sunscreen ingredients such as oxybenzone can exhibit hormone-disrupting properties and neurotoxic effects (Collaris & Frank, Krause et al., 2012; J. Wang et al., 2016). Synthetic anti-UV chemicals can also affect living organisms. For example, oxybenzone and octinoxate have been linked to coral reef bleaching (Danovaro et al., 2008; Schneider & Lim, 2019), leading to bans in regions like Hawaii and Key West (Levine, 2020; Ouchene et al., 2019). While physical anti-UV agents are generally considered less toxic (Nohynek et al., 2008; Smijs & Pavel, 2011), these metal oxides can generate significant hydrogen peroxide levels, potentially stressing living organisms (Jeon et al., 2016; Osmond & Mccall, 2010; Sánchez-Quiles & Tovar-Sánchez, 2014). These concerns underscore the need for the development of safe, biodegradable, and environmentally friendly anti-UV compounds.

Many organisms, especially microbes lacking inherent defenses like skin or shells against UV radiation, have evolved diverse strategies for UV protection. The most prevalent strategy is remediation, such as DNA repair mechanisms (Rastogi et al., 2010) and the replacement of damaged protein targets. Other common strategies involve preventative mechanisms, such as ROS detoxification systems (He & Häder, 2002) and antioxidant production (G. Wang et al., 2007), and behavioral adaptations (Kruschel & Castenholz, 1998; G. Wang et al., 2007). Another common protective strategy is the synthesis and accumulation of UV-absorbing secondary metabolites that absorb UV radiation and dissipate energy through harmless thermal de-excitation. Both aromatic polyketides and polymeric substances (e.g., melanins) have demonstrated anti-UV activities (Butler & Day, 1998; Nguyen et al., 2013). Terpenoids, including carotenoids, also serve as UV protectants and antioxidants (Demmig-Adams & Adams, 1992). Other notable examples of anti-UV natural products include scytonemin, a shikimate pathway derivative, and mycosporine-like amino acids (MAAs), both of which are produced by many aquatic microorganisms. Scytonemin, a yellow-brown pigment, is highly lipid soluble (Pathak et al., 2020). In contrast, MAAs are colorless, water-soluble compounds with considerable structural diversity, making them attractive for natural sunscreen product development. Here, we will introduce MAAs as natural sunscreen molecules and discuss recent progress in understanding their biosynthesis.

MAAs as Natural Sunscreens

MAAs are a family of potent UV protectants recognized for their thermal and photochemical stability (Carreto & Carignan, 2011). Since their initial identification from a terrestrial fungal species, over 70 MAA analogs have been identified in taxonomically diverse marine and terrestrial organisms, including cyanobacteria, eukaryotic algae, corals, plants, and vertebrates (Geraldes & Pinto, 2021; Sinha et al., 2007). MAAs can efficiently convert absorbed energy into heat, sidestepping the generation of free oxygen species (Conde et al., 2004). Despite their notable structural diversity, MAA analogs display absorption maxima between 310 and 362 nm and possess extinction coefficients reaching 50 000 $M^{-1}{\cdot}cm^{-1}$ (Fig. 1A), positioning them among the most powerful known UV-absorbing compounds. Quantum chemical calculations have delineated the ultrafast deexcitation pathway of a representative MAA, porphyra-334, involving a significant structural transformation from an extensively π conjugated planar structure to a nonplanar boat structure (Fig. 1B) (Hatakeyama et al., 2019). This analysis has further revealed the crucial structural features of MAAs underpinning their UV absorption profile, including the linear hetero-π conjugation of the C = N and C = C bonds, coupled with the nonaromatic ring facilitating a drastic molecular structure alteration upon electronic excitation (Hatakeyama & Nakamura, 2022). Beyond their anti-UV properties, MAAs have demonstrated a spectrum of potential benefits, including antioxidative, anti-inflammatory, and antiaging activities, offering another photoprotective mechanism (Suh et al., 2014).

Given their potent UV protective properties, MAAs have garnered considerable interest in the formulation of next-generation sunscreens. Currently, at least two commercial sunscreen products (Helioguard™ 365 and Helionori®) contain shinorine and porhyra-334 as active ingredients (Becker et al., 2016; Hartmann et al., 2017). However, the widespread application of MAAs in the cosmetic industry encounters a significant problem primarily due to the challenges associated with isolating these compounds from their natural sources. MAAs currently used in commercial applications are predominantly extracted from the red alga *Porphyra umbilicalis* (Lüning et al., 1997). However, the isolation is generally laborious and the production can be influenced by environmental factors (Lüning et al., 1997). Addressing and overcoming the supply challenge can potentially catalyze the broader applications of MAAs in various industrial sectors.

Chemical Synthesis of MAAs

Currently, only mycosporine-glycine (MG) has been successfully synthesized by White et al. (White et al., 1989, 1995). The synthesis route started with D-(-)-quinic acid carrying a favored *S* configuration at the C5 position along with a contiguous triol system (Fig. 2A). The triol system on C1-C3 can easily lead to aromatization, forming a benzene-like structure. The synthetic route was initiated by integrating a bridging γ-lactone between the carboxylic acid group at C5 and C1-OH, thereby sterically locking the cyclohexane ring. Subsequently, the *cis*-diols at C2 and C3 were protected by *O*-benzylidene acetals, enabling the selective generation of 3-bromo benzoate and eventual C3-oxidation to form the enolone. The Staudinger reaction, followed by reductive amination, facilitated the synthesis of MG. This pathway includes 13 steps, resulting in a total yield of less than 5%. Notably, the enantioselective synthesis of MG remains unattained. On the other hand, the Sampedro group recently reported a more direct synthesis route for MAA derivatives lacking a stereocenter at C5 (Losantos et al., 2017). Initially, the basic scaffold of diverse MAA derivatives underwent *in silico* evaluation, focusing on photostability, radiative processes, and excited-state lifetime. A total of

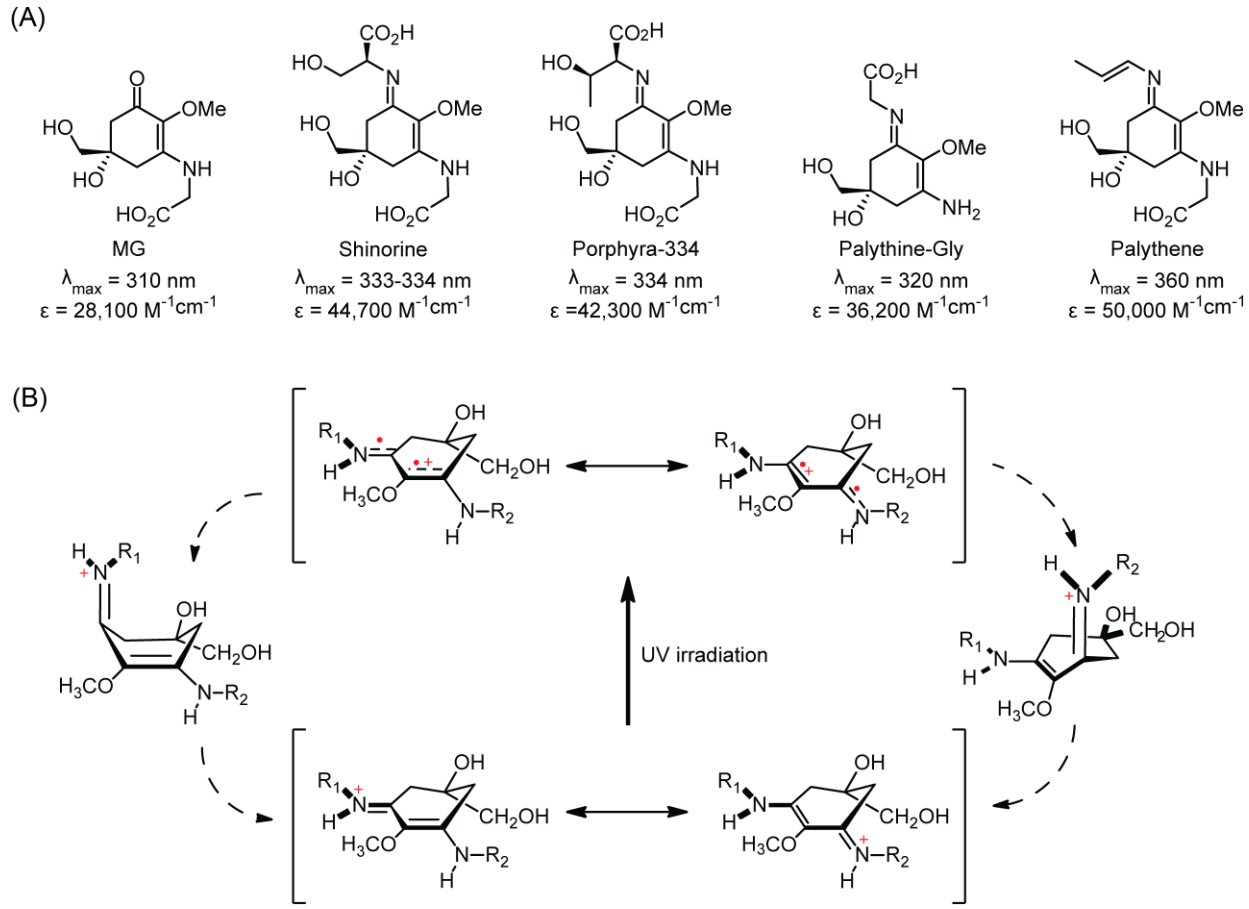

Fig. 1. MAAs as natural sunscreens. (A) Chemical structures of selected MAAs with corresponding maximal absorbance wavelengths and extinction coefficients. (B) Representative steps of the ultrafast deexcitation pathway of MAAs involving significant structural changes.

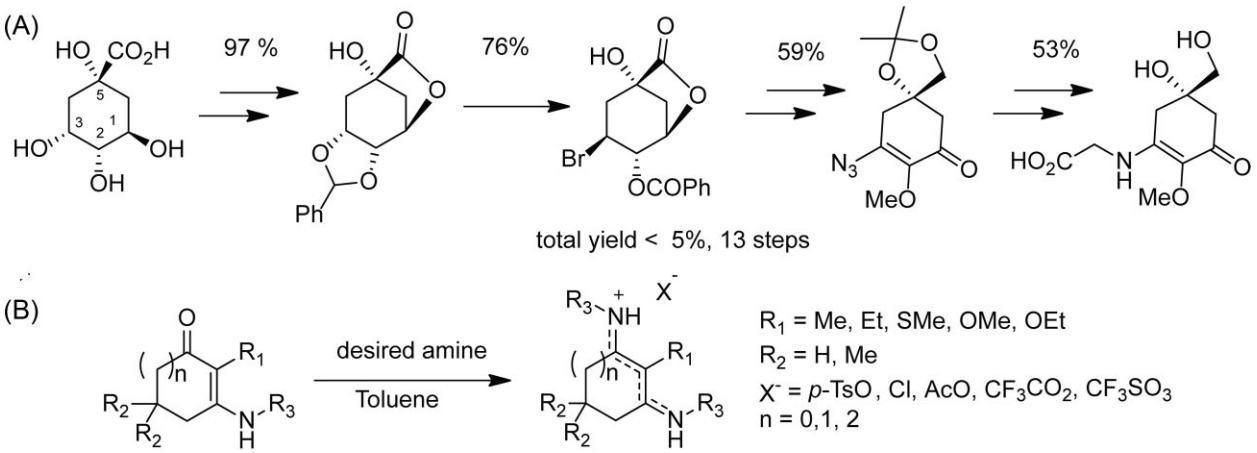

Fig. 2. Synthetic routes of MG starting from D-(-)-quinic acid in 13 steps (A) and MAA derivatives lacking a stereocenter at C5 within five steps (B).

20 compounds featuring the cyclohexenimine scaffold were then synthesized from readily available and economical materials through a maximum of five uncomplicated steps (Fig. 2B). These synthesized compounds displayed strong thermostability, enduring temperatures up to 270°C. A blend of two synthetic compounds at a 10% concentration showed modest sun protection but remarkably enhanced the efficacy of synthetic anti-UV compounds octinoxate (10%) and avobenzone (5%) by two to threefolds. These findings underscore the promising potential applications of these synthetic MAA derivatives.

General MAA Biosynthetic Pathway

The first biochemical characterization of the MAA biosynthesis came from the Walsh group (Balskus & Walsh, 2010).

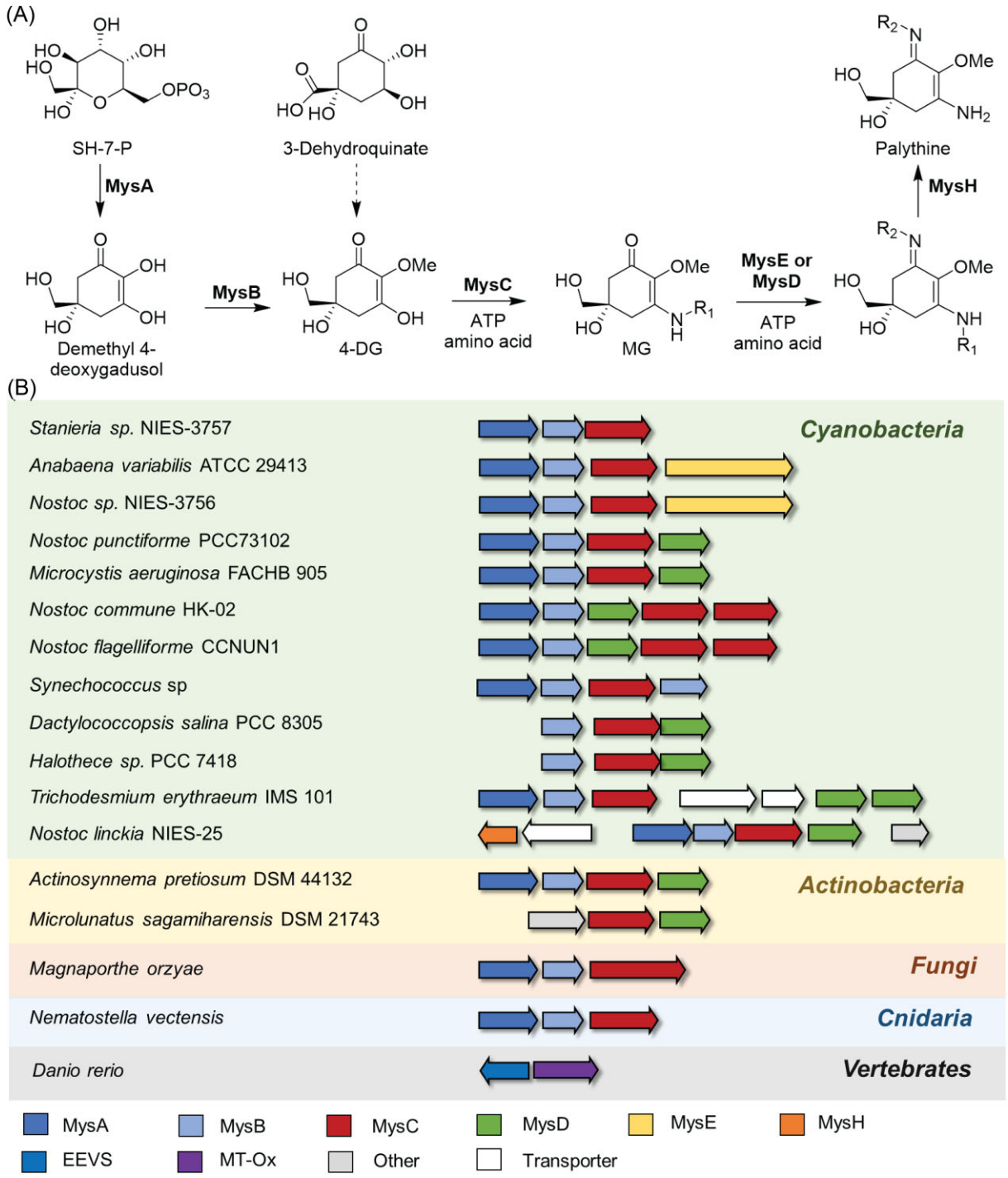

Fig. 3. A general MAA biosynthetic pathway catalyzed by MysA-E and MysH (A) and the diversity of MAA BGCs in different organisms (B).

Inspired by two co-localized genes encoding a dehydroquinate synthase homolog (DHQS) and an *O*-methyltransferase (*O*-MT) in the sea anemone genome, they queried them against publicly available genomes and identified the MAA biosynthetic gene cluster (BGC) in the genome of *Anabaena variabilis* ATCC 29413 (Fig. 3). The cluster encodes a DHQS homolog (Ava_3858; MysA), a putative *O*-MT (Ava_3857; MysB), a predicted ATP-grasp ligase (Ava_3856; MysC) and a nonribosomal peptide synthetase (NRPS)-like enzyme (Ava_3855; MysE) (Balskus & Walsh, 2010). MysA and MysB together synthesize 4-deoxygadusol (4-DG) from the pentose phosphate pathway intermediate sedoheptulose 7-phosphate (SH-7-P). Subsequently, MysC catalyzes the condensation between C3 of 4-DG and glycine to generate MG. Finally, shinorine is produced in the MysE reaction by modifying C1 of MG with L-Ser (Fig. 3A). On the other hand, several disubstituted MAA analogs, such as shinorine, porphyra-334, and mycosporine-2-glycine, are derived from MG by a D-Ala-D-Ala Ligase homolog (MysD) in other microorganisms (Fig. 3B), indicating the substrate flexibility of this enzyme (Gao & Garcia-Pichel, 2011).

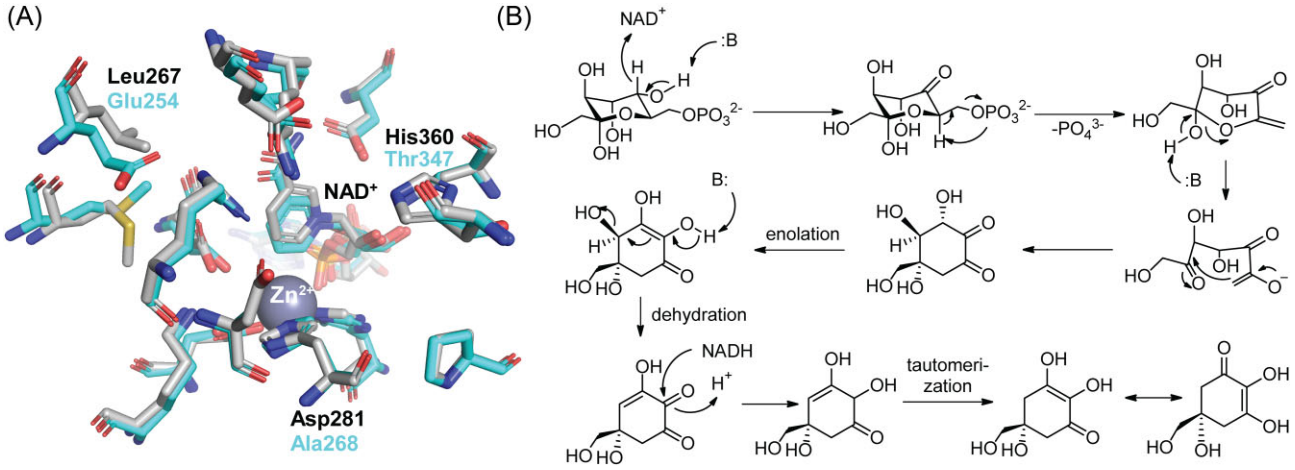

Fig. 4. MysA initiates the MAA biosynthesis. (A) Superimposing the active sites of MysA (PDB ID 5TPR, cyan) and EEVS (PDB ID 4P53, grey) revealed the difference of three residues. Zinc ion (Zn^{2+}) was shown as a dark grey sphere. The cofactor NAD^+ was shown as sticks with backbone carbons colored according to corresponding structures. (B) Proposed MysA reaction pathway starting from SH-7-P. The figure is modified from the previous work (Osborn et al., 2017).

Intriguingly, despite the confirmation of SH-7-P as the synthetic precursor by biochemical and genetic studies (Balskus & Walsh, 2010), early isotopic labeling studies indicated 3-dehydroquinate (3-DHQ) from the shikimate pathway as the precursor of fungal mycosporines (Favre-Bonvin et al., 1987). In addition, a subsequent study in *A. variabilis* ATCC 29413 revealed that even the *mysA* deleted strain continues to produce MAAs at a comparable level to the wild type, suggesting an alternative biosynthetic route (Spence et al., 2012). This hypothesis is further supported by the observation that chemical inhibition of the shikimate pathway markedly reduces MAA content across diverse cyanobacterial species, underscoring the potential significance of this pathway in providing essential building blocks like 3-DHQ for the MAA biosynthesis (Pope et al., 2015; Portwich & Garcia-Pichel, 2003). However, the mechanism through which the shikimate pathway intermediate transforms into 4-DG remains to be discovered.

Since the seminal studies of the Walsh group (Balskus & Walsh, 2010), the functions and mechanisms of the MAA biosynthetic enzymes have been further investigated by several research groups, and tailoring enzymes have been identified to participate in the MAA biosynthesis. Here, we discuss the recent progress of each MAA biosynthetic enzyme, except for the O-MT MysB whose mechanistic or structural characterization remains lacking.

Current Understanding of MAA Core Biosynthetic Enzymes

MysA

MysA was initially proposed as a DHQS based on sequence homology and the assumption that the MAA biosynthesis is rooted in the shikimate pathway (Balskus & Walsh, 2010; Favre-Bonvin et al., 1987). However, attempts to produce 4-DG from 3-DHQ by recombinant MysA were unsuccessful *in vitro* (Balskus & Walsh, 2010). Careful inspection of the enzyme active site residues suggests that MysA aligns more closely with the DHQS homolog 2-*epi*-5-*epi*-valiolone synthase (EEVS), potentially accepting the EEVS substrate SH-7-P (Fig. 3A). This hypothesis was confirmed by the production of 4-DG from SH-7-P in the MysA and MysB reaction in the presence of cofactors S-adenosylmethionine (SAM), nicotinamide adenine dinucleotide (NAD^+), and Co^{2+} (Balskus & Walsh, 2010). EEVS homologs play a pivotal role in the biosynthesis of many natural products. Interestingly, one EEVS homolog along with a methyltransferase-oxidoreductase (MT-Ox) enzyme converts SH-7-P into gadusol (Fig. 3B), a molecule exhibiting UV protection and structural similarity to 4-DG. The gadusol biosynthetic pathway is widely distributed across diverse bacteria and eukarya including vertebrates (Osborn & Mahmud, 2019; Osborn et al., 2015). Of note, the discovery of the *EEVS* gene in vertebrate genomes, such as those of fish, was unexpected, as these enzymes are likely evolved from DHQS but the shikimate pathway is missing in vertebrates, suggesting horizontal gene transfer events (Osborn et al., 2017). The Mahmud group recently elucidated the X-ray crystal structure of MysA from *A. variabilis* ATCC 29413 (PDB entry 5TPR), revealing consistency with the EEVS structure (PDB entry 4P53) (Fig. 4A) (Osborn et al., 2017). Although the active site residues of the two enzymes are highly conserved, subtle differences might be influential in determining their reaction products. In particular, three key active site residues His360, Asp281 and Leu267 in EEVS are respectively replaced by Thr347, Ala268 and Glu254 in MysA. Site-directed mutagenesis has confirmed the significance of both Asp281/Ala268 and Leu267/Glu254 in the reaction. MysA is proposed to catalyze the reaction similar to EEVS, but additional enolization, dehydration, and tautomerization steps are required (Fig. 4B).

Recent genome mining efforts have identified multiple MAA BGCs lacking the *mysA* gene such as the one identified in *Halothece sp.* PCC 7418 (Fig. 3B). This observation suggests an alternative pathway for 4-DG synthesis (Spence et al., 2012). One untested hypothesis is that the DHQS enzyme in microorganisms carrying the *mysA*-less MAA BGC could convert the shikimate pathway metabolite to 4-DG (Mogany et al., 2022).

MysC

MysC and MysD both belong to the ATP-grasp ligase superfamily, which carries diverse functions and is widely involved in central biological pathways (Fawaz et al., 2011). The characteristic mechanism of ATP-grasp ligases starts with the phosphorylation of a carboxylate to yield an acylphosphate intermediate, which is then attacked by a nucleophile such as an amine, hydroxyl, or thiol group (Fawaz et al., 2011). Uniquely within this enzyme superfamily, MysC and MysD in the MAA biosynthesis catalyze the

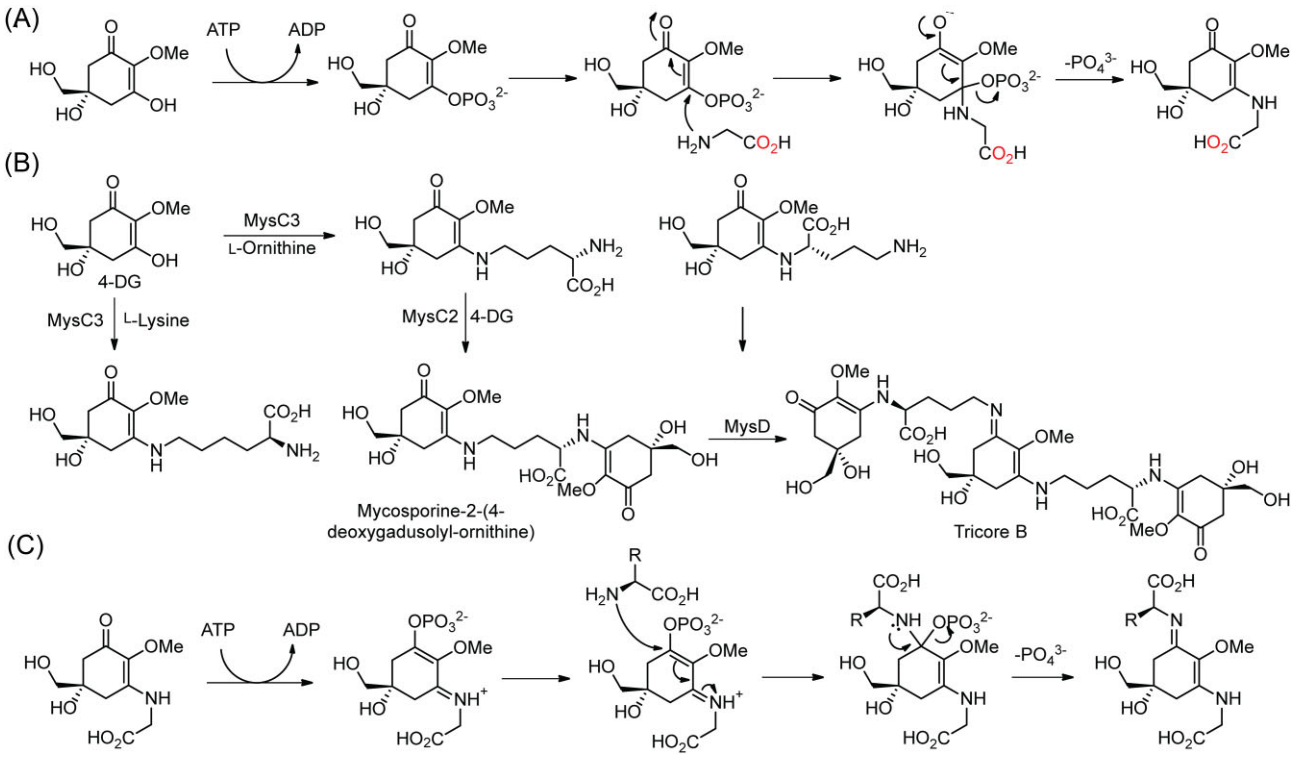

Fig. 5. ATP-grasp enzymes MysC and MysD respectively decorate C3 and C1 of the MAA scaffold. (A) MysC reaction pathway involving C3-phosphorylation. (B) MysC and MysD homologs synthesize multicore MAAs. (C) Proposed MysD reaction pathway.

formation of enamine or imine products. Specifically, MysC from *A. variabilis* ATCC 29413 has been biochemically characterized to convert 4-DG and glycine into MG (Balskus & Walsh, 2010). This reaction can proceed through the phosphorylation of the 4-DG C3-OH or the glycine carboxylic group. To distinguish the two potential routes, the Walsh group used ^{18}O-labeled glycine in the MysC reaction and observed that both labeled oxygen atoms are retained in the MG glycyl moiety, indicating that the 4-DG C3-OH is phosphorylated in the reaction (Fig. 5A) (Balskus & Walsh, 2010).

The majority of known MAAs carry a C3-glycine but different C3 moieties also appear, such as L-Ala, L-Ser, L-Glu, L-glutamicol, L-Lys, and ornithine, suggesting the substrate flexibility of MysC homologs (Katoch et al., 2016; Orfanoudaki et al., 2019; Sun et al., 2020). Recent cyanobacterial genome mining disclosed MAA BGCs with duplicated *mysC* genes, named *mysC2* and *mysC3* (Fig. 3B) (Zhang et al., 2021). In the phylogenic analysis, the homologs of MysC2 and MysC3 form two distinct clades, both divergent from the previously characterized MysC homologs named MysC1. Interestingly, the BGCs with duplicated *mysC* genes are exclusive to drought-tolerant cyanobacteria such as the desert cyanobacterium *Nostoc flagelliforme* (Fig. 3B). Heterologous expression in *E. coli* showed that MysC3 incorporates ornithine or L-Lys onto C3 of 4-DG through their δ- or ε-amino group, while MysC2 connects the α-amino group of mycosporine-ornithine to another 4-DG, forming the dual-core MAA analog mycosporine-2-(4-deoxygadusolyl-ornithine) (Fig. 5B) (Zhang et al., 2021). Furthermore, another study reported a discontiguous MAA BGC carrying all three types of MysCs in a lichen-symbiont *Nostoc* sp. UHCC 0926 (Arsın et al., 2023). These MysC homologs lead to the synthesis of multicore MAA analogs such as Tricore B carrying three 4-DG cores linked by two ornithine moieties (Fig. 5B) (Arsın et al., 2023; Zhang et al., 2021). The diverse function of MysC homologs enriches the chemical complexity of MAA analogs. The synthesis of such multicore MAAs may represent an adaptive strategy employed by microorganisms to thrive in harsh environments (Zhang et al., 2021).

MysD

The significant structural diversity of MAA analogs at C1 indicates the diverse substrate selectivity of MysD. Heterologous expression of the MysD-type MAA BGC from *Nostoc punctiforme* ATCC 29133 has affirmed that MysD accepts L-Gly, L-Ser, and L-Thr as the amino acid substrate (Gao & Garcia-Pichel, 2011). Our group recently characterized the function of MysD from *N. linckia* NIES-25 *in vitro*, and found that recombinant MysD utilizes at least six out of twenty natural amino acids (Chen et al., 2021). The enzyme showed the highest activity toward L-Thr, followed by L-Ser, L-Cys, L-Ala, L-Arg and L-Gly. Remarkably, the isolation of di- or tri-core MAA analogs 2-mycosporine-ornithine and Tricore B from *Nostoc* sp. UHCC 0926 suggests that some MysD homologs can accept a large amino nucleophile such as mycosporine-ornithine and 2-mycosporine-2-ornithine (Fig. 5B) (Arsın et al., 2023).

Given the chemical transformations catalyzed by MysC and MysD are similar, it is reasonable to hypothesize a parallel reaction mechanism between these two enzymes. In the MysD reaction, it is speculated that the MG C1 oxo group may undergo phosphorylation and subsequently, the amino group of the amino acid substrate could attack the phosphorylated intermediate, forming the imine bond (Fig. 5C). The structural characterization of MysC and MysD can provide useful insights into their reaction mechanisms and illuminate key residues crucial for catalysis and substrate binding. This information could be invaluable for understanding the versatility and specificity of these enzymes in the MAA biosynthesis and in synthesizing diverse MAA analogs.

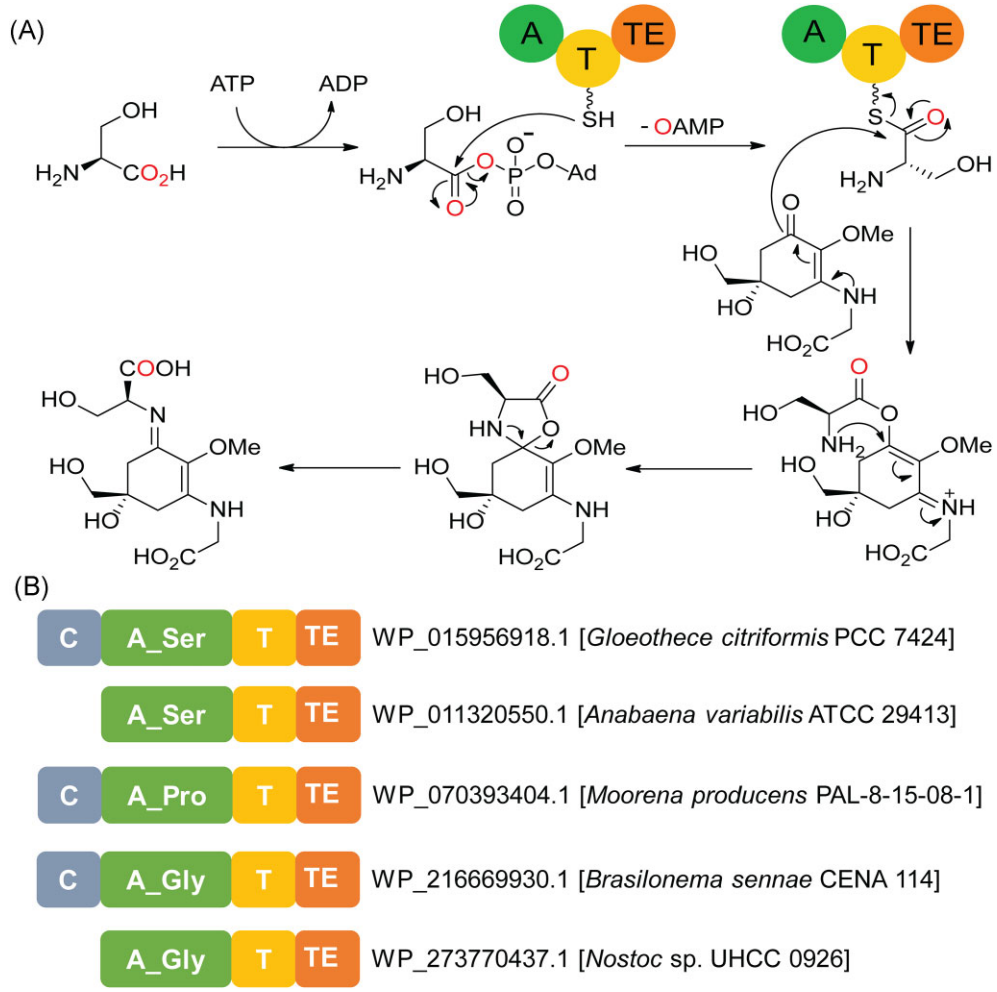

Fig. 6. MysE modifies the C1 of MG, producing disubstituted MAA analogs. (A) Proposed reaction mechanism of MysE involving ATP-dependent amino acid loading. (B) Domain organization of representative MysE homologs identified from cyanobacterial genomes.

MysE

The NRPS-like enzyme MysE from *A. variabilis* ATCC 29413 is composed of an adenylation (A), a thiolation (T), and a thioesterase (TE) domain. The function of this enzyme in converting MG and L-Ser into shinorine has been confirmed in biochemical studies and heterologous expression (Balskus & Walsh, 2010). Our group further confirmed the function of its homolog in the filamentous cyanobacterium *Fischerella* sp. PCC 9339 by the heterologous expression of its MAA BGC in *Synechocystis* sp. PCC 6803 (Yang et al., 2018). To elucidate the reaction mechanism of MysE, the Walsh group used [carboxy-$^{18}O_2$]-L-Ser as the substrate and observed that the product mass was two Daltons heavier compared to the unlabeled product (Balskus & Walsh, 2010). This result indicated that MysE loads L-Ser onto its T domain through the ATP-dependent activation by its A domain (Fig. 6A). One ^{18}O atom of [carboxy-$^{18}O_2$]-L-Ser is discarded as part of AMP during the process. It is hypothesized that the TE domain of MysE may catalyze the formation of an enol ester intermediate, which leads to subsequent *O*- to *-N* rearrangement via 1,4-addition of the L-Ser nitrogen to the activated cyclohexenimine core (Fig. 6A). However, this proposed mechanism depends on further structural and mechanistic investigations for validation.

In contrast to the wide distribution of MysD homologs across diverse microorganisms (Fig. 3B), MysE homologs seem to be exclusively located in cyanobacterial genomes. Our bioinformatic prediction suggested that the majority of the MysE A domain is specific for L-Ser as the substrate. Indeed, a recent study has identified 20 MysE homologs from complete cyanobacterial genomes, with 12 predicted to be specific for L-Ser, seven for glycine, and one for L-Pro (Arsın et al., 2023). We also observed that some MysE homologs carry an additional condensation (C) domain (Fig. 6B).

New Tailoring Biosynthetic Enzymes of MAAs

The four-step biosynthetic route offers insights into the synthesis of disubstituted MAA analogs (Fig. 3A), but it does not encompass the full range of structural diversity at C1 and C3 positions of these molecules, such as amino alcohol (e.g., asterina-330) and enaminone (e.g., palythene). These modifications change the UV absorption profiles of MAA analogs, potentially providing broad-spectrum UV protection. To identify additional MAA biosynthetic enzymes, we applied genome neighborhood analysis to classify the genes that are frequently co-localized with the known MAA biosynthetic genes (Chen et al., 2021). This approach led to the identification of a high cooccurrence of nonheme iron(II)- and 2-oxoglutarate-dependent dioxygenases (Fe(II)/2OG-dependent dioxygenases) with MysC homologs. We mined one MAA BGC from the genome of *N. linckia* NIES-25, which contains the gene of Fe(II)/2OG-dependent dioxygenase named MysH (Fig. 3B). Heterologous expression of *mysH* with *mysABCD* in *E. coli* revealed that MysH converts disubstituted MAAs into

corresponding palythines by oxidatively decarboxylating the MAA C3 glycyl moiety (Fig. 3A). Fe(II)/2OG-dependent dioxygenases catalyze diverse oxidative reactions including but not limited to hydroxylation, desaturation, epoxidation, and halogenation (Islam et al., 2018). We propose that MysH catalyzes an α-hydroxylation on the C3-L-Gly moiety, followed by automatic hydrolysis to release palythines and glyoxylic acid. A similar enzyme, MysI, from *Nostoc* sp. UHCC 0926, has also been suggested to catalyze the same reaction on mycosporine-2-glycine (Arsın et al., 2023). Despite the high function similarity, MysH and MysI homologs were grouped into two clades in a phylogenic analysis. Additionally, an *N*-methyltransferase MysF is predicted to methylate the palythine C3 amino group (Arsın et al., 2023), producing aplysiapalythine C.

Aside from the Fe(II)/2OG-dependent dioxygenases and methyltransferases, we also observed the frequent occurrence of glycosyltransferase (GlyT) genes in the MAA BGCs (Chen et al., 2021). Many glycosylated MAA analogs have been reported (D'Agostino et al., 2016; Nazifi et al., 2013), but corresponding GlyTs have not been identified. Glycosylation could occur on the MAA C7-OH or the L-Ser/Thr side chain. The presence of short-chain dehydrogenases/reductases in many MAA BGCs is also noted (Chen et al., 2021), but their specific roles in the MAA biosynthesis remain unconfirmed. The diversity of tailoring enzymes underscores the complexity and adaptability of the biosynthetic pathways leading to the formation of diverse MAA analogs, potentially reflecting the adaptive strategies of microorganisms in various environments.

Concluding Remarks and Perspectives

With distinguishing anti-UV properties, MAAs can protect producing organisms in nature and have the potential to be developed as novel sunscreen active ingredients. The characterization of the MAA biosynthesis opens opportunities to address the difficulty in isolating or chemically synthesizing these molecules for commercial applications. For example, our group has demonstrated controllable production of shinorine in the model cyanobacterium *Synechocystis* sp. PCC 6803 with a yield comparable to the commercially used producer red algae (2.37 mg/g DCW) (Yang et al., 2018). Another research described the production of 31.0 mg/L (9.62 mg/g DCW) of shinorine in *Saccharomyces cerevisiae* after increasing the SH-7-P pool (Park et al., 2019). The synthetic biology studies further led to the production of up to 1.1 g/L of gadusol in *Streptomyces coelicolor*, a significant achievement for commercialization (Osborn & Mahmud, 2019). Recent advances in genome mining and bioinformatics analysis have facilitated the advanced understanding of the MAA biosynthesis, uncovering different clades of core biosynthetic enzymes and new tailoring enzymes. This knowledge paves the way for innovative synthetic biology and biocatalysis strategies to sustainably produce a diverse array of MAA analogs with tailored properties.

One key question regarding the MAA biosynthesis centers on the diversion of the shikimate pathway intermediate to form 4-DG. Identifying the enzyme(s) mediating this conversion is crucial for boosting MAA production through metabolic engineering. MAA BGCs are surprisingly diverse on both the pathway level (shikimate pathway vs. pentose phosphate pathway to supply the precursor) and the enzyme level (MysD vs. MysE). Notably, it is unclear why distinct types of core enzymes are utilized in nature to produce structurally similar compounds. Nonetheless, the widespread distribution and diversity of MAA BGCs illuminate the significant biological importance of these molecules, likely extending beyond UV protection.

Multiple MAA biosynthetic enzymes, such as the ATP-grasp ligases and the NRPS-like enzymes, show unique reaction mechanisms compared to other members of the same enzyme families. The mechanistic studies would not only facilitate enzyme engineering to produce MAA analogs but also advance our knowledge of the principles governing the formation of novel enzyme chemistry from the same protein scaffolds. As genome sequencing and mining become commonplace, the discovery and characterization of more MAA BGCs and novel biosynthetic enzymes are anticipated. This progress will facilitate further exploration of their biosynthesis, ecological roles, and potential applications, ultimately contributing to the development of new compounds with protective properties against UV radiation and potentially other beneficial uses.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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