


Review

# Bioactive Metabolites Produced by Cyanobacteria for Growth Adaptation and Their Pharmacological Properties

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**Simple Summary:** Cyanobacteria are known as oxygenic microorganisms are able to release oxygen as a byproduct during photosynthesis. Rapidly changing environmental conditions require cyanobacteria to have dynamic adaptation strategies. They synthesize bioactive metabolites that are responsible for protection against harmful environmental conditions and to colonize in various habitats. This review focuses on the roles of bioactive metabolites for cyanobacterial survival and also discusses the bioactivities of these compounds for the treatment of numerous diseases.

**Abstract:** Cyanobacteria are the most abundant oxygenic photosynthetic organisms inhabiting various ecosystems on earth. As with all other photosynthetic organisms, cyanobacteria release oxygen as a byproduct during photosynthesis. In fact, some cyanobacterial species are involved in the global nitrogen cycles by fixing atmospheric nitrogen. Environmental factors influence the dynamic, physiological characteristics, and metabolic profiles of cyanobacteria, which results in their great adaptation ability to survive in diverse ecosystems. The evolution of these primitive bacteria resulted from the unique settings of photosynthetic machineries and the production of bioactive compounds. Specifically, bioactive compounds play roles as regulators to provide protection against extrinsic factors and act as intracellular signaling molecules to promote colonization. In addition to the roles of bioactive metabolites as indole alkaloids, terpenoids, mycosporine-like amino acids, non-ribosomal peptides, polyketides, ribosomal peptides, phenolic acid, flavonoids, vitamins, and antimetabolites for cyanobacterial survival in numerous habitats, which is the focus of this review, the bioactivities of these compounds for the treatment of various diseases are also discussed.

**Keywords:** cyanobacteria; habitat; adaptation strategies; bioactive metabolites



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## 1. Introduction

Cyanobacteria are photosynthetic microorganisms that possess various cellular strategies and physiological capacities to facilitate their adaptations for colonization in diverse environments on Earth. As a result, these photosynthetic microbes can exist in marine, terrestrial, and freshwater habitats. Furthermore, cyanobacteria are the most versatile ancient microorganisms that can thrive in extreme environments such as deserts, polar environments, geothermal springs, hypersaline lakes, and soils with high metal concentrations. They can be classified according to their ability to grow in high pH (alkaliphiles), beneath rock (endolithics), in high salinity (halophiles), under low nutrients (oligotrophics), in low (psychrophiles) or high (thermophiles) temperatures, and under high radiation levels (radiophiles) (Table 1).

**Table 1.** Different classes of cyanobacterial species based on their physiological characteristics.

Class	Habitats	Cyanobacteria	References
Alkaliphiles	Hypersaline swamps, alkaline-saline lake or ponds, hot spring, alkaline hot spring, alkaline-saline volcanic lake, soda deserts	<i>Microcoleus</i> sp., <i>Pleurocapsa</i> sp., <i>Synechococcus</i> sp., <i>Cyanobacterium</i> sp., <i>Spirulina subsalsa</i> , <i>Spirulina platensis</i> , <i>Spirulina maxima</i> , and <i>Arthrospira</i> sp.	[1–10]
Acidophiles	Sulfuric pools and acid mine drainage	Cyanobacteria cannot survive under this condition.	[11–13]
Endolithic	Rocks, granites and quartzites in desert, freshwater	<i>Chroococcidiopsis</i> -like cyanobacterium	[14]
Halophilic	Hypersaline lakes, coastal hypersaline lagoons, saline springs, salt flats and ponds	<i>Synechococcus</i> sp., <i>Leptolyngbya</i> sp., <i>Nodosilinea</i> sp., and <i>Geitlerinema</i> sp.	[15]
Oligotrophics	Coastal regions of marine and freshwater	<i>Dolichospermum lemmermanii</i>	[16,17]
Psychrophilic	Alpines and polar regions	<i>Nostoc</i> sp., <i>Leptolyngba</i> sp., <i>Oscillatoria</i> sp. and <i>Phormidium</i> sp.	[18–20]
Thermophilic	Thermal springs and soil crusts of deserted area	<i>Synechococcus</i> sp., <i>Thermosynechococcus vulcanus</i> , <i>Leptolyngbya</i> sp., <i>Thermosynechococcus elongatus</i> , and <i>Phormidium</i> sp.	[21–25]
Radiophiles	Marine, freshwater and desert	<i>Synechocystis</i> sp., <i>Chroococcus minutus</i> , <i>Leptolyngbya</i> sp., <i>Trichodesmium</i> and <i>Crocospaera</i>	[26–28]

Through centuries of evolution, cyanobacteria developed various sophisticated molecular, physiological, and metabolic characteristics for thriving in their habitats. The main aim of this paper is to review the roles of bioactive metabolites in addition to molecular machineries and physiological characteristics in ensuring the adaptation of cyanobacteria to environmental conditions. It is noteworthy that numerous studies have identified the potentials of cyanobacteria for modern drug discovery due to the bioactivities exhibited by cyanobacterial metabolites.

## 2. Adaptation Strategies of Cyanobacteria

### 2.1. Physiological Adaptation

Cyanobacteria possess the capacity to switch from one mode of metabolic approach to another. Most cyanobacteria conduct oxygenic photosynthetic mode. However, some can switch to anoxygenic photosynthetic mode [29]. For example, a filamentous mat of *Leptolyngbya* sp. and a cyanobacterial community of *Planktothrix* sp. and *Annamia* sp. dominating the sulfidic water column can conduct anoxygenic photosynthesis using sulfide as an electron donor [30,31]. Moreover, some cyanobacteria can carry out the fermentation processes under anoxic conditions and in the dark [32]. On the other hand, many cyanobacteria species form heterocysts, the cells that carry out atmospheric nitrogen fixation, especially during nitrogen deprivation [33]. This uniquely differentiated cell

results in the dispersion of cyanobacterial genera in various ecosystems; for example, *Anabaena* and *Trichodesmium* inhabit open oceans, thermal springs and freshwaters [34,35], whereas *Leptolyngbya* grows in geothermal springs, hot deserts, and surface crusts of semi-deserts [36,37].

The high adaptability of cyanobacteria to high temperature environments might be related to their photosynthetic machinery acclimation throughout many years of evolution. Previous studies have identified that light-harvesting phycobilisome (PBS) and photosystem II (PSII) are the main components that contribute to the survival of thermophilic cyanobacteria. *Synechococcus* A/B clade, *Mastigocladus laminosus*, *Synechococcus lividus* and *Synechococcus vulcanus* have developed PBS with a greater thermostability during the evolutionary divergence [38]. The rigidity of the phycocyanin complex is important in achieving PBS thermostability [39]. On the other hand, D1 protein and PsbU, the key subunits of PSII, provide stability to PSII from denaturation at a high temperature [40,41]. Previous studies have also reported that filamentous cyanobacteria are thermostability related to metabolic mechanisms, which enables them to survive at high temperatures [42,43].

Additionally, some marine planktonic cyanobacteria, for example, *Synechococcus* sp. PCC 7942, exhibit DNA repair mechanisms, including detoxifying enzymes and pigments [44] and UV-absorbing sunscreen molecules [45] to release the damage caused by UV radiation and to protect them from harmful radiation pollutants [46]. Many planktonic cyanobacteria possess gas vesicles for position adjustment in the water column. Cyanobacteria use these gas-filled structures in connection to different environmental stimuli such as photic, gravitational, chemical and thermal to find a suitable niche [47].

## 2.2. Cellular Morphological Adaptation

Cyanobacteria exist in different morphological structures: unicellular in a single cell or colony with or without mucilaginous envelope, unbranched filamentous with single or multiple trichomes with or without sheath, and branched filamentous [48]. Furthermore, cyanobacteria have been subdivided into five subsections according to their morphological characteristics, subsection I (unicellular), subsection II (unicellular with baeocytes), subsection III (unbranched filamentous without heterocyst), subsection IV (false-branched or unbranched filamentous with heterocysts) and subsection V (branched filamentous with heterocysts) [49]. Although the forms are not habitat dependent, these physical characteristics might have contributed to cyanobacterial evolutionary adaptations. The earliest cyanobacterial genera are unicellular with sheath living in freshwater habitats [50]. The sheath enables benthic or sessile cyanobacteria such as *Gloeocapsa*, *Synechococcus*, *Prochlorococcus* and *Aphanothece* to form epilithic/endolithic biofilms in water bodies. This thick protective layer also provides high irradiance and UV light defense to the cells. Remarkably, some unicellular cyanobacteria possess thin firm colorless sheath for adaptations in extreme habitats, such as *Chroococidiopsis*, which can be found in thermal and mineral springs, alkaline hypersaline swamps and hot or Antarctic deserts [51] as well as *Chroococcus*, which can be found in thermal springs and calcite speleotherms [52,53]. In contrast, the solitary cells or small groups of *Halothece* that inhabit coastal salty habitats lack mucilaginous envelope [54]. Noteworthy, most filamentous cyanobacteria produce extracellular sheath as a method of adaptation, especially to water level fluctuation and high solute concentration, by providing a microenvironment for trichomes. For example, *Microcoleus*, *Trichocoleus*, *Oscillatoria* and some *Schizothrix* covered by thick sheath grow in saline soil crusts, semi-desert regions, soil crusts of desert and polar environments [35,55,56]. However, some mat-forming *Schizothrix* and *Oscillatoria* enveloped by firm and thin sheaths inhabit diverse aquatic environments, freshwater, marine environments, thermal springs and polar water bodies [55]. Moreover, heterocystous cyanobacteria, such as *Anabaena* and *Trichormus*, have filaments without sheath or gelatinous envelope, which are necessary to allow more light penetration into the cells. In the case of cyanobacterial symbionts (cyanobionts), the absence of sheath or gelatinous envelope is important to enhance nitrogen and carbon transfer between the symbiotic partners [55].

### 2.3. Bioactive Metabolites for Cyanobacterial Adaptations and Their Pharmacological Properties

#### 2.3.1. Indole Alkaloids

Alkaloids are ubiquitous in plants, bacteria, fungi and animals. In plants, alkaloids are produced as secondary metabolites in response to biotic or abiotic stresses [57]. Indole alkaloids are one of the alkaloid classes consisting of one indole structural moiety and are known for their bioactivities [58]. Many studies were conducted on the pharmacological properties of indole alkaloids from plants, fungi and animals, for example, antitumor activities showed by vinblastine and vincristine from *Catharanthus roseus* [59] and UV protective function by pityriacitrin from yeast *Malassezia furfur* [60], as well as the anti-inflammatory effect produced by conicamin from tunicate [61], lepadiformines A and B from ascidian [62], manzamine and carteramine A from sponges [63,64], and ascidiathiazones A and B from ascidian [65,66].

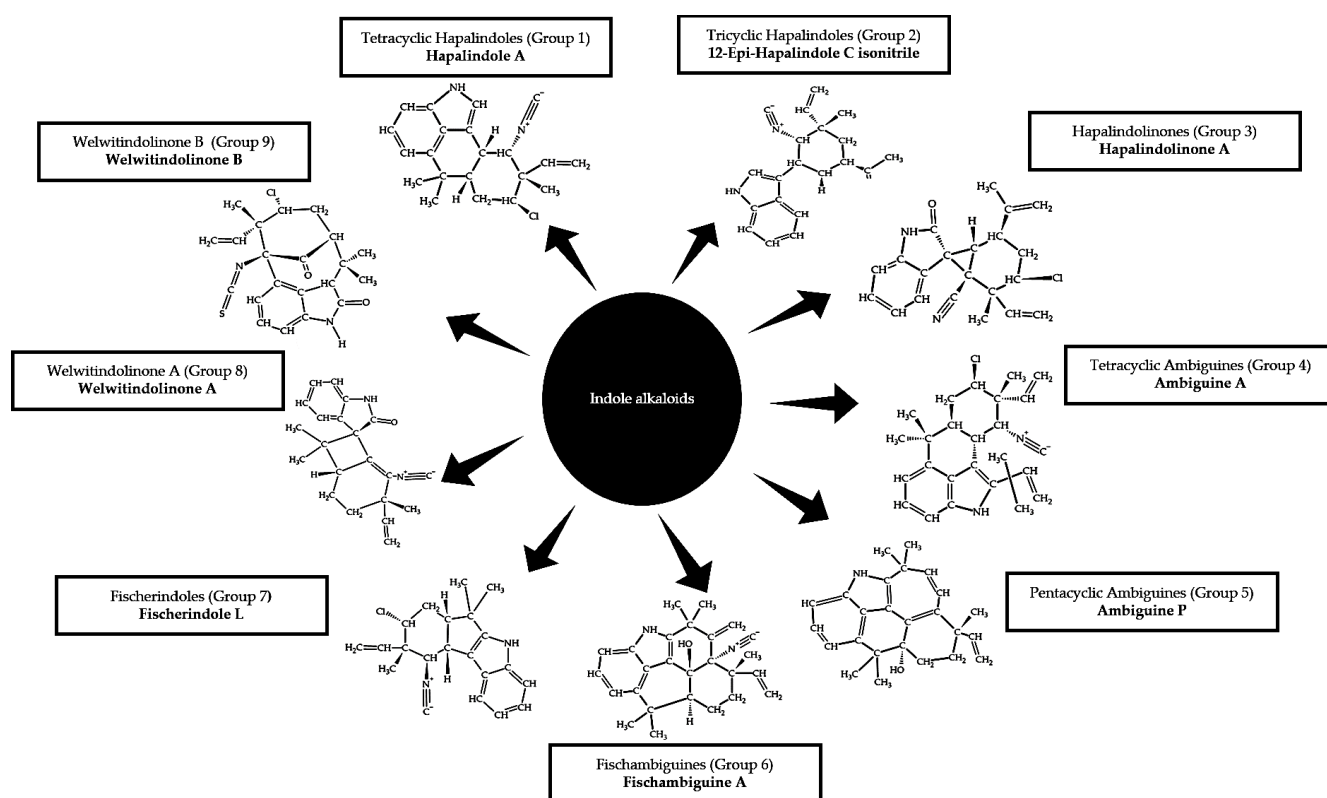
A diverse class of indole alkaloids synthesized by cyanobacteria have been reported as the bioactive secondary metabolites that possess pharmacological and biological properties (Table 2).

**Table 2.** List of cyanobacteria producing diverse class of indole alkaloids.

Cyanobacteria species	Habitat	Compounds	Bioactivities	References
<i>Hapalosiphon</i> sp. CBT1235	Terrestrial	Hapalindoles	Inhibit T Cell Proliferation	[67]
<i>Hapalosiphon fontinalis</i>	Soil	Hapalindoles	Antibacterial and antimycotic	[68]
<i>Hapalosiphon fontinalis</i>	Soil	Hapalindoles	Antialgal	[69]
<i>Westiellopsis</i> sp. (SAG 20.93) and <i>Fischerella muscicola</i> (UTEX LB1829)	Freshwater and terrestrial	Hapalindoles	Antibacterial	[70]
<i>Fischerella ambigua</i> UTEX1903	Terrestrial	Ambiguine	Unknown	[71]
<i>Hapalosiphon welwitschii</i> UTEX B1830	Freshwater	Welwitindolinone	Unknown	[72]
<i>Westiella intricata</i> UH strain HT-29-1	Freshwater	Welwitindolinone	Unknown	[73]
<i>Fischerella ambigua</i> (UTEX 1903), <i>Westiellopsis prolifica</i> and <i>Hapalosiphon hibernicus</i> BZ-3-1	Terrestrial	Ambiguine Isonitriles	Fungicidal	[74]
<i>Fischerella muscicola</i>	Terrestrial	Fischerindole	Antifungal	[75]
<i>Fischerella ambigua</i> (UTEX 1903)	Terrestrial	Fischambiguines and ambiguines	Antibacterial	[76]
<i>Fischerella</i> sp.	Terrestrial	Welwitindolinones	Multi-drug resistance reversing activity	[77]
<i>Hapalosiphon welwitschia</i> and <i>Westiella intricata</i>	Soil	Welwitindolinones	Multi-drug resistance reversing activity and insecticidal activity	[78]

Thus far, 80 variants of indole alkaloids have been identified exclusively produced by the genera *Westiella*, *Westiellopsis*, *Fischerella* and *Hapalosiphon* (belonging to subsection V formerly order Stigonematales) [79–81]. The variants belong to nine different groups

based on their carbon skeletons (Figure 1). Hapalindoles are the largest group of alkaloid indoles produced by cyanobacteria, which make up Group 1 (tetracyclic hapalindoles) and Group 2 (tricyclic hapalindoles). Furthermore, the hapalindoles are the precursors for the other groups, so-called hapalindole-type alkaloids: the hapalindolinones (Group 3), the ambiguines (Group 4 and Group 5), fischambiguines (Group 6), fischerindoles (Group 7) and welwitindolinones (Group 8 and Group 9). Such an extensive list of indole alkaloids suggests the important roles of these secondary metabolites in ensuring the survival of the cyanobacterial genera. Although most of the indole alkaloids are identified from the terrestrial and freshwater cyanobacteria in the genera *Westiella*, *Westiellopsis*, *Fischerella* and *Hapalosiphon*, it is tempting to speculate that these secondary metabolites are also produced by these genera inhabiting the other ecosystems, especially by those thriving in the extreme environments. Remarkably, the hapalindole family appears to be inherited vertically and thus, suggests the inheritance of hapalindole biosynthetic genes within the Subsection V [73].



**Figure 1.** Classification of indole alkaloids from Stigonematales order of cyanobacteria [81].

Interestingly, scytonemin, an indole alkaloid UV-filtering pigment, is predominantly produced by cyanobacteria [82,83]. A recent study reported that an unculturable *Halothece* produced scytonemin in response to UV-A radiation at the driest Salar Grande, Atacama Desert [84]. In addition, scytonemin found in the terrestrial *Lyngbya* sp. CU2555, showed high resistance toward UV-B and heat, thus protecting the cells against harsh environmental conditions. This strong oxidizing agent not only functions as a photoprotective compound against harmful UV radiation but also provides protection against deleterious short-wavelength radiation [85]. Notably, the accumulation of scytonemin in the unicellular *Chroococcidiopsis*-like cyanobacterial isolate from an epilithic desert crust occurred due to the increase in both temperature and photooxidative conditions together with UV-A exposure. However, the increased salt concentration under UV-A radiance blocked the production of scytonemin [86].



*spongelliae* are suggested to be responsible for the symbiotic interaction with the tropical marine sponge [101].

Triterpenoids, such as 2-methylhopanoids (2-MeBHPs), were discovered in a significant quantity in both laboratory cyanobacterial cultures and natural cyanobacterium-dominated microbial mats [102,103]. 2-MeBHPs is an example of pentacyclic triterpenoids, which play the role of biomarkers for modern cyanobacteria in some environmental settings [103]. Moreover, 2-MeBHP promotes osmotic, pH stress and freezing/thawing resistance in cyanobacteria to ensure their survival in desert soil crusts, hot springs, hypersaline lake, Antarctic water, and Arctic soil [100]. Apparently, the deletion of *hpnP*, the gene coding for the hopanoids protein responsible in C-2 methylation, caused a decrease in osmotic and pH stress tolerance by *Nostoc punctiforme* ATCC 29133S [104].

Tetraterpenoids, also known as carotenoids, are ubiquitous in most photosynthetic organisms and are essential for light-harvesting and energy dissipation during the photosynthesis process [105,106].  $\beta$ -carotene, zeaxanthin, and echinenone are common carotenoids produced by cyanobacteria. The freshwater *Aphanothece microscopica Nageli* (RSMa92) [107] and both the marine *Cyanobium* sp. LEGE 06113 [108] and *Trichodesmium* sp. [109] are also excellent sources of these terpenes. Carotenoids are lipophilic secondary metabolites from the isoprenoid pathway that are necessary to facilitate cyanobacteria against direct UV light exposure and photooxidative damage while conducting photosynthesis. In particular, it was suggested that echinenone and zeaxanthin protect PSII against singlet oxygen [110]. In addition, *Pseudanabaena* sp. CCNU1, inhabiting the arid and exposed region in Chetmari, Niger, produces carotenoids, specifically,  $\beta$ -carotene, echinenone, canthaxanthin, zeaxanthin, synechoxanthin, and three myxoxanthophyll derivatives, as a method of protection against UV-B radiation [111]. Moreover, carotenoids also play important roles in the survival of endolithic cyanobacteria, *Chroococciopsis* sp. at the Atacama Desert [112].

Recent studies have reported the biological activities of cyanobacterial carotenoids for the treatment of various diseases. Several cyanobacteria strains, including the freshwater *Alkalinema aff. pantanalense* LEGE15481, *Cyanobium gracile* LEGE12431, *Cuspidothrix issatschenkoi* LEGE03282, the terrestrial *Nodosilinea (Leptolyngbya) antarctica* LEGE13457 and the marine *Leptolyngbya*-like sp. LEGE13412, have been characterized for their high content of carotenoids [113]. Remarkably, carotenoids and their derivatives extracted from terrestrial and marine cyanobacteria showed high superoxide anion radical ( $O_2^{\bullet-}$ ) scavenging and anti-inflammatory effects that enabled the treatment of psoriasis [113]. A high number of carotenoids was also detected in *Cyanobium* sp. LEGE 07175 and *Tychonema* sp. LEGE 07175 [114]. Both cyanobacterial extracts showed strong antiaging effects by inhibiting hyaluronidase, the enzyme that stimulates the depolymerization of hyaluronic acid under oxidative stress [114]. Although the information on the biochemical mechanisms of carotenoids in cell apoptosis and proliferation is still scarce, their antioxidant capacity might be a contributing factor in anticancer and anti-aging effects.

Moreover, scytonemide (also known as an antimicrobial sesterterpene) from *Scytonema* sp. (UTEX 1163) culture showed growth inhibition against *Bacillus anthracis*, *Staphylococcus aureus*, *Escherichia coli*, *Candida albicans*, and *Mycobacterium tuberculosis* [115]. In addition, cybastacines A and B found in *Nostoc* sp. BEA-0956 also showed antibacterial activities against some clinical pathogenic bacteria [116]. Remarkably, scytonemides A and B extracted from the freshwater *Scytonema hofmannii* (UTEX 1834) have been identified and can function as an anticancer agent through the inhibition of 20S proteasome, the catalytic core of the proteasome complex that catalyzes the degradation of regulatory proteins [117].

### 2.3.3. Mycosporine-Like Amino Acids (MAAs)

Mycosporine-like amino acids (MAAs) are UV-absorbing compounds involved in the evolution of organisms living in environments with high exposure to sunlight, such as cyanobacteria, microalgae, fungi, seaweeds, corals, and lichens [118–121]. These small water-soluble compounds (generally <400 Da) provide protection against ultraviolet radiation (UVR) exposure. In fact, the production of MAAs is induced by UV radiation

and osmotic stresses; however, the mechanism remains poorly understood [122]. On the other hand, these photoprotective compounds also exhibit antioxidant activity [123–125].

*Synechococcales*, *Chroococcales*, *Oscillatoriales*, and *Nostocales* are efficient producers of MAAs for adaptations [118,126]. For example, a study found that MAAs produced by the benthic filamentous cyanobacteria in the Alpine Lake Gossenköllesee function as a protective shield against UVR. Despite a very low turnover of the synthesis of MAAs by the benthic filamentous cyanobacteria, especially during the ice-free season, these secondary metabolites reduce the transmission of UVR wavelengths received by the cyanobacteria in the clear Alpine lakes [127]. MAAs also provide protection against the damaging effects of solar UVR to the cyanobacterial mats in the Arctic [128]. Moreover, the MAA *mys* gene cluster in the filamentous *Chlorogloeopsis fritschii* PCC 6912 was up-regulated when simultaneously exposed to both UV and far-red lights. This suggests that MAAs may be involved in photon dissipation and thermodynamic optimization, which are important in regulating the heat from affecting the climate [129,130].

Recently, an usual mycosporine-glycine-alanine (MGA), an MAA derivative, was found in *Sphaerospermopsis torques-reginae* ITP-024 [123]. Inhabiting freshwater with low salinity, this heterocystous filamentous cyanobacterium also produces the imino-mycosporines, shinorine and porphyra-334, as an acclamatory response to UV exposure [123]. Other than providing protection against UV light, rear mycosporine-2-glycine (M2G), isolated from the halotolerant *Aphanothece halophytica*, possesses biological functions, such as free radical scavenging [131], oxidative stress protection [132], and osmoregulation [133], as well as inhibition of collagenase activity and protein glycation [134].

Interestingly, MAAs are attractive to cosmetic industries as the active ingredients for sunscreens and anti-aging products due to their characteristics [119,135]. For example, a recent in vitro study identified the protection activity of human keratinocytes against UV radiation by a novel MAA (13-O- $\beta$ -galactosyl-porphyrin-334) from *Nostoc sphaericum* [136]. This novel MAA also possesses radical scavenging activity that can reduce the damage caused by ROS in order to prevent photoaging. Nevertheless, MAAs have yet to be exploited for industrial production, with only a few edible products currently available. For example, both Helioguard 365® and Helionori® extracted from the red seaweed *Porphyra umbilicalis* [137,138] have been used as ingredients for the production of sunscreens. The in vivo study using Helioguard 365® from the red seaweed showed improvements in skin firmness and smoothness [138], whereas Helionori® offered protection against DNA damage due to UV radiation [139]. Nevertheless, these products are able to provide maximal protection in the UVA range but only allow minimum protection in the more damaging UVB range [125].

#### 2.3.4. Non-Ribosomal Peptides and Polyketides

Biosynthesis of non-ribosomal peptides (NRPs) and polyketides (PKs) are catalyzed by non-ribosomal peptide synthases (NRPS) and polyketide synthases (PKS), respectively [140]. Notably, the gene clusters of NRPS and PKS were more frequently found in bacteria, including cyanobacteria, than archaea and eukarya [141]. The gene clusters have been found in the genera *Lyngbya*, *Microcystis*, *Planktothrix*, *Nodularia*, *Nostoc*, *Pleurocapsa*, and *Anabaena* [141,142]. *Pleurocapsa* and *Nostoc* species are the most common cyanobacteria producing NRP/PK [141]. However, cyanobacteria with genomes fewer than 3 Mbp, such as *Prochlorococcus marinus* SS120 and *Synechococcus* sp. WH8109, might not possess these clusters due to the extra metabolic burdens [141,143,144].

The biosynthesis of peptides and polyketides in microorganisms is a unique modular pathway regulated by NRPS and PKS. NRPS comprises modules, each of which integrates proteinogenic amino acids with non-proteinogenic amino acids, fatty acids, carbohydrates and other building blocks into peptide chains [142]. These peptide-synthesizing enzymes accept approximately 300 proteinogenic and nonproteinogenic substrates during the biosynthesis of non-ribosomal peptides [145]. In bacteria, PKS Type I are widely found to be responsible for polyketide chain elongation, processing and termination [146]. These mod-



ular enzymes are involved in the recognition, activation and condensation of coenzyme A (CoA) derivatives as the building blocks [141,146]. Not only are the secondary metabolites produced through this unique natural combinatorial biosynthetic pathway are important for growth, symbiotic interactions and protection against biotic and abiotic stresses, but they also possess various therapeutic activities (Table 3). Some of the compounds have been applied for the treatment of various acute and chronic diseases.

**Table 3.** Bioactivities of non-ribosomal peptides (NRPS) and polyketides (PKS) produced by cyanobacteria.

Cyanobacteria species	Habitat	Compounds	Bioactivities	References
<i>Microcystis aeruginosa</i>	Freshwater	Microcystins	Inhibit eukaryotic types 1 and 2A phosphatases, cytoskeletal collapse, massive hepatic bleeding, potential tumor promoters and carcinogens	[147–149]
<i>Planktothrix agardhii</i> NIVA-CYA 126	Freshwater	Aeruginosin	Inhibit serine proteases	[150]
<i>Cylindrospermopsis raciborskii</i> , <i>Aphanizomenon ovalisporum</i> and <i>Aphanizomenon flos-aquae</i>	Freshwater	Cylindrospermopsisin	Cytotoxic, neurotoxic effects and carcinogen	[151]
<i>Anabaena</i> sp. 90	Freshwater	Anabaenopeptin	Inhibit proteases	[152]
<i>Lyngbya bouillonii</i>	Marine	Apratoxin	Reversible inhibition of several cancer-associated receptors	[153,154]
<i>Lyngbya majuscula</i>	Marine	Lyngbyatoxin	Potent skin irritant	[155]
<i>Lyngbya majuscula</i> JHB	Marine	Hectochlorin	Antifungal and anticancer activity	[156]
<i>Lyngbya majuscula</i> 19L	Marine	Barbamide	Anti-molluscidal	[157]
<i>Lyngbya majuscula</i> 19L	Marine	Curacin A	Antiproliferative and cytotoxic activities	[158]
<i>Lyngbya majuscula</i> JHB	Marine	Jamaicamide	Block sodium-channel	[159]
<i>Nostoc</i> sp. GSV 224	Terrestrial	Nostopeptolide	No cytotoxic, antifungal and inhibit protease activities	[160]
<i>Nostoc</i> sp. ATCC 53789	Terrestrial	Nostocyclopeptide	Antitoxin activity	[161]
<i>Nostoc</i> sp. ATCC 53789	Terrestrial	Cryptophycins	Tubulin-destabilizing compound	[162]
<i>Cylindrospermum alatosporum</i> CCALA 988	Terrestrial	Puwainaphycins	Cytotoxic	[163]
<i>Nostoc calcicola</i>	Wastewater	Nostophycin	Antibacterial and antifungal	[164]
<i>Nodularia spumigena</i> NSOR10	Freshwater	Nodularin	Inhibits phosphatase type 1 and 2A, cytoskeletal collapse, massive hepatic bleeding, potential tumor promoters and carcinogens	[165]

### 2.3.5. Ribosomal Peptides

Ribosomal peptides (RPs) are peptide chains of proteinogenic amino acids that can be found on ribosomes. In contrast to the biosynthesis of NRPs, only 20 proteinogenic amino acids are used as the building blocks during the biosynthesis of RPs [145]. There are three major RP families: cyanobactin, microviridins, and lantipeptides. Cyanobactin is diversely present in symbiotic and planktonic cyanobacteria [166]. Microviridins are the largest RPs, consisting of between 12 and 20 amino acids, which have been classified into four classes (Group I–IV) and are found in freshwater cyanobacteria [167]. Lantipeptides can be produced by four different classes (Class I–IV) of lantipeptidase in the cytosol of producing strains. Few studies have been conducted on cyanobacteria producing lantipeptides. However, comparative genomic analyses revealed that the marine *Prochlorococcus* and *Synechococcus* possess Class II lantipeptidase, ProcM [168,169]. The heterologous expression of *procM* and *procA* genes identified that ProcM can catalyze the dehydration and cyclization of all 29 different ProcA precursor peptides to produce the lantipeptides called prochlorosins [170]. Such an efficient biosynthetic pathway for generating prochlorosins with structural diversity is necessary for *Prochlorococcus* strains MIT9313 and MIT9303, as well as *Synechococcus* strain RS9916, which has a small genome size. Remarkably, RPs exhibit biological activities that could be used as natural drugs in the future (Table 4).

**Table 4.** Bioactivities of ribosomal peptides (RPs) produced by cyanobacteria.

Cyanobacteria Species	Habitat	Compounds	Bioactivities	References
Cyanobactin				
<i>Microcystis aeruginosa</i>	Freshwater	Aerucyclamide A, B, C and D	Cytotoxic and antimalarial	[171–173]
<i>Stigonema dendroideum</i>	Terrestrial	Dendroamide A	Multidrug-resistance reversing activity	[174]
<i>Trichodesmium erythraeum</i>	Marine	Trichamide	No biological effects found	[175]
<i>Prochloron didemnid</i> (symbioant)	Marine	Patellamide A and C	Cytotoxic	[176]
<i>Anabaena</i> sp. 90	Freshwater	Anacyclamide	Cytotoxic	[177]
<i>Microcystis aeruginosa</i> PCC 7806	Freshwater	Microcyclamide	No biological effects found	[171]
Microviridin				
<i>Microcystis aeruginosa</i> NIES-298	Freshwater	Microviridios B and C	Inhibits elastase	[178]
Lantipeptides				
<i>Prochlorococcus</i> MIT9313	Marine	Prochlorosins	Bacteriocidal and act as signaling molecules	[168,170,179]

It is unclear on how the NRPs, PKs and RPs are involved in the survival of cyanobacteria; however, these posttranslational modified compounds are well known for their antibacterial properties, which could be important when in competition with other microbial species in the ecosystem [170]. For example, under poor nutrient conditions in hot springs, cyanobacteria and other bacterial classes, such as Deinococci, Alphaproteobacteria, Ignavibacteria, and Betaproteobacteria [180], may compete for organic and non-organic matters, as well as space for either exposure to sunlight or cover from direct sunlight. Additionally, benthic or sessile cyanobacteria may produce NRPs, PKs, and RPs for cell signaling in order to form epilithic/endolithic biofilms in water bodies, saline soil crusts or soil crusts of desert and polar environments. Moreover, the oligopeptides produced by

cyanobacteria could be crucial for other organisms, such as eukaryotic algae, sponges, and plants, used as precursors for their metabolic pathways.

### 2.3.6. Phenolic Acids

Phenolic acids consist of one carboxyl group and one or more hydroxyl groups joined to the aromatic ring. These secondary metabolites are one of the largest groups of phenolic compounds. Phenolic acids are represented by hydrocinnamic acid, hydrobenzoic acid, phenylacetic acid and phenylpropionic acid derivatives from the shikimate pathway [181,182]. Phenolic acids produced by photosynthetic organisms are necessary for protection against oxidative damage that might be caused by reactive oxygen species (ROS) and the hydroxyl radical (OH).

In cyanobacteria, the accumulation of phenolic acids ensures the tolerance and adaptability of these photosynthetic microbes to various environmental stresses, which can cause the deposit of free radicals in cells, as well as chemical damage to deoxyribose and DNA. Notably, the accumulation of gallic acid, caffeic acid, chlorogenic, ferulic acid, and vanillic acid was detected when a high concentration of NaCl was supplied into the cultures of *Plectonema boryanum*, *Haplosiphon intricatus*, *Anabaena doliolum*, and *Oscillatoria acuta* [183], and thus suggesting that these phenolic acids play roles in the scavenging of free radicals under salt stress conditions. A recent study reported that the abundance of phenolic compounds in response to both cold and hot shocks might have stimulated the antioxidant capacity in halotolerant *Halotheca* sp. PCC 7418 [184]. It is noteworthy that the synergistic effect of phenolic acids and other antioxidative compounds (flavonoids, MAAs and phycobiliproteins) is necessary for the response.

As with other phenolic compounds, many studies identified that plant phenolic acids also manifest antimicrobial [185] and antiviral properties [186]. Due to their ability to reduce oxidative damage or stress in cells, phenolic acids such as gentisic acid, gallic acid and syringic acid exhibit good recovery in heart failure [187], memory loss [188] and wound healing [189], respectively. Previous studies have also reported that ferulic acids can produce skin whitening and anti-wrinkle effects [190] whereas gallic acid has anti-aging properties [191]. These therapeutic effects might also be produced by cyanobacterial phenolic acids due to their abilities to detoxify ROS and scavenge free radicals [183,184].

### 2.3.7. Flavonoids

Flavonoids are polyphenolic compounds that are widely distributed in plants [192]. These secondary metabolites can be classified into different subclasses: chalcones, flavanols, flavanones, flavones, isoflavones, flavonols, and anthocyanins. Remarkably, plant flavonoids exhibit antioxidant, anticancer, antiviral and anti-inflammatory properties [193,194].

In addition to phenolic acids, flavonoids are also antioxidants that are important for the survival of cyanobacteria. These antioxidative molecules, particularly quercetin and lutein, might facilitate *Plectonema boryanum*, *Haplosiphon intricatus*, *Anabaena doliolum*, and *Oscillatoria acuta* in salt acclimation mechanisms [183]. On the other hand, the chromatographic analysis identified that the thermophilic *Leptolyngbya* sp. produces a high amount of luteolin-7-glucoside and naringenin [195], which could protect the cells from oxidative damage due to high temperatures. Additionally, naringenin not only plays a role as a strong free radical scavenger but also affects the growth and physiological functions of the halophilic *Spirulina platensis* and *Arthrospira maxima* and the freshwater *Anabaena* sp. by altering the cell wall and cellular membrane permeability [196]. These features are crucial to allow the secretion of exopolysaccharides (EPS) onto the surface of cyanobacterial cells for protection against unfavorable environmental conditions [196]. The oxidative power of the total flavonoids produced by cyanobacterial strains [183,184,195,197,198] suggests that these strong antioxidative compounds might also have pharmacological potentials similar to the plants flavonoids, such as nephroprotective [199], neuroprotective [200], anticancer [201], and antiatherosclerotic properties [202,203].

### 2.3.8. Vitamins

Vitamins are commonly synthesized by photosynthetic organisms. Vitamin B: B1 (thiamin), B2 (riboflavin), B3 (niacin), B5 (pantothenic acid), B6 (pyridoxine), B7 (biotin), B9 (folic acid), B12 (cobalamin), and C are water-soluble compounds, whereas vitamin A, D, E, and K are lipid-soluble compounds. Plants produce vitamin A, B, C, E, and K in most organ parts to alleviate the effects of environmental stresses [204]. However, not all plants produce all vitamins and in fact, vitamin D and K, as well as some types of vitamin B are scarcely present [205]. By contrast, microalgae including cyanobacteria can produce vitamin D, K and B12, which are not present in higher plants [205].

*Arthrospira maxima*, *Anabaena cylindrica*, and *Synechococcus* sp. displayed high contents of  $\beta$ -carotene (pro-vitamin A) [206,207]. Remarkably, these cyanobacteria produce much higher  $\beta$ -carotene than some fruits, such as carrots and oranges [205]. Similarly in plants, this pro-vitamin A carotenoid compound produced by the cyanobacteria possesses a great oxidative efficacy against ROS, which is important for photooxidative protection. It is noteworthy that the efficacy of  $O_2^{\bullet-}$  scavenging by  $\beta$ -carotene is greater than vitamin E and C [205].

Cyanobacteria are the major sources of B vitamins in marine and freshwater ecosystems. These water-soluble vitamins secreted by some cyanobacteria into the water bodies are important nutrients for other aquatic organisms [206,208,209]. Additionally, B vitamins might also be necessary in the metabolic pathways of cyanobacteria [205], as a high content of B2, B5 and B6 was detected in the freshwater *Anabaena cylindrica* [206] whereas, a marine *Anabaena cylindrica* was found to produce a high amount of B12. On the other hand, chromatographic analysis detected a high content of B2, B3, B9 and B12 in dried biomass of commercial *Arthrospira maxima* and *Arthrospira platensis* [210]. Notably, vitamin B also plays a role in cyanobacterial adaptation to environmental stresses. *Nodularia spumegina* accumulates B1 in response to salinity and temperature stresses [208]. Together with  $\beta$ -carotene, B1 ensures that this planktonic cyanobacterium is able to survive under high UV radiation [208].

Other than the higher plants, *Anabaena cylindrica* is also an excellent source of vitamin C [206]. This well-known antioxidant compound may provide protection against oxidative compounds in cyanobacteria.

A very low amount of vitamin D was detected in *Arthrospira* sp. [211]. As characterized in other algae species, this lipid-soluble vitamin might be important to ease the damage or degradation of cell membranes in cyanobacteria caused by UV radiation.

A high amount of vitamin E has been found in *Nostoc* sp. PCC 7120, *Synechocystis* sp. PCC 6803, *Anabaena cylindrica*, *Synechococcus* sp. PCC 7942 and *Arthrospira maxima* [206,207,212,213]. Remarkably, the vitamin E content is higher in these cyanobacteria compared to some common food sources [206]. The production of vitamin E is necessary for protection against photooxidative damage to PSII [214]. The accumulation of  $\alpha$ -tocopherol was stimulated by the light intensity when *Synechocystis* sp. PCC 6803 was grown under photoautotrophic conditions [212]. Additionally, vitamin E also facilitates cyanobacteria to survive an emerging nutrient limitation. A study showed that *Arthrospira maxima*, *Nostoc* sp. PCC 7120 and *Synechocystis* sp. PCC 6803 produce low amount of vitamin E under optimum nitrogen availability [213]. However, *Arthrospira* sp. and *Oscillatoria* sp. synthesize high amounts of vitamin E in response to nitrogen deficiency at their logarithmic growth phase. Moreover, it is known that microalgae also produce vitamin E in response to nutrient limitation [215]. It is noteworthy that the production of vitamin E in microalgae is also a reaction in response to oxidative stress caused by metals [216,217]. This same antioxidative response could also happen in cyanobacteria, although so far, no study has been reported in these photosynthetic bacteria.

It was proposed that the marine *Anabaena cylindrica* possess a higher content of vitamin K1 than spinach and parsley [218]. Conversely, *Spirulina* sp. CS-785 produces a low amount of K1. Phylloquinone (vitamin K1) is synthesized by most cyanobacteria such as *Anabaena variabilis*, *Mastigocladus laminosus*, *Nostoc muscorum*, *Prochlorococcus* sp., *Anacystis nidulans*

and *Synechocystis* sp. PCC 6803 [219–221]. Phylloquinone not only acts as an one-electron carrier at the A1 binding site of PSI, but it also provides protection against growth damage at high light intensity [222]. Similar to vitamin K1, menaquinone (vitamin K2) acts as a secondary electron acceptor of PSI in *Gloeobacter violaceus* and *Synechococcus* sp. PCC 7002 [223,224]. Although phylloquinone and menaquinone exhibit structural similarity, the latter compound was absent in *Synechococcus* sp. PCC 7002, and two enzymes involved in its biosynthesis were missing in *Gloeobacter violaceus*.

Humans obtain vitamins through their diet. Vegetables, fruit, fish, and meat are great sources of vitamins. Currently, vitamin deficiencies occurring in humans are treated with synthetic vitamin analogs. For example, intramuscular injections or oral vitamin B<sub>12</sub> therapy are the most common treatments for patients with vitamin B<sub>12</sub> deficiency [225]. Those with vitamin D deficiency can be treated with oral ergocalciferol (vitamin D<sub>2</sub>) [226]. For adults with vitamin C deficiency and scurvy signs, oral ascorbic acid followed by a nutritious diet are always recommended [227,228]. Moreover, vitamin K1 can be administered via intramuscular injection or orally for people with vitamin K deficiency [229]. For adults with deficiency of vitamin A, vitamin A palmitate in oil is the most common method of treatment [230,231].

To date, only *Spirulina* (*Arthrospira* sp.) has been made available for consumption by humans as a supplementary diet. Indeed, several in vivo studies have showed the health benefits of well-characterized *Spirulina*, a rich source of vitamin B<sub>12</sub>,  $\beta$ -carotene and vitamin E. For example, *Spirulina* can improve bone strength and stiffness due to vitamin B<sub>12</sub> deficiency [232], prevent ulcer formation [233] and recover blood retinol status [234].

### 2.3.9. Antimetabolites

Antimetabolites are small molecules that inhibit the biosynthetic pathway by binding to the active site of the target molecule. An unusual deoxy sugar, 7-deoxy-D-altro-2-heptulose (7-deoxysedoheptulose, 7dSh) obtained from the *Synechococcus elongatus* PCC 7942 culture supernatant was identified to show biological activity against several wild type organisms, specifically, *Anabaena variabilis*, *Saccharomyces cerevisiae* and *Arabidopsis thaliana* [235]. In vitro analysis suggested that this antimetabolite mimics 3-deoxy-D-arabino-heptulosonate 7-phosphate (DAHP), the substrate of 3-dehydroquinate (DHQ) synthase. The binding of 7dSH on DHQ synthase leads to the inhibition of the enzyme and consequently blocks the shikimate pathway [235]. Additionally, a recent study detected the accumulation of 5-deoxyribose (5dR) and then 7dSh in the *Synechococcus elongatus* PCC 7942 culture supernatant under elevated CO<sub>2</sub> conditions [236]. The formation of 5dR was reported to be derived from the 5-deoxyadenosine (5dAdo) salvage pathway as a detoxification strategy in order to protect the radical S-adenosyl-L-methionine (SAM) enzymes from feedback inhibition [236]. In fact, 5dR is continuously imported and exported by the cells and serves as a precursor for 7dSH, which is metabolized by transketolase activity when a relatively high extracellular 5dR concentration is reached [236]. This unique biosynthesis pathway strategy enables cyanobacteria to survive a niche competition by inhibiting the growth of other microalgae or bacteria and is especially crucial for the unicellular cyanobacteria with small genome sizes and fewer plasmids [236].

Another cyanobacterial antimetabolite, a nonprotein amino acid  $\beta$ -methylamino-L-alanine (BMAA), may be involved in the nitrogen metabolism of cyanobacteria in order for the nitrogen-fixing microbes to survive under nutrient deprivation. Previous studies have suggested that the production of BMAA is correlated with nitrogen starvation under both natural and culture conditions, which results in the inhibition of the nitrogen assimilation pathway [237–240]. In turn, the concentration of BMAA was declined when a nitrogen source was added to the nitrogen-starved *Microcystis* PCC 7806 culture [241]. Although very little is known regarding the biological function of BMAA in cyanobacteria, *Synechococcus* sp. TAU-MAC 0499, *Synechocystis* PCC 6803 and *Anabaena* sp. PCC 7120 have been found to rapidly import exogenous BMAA [237,238,240]. BMAA was suggested to impair the activity of glutamine synthetase-glutamine-oxoglutarate aminotransferase (GS-GOGAT),

the sequentially functioning enzymes that are involved in nitrogen assimilation, in the non-BMAA producer *Synechococcus* sp. TAU-MAC 0499 and the BMAA producer *Synechocystis* PCC 6803 [237,242]. Specifically, BMAA competes with glutamine to bind to GOGAT and acts as an inactivating factor [242]. On the other hand, nitrogenase activity was inhibited in *Anabaena* sp. PCC 7120 culture supplied with exogenous BMAA and the cyanobacterial growth was retarded by forming chlorotic cells. Similarly, the growth of BMAA producer *Synechocystis* PCC 6803 was arrested and the formation of chlorotic cells increased in the presence of exogenous BMAA [238]. Chlorotic is a dormant state of cyanobacterial cells in order to prolong their survival period under nitrogen starvation [243]. On the contrary, exogenous BMAA does not affect the physiology of *Synechococcus* sp. TAU-MAC 0499 [237]. A recent study reported a different response of growth retardation by the non-BMAA producers *Microcystis aeruginosa* (FACHB-836 and 905) [244] compared to *Synechococcus* sp. TAU-MAC 0499, whereas BMAA has no negative impacts on the BMAA producers *Anabaena* sp. FACHB-418 and *Microcystis wesenbergii* FACHB-908 [244]. To date, little is known about the effects of BMAA on cyanobacteria. However, it is tempting to speculate that cyanobacteria synthesize BMAA as a response to nutrient-limited conditions by either eliminating the competitors or forming dormant cells [237,238,244,245]. Additionally, the fact that a low concentration of bound BMAA was detected in the non-nitrogen-fixing *Microcystis wesenbergii* (FACHB-908) and *Synechocystis* (FACHB-898) suggested that BMAA may be involved in the formation of cyanobacterial proteins [244].

Remarkably, antibacterial, antifungal, and herbicidal properties exhibited by the unusual deoxy sugar 7dSh [235] suggest its applications in various fields including agriculture, water management, veterinary medicine, and human medicine. On the other hand, further confirmation on the biological function of BMAA in cyanobacteria could provide solutions to control cyanobacterial bloom and subsequently overcome its neurotoxic effects on humans, which are associated with amyotrophic lateral sclerosis, Parkinson's disease, and Alzheimer's disease [246].

### 3. Conclusions

Pharmacological effects exhibited by plant natural bioactive metabolites have led to their numerous applications in the treatment of serious and chronic diseases. In plants, bioactive metabolites are typically produced in low amounts as secondary metabolites. Therefore, a large amount of plant resources is required for traditional extraction methods of these compounds to obtain the industrial yield. However, these methods are known to be unsustainable. For decades, important discoveries of the biological activities possessed by the bioactive metabolites produced by cyanobacteria has attracted attention for modern therapy. These oxygenic photosynthetic microbes produce bioactive metabolites as a response to environmental stresses. Some of the compounds are produced in abundance to release the stress effects. Moreover, the emergence of synthetic biology tools has allowed the combinatorial synthesis of plant-derived biosynthetic genes involved in metabolic pathways to be heterologously expressed in cyanobacteria. In fact, the capacity to express P450, an enzyme involved in secondary metabolite production in plants, is beneficial in the metabolic engineering of cyanobacteria for the heterologous expression of the plant bioactive metabolic pathway. Together with this synthetic biology approach, the advancement in bioprocess engineering can produce natural bioactive compounds using sustainable approaches in order to meet industrial demands in the future.

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## References

1. Cho, S.M.; Jeoung, S.C.; Song, J.-Y.; Kupriyanova, E.V.; Pronina, N.A.; Lee, B.-W.; Jo, S.-W.; Park, B.-S.; Choi, S.-B.; Song, J.-J. Genomic survey and biochemical analysis of recombinant candidate cyanobacteriochromes reveals enrichment for near UV/violet sensors in the halotolerant and alkaliphilic cyanobacterium *Microcoleus* IPPAS B353. *J. Biol. Chem.* **2015**, *290*, 28502–28514. [[CrossRef](#)]
2. Herbert, R.A.; Codd, G.A. *Microbes in Extreme Environments*; Academic Press: London, UK, 1986.
3. Shih, P.M.; Wu, D.; Latifi, A.; Axen, S.D.; Fewer, D.P.; Talla, E.; Calteau, A.; Cai, F.; De Marsac, N.T.; Rippka, R. Improving the coverage of the cyanobacterial phylum using diversity-driven genome sequencing. *Proc. Natl. Acad. Sci. USA* **2013**, *110*, 1053–1058. [[CrossRef](#)] [[PubMed](#)]
4. Bhaya, D.; Grossman, A.R.; Steunou, A.-S.; Khuri, N.; Cohan, F.M.; Hamamura, N.; Melendrez, M.C.; Bateson, M.M.; Ward, D.M.; Heidelberg, J.F. Population level functional diversity in a microbial community revealed by comparative genomic and metagenomic analyses. *ISME J.* **2007**, *1*, 703–713. [[CrossRef](#)] [[PubMed](#)]
5. Cheevadhanarak, S.; Paithoonrangsarid, K.; Prommeenate, P.; Kaewngam, W.; Musigkain, A.; Tragoonrung, S.; Tabata, S.; Kaneko, T.; Chaijaruwanich, J.; Sangsrakru, D. Draft genome sequence of *Arthrospira platensis* C1 (PCC 9438). *Stand. Genom. Sci.* **2012**, *6*, 43–53. [[CrossRef](#)]
6. Fujisawa, T.; Narikawa, R.; Okamoto, S.; Ehira, S.; Yoshimura, H.; Suzuki, I.; Masuda, T.; Mochimaru, M.; Takaichi, S.; Awai, K. Genomic structure of an economically important cyanobacterium, *Arthrospira* (Spirulina) *platensis* NIES-39. *DNA Res.* **2010**, *17*, 85–103. [[CrossRef](#)] [[PubMed](#)]
7. Lefort, F.; Calmin, G.; Crovadore, J.; Falquet, J.; Hurni, J.-P.; Osteras, M.; Haldemann, F.; Farinelli, L. Whole-genome shotgun sequence of *Arthrospira platensis* strain Paraca, a cultivated and edible cyanobacterium. *Genome Announc.* **2014**, *2*, e00751-14. [[CrossRef](#)] [[PubMed](#)]
8. Carrieri, D.; Ananyev, G.; Lenz, O.; Bryant, D.A.; Dismukes, G.C. Contribution of a sodium ion gradient to energy conservation during fermentation in the cyanobacterium *Arthrospira* (Spirulina) *maxima* CS-328. *Appl. Environ. Microbiol.* **2011**, *77*, 7185–7194. [[CrossRef](#)] [[PubMed](#)]
9. Janssen, P.J.; Morin, N.; Mergeay, M.; Leroy, B.; Wattiez, R.; Vallaeys, T.; Waleron, K.; Waleron, M.; Wilmotte, A.; Quillardet, P. Genome sequence of the edible cyanobacterium *Arthrospira* sp. PCC 8005. *J. Bacteriol.* **2010**, *192*, 2465–2466. [[CrossRef](#)]
10. Dong, S.; Chen, J.; Wang, S.; Wu, Y.; Hou, H.; Li, M.; Yan, C. Draft genome sequence of cyanobacteria *Arthrospira* sp. TJS091 isolated from seaside wetland. *Mar. Genom.* **2015**, *24*, 197–198. [[CrossRef](#)]
11. Hirooka, S.; Hirose, Y.; Kanesaki, Y.; Higuchi, S.; Fujiwara, T.; Onuma, R.; Era, A.; Ohbayashi, R.; Uzuka, A.; Nozaki, H. Acidophilic green algal genome provides insights into adaptation to an acidic environment. *Proc. Natl. Acad. Sci. USA* **2017**, *114*, E8304–E8313. [[CrossRef](#)]
12. Gross, W. Ecophysiology of algae living in highly acidic environments. *Hydrobiologia* **2000**, *433*, 31–37. [[CrossRef](#)]
13. Ferris, M.J.; Sheehan, K.B.; Kuhl, M.; Cooksey, K.; Wigglesworth-Cooksey, B.; Harvey, R.; Henson, J.M. Algal species and light microenvironment in a low-pH, geothermal microbial mat community. *Appl. Environ. Microbiol.* **2005**, *71*, 7164–7171. [[CrossRef](#)]
14. Khomutovska, N.; de Los Ríos, A.; Jasser, I. Diversity and Colonization Strategies of Endolithic Cyanobacteria in the Cold Mountain Desert of Pamir. *Microorganisms* **2021**, *9*, 6. [[CrossRef](#)] [[PubMed](#)]
15. Ramos, V.; Castelo-Branco, R.; Leao, P.N.; Martins, J.; Carvalhal-Gomes, S.; Sobrinho da Silva, F.; Mendonca Filho, J.G.; Vasconcelos, V.M. Cyanobacterial diversity in microbial mats from the hypersaline lagoon system of Araruama, Brazil: An in-depth polyphasic study. *Front. Microbiol.* **2017**, *8*, 1233. [[CrossRef](#)]
16. Sterner, R.W.; Reinl, K.L.; Lafrancois, B.M.; Brovold, S.; Miller, T.R. A first assessment of cyanobacterial blooms in oligotrophic Lake Superior. *Limnol. Oceanogr.* **2020**, *65*, 2984–2998. [[CrossRef](#)]
17. Reinl, K.L.; Sterner, R.W.; Lafrancois, B.M.; Brovold, S. Fluvial seeding of cyanobacterial blooms in oligotrophic Lake Superior. *Harmful Algae* **2020**, *100*, 101941. [[CrossRef](#)] [[PubMed](#)]
18. Nadeau, T.L.; Castenholz, R.W. Characterization of psychrophilic oscillatorians (cyanobacteria) from Antarctic meltwater ponds. *J. Phycol.* **2000**, *36*, 914–923. [[CrossRef](#)]
19. Singh, S.M.; Elster, J. Cyanobacteria in Antarctic lake environments. In *Algae and Cyanobacteria in Extreme Environments. Cellular Origin, Life in Extreme Habitats and Astrobiology*; Seckbach, J., Ed.; Springer: Dordrecht, The Netherlands, 2007; Volume 11, pp. 303–320.
20. Thangaraj, B.; Rajasekar, D.P.; Vijayaraghavan, R.; Garlapati, D.; Devanesan, A.A.; Lakshmanan, U.; Dharmar, P. Cytomorphological and nitrogen metabolic enzyme analysis of psychrophilic and mesophilic *Nostoc* sp.: A comparative outlook. *3 Biotech* **2017**, *7*, 107. [[CrossRef](#)] [[PubMed](#)]
21. Pedersen, D.; Miller, S.R. Photosynthetic temperature adaptation during niche diversification of the thermophilic cyanobacterium *Synechococcus* A/B clade. *ISME J.* **2017**, *11*, 1053–1057. [[CrossRef](#)] [[PubMed](#)]
22. Maeda, K.; Tamura, J.; Okuda, Y.; Narikawa, R.; Midorikawa, T.; Ikeuchi, M. Genetic identification of factors for extracellular cellulose accumulation in the thermophilic cyanobacterium *Thermo Synechococcus vulcanus*: Proposal of a novel tripartite secretion system. *Mol. Microbiol.* **2018**, *109*, 121–134. [[CrossRef](#)]

23. Tyagi, S.; Singh, R.K.; Tiwari, S.P. Anti-enterococcal and anti-oxidative potential of a thermophilic cyanobacterium, *Leptolyngbya* sp. HNBGU 003. *Saudi J. Biol. Sci.* **2021**, *28*, 4022–4028. [[CrossRef](#)]
24. Karatay, S.E.; Dönmez, G.; Aksu, Z. Effective biosorption of phenol by the thermophilic cyanobacterium *Phormidium* sp. *Water Sci. Technol.* **2017**, *76*, 3190–3194. [[CrossRef](#)] [[PubMed](#)]
25. El-Mohsnawy, E.; Abu-Khudir, R. A highly purified C-phycocyanin from thermophilic cyanobacterium *Thermo Synechococcus elongatus* and its cytotoxic activity assessment using an in vitro cell-based approach. *J. Taibah Univ. Sci.* **2020**, *14*, 1218–1225. [[CrossRef](#)]
26. Ahmed, O.M.; Mahmoud, A.M.; Abdel-Moneim, A.; Ashour, M.B. Antidiabetic effects of hesperidin and naringin in type 2 diabetic rats. *Diabetol. Croat.* **2012**, *41*, 53–67.
27. Zhu, Z.; Fu, F.; Qu, P.; Mak, E.W.K.; Jiang, H.; Zhang, R.; Zhu, Z.; Gao, K.; Hutchins, D.A. Interactions between ultraviolet radiation exposure and phosphorus limitation in the marine nitrogen-fixing cyanobacteria *Trichodesmium* and *Crocosphaera*. *Limnol. Oceanogr.* **2020**, *65*, 363–376. [[CrossRef](#)]
28. Song, W.; Zhao, C.; Zhang, D.; Mu, S.; Pan, X. Different resistance to UV-B radiation of extracellular polymeric substances of two cyanobacteria from contrasting habitats. *Front. Microbiol.* **2016**, *7*, 1208. [[CrossRef](#)]
29. Cohen, Y.; Jørgensen, B.B.; Revsbech, N.P.; Poplawski, R. Adaptation to hydrogen sulfide of oxygenic and anoxygenic photosynthesis among cyanobacteria. *Appl. Environ. Microbiol.* **1986**, *51*, 398–407. [[CrossRef](#)]
30. Hamilton, T.L.; Klatt, J.M.; De Beer, D.; Macalady, J.L. Cyanobacterial photosynthesis under sulfidic conditions: Insights from the isolate *Leptolyngbya* sp. strain hensonii. *ISME J.* **2018**, *12*, 568–584. [[CrossRef](#)]
31. Klatt, J.M.; Gomez-Saez, G.V.; Meyer, S.; Ristova, P.P.; Yilmaz, P.; Granitsiotis, M.S.; Macalady, J.L.; Lavik, G.; Polerecky, L.; Bühring, S.I. Versatile cyanobacteria control the timing and extent of sulfide production in a Proterozoic analog microbial mat. *ISME J.* **2020**, *14*, 3024–3037. [[CrossRef](#)]
32. Stal, L.J.; Moezelaar, R. Fermentation in cyanobacteria. *FEMS Microbiol. Rev.* **1997**, *21*, 179–211. [[CrossRef](#)]
33. Capone, D.G.; Burns, J.A.; Montoya, J.P.; Subramaniam, A.; Mahaffey, C.; Gunderson, T.; Michaels, A.F.; Carpenter, E.J. Nitrogen fixation by *Trichodesmium* spp.: An important source of new nitrogen to the tropical and subtropical North Atlantic Ocean. *Glob. Biogeochem. Cycles* **2005**, *19*. [[CrossRef](#)]
34. Herrero, A.; Stavans, J.; Flores, E. The multicellular nature of filamentous heterocyst-forming cyanobacteria. *FEMS Microbiol. Rev.* **2016**, *40*, 831–854. [[CrossRef](#)] [[PubMed](#)]
35. Mehda, S.; Muñoz-Martín, M.; Oustani, M.; Hamdi-Aïssa, B.; Perona, E.; Mateo, P. Microenvironmental Conditions Drive the Differential Cyanobacterial Community Composition of Biocrusts from the Sahara Desert. *Microorganisms* **2021**, *9*, 487. [[CrossRef](#)] [[PubMed](#)]
36. Pushkareva, E.; Pessi, I.S.; Wilmette, A.; Elster, J. Cyanobacterial community composition in Arctic soil crusts at different stages of development. *FEMS Microbiol. Ecol.* **2015**, *91*, fiv143. [[CrossRef](#)] [[PubMed](#)]
37. Amarouche-Yala, S.; Benouadah, A.; López-García, P. Morphological and phylogenetic diversity of thermophilic cyanobacteria in Algerian hot springs. *Extremophiles* **2014**, *18*, 1035–1047. [[CrossRef](#)]
38. Eisenberg, I.; Caycedo-Soler, F.; Harris, D.; Yochelis, S.; Huelga, S.F.; Plenio, M.B.; Adir, N.; Keren, N.; Paltiel, Y. Regulating the energy flow in a cyanobacterial light-harvesting antenna complex. *J. Phys. Chem. B* **2017**, *121*, 1240–1247. [[CrossRef](#)]
39. Adir, N.; Dobrovetsky, Y.; Lerner, N. Structure of C-phycocyanin from the thermophilic cyanobacterium *Synechococcus vulcanus* at 2.5 Å: Structural implications for thermal stability in phycobilisome assembly. *J. Mol. Biol.* **2001**, *313*, 71–81. [[CrossRef](#)]
40. Komenda, J. Role of two forms of the D1 protein in the recovery from photoinhibition of photosystem II in the cyanobacterium *Synechococcus* PCC 7942. *Biochim. Biophys. Acta (BBA)-Bioenerg.* **2000**, *1457*, 243–252. [[CrossRef](#)]
41. Nishiyama, Y.; Los, D.A.; Hayashi, H.; Murata, N. Thermal protection of the oxygen-evolving machinery by PsbU, an extrinsic protein of photosystem II, in *Synechococcus* species PCC 7002. *Plant Physiol.* **1997**, *115*, 1473–1480. [[CrossRef](#)]
42. Prihantini, N.B.; Fitrianti, A.N.; Sjamsuridzal, W.; Yokota, A. Growth temperature of hot springs filamentous cyanobacteria in artificial media. *AIP Conf. Proc.* **2020**, *2242*, 050012.
43. Strunecký, O.; Kopejtká, K.; Goecke, F.; Tomasch, J.; Lukavský, J.; Neori, A.; Kahl, S.; Pieper, D.H.; Pilarski, P.; Kaftan, D. High diversity of thermophilic cyanobacteria in Rupite hot spring identified by microscopy, cultivation, single-cell PCR and amplicon sequencing. *Extremophiles* **2019**, *23*, 35–48. [[CrossRef](#)]
44. Mittler, R.; Tel-or, E. Oxidative stress responses in the unicellular cyanobacterium *Synechococcus* PCC 7942. *Free Radic. Res. Commun.* **1991**, *13*, 845–850. [[CrossRef](#)]
45. Ehling-Schulz, M.; Bilger, W.; Scherer, S. UV-B-induced synthesis of photoprotective pigments and extracellular polysaccharides in the terrestrial cyanobacterium *Nostoc commune*. *J. Bacteriol.* **1997**, *179*, 1940–1945. [[CrossRef](#)]
46. Mloszewski, A.M.; Cole, D.B.; Planavsky, N.J.; Kappler, A.; Whitford, D.S.; Owttrim, G.W.; Konhauser, K.O. UV radiation limited the expansion of cyanobacteria in early marine photic environments. *Nat. Commun.* **2018**, *9*, 3088. [[CrossRef](#)]
47. Mur, R.; Skulberg, O.M.; Utkilen, H. Cyanobacteria in the Environment. In *Toxic Cyanobacteria in Water: A Guide to Their Public Health Consequences, Monitoring, and Management*; Chorus, I., Bartram, J., Eds.; World Health Organization, Routledge: London, UK, 1999.
48. Thajuddin, N.; Subramanian, G. Cyanobacterial biodiversity and potential applications in biotechnology. *Curr. Sci.* **2005**, *89*, 47–57.



49. Rippka, R.; Deruelles, J.; Waterbury, J.B.; Herdman, M.; Stanier, R.Y. Generic assignments, strain histories and properties of pure cultures of cyanobacteria. *Microbiology* **1979**, *111*, 1–61. [[CrossRef](#)]
50. Uyeda, J.C.; Harmon, L.J.; Blank, C.E. A comprehensive study of cyanobacterial morphological and ecological evolutionary dynamics through deep geologic time. *PLoS ONE* **2016**, *11*, e0162539. [[CrossRef](#)]
51. Tiwari, G.L. On the morphology and life-history of a new species of Chroococciopsis Geitler (Chroococcales). *Hydrobiologia* **1972**, *40*, 177–182. [[CrossRef](#)]
52. Demoulin, C.F.; Lara, Y.J.; Cornet, L.; François, C.; Baurain, D.; Wilmette, A.; Javaux, E.J. Cyanobacteria evolution: Insight from the fossil record. *Free Radic. Biol. Med.* **2019**, *140*, 206–223. [[CrossRef](#)] [[PubMed](#)]
53. Roldán, M.; Ramírez, M.; Del Campo, J.; Hernández-Mariné, M.; Komárek, J. *Chalicogloea cavernicola* gen. nov., sp. nov. (Chroococcales, Cyanobacteria), from low-light aerophytic environments: Combined molecular, phenotypic and ecological criteria. *Int. J. Syst. Evol. Microbiol.* **2013**, *63*, 2326–2333. [[CrossRef](#)] [[PubMed](#)]
54. Margheri, M.C.; Ventura, S.; Kaštokský, J.; Komárek, J. The taxonomic validation of the cyanobacterial genus *Halothece*. *Phycologia* **2008**, *47*, 477–486. [[CrossRef](#)]
55. Berrendero, E.; Valiente, E.F.; Perona, E.; Gómez, C.L.; Loza, V.; Muñoz-Martín, M.Á.; Mateo, P. Nitrogen fixation in a non-heterocystous cyanobacterial mat from a mountain river. *Sci. Rep.* **2016**, *6*, 30920. [[CrossRef](#)] [[PubMed](#)]
56. Zhang, X.-J.; Feng, J.; Wang, G.-H.; Xie, S.-L. A morphological and phylogenetic study of a filamentous cyanobacterium, *Microcoleus vaginatus*, associated with the moss *Mnium cuspidatum*. *Symbiosis* **2014**, *64*, 43–51. [[CrossRef](#)]
57. Taha, H.S.; El Bahr, M.K.; Seif, E.L.N.M.M. In Vitro Studies on Egyptian *Catharanthus roseus* (L.). II. Effect of Biotic and Abiotic Stress on Indole Alkaloids Production. *J. Appl. Sci. Res.* **2009**, *3*, 3137–3144.
58. Singh, B.; A Sharma, R.; K Vyas, G. Antimicrobial, Antineoplastic and Cytotoxic Activities of Indole Alkaloids from *Tabernaemontana divaricata* (L.) R. Br. *Curr. Pharm. Anal.* **2011**, *7*, 125–132. [[CrossRef](#)]
59. El-Sayed, M.; Verpoorte, R. *Catharanthus* terpenoid indole alkaloids: Biosynthesis and regulation. *Phytochem. Rev.* **2007**, *6*, 277–305. [[CrossRef](#)]
60. Mayser, P.; Schäfer, U.; Krämer, H.-J.; Irlinger, B.; Steglich, W. Pityriacitrin—an ultraviolet-absorbing indole alkaloid from the yeast *Malassezia furfur*. *Arch. Dermatol. Res.* **2002**, *294*, 131–134. [[CrossRef](#)]
61. Aiello, A.; Borrelli, F.; Capasso, R.; Fattorusso, E.; Luciano, P.; Menna, M. Conicamin, a novel histamine antagonist from the mediterranean tunicate *Aplidium conicum*. *Bioorganic Med. Chem. Lett.* **2003**, *13*, 4481–4483. [[CrossRef](#)] [[PubMed](#)]
62. Sauviat, M.-P.; Vercauteren, J.; Grimaud, N.; Jugé, M.; Nabil, M.; Petit, J.-Y.; Biard, J.-F. Sensitivity of cardiac background inward rectifying K<sup>+</sup> outward current (I<sub>K1</sub>) to the alkaloids lepadiformines A, B, and C. *J. Nat. Prod.* **2006**, *69*, 558–562. [[CrossRef](#)]
63. Kobayashi, H.; Kitamura, K.; Nagai, K.; Nakao, Y.; Fusetani, N.; van Soest, R.W.M.; Matsunaga, S. Carteramine A, an inhibitor of neutrophil chemotaxis, from the marine sponge *Stylissa carteri*. *Tetrahedron Lett.* **2007**, *48*, 2127–2129. [[CrossRef](#)]
64. Sayed, K.A.E.; Khalil, A.A.; Yousaf, M.; Labadie, G.; Kumar, G.M.; Franzblau, S.G.; Mayer, A.M.S.; Avery, M.A.; Hamann, M.T. Semisynthetic studies on the manzamine alkaloids. *J. Nat. Prod.* **2008**, *71*, 300–308. [[CrossRef](#)] [[PubMed](#)]
65. Pearce, A.N.; Chia, E.W.; Berridge, M.V.; Clark, G.R.; Harper, J.L.; Larsen, L.; Maas, E.W.; Page, M.J.; Perry, N.B.; Webb, V.L. Anti-inflammatory thiazine alkaloids isolated from the New Zealand ascidian *Aplidium* sp.: Inhibitors of the neutrophil respiratory burst in a model of gouty arthritis. *J. Nat. Prod.* **2007**, *70*, 936–940. [[CrossRef](#)] [[PubMed](#)]
66. Pearce, A.N.; Chia, E.W.; Berridge, M.V.; Maas, E.W.; Page, M.J.; Webb, V.L.; Harper, J.L.; Copp, B.R. E/Z-rubrolide O, an anti-inflammatory halogenated furanone from the New Zealand ascidian *Synoicum* n. sp. *J. Nat. Prod.* **2007**, *70*, 111–113. [[CrossRef](#)] [[PubMed](#)]
67. Chilczuk, T.; Steinborn, C.; Breinlinger, S.; Zimmermann-Klemd, A.M.; Huber, R.; Enke, H.; Enke, D.; Niedermeyer, T.H.J.; Gründemann, C. Hapalindoles from the cyanobacterium *Hapalosiphon* sp. inhibit T cell proliferation. *Planta Med.* **2020**, *86*, 96–103. [[CrossRef](#)] [[PubMed](#)]
68. Moore, R.E.; Cheuk, C.; Yang, X.Q.G.; Patterson, G.M.L.; Bonjouklian, R.; Smitka, T.A.; Mynderse, J.S.; Foster, R.S.; Jones, N.D.; Swartzendruber, J.K. Hapalindoles, antibacterial and antimycotic alkaloids from the cyanophyte *Hapalosiphon fontinalis*. *J. Org. Chem.* **1987**, *52*, 1036–1043. [[CrossRef](#)]
69. Moore, R.E.; Cheuk, C.; Patterson, G.M.L. Hapalindoles: New alkaloids from the blue-green alga *Hapalosiphon fontinalis*. *J. Am. Chem. Soc.* **1984**, *106*, 6456–6457. [[CrossRef](#)]
70. Kim, H.; Lantvit, D.; Hwang, C.H.; Kroll, D.J.; Swanson, S.M.; Franzblau, S.G.; Orjala, J. Indole alkaloids from two cultured cyanobacteria, *Westiellopsis* sp. and *Fischerella muscicola*. *Bioorganic Med. Chem.* **2012**, *20*, 5290–5295. [[CrossRef](#)] [[PubMed](#)]
71. Hillwig, M.L.; Zhu, Q.; Liu, X. Biosynthesis of ambiguine indole alkaloids in cyanobacterium *Fischerella ambigua*. *ACS Chem. Biol.* **2014**, *9*, 372–377. [[CrossRef](#)]
72. Hillwig, M.L.; Fuhrman, H.A.; Ittiarnornkul, K.; Sevco, T.J.; Kwak, D.H.; Liu, X. Identification and characterization of a welwitindolinone alkaloid biosynthetic gene cluster in the stigonematalean cyanobacterium *Hapalosiphon welwitschii*. *ChemBioChem* **2014**, *15*, 665–669. [[CrossRef](#)]
73. Micallef, M.L.; Sharma, D.; Bunn, B.M.; Gerwick, L.; Viswanathan, R.; Moffitt, M.C. Comparative analysis of hapalindole, ambiguine and welwitindolinone gene clusters and reconstitution of indole-isonitrile biosynthesis from cyanobacteria. *BMC Microbiol.* **2014**, *14*, 1–18. [[CrossRef](#)]

74. Smitka, T.A.; Bonjouklian, R.; Doolin, L.; Jones, N.D.; Deeter, J.B.; Yoshida, W.Y.; Prinsep, M.R.; Moore, R.E.; Patterson, G.M.L. Ambiguine isonitriles, fungicidal hapalindole-type alkaloids from three genera of blue-green algae belonging to the Stigonemataceae. *J. Org. Chem.* **1992**, *57*, 857–861. [[CrossRef](#)]
75. Park, A.; Moore, R.E.; Patterson, G.M.L. Fischerindole L, a new isonitrile from the terrestrial blue-green alga *Fischerella muscicola*. *Tetrahedron Lett.* **1992**, *33*, 3257–3260. [[CrossRef](#)]
76. Mo, S.; Krunic, A.; Santarsiero, B.D.; Franzblau, S.G.; Orjala, J. Hapalindole-related alkaloids from the cultured cyanobacterium *Fischerella ambigua*. *Phytochemistry* **2010**, *71*, 2116–2123. [[CrossRef](#)]
77. Jimenez, J.I.; Huber, U.; Moore, R.E.; Patterson, G.M.L. Oxidized welwitindolinones from terrestrial fischerella spp. *J. Nat. Prod.* **1999**, *62*, 569–572. [[CrossRef](#)]
78. Stratmann, K.; Moore, R.E.; Bonjouklian, R.; Deeter, J.B.; Patterson, G.M.L.; Shaffer, S.; Smith, C.D.; Smitka, T.A. Welwitindolinones, unusual alkaloids from the blue-green algae *Hapalosiphon welwitschii* and *Westiella intricata*. Relationship to fischerindoles and hapalindoles. *J. Am. Chem. Soc.* **1994**, *116*, 9935–9942. [[CrossRef](#)]
79. Richter, J.M.; Ishihara, Y.; Masuda, T.; Whitefield, B.W.; Llamas, T.; Pohjakallio, A.; Baran, P.S. Enantiospecific total synthesis of the hapalindoles, fischerindoles, and welwitindolinones via a redox economic approach. *J. Am. Chem. Soc.* **2008**, *130*, 17938–17954. [[CrossRef](#)]
80. Demay, J.; Bernard, C.; Reinhardt, A.; Marie, B. Natural products from cyanobacteria: Focus on beneficial activities. *Mar. Drugs* **2019**, *17*, 320. [[CrossRef](#)] [[PubMed](#)]
81. Walton, K.; Berry, J.P. Indole alkaloids of the *Stigonematales* (Cyanophyta): Chemical diversity, biosynthesis and biological activity. *Mar. Drugs* **2016**, *14*, 73. [[CrossRef](#)] [[PubMed](#)]
82. Castenholz, R.W.; Garcia-Pichel, F. Cyanobacterial responses to UV radiation. In *Ecology of Cyanobacteria II*; Whitton, B.A., Ed.; Springer: Dordrecht, The Netherlands, 2012; pp. 481–499.
83. Nägeli, C. *Gattungen Einzelliger Algen: Physiologisch und Systematisch Bearbeitet*; Friedrich Schulthess: Zürich, Switzerland, 1849.
84. Orellana, G.; Gómez-Silva, B.; Urrutia, M.; Galetović, A. UV-A Irradiation Increases Scytonemin Biosynthesis in Cyanobacteria Inhabiting Halites at Salar Grande, Atacama Desert. *Microorganisms* **2020**, *8*, 1690. [[CrossRef](#)]
85. Rastogi, R.P.; Incharoensakdi, A. Characterization of UV-screening compounds, mycosporine-like amino acids, and scytonemin in the cyanobacterium *Lyngbya* sp. CU2555. *FEMS Microbiol. Ecol.* **2014**, *87*, 244–256. [[CrossRef](#)]
86. Dillon, J.G.; Tatsumi, C.M.; Tandingan, P.G.; Castenholz, R.W. Effect of environmental factors on the synthesis of scytonemin, a UV-screening pigment, in a cyanobacterium (*Chroococcidiopsis* sp.). *Arch. Microbiol.* **2002**, *177*, 322–331. [[CrossRef](#)]
87. Cao, R.; Peng, W.; Wang, Z.; Xu, A.  $\beta$ -Carboline alkaloids: Biochemical and pharmacological functions. *Curr. Med. Chem.* **2007**, *14*, 479–500. [[CrossRef](#)]
88. Volk, R.-B. Screening of microalgal culture media for the presence of algicidal compounds and isolation and identification of two bioactive metabolites, excreted by the cyanobacteria *Nostoc insulare* and *Nodularia harveyana*. *J. Appl. Phycol.* **2005**, *17*, 339–347. [[CrossRef](#)]
89. Volk, R.-B.; Furkert, F.H. Antialgal, antibacterial and antifungal activity of two metabolites produced and excreted by cyanobacteria during growth. *Microbiol. Res.* **2006**, *161*, 180–186. [[CrossRef](#)]
90. Becher, P.G.; Baumann, H.I.; Gademann, K.; Jüttner, F. The cyanobacterial alkaloid nostocarboline: An inhibitor of acetylcholinesterase and trypsin. *J. Appl. Phycol.* **2009**, *21*, 103–110. [[CrossRef](#)]
91. Breitmaier, E. Terpenes: Importance, general structure, and biosynthesis. *Terpenes Flavors Fragr. Pharmaca Pheromones* **2006**, *1*, 1–3.
92. Kandi, S.; Godishala, V.; Rao, P.; Ramana, K.V. Biomedical significance of terpenes: An insight. *Biomedicine* **2015**, *3*, 8–10.
93. Abdallah, I.I.; Quax, W.J. A Glimpse into the Biosynthesis of Terpenoids. In Proceedings of the International Conference on Natural Resources and Life Sciences (2016), Surabaya, Indonesia, 20–21 October 2016; KnE Life Sciences: Dubai, United Arab Emirates, 2017; pp. 81–98.
94. Gershenzon, J.; Dudareva, N. The function of terpene natural products in the natural world. *Nat. Chem. Biol.* **2007**, *3*, 408–414. [[CrossRef](#)] [[PubMed](#)]
95. Dittmann, E.; Gugger, M.; Sivonen, K.; Fewer, D.P. Natural product biosynthetic diversity and comparative genomics of the cyanobacteria. *Trends Microbiol.* **2015**, *23*, 642–652. [[CrossRef](#)] [[PubMed](#)]
96. Yamada, Y.; Kuzuyama, T.; Komatsu, M.; Shin-Ya, K.; Omura, S.; Cane, D.E.; Ikeda, H. Terpene synthases are widely distributed in bacteria. *Proc. Natl. Acad. Sci. USA* **2015**, *112*, 857–862. [[CrossRef](#)]
97. Devi, S.; Rani, N.; Sagar, A. GC-MS Analysis and antioxidant activity of two species of cyanobacteria isolated from Drang salt mine of district Mandi, Himachal Pradesh, India. *Plant Arch.* **2020**, *20*, 7505–7510.
98. Höckelmann, C.; Becher, P.G.; von Reuss, S.H.; Jüttner, F. Sesquiterpenes of the geosmin-producing cyanobacterium *Calothrix* PCC 7507 and their toxicity to invertebrates. *Z. Nat. C* **2009**, *64*, 49–55. [[CrossRef](#)]
99. Dienst, D.; Wichmann, J.; Mantovani, O.; Rodrigues, J.S.; Lindberg, P. High density cultivation for efficient sesquiterpenoid biosynthesis in *Synechocystis* sp. PCC 6803. *Sci. Rep.* **2020**, *10*, 5932. [[CrossRef](#)]
100. Agger, S.A.; Lopez-Gallego, F.; Hoyer, T.R.; Schmidt-Dannert, C. Identification of sesquiterpene synthases from *Nostoc punctiforme* PCC 73102 and *Nostoc* sp. strain PCC 7120. *J. Bacteriol.* **2008**, *190*, 6084–6096. [[CrossRef](#)] [[PubMed](#)]
101. Unson, M.D.; Faulkner, D.J. Cyanobacterial symbiont biosynthesis of chlorinated metabolites from *Dysidea herbacea* (Porifera). *Experientia* **1993**, *49*, 349–353. [[CrossRef](#)]

102. Jahnke, L.L.; Embaye, T.; Hope, J.; Turk, K.A.; Van Zuilen, M.; Des Marais, D.J.; Farmer, J.D.; Summons, R.E. Lipid biomarker and carbon isotopic signatures for stromatolite-forming, microbial mat communities and *Phormidium* cultures from Yellowstone National Park. *Geobiology* **2004**, *2*, 31–47. [[CrossRef](#)]
103. Summons, R.E.; Jahnke, L.L.; Hope, J.M.; Logan, G.A. 2-Methylhopanoids as biomarkers for cyanobacterial oxygenic photosynthesis. *Nature* **1999**, *400*, 554–557. [[CrossRef](#)] [[PubMed](#)]
104. Garby, T.J.; Matys, E.D.; Ongley, S.E.; Salih, A.; Larkum, A.W.D.; Walter, M.R.; Summons, R.E.; Neilan, B.A. Lack of methylated hopanoids renders the cyanobacterium *Nostoc punctiforme* sensitive to osmotic and pH stress. *Appl. Environ. Microbiol.* **2017**, *83*, e00777-17. [[CrossRef](#)] [[PubMed](#)]
105. Hirschberg, J.; Chamovitz, D. Carotenoids in cyanobacteria. In *The Molecular Biology of Cyanobacteria. Advances in Photosynthesis*, 1st ed.; Bryant, D.A., Ed.; Springer: Dordrecht, Netherlands, 1994; Volume 1, pp. 559–579.
106. Merhan, O. The biochemistry and antioxidant properties of carotenoids. *Carotenoids* **2017**, *5*, 51.
107. Patias, L.D.; Fernandes, A.S.; Petry, F.C.; Mercadante, A.Z.; Jacob-Lopes, E.; Zepka, L.Q. Carotenoid profile of three microalgae/cyanobacteria species with peroxy radical scavenger capacity. *Food Res. Int.* **2017**, *100*, 260–266. [[CrossRef](#)] [[PubMed](#)]
108. Pagels, F.; Salvaterra, D.; Amaro, H.M.; Lopes, G.; Sousa-Pinto, I.; Vasconcelos, V.; Guedes, A.C. Bioactive potential of *Cyanobium* sp. pigment-rich extracts. *J. Appl. Phycol.* **2020**, *32*, 3031–3040. [[CrossRef](#)]
109. Kelman, D.; Ben-Amotz, A.; Berman-Frank, I. Carotenoids provide the major antioxidant defence in the globally significant N<sub>2</sub>-fixing marine cyanobacterium *Trichodesmium*. *Environ. Microbiol.* **2009**, *11*, 1897–1908. [[CrossRef](#)] [[PubMed](#)]
110. Kusama, Y.; Inoue, S.; Jimbo, H.; Takaichi, S.; Sonoike, K.; Hihara, Y.; Nishiyama, Y. Zeaxanthin and echinenone protect the repair of photosystem II from inhibition by singlet oxygen in *Synechocystis* sp. PCC 6803. *Plant Cell Physiol.* **2015**, *56*, 906–916. [[CrossRef](#)] [[PubMed](#)]
111. Boucar, M.C.M.; Shen, L.-Q.; Wang, K.; Zhang, Z.-C.; Qiu, B.-S. UV-B irradiation enhances the production of unique mycosporine-like amino acids and carotenoids in the subaerial cyanobacterium *Pseudanabaena* sp. CCNU1. *Eur. J. Phycol.* **2021**, *56*, 316–323. [[CrossRef](#)]
112. Vitek, P.; Ascaso, C.; Artieda, O.; Casero, M.C.; Wierchos, J. Discovery of carotenoid red-shift in endolithic cyanobacteria from the Atacama Desert. *Sci. Rep.* **2017**, *7*, 11116. [[CrossRef](#)] [[PubMed](#)]
113. Lopes, G.; Clarinha, D.; Vasconcelos, V. Carotenoids from cyanobacteria: A biotechnological approach for the topical treatment of psoriasis. *Microorganisms* **2020**, *8*, 302. [[CrossRef](#)] [[PubMed](#)]
114. Morone, J.; Lopes, G.; Preto, M.; Vasconcelos, V.; Martins, R. Exploitation of Filamentous and Picoplanktonic Cyanobacteria for Cosmetic Applications: Potential to Improve Skin Structure and Preserve Dermal Matrix Components. *Mar. Drugs* **2020**, *18*, 486. [[CrossRef](#)]
115. Mo, S.; Kronic, A.; Pegan, S.D.; Franzblau, S.G.; Orjala, J. An antimicrobial guanidine-bearing sesterterpene from the cultured cyanobacterium *Scytonema* sp. *J. Nat. Prod.* **2009**, *72*, 2043–2045. [[CrossRef](#)]
116. Cabanillas, A.H.; Tena Pérez, V.C.; Maderuelo Corral, S.; Rosero Valencia, D.F.; Martel Quintana, A.; Ortega Doménech, M.; Rumbero Sánchez, A.n. Cybastacines A and B: Antibiotic sesterterpenes from a *Nostoc* sp. cyanobacterium. *J. Nat. Prod.* **2018**, *81*, 410–413. [[CrossRef](#)]
117. Kronic, A.; Vallat, A.; Mo, S.; Lantvit, D.D.; Swanson, S.M.; Orjala, J. Scytonemides A and B, cyclic peptides with 20S proteasome inhibitory activity from the cultured cyanobacterium *Scytonema hofmannii*. *J. Nat. Prod.* **2010**, *73*, 1927–1932. [[CrossRef](#)]
118. Gerald, V.; Jacinavicius, F.R.; Genuário, D.B.; Pinto, E. Identification and distribution of mycosporine-like amino acids in Brazilian cyanobacteria using ultrahigh-performance liquid chromatography with diode array detection coupled to quadrupole time-of-flight mass spectrometry. *Rapid Commun. Mass Spectrom.* **2020**, *34*, e8634. [[CrossRef](#)]
119. Chrapusta, E.; Kaminski, A.; Duchnik, K.; Bober, B.; Adamski, M.; Bialczyk, J. Mycosporine-like amino acids: Potential health and beauty ingredients. *Mar. Drugs* **2017**, *15*, 326. [[CrossRef](#)]
120. D’Agostino, P.M.; Javalkote, V.S.; Mazmouz, R.; Pickford, R.; Puranik, P.R.; Neilan, B.A. Comparative profiling and discovery of novel glycosylated mycosporine-like amino acids in two strains of the cyanobacterium *Scytonema* cf. *crispum*. *Appl. Environ. Microbiol.* **2016**, *82*, 5951–5959. [[CrossRef](#)]
121. Shukla, V.; Kumari, R.; Patel, D.K.; Upreti, D.K. Characterization of the diversity of mycosporine-like amino acids in lichens from high altitude region of Himalaya. *Amino Acids* **2016**, *48*, 129–136. [[CrossRef](#)]
122. Pathak, J.; Ahmed, H.; Singh, S.P.; Häder, D.-P.; Sinha, R.P. Genetic regulation of scytonemin and mycosporine-like amino acids (MAAs) biosynthesis in cyanobacteria. *Plant Gene* **2019**, *17*, 100172. [[CrossRef](#)]
123. Gerald, V.; de Medeiros, L.S.; Lima, S.T.; Alvarenga, D.O.; Gacesa, R.; Long, P.F.; Fiore, M.F.; Pinto, E. Genetic and biochemical evidence for redundant pathways leading to mycosporine-like amino acid biosynthesis in the cyanobacterium *Sphaerospermopsis torques-reginae* ITP-024. *Harmful Algae* **2020**, *35*, 177–187.
124. Gacesa, R.; Lawrence, K.P.; Georgakopoulos, N.D.; Yabe, K.; Dunlap, W.C.; Barlow, D.J.; Wells, G.; Young, A.R.; Long, P.F. The mycosporine-like amino acids porphyra-334 and shinorine are antioxidants and direct antagonists of Keap1-Nrf2 binding. *Biochimie* **2018**, *154*, 35–44. [[CrossRef](#)]
125. Lawrence, K.P.; Long, P.F.; Young, A.R. Mycosporine-like amino acids for skin photoprotection. *Curr. Med. Chem.* **2018**, *25*, 5512–5527. [[CrossRef](#)] [[PubMed](#)]
126. Jain, S.; Prajapat, G.; Abrar, M.; Ledwani, L.; Singh, A.; Agrawal, A. Cyanobacteria as efficient producers of mycosporine-like amino acids. *J. Basic Microbiol.* **2017**, *57*, 715–727. [[CrossRef](#)] [[PubMed](#)]

127. Werner, N.; Orfanoudaki, M.; Hartmann, A.; Ganzera, M.; Sommaruga, R. Low temporal dynamics of mycosporine-like amino acids in benthic cyanobacteria from an alpine lake. *Freshwat. Biol.* **2021**, *66*, 169–176. [[CrossRef](#)] [[PubMed](#)]
128. Mueller, D.R.; Vincent, W.F.; Bonilla, S.; Laurion, I. Extremotrophs, extremophiles and broadband pigmentation strategies in a high arctic ice shelf ecosystem. *FEMS Microbiol. Ecol.* **2005**, *53*, 73–87. [[CrossRef](#)]
129. Llewellyn, C.A.; Greig, C.; Silkina, A.; Kultschar, B.; Hitchings, M.D.; Farnham, G. Mycosporine-like amino acid and aromatic amino acid transcriptome response to UV and far-red light in the cyanobacterium *Chlorogloeopsis fritschii* PCC 6912. *Sci. Rep.* **2020**, *10*, 20638. [[CrossRef](#)]
130. Couradeau, E.; Karaoz, U.; Lim, H.C.; Da Rocha, U.N.; Northen, T.; Brodie, E.; Garcia-Pichel, F. Bacteria increase arid-land soil surface temperature through the production of sunscreens. *Nat. Commun.* **2016**, *7*, 10373. [[CrossRef](#)]
131. Nishida, Y.; Kumagai, Y.; Michiba, S.; Yasui, H.; Kishimura, H. Efficient extraction and antioxidant capacity of mycosporine-like amino acids from red alga *Dulse Palmaria palmata* in Japan. *Mar. Drugs* **2020**, *18*, 502. [[CrossRef](#)] [[PubMed](#)]
132. Cheewinathamrongrod, V.; Kageyama, H.; Palaga, T.; Takabe, T.; Waditee-Sirisattha, R. 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 Biol.* **2016**, *164*, 289–295. [[CrossRef](#)] [[PubMed](#)]
133. Patipong, T.; Hibino, T.; Waditee-Sirisattha, R.; Kageyama, H. Efficient bioproduction of mycosporine-2-glycine, which functions as potential osmoprotectant, using *Escherichia coli* cells. *Nat. Prod. Commun.* **2017**, *12*. [[CrossRef](#)]
134. Tarasuntisuk, S.; Patipong, T.; Hibino, T.; Waditee-Sirisattha, R.; Kageyama, H. Inhibitory effects of mycosporine-2-glycine isolated from a halotolerant cyanobacterium on protein glycation and collagenase activity. *Lett. Appl. Microbiol.* **2018**, *67*, 314–320. [[CrossRef](#)]
135. Kageyama, H.; Waditee-Sirisattha, R. Mycosporine-like amino acids as multifunctional secondary metabolites in cyanobacteria: From biochemical to application aspects. *Stud. Nat. Prod. Chem.* **2018**, *59*, 153–194.
136. Ishihara, K.; Watanabe, R.; Uchida, H.; Suzuki, T.; Yamashita, M.; Takenaka, H.; Nazifi, E.; Matsugo, S.; Yamaba, M.; Sakamoto, T. 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. *J. Photochem. Photobiol. B Biol.* **2017**, *172*, 102–108. [[CrossRef](#)]
137. Soule, T.; Garcia-Pichel, F. Ultraviolet photoprotective compounds from cyanobacteria in biomedical applications. *Cyanobacteria Econ. Perspect.* **2014**, 119–143. [[CrossRef](#)]
138. Daniel, S.; Cornelia, S.; Fred, Z. UV-A sunscreen from red algae for protection against premature skin aging. *Cosmet Toilet. Manuf. Worldw.* **2004**, 139–143.
139. Andre, G.; Pellegrini, M.; Pellegrini, L. *Algal Extracts Containing Amino Acid Analogs of Mycosporin Are Useful as Dermatological Protecting Agents against Ultraviolet Radiation*; Institut National De La Propriete Industrielle: Courbevoie, France, 2001; pp. 1–22.
140. Maurya, S.K.; Mishra, R. Importance of bioinformatics in genome Mining of Cyanobacteria for production of bioactive compounds. In *Cyanobacteria*, 1st ed.; Academic Press: London, UK, 2019; pp. 477–506.
141. Wang, H.; Fewer, D.P.; Holm, L.; Rouhiainen, L.; Sivonen, K. Atlas of nonribosomal peptide and polyketide biosynthetic pathways reveals common occurrence of nonmodular enzymes. *Proc. Natl. Acad. Sci. USA* **2014**, *111*, 9259–9264. [[CrossRef](#)]
142. Welker, M.; Von Döhren, H. Cyanobacterial peptides—nature’s own combinatorial biosynthesis. *FEMS Microbiol. Rev.* **2006**, *30*, 530–563. [[CrossRef](#)]
143. Larsson, J.; Nylander, J.A.; Bergman, B. Genome fluctuations in cyanobacteria reflect evolutionary, developmental and adaptive traits. *BMC Evol. Biol.* **2011**, *11*, 187. [[CrossRef](#)] [[PubMed](#)]
144. Dufresne, A.; Salanoubat, M.; Partensky, F.; Artiguenave, F.; Axmann, I.M.; Barbe, V.; Duprat, S.; Galperin, M.Y.; Koonin, E.V.; Le Gall, F. Genome sequence of the cyanobacterium *Prochlorococcus marinus* SS120, a nearly minimal oxypototrophic genome. *Proc. Natl. Acad. Sci. USA* **2003**, *100*, 10020–10025. [[CrossRef](#)]
145. Kehr, J.-C.; Picchi, D.G.; Dittmann, E. Natural product biosyntheses in cyanobacteria: A treasure trove of unique enzymes. *Beilstein J. Org. Chem.* **2011**, *7*, 1622–1635. [[CrossRef](#)]
146. Dutta, S.; Whicher, J.R.; Hansen, D.A.; Hale, W.A.; Chemler, J.A.; Congdon, G.R.; Narayan, A.R.H.; Håkansson, K.; Sherman, D.H.; Smith, J.L. Structure of a modular polyketide synthase. *Nature* **2014**, *510*, 512–517. [[CrossRef](#)] [[PubMed](#)]
147. Nishizawa, T.; Asayama, M.; Fujii, K.; Harada, K.-I.; Shirai, M. Genetic analysis of the peptide synthetase genes for a cyclic heptapeptide microcystin in *Microcystis* spp. *J. Biochem.* **1999**, *126*, 520–529. [[CrossRef](#)] [[PubMed](#)]
148. Nishizawa, T.; Ueda, A.; Asayama, M.; Fujii, K.; Harada, K.-I.; Ochi, K.; Shirai, M. Polyketide synthase gene coupled to the peptide synthetase module involved in the biosynthesis of the cyclic heptapeptide microcystin. *J. Biochem.* **2000**, *127*, 779–789. [[CrossRef](#)]
149. Tillett, D.; Dittmann, E.; Erhard, M.; Von Döhren, H.; Börner, T.; Neilan, B.A. Structural organization of microcystin biosynthesis in *Microcystis aeruginosa* PCC 7806: An integrated peptide–polyketide synthetase system. *Chem. Biol.* **2000**, *7*, 753–764. [[CrossRef](#)]
150. Ishida, K.; Christiansen, G.; Yoshida, W.Y.; Kurmayer, R.; Welker, M.; Valls, N.; Bonjoch, J.; Hertweck, C.; Börner, T.; Hemscheidt, T. Biosynthesis and structure of aeruginoside 126A and 126B, cyanobacterial peptide glycosides bearing a 2-carboxy-6-hydroxyoctahydroindole moiety. *Chem. Biol.* **2007**, *14*, 565–576. [[CrossRef](#)]
151. Mihali, T.K.; Kellmann, R.; Muenchhoff, J.; Barrow, K.D.; Neilan, B.A. Characterization of the gene cluster responsible for cylindrospermopsin biosynthesis. *Appl. Environ. Microbiol.* **2008**, *74*, 716–722. [[CrossRef](#)]

152. Rouhiainen, L.; Jokela, J.; Fewer, D.P.; Urmann, M.; Sivonen, K. Two alternative starter modules for the non-ribosomal biosynthesis of specific anabaenopeptin variants in *Anabaena* (Cyanobacteria). *Chem. Biol.* **2010**, *17*, 265–273. [[CrossRef](#)] [[PubMed](#)]
153. Tidgewell, K.; Engene, N.; Byrum, T.; Media, J.; Doi, T.; Valeriote, F.A.; Gerwick, W.H. Evolved diversification of a modular natural product pathway: Apratoxins F and G, two cytotoxic cyclic depsipeptides from a Palmyra collection of *Lyngbya bouillonii*. *ChemBioChem* **2010**, *11*, 1458–1466. [[CrossRef](#)] [[PubMed](#)]
154. Grindberg, R.V.; Ishoey, T.; Brinza, D.; Esquenazi, E.; Coates, R.C.; Liu, W.-T.; Gerwick, L.; Dorrestein, P.C.; Pevzner, P.; Lasken, R. Single cell genome amplification accelerates identification of the apratoxin biosynthetic pathway from a complex microbial assemblage. *PLoS ONE* **2011**, *6*, e18565. [[CrossRef](#)] [[PubMed](#)]
155. Edwards, D.J.; Gerwick, W.H. Lyngbyatoxin biosynthesis: Sequence of biosynthetic gene cluster and identification of a novel aromatic prenyltransferase. *J. Am. Chem. Soc.* **2004**, *126*, 11432–11433. [[CrossRef](#)] [[PubMed](#)]
156. Ramaswamy, A.V.; Sorrels, C.M.; Gerwick, W.H. Cloning and biochemical characterization of the hectochlorin biosynthetic gene cluster from the marine cyanobacterium *Lyngbya majuscula*. *J. Nat. Prod.* **2007**, *70*, 1977–1986. [[CrossRef](#)] [[PubMed](#)]
157. Chang, Z.; Flatt, P.; Gerwick, W.H.; Nguyen, V.-A.; Willis, C.L.; Sherman, D.H. The barbamide biosynthetic gene cluster: A novel marine cyanobacterial system of mixed polyketide synthase (PKS)-non-ribosomal peptide synthetase (NRPS) origin involving an unusual trichloroleucyl starter unit. *Gene* **2002**, *296*, 235–247. [[CrossRef](#)]
158. Chang, Z.; Sitachitta, N.; Rossi, J.V.; Roberts, M.A.; Flatt, P.M.; Jia, J.; Sherman, D.H.; Gerwick, W.H. Biosynthetic Pathway and Gene Cluster Analysis of Curacin A, an Antitubulin Natural Product from the Tropical Marine Cyanobacterium *Lyngbya majuscula*. *J. Nat. Prod.* **2004**, *67*, 1356–1367. [[CrossRef](#)]
159. Edwards, D.J.; Marquez, B.L.; Nogle, L.M.; McPhail, K.; Goeger, D.E.; Roberts, M.A.; Gerwick, W.H. Structure and biosynthesis of the jamaicamides, new mixed polyketide-peptide neurotoxins from the marine cyanobacterium *Lyngbya majuscula*. *Chem. Biol.* **2004**, *11*, 817–833. [[CrossRef](#)]
160. Hoffmann, D.; Hevel, J.M.; Moore, R.E.; Moore, B.S. Sequence analysis and biochemical characterization of the nostopeptolide A biosynthetic gene cluster from *Nostoc* sp. GSV224. *Gene* **2003**, *311*, 171–180. [[CrossRef](#)]
161. Becker, J.E.; Moore, R.E.; Moore, B.S. Cloning, sequencing, and biochemical characterization of the nostocyclopeptide biosynthetic gene cluster: Molecular basis for imine macrocyclization. *Gene* **2004**, *325*, 35–42. [[CrossRef](#)]
162. Magarvey, N.A.; Beck, Z.Q.; Golakoti, T.; Ding, Y.; Huber, U.; Hemscheidt, T.K.; Abelson, D.; Moore, R.E.; Sherman, D.H. Biosynthetic characterization and chemoenzymatic assembly of the cryptophycins. Potent anticancer agents from *Nostoc* cyanobionts. *ACS Chem. Biol.* **2006**, *1*, 766–779. [[CrossRef](#)]
163. Mareš, J.; Hájek, J.; Urajová, P.; Kopecký, J.; Hrouzek, P. A hybrid non-ribosomal peptide/polyketide synthetase containing fatty-acyl ligase (FAAL) synthesizes the  $\beta$ -amino fatty acid lipopeptides puwainaphycins in the Cyanobacterium *Cylindrospermum alatosporum*. *PLoS ONE* **2014**, *9*, e111904. [[CrossRef](#)]
164. Gupta, V.; Vyas, D. Antimicrobial effect of a cyclic peptide Nostophycin isolated from wastewater cyanobacteria, *Nostoc calcicola*. *Curr. Bot.* **2021**, *12*, 94–101. [[CrossRef](#)]
165. Moffitt, M.C.; Neilan, B.A. Characterization of the nodularin synthetase gene cluster and proposed theory of the evolution of cyanobacterial hepatotoxins. *Appl. Environ. Microbiol.* **2004**, *70*, 6353–6362. [[CrossRef](#)] [[PubMed](#)]
166. Sivonen, K.; Leikoski, N.; Fewer, D.P.; Jokela, J. Cyanobactins—ribosomal cyclic peptides produced by cyanobacteria. *Appl. Microbiol. Biotechnol.* **2010**, *86*, 1213–1225. [[CrossRef](#)] [[PubMed](#)]
167. do Amaral, S.C.; Monteiro, P.R.; Neto, J.d.S.P.; Serra, G.M.; Gonçalves, E.C.; Xavier, L.P.; Santos, A.V. Current knowledge on microviridin from cyanobacteria. *Mar. Drugs* **2021**, *19*, 17. [[CrossRef](#)]
168. Cubillos-Ruiz, A.; Berta-Thompson, J.W.; Becker, J.W.; Van Der Donk, W.A.; Chisholm, S.W. Evolutionary radiation of lanthipeptides in marine cyanobacteria. *Proc. Natl. Acad. Sci. USA* **2017**, *114*, E5424–E5433. [[CrossRef](#)]
169. Knerr, P.J.; van der Donk, W.A. Discovery, biosynthesis, and engineering of lantipeptides. *Annu. Rev. Biochem.* **2012**, *81*, 479–505. [[CrossRef](#)]
170. Li, B.; Sher, D.; Kelly, L.; Shi, Y.; Huang, K.; Knerr, P.J.; Joewono, I.; Rusch, D.; Chisholm, S.W.; Van Der Donk, W.A. Catalytic promiscuity in the biosynthesis of cyclic peptide secondary metabolites in planktonic marine cyanobacteria. *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 10430–10435. [[CrossRef](#)]
171. Ziemert, N.; Ishida, K.; Quillardet, P.; Bouchier, C.; Hertweck, C.; de Marsac, N.T.; Dittmann, E. Microcyclamide biosynthesis in two strains of *Microcystis aeruginosa*: From structure to genes and vice versa. *Appl. Environ. Microbiol.* **2008**, *74*, 1791–1797. [[CrossRef](#)]
172. Portmann, C.; Blom, J.F.; Gademann, K.; Jüttner, F. Aerucyclamides A and B: Isolation and synthesis of toxic ribosomal heterocyclic peptides from the cyanobacterium *Microcystis aeruginosa* PCC 7806. *J. Nat. Prod.* **2008**, *71*, 1193–1196. [[CrossRef](#)] [[PubMed](#)]
173. Portmann, C.; Blom, J.F.; Kaiser, M.; Brun, R.; Jüttner, F.; Gademann, K. Isolation of aerucyclamides C and D and structure revision of microcyclamide 7806A: Heterocyclic ribosomal peptides from *Microcystis aeruginosa* PCC 7806 and their antiparasite evaluation. *J. Nat. Prod.* **2008**, *71*, 1891–1896. [[CrossRef](#)]
174. Ogino, J.; Moore, R.E.; Patterson, G.M.L.; Smith, C.D. Dendroamides, new cyclic hexapeptides from a blue-green alga. Multidrug-resistance reversing activity of dendroamide A. *J. Nat. Prod.* **1996**, *59*, 581–586. [[CrossRef](#)] [[PubMed](#)]
175. Sudek, S.; Haygood, M.G.; Youssef, D.T.A.; Schmidt, E.W. Structure of trichamide, a cyclic peptide from the bloom-forming cyanobacterium *Trichodesmium erythraeum*, predicted from the genome sequence. *Appl. Environ. Microbiol.* **2006**, *72*, 4382–4387. [[CrossRef](#)] [[PubMed](#)]

176. Schmidt, E.W.; Nelson, J.T.; Rasko, D.A.; Sudek, S.; Eisen, J.A.; Haygood, M.G.; Ravel, J. Patellamide A and C biosynthesis by a microcin-like pathway in *Prochloron didemni*, the cyanobacterial symbiont of *Lissoclinum patella*. *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 7315–7320. [[CrossRef](#)]
177. Leikoski, N.; Fewer, D.P.; Jokela, J.; Wahlsten, M.; Rouhiainen, L.; Sivonen, K. Highly diverse cyanobactins in strains of the genus *Anabaena*. *Appl. Environ. Microbiol.* **2010**, *76*, 701–709. [[CrossRef](#)]
178. Okino, T.; Matsuda, H.; Murakami, M.; Yamaguchi, K. New microviridins, elastase inhibitors from the blue-green alga *Microcystis aeruginosa*. *Tetrahedron* **1995**, *51*, 10679–10686. [[CrossRef](#)]
179. Tang, W.; Van Der Donk, W.A. Structural characterization of four prochlorosins: A novel class of lantipeptides produced by planktonic marine cyanobacteria. *Biochemistry* **2012**, *51*, 4271–4279. [[CrossRef](#)]
180. Schuler, C.G.; Havig, J.R.; Hamilton, T.L. Hot spring microbial community composition, morphology, and carbon fixation: Implications for interpreting the ancient rock record. *Front. Earth Sci.* **2017**, *5*, 97. [[CrossRef](#)]
181. Teodoro, G.R.; Ellepola, K.; Seneviratne, C.J.; Koga-Ito, C.Y. Potential use of phenolic acids as anti-Candida agents: A review. *Front. Microbiol.* **2015**, *6*, 1420. [[CrossRef](#)] [[PubMed](#)]
182. Kumar, N.; Goel, N. Phenolic acids: Natural versatile molecules with promising therapeutic applications. *Biotechnol. Rep.* **2019**, *24*, e00370. [[CrossRef](#)] [[PubMed](#)]
183. Singh, D.P.; Prabha, R.; Meena, K.K.; Sharma, L.; Sharma, A.K. Induced accumulation of polyphenolics and flavonoids in cyanobacteria under salt stress protects organisms through enhanced antioxidant activity. *Am. J. Plant Sci.* **2014**, *2014*, 43916. [[CrossRef](#)]
184. Patipong, T.; Hibino, T.; Waditee-Sirisattha, R.; Kageyama, H. Induction of antioxidative activity and antioxidant molecules in the halotolerant cyanobacterium *Halotheca* sp. PCC 7418 by temperature shift. *Nat. Prod. Commun.* **2019**, *14*, 1934578X19865680. [[CrossRef](#)]
185. Monroe, M.B.B.; Easley, A.D.; Grant, K.; Fletcher, G.K.; Boyer, C.; Maitland, D.J. Multifunctional shape-memory polymer foams with bio-inspired antimicrobials. *ChemPhysChem* **2018**, *19*, 1999–2008. [[CrossRef](#)]
186. Li, R.; Narita, R.; Nishimura, H.; Marumoto, S.; Yamamoto, S.P.; Ouda, R.; Yatagai, M.; Fujita, T.; Watanabe, T. Antiviral activity of phenolic derivatives in pyroligneous acid from hardwood, softwood, and bamboo. *ACS Sustain. Chem. Eng.* **2018**, *6*, 119–126. [[CrossRef](#)]
187. Sun, S.; Kee, H.J.; Ryu, Y.; Choi, S.Y.; Kim, G.R.; Kim, H.-S.; Kee, S.-J.; Jeong, M.H. Gentisic acid prevents the transition from pressure overload-induced cardiac hypertrophy to heart failure. *Sci. Rep.* **2019**, *9*, 3018. [[CrossRef](#)]
188. Mori, T.; Koyama, N.; Yokoo, T.; Segawa, T.; Maeda, M.; Sawmiller, D.; Tan, J.; Town, T. Gallic acid is a dual  $\alpha/\beta$ -secretase modulator that reverses cognitive impairment and remediates pathology in Alzheimer mice. *J. Biol. Chem.* **2020**, *295*, 16251–16266. [[CrossRef](#)]
189. Ren, J.; Yang, M.; Xu, F.; Chen, J.; Ma, S. Acceleration of wound healing activity with syringic acid in streptozotocin induced diabetic rats. *Life Sci.* **2019**, *233*, 116728. [[CrossRef](#)]
190. Park, H.-J.; Cho, J.-H.; Hong, S.-H.; Kim, D.-H.; Jung, H.-Y.; Kang, I.-K.; Cho, Y.-J. Whitening and anti-wrinkle activities of ferulic acid isolated from *Tetragonia tetragonioides* in B16F10 melanoma and CCD-986sk fibroblast cells. *J. Nat. Med.* **2018**, *72*, 127–135. [[CrossRef](#)] [[PubMed](#)]
191. Monteiro e Silva, S.A.; Calixto, G.M.F.; Cajado, J.; De Carvalho, P.C.A.; Rodero, C.F.; Chorilli, M.; Leonardi, G.R. Gallic acid-loaded gel formulation combats skin oxidative stress: Development, characterization and ex vivo biological assays. *Polymers* **2017**, *9*, 391. [[CrossRef](#)] [[PubMed](#)]
192. Singh, B.; Kumar, A.; Malik, A.K. Flavonoids biosynthesis in plants and its further analysis by capillary electrophoresis. *Electrophoresis* **2017**, *38*, 820–832. [[CrossRef](#)] [[PubMed](#)]
193. Ruiz-Cruz, S.; Chaparro-Hernández, S.; Hernández-Ruiz, K.L.; Cira-Chávez, L.A.; Estrada-Alvarado, M.I.; Ortega, L.E.G.; Mata, M.A.L. Flavonoids: Important biocompounds in food. In *Flavonoids: From Biosynthesis to Human Health*; Justino, J.G., Ed.; IntechOpen: London, UK, 2017; pp. 353–369.
194. Wang, T.-Y.; Li, Q.; Bi, K.-S. Bioactive flavonoids in medicinal plants: Structure, activity and biological fate. *Asian J. Pharm. Sci.* **2018**, *13*, 12–23. [[CrossRef](#)] [[PubMed](#)]
195. Trabelsi, L.; Mnari, A.; Abdel-Daim, M.M.; Abid-Essafi, S.; Aleya, L. Therapeutic properties in Tunisian hot springs: First evidence of phenolic compounds in the cyanobacterium *Leptolyngbya* sp. biomass, capsular polysaccharides and releasing polysaccharides. *BMC Complementary Altern. Med.* **2016**, *16*, 515. [[CrossRef](#)]
196. Żyszcza, B.; Anioł, M.; Lipok, J. Modulation of the growth and metabolic response of cyanobacteria by the multifaceted activity of naringenin. *PLoS ONE* **2017**, *12*, e0177631. [[CrossRef](#)]
197. Jerez-Martel, I.; García-Poza, S.; Rodríguez-Martel, G.; Rico, M.; Afonso-Olivares, C.; Gómez-Pinchetti, J.L. Phenolic profile and antioxidant activity of crude extracts from microalgae and cyanobacteria strains. *J. Food Qual.* **2017**, *2017*, 2924508. [[CrossRef](#)]
198. Mallick, N.; Mohn, F.H. Reactive oxygen species: Response of algal cells. *J. Plant Physiol.* **2000**, *157*, 183–193. [[CrossRef](#)]
199. Hernández-Aquino, E.; Muriel, P. Beneficial effects of naringenin in liver diseases: Molecular mechanisms. *World J. Gastroenterol.* **2018**, *24*, 1679. [[CrossRef](#)]
200. Sugumar, M.; Sevanan, M.; Sekar, S. Neuroprotective effect of naringenin against MPTP-induced oxidative stress. *Int. J. Neurosci.* **2019**, *129*, 534–539. [[CrossRef](#)]

201. Choi, J.; Lee, D.-H.; Jang, H.; Park, S.-Y.; Seol, J.-W. Naringenin exerts anticancer effects by inducing tumor cell death and inhibiting angiogenesis in malignant melanoma. *Int. J. Med. Sci.* **2020**, *17*, 3049. [[CrossRef](#)]
202. Mulvihill, E.E.; Assini, J.M.; Sutherland, B.G.; DiMattia, A.S.; Khami, M.; Koppes, J.B.; Sawyez, C.G.; Whitman, S.C.; Huff, M.W. Naringenin decreases progression of atherosclerosis by improving dyslipidemia in high-fat-fed low-density lipoprotein receptor-null mice. *Arterioscler. Thromb. Vasc. Biol.* **2010**, *30*, 742–748. [[CrossRef](#)]
203. Assini, J.M.; Mulvihill, E.E.; Huff, M.W. Citrus flavonoids and lipid metabolism. *Curr. Opin. Lipidol.* **2013**, *24*, 34–40. [[CrossRef](#)] [[PubMed](#)]
204. Asensi-Fabado, M.A.; Munné-Bosch, S. Vitamins in plants: Occurrence, biosynthesis and antioxidant function. *Trends Plant Sci.* **2010**, *15*, 582–592. [[CrossRef](#)] [[PubMed](#)]
205. Del Mondo, A.; Smerilli, A.; Sané, E.; Sansone, C.; Brunet, C. Challenging microalgal vitamins for human health. *Microb. Cell Factories* **2020**, *19*, 201. [[CrossRef](#)]
206. Aaronson, S.; Dhawale, S.W.; Patni, N.J.; DeAngelis, B.; Frank, O.; Baker, H. The cell content and secretion of water-soluble vitamins by several freshwater algae. *Arch. Microbiol.* **1977**, *112*, 57–59. [[CrossRef](#)]
207. Santiago-Morales, I.S.; Trujillo-Valle, L.; Márquez-Rocha, F.J.; Hernández, J.F.L. Tocopherols, phycocyanin and superoxide dismutase from microalgae: As potential food antioxidants. *Appl. Food Biotechnol.* **2018**, *5*, 19–27.
208. Sylvander, P.; Häubner, N.; Snoeijs, P. The thiamine content of phytoplankton cells is affected by abiotic stress and growth rate. *Microb. Ecol.* **2013**, *65*, 566–577. [[CrossRef](#)] [[PubMed](#)]
209. Helliwell, K.E.; Lawrence, A.D.; Holzer, A.; Kudahl, U.J.; Sasso, S.; Kräutler, B.; Scanlan, D.J.; Warren, M.J.; Smith, A.G. Cyanobacteria and eukaryotic algae use different chemical variants of vitamin B12. *Curr. Biol.* **2016**, *26*, 999–1008. [[CrossRef](#)]
210. Edelmann, M.; Aalto, S.; Chamlagain, B.; Kariluoto, S.; Piironen, V. Riboflavin, niacin, folate and vitamin B12 in commercial microalgae powders. *J. Food Compos. Anal.* **2019**, *82*, 103226. [[CrossRef](#)]
211. Ljubic, A.; Jacobsen, C.; Holdt, S.L.; Jakobsen, J. Microalgae *Nannochloropsis oceanica* as a future new natural source of vitamin D3. *Food Chem.* **2020**, *320*, 126627. [[CrossRef](#)] [[PubMed](#)]
212. Backasch, N.; Schulz-Friedrich, R.; Appel, J. Influences on tocopherol biosynthesis in the cyanobacterium *Synechocystis* sp. PCC 6803. *J. Plant Physiol.* **2005**, *162*, 758–766. [[CrossRef](#)] [[PubMed](#)]
213. Mudimu, O.; Koopmann, I.K.; Rybalka, N.; Friedl, T.; Schulz, R.; Bilger, W. Screening of microalgae and cyanobacteria strains for  $\alpha$ -tocopherol content at different growth phases and the influence of nitrate reduction on  $\alpha$ -tocopherol production. *J. Appl. Phycol.* **2017**, *29*, 2867–2875. [[CrossRef](#)]
214. Krieger-Liszczay, A.; Trebst, A. Tocopherol is the scavenger of singlet oxygen produced by the triplet states of chlorophyll in the PSII reaction centre. *J. Exp. Bot.* **2006**, *57*, 1677–1684. [[CrossRef](#)]
215. Goiris, K.; Van Colen, W.; Wilches, I.; León-Tamariz, F.; De Cooman, L.; Muylaert, K. Impact of nutrient stress on antioxidant production in three species of microalgae. *Algal Res.* **2015**, *7*, 51–57. [[CrossRef](#)]
216. Hamed, S.M.; Selim, S.; Klöck, G.; AbdElgawad, H. Sensitivity of two green microalgae to copper stress: Growth, oxidative and antioxidants analyses. *Ecotoxicol. Environ. Saf.* **2017**, *144*, 19–25. [[CrossRef](#)]
217. Strejckova, A.; Dvorak, M.; Klejdus, B.; Krystofova, O.; Hedbavny, J.; Adam, V.; Huska, D. The strong reaction of simple phenolic acids during oxidative stress caused by nickel, cadmium and copper in the microalga *Scenedesmus quadricauda*. *New Biotechnol.* **2019**, *48*, 66–75. [[CrossRef](#)]
218. Tarento, T.D.C.; McClure, D.D.; Vasiljevski, E.; Schindeler, A.; Dehghani, F.; Kavanagh, J.M. Microalgae as a source of vitamin K1. *Algal Res.* **2018**, *36*, 77–87. [[CrossRef](#)]
219. Collins, M.D.; Jones, D. Distribution of isoprenoid quinone structural types in bacteria and their taxonomic implication. *Microbiol. Rev.* **1981**, *45*, 316–354. [[CrossRef](#)]
220. Sakuragi, Y.; Bryant, D.A. Genetic manipulation of quinone biosynthesis in cyanobacteria. In *Photosystem I: The Light-Driven Plastocyanin: Ferredoxin Oxidoreductase*; Golbeck, J.H., Ed.; Springer: Dordrecht, The Netherlands, 2006; pp. 205–222.
221. Joliot, P.; Joliot, A.; Johnson, G. *Cyclic Electron Transfer around Photosystem I*; Springer: Berlin/Heidelberg, Germany, 2006; pp. 639–656.
222. Widhalm, J.R.; van Oostende, C.; Furt, F.; Basset, G.J.C. A dedicated thioesterase of the Hotdog-fold family is required for the biosynthesis of the naphthoquinone ring of vitamin K1. *Proc. Natl. Acad. Sci. USA* **2009**, *106*, 5599–5603. [[CrossRef](#)]
223. Mimuro, M.; Tsuchiya, T.; Inoue, H.; Sakuragi, Y.; Itoh, Y.; Gotoh, T.; Miyashita, H.; Bryant, D.A.; Kobayashi, M. The secondary electron acceptor of photosystem I in *Gloeobacter violaceus* PCC 7421 is menaquinone-4 that is synthesized by a unique but unknown pathway. *FEBS Lett.* **2005**, *579*, 3493–3496. [[CrossRef](#)]
224. Sakuragi, Y.; Zybailov, B.; Shen, G.; Bryant, D.A.; Golbeck, J.H.; Diner, B.A.; Karygina, I.; Pushkar, Y.; Stehlik, D. Recruitment of a foreign quinone into the A1 site of photosystem I: Characterization of a menB rubA double deletion mutant in *Synechococcus* sp. PCC 7002 devoid of FX, FA, and FB and containing plastoquinone or exchanged 9, 10-anthraquinone. *J. Biol. Chem.* **2005**, *280*, 12371–12381. [[CrossRef](#)] [[PubMed](#)]
225. Langan, R.C.; Goodbred, A.J. Vitamin B12 deficiency: Recognition and management. *Am. Fam. Physician* **2017**, *96*, 384–389. [[PubMed](#)]
226. Bordelon, P.; Ghetu, M.V.; Langan, R.C. Recognition and management of vitamin D deficiency. *Am. Fam. Physician* **2009**, *80*, 841–846. [[PubMed](#)]
227. Maxfield, L.; Crane, J.S. *Vitamin C Deficiency (Scurvy)*; StatPearls; StatPearls Publishing: Treasure Island, FL, USA, 2020.

228. Golriz, F.; Donnelly, L.F.; Devaraj, S.; Krishnamurthy, R. Modern American scurvy—experience with vitamin C deficiency at a large children’s hospital. *Pediatric Radiol.* **2017**, *47*, 214–220. [[CrossRef](#)]
229. Eden, R.E.; Coviello, J.M. *Vitamin K Deficiency*; StatPearls; StatPearls Publishing: Treasure Island, FL, USA, 2019.
230. Kishimoto, N.; Hayashi, T.; Mizobuchi, K.; Kubota, M.; Nakano, T. Vitamin A deficiency after prolonged intake of an unbalanced diet in a Japanese hemodialysis patient. *Doc. Ophthalmol.* **2021**, *143*, 85–91. [[CrossRef](#)]
231. Cordeiro, A.; Bento, C.; de Matos, A.C.; Ramalho, A. Vitamin A deficiency is associated with body mass index and body adiposity in women with recommended intake of vitamin A. *Nutr. Hosp. Organo Of. Soc. Española Nutr. Parenter. Enter.* **2018**, *35*, 1072–1078. [[CrossRef](#)]
232. Ekeuku, S.O.; Chong, P.N.; Chan, H.K.; Mohamed, N.; Froemming, G.R.A.; Okechukwu, P.N. Spirulina supplementation improves bone structural strength and stiffness in streptozocin-induced diabetic rats. *J. Tradit. Complementary Med.* **2021**, in press. [[CrossRef](#)]
233. Anantharajappa, K.; Dharmesh, S.M.; Ravi, S. Gastro-protective potentials of Spirulina: Role of vitamin B 12. *J. Food Sci. Technol.* **2020**, *57*, 745–753. [[CrossRef](#)]
234. Soudy, I.D.; Minet-Quinard, R.; Mahamat, A.D.; Ngoua, H.F.; Izzedine, A.A.; Tidjani, A.; Ngo Bum, E.; Lambert, C.; Pereira, B.; Desjeux, J.-F. Vitamin A status in healthy women eating traditionally prepared spirulina (Dihé) in the Chad Lake area. *PLoS ONE* **2018**, *13*, e0191887. [[CrossRef](#)]
235. Brilisauer, K.; Rapp, J.; Rath, P.; Schöllhorn, A.; Bleul, L.; Weiß, E.; Stahl, M.; Grond, S.; Forchhammer, K. Cyanobacterial antimetabolite 7-deoxy-sedoheptulose blocks the shikimate pathway to inhibit the growth of prototrophic organisms. *Nat. Commun.* **2019**, *10*, 545. [[CrossRef](#)] [[PubMed](#)]
236. Rapp, J.; Rath, P.; Kilian, J.; Brilisauer, K.; Grond, S.; Forchhammer, K. A bioactive molecule made by unusual salvage of radical SAM enzyme byproduct 5-deoxyadenosine blurs the boundary of primary and secondary metabolism. *J. Biol. Chem.* **2021**, *296*, 100621. [[CrossRef](#)] [[PubMed](#)]
237. Vergou, Y.; Touraki, M.; Paraskevopoulou, A.; Triantis, T.M.; Hiskia, A.; Gkelis, S.  $\beta$ -N-Methylamino-L-alanine interferes with nitrogen assimilation in the cyanobacterium, non-BMAA producer, *Synechococcus* sp. TAU-MAC 0499. *Toxicon* **2020**, *185*, 147–155. [[CrossRef](#)] [[PubMed](#)]
238. Downing, S.; van de Venter, M.; Downing, T.G. The effect of exogenous  $\beta$ -N-methylamino-L-alanine on the growth of *Synechocystis* PCC 6803. *Microb. Ecol.* **2012**, *63*, 149–156. [[CrossRef](#)] [[PubMed](#)]
239. Scott, L.; Downing, S.; Phelan, R.; Downing, T. Environmental modulation of microcystin and  $\beta$ -N-methylamino-l-alanine as a function of nitrogen availability. *Toxicon* **2014**, *87*, 1–5. [[CrossRef](#)]
240. Berntzon, L.; Erasmie, S.; Celepli, N.; Eriksson, J.; Rasmussen, U.; Bergman, B. BMAA inhibits nitrogen fixation in the cyanobacterium *Nostoc* sp. PCC 7120. *Mar. Drugs* **2013**, *11*, 3091–3108. [[CrossRef](#)] [[PubMed](#)]
241. Downing, S.; Banack, S.; Metcalf, J.; Cox, P.; Downing, T. Nitrogen starvation of cyanobacteria results in the production of  $\beta$ -N-methylamino-L-alanine. *Toxicon* **2011**, *58*, 187–194. [[CrossRef](#)] [[PubMed](#)]
242. Downing, S.; Downing, T.G. The metabolism of the non-proteinogenic amino acid  $\beta$ -N-methylamino-L-alanine (BMAA) in the cyanobacterium *Synechocystis* PCC 6803. *Toxicon* **2016**, *115*, 41–48. [[CrossRef](#)]
243. Forchhammer, K.; Schwarz, R. Nitrogen chlorosis in unicellular cyanobacteria—a developmental program for surviving nitrogen deprivation. *Environ. Microbiol.* **2019**, *21*, 1173–1184. [[CrossRef](#)]
244. Yan, B.; Liu, Z.; Huang, R.; Xu, Y.; Liu, D.; Wang, W.; Zhao, Z.; Cui, F.; Shi, W. Impact factors on the production of  $\beta$ -methylamino-L-alanine (BMAA) by cyanobacteria. *Chemosphere* **2020**, *243*, 125355. [[CrossRef](#)]
245. Cox, P.A.; Banack, S.A.; Murch, S.J.; Rasmussen, U.; Tien, G.; Bidigare, R.R.; Metcalf, J.S.; Morrison, L.F.; Codd, G.A.; Bergman, B. Diverse taxa of cyanobacteria produce  $\beta$ -N-methylamino-L-alanine, a neurotoxic amino acid. *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 5074–5078. [[CrossRef](#)]
246. Cox, P.A.; Banack, S.A.; Murch, S.J. Biomagnification of cyanobacterial neurotoxins and neurodegenerative disease among the Chamorro people of Guam. *Proc. Natl. Acad. Sci. USA* **2003**, *100*, 13380–13383. [[CrossRef](#)]