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# Secondary Metabolites in Cyanobacteria

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## Abstract

Cyanobacteria are a diverse group of photosynthetic bacteria found in marine, freshwater and terrestrial habitats. Secondary metabolites are produced by cyanobacteria enabling them to survive in a wide range of environments including those which are extreme. Often production of secondary metabolites is enhanced in response to abiotic or biotic stress factors. The structural diversity of secondary metabolites in cyanobacteria ranges from low molecular weight, for example, with the photoprotective mycosporine-like amino acids to more complex molecular structures found, for example, with cyanotoxins. Here a short overview on the main groups of secondary metabolites according to chemical structure and according to functionality. Secondary metabolites are introduced covering non-ribosomal peptides, polyketides, ribosomal peptides, alkaloids and isoprenoids. Functionality covers production of cyanotoxins, photoprotection and antioxidant activity. We conclude with a short introduction on how secondary metabolites from cyanobacteria are increasingly being sought by industry including their value for the pharmaceutical and cosmetics industries.

**Keywords:** cyanobacteria, secondary metabolites, nonribosomal peptides, polyketides, alkaloids, isoprenoids, cyanotoxins, mycosporine-like amino acids, scytonemin, phycobiliproteins, biotechnology, pharmaceuticals, cosmetics

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## 1. Introduction

### 1.1. Cyanobacteria

Cyanobacteria are a diverse group of gram-negative photosynthetic prokaryotes. They are thought to be one of the oldest photosynthetic organisms creating the conditions that resulted in the evolution of aerobic metabolism and eukaryotic photosynthesis [1, 2]. They

are primarily photoautotrophic performing oxygenic photosynthesis using photosystems I and II to produce energy, requiring water, carbon dioxide, inorganic compounds and light to grow. They are also able to grow under heterotrophic conditions without light using an organic carbon substrate to obtain energy [3].

Morphologically cyanobacteria can be unicellular or filamentous and have spherical, rod and spiral shapes [4, 5]. Taxonomically they are divided broadly into five major sub-sections using morphological and physiological characteristics as described in [5]: Subsection I (order: Chroococcales), II (order: Pleurocapsales), III (order: Oscillatoriales), IV (order: Nostocales) and V (order: Stigonematales). Subsections I and II are unicellular as single cells or aggregates that reproduce by binary fission or budding (I) and multiple fission or both binary and multiple fission (II). Subsections III-V are filamentous, which are composed of trichomes (chain of cells), these reproduce by trichome breakages to produce short motile fragments known as hormogonia. Subsection III cyanobacteria divide in one plane only and are composed of vegetative cells only whereas subsections IV and V are capable of cell differentiation. An example includes the production of heterocysts in the absence of a nitrogen source, which is used for nitrogen fixation [5]. The classification of cyanobacteria is constantly evolving with newer systems based on phylogenetic analyses [6].

Cyanobacteria live in a wide range of habitats encompassing freshwater, marine and terrestrial ecosystems (**Table 1**). A key feature of cyanobacteria is their ability to thrive under extreme conditions and their ability to adapt and evolve to cope with abiotic stress factors such as high light, UV and extreme temperatures. As extremophiles cyanobacteria can exist as thermophiles (high temperature tolerant) e.g. *Synechococcus* found in hot springs and geotherms, psychrophiles (cold tolerant), acidophiles (low pH tolerant), alkaliphiles (high pH tolerant) and halophiles (salt tolerant) [7].

Species of cyanobacteria	Order	Habitat
Unicellular		
<i>Microcystis</i> sp.	Chroococcales	Freshwater
<i>Synechococcus</i> sp.	Chroococcales	Marine
<i>Synechocystis</i> sp.	Chroococcales	Freshwater
<i>Hyella caespitosa</i>	Pleurocapsales	Marine
Filamentous		
<i>Lyngbya majuscula</i>	Oscillatoriales	Marine (tropical)
<i>Oscillatoria</i> sp.	Oscillatoriales	Freshwater
<i>Anabaena</i> sp.	Nostocales	Freshwater
<i>Nostoc</i> sp.	Nostocales	Terrestrial
<i>Fischerella muscicola</i>	Stigonematales	Freshwater

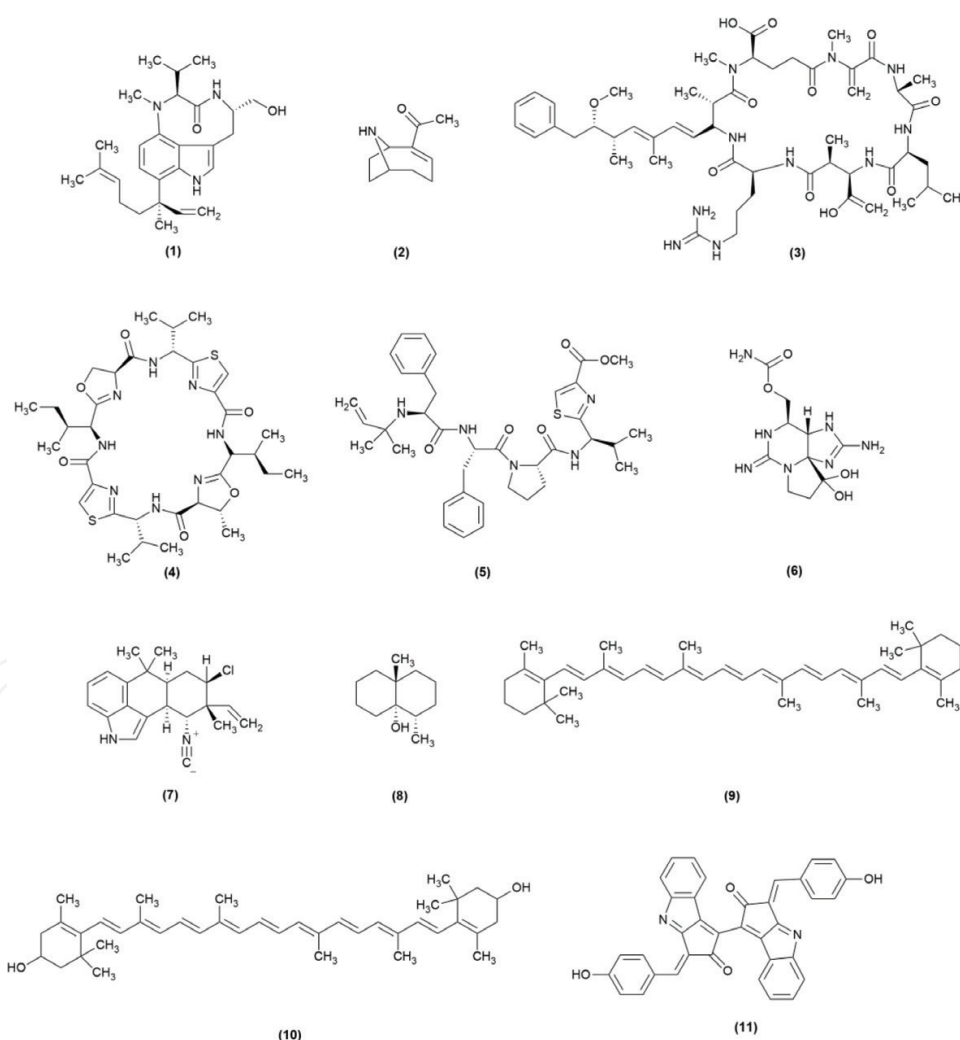
**Table 1.** Cyanobacterial species by morphology, order and habitat.

## 1.2. Cyanobacterial secondary metabolites

Secondary metabolites, also described as natural products, are usually described as compounds that are not directly required for an organism's primary metabolism. These secondary metabolites are usually unique to specific organisms and are not present during all environmental conditions.

Although most metabolites can be categorised as primary or secondary there is some overlap between the two. Some are essential for primary metabolism but are only synthesised by specific species and are therefore also secondary metabolites.

Secondary metabolites are often produced by cyanobacteria in response to biotic or abiotic stress in the surrounding environment by providing protection and aiding in survival giving an advantage over other species [2, 8]. Because of their ability to survive under a diversity of environments, cyanobacteria are a rich source of secondary metabolites. Different suites



**Figure 1.** Chemical structures of a variety of secondary metabolites; lyngbyatoxin-a (1), anatoxin-a (2), microcystin-LR (3), patellamide-a (4), aeruginosamide (5), saxitoxin (6), hapalindole-a (7), geosmin (8),  $\beta$ -carotene (9), zeaxanthin (10) and scytonemin (11).

of secondary metabolites can be produced according to the stress environment with a high degree of structural variation across the different compound classes. These suites of metabolites include; peptides, polyketides, alkaloids, terpenoids and UV-absorbing (**Figure 1**). Accordingly they possess a wide variety of functions to protect the cells such as; defence against predators and grazers, chemosensory, photoprotection and antioxidant roles. These properties can be utilized in industrial biotechnology as nutraceuticals, cosmeceuticals and pharmaceuticals.

## 2. Cyanobacterial secondary metabolites by chemical structure and biosynthesis

### 2.1. Nonribosomal peptides and polyketides

Commonly occurring as secondary metabolites in cyanobacteria are nonribosomal peptides NRPs. These are produced using specialised nonribosomal peptide synthases (NRPS). NRPS contains modules, which are responsible for integrating specific amino acids into peptide chains. These modules consist of an adenylation domain, peptidyl carrier domain and a condensation domain, which incorporates proteinogenic and nonproteinogenic amino acids. Other domains can also be present for further modifications such as N-methylation, epimerization and cyclisation of the amino acid backbone, which gives rise to the intricate chemical structures produced [9]. Lyngbyatoxins, such as lyngbyatoxin-a (**Figure 1 (1)**), are biosynthesised *via* NRPS pathway in *Lyngbya majuscula* and comprise of an indolactam ring composed of L-valine, L-tryptophan and methionine [10]. Lyngbyatoxin-a is a dermatotoxin with potent tumour promoting activity by activation of protein kinase C (PKC) [11].

Another large class of secondary metabolites found in cyanobacteria are the polyketides, which are biosynthesised from acetyl-CoA using polyketide synthases (PKS). Similarly to NRPS, PKS modules consist of an acyltransferase domain, acyl carrier protein domain and ketosynthase domain as well as additional domains for further modification [12]. The neurotoxin anatoxin-a (**Figure 1 (2)**) from *Anabaena* sp. Binds irreversibly to nicotinic acetylcholine receptors and is biosynthesised from L-proline using three PKS modules [9].

Hybrid metabolites are primarily derived from the attachment of polyketide or fatty acids using PKS to nonribosomal peptides in a natural combinatorial biosynthetic pathway to produce an array of chemical structures with specific roles and bioactivity. Microcystin-LR (**Figure 1 (3)**) is biosynthesised using multi-enzymes of NRPS and PKS modules and has potential as a lead compound for the treatment of cancer due to its cytotoxicity [13].

### 2.2. Ribosomal peptides

Ribosomal peptides (RPs) are synthesised on the ribosome and only use proteinogenic amino acid. They are similar to NRPs due to their posttranslational modifications. A prevalent group of ribosomal peptides found in cyanobacteria are the cyanobactin. These are cyclic and less commonly linear peptides formed through the post-ribosomal peptide synthesis (PRPS) pathway, which then undergoes post modifications to form their final complex structures [14],

formally known as ribosomally synthesised and posttranslationally modified peptides (RiPP). Examples include the cyclic peptides patellamides, such as patellamide A (**Figure 1 (4)**) and the linear peptide aeruginosamide (**Figure 1 (5)**) [9].

### 2.3. Alkaloids

Alkaloids are nitrogen containing natural compounds, which usually have toxic properties, an example includes the saxitoxins also known as paralytic shellfish poisons (**Figure 1 (6)**), which are neurotoxins found in a number of cyanobacteria [15].

Indole alkaloids are a class of alkaloids containing an indole moiety such as the hapalindoles (hapalindole-A, **Figure 1 (7)**), hapalindolinones, ambiguines, fischambiguines, fisherindoles, and welwitindolinones, which are only found in cyanobacteria of subsection V. Their structural diversity is due to the cyclisation, methylation, oxygenation and chlorination of terpene precursors [16]. Hapalindole isolated from *Fischerella* sp. has been found to possess antibacterial activity against gram negative and gram positive bacteria such as; *Escherichia coli* ATCC25992 and *Staphylococcus aureus* ATCC25923 [13].

### 2.4. Isoprenoids

A wide range of isoprenoids (also known as terpenoids) are produced by cyanobacteria, which have a common pathway utilising isoprene diphosphate (IDP) and dimethylallyl triphosphate (DMADP) precursors. These have many possible configurations resulting in high structural diversity due to modification by cyclisation, rearrangements and oxidation [17]. They are biosynthesized through the methylerythritol-phosphate (MEP) pathway. Using glyceraldehyde-3-phosphate and pyruvate produced from photosynthesis, the five carbon building blocks IPD and DMADP are formed [17].

The smallest group of isoprenoids is the hemiterpenes, which are formed from a single isoprene unit composed of five carbons. Monoterpenes have 10 carbons and are formed from IDP and DMADP or two molecules of DMADP monomers to form geranyl diphosphate (GDP). An example includes 2-methylisabomeol, which gives taste and odour to water. Geosmin (**Figure 1 (8)**) is an odorous sesquiterpene found in *Nostoc punctiforme* PCC 73102, which gives rise to its earthy smell and is synthesised from the condensation of an IDP molecule to the monoterpene GDP to form farnesyl diphosphate (FDP) [17, 18].

An abundant group of isoprenoids found in cyanobacteria are the carotenoids. These are tetraterpenes formed from the head to head condensation of two geranyl geranyl diphosphate (GGDP) molecules [17]. Located within cell membranes due to their hydrophobic nature, this group of metabolites can be divided into two classes; carotenes, hydrocarbon carotenoids such as  $\beta$ -carotene (**Figure 1 (9)**) and xanthophylls, which are oxygenated derivatives of hydrocarbon carotenoids such as zeaxanthin (**Figure 1 (10)**). Other carotenoids commonly found within cyanobacteria are echinenone, canthaxanthin and myxoxanthophyll. In many cases individual carotenoids could be considered as primary rather than secondary metabolites because of their role in photosynthesis however, other carotenoids are more specifically involved in photoprotection and in antioxidant protection and therefore fall into the secondary metabolites category [19].



3. Cyanobacterial secondary metabolites by function

3.1. Toxic metabolites

A wide variety of toxic metabolites (**Table 2**) are produced by cyanobacteria that have a negative effect on target species in their surrounding areas and are referred to as cyanotoxins [2]. These toxins are found during cyanobacterial blooms on stagnant surface water bodies. Cyanobacteria that bloom include the unicellular *Microcystis* and the filamentous *Anabaena*, and *Nostoc* [20].

Cyanotoxins have a diverse range of chemical structures including ribosomal peptides and NRPs, polyketides alkaloids and lipopolysaccharides. These toxins can be classified according to their biological effect; neurotoxins targeting the nervous system, hepatotoxins targeting the liver, cytotoxins targeting cells, dermatotoxins targeting the skin or endotoxins, which are irritants [15]. The most prevalent and potent hepatotoxins are the cyclic peptides microcystins, which are produced through NRPS in *Microcystis*, *Anabaena*, *Planktothrix* and *Nostoc* [15].

An example of a non-protein amino acid neurotoxin is  $\beta$ -N-methylamino-L-alanine, which can be produced by a variety of cyanobacteria [21]. It was originally isolated from cycad seeds in Guam and many investigations have implicated this neurotoxin in neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS) and Parkinsonism dementia complex (PDC) [22]. Other neurotoxins include saxitoxin (paralytic shellfish poisons) and the anatoxins [15].

Cyanotoxin	Biological effects	Cyanobacteria
Microcystin	Hepatotoxin, inhibits eukaryotic protein phosphatases (types 1 and 2A)	<i>Microcystis</i> , <i>Anabaenopsis</i> , <i>Nostoc</i>
Nodularin	Hepatotoxin, inhibits eukaryotic protein phosphatases (types 1 and 2A)	<i>Nodularia</i>
Saxitoxin	Neurotoxin, binds to voltage-gated Na <sup>+</sup> channels, causing neuronal communication blockage	<i>Aphanizomenon</i> , <i>Anabaena</i> , <i>Lyngbya</i>
Anatoxin-a	Neurotoxin, binds to nicotinic acetylcholine receptors irreversibly	<i>Cylindrospermum</i> , <i>Planktothrix</i> , <i>Oscillatoria</i>
$\beta$ -N-methylamino-L-alanine	Neurotoxin, damages motor neurons	Many species including; <i>Anabaena</i> , <i>Nostoc</i> , [24]
Lyngbyatoxin	Cytotoxin, binds to protein kinase C, tumour promoting	<i>Lyngbya majuscula</i>
Aplysiatoxins	Cytotoxin, binds to protein kinase C, tumour promoting	<i>Lyngbya majuscula</i>
Lipopolysaccharides	Endotoxin, irritant	<i>Microcystis</i> , <i>Anabaena</i> , <i>Spirulina</i> , <i>Oscillatoria</i>

**Table 2.** Cyanotoxins and their biological effect.

Although dangerous to animals, fish and humans, these toxins have potential uses as biocides (algacides, fungicides, herbicides and insecticides) and pharmaceuticals (antimicrobial, anti-cancer, antiviral and immunosuppressant) [15, 23].

### 3.2. Photoprotective metabolites: Mycosporine-like amino acids (MAAs) and scytonemin

Mycosporine-like amino acids (MAAs) are a group of about 30 colourless, water soluble, low molecular weight molecules found primarily within the cytosol of cells and sometimes found glycosylated on the outer cell membrane such as in *Nostoc commune* [25]. MAAs have strong absorption in the UV region between 310 and 365 nm [2] with high molar extinction coefficients ( $\epsilon = 28,100\text{--}50,000 \text{ l}\cdot\text{mol}^{-1}\cdot\text{cm}^{-1}$ ) providing photoprotection with the ability to disperse energy without producing reactive oxygen species (ROS) [26].

They consist of cyclohexenone or cyclohexenimine chromophores conjugated to nitrogen substituents from amino acids or imino alcohols. The variety in absorption is due to the differing nitrogen substituents and side groups [27, 28] (**Table 3**).

There are two biosynthetic routes involved in the production of MAAs. The first is the shikimate pathway (biosynthesis of aromatic acids) [29], by first forming deoxy-D-arabinoheptulose-7-phosphate (DAHP) from phosphoenolpyruvate (PEP) and erythrose-4-phosphate (E4P) using DAHP synthase. DAHP is then converted to 3-dehydroquinate and subsequent transformation into 4-deoxygadusol (4-DG). The primary MAA mycosporine-glycine is then formed from the reaction of 4-DG with glycine, which can then be converted into a secondary MAA by addition of other amino acids such as serine (to produce shinorine) and threonine (to produce porphyra-334) [25]. The other pathway involved is the pentose-phosphate pathway, which also produces the intermediate 4-DG from sedoheptulose-7-phosphate *via* 2-*epi*-5-*epi*-violiolone [19].

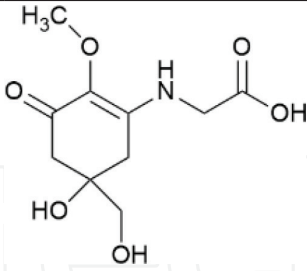
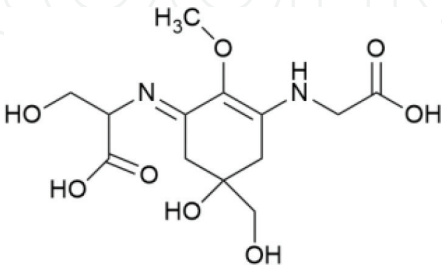
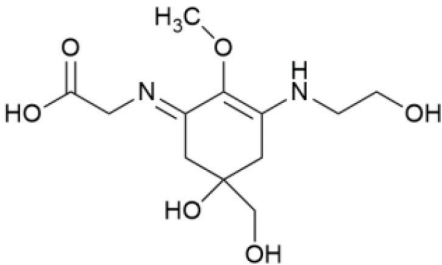
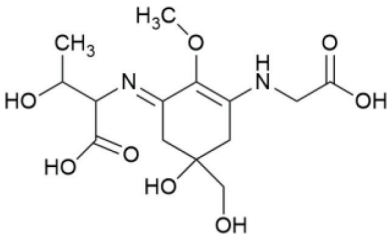
Another photoprotective metabolite produced by cyanobacteria alone is scytonemin (**Figure 1 (11)**), this is located in the extracellular polysaccharide sheath of cyanobacteria [19]. With a molecular weight of 544 Da it is a hydrophobic alkaloid comprising of idolic and phenolic substituents usually linked by a carbon-carbon double bond. It has an absorption maximum at 380 nm [2, 26]. Scytonemin has an extinction coefficient of  $136,000 \text{ l}\cdot\text{mol}^{-1} \text{ cm}^{-1}$  at 384 nm, which makes it an excellent photo-protective compound. It is biosynthesized in response to UV-A and has two major forms, an oxidised state (brown) and reduced state (red).

### 3.3. Antioxidants

Unavoidably ROS are produced by cyanobacteria during photosynthesis and respiration. Abiotic factors that produce these species include UVR, osmotic perturbations, desiccation and heat. Hydrogen peroxides ( $\text{H}_2\text{O}_2$ ), superoxides ( $\text{O}_2^{\bullet-}$ ) and hydroxyl radicals ( $\text{OH}^{\bullet}$ ) which damage biomolecules within cells are all examples of ROS [30].

Cyanobacteria require multiple approaches to prevent inhibitory effects of stressful environments. They can prevent the production of ROS by energy dissipation in the photosynthetic



MAA	Molecular structure	$\lambda_{\text{max}}$ (nm), $\epsilon$ ( $\text{l}\cdot\text{mol}^{-1}\cdot\text{cm}^{-1}$ )	Species of cyanobacteria
Mycosporine-glycine		310, 28,800	<i>Nostoc commune</i>
Shinorine		334, 44,668	<i>Anabaena</i> sp.
Asterina-330		330, 43,800	<i>Gloeocapsa</i> sp.
Porphyra-334		334, 42,300	<i>Nodularina baltica</i>

**Table 3.** Example of MAAs [27, 28].

apparatus. One mechanism is the non-photochemical quenching (NPQ) of excitation energy *via* photosystem II using the carotenoid zeaxanthin. They also produce enzymatic antioxidants such as; superoxide dismutases (SOD), catalases and peroxidases) as well as non-enzymatic antioxidants such as; carotenoids, phycobiliproteins, tocopherols and ascorbic acid [31].

Carotenoids absorb light in the region of 400–500 nm and have several roles including sun-screening, singlet oxygen quenching, releasing excessive light as heat through the xanthophyll cycle and radical scavenging [30].

Another group of antioxidants are the phycobiliproteins (PBP). These are present only in cyanobacteria and are primarily used as major light harvesting antennae but also have antioxidant

roles within the cells [32]. They are water soluble proteins that are brightly coloured due to the covalently attached linear tetrapyrrole prosthetic groups called bilins, which gives rise to cyanobacteria prominent colour. They, along with linker protein are able to form giant supra-molecular structures known as phycobilisomes [33].

## 4. Potential of cyanobacterial secondary metabolites in industrial biotechnology

Sustainability in industry is increasingly important due to global warming and the depletion of fossil fuels. A considerable amount of research has been conducted to find new sources of industrially important compounds to reduce the carbon footprint and increase sustainability.

Cyanobacteria has received much interest in becoming a promising alternative due to their diversity, simple growth needs and simple genetic background, which are easily manipulated to form cell factories [34].

Some strains of cyanobacteria are already being used in industry, examples include the edible *Arthrospira* (*Spirulina*) and *Nostoc*, which have been used as a food source for thousands of years [35].

*Spirulina* has been well researched for its application within industry. It is used as a health food due to its extensive source of proteins, polyunsaturated fatty acids ( $\gamma$ -linoleic acid, GLA), antioxidants (phycocyanin and carotenoids) and vitamins [36].

A challenge remains in assessing and understanding the ability of cyanobacteria to produce target metabolites in sufficient quantities to be of use under standard and repeatable conditions. This will be easier moving into the future as 'omic' studies enable improved understanding on metabolite pathways using a whole systems approach.

### 4.1. Pharmaceuticals and cosmetics

Natural products have been used to treat disease for thousands of years and are a useful source of bioactive compounds used in the pharmaceutical industry as leading compounds in drug discovery. They can be used as templates for synthesis of new drugs to treat complex diseases. Cyanobacteria have been widely researched for their applications in this field. They have found to possess a wide range of potential antimicrobial, anticancer, antiviral and anti-inflammatory activities [37]. Some known bioactives are listed below (**Table 4**) [11].

Chemotherapies currently used in the treatment of cancer cause serious side effects; naturally derived alternatives give opportunities for synthesising new highly potent drugs with fewer side effects [15, 42]. Cytotoxic metabolites produced by cyanobacteria usually target tubulin or actin filaments in eukaryotic cells, which make them promising anticancer agents. Dolastatins found within *Leptolyngbya* and *Simploca* sp. are synthesised by NRPS-PKS enzymes and are able to disrupt microtubule formation. Other cyanobacterial metabolites act as proteases inhibitors such as the lyngbyastatins, which are cyclic depsipeptide derivatives, which are

Species of cyanobacteria	Bioactive compound	Biological activity	References
<i>Spirulina platensis</i>	Spirulan	Antiviral	[38]
	$\gamma$ -linolenic acid	Precursor to prostaglandins	[39]
	Phycocyanin	Cosmetic colourants	[1]
<i>Lyngbya majuscula</i>	Apratoxins	Anticancer	[23]
<i>Nostoc commune</i>	Nostodione	Antifungal	[38]
	Carotenoids	Antioxidant	[36]
	MAAs	Sunscreen	[40]
<i>Anabaena circinalis</i>	Anatoxin-a	Anti-Inflammatory	[11, 38]
<i>Fischerella muscicola</i>	Fischerellin	Antifungal	[11]
	Scytonemin	Anti-inflammatory, Anti-proliferation	[41]

**Table 4.** Potential applications of cyanobacterial natural products in pharmaceutical and cosmetics industry.

thought to be elastase inhibitors. Apratoxins such as Apratoxin-a from *Lyngbya majuscula* is another metabolites biosynthesized from a hybrid NRPS-PKS pathway. It is cytotoxic due its ability to induce G1-phase cell cycle arrest and apoptosis [42].

Antibacterial metabolites produced by cyanobacteria are effective against gram negative and gram positive bacteria. In the age of antibacterial resistance, new drugs are essential to combat bacterial infections. The hapalindole-type class of indole alkaloids has been found to possess antimicrobial (bacteria, fungi) and antialgal activity [16].

Secondary metabolites can be used as natural ingredients in the cosmetics industry. Uses include the photoprotective MAAs in sunscreens to protect the skin from harmful UVR. Pigments such as carotenoids and phycobiliproteins could be used as natural colourants but also as antioxidants to protect the skin from damage caused by UV exposure [11].

Other potential uses for cyanobacterial secondary metabolites include their use in the nutraceutical and agricultural industry [11, 43].

## 5. Conclusion

Cyanobacteria have a long evolutionary history and have adapted to deal with natural and anthropogenic stress. The morphological, biochemical and physiological diversity of cyanobacteria gives rise to the vast amount of secondary metabolites produced all with their own specific functions that aid in the organism's survival. These secondary metabolites can also be utilised in drug discovery as lead compounds due to their complex structures and varied bioactivities. New natural products can be identified through biosynthetic pathway analysis using genomic data with around 208 cyanobacterial genomes sequences publically available [12]. Although extensive research has been conducted on cyanobacterial secondary metabolites

there is still a large selection of species, which have yet to be sequenced and investigated with many potentially important secondary metabolites yet to be discovered.

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## Conflict of interest

No conflict of interest.

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