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Review

Natural products from cyanobacteria: focus on beneficial activities

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Abstract: Cyanobacteria are photosynthetic microorganisms that colonize diverse environments worldwide, ranging from ocean to freshwaters, soils, and extreme environments. Their adaptation capacities and the diversity of natural products (molecules, metabolites, or compounds) that they synthesize support the cyanobacterial success for the colonization of their respective ecological niches. Although cyanobacteria are well-known for their toxin production and their relative deleterious consequences, they also produce a large variety of molecules that exhibit beneficial properties with high potential for various fields of application (e.g., synthetic analog of the dolastatin 10 used against Hodgkin lymphoma). The present review specially focuses on the beneficial activities of cyanobacterial molecules described so far. Based on an analysis of 670 papers, it appears that more than 90 genera of cyanobacteria have been found to produce compounds with potential beneficial activities, most of them belonging to the orders Oscillatoriales, Nostocales Chroococcales, and Synechococcales. The rest of the cyanobacterial orders (i.e., Pleurocapsales, Chroococcidiopsales, and Gloeobacterales) remain poorly explored in terms of their molecular diversity and relative bioactivity. The diverse cyanobacterial molecules presenting beneficial bioactivities belong to 10 different chemical classes (alkaloids, depsipeptides, lipopeptides, macrolides/lactones, peptides, terpenes, polysaccharides, lipids, polyketides, and others) that exhibit 14 major kinds of bioactivity. However, no direct relation between the chemical class and the bioactivity of these molecules has been demonstrated. We further selected and specifically described 50 molecule families according to their specific bioactivities and their potential uses in pharmacology, cosmetology, agriculture, or other specific fields of interest. This up-to-date review takes advantage of the recent progresses in genome sequencing and biosynthetic pathway elucidation, and presents new perspectives for the rational discovery of new cyanobacterial metabolites with beneficial bioactivity.

Keywords: cyanobacteria; natural products; metabolites; biological activities; producers; chemical classes

1. Introduction

Cyanobacteria belong to an ancient group of photosynthetic prokaryotes presenting a very wide range of cellular strategies, physiological capacities, and adaptations that support their colonization of very diverse microenvironments that are spread worldwide. As a consequence, cyanobacteria occur in varied and often even extreme habitats and are then able to settle in diverse biotopes (e.g., marine, terrestrial, freshwater, thermal springs) [1–3]. They are also well known for their production of a wide variety of natural bioactive products, including some potent toxins (e.g., microcystins, anatoxins, saxitoxins) [2,3]. Due to the remarkable capability of cyanobacteria to proliferate and form toxic blooms that induce potential human health consequences [4], numerous studies have been conducted to develop tools for the monitoring of cyanobacterial blooms [5,6] or effective strategies for the mitigation of their overgrowth [7]. On the contrary, cyanotoxins could also constitute a promising opportunity for drug development, notably for certain cancer therapies [8].

Two main aspects, the chemical diversity and the related bioactivity, have to be considered when considering the application potential of natural products (molecules, metabolites, or compounds)

produced by cyanobacteria. The chemical diversity of metabolites produced by cyanobacteria has been largely described and about fifteen reviews have been already published in the past twenty years dealing with their structural and chemical diversity [9–14] or their corresponding biosynthetic pathways [15,16]. Beyond the notorious harmful effects of cyanotoxins, other cyanobacterial natural products show a wide range of bioactivities that could be potentially useful for diverse application fields [17–21]. So far, among the existing reviews related to the diversity of cyanobacterial metabolites, only one has addressed the relative taxonomical positions of the producing strains [9]. Few taxa appear to be especially prolific producers of a large set of metabolites, while others still remain to be investigated. Recent genomics approaches and genome sequencing have been important steps in the elucidation of the pathways implicated in the biosynthesis of natural products. The wide structural diversity has been described as a consequence of the numerous biosynthetic pathway developed by cyanobacteria in order to produce these metabolites [15]. Most of the active cyanobacterial molecules are considered as being produced either through the non-ribosomal peptide (NRP) or the hybrid polyketide-NRP biosynthetic pathways [10], or by the ribosomal synthesis of pro-peptides that are post-translationally modified (RiPP). Previous genome analysis demonstrated that the diversity of the known metabolites is just a fraction of the true metabolic potential of cyanobacteria [15]. Concerning the bioactivity, cyanobacteria have long been a source of molecules with a potent nutritional virtue [18]. Indeed, Aztec civilizations consumed cyanobacteria (*Spirulina*) in their routine diet [22], and Chadian populations still use them as one of their substantial food sources [23]. Besides nutritional and probiotic purposes [13,21], they are well-known as a powerful source of metabolites with technological applications in the biotechnical or pharmaceutical fields, leading to an increase in interest in these research realms [10]. The most notorious bioactivities described to date are the antibacterial, antifungal, anticancerous, immunosuppressive, anti-inflammatory, and antituberculosis activities that have the potential to be used in rising fields such as pharmacology, cosmetology, agriculture, the food industry, or as biofuels [17]. Cyanobacteria cells, such as microalgae, already represent a sustainable resource for biotechnology due to their photosynthetic, N-fixation, and autotrophic capacities [17,18,24]. Due to the current increase in their pharmaceutical value and in their application prospects for use in medicine or biotechnology, the exploration of uncovered cyanobacterial taxa constitutes a promising strategy to efficiently explore the chemical diversity of their bioactive compounds.

The present review globally and systematically describes current knowledge on the biological activities described for cyanobacterial natural products, and thanks to the construction of a specific and freely available molecular database, regroups all information described so far concerning the chemical structures, the producing organisms, and the various bioactivities of all the different cyanobacterial metabolite families. This original material allows us to depict, from data based on exhaustive literature, which kinds of bioactive metabolite are potentially produced by the different cyanobacterial taxa. Here, the producer organisms were considered at different taxonomic levels (family, order, and genus) and are referenced according to their original habitats (freshwater, marine, and others). The chemical diversity is described with respect to the different kinds of bioactivity and the potential links between them are questioned, according to their potential or effective molecular mechanisms of action. A specific focus on 50 cyanobacterial compounds presenting beneficial bioactivities is detailed and discussed regarding their potential interest in pharmaceutical, cosmetical, biotechnical, and agricultural applications, opening new perspectives on the discovery of new potent bioactive cyanobacterial molecules.

2. Methods for dataset construction

A database was constructed using different search engines, notably PubMed and Google Scholar. The keywords used were “cyanobacteria”, “metabolite” or “natural product”, “beneficial” and “activity”, or “biological properties”. The database was first based on reviews and further completed with recent publications dealing with the isolation of new compounds from cyanobacteria.

The main entries into the database were the names of the metabolites. To avoid bias in the counting of metabolites, we stored all the data of each molecule and its variants as a “family”

according to their structures, in accordance with the proposal of Boudreau et al., 2012 [25] for the kulolide-like family. For example, all the properties of microcystin variants are contained in one line of the database.

The data collected were then classified depending on the chemical class of the compound, the chemical structure, and the strain producing the metabolites with all the taxonomic information (species, genus, family, and order), in accordance with Komarek et al. (2014) [26]. In addition, we collected the demonstrated activities for the purified compounds. Fourteen classes of activity were predominant: lethality (against brine shrimp, and other small invertebrates), neurotoxicity, hepatotoxicity, dermal toxicity, cytotoxicity, anti-inflammatory activity, antioxidant activity, antiviral, antibacterial, antifungal, antialgal, antiprotozoal, serine protease inhibition, and other types of enzyme inhibition.

Six hundred and seventy publications were analyzed, dating from the 1970s until today, and 260 families of metabolites were listed. To validate the knowledge depth of our work, a rarefaction curve of the number of molecule families was constructed using the number of analyzed publications (Figure 1).

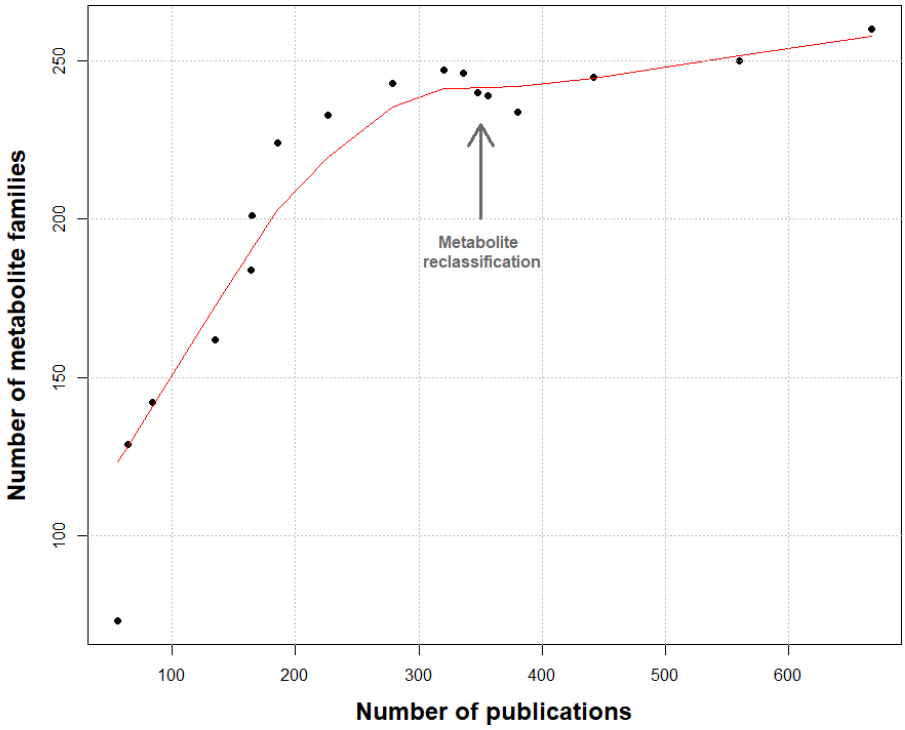

Figure 1. Evolution of the cumulative number of metabolite families according to the number of analyzed publications used for the construction of the database. The arrow indicates reclassification event of all the structural variants of one molecule in a unique entry of "family", according to the work of Boudreau et al. 2012 [25] with the kulolide family. We observed a progressive stabilization of the number of compounds family in the database that supports the postulation of the exhaustiveness of the present database.

3. Taxonomy of the producing strains

The 260 families of molecules were attributed to cyanobacteria at their different taxonomic levels (order, family, and genus) (Figure 2). Some families of compounds can be produced by different strains and thus, occur at different taxonomical level. For example, microcystins are produced by various strains belonging to seven different genera, five families, and three orders.

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The Oscillatoriales produces the largest number: 153 families of metabolites (46.5%). The strains belonging to the Nostocales are also considerable producers of metabolites with 98 families (29.7%). The other main producers are the strains belonging to Chroococcales and Synechococcales, which exhibit, respectively, 34 and 31 described molecules (10.3% and 9.4%). It is interesting that except for these four orders, the others (i.e., Pleurocapsales, Chroococcidiopsales, Gloeobacterales, and Spirulinales) are weakly represented in the database: less than five families of metabolite have been reported so far for all of them. Some metabolites have been isolated from cyanobacterial assemblage without accurate identification of the producer organisms. For these cases, the authors identified the genera of the two dominant cyanobacteria of the assemblage but could not accurately determine which one of them produces which molecule [27–39]. Tidgewell et al. (2010) [9] also identified the prevalence of the marine cyanobacterial products within Oscillatoriales and Nostocales with 58% and 24% of the isolated molecules, respectively. Within Oscillatoriales, members of the genus *Lyngbya*, and notably, *Lyngbya majuscula* produce the highest number of metabolites. This benthic genus is widely spread through the marine tropical ecosystem and has been widely studied because of its toxicity and implication in many dermatitis cases around the world [40,41]. A number of studies have been conducted on this genus, and a high number of new metabolites have been described. Nevertheless, *Lyngbya* is, to date, the most productive genus of bioactive cyanobacteria compounds (Figure 2.B). Recent studies showed that *Lyngbya* is polyphyletic [26,42] and using polyphasic approaches, *Lyngbya* have been split in four new genera: *Moorea* [43], *Okeania* [44], *Limnoraphis* [45], and *Microseira* [46]. Some marine strains previously identified morphologically as *Lyngbya majuscula* and *Lyngbya sordida* were therefore renamed to *Moorea producens,* and some strains of *Lyngbya bouillonii* were renamed to *Moorea bouillonii* on the basis of molecular and phylogenetic analyses [43]. In the same way, some freshwater strains morphologically identified as *Lyngbya wollei* were separate from the *Lyngbya* genus and described as *Microseira wollei* after analysis of their phylogeny [46].

According to this information, we decided to present the number of metabolite families produced by the *Lyngbya* and the *Moorea* genera together (reported as *Lyngbya-Moorea* in Figure 2.B), given that the majority of families isolated from *Lyngbya* species were reported to be from *Lyngbya majuscula* (46 of 78 described from all the *Lyngbya*) or from *Lyngbya* spp. strains sampled from tropical marine environments (22 of 78), as described for the *Moorea* genus and were possibly misidentified in regard to this newly described genus [43].

At the family level, the main producers of known bioactive compounds belong to Oscillatoriaceae (30.3%, representing 122 families of compounds), followed by Nostocaceae and Microcoleaceae (17.2% and 10.9% for 69 and 48 molecule families, respectively) (Figure 2.A). At the genus level (Figure 2.B), *Lyngbya-Moorea* exhibits the highest number of isolated compounds (85 families of metabolites representing 20.6%), in accordance with the perceived richness production for the *Lyngbya* genus due to its polyphyletic status [47]. *Nostoc* is the second most prolific genus of bioactive compound families with 50 isolated families so far (12.1% of the families of metabolites). The other most important genera are *Anabaena*, *Oscillatoria,* and *Microcystis* (with 32, 31, and 27 families of molecules, respectively, representing 7.8%, 7.5% and 6.6%) (Figure 2.B).

When looking at the habitats of these Cyanobacteria, a large number of compounds were isolated from marine environments (148 families of metabolite in the database, meaning 53% of the families of metabolites) in comparison to the number of strains isolated from freshwater environments (77 families of metabolites, 27.6%) (Figure 2.B). However, this difference might be at least partly due to the high number of compounds isolated from the marine species *Lyngbya majuscula-Moorea producens* (49 families of molecules, 18.8% of the families in the database) and to the existence of various research programs focused on marine species (e.g., the Panama International Cooperative Biodiversity Group, ICBG).

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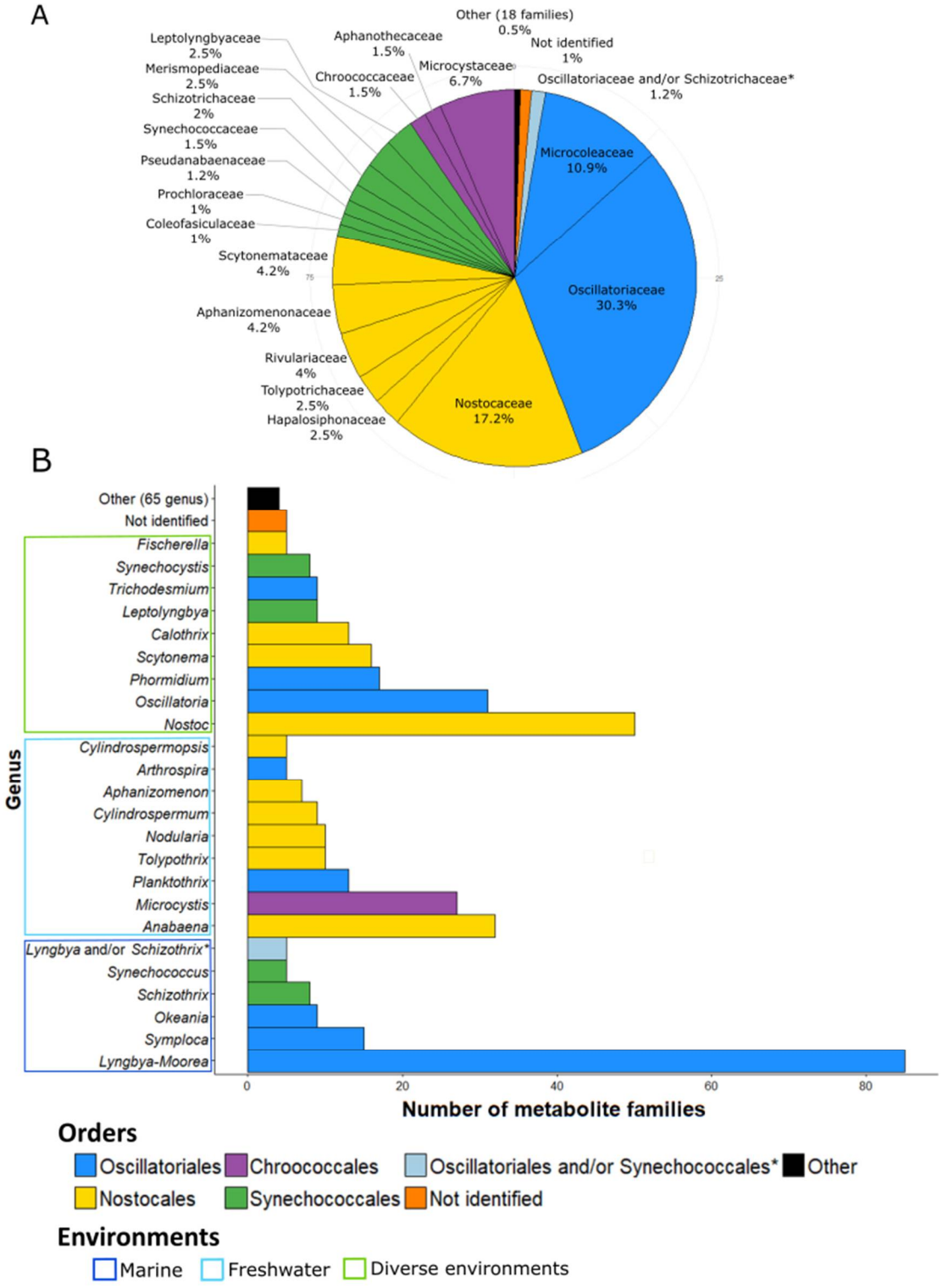

Figure 2. Proportion of families of compound by taxonomical level. A/ The pie chart represents the percentage of compound families for each taxonomical family. Remark that some compound families can be produced by several cyanobacterial families. The "Other" category concerns other taxonomical families that produce less than 2 compound families. B/ The histogram shows the number of compound families for each genus. The "Other" category corresponds to genera producing less than 4 compound families. * indicates cyanobacterial assemblages whom the real metabolite producer is undetermined. The boxes indicate the environmental origins for the corresponding genera. For both charts, the colors correspond to the taxonomical order of each genus or family.

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Overall, we observed that diversity at the genus level is important, as illustrated by the 90 different genera present in the database. Moreover, 65 different genera have been reported to produce less than four molecules (Figure 2.B). We also noticed that five molecules were isolated from *Lyngbya/Schizothrix* assemblages and five others from unidentified strains of cyanobacteria (Figure 2.B). These two observations allowed us to conclude that, at the genus level, the diversity of producers is large with a high number of genera studied. Nevertheless, the covered diversity appears not to be exhaustive and can still be increased. For example, among the Pleurocapsales order, only four genera have been reported to produce metabolites.

According to Shih et al. (2013) [48], the genomic potential of cyanobacteria to produce secondary metabolites is high with over above 70% of the studied strains presenting non-ribosomal peptide synthase (NRPS) or polyketide synthase (PKS) gene clusters in their genomes. In particular, they identified one strain belonging to the *Fischerella* genus (*Fischerella* sp. PCC 9339) that exhibits 22 NRPS/PKS clusters in its genome. On the contrary, only five compound families have been isolated from the genus *Fischerella* so far and are listed on the present database. Moreover, it is interesting to note that among the 126 strains analyzed by Shih et al. (2013) [48], only 14 were formally reported to produce characterized metabolites.

On the other side, the best producer genus, *Lyngbya-Moorea*, remains rarely studied at the genomic level: four genomes are available in Genbank database and another three are available on the Microscope platform [49]. Considering the number of compounds isolated from the *Lyngbya-Moorea* genus (85 compound families), most of the links between the identified molecules and the responsible biosynthetic gene clusters remain to be characterized. We also compared our collected data with those reported by Dittman et al. (2015) [15] in order to determine when the isolated molecule families are linked with a specific gene cluster for biosynthesis. This review showed that less than 20% of the molecule families from the database are associated with specific identified production of gene clusters. Thus, the biosynthesis of a large majority of compounds is still unknown as well as the regulation mechanisms controlling their biosynthesis. Therefore, these observations highlight part of the remaining possibilities for the discovery of new molecules, gene production, and biosynthesis pathways.

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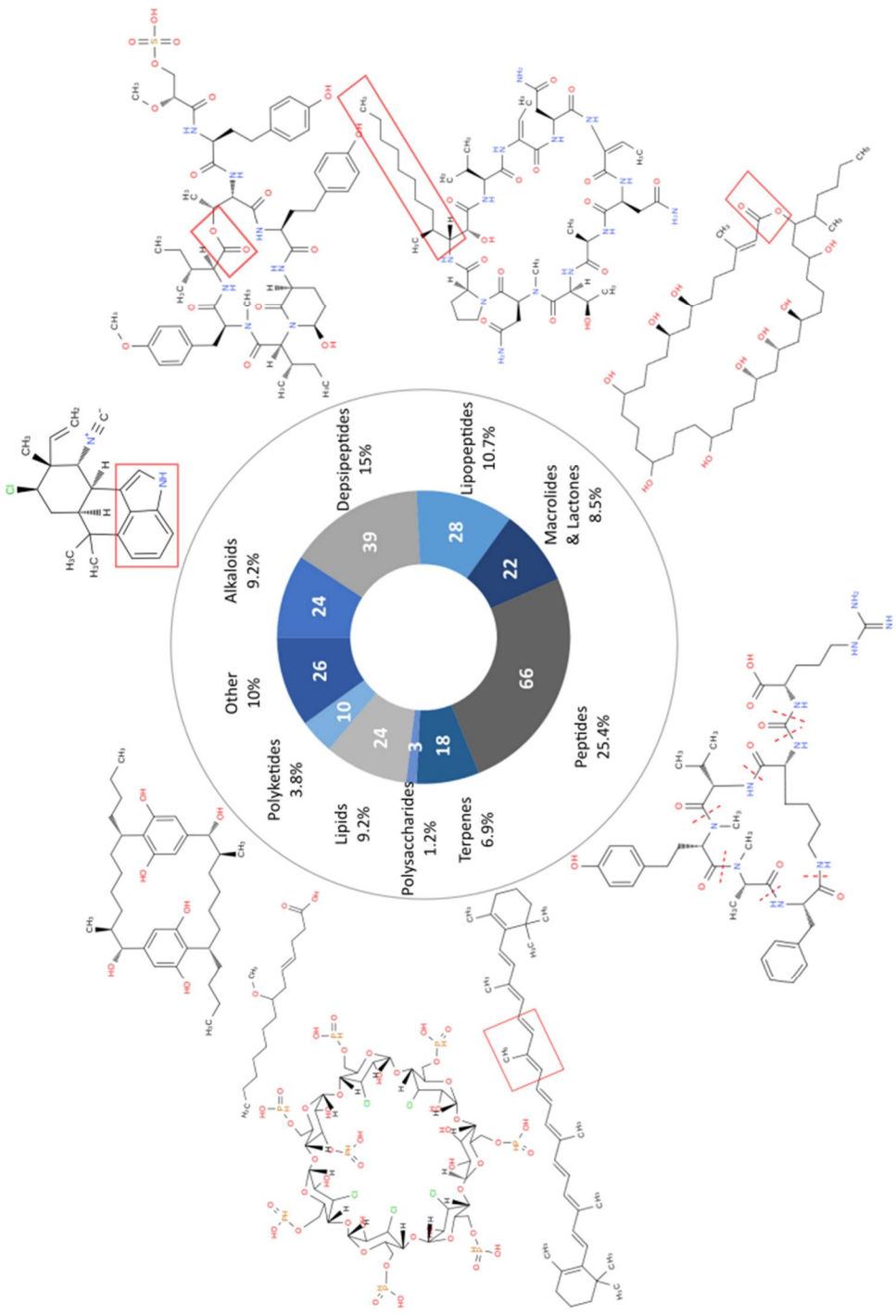

Figure 3. Classification of the 260 cyanobacterial metabolite families according to their respective chemical classes. All the molecules have been classified into these different classes according to their respective structural characteristics. For example, the depsipeptides are a class of peptide containing ester bond. The lipopeptides are a class of peptides which are linked to a lipid. Macrolides are molecules exhibiting a macrocycle and one or more lactone functions. The alkaloids are a class of compounds without presenting a specific structure, but some of them share remarkable features: small size, high activities and presence of some structure like indole, pyrrolidine, tropane etc… Terpenes are derived from the polymerization of isopentenyl-pyrophosphate. Polyketides are carbon molecules synthesized by polyketide synthase (PKS). Some examples of cyanobacterial molecules belonging to these classes are illustrated: Hapalindole A (alkaloids), Oscillapeptin A (depsipeptides), Minutissamide A (lipopeptides), Caylobolide B (macrolides/lactones), Anabaenopeptin E (peptides), β-carotene (terpenes), Cyclodextrin phosphate (polysaccharides), Lyngbic acid (lipids) and Cylindrocyclophane A (polyketides). The main characteristics of each chemical classes are highlight in red. All the structures were obtained from ChEMBL Database [353]

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4. Chemical diversity and bioactivity of natural products from cyanobacteria

Each of the 260 families of compounds was classified by chemical classes and bioactivity (Figure 3 & 4). The 260 families of compounds were classified by their chemical classes, and 10 classes were listed: alkaloids, depsipeptides, lipopeptides, macrolides/lactones, peptides, terpenes, polysaccharides, lipids, polyketides, and others (Figure 3). Of the 260 metabolite families, 66 belong to the peptide class. Together with the depsipeptide and lipopeptide classes, they represent 133 families of compounds (51%) derived from peptides. This is not surprising, regarding the diversity of biosynthetic pathways described in cyanobacteria: NRPS (non-ribosomal peptide synthase), PKS (polyketide synthase) and RiPPs (ribosomally synthesized and post-translationally modified peptides) with the ability to produce a wide range of metabolites and notable peptides [15] (Figure 3). Fourteen major activities have been listed from the literature (lethality, neuro-, hepato-, dermato- and cytotoxicity, anti-inflammatory, antioxidant, antiviral, antimicroalgal, antibacterial, antifungal and antiprotozoal activities as well as protease and enzyme inhibition activities). Cytotoxic activity against various cell lines is the most frequently detected type with up to 110 families of the 260 listed. On the other side, lethal and the antibacterial activities have been detected for 54 and 43 compound families, respectively (Figure 4).

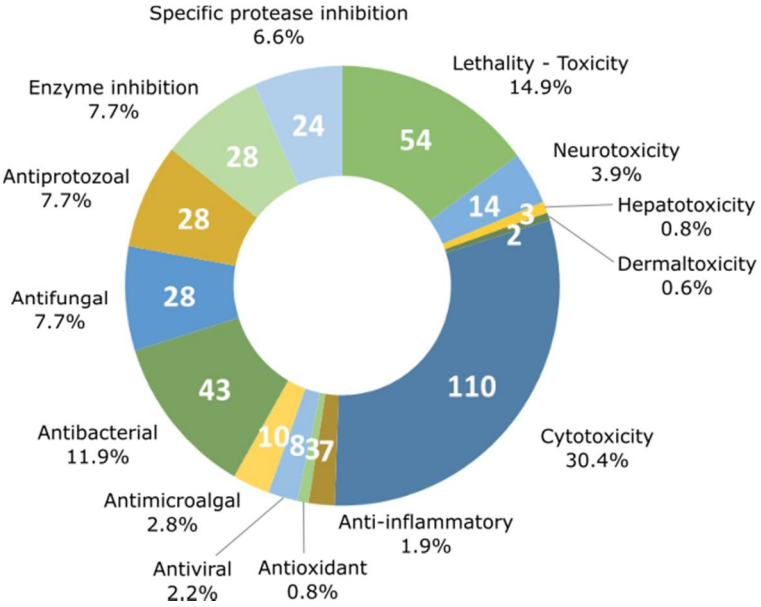

Figure 4. Number of metabolite families observed for each class of activity. The percentage represent the proportion of one activity compared to the whole occurrence of activities detected (n=362), some compounds presenting various activities and are considered several times.

The number of compounds displaying each tested activity is shown in Figure 5. The activities of molecules have been tested against different targets ranging from specific cellular mechanism to whole organism. For example, the inhibitory activity of proteases and other enzymes was shown to target enzymatic processes when the lethality and antimicrobial activity were tested against whole "organisms". The lethality tests were generally realized against small invertebrates such as the brine shrimp crustacean *Artemia salina,* the gastropod mollusk *Biomphalaria glabrata,* and the crustacean *Thamnocephalus platyurus*. This analysis confirms preceding observations (i.e., that cytotoxicity is the most commonly detected activity, followed by lethality and antibacterial activity). Some activities were detected only for a restricted number of compounds: dermatotoxicity concerned only two families of metabolites (aplysiatoxins and lyngbyatoxins) [50,51], hepatotoxicity was observed for three families (cylindrospermopsins, microcystins, and nodularins) [52–54], antioxidant and anti-inflammatory activities were observed for four (carotenoids, chlorophylls, mycosporine-like amino acids, phycocyanins) [55–58] and seven metabolite families (coibacins, honaucins, aeruginosins, malyngamides, phycocyanin, scytonemin, tolypodiol) [59–65], respectively. Nevertheless, there are

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only a few examples of these activities being tested by authors in comparison with cytotoxicity and lethality, which have been investigated far more regularly. In terms of anti-inflammatory activity, all seven tested molecules cited above were positive for this type of activity, and 53% of the studied molecule families have been tested for cytotoxic activity, while only 2.7% have been tested for anti-inflammatory activity. In parallel, some of these metabolite families can exhibit more than one activity. In fact, a total of 362 activities have been detected for all metabolite families.

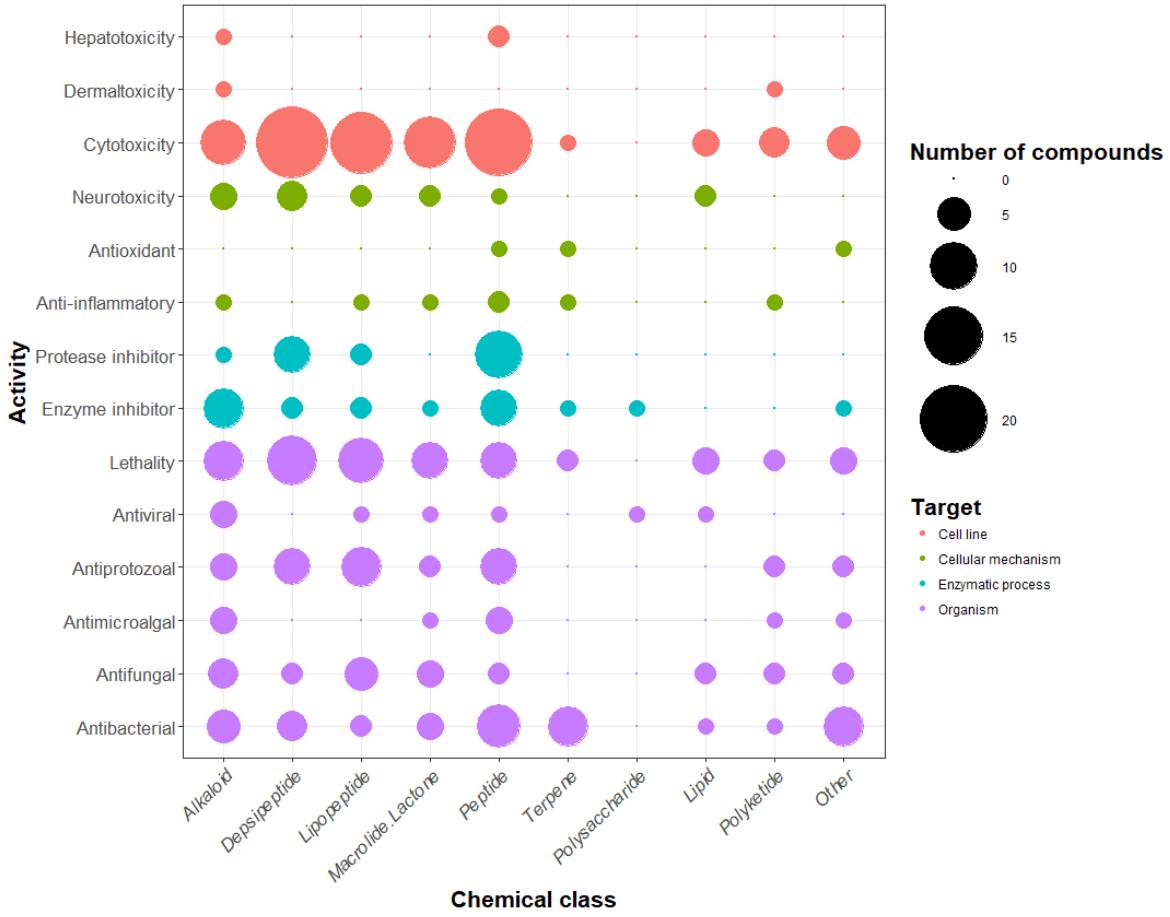

Figure 5. Classification of the 260 metabolite families according to their respective activities and chemical classes. The number of metabolite families is symbolized by the disc diameters, for each activity and each chemical class. For example, the first circle represents the number of alkaloids who has a hepatotoxic activity (in this case, 1 family of metabolites). Colors corresponds to the different category of activity targets. For example, cytotoxicity and hepatotoxicity are tested *in vitro* against cell lines while neurotoxicity, antioxidant and anti-inflammatory activities are biochemically tested for specific cellular mechanisms (such as the sodium influx, the scavenging of ROS (reactive oxygen species) and the inhibition of cytokines).

Focusing on the chemical class, it appears that there is no specific indication that one chemical class exhibits specific activities with regard to other classes. The results from the review showed that the polysaccharide class has only two activities (enzyme inhibition and antiviral activity), but only three types of polysaccharide isolated from cyanobacteria have been observed so far (calcium spirulan, cyclodextrins, iminotetrasaccharide) [66–68]. Five chemical classes, the alkaloids, the depsipeptides, the lipopeptides, the macrolides, and the peptides, seem to present a very large set of activities. When comparing the number of detected activities with the number of molecules belonging to each chemical class, the most bioactive molecules were shown to be the alkaloids, the lipopeptides, and the polyketides. Indeed, molecules belonging to the alkaloid class actually exhibit an average of 2.2 activities per molecule family, while the lipopeptides, the polyketides, and the peptides exhibit averages of 1.9, 1.8, and 1.2 bioactivities per molecule class, respectively.

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These observations highlight a bias in the bioactivities searched from the isolated molecules. Only the tested activities are finally reported. This obvious ascertainment remains the main limitation for the description of the potential applications of the bioactive molecules. In addition, there is still no consensus concerning the dose and dilution threshold that should be considered for each individual bioactivity test. In some cases, the concentration difference, used to determine if two distinct molecules are active, is important. For example, odoamide [69], a cyclic depsipeptide member of the aurilides family, and scytoscalarol [70], a sesterterpene, have both described as being "cytotoxic". However, their respective IC_{50} values appear to be very different: 26.3 nM against HeLa S3 human cervical cancer cells for odoamide and 135 μM against Vero cells for scytoscalarol, which represents a concentration difference of 500 times between their respective inhibition potentials. Furthermore, tests can be realized against several cell lines and strains with different responses, which limit comparison between results.

With 10 chemical classes and 14 types of bioactivity, the cyanobacterial metabolites are diverse and highly active. However, half of the families of metabolites listed in the database are peptides or peptide derivatives. This could be due to the importance of the peptide biosynthetic pathway (NRPS, PKS, and RiPPs) or the extraction methods used, which can eventually favor peptide extraction. We did not observe a link between chemical classes and activities, but this observation must be considered carefully in regard to the weak number of molecules in some classes (i.e., polyketides, polysaccharides, terpenes). The most frequently detected activity for cyanobacterial metabolites is cytotoxicity (42% of the metabolite families), whereas antioxidant or anti-inflammatory activities were detected for only 1.5% and 2.7% of the families. This imbalance is due to the frequency at which tests were carried out. In fact, cytotoxicity was tested for 53% of the molecules, while anti-inflammatory activity was only tested in 2.7%. This observation may reflect the research inclination to find new pharmaceutical compounds, notably cytotoxic compounds that are usable in cancer therapy, and suggests the potential for the discovery of new activities for application in other fields.

5. Beneficial activities of natural products produced by cyanobacteria

In this review, we further considered and developed examples of molecules that are considered as exhibiting potential beneficial activities for several purposes. The 260 families of compounds could have a large field of applications, e.g., agriculture, pharmacology, cosmetology, or in the food industry. For potential applications in agriculture, cyanobacterial compounds could be useful for alternative soil fertilization methods and as chemical pesticides [18]. The potential pharmaceutical applications of cyanobacterial metabolites include the development of new antibiotics or antibacterial or antiviral drugs [21].

5.1. Antimicrobial activity

Antimicrobial compounds that do not also present toxic effects are particularly of interest for applications in the food industry in order to clean processing equipment or for food preservation [71,72]. Cyanobacteria produce 85 families of metabolites isolated from various strains which display potent antimicrobial activity (representing a third of the 260 listed in the database) [18]. Below, we summarize the different antimicrobial metabolites (ranging by type of antimicrobial activity) that have been isolated from cyanobacteria so far and the corresponding available information. We also detail some examples of specific molecules that exhibit interesting bioactivity profiles.

5.1.1. Antibacterial activity

Among the metabolite families listed, 43 molecules have antibacterial activity, representing 17% of the families. These components were, in general, tested against different types of bacteria: GRAM-, GRAM+, mycobacterium, and cyanobacteria.

Among the 43 molecules, 22 are also cytotoxic and 16 have lethal activity against small invertebrates. Only three of them—eucapsitrione, kulolide-like, abietic acid—may have specific antimicrobial activity and produce negative results against other microorganisms.

316 **Table 1.** Antibacterial molecules extracted from the database and discussed in this review

Molecule family	Chemical classes	Activity	Producing organisms	References
Eucapsitrione	Anthraquinone derivative	- Antibacterial - No antimicrobial - Cytotoxic	*Eucapsis* sp. UTEX 1519	[73]
Kulolide-like	Depsipeptide	- Antibacterial - No antifungal - Antiprotozoal - Lethal - Cytotoxic - VGSC (Voltage Gate Sodium Channel) activation	*Lyngbya majuscula;* *Rivularia* sp.; *Moorea producens;* *Okeania* sp.; *Symploca hydnoides;* *Oscillatoria margaritifera*	[25,74–85]
Abietic acids	Terpene	- Antibacterial - No lethality - No antialgal	*Plectonema radiosum* LEGE 06105; *Nostoc* sp. LEGE 06077 and LEGE 07365; *Chroococcidiopsis* sp. LEGE 06174; *Synechocystis* sp. LEGE 06079; *Synechocystis salina* LEGE 06099; *Leptolyngbya ectocarpi* LEGE 11425; *Nodosilinea* sp. LEGE 13457; *Nodosilinea nodulosa* LEGE 07084	[86]
Hapalindole-like	Alkaloid	- Antibacterial - Antifungal - Antialgal - Cytotoxic - Insecticidal - Lethal activity - Reverse drug resistance (MDR) - VGSC modulator	*Hapalosiphon fontinalis;* *Westiellopsis* sp.; *Fischerella musicola;* *Hapalosiphon welwitschii;* *Westiella intricata;* *Fischerella ambigua;* *Hapalosiphon delicatulus;* *Hapalosiphon hibernicus;* *Westiellopsis prolifica;* *Fischerella* sp.; *Hapalosiphon laingii*	[87–112]

317 More details about molecule activities are available in supplementary data

318 Eucapsitrione and kulolide-like molecules (Table 1) show antibacterial activity (against
319 *Mycobacterium tuberculosis*) without inhibitory activity against the yeast *Candida albicans* [73,78].
320 Eucapsitrione is a molecule isolated from the cyanobacteria *Eucapsis* sp. (UTEX 1519) [73] and seems
321 to be a derivative of anthraquinones. This phenolic compound family is well-known in plants and
322 some microorganisms, and has demonstrated a large range of bioactivities, including antimicrobial,
323 antioxidant, anti-inflammatory, and potent anticancer properties [113–116]. This opens up other
324 perspectives and applications for these anthraquinone derivatives isolated from cyanobacteria, such
325 as eucapsitrione, but, so far, its other potential bioactivities have not been tested.
326 The kulolide-like family includes 44 related molecules. The first discovered molecule of the
327 family, kulolide, was isolated from a cephalaspidean mollusk *Philinopsis speciosa* [74]. Luesch and co-
328 workers (2001) discovered the first cyanobacterial analogues of this family, naming them the
329 pitipeptolides, and proposed a cyanobacterial origin for kulolide, which had been isolated earlier
330 from the mollusk [76]. All members of the kulolide-like family share chemical similarities and can be
331 categorized into two subgroups: those containing 2,2-dimethyl-3-hydroxy-7-octynoic acid (Dhoya)
332 and those containing 3-hydroxy-2-methyl-7-octynoid acid (Hmoya) [25]. The same activities were not

tested for all analogues, but some of them have shown antibacterial, antiprotozoal, cytotoxic, and even lethal activities (Table 1).

The third example of a molecule family presenting a specific anti-bacterial activity is abietic acid (Table 1). This molecule is a terpene that is generally found in resin and used by conifers as a defense metabolite [86]. Abietic acid presents anticyanobacterial activity against *Synechococcus nidulans*, and it seems to be non-toxic for *Chlorella vulgaris* and the brine shrimp *Artemia salina* (Table 1). Authors have suggested that its activity and defense mechanisms could be equivalent to those of conifer plants, i.e., trapping microorganisms or acting like allelochemical compounds. These non-toxic properties are interesting for the development of specific anti-cyanobacterial products.

The hapalindole-like group is a family of alkaloids, which contains around 80 related molecules ([87–112]) (Table 1). These metabolites were only previously isolated from *Hapalosiphon*, *Fischerella*, *Westiellopsis*, and *Westiella* genera. They show a wide range of activity, most notably, antibacterial activity against 27 various bacterial strains, together with antifungal and antialgal activities. They are also cytotoxic and exhibit additional insecticidal activity. Some of them were even able to reverse drug resistance in cancer cell lines [104,108] (Table 1). They probably exhibit modulatory activity on the sodium channels [106], which could explain their large set of diverse bio-activities.

5.1.2 Antialgal activity

Table 2. Antialgal molecules extracted from the database

Molecule family	Chemical classes	Activity	Producing organisms	References
Cyanobacterin	Lactone derivative	-Antialgal -Anticyanobacterial -Growth inhibition	*Scytonema hofmanni* UTEX 2349; *Nostoc linckia* CALU 892	[117–119,128]
Fischerellins	Polyketide	-Antialgal -Anticyanobacterial -Antifungal -Lethal -Growth inhibition	*Fischerella musicola*; *Fischerella* sp.; *Fischerella ambigua*; *Fischerella tesserantii*	[120,129–131]
Westiellamide-like	Peptide	-Antialgal -Anticyanobacterial -No antifungal -Lethal activity -Cytotoxic	*Westiellopsis prolifica* EN-3-1; *Nostoc* sp. 31; *Stigonema dendroideum* IA-45-3; *Oscillatoria raoi* TAU IL-76-1-2; *Nostoc spongiaeforme* var. *tenue* str. Carmeli	[122–127]
Ambigols	Alkaloid	-Antialgal -Antibacterial -Antifungal -Antiprotozoal -Lethal activity -Cytotoxicity -Enzyme inhibition	*Fischerella ambigua* 108b	[132,133]
Schizotrin-like	Peptide	-Antialgal -Antibacterial -Antifungal -Antiprotozoal -Lethal activity -Cytotoxicity	*Schizothrix* sp. TAU IL-82-2; *Lyngbya* sp. 36.91; *Phormidium* sp. LEGE 05292; *Tychonema* sp. CCAP 1462/13	[134–141]

Antialgal activity was tested generally against microalgae, and 10 families of metabolites were shown to present such activity. Among these 10 families, four also exhibited anticyanobacterial activity, and it can be supposed that these molecules may be acting against general photosynthesis

mechanisms. For example, cyanobacterins isolated from two strains, *Scytonema hofmanni* UTEX 2349 and *Nostoc linckia* CALU 892 [117,118], were shown to present significant antimicrobial activity directed against a large panel of microalgal and cyanobacterial strains (Table 2). These compounds also inhibit the growth of eight angiosperm plants, such as duckweed (*Lemna* genus), pea, corn, sorrel, black bindweed, wild oat, and green foxtail [119] (Table 2). Gleason and Case (1986) showed that this activity is due to the inhibition of the Hill reaction in photosystem II without inhibition of photosystem I [119].

Another example is the fischerellins family. These compounds were observed in four strains belonging to the *Fischerella* genus. They show a large range of activities comprising growth inhibition of *Lemna minor*, antifungal and lethal activities, and antialgal and anticyanobacterial activities. Hagmann & Jüttner (1996) showed that the fischerellins A is an effective inhibitor of the photosystem II [120] (Table 2).

The westiellamide-like family that gather 12 related cyclic peptides isolated from five strains belong to four different genera (Table 2). The related molecules, the bistratamides, were previously isolated from the ascidian *Lissoclinum bistratum* [121], and authors hypothesized a cyanobacterial symbiont origin for this molecules [122]. This family of compounds have been shown to have antialgal and anticyanobacterial activities (Table 2), but they did not show any antifungal activity against the yeast *Saccharomyces cerevisiae* ([122–127]). Moreover, one of them, dendroamide A, has shown the ability to reverse the multidrug resistance of a human breast carcinoma cell line (MCF-7/ADR) [123]. Indeed, the MCF-7/ACR cell line overexpress the P-glycoprotein pump, which transport drugs outside of the cell providing higher resistance to chemical treatment. Dendroamide A is able to specifically inhibit the action of the P-glycoprotein pump, allowing the drug to penetrate and lyse the cells with interesting potential anticancer applications.

Among the antialgal compounds, two have a remarkably broad spectrum of antimicrobial activities: the ambigols and the schizotrin-like families, both showing antialgal, antibacterial, antifungal, and antiprotozoal activities (Table 2). Three ambigol variants were isolated from *Fischerella ambigua* str. 108b, while the schizotrin-like family includes 13 structurally related molecules isolated from four different strains (Table 2). In addition to these antimicrobial activities, the ambigols also have enzyme inhibition activity against cyclooxygenases and HIV-1 reverse transcriptase. The members of the schizotrin-like family, the portoamides (isolated from *Phormidium* sp. LEGE 05292), have also shown mitochondrial metabolism inhibition activity, which induces a further decrease in the cellular ATP content in cells exposed to portoamides [140]. This property is also promising for the development of drugs acting against tumors and cancers [142].

Via their main antialgal action (i.e., photosynthesis inhibition), the molecules have been shown to present other potential uses and could be used as alternatives to chemical herbicides, for example, based on PSII inhibition (e.g., DCMU). These families of compounds could be used to develop new algaecides and herbicides and/or to develop new pharmaceutical drugs.

5.1.3 Antifungal activity

Twenty-eight families of compounds showed antifungal activities. Toxicity tests were carried out against diverse fungal species, mostly pathogenic ones, such as the well-known *Candida albicans*, *Saccharomyces cerevisiae*, *Penicillium notatum*, *Aspergillus oryzae*, and the less-known *Trichophyton mentagrophytes* and *Ustilago violacea*. Among these compounds, 11 showed several other types of antimicrobial activity in addition to antifungal activity. Only two metabolites, hassallidins and lyngbyabellins, demonstrated specific antifungal activity without presenting any antibacterial activity. The hassallidins are cyclic glycolipopeptides isolated from three strains belong to the Nostocales order (Table 3). Four variants have been characterized so far [143–147], and the non-ribosomal peptide gene cluster responsible for hassallidins synthesis has been identified. Thus, the hassallidins cluster was detected by bioinformatics analysis of the genomes of four heterocytous cyanobacteria, *Aphanizomenon gracile*, *Cylindrospermopsis raciborskii*, *Nostoc* sp., and *Tolypothrix* sp., and hassallidins production was confirmed by LC/MS analysis (Table 3). Recently, Pancrace et al. (2017) identified the hassallidins gene cluster and characterized a new hassallidins variant from

405 *Planktothrix serta* (PCC 8927), a nitrogen-fixing, non-heterocytous forming strain [146]. They
406 concluded that the strain gain of the cluster occurred by horizontal transfer and therefore questioned
407 the natural product distribution and diversity among cyanobacteria.

408 **Table 3.** Antifungal molecules extracted from the database

Molecule family	Chemical classes	Activity	Producing organisms	References
Hassallidins	Glycolipopeptide	-Antifungal -No antibacterial activity	*Hassalia* sp. B02-07; *Anabaena* sp. (SYKE 748A, 90y1998, 90M3, 299B, 258, SYKE763A, 0TU33S16, 0TU43S8, 1TU33S8, 1TU35S12, 1TU44S9, 1TU44S16, SYKE971/6, NIVA-CYA269/2, NIVA-CYA269/6, XPORK5C, XSPORK7B, XSPORK36B, XSPORK14D, BECID19); *Anabaena cylindrica* Bio33 *Cylindrospermopsis raciborskii* (ATC-9502 & CS-505); *Aphanizomenon gracile* Heaney/Camb 1986 140 1/1; *Nostoc* sp. (159 & 113.5); *Tolypothrix* sp. PCC 9009 *Planktothix serta* PCC 8927	[143–147]
Lyngbyabellins	Depsipeptide	-Antifungal -No antibacterial activity -Lethal activity -Cytotoxic	*Lyngbya majuscula* *Lyngbya* sp.; *Lyngbya bouillonii* *Moorea bouillonii*	[148–155]
Microguanidines	Guanidine derivative	-Antifungal -No cytotoxicity -No protease inhibition	*Microcystis* sp. TAU IL-306; *Microcystis aeruginosa* TAU IL-374	[156–158]
Majusculamides	Lipopeptide	-Antifungal -Cytotoxic -Immunosuppressive activity -Actin filaments disrupting -Anti-settlement activity	*Lyngbya majuscula*; *Lyngbya polychroa*	[159–165]

409 The lyngbyabellins are cyclic depsipeptides. They were isolated from *Lyngbya* and *Moorea*
410 species (Table 3). Hectochlorin is the only member of the family who was tested for antibacterial and
411 antifungal activity, showing no antibacterial activity but presenting antifungal activity against
412 *Candida albicans* [151]. The distinctive feature of the lyngbyabellins is that they can also disrupt actin
413 filaments. Luesch et al. (2000) [150] and Han et al. (2005) [149] showed that cells exposed to
414 lyngbyabellin A and E lost their microfilament network and caused cell cycle arrest at the cytokinesis
415 phase. Marquez et al. (2002) [151] showed that the same process appears with cells exposed to
416 hectochlorin. They also demonstrated that the molecule stimulates actin polymerization and then
417 induces cellular cycle disorders.
418 Microguanidines are guanidine derivatives isolated from two strains of *Microcystis* (Table 3).
419 These molecules showed antifungal activity against *Saccharomyces cerevisiae* E4orf4 without cytotoxic

activity. This specificity could be of interest for the development of new specific antifungal products [157].

Majusculamides are lipopeptides produced by *Lyngbya majuscula* and *Lyngbya polychroa*. These metabolites combine antifungal and cytotoxic activities with immunosuppressive and anti-settlement properties [159–165]. Simmons et al. (2009) [164] also demonstrated the ability of majusculamides to disrupt actin filaments that may explain these specific properties (Table 3).

5.1.4 Antiviral activity

Viral diseases are one of the main concerns around the world. According to the World Health Organization (WHO), HIV and AIDS caused around one million deaths in 2017 [166]. We noted that eight families of cyanobacterial compounds have shown antiviral activity. Antiviral activity was generally determined by testing against the human immunodeficiency virus (HIV-1 or HIV-2) or the herpes simplex virus (HSV-1 or HSV-2). One of them, the aplysiatoxins, showed activity against Chikungunya's virus (CHIKV) [167] (Table 4). Nevertheless, the aplysiatoxins are a family of very active dermatotoxins [50,168]. They are also tumor-promoting molecules due to their capacity to activate protein kinase C (PKC), an enzyme that plays roles in cell proliferation, differentiation, and apoptosis [167] (Table 4). Recently, Han et al., 2018 demonstrated that two aplysiatoxin analogues showed the capability to inhibit the potassium channels [169], opening interesting perspectives for the study and use of these molecules for drug development.

Table 4. Antiviral molecules extracted from the database

Molecule family	Chemical classes	Activity	Producing organisms	References
Aplysiatoxins	Alkaloid	-Antiviral -Dermatitis and swimmer itch agents -Cytotoxic	*Lyngbya majuscula;* *Schizothrix calcicola;* *Oscillatoria nigro-viridis;* *Trichodesmium erythaeum*	[50,167,169–172]
Cyanovirin-N	Protein	-Antiviral -No cytotoxicity -Stop fusion and transmission of HIV-1 virus	*Nostoc ellipsosporum*	[173–175]
Calcium spirulan	Polysaccharide	-Antiviral -No cytotoxicity -Low anticoagulant activity	*Arthrospira platensis*	[66,176,177]

Two other families of molecules have shown antiviral activity against a large panel of viruses. The first one, cyanovirin-N, has been isolated from *Nostoc ellipsosporum* [173] and *Cyanothece* sp. [175] (Table 4). These molecules are proteins belonging to the lectins class because of their ability to bind glycans. Cyanovirins show inhibitory activity against HIV-1, HIV-2, simian immunodeficiency virus (SIV), feline immunodeficiency virus, HHV-6, and measles virus [173,174]. Also, they inhibit Ebola and influenza viruses [175]. Nevertheless, cyanovirins are not active against some viruses, such as human herpesvirus A (HHV-1), cytomegalovirus, and adenovirus type 5 [174]. Cyanovirins are also non-cytotoxic for non-infected cells (at concentrations required for antiviral activity) [173,174] (Table 4). In fact, cyanovirin-N binds gp120, a glycoprotein component of the HIV envelope. As a result, the molecule inhibits membrane fusion into target cells and stops virus transmission. Calcium spirulan has been isolated from *Arthrospira platensis* (anc. *Spirulina platensis*). Calcium spirulan belongs to the chemical class of sulphated polysaccharides. It shows antiviral activity against a wide range of

viruses including HIV-1, HSV-1, the human cytomegalovirus (HCMV), measles virus, mumps virus, and influenza virus in addition to a low cytotoxicity against several cell lines (Table 4) [66,177]. Interestingly, calcium spirulan seems inactive against poliovirus and coxsackievirus, two non-enveloped viruses, meaning that it probably has selective activity for enveloped viruses. Hayashi et al. (1996) [66] also showed that this molecule inhibits virus penetration in targeted cells. Other sulphated polysaccharides are known for their anticoagulant and antiviral activity, such as heparin or dextran sulphate [178,179]. In comparison to these molecules, calcium spirulan showed a lower anticoagulant activity and a longer half-life in blood [176], confirming its promising potential for the development of new specific antiviral drugs.

5.1.5 Antiprotozoal activity (against malaria, leishmaniosis, Chagas disease)

The last kind of antimicrobial properties listed is related to the antiprotozoal activity. Protozoans are eukaryotic microorganisms. Some of them have parasitic lifestyles and are well-known for their involvement in human diseases such as malaria, leishmaniosis, Chagas disease, and trypanosomiasis. These diseases represent a huge problem in tropical countries where the parasite is transmitted by mosquitoes. The World Health Organization identified more than 210 million malaria cases in 2016 [180]. Therein, molecules with antiprotozoal activity are actively being sought in order to develop new drugs against these diseases.

Table 5. Antiprotozoal molecules extracted from the database

Molecule family	Chemical classes	Activity	Producing organisms	References
Companeramides	Depsipeptide	-Antiprotozoal -No significant cytotoxicity	*Leptolyngbya* sp. or « *Hyalidium* »	[28]
Hoshinolactam	Lactam	-Antiprotozoal -No cytotoxicity	*Oscillatoria* sp.	[181]
Dolastatins	Peptide	-Antiprotozoal -Lethal -Cytotoxic	*Lyngbya majuscula*; *Symploca hydnoides*; *Lyngbya* sp.; *Symploca* sp. VP642; *Lyngbya-Schizothrix* assemblage	[32,34,78,182–188]

From the review, 28 cyanobacterial metabolites showed antiprotozoal activities. Tests have been conducted against several strains of *Plasmodium falciparum* (causative agent of malaria), *Leishamania donovani* (leishmaniosis), *Trypanosoma cruzi* (Chagas disease), and *Trypanosoma brucei* (sleeping sickness). Among the 28 concerned families of molecules, 19 showed antiprotozoal activity against drug-resistant strains, particularly against chloroquine-resistant strains of *Plasmodium falciparum* (see Table 5). Nevertheless, most of them are less active than the antibiotics currently used. For example, companeramides are cyclic depsipeptides produced by a cyanobacterium previously identified as *Leptolyngbya* sp. (now *Hyalidium*) [28] (Table 5). Companeramides showed antimalarial activity against three strains of chloroquine-resistant *Plasmodium falciparum*. They also showed no significant cytotoxicity against the cell lines used in the test, which constitutes an interesting property for the development of specific but non-toxic antimalarial drugs. Unfortunately, the activity of companeramides against the parasite is 100-fold lower than that of chloroquine (a commonly used drug), reducing their potential utilization.

However, some molecules show promise as substitutes for antibiotic treatment because of their strong activity against the parasite. This is the case for hoshinolactam and dolastatins. Hoshinolactam is an aromatic molecule belonging to the lactam chemical class [181]. It was isolated from an environmental sample rich in *Oscillatoria* sp. and has shown antiprotozoal activity against *Trypanosoma brucei* (IC_{50} = 3.9 nM) with no cytotoxicity against MDR-5 (the host cell, IC_{50} > 25 µM) (Table 5). Interestingly, the IC_{50} of pentamidine (another commonly used drug) against *Trypanosoma* species is 4.7 nM. Thus, the activity of hoshinolactam is equivalent to that of the antibiotics, and

hoshinolactam represents a promising alternative to pentamidine for trypanosomiasis treatment [181].

Dolastatins are a well-studied family of peptides. The first members of this family were isolated in 1977 from the sea hare *Dolabella auricularia* [189]. In 1998, other molecules belonging to the dolastatins family were isolated from the cyanobacteria *Lyngbya majuscula* and *Symploca hydnoides*, leading to the hypothesis that dolastatins isolated from the mollusk have a cyanobacterial dietary origin [190]. Dolastin 10, one of the dolastatin-related molecules, is the most potent antiprotozoal metabolite discovered so far from cyanobacteria, exhibiting an IC_{50} of 0.1 nM (the IC_{50} of chloroquine is, on average, 5 nM for the chloroquine-sensitive strain of *P. falciparum*) [183]. Dolastatins are also strong cytotoxic molecules (Table 5). They are able to inhibit tubulin polymerization, which induces cellular cycle arrest and apoptosis [191]. Antiprotozoal and cytotoxic activities are both the result of this property. Therefore, there is no apparent specificity for this molecule to act directly against the parasite itself, the cellular host being probably the most potent target of dolastatins. For this reason, Fennel et al. (2003) [183] concluded that dolastatins do not constitute a promising antiprotozoal drug despite their strong activity.

5.2. Potential anticancer

Nowadays, tumors and cancers constitute the most important problems concerning non-transmittable diseases worldwide. According to the WHO, cancer was the cause of one in six deaths (9.6 million) in 2018 [192]. The annual cost of cancer in 2010 was estimated to be US$ 1.16 trillion [193]. That is why, numerous studies have been conducted to understand the physiology of the different cancers and to find new efficient anticancer drugs. For this purpose, researchers are looking for molecules, and notably, natural products, that are able to kill cells or inhibit cell proliferation.

5.2.1 Cytotoxic activity

The first type of activity test was performed to determine the potential of molecules as anticancer agents due to cytotoxic activity. Tests have been made against different cell lines derived from tumor cells, like the HeLa cell line (derived from cervical cancer), KB (HeLa derivative), LoVo (human colon tumor), H-460 (human lung cancer) and MCF-7 (human breast cancer). Most of the time, the investigated molecules were tested against two or more cell lines to detect a potent specificity and to evaluate their potential for drug development. According to this review, 110 families of metabolites isolated from cyanobacteria showed cytotoxicity, representing 43% of the molecule families listed in the database.

The best example of potent anticancer molecules derived from cyanobacteria is the dolastatins family [190]. One synthetic analogue of dolastatin 10, monomethyl auristatin E, is actually used to treat Hodgkin lymphoma in the drug Brentuximab vedotin [190]. Luesch et al. (2001) [186] showed that dolastatin 10 and symplostatin 1 are 100-fold more efficient than vinblastine (anticancer drug extracted originally from the Madagascar periwinkle) against the same cell line due to their ability to depolymerize microtubules. Unfortunately, dolastatins also have strong cytotoxicity [186,194]. Researchers found a way to reduce this toxicity by coupling monomethyl auristatin E with a chimeric antibody against CD30 (tumor necrosis factor receptor, highly expressed in Hodgkin lymphoma) in order to target only tumor cells [195]. Since then, other antibody drugs linked (ADC) with monomethyl auristatin E have been developed. For example, glembatumumab vedotin is currently under clinical trial. This drug targets GPNMB (glyprotein non-metastatic melanoma protein B), a glycoprotein expressed in melanoma and breast tumors, [196]. In addition to the dolastatins, other cyanobacterial metabolites destabilize the microtubule network. Notably, one such metabolite is tubercidin, a nucleoside produced by *Tolypothrix byssoidea*, *Tolypothrix distorta*, *Plectonema radiosum,* and *Scytonema saleyeriense* var. *indica* [197,198]. This molecule was previously isolated from the bacterium *Streptomyces tubercidicus*. Tubercidin has shown inhibition of cell proliferation with an IC_{50} of 248 nM (Table 6). Interestingly, tubercidin acts against dolastatins showing a microtubule stabilizing activity comparable to taxol bioactivity [199]. Its cytotoxicity is due to its stabilizing property, causing mitotic arrest at G2/M transition and stopping growth [200].

Table 6. Cytotoxic metabolites extracted from the database

Molecule family	Chemical classes	Activity	Producing organisms	References
Tubercidin	Nucleoside	-Cytotoxic -Microtubule stabilizer	*Tolypothrix byssoidea* H-6-2; *Scytonema saleyeriense* var. *indica* CV-14-1; *Plectonema radiosum* DF-6-1; *Tolypothrix distorta* BL-11-2	[197–199]
Aurilides	Depsipeptide	- Cytotoxic -Lethal activity -Anti-swarming -Antiprotozoal -Induce loss of microfilament network	*Lyngbya majuscula*; *Okeania* sp.; *Lyngbya* sp.	[69,201–204]
Swinholide-type	Macrolide	-Cytotoxic -Actin microfilament disruption	*Symploca* sp.; *Geitlerinema* sp.; *Nostoc* sp. UHCC0451; *Phormidium* sp.	[205–207]
Anabaenolysins	Lipopeptide	-Cytotoxic -Antifungal -Hemolytic activity -Ability to permeabilize cell membranes	*Anabaena* sp. XPORK 15F; *Anabaena* sp. XSPORK 27C	[208,209]

Another mechanism of cytotoxicity noted from cyanobacterial metabolites is the destabilization of actin microfilaments. As tubulin microtubules, actin microfilaments are key cytoskeleton components of cells. Microfilaments are involved in several mechanisms: cell division (cytokinesis), cell motility, cell adhesion, exocytosis, and endocytosis [210]. Thus, molecules with actin-modulating activity are sought in order to develop anticancer drugs because of their ability to induce apoptosis [210]. Four cyanobacterial metabolite families have shown disrupting activity of the actin microfilament network: the lyngbyabellins, the majusculamides, the aurilides, and the swinholide-type molecules (Table 6).

Lyngbyabellins and majusculamides, as mentioned above, have shown antifungal activity that probably corresponds to their ability to modulate actin polymerization [149–151,164]. Aurilides are cyclic depsipeptides, and the first member of this family was isolated from the sea hare *Dolabella auricularia* [211]. Since then, seven other related molecules have been isolated from two cyanobacterial genera: *Lyngbya* and *Okeania* [69,201–204], and one from *Philinopsis speciosa* (cephalaspidean mollusk) [212]. Aurilides showed nanomolar cytotoxic activity associated with a moderate toxicity to *Artemia salina*. Two analogues, lagunamides A and B, have also shown antimalarial activity and antiswarming activity against *Pseudomonas aeruginosa* [202] (Table 6). Han et al. (2006) [201] showed that aurilides induce microfilament disruption at the micromolar level; they concluded that this disrupting activity is probably related to their toxic and antimicrobial activities.

Swinholide-type molecules were macrolides, originally isolated from sponge *Theonella swinhoei* [213]. In 2005, Andrianasolo et al. (2005) [205] succeeded in isolating swinholide A and two new related molecules (ankaraholides A and B) from two cyanobacteria (*Symploca* sp. and *Geitlerinema* sp., respectively) leading to the hypothesis of a symbiotic origin of the compounds isolated from sponge [205] (Table 6). More recently, Humisto et al. (2018) identified the swinholide biosynthetic cluster in *Nostoc* sp. (Table 6) [206], and Tao et al. (2018) isolated nine swinholide-related metabolites from a marine *Phormidium* sp. [207]. Swinholide A, isolated from the marine sponge, showed microfilament-disrupting activity by stabilizing actin dimers [214]. In addition to their cytotoxic activity,

cyanobacterial swinholides showed also the same actin disrupting activity, which is of interest for the development of related anticancer drugs [205].

Other metabolites with noticeable cytotoxicity are anabaenolysins, which are lipopeptides isolated from two strains of the *Anabaena* genus [209] (Table 6). Anabaenolysins showed cytotoxicity against all of the ten cell lines tested, with LC_{50} between 4 and 20 μM depending on the cell lines and the anabaenolysin variants [209]. In addition, using a trypan dye exclusion assay, these authors showed that anabaenolysins have an interesting profile. Instead of excluding the dye, cells showed an influx of trypan dye meaning that anabaenolysins permeabilize cell membranes until necrotic death [209]. Anabaenolysins are able to solubilize the lipid component of the cell membrane, probably acting with same mechanisms as the detergent digitonin. Anabaenolysins particularly target cholesterol-containing membranes and do not induce permeabilization of mitochondria membranes. As detergents, anabaenolysins also show hemolytic activity but at lower concentrations than digitonin and surfactin [208]. In addition, Oftedal et al. (2012) showed that the permeabilization ability of anabaenolysins also allows the internalization of nodularin [208]. This property is of interest for the development of a drug administration strategy involving anabaenolysins as a synergistic compound and other bioactive molecules that cannot be passed through the membrane within the targeted cells alone.

Six cyanobacterial families of compounds showed the ability to reverse multidrug resistance (MDR) in addition to their cytotoxicity properties. These include the cryptophycins [215], the hapalindole-like metabolites [104], hapalosin [216], the patellamides [217,218], the tolyporphins [219,220], and the westiellamide-like [123] molecules. Among them, five families carried out reverse MDR by acting on the P-glycoprotein pumps (except for cryptophycins and patellamides for which the reverse MDR mechanisms have still not been described). P-glycoprotein is a glycosylated transmembrane protein that transports drugs and toxins out of the cell. This protein is often overexpressed in cancer cells and leads to resistance against standard chemotherapeutics, because of its lower accumulation in targeted cells [221]. Thus, metabolites with the ability to inhibit this efflux pump are of interest for the development of anticancer drug or to supplement current chemotherapeutic strategies in order to increase their efficiency on resistant cancer cells.

5.2.2 Protease inhibitory activity

Proteases are a widespread family of enzymes found in most, if not all, organisms. They are involved in a large number of pathways including coagulation, inflammation, digestion, haemostasis, and blood pressure regulation [222,223]. There are several types of proteases that are classified by their specific hydrolysis mechanisms. The major groups are the metalloproteinases, the serine proteases, the cysteine proteases, the threonine proteases, and the aspartic acid proteases [223]. Because of their ubiquity, these enzymes are attractive targets for the development of new drugs against diverse diseases [222]. Some proteases have also shown the potential to act against thrombotic diseases [222], hypertension [223], pulmonary diseases [224], asthma [225], pathogenic microorganisms [226,227], and even cancers [223,228]. According to our investigation, 24 family of metabolites presenting diverse protease inhibitor activities have been isolated from cyanobacteria so far. These compounds have shown inhibitory activity against a wide range of proteases, including enzymes belonging to the cathepsin family or the well-known serine proteases trypsin, chymotrypsin, and thrombin. Only three metabolite families have shown inhibitory activity against cathepsins. Cathepsins are frequently overexpressed in cancer cells and are involved in tumorigenesis, cell invasion, and metastasis [229–234]. One of them, the spumigins, isolated from *Nodularia spumigena* and *Anabaena compacta* [235–237], is a set of linear peptides that are structurally similar to the aeruginosins family (Table 7). They showed protease inhibitory activity against several proteases including trypsin, thrombin, plasmin, and cathepsin B to a better extent [236]. All of these proteases are potentially involved in cancer cell processes, and notably, cathepsin B, has been proposed to be a promising target for anticancer drug development [230,238].

Table 7. Serine protease inhibitor metabolites extracted from the database

Molecule family	Chemical classes	Activity	Producing organisms	References
Spumigins	Peptide	-Proteases inhibitory activity	*Nodularia spumigena* AV1 & CCY 9414; *Anabaena compacta* NIES-835	[235–237]
Cyanopeptolin-like	Depsipeptide	-Protease inhibitory activity -Other enzyme inhibition -Cytotoxic -Lethal -Antibacterial -Antifungal -Antiprotozoal	*Microcystis* sp.; *Microcystis aeruginosa;* *Aphanocapsa* sp.; *Microchaete loktahensis*; *Planktothrix agardhii*; *Scytonema hofmanni*; *Lyngbya* sp.; *Lyngbya confervoides*; *Lyngbya* spp.; *Lyngbya semiplena*; *Microcystis viridis*; *Dichothrix utahensis*; *Nostoc* sp.; *Nostoc minutum*; *Planktothrix rubescens;* *Lyngbya majuscula-Schizothrix* sp. (Assemblage); *Stigonema* sp.; *Symploca* sp.; *Symploca hydnoides*; *Nostoc insulare*	[32,33,158,184,185,187,239–288]
Carmaphycins	Peptide	-Protease inhibition -Cytotoxic -Antiprotozoal	*Symploca* sp. WHG NAC15/Dec/08–5	[289,290]

Another example of interesting metabolites is the cyanopeptolin-like family. This family is the second in terms of the number of structural analogues isolated, after the microcystins (respectively 140 and 246 molecular variants described so far). Currently, more than 50 papers have reported on the isolation and activities of these metabolites. They are cyclic depsipeptides isolated from 12 different cyanobacterial genera (Table 7). Among the large number of analogs, a wide range of activity has been reported for these cyanobacterial metabolites including protease activity and other types of enzyme inhibition, cytotoxicity, lethal activity, and antimicrobial activity, opening various possibilities for the development of therapies targeting cancer cells or microorganisms or those that fight some disease like emphysema [269], pancreatitis [291] or thrombosis [292]. Nevertheless, this large number of activities can also represent a problem, namely, how to develop therapeutic drug exhibiting a specific activity. It would be interesting to study some analogs more in-depth or to conduct a structure–activity relationship study in order to increase the specificity of synthetic variants.

Finally, another class of inhibitors that would be of interests for the development of new therapeutics against tumors is the proteasome inhibitors. Proteasome or ubiquitin-proteasome is a multi-enzymatic complex of eukaryotes. It is involved in protein degradation in a different way than the lysosomes [292]. Because proteasome catalysis is involved in a wide variety of essential pathways, including cell-cycle progression and the regulation of the apoptosis, it is a potent target for cancer therapy. Moreover, malignant cells have been shown to be more affected by proteasome inhibitors than normal cells, reducing the potential deleterious side effects of these molecules [228]. Four cyanobacterial families of metabolites were described to inhibit the 20S core of proteasome: the carmaphycins, the cylindrocyclophanes, the nostocyclopeptides, and nostodione. Among them, the

most efficient 20S proteasome inhibitors are the carmaphycins, which exhibit a IC_{50} of around 2.5 nM [289], whereas the other compounds present a micromolar range of action [168,293,294] (Table 7). Only two carmaphycin variants (A and B) have been isolated from *Symploca* sp., so far. These molecules are linear peptides with cytotoxic and antiprotozoal activities. They show the additional ability to inhibit the 20S proteasome activity in yeast and *Plasmodium* through interaction with the β5 subunit [289,290]. These bioactivities are interesting for the use of carmaphycins as anticancer or antimalarial therapeutics. Two studies were conducted to enhance the specificity of carmaphycins for either applications. To develop a specific antimalarial drug, LaMonte et al. (2017) synthesized synthetic analogues of carmaphycin B and identified one analog with a selectivity index of 380 for antiprotozoal activity against cytotoxic activity [290]. On the other hand, Almaliti et al. (2018) studied the potential of carmaphycins as anticancer drugs and as an antibody–drug conjugate (ADC) in order to enhance the selectivity of the molecules for cancer cells and to reduce the potential side effects [295].

Then, cyanobacterial metabolites with protease inhibition activities were shown to be not enough specific for further use, but the synthesis of synthetic analogs increased the selectivity of some of these molecules.

5.2.3 Histone deacetylase inhibitors

Histone deacetylases (HDACs) are enzymes involved in remodeling the chromatin and the acetylation/deacetylation of histone and non-histone proteins. Furthermore, histone deacetylases play a key role in histone–DNA interactions and in the binding to transcription factors. HDACs have also been identified as potent regulators of gene expression [296,297]. Because cancer generally emerges from genetic mutations inducing hyperactivation of oncogenes or loss of tumor-suppressor genes, targeting mechanisms that are involved in the epigenetic regulation of genes is a promising strategy for the development of antitumor drugs [297].

Table 8. HDACs inhibitor metabolites extracted from the database

Molecule family	Chemical classes	Activity	Producing organisms	References
Largazole	Depsipeptide	-Histone deacetylases inhibitor -Cytotoxic -Other enzyme inhibition -Pro-drug	*Symploca* sp.	[298–303]
Santacruzamate A	Carboxylic acid derived	-Histone deacetylases inhibitor - Cytotoxic	*Symploca* sp. PAC-19-FEB-10-1	[304]

Two molecules showing histone deacetylase inhibitory activity have been isolated from cyanobacteria so far, largazole and santacruzamate A, both from *Symploca* sp. strains (Table 8). Largazole has shown inhibition activity against 12 class I HDACs in addition to inhibition of the ubiquitin-activating enzyme (E1). It has also shown cytotoxic activity against several cell lines (Table 8). Largazole acts as a pro-drug—the molecule needed to be activated by hydrolysis to release its active form, the largazole thiol [296]. Santacruzamate A has also shown histone deacetylase inhibition and cytotoxic activity. It shares some structural features with suberoylanilide hydroxamic acid (SAHA), a clinically approved HDAC inhibitor that is used to treat refractory cutaneous T-cell lymphoma [304]. Salvador-Reyes and Luesch (2015) performed an in-depth review of the activities and mechanisms of action of these two metabolites [296]. They highlighted the high potency of largazole in anticancer drug development, while the potency of santacruzamate seems to remain more limited.

5.3. Anti-inflammatory and antioxidant activity

5.3.1 Anti-inflammatory activity

According to our review, seven metabolite families isolated from cyanobacteria were found to have anti-inflammatory activity (aeruginosins, coibacins, honaucins, malyngamides, phycocyanin, scytonemin, and tolypodiol). Nowadays, anti-inflammatory molecules have been widely studied in order to develop new therapeutics directed against chronic inflammatory diseases, such as rheumatoid arthritis, psoriasis, chronic obstructive pulmonary disease, multiple sclerosis, and inflammatory bowel disease [305]. Anti-inflammatory compounds can also be useful against cardiovascular diseases, notably arthrosclerosis [306], and neurodegenerative diseases such as Parkinson's disease [307].

Table 9. Anti-inflammatory metabolites extracted from the database

Molecule family	Chemical classes	Activity	Producing organisms	References
Aeruginosins	Peptide	-Anti-inflammatory activity -Protease inhibitor -No cytotoxicity	*Microcystis aeruginosa* NIES-98, NIES-298, NIES-101, NIES-89; *Microcystis viridis* NIES-102_ *Planktothrix agardhii* CYA 126/8; *Nodularia spumigena* CCY9414; *Nostoc* sp. Lukesova 30/93	[61,310,311,315]
Phycocyanin	Peptide	-Anti-inflammatory -Antioxidant -Specific inhibitor of COX-2 -No lethality	All	[58,63,316–318]
Scytonemin	Alkaloid	-Anti-inflammatory -Enzyme inhibition -No cytotoxicity	*Stigonema* sp.; *Nostoc punctiforme*; *Anabaena variabilis*; *Anabaena ambigua*; *Aphanocapsa*/*Synechocystis* sp. (assembly); *Aulosira fertilissima*; *Calothrix* sp.; *Calothrix parietina*; *Calothrix crustacea*; *Chlorogloeopsis* sp.; *Chroococcidiopsis* sp.; *Chroococcus* sp.; *Cylindrospermum* sp.; *Diplocolon* sp.; *Entophysalis granulos*; *Gloeocapsa* sp.; *Hapalosiphon* sp.; *Hapalosiphon fontinalis*; *Lyngbya* sp.; *Lyngbya aestuarii*; *Nostoc parmelioides*; *Nostoc commune*; *Nostoc microscopium*; *Nostoc pruniforme*; *Phormidium* sp.; *Pleurocapsa* sp.; *Rivularia* atra; *Rivularia* sp.; *Schizothrix* sp.; *Scytonema* sp.; *Tolyothrix* sp.; *Tolypothrix tenni*; *Westiellopsis prolifica*; *Scytonema hoffmani*	[64,309,319–322]

Anti-inflammatory tests have been performed in vitro or in vivo in mice. For example, malyngamides have been shown to inhibit superoxide production generated by inflammation-promoting agents [308], and honaucins inhibit pro-inflammatory cytokine expression [60] in the murine macrophage cell line RAW264.7. The mouse ear edema assay has been performed in vivo by observing the resorption of ear edema in the presence of anti-inflammatory compounds, such as phycocyanin [63], scytonemin [309] and tolypodiol [65], which have shown noteworthy activities using this assay.

Three metabolites seem to be particularly interesting according to their specific bioactivity profiles: the aeruginosins, phycocyanin, and scytonemin, which additionally, have not shown any toxicity when tested in vitro or in vivo. Aeruginosins have shown anti-inflammatory properties using the AlphaLISA assay; they are able to down-regulate the level of pro-inflammatory mediators (IL-8 and ICAM-1) in stimulated endothelial cells [61] without affecting the viability of two different cell lines [61] (Table 9). Aeruginosins have also shown serine protease inhibitory activity against trypsin, thrombin, and plasmin [310], and their corresponding biosynthetic gene cluster was first identified in Planktothrix agardhii and Nodularia spumigena (Table 9) [237,311]. Nowadays, the obtained data do not seem to support the correlation between serine protease inhibition and the anti-inflammatory activity of aeruginosins. However, on neutrophils, it has been shown that some serine proteases (elastase, cathepsin G, and proteinase 3) are responsible for the conversion and activation of proinflammatory chemokines (and notably, interleukine-8 (IL-8)) and are able to conserve or enhance the inflammation response [312–314]. In this regard, it will be interesting to further test whether aeruginosins are capable of inhibiting other serine proteases, notably elastase, cathepsin G, and proteinase 3, in order to determine whether the down-regulation of IL-8 induced by the aeruginosins is mediated through serine protease inhibition processes.

Phycocyanin is a phycobiliprotein, constituting one of the major cyanobacterial pigments, together with the chlorophylls and phycoerythrin. It is involved in light-harvesting and the energy transfer of phycobilisomes within the outer membrane of thylakoids. In addition, phycocyanin has shown a wide variety of beneficial properties including antioxidant, anti-inflammatory, neuroprotective, and hepatoprotective activities [63] (Table 9). Authors of phycocyanin studies have reviewed the main features of phycocyanin anti-inflammatory mechanisms. Phycocyanin is able to scavenge ROS, has anti-lipoperoxydative effects, and inhibits cyclooxygenases (specifically COX-2) as well as TNF-α release. All of these properties are interesting from the perspective of new therapeutics development targeting neurodegenerative diseases such as Alzheimer's, Parkinson's or Huntington's disorders, or as an anti-inflammatory agent [63].

Scytonemin is an alkaloid pigment found in the sheath of some cyanobacteria and particularly on some organisms living in extreme environments [64]. Scytonemin synthesis is mainly induced by UV-A exposure in order to reduce heating and the oxidative stress [64]. Scytonemin is mainly involved in photoprotection by UV-absorption [64]. It has also been shown to have anti-inflammatory activity with no cytotoxicity against non-proliferating cells [64,309,322]. In addition, scytonemin has been shown to inhibit polo-like kinase 1 (PLK1), an enzyme involved in the phosphorylation and activation of proteins, notably, of cdc25C, which is involved in cell cycle progression and the G2/M transition in the cell cycle (Table 9). As a consequence, scytonemin can repressed cell proliferation [64,309,322]. Therefore, scytonemin could be a promising compound for use in the development of anticancer therapeutics, sunscreen agents, or anti-inflammatory drugs.

Last but not least, as mentioned above, ambigol have been shown to inhibit cyclooxygenases. Cyclooxygenases are enzymes belonging to the oxydoreductase enzymatic class; two related isoforms, COX-1 and COX-2 [323], have been discovered so far and are involved in inflammation processes through the synthesis of prostaglandins from arachidonic acid. Some classical anti-inflammatory molecules are known to target COX. For example, aspirin, the most famous COX inhibitor discovered so far, is a nonsteroidal anti-inflammatory drug (NSAID) [324]. For these reasons, ambigol is a promising cyanobacterial anti-inflammatory compound. Nevertheless, further studies are still needed in order to describe its activities and potential unexpected side effects in-depth [325].

5.3.1 Antioxidant activity

Oxidative stress is widely recognized to be implicated in neurodegenerative diseases [326,327], metabolic disorders [328], hypertension [329], liver diseases [330], and cardiovascular diseases [331]. Thus, antioxidant molecules are required to develop or supplement therapy for reducing the harmful effects of oxidative stress.

According to our review, only four compounds isolated from cyanobacteria show antioxidant properties. As mentioned above, this weak number in comparison to cytotoxic or antimicrobial compounds might be due to the fact this activity has been poorly tested in secondary metabolites and its testing has generally been limited to pigments or molecules implicated in light-harvesting or UV protection. Indeed, antioxidant activity has been characterized for the carotenoids, chlorophyll, the mycosporine-like amino acids (MAAs), and the phycobiliproteins such as phycocyanin (Table 10).

Table 10. Antioxidant metabolites extracted from the database

Molecule family	Chemical classes	Activity	Producing organisms	References
Carotenoids	Terpenoid	-Antioxidant -Sunscreens	All	[55,332,333]
Chlorophylls	Chlorin	-Photosynthesis -Antioxidant -Pro-oxidant (sensitizer for singlet oxygen production)	All	[56,332]
MAAs	Cyclohexenone linked with an amino acid	-Antioxidant -Sunscreens	*Synechocystis* sp. PCC 6803; *Gloeocapsa* sp. CU-2556; *Aphanothece halophytica*; *Gloeocapsa* sp.; *Euhalothece* sp.; *Microcystis aeruginosa*; *Arthrospira* sp. CU2556; *Lyngbya* sp. CU2555; *Leptolyngbya* sp.; *Phormidium* sp.; *Lyngbya* cf. *aestuarii*; *Microcoleus chthonoplastes*; *Microcoleus* sp.; *Oscillatoria spongelidae*; *Trichodesmium* spp.; *Anabaena* sp.; *Anabaena doliolum*; *Anabaena variabilis* PCC 7937; *Nostoc* sp.; *Nostoc commune* var. Vaucher; *Nostoc commune*; *Scytonema* sp.; *Nostoc punctiforme* ATCC 29133; *Nostoc* sp. HKAR-2 and HKAR-6; *Nodularia baltica*; *Nodularia harveyana*; *Nodularia spumigena*; *Aphanizomenon flos-aquae*; *Chlorogloeopsis* PCC 6912	[57,332,334,335]
Phycocyanin	Peptide	- Anti-inflammatory - Antioxidant - Specific inhibitor of COX-2 - No lethality	All	[58,63,316–318]

Carotenoids are orange pigments that are localized in the thylakoid membrane. They absorb light between 400 and 500 nm and are involved in photosynthesis by transferring energy to chlorophyll through a single-singlet energy transfer mechanism [333,336]. Five carotenoids are found in the majority of cyanobacteria: β-carotene, zeaxanthin, nostoxanthin, echinenone, and canthaxanthin [332]. In addition to their role in light harvesting, carotenoids act as potent photoprotectant molecules and show antioxidant activity through ROS scavenging [332,336] (Table 10).

Chlorophylls are the ubiquitous pigments of photosynthetic organisms. Chlorophyll *a* is the major isoform used by cyanobacteria with most absorbing light at 660 nm [332]. Chlorophylls are mainly involved in photosynthesis, but they have also shown antioxidant activity *in vitro* via radical

scavenging and, on the contrary, singlet oxygen production under high light conditions, mitigating their potential use as antioxidant therapeutics [332] (Table 10).

Mycosporine-like amino acids (MAAs) are pigments that are widely produced by cyanobacteria (Table 10) and other algae [57,332]. They absorb light in the UV-A and UV-B ranges with a maximum absorbance between 310 and 360 nm [57]. The primary function of MAAs is to protect cells from damage by absorbing UV and to dissipate energy without generating ROS [332,335]. In addition, MAAs show other interesting properties. They have been demonstrated to have antioxidant activity through ROS scavenging, are able to protect skin from UV damage, and are involved in osmotic regulation, desiccation, and defense against oxidative and thermal stresses. They are also able to protect fibroblasts against UV-induced cell death [57,335]. Jain et al. (2017) stated that two products containing MAAs have been commercialized as sunscreen agents for cosmetics and for use in plastics, paints, and varnishes as a photostabilizer [57].

Finally, as mentioned above, phycocyanins are antioxidant molecules with the ability to scavenge ROS. In addition to their anti-inflammatory activity, this antioxidant property increases the potential of phycocyanins to be used for pharmaceutical applications [317].

5.4. Other metabolites with potential beneficial properties

To close this review on the beneficial activities demonstrated for cyanobacterial metabolites, we highlight a few other compounds that are of potential interest for various fields of application.

For instance, grassystatins-tasiamides constitutes a depsipeptide group of related compounds isolated from *Lyngbya* and *Symploca* tropical species [337–343]. These metabolites have shown protease inhibitory activity against cathepsin D, cathepsin E, and the β-amyloid precursor protein-cleaving enzyme A (BACE1) for tasiamides B and F [337,338] (Table 11). In addition, these compounds have shown moderate or no cytotoxicity at concentrations higher than that of protease inhibitory activity [340,341,343]. Cathepsin D is an aspartic protease that is localized in the lysosome. This enzyme is considered a biomarker of some forms of metastatic breast cancer because of its related overexpression [232]. Cathepsin D has also been shown to promote proliferation and metastasis [232]. Cathepsin E, being also an aspartic protease, is mainly localized in immune system cells and notably in antigen-presenting cells [344]. Grassystatin A induces the reduction of antigen presentation in dendritic cells [339], which is correlated with the involvement of cathepsin E in this process and has led to the hypothesis that grassystatin could modulate the immune response. Alzheimer's disease pathogenesis is mediated by the accumulation of amyloid β peptide (Aβ) in the brain. BACE1 is responsible for Aβ formation by cleaving the amyloid precursor protein (APP). As a result, BACE1 inhibitors could be promising targets for the development of new therapeutics against Alzheimer's disease [338,345]. Considering these activities, we assume that members of the grassystatins-tasiamides family constitute promising components for the development of antiproliferative agents, immune response modulatory compounds, and therapeutics for Alzheimer's disease treatment.

During the process of database construction, we noticed that five metabolite families showed a remarkable ability to bind to cannabinoid receptors (CB1 and CB2). These metabolites were grenadamide [346], the semiplenamides [347], serinolamide A [348], mooreamide A [349], and the columbamides [350]. CB1 and CB2 are cell membrane receptors that belong to the endocannabinoid system (ECS), an important part of the human physiological system. It is involved in a wide range of different processes, such as brain plasticity, memory, nociception, appetite regulation, the sleep–wake cycle, the regulation of emotions and stress, addiction, etc. This ubiquity for the regulation of various vital processes makes exogenous CB1 and CB2 ligands attractive as modulators of this system for the management of the pain, diabetes, obesity, cancer, epilepsy, or Alzheimer's disease, or to develop new anxiolytics [351,352]. Columbamides are the most potent CB1/CB2 ligands from cyanobacteria discovered so far (table 11) [350]. They are linear acyl amides that have been isolated from *Moorea bouillonii* PNG05-198 using a genome mining approach [350]. To date, only the CB1- and CB2-binding activity of columbamides has been tested, and other investigations are required in order

to look deeper into the activity profiles of these molecules, as they still remain promising compounds for therapeutic developments.

Table 11. Other interesting metabolites extracted from our database

Molecule family	Chemical classes	Activity	Producing organisms	References
Grassystatins-Tasiamides	Depsipeptide	-Protease inhibitory activity -Cytotoxic -Reduce antigen presentation in dendritic cells	*Lyngbya confervoides*, *Symploca* sp., *Symploca* sp. NHI304, *Lyngbya* sp. NIH399	[337–343]
Columbamides	Acyl amide	-CB1 and CB2 ligands	*Moorea bouillonii* PNG05-198	[350]

6. Conclusion

In this review, all available information concerning the beneficial activities of natural products of cyanobacteria was gathered. To write this review, a molecular database of the various families of metabolites isolated from cyanobacteria was constructed from the systematic analysis of 670 articles. The derived database represents 260 families of metabolites. It groups various types of information concerning the taxonomy of producing strains, the respective chemical classes, the origin strain habitats, and the tested/demonstrated activities for each member of the family, together with the related full references.

According to this review, from the above 300 different genera of cyanobacteria (referenced by the taxonomy published by Komarek et al. in 2014) [26], 90 have so far been reported to produce bioactive metabolites. Some of them have been shown to produce a high number of compounds, such as those from the genus *Lyngbya-Moorea*, which includes 85 families of metabolites isolated so far. However, the *Lyngbya* genus is a polyphyletic group and its taxonomy position is under revision; this number might be re-evaluated and distributed within distinctive new genera. The genomes of the producing strains are not available in the majority of cases, whereas Shih et al. (2013) demonstrated the large genomic potential of numerous cyanobacteria thanks to the biosynthetic pathways of metabolites highlighted by genome mining analyses [48]. Therefore, the potential for the discovery of new natural molecules and new biosynthetic pathways from cyanobacteria still remains very important and needs to be systematically explored.

Cyanobacterial metabolites belong to 10 chemical classes (including peptides, alkaloids, terpenes, and lipids), most of the families of metabolites being peptide derivatives (above 50% of the families). Fourteen different types of activities can be distinguished for cyanobacterial metabolites (e.g., antimicrobial, lethality, cytotoxicity, antioxidant). The large majority of the components are cytotoxic (110 families), whereas some activities have only been tested rarely, and their occurrence appears to be weakly demonstrated. Globally, no clear correlation has been observed between chemical classes and the specificity of the respective types of bioactivity, and further studies are needed in order to precisely understand the mechanisms of action of cyanobacterial metabolites, potentially linking bioactivity with structural features in order to support the new hypothesis on the biological function of the production of these components for organisms.

Finally, 50 metabolites isolated from cyanobacteria, presenting remarkable interest for diverse fields of application, were investigated further in the present literature review. For example, hassallidins, which show specific antifungal activity without antibacterial activity, and scytonemin, which has anti-inflammatory properties with no cytotoxicity, were detailed. These metabolites are potentially useful for the development of new concrete applications for cyanobacterial natural products and illustrate the interest in cyanobacteria as a prolific source of bioactive molecules.

Supplementary Materials: The following are available online at www.mdpi.com/xxx/s1, Table S1: Activities of metabolites described.

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References

1. Whitton, B.A.; Potts, M. *Ecology of Cyanobacteria II: Their Diversity in Space and Time*. Kluwer Academic Publishers: Dordrecht 2012, pp. 1–13.

2. Kurmayer, R.; Deng, L.; Entfellner, E. Role of toxic and bioactive secondary metabolites in colonization and bloom formation by filamentous cyanobacteria Planktothrix. *Harmful Algae* 2016, *54*, 69–86.

3. Mazard, S.; Penesyan, A.; Ostrowski, M.; Paulsen, I.T.; Egan, S. Tiny Microbes with a Big Impact: The Role of Cyanobacteria and Their Metabolites in Shaping Our Future. *Mar. Drugs* 2016, *14*.

4. Buratti, F.M.; Manganelli, M.; Vichi, S.; Stefanelli, M.; Scardala, S.; Testai, E.; Funari, E. Cyanotoxins: producing organisms, occurrence, toxicity, mechanism of action and human health toxicological risk evaluation. *Arch. Toxicol.* **2017**, *91*, 1049–1130.

5. Humbert, J.-F.; Törökné, A. New Tools for the Monitoring of Cyanobacteria in Freshwater Ecosystems. In *Handbook of Cyanobacterial Monitoring and Cyanotoxin Analysis*; John Wiley & Sons, Ltd: Chichester, UK, 2017; pp. 84–88.

6. Salmaso, N.; Bernard, C.; Humbert, J.-F.; Akçaalan, R.; Albay, M.; Ballot, A.; Catherine, A.; Fastner, J.; Häggqvist, K.; Horecká, M.; et al. Basic Guide to Detection and Monitoring of Potentially Toxic Cyanobacteria. In *Handbook of Cyanobacterial Monitoring and Cyanotoxin Analysis*; John Wiley & Sons, Ltd: Chichester, UK, 2017; pp. 46–69 ISBN 0-7803-8560-8.

7. Paerl, H.W.; Otten, T.G. Harmful Cyanobacterial Blooms: Causes, Consequences, and Controls. *Microb. Ecol.* **2013**, *65*, 995–1010.

8. Zanchett, G.; Oliveira-Filho, E.C. Cyanobacteria and cyanotoxins: From impacts on aquatic ecosystems and human health to anticarcinogenic effects. *Toxins (Basel).* 2013, *5*, 1896–1917.

9. Tidgewell, K.; Clark, B.R.; Gerwick, W.H. The natural products chemistry of cyanobacteria. In *Comprehensive Natural Products II Chemistry and Biology*; 2010; Vol. 2, pp. 141–188.

10. Ali Shah, S.A.; Akhter, N.; Auckloo, B.N.; Khan, I.; Lu, Y.; Wang, K.; Wu, B.; Guo, Y.W. Structural diversity, biological properties and applications of natural products from

885 cyanobacteria. A review. *Mar. Drugs* 2017, *15*, 354.

886 11. Mi, Y.; Zhang, J.; He, S.; Yan, X. New peptides isolated from marine cyanobacteria, an
887 overview over the past decade. *Mar. Drugs* **2017**, *15*.

888 12. Wang, M.; Zhang, J.; He, S.; Yan, X. A review study on macrolides isolated from cyanobacteria.
889 *Mar. Drugs* 2017, *15*.

890 13. Chlipala, G.E.; Mo, S.; Orjala, J. Chemodiversity in freshwater and terrestrial cyanobacteria -
891 a source for drug discovery. *Curr. Drug Targets* **2011**, *12*, 1654–73.

892 14. Sivonen, K.; Leikoski, N.; Fewer, D.P.; Jokela, J. Cyanobactins-ribosomal cyclic peptides
893 produced by cyanobacteria. *Appl. Microbiol. Biotechnol.* 2010, *86*, 1213–1225.

894 15. Dittmann, E.; Gugger, M.; Sivonen, K.; Fewer, D.P. Natural Product Biosynthetic Diversity
895 and Comparative Genomics of the Cyanobacteria. *Trends Microbiol.* **2015**, *23*, 642–652.

896 16. Pattanaik, B.; Lindberg, P. Terpenoids and Their Biosynthesis in Cyanobacteria. *Life* **2015**, *5*,
897 269–293.

898 17. Singh, R.; Parihar, P.; Singh, M.; Bajguz, A.; Kumar, J.; Singh, S.; Singh, V.P.; Prasad, S.M.
899 Uncovering potential applications of cyanobacteria and algal metabolites in biology,
900 agriculture and medicine: Current status and future prospects. *Front. Microbiol.* 2017, *8*, 515.

901 18. Singh, J.S.; Kumar, A.; Rai, A.N.; Singh, D.P. Cyanobacteria: A precious bio-resource in
902 agriculture, ecosystem, and environmental sustainability. *Front. Microbiol.* **2016**, *7*, 1–19.

903 19. Gerwick, W.H.; Fenner, A.M. Drug Discovery from Marine Microbes. *Microb Ecol* **2013**, 800–
904 806.

905 20. Shishido, T.K.; Humisto, A.; Jokela, J.; Liu, L.; Wahlsten, M.; Tamrakar, A.; Fewer, D.P.; Permi,
906 P.; Andreote, A.P.D.; Fiore, M.F.; et al. Antifungal compounds from cyanobacteria. *Mar. Drugs*
907 **2015**, *13*, 2124–2140.

908 21. Vijayakumar, S.; Menakha, M. Pharmaceutical applications of cyanobacteria-A review. *J.*
909 *Acute Med.* 2015, *5*, 15–23.

910 22. Ciferri, O.; Tiboni, O. The Biochemistry and Industrial Potential of Spirulina. *Annu. Rev.*
911 *Microbiol.* **1985**, *39*, 503–526.

912 23. Abdulqader, G.; Barsanti, L.; Tredici, M.R. Harvest of Arthrospira platensis from Lake
913 Kossorom (Chad) and its household usage among the Kanembu. *J. Appl. Phycol.* **2000**, *12*, 493–
914 498.

915 24. Lau, N.-S.; Matsui, M.; Abdullah, A.A.-A. Cyanobacteria: Photoautotrophic Microbial
916 Factories for the Sustainable Synthesis of Industrial Products. *Biomed Res. Int.* **2015**, *2015*, 1–9.

25. Boudreau, P.D.; Byrum, T.; Liu, W.T.; Dorrestein, P.C.; Gerwick, W.H. Viequeamide a, a cytotoxic member of the kulolide superfamily of cyclic depsipeptides from a marine button cyanobacterium. *J. Nat. Prod.* **2012**, *75*, 1560–1570.

26. Komarek, J.; Kastovsky, J.; Mares, J.; Johansen, J.R. Taxonomic classification of cyanoprokaryotes (cyanobacterial genera) 2014, using a polyphasic approach. *Preslia* **2014**, 295–335.

27. Soares, A.R.; Engene, N.; Gunasekera, S.P.; Sneed, J.M.; Paul, V.J. Carriebowlinol, an Antimicrobial Tetrahydroquinolinol from an Assemblage of Marine Cyanobacteria Containing a Novel Taxon. *J. Nat. Prod.* **2014**, 534–538.

28. Vining, O.B.; Medina, R.A.; Mitchell, E.A.; Videau, P.; Li, D.; Serrill, J.D.; Kelly, J.X.; Gerwick, W.H.; Proteau, P.J.; Ishmael, J.E.; et al. Depsipeptide companeramides from a panamanian marine cyanobacterium associated with the coibamide producer. *J. Nat. Prod.* **2015**, *78*, 413–420.

29. Williamson, R.T.; Singh, I.P.; Gerwick, W.H. Taveuniamides: New chlorinated toxins from a mixed assemblage of marine cyanobacteria. *Tetrahedron* **2004**, *60*, 7025–7033.

30. Harrigan, G.G.; Luesch, H.; Yoshida, W.Y.; Moore, R.E.; Nagle, D.G.; Biggs, J.; Park, P.U.; Paul, V.J. Tumonoic acids, novel metabolites from a cyanobacterial assemblage of Lyngbya majuscula and Schizothrix calcicola. *J. Nat. Prod.* **1999**, *62*, 464–467.

31. Sitachitta, N.; Williamson, R.T.; Gerwick, W.H. Yanucamides A and B, two new depsipeptides from an assemblage of the marine cyanobacteria Lyngbya majuscula and Schizothrix species. *J. Nat. Prod.* **2000**, *63*, 197–200.

32. Nogle, L.M.; Williamson, R.T.; Gerwick, W.H. Somamides A and B, two new depsipeptide analogues of dolastatin 13 from a Fijian cyanobacterial assemblage of Lyngbya majuscula and Schizothrix species. *J. Nat. Prod.* **2001**, *64*, 716–719.

33. Iwasaki, A.; Sumimoto, S.; Ohno, O.; Suda, S.; Suenaga, K. Kurahamide, a cyclic depsipeptide analog of dolastatin 13 from a marine cyanobacterial assemblage of Lyngbya sp. *Bull. Chem. Soc. Jpn.* **2014**, *87*, 609–613.

34. Harrigan, G.G.; Yoshida, W.Y.; Moore, R.E.; Nagle, D.G.; Park, P.U.; Biggs, J.; Paul, V.J.; Mooberry, S.L.; Corbett, T.H.; Valeriote, F.A. Isolation, structure determination, and biological activity of dolastatin 12 and lyngbyastatin 1 from Lyngbya majuscula/Schizothrix calcicola cyanobacterial assemblages. *J. Nat. Prod.* **1998**, *61*, 1221–1225.

35. Pereira, A.; Cao, Z.; Murray, T.F.; Gerwick, W.H. Hoiamide A, a Sodium Channel Activator of Unusual Architecture from a Consortium of Two Papua New Guinea Cyanobacteria. *Chem. Biol.* **2009**, *16*, 893–906.

36. Graber, M.A.; Gerwick, W.H. Kalkipyrone, a toxic gamma-pyrone from an assemblage of the

952 marine cyanobacteria Lyngbya majuscula and Tolypothrix sp. *J. Nat. Prod.* **1998**, *61*, 677–680.

953 37. Pereira, A.R.; Cao, Z.; Engene, N.; Soria-Mercado, I.E.; Murray, T.F.; Gerwick, W.H.
954 Palmyrolide A, an unusually stabilized neuroactive macrolide from palmyra atoll
955 cyanobacteria. *Org. Lett.* **2010**, *12*, 4490–4493.

956 38. Pereira, A.R.; Etzbach, L.; Engene, N.; Müller, R.; Gerwick, W.H. Molluscicidal metabolites
957 from an assemblage of Palmyra Atoll cyanobacteria. *J. Nat. Prod.* **2011**, *74*, 1175–1181.

958 39. Nogle, L.M.; Gerwick, W.H. Somocystinamide A, a Novel Cytotoxic Disulfide Dimer from a
959 Fijian Marine Cyanobacterial Mixed Assemblage. *Org. Lett.* **2002**, *4*, 1095–1098.

960 40. Osborne, N.J.; Shaw, G.R.; Webb, P.M. Health effects of recreational exposure to Moreton Bay,
961 Australia waters during a Lyngbya majuscula bloom. *Environ. Int.* **2007**, *33*, 309–314.

962 41. Osborne, N.J.; Shaw, G.R. Dermatitis associated with exposure to a marine cyanobacterium
963 during recreational water exposure. *BMC Dermatol.* **2008**, *8*, 5.

964 42. Engene, N.; Cameron Coates, R.; Gerwick, W.H. 16S Rrna gene heterogeneity in the
965 filamentous marine cyanobacterial genus lyngbya. *J. Phycol.* **2010**, *46*, 591–601.

966 43. Engene, N.; Rottacker, E.C.; Kaštovský, J.; Byrum, T.; Choi, H.; Ellisman, M.H.; Komárek, J.;
967 Gerwick, W.H. Moorea producens gen. nov., sp. nov. and Moorea bouillonii comb. nov.,
968 tropical marine cyanobacteria rich in bioactive secondary metabolites. *Int. J. Syst. Evol.*
969 *Microbiol.* **2012**, *62*, 1171–1178.

970 44. Engene, N.; Paul, V.J.; Byrum, T.; Gerwick, W.H.; Thor, A.; Ellisman, M.H. Five chemically
971 rich species of tropical marine cyanobacteria of the genus Okeania gen. nov. (Oscillatoriales,
972 Cyanoprokaryota). *J. Phycol.* **2013**, *49*, 1095–1106.

973 45. Komarek, J.; Zapomelova, E.; Smarda, J.; Kopecky, J.; Rejmankova, E.; Woodhouse, J.; Neilan,
974 B.A.; Komarkova, J. Polyphasic evaluation of Limnoraphis robusta, a water-bloom forming
975 cyanobacterium from Lake Atitlan, Guatemala, with a description of Limnoraphis gen. nov.
976 *Fottea* **2013**, *13*, 39–52.

977 46. Mcgregor, G.B.; Sendall, B.C. Phylogeny and toxicology of Lyngbya wollei (Cyanobacteria,
978 Oscillatoriales) from north-eastern Australia, with a description of Microseira gen. nov. *J.*
979 *Phycol.* **2015**, *51*, 109–119.

980 47. Engene, N.; Choi, H.; Esquenazi, E.; Rottacker, E.C.; Ellisman, M.H.; Dorrestein, P.C.; Gerwick,
981 W.H. Underestimated biodiversity as a major explanation for the perceived rich secondary
982 metabolite capacity of the cyanobacterial genus Lyngbya. *Environ. Microbiol.* **2011**, *13*, 1601–
983 1610.

984 48. Shih, P.M.; Wu, D.; Latifi, A.; Axen, S.D.; Fewer, D.P.; Talla, E.; Calteau, A.; Cai, F.; Tandeau
985 de Marsac, N.; Rippka, R.; et al. Improving the coverage of the cyanobacterial phylum using
986 diversity-driven genome sequencing. *Proc. Natl. Acad. Sci.* **2013**, *110*, 1053–1058.

49. Médigue, C.; Calteau, A.; Cruveiller, S.; Gachet, M.; Gautreau, G.; Josso, A.; Lajus, A.; Langlois, J.; Pereira, H.; Planel, R.; et al. MicroScope—an integrated resource for community expertise of gene functions and comparative analysis of microbial genomic and metabolic data. *Brief. Bioinform.* **2017**.

50. Moore, R.E.; Blackman, A.J.; Cheuk, C.E.; Mynderse, J.S.; Matsumoto, G.K.; Clardy, J.; Woodard, R.W.; Craig, J.C. Absolute Stereochemistries of the Aplysiatoxins and Oscillatoxin A. *J. Org. Chem.* **1984**, *49*, 2484–2489.

51. Cardellina, J.H.; Marner, F.-J.; Moore, R.E. Seaweed dermatitis: structure of lyngbyatoxin A. *Science (80-.).* **1979**, *204*, 193–195.

52. Ohtani, I.; Moore, R.E.; Runnegar, M.T.C. Cylindrospermopsin: A Potent Hepatotoxin from the Blue-Green Alga Cylindrospermopsis raciborskii. *J. Am. Chem. Soc.* **1992**, *114*, 7941–7942.

53. MacKintosh, C.; Beattie, K.A.; Klumpp, S.; Cohen, P.; Codd, G.A. Cyanobacterial microcystin-LR is a potent and specific inhibitor of protein phosphatases 1 and 2A from both mammals and higher plants. *FEBS Lett.* **1990**, *264*, 187–192.

54. Jokela, J.; Heinilä, L.M.P.; Shishido, T.K.; Wahlsten, M.; Fewer, D.P.; Fiore, M.F.; Wang, H.; Haapaniemi, E.; Permi, P.; Sivonen, K. Production of high amounts of hepatotoxin nodularin and new protease inhibitors pseudospumigins by the brazilian benthic nostoc sp. CENA543. *Front. Microbiol.* **2017**, *8*, 1963.

55. Stahl, W.; Sies, H. Antioxidant activity of carotenoids. *Mol. Aspects Med.* 2003, *24*, 345–351.

56. Lanfer-Marquez, U.M.; Barros, R.M.C.; Sinnecker, P. Antioxidant activity of chlorophylls and their derivatives. In Proceedings of the Food Research International; Elsevier, 2005; Vol. 38, pp. 885–891.

57. 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.

58. Romay, C.; Armesto, J.; Remirez, D.; González, R.; Ledon, N.; García, I. Antioxidant and anti-inflammatory properties of C-phycocyanin from blue-green algae. *Inflamm. Res.* **1998**, *47*, 36–41.

59. Balunas, M.J.; Grosso, M.F.; Villa, F.A.; Engene, N.; McPhail, K.L.; Tidgewell, K.; Pineda, L.M.; Gerwick, L.; Spadafora, C.; Kyle, D.E.; et al. Coibacins A-D, antileishmanial marine cyanobacterial polyketides with intriguing biosynthetic origins. *Org. Lett.* **2012**, *14*, 3878–3881.

60. Choi, H.; Mascuch, S.J.; Villa, F.A.; Byrum, T.; Teasdale, M.E.; Smith, J.E.; Preskitt, L.B.; Rowley, D.C.; Gerwick, L.; Gerwick, W.H. Honaucins A-C, potent inhibitors of inflammation and bacterial quorum sensing: Synthetic derivatives and structure-activity relationships. *Chem. Biol.* **2012**, *19*, 589–598.

61. Kapuścik, A.; Hrouzek, P.; Kuzma, M.; Bártová, S.; Novák, P.; Jokela, J.; Pflüger, M.; Eger, A.;

Hundsberger, H.; Kopecký, J. Novel Aeruginosin-865 from *Nostoc* sp. as a Potent Anti-inflammatory Agent. *ChemBioChem* **2013**, *14*, 2329–2337.

62. Shaala, L.A.; Youssef, D.T.A.; McPhail, K.L.; Elbandy, M. Malyngamide 4, a new lipopeptide from the Red Sea marine cyanobacterium Moorea producens (formerly Lyngbya majuscula). *Phytochem. Lett.* **2013**, *6*, 183–188.

63. Romay, C.; Gonzalez, R.; Ledon, N.; Remirez, D.; Rimbau, V. C-Phycocyanin: A Biliprotein with Antioxidant, Anti-Inflammatory and Neuroprotective Effects. *Curr. Protein Pept. Sci.* **2003**, *4*, 207–216.

64. Rastogi, R.P.; Sonani, R.R.; Madamwar, D. Cyanobacterial Sunscreen Scytonemin: Role in Photoprotection and Biomedical Research. *Appl. Biochem. Biotechnol.* 2015, *176*, 1551–1563.

65. Prinsep, M.R.; Thomson, R.A.; West, M.L.; Wylie, B.L. Tolypodiol, an antiinflammatory diterpenoid from the cyanobacterium Tolypothrix nodosa. *J. Nat. Prod.* **1996**, *59*, 786–788.

66. Hayashi, T.; Hayashi, K.; Maeda, M.; Kojima, I. Calcium spirulan, an inhibitor of enveloped virus replication, from a blue-green alga Spirulina platensis. *J. Nat. Prod.* **1996**, *59*, 83–87.

67. Entzeroth, M.; Moore, R.E.; Niemczura, W.P.; Patterson, G.M.L.; Shoolery, J.N. O-Acetyl-O-butyryl-O-carbamoyl-O,O-dimethyl-.alpha.-cyclodextrins from the cyanophyte Tolypothrix byssoidea. *J. Org. Chem.* **1986**, *51*, 5307–5310.

68. Thammana, S.; Suzuki, H.; Lobkovsky, E.; Clardy, J.; Shimizu, Y. Isolation and structure assignment of an iminotetrasaccharide from a cultured filamentous cyanobacterium Anabaena sp. *J. Nat. Prod.* **2006**, *69*, 365–368.

69. Sueyoshi, K.; Kaneda, M.; Sumimoto, S.; Oishi, S.; Fujii, N.; Suenaga, K.; Teruya, T. Odoamide, a cytotoxic cyclodepsipeptide from the marine cyanobacterium Okeania sp. *Tetrahedron* **2016**, *72*, 5472–5478.

70. Mo, S.; Krunic, 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.

71. Sung, S.Y.; Sin, L.T.; Tee, T.T.; Bee, S.T.; Rahmat, A.R.; Rahman, W.A.W.A.; Tan, A.C.; Vikhraman, M. Antimicrobial agents for food packaging applications. *Trends Food Sci. Technol.* 2013, *33*, 110–123.

72. Abushelaibi, A.A.; Al Shamsi, M.S.; Afifi, H.S. Use of antimicrobial agents in food processing systems. *Recent Pat. Food. Nutr. Agric.* **2012**, *4*, 2–7.

73. Sturdy, M.; Krunic, A.; Cho, S.; Franzblau, S.; Orjala, J. Eucapsitrione, an anti- mycobacterium tuberculosis anthraquinone derivative from the cultured freshwater cyanobacterium Eucapsis sp. *J. Nat. Prod.* **2010**, *73*, 1441–1443.

74. Reese, M.T.; Gulavita, N.K.; Nakao, Y.; Hamann, M.T.; Yoshida, W.Y.; Coval, S.J.; Scheuer, P.J. Kulolide : A Cytotoxic Depsipeptide from a Cephalaspidean. *J. Am. Chem. Soc.* **1996**, *7863*, 11081–11084.

75. Iwasaki, A.; Shiota, I.; Sumimoto, S.; Matsubara, T.; Sato, T.; Suenaga, K. Kohamamides A, B, and C, Cyclic Depsipeptides from an Okeania sp. Marine Cyanobacterium. *J. Nat. Prod.* **2017**, *80*, 1948–1952.

76. Luesch, H.; Pangilinan, R.; Yoshida, W.Y.; Moore, R.E.; Paul, V.J. Pitipeptolides A and B, new cyclodepsipeptides from the marine cyanobacterium Lyngbya majuscula. *J. Nat. Prod.* **2001**, *64*, 304–307.

77. Medina, R.A. Biologically active cyclic depsipeptides from marine cyanobacteria. **2009**, 160.

78. Nogle, L.M.; Gerwick, W.H. Isolation of four new cyclic depsipeptides, antanapeptins A-D, and dolastatin 16 from a Madagascan collection of Lyngbya majuscula. *J. Nat. Prod.* **2002**, *65*, 21–24.

79. Bunyajetpong, S.; Yoshida, W.Y.; Sitachitta, N.; Kaya, K. Trungapeptins A-C, cyclodepsipeptides from the marine cyanobacterium Lyngbya majuscula. *J. Nat. Prod.* **2006**, *69*, 1539–1542.

80. Tripathi, A.; Puddick, J.; Prinsep, M.R.; Lee, P.P.F.; Tan, L.T. Hantupeptins B and C, cytotoxic cyclodepsipeptides from the marine cyanobacterium Lyngbya majuscula. *Phytochemistry* **2010**, *71*, 307–311.

81. Malloy, K.L. UC San Diego UC San Diego Electronic Theses and Dissertations Title Structure elucidation of biomedically relevant marine cyanobacterial natural products, 2011.

82. Mevers, E.; Liu, W.T.; Engene, N.; Mohimani, H.; Byrum, T.; Pevzner, P.A.; Dorrestein, P.C.; Spadafora, C.; Gerwick, W.H. Cytotoxic veraguamides, alkynyl bromide-containing cyclic depsipeptides from the marine cyanobacterium cf. Oscillatoria margaritifera. *J. Nat. Prod.* **2011**, *74*, 928–936.

83. Montaser, R.; Paul, V.J.; Luesch, H. Pitipeptolides C-F, antimycobacterial cyclodepsipeptides from the marine cyanobacterium Lyngbya majuscula from Guam. *Phytochemistry* **2011**, *72*, 2068–2074.

84. Salvador, L.A.; Biggs, J.S.; Paul, V.J.; Luesch, H. Veraguamides A-G, cyclic hexadepsipeptides from a dolastatin 16-producing cyanobacterium Symploca cf. hydnoides from Guam. *J. Nat. Prod.* **2011**, *74*, 917–927.

85. Almaliti, J.; Malloy, K.L.; Glukhov, E.; Spadafora, C.; Gutiérrez, M.; Gerwick, W.H. Dudawalamides A-D, Antiparasitic Cyclic Depsipeptides from the Marine Cyanobacterium Moorea producens. *J. Nat. Prod.* **2017**, *80*, 1827–1836.

86. Costa, M.S.; Rego, A.; Ramos, V.; Afonso, T.B.; Freitas, S.; Preto, M.; Lopes, V.; Vasconcelos,

V.; Magalhães, C.; Leaõ, P.N. The conifer biomarkers dehydroabietic and abietic acids are widespread in Cyanobacteria. *Sci. Rep.* **2016**, *6*, 23436.

87. Acuña, U.M.; Zi, J.; Orjala, J.; Carcache de Blanco, E.J. Ambiguine I Isonitrile from Fischerella ambigua Induces Caspase-Independent Cell Death in MCF-7 Hormone Dependent Breast Cancer Cells. *Int. J. cancer Res.* **2015**, *49*, 1655–1662.

88. Becher, P.G.; Jüttner, F. Insecticidal compounds of the biofilm-forming cyanobacteriumFischerella sp. (ATCC 43239). *Environ. Toxicol.* **2005**, *20*, 363–372.

89. Klein, D.; Daloze, D.; Braekman, J.C.; Hoffmann, L.; Demoulin, V. New hapalindoles from the cyanophyte hapalosiphon laingii. *J. Nat. Prod.* **1995**, *58*, 1781–1785.

90. Koodkaew, I.; Sunohara, Y.; Matsuyama, S.; Matsumoto, H. Isolation of ambiguine D isonitrile from Hapalosiphon sp. and characterization of its phytotoxic activity. *Plant Growth Regul.* **2012**, *68*, 141–150.

91. 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*, 213.

92. Micallef, M.L.; D'Agostino, P.M.; Sharma, D.; Viswanathan, R.; Moffitt, M.C. Genome mining for natural product biosynthetic gene clusters in the Subsection V cyanobacteria. *BMC Genomics* **2015**, *16*, 669.

93. Mo, S.; Krunic, A.; Chlipala, G.; Orjala, J. Antimicrobial ambiguine isonitriles from the cyanobacterium Fischerella ambigua. *J. Nat. Prod.* **2009**, *72*, 894–9.

94. Mo, S.; Krunic, A.; Santarsiero, B.D.; Franzblau, S.G.; Orjala, J. Hapalindole-related alkaloids from the cultured cyanobacterium Fischerella ambigua. *Phytochemistry* **2010**, *71*, 2116–23.

95. 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.

96. Moore, R.E.; Yang, X.Q.G.; Patterson, G.M.L. Fontonamide and Anhydrohapaloxindole A, Two New Alkaloids from the Blue-Green Alga Hapalosiphon fontinalis. *J. Org. Chem.* **1987**, *52*, 3773–3777.

97. Moore, R.E.; Cheuk, C.; Yang, X.Q.G.; Patterson, G.M.L.; Bonjouklian, R.; Smitka, T.A.; Mvnderse, J.S.; Foster, R.S.; Jones, N.D.; Swartzendruber, J.K.; et al. Hapalindoles, Antibacterial and Antimycotic Alkaloids from the Cyanophyte Hapalosiphon fontinalis. *J. Org. Chem.* **1987**, *52*, 1036–1043.

98. Moore, R.E.; Yang, X.Q.G.; Patterson, G.M.L.; Bonjouklian, R.; Smitka, T.A. Hapalonamides and other oxidized hapalindoles from Hapalosiphon fontinalis. *Phytochemistry* **1989**, *28*, 1565–1567.

99. Becher, P.G.; Keller, S.; Jung, G.; Süssmuth, R.D.; Jüttner, F. Insecticidal activity of 12-epi-hapalindole J isonitrile. *Phytochemistry* **2007**, *68*, 2493–2497.

100. Park, A.; Moore, R.E.; Patterson, G.M.. Fischerindole L, a new isonitrile from the terrestrial blue-green alga fischerella muscicola. *Tetrahedron Lett.* **1992**, *33*, 3257–3260.

101. Raveh, A.; Carmeli, S. Antimicrobial ambiguines from the cyanobacterium Fischerella sp. collected in Israel. *J. Nat. Prod.* **2007**, *70*, 196–201.

102. Schwartz, R.E.; Hirsch, C.F.; Pettibone, D.J.; Zink, D.L.; Springer, J.P. Unusual Cyclopropane-Containing Hapalindolinones from a Cultured Cyanobacterium. *J. Org. Chem.* **1987**, *52*, 3704–3706.

103. 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.

104. Stratmann, K.; Moore, R.E.; Patterson, G.M.L.; Bonjouklian, R.; Deeter, J.B.; Shaffer, S.; Smitka, T.A.; Smith, C.D. Welwitindolinones, Unusual Alkaloids from the Blue-Green Algae Hapalosiphon welwitschii and Westiella intricata. Relationship to Fischerindoles and Hapalinodoles. *J. Am. Chem. Soc.* **1994**, *116*, 9935–9942.

105. Walton, K.; Gantar, M.; Gibbs, P.D.L.; Schmale, M.C.; Berry, J.P. Indole alkaloids from Fischerella inhibit vertebrate development in the zebrafish (Danio rerio) embryo model. *Toxins (Basel).* **2014**, *6*, 3568–3581.

106. Cagide, E.; Becher, P.G.; Louzao, M.C.; Espiña, B.; Vieytes, M.R.; Jüttner, F.; Botana, L.M. Hapalindoles from the cyanobacterium Fischerella: Potential sodium channel modulators. *Chem. Res. Toxicol.* **2014**, *27*, 1696–1706.

107. Etchegaray, A.; Rabello, E.; Dieckmann, R.; Moon, D.H.; Fiore, M.F.; Von Döhren, H.; Tsai, S.M.; Neilan, B.A. Algicide production by the filamentous cyanobacterium Fischerella sp. CENA 19. *J. Appl. Phycol.* **2004**, *16*, 237–243.

108. Hillwig, M.L.; Zhu, Q.; Liu, X. Biosynthesis of Ambiguine Indole Alkaloids in Cyanobacterium Fischerella ambigua. *ACS Chem. Biol.* **2014**, *9*, 372–377.

109. Hillwig, M.L.; Fuhrman, H.A.; Ittiamornkul, 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.

110. Huber, U.; Moore, R.E.; Patterson, G.M.L. Isolation of a nitrile-containing indole alkaloid from the terrestrial blue-green alga Hapalosiphon delicatulus. *J. Nat. Prod.* **1998**, *61*, 1304–1306.

111. 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.

Bioorg. Med. Chem. **2012**, *20*, 5290–5295.

112. Kim, H.; Krunic, A.; Lantvit, D.; Shen, Q.; Kroll, D.J.; Swanson, S.M.; Orjala, J. Nitrile-containing fischerindoles from the cultured cyanobacterium Fischerella sp. *Tetrahedron* **2012**, *68*, 3205–3209.

113. Kosalec, I.; Kremer, D.; Locatelli, M.; Epifano, F.; Genovese, S.; Carlucci, G.; Randić, M.; Zovko Končić, M. Anthraquinone profile, antioxidant and antimicrobial activity of bark extracts of Rhamnus alaternus, R. fallax, R. intermedia and R. pumila. *Food Chem.* **2013**, *136*, 335–341.

114. Yang, E.J.; Kim, S.H.; Lee, K.Y.; Song, K.S. Neuroprotective and anti-neuroinflammatory activities of anthraquinones isolated from Photorhabdus temperata culture broth. *J. Microbiol. Biotechnol.* **2018**, *28*, 12–21.

115. Park, J.G.; Kim, S.C.; Kim, Y.H.; Yang, W.S.; Kim, Y.; Hong, S.; Kim, K.H.; Yoo, B.C.; Kim, S.H.; Kim, J.H.; et al. Anti-Inflammatory and Antinociceptive Activities of Anthraquinone-2-Carboxylic Acid. *Mediators Inflamm.* **2016**, *2016*, 1–12.

116. Yen, G.C.; Duh, P. Der; Chuang, D.Y. Antioxidant activity of anthraquinones and anthrone. *Food Chem.* **2000**, *70*, 437–441.

117. Mason, C.P.; Edwards, K.R.; Carlson, R.E.; Pignatello, J.; Gleason, F.K.; Wood, J.M. Isolation of Chlorine-Containing Antibiotic from the Freshwater Cyanobacterium Scytonema hofmanni. *Science (80-.).* **1982**, *215*, 400–402.

118. Gromov, B. V.; Vepritskiy, A.A.; Titova, N.N.; Mamkayeva, K.A.; Alexandrova, O. V. Production of the antibiotic cyanobacterin LU-1 by Nostoc linckia CALU 892 (cyanobacterium). *J. Appl. Phycol.* **1991**, *3*, 55–59.

119. Gleason, F.K.; Case, D.E. Activity of the natural algicide, cyanobacterin, on angiosperms. *Plant Physiol.* **1986**, *80*, 834–7.

120. Hagmann, L.; Jüttner, F. Fischerellin A, a novel photosystem-II-inhibiting allelochemical of the cyanobacterium Fischerella muscicola with antifungal and herbicidal activity. *Tetrahedron Lett.* **1996**, *37*, 6539–6542.

121. Foster, M.P.; Concepción, G.P.; Caraan, G.B.; Ireland, C.M. Bistratamides C and D. Two New Oxazole-Containing Cyclic Hexapeptides Isolated from a Philippine Lissoclinum bistratum Ascidian. *J. Org. Chem.* **1992**, *57*, 6671–6675.

122. Prinsep, M.R.; Moore, R.E.; Levine, I.A.; Patterson, G.M.L. Westiellamide, a bistratamide-related cyclic peptide from the blue-green alga westiellopsis prolifica. *J. Nat. Prod.* **1992**, *55*, 140–142.

123. 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.

124. Todorova, A.K.; Jüttner, F.; Linden, A.; Plüiss, T.; von Philipsborn, W. Nostocyclamide: A New Macrocyclic, Thiazole-Containing Allelochemical from Nostoc sp. 31 (Cyanobacteria). *J. Org. Chem.* **1995**, *60*, 7891–7895.

125. Admi, V.; Afek, U.; Carmeli, S. Raocyclamides A and B, novel cyclic hexapeptides isolated from the cyanobacterium Oscillatoria raoi. *J. Nat. Prod.* **1996**, *59*, 396–399.

126. Banker, R.; Carmeli, S. Tenuecyclamides A−D, Cyclic Hexapeptides from the Cyanobacterium Nostoc spongiaeforme var. tenue. *J. Nat. Prod.* **1998**, *61*, 1248–1251.

127. Jüttner, F.; Todorova, A.K.; Walch, N.; Von Philipsborn, W. Nostocyclamide M: A cyanobacterial cyclic peptide with allelopathic activity from Nostoc 31. *Phytochemistry* **2001**, *57*, 613–619.

128. Ishibashi, F.; Park, S.; Kusano, T.; Kuwano, K. Synthesis and algicidal activity of (+)-cyanobacterin and its stereoisomer. *Biosci. Biotechnol. Biochem.* **2005**, *69*, 391–6.

129. Gross, E.M.; Wolk, C.P.; Jüttner, F. Fischerellin, a new allelochemical from the freshwater cyanobacterium Fischerella muscicola. *J. Phycol.* **1991**, *27*, 686–692.

130. Papke, U.; Gross, E.M.; Francke, W. Isolation, identification and determination of the absolute configuration of Fischerellin B. A new algicide from the freshwater cyanobacterium Fischerella muscicola (Thuret). *Tetrahedron Lett.* **1997**, *38*, 379–382.

131. Srivastava, V.C.; Manderson, G.J.; Bhamidimarri, R. Inhibitory metabolites production by the cyanobacterium Fischerella muscicola. *Microbiol. Res.* **1999**, *153*, 309–317.

132. Falch, B.S.; König, G.M.; Wright, A.D.; Sticher, O.; Röegger, H.; Bernardinelli, G. Ambigol A and B: New Biologically Active Polychlorinated Aromatic Compounds from the Terrestrial Blue-Green Alga Fischerella ambigua. *J. Org. Chem.* **1993**, *58*, 6570–6575.

133. Wright, A.D.; Papendorf, O.; König, G.M. Ambigol C and 2, 4 dichlorobenzoic acid, natural products produced by terrestrial cyanobacterium Fischerella ambigua. *J. Nat. Prod.* **2005**, *68*, 459–461.

134. An, T.; Kumar, T.K.S.; Wang, M.; Liu, L.; Lay, J.O.; Liyanage, R.; Berry, J.; Gantar, M.; Marks, V.; Gawley, R.E.; et al. Structures of pahayokolides A and B, cyclic peptides from a Lyngbya sp. *J. Nat. Prod.* **2007**, *70*, 730–735.

135. Berry, J.P.; Gantar, M.; Gawley, R.E.; Wang, M.; Rein, K.S. Pharmacology and toxicology of pahayokolide A, a bioactive metabolite from a freshwater species of Lyngbya isolated from the Florida Everglades. *Comp. Biochem. Physiol. - C Toxicol. Pharmacol.* **2004**, *139*, 231–238.

136. Dias, F.; Antunes, J.T.; Ribeiro, T.; Azevedo, J.; Vasconcelos, V.; Leão, P.N. Cyanobacterial allelochemicals but not cyanobacterial cells markedly reduce microbial community diversity. *Front. Microbiol.* **2017**, *8*, 1495.

137. Leao, P.N.; Pereira, A.R.; Liu, W.-T.; Ng, J.; Pevzner, P.A.; Dorrestein, P.C.; Konig, G.M.; Vasconcelos, V.M.; Gerwick, W.H. Synergistic allelochemicals from a freshwater cyanobacterium. *Proc. Natl. Acad. Sci.* **2010**, *107*, 11183–11188.

138. Mehner, C.; Müller, D.; Krick, A.; Kehraus, S.; Löser, R.; Gütschow, M.; Maier, A.; Fiebig, H.H.; Brun, R.; König, G.M. A novel β-amino acid in cytotoxic peptides from the cyanobacterium Tychonema sp. *European J. Org. Chem.* **2008**, *2008*, 1732–1739.

139. Pergament, I.; Carmeli, S. Schizotrin A ; a Nwel Antimicrobial Cyclic Peptide from a Cyanobacterium. *Tetrahedron Lett.* **1994**, *35*, 8473–8476.

140. Ribeiro, T.; Lemos, F.; Preto, M.; Azevedo, J.; Sousa, M.L.; Leão, P.N.; Campos, A.; Linder, S.; Vitorino, R.; Vasconcelos, V.; et al. Cytotoxicity of portoamides in human cancer cells and analysis of the molecular mechanisms of action. *PLoS One* **2017**, *12*, e0188817.

141. Zainuddin, E.N.; Jansen, R.; Nimtz, M.; Wray, V.; Preisitsch, M.; Lalk, M.; Mundt, S. Lyngbyazothrins A-D, antimicrobial cyclic undecapeptides from the cultured cyanobacterium Lyngbya sp. *J. Nat. Prod.* **2009**, *72*, 1373–1378.

142. Ramsay, E.E.; Hogg, P.J.; Dilda, P.J. Mitochondrial metabolism inhibitors for cancer therapy. *Pharm. Res.* 2011, *28*, 2731–2744.

143. Bui, T.H.; Wray, V.; Nimtz, M.; Fossen, T.; Preisitsch, M.; Schröder, G.; Wende, K.; Heiden, S.E.; Mundt, S. Balticidins A-D, antifungal hassallidin-like lipopeptides from the Baltic Sea cyanobacterium Anabaena cylindrica Bio33. *J. Nat. Prod.* **2014**, *77*, 1287–1296.

144. Neuhof, T.; Schmieder, P.; Seibold, M.; Preussel, K.; Von Dö Hren, H. Hassallidin B—Second antifungal member of the Hassallidin family. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4220–4222.

145. Neuhof, T.; Schmieder, P.; Preussel, K.; Dieckmann, R.; Pham, H.; Bartl, F.; Von Döhren, H. Hassallidin A, a Glycosylated Lipopeptide with Antifungal Activity from the Cyanobacterium Hassallia sp. *J. Nat. Prod.* **2005**, *68*, 695–700.

146. Pancrace, C.; Jokela, J.; Sassoon, N.; Ganneau, C.; Desnos-Ollivier, M.; Wahlsten, M.; Humisto, A.; Calteau, A.; Bay, S.; Fewer, D.P.; et al. Rearranged Biosynthetic Gene Cluster and Synthesis of Hassallidin e in Planktothrix serta PCC 8927. *ACS Chem. Biol.* **2017**, *12*, 1796–1804.

147. Vestola, J.; Shishido, T.K.; Jokela, J.; Fewer, D.P.; Aitio, O.; Permi, P.; Wahlsten, M.; Wang, H.; Rouhiainen, L.; Sivonen, K. Hassallidins, antifungal glycolipopeptides, are widespread among cyanobacteria and are the end-product of a nonribosomal pathway. *Proc. Natl. Acad. Sci. U. S. A.* **2014**, *111*, E1909-17.

148. Choi, H.; Mevers, E.; Byrum, T.; Valeriote, F.A.; Gerwick, W.H. Lyngbyabellins K-N from two Palmyra atoll collections of the marine cyanobacterium Moorea bouillonii. *European J. Org. Chem.* **2012**, *2012*, 5141–5150.

149. Han, B.; McPhail, K.L.; Gross, H.; Goeger, D.E.; Mooberry, S.L.; Gerwick, W.H. Isolation and

structure of five lyngbyabellin derivatives from a Papua New Guinea collection of the marine cyanobacterium Lyngbya majuscula. *Tetrahedron* **2005**, *61*, 11723–11729.

150. Luesch, H.; Yoshida, W.Y.; Moore, R.E.; Paul, V.J.; Mooberry, S.L. Isolation, structure determination, and biological activity of lyngbyabellin A from the marine cyanobacterium Lyngbya majuscula. *J. Nat. Prod.* **2000**, *63*, 611–615.

151. Marquez, B.L.; Watts, K.S.; Yokochi, A.; Roberts, M.A.; Verdier-Pinard, P.; Jimenez, J.I.; Hamel, E.; Scheuer, P.J.; Gerwick, W.H. Structure and absolute stereochemistry of hectochlorin, a potent stimulator of actin assembly. *J. Nat. Prod.* **2002**, *65*, 866–871.

152. Milligan, K.E.; Marquez, B.L.; Williamson, R.T.; Gerwick, W.H. Lyngbyabellin B, a toxic and antifungal secondary metabolite from the marine cyanobacterium Lyngbya mojuscula. *J. Nat. Prod.* **2000**, *63*, 1440–1443.

153. 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**, 1977–1986.

154. Williams, P.G.; Luesch, H.; Yoshida, W.Y.; Moore, R.E.; Paul, V.J. Continuing studies on the cyanobacterium Lyngbya sp.: Isolation and structure determination of 15-norlyngbyapeptin A and lyngbyabellin D. *J. Nat. Prod.* **2003**, *66*, 595–598.

155. Matthew, S.; Salvador, L.A.; Schupp, P.J.; Paul, V.J.; Luesch, H. Cytotoxic halogenated macrolides and modified peptides from the apratoxin-producing marine cyanobacterium Lyngbya bouillonii from Guam. *J. Nat. Prod.* **2010**, *73*, 1544–1552.

156. Adiv, S.; Carmeli, S. Protease inhibitors from microcystis aeruginosa bloom material collected from the dalton reservoir, israel. *J. Nat. Prod.* **2013**, *76*, 2307–2315.

157. Gesner-Apter, S.; Carmeli, S. Three novel metabolites from a bloom of the cyanobacterium Microcystis sp. *Tetrahedron* **2008**, *64*, 6628–6634.

158. Lifshits, M.; Carmeli, S. Metabolites of microcystis aeruginosa bloom material from Lake Kinneret, Israel. *J. Nat. Prod.* **2012**, *75*, 209–219.

159. Marner, F.J.; Moore, R.E.; Hirotsu, K.; Clardy, J. Majusculamides A and B, Two Epimeric Lipodipeptides from Lyngbya majuscula Gomont. *J. Org. Chem.* **1977**, *42*, 2815–2819.

160. Carter, D.C.; Moore, R.E.; Mynderse, J.S.; Niemczura, W.P.; Todd, J.S. Structure of Majusculamide C, a Cyclic Depsipeptide from Lyngbya majuscula. *J. Org. Chem.* **1984**, *49*, 236–241.

161. Moore, R.E.; Entzeroth, M. Majusculamide D and deoxymajusculamide D, two cytotoxins from Lyngbya majuscula. *Phytochemistry* **1988**, *27*, 3101–3103.

162. Koehn, F.E.; Longley, R.E.; Reed, J.K. Microcolins a and b, new immunosuppressive peptides

from the blue-green alga lyngbya majuscula. *J. Nat. Prod.* **1992**, *55*, 613–619.

163. Meickle, T.; Matthew, S.; Ross, C.; Luesch, H.; Paul, V. Bioassay-guided isolation and identification of desacetylmicrocolin B from lyngbya cf. polychroa. *Planta Med.* **2009**, *75*, 1427–1430.

164. Simmons, T.L.; Nogle, L.M.; Media, J.; Valeriote, F.A.; Mooberry, S.L.; Gerwick, W.H. Desmethoxymajusculamide C, a cyanobacterial depsipeptide with potent cytotoxicity in both cyclic and ring-opened forms. *J. Nat. Prod.* **2009**, *72*, 1011–1016.

165. Tan, L.T.; Goh, B.P.L.; Tripathi, A.; Lim, M.G.; Dickinson, G.H.; Lee, S.S.C.; Teo, S.L.M. Natural antifoulants from the marine cyanobacterium Lyngbya majuscula. *Biofouling* **2010**, *26*, 685–695.

166. World Health Organisation WHO | Number of deaths due to HIV/AIDS Available online: https://www.who.int/gho/hiv/epidemic_status/deaths_text/en/ (accessed on Apr 9, 2019).

167. Gupta, D.K.; Kaur, P.; Leong, S.T.; Tan, L.T.; Prinsep, M.R.; Chu, J.J.H. Anti-Chikungunya viral activities of aplysiatoxin-related compounds from the marine cyanobacterium Trichodesmium erythraeum. *Mar. Drugs* **2014**, *12*, 115–127.

168. Chlipala, G.E.; Sturdy, M.; Krunic, A.; Lantvit, D.D.; Shen, Q.; Porter, K.; Swanson, S.M.; Orjala, J. Cylindrocyclophanes with proteasome inhibitory activity from the Cyanobacterium Nostoc sp. *J. Nat. Prod.* **2010**, *73*, 1529–37.

169. Han, B.N.; Liang, T.T.; Keen, L.J.; Fan, T.T.; Zhang, X.D.; Xu, L.; Zhao, Q.; Wang, S.P.; Lin, H.W. Two Marine Cyanobacterial Aplysiatoxin Polyketides, Neo-debromoaplysiatoxin A and B, with K+Channel Inhibition Activity. *Org. Lett.* **2018**, *20*, 578–581.

170. Rastogi, R.P.; Madamwar, D.; Incharoensakdi, A. Bloom Dynamics of Cyanobacteria and Their Toxins: Environmental Health Impacts and Mitigation Strategies. *Front. Microbiol.* **2015**, *6*, 1254.

171. Chlipala, G.E.; Tri, P.H.; Hung, N. Van; Krunic, A.; Shim, S.H.; Soejarto, D.D.; Orjala, J. Nhatrangins A and B, aplysiatoxin-related metabolites from the marine cyanobacterium lyngbya majuscula from Vietnam. *J. Nat. Prod.* **2010**, *73*, 784–787.

172. Mynderse, J.S.; Moore, R.E.; Kashiwagi, M.; Norton, T.R. Antileukemia activity in the Oscillatoriaceae: Isolation of debromoaplysiatoxin from Lyngbya. *Science (80-.).* **1977**, *196*, 538–540.

173. Boyd, M.R.; Gustafson, K.R.; McMahon, J.B.; Shoemaker, R.H.; O'Keefe, B.R.; Mori, T.; Gulakowski, R.J.; Wu, L.; Rivera, M.I.; Laurencot, C.M.; et al. Discovery of cyanovirin-N, a novel human immunodeficiency virus- inactivating protein that binds viral surface envelope glycoprotein gp120: Potential applications to microbicide development. *Antimicrob. Agents Chemother.* **1997**, *41*, 1521–1530.

174. Dey, B.; Lerner, D.L.; Lusso, P.; Boyd, M.R.; Elder, J.H.; Berger, E.A. Multiple antiviral activities of cyanovirin-N: blocking of human immunodeficiency virus type 1 gp120 interaction with CD4 and coreceptor and inhibition of diverse enveloped viruses. *J. Virol.* **2000**, *74*, 4562–4569.

175. Matei, E.; Basu, R.; Furey, W.; Shi, J.; Calnan, C.; Aiken, C.; Gronenborn, A.M. Structure and glycan binding of a new cyanovirin-N homolog. *J. Biol. Chem.* **2016**, *291*, 18967–18976.

176. Hayashi, K.; Hayashi, T.; Kojima, I. A Natural Sulfated Polysaccharide, Calcium Spirulan, Isolated from Spirulina platensis: In Vitro and ex Vivo Evaluation of Anti-Herpes Simplex Virus and Anti-Human Immunodeficiency Virus Activities. *AIDS Res. Hum. Retroviruses* **1996**, *12*, 1463–1471.

177. Mader, J.; Gallo, A.; Schommartz, T.; Handke, W.; Nagel, C.H.; Günther, P.; Brune, W.; Reich, K. Calcium spirulan derived from Spirulina platensis inhibits herpes simplex virus 1 attachment to human keratinocytes and protects against herpes labialis. *J. Allergy Clin. Immunol.* **2016**, *137*, 197-203.e3.

178. Wijesekara, I.; Pangestuti, R.; Kim, S.K. Biological activities and potential health benefits of sulfated polysaccharides derived from marine algae. *Carbohydr. Polym.* 2011, *84*, 14–21.

179. Baba, M.; Pauwels, R.; Balzarini, J.; Arnout, J.; Desmyter, J.; De Clercq, E. Mechanism of inhibitory effect of dextran sulfate and heparin on replication of human immunodeficiency virus in vitro. *Proc. Natl. Acad. Sci.* **1988**, *85*, 6132–6136.

180. World Health Organisation Malaria Available online: https://www.who.int/news-room/fact-sheets/detail/malaria (accessed on Apr 10, 2019).

181. Ogawa, H.; Iwasaki, A.; Sumimoto, S.; Iwatsuki, M.; Ishiyama, A.; Hokari, R.; Otoguro, K.; Omura, S.; Suenaga, K. Isolation and Total Synthesis of Hoshinolactam, an Antitrypanosomal Lactam from a Marine Cyanobacterium. *Org. Lett.* **2017**, *19*, 890–893.

182. Davies-Coleman, M.T.; Dzeha, T.M.; Gray, C.A.; Hess, S.; Pannell, L.K.; Hendricks, D.T.; Arendse, C.E. Isolation of homodolastatin 16, a new cyclic depsipeptide from a Kenyan collection of Lyngbya majuscula. *J. Nat. Prod.* **2003**, *66*, 712–715.

183. Fennell, B.J.; Carolan, S.; Pettit, G.R.; Bell, A. Effects of the antimitotic natural product dolastatin 10, and related peptides, on the human malarial parasite Plasmodium falciparum. *J. Antimicrob. Chemother.* **2003**, *51*, 833–841.

184. Harrigan, G.G.; Luesch, H.; Yoshida, W.Y.; Moore, R.E.; Nagle, D.G.; Paul, V.J.; Mooberry, S.L.; Corbett, T.H.; Valeriote, F.A. Symplostatin 1: A Dolastatin 10 Analogue from the Marine Cyanobacterium Symploca hydnoides. *J. Nat. Prod.* **1998**, *61*, 1075–1077.

185. Harrigan, G.G.; Luesch, H.; Yoshida, W.Y.; Moore, R.E.; Nagle, D.G.; Paul, V.J. Symplostatin 2: A dolastatin 13 analogue from the marine cyanobacterium Symploca hydnoides. *J. Nat.*

Prod. **1999**, *62*, 655–658.

186. Luesch, H.; Moore, R.E.; Paul, V.J.; Mooberry, S.L.; Corbett, T.H. Isolation of dolastatin 10 from the marine cyanobacterium Symploca species VP642 and total stereochemistry and biological evaluation of its analogue symplostatin 1. *J. Nat. Prod.* **2001**, *64*, 907–910.

187. Luesch, H.; Yoshida, W.Y.; Moore, R.E.; Paul, V.J.; Mooberry, S.L.; Corbett, T.H. Symplostatin 3, a new dolastatin 10 analogue from the marine cyanobacterium Symploca sp. VP452. *J. Nat. Prod.* **2002**, *65*, 16–20.

188. Mitchell, S.S.; Faulkner, D.J.; Rubins, K.; Bushman, F.D. Dolastatin 3 and two novel cyclic peptides from a palauan collection of Lyngbya majuscula. *J. Nat. Prod.* **2000**, *63*, 279–282.

189. Pettit, G.R. The Dolastatins. *Prog. Chem. Org. Nat. Prod.* **1997**, *70*, 2–79.

190. Flahive, E.; Srirangam, J. The Dolastatins: Novel Antitumor Agents from Dolabella auricularia. In *Anticancer Agents from Natural Products*; CRC Press, 2005; p. 600.

191. Bai, R.; Pettit, G.R.; Hamel, E. Structure-activity studies with chiral isomers and with segments of the antimitotic marine peptide dolastatin 10. *Biochem. Pharmacol.* **1990**, *40*, 1859–1864.

192. World Health Organisation Cancer Available online: https://www.who.int/news-room/fact-sheets/detail/cancer.

193. *World cancer report 2014*; Stewart, B.W., Wild, C.P., Eds.; 2014; ISBN 978-92-832-0443-5.

194. Mirsalis, J.C.; Schindler-Horvat, J.; Hill, J.R.; Tomaszewski, J.E.; Donohue, S.J.; Tyson, C.A. Toxicity of dolastatin 10 in mice, rats and dogs and its clinical relevance. *Cancer Chemother. Pharmacol.* **1999**, *44*, 395–402.

195. Francisco, J.A.; Cerveny, C.G.; Meyer, D.L.; Mixan, B.J.; Klussman, K.; Chace, D.F.; Rejniak, S.X.; Gordon, K.A.; DeBlanc, R.; Toki, B.E.; et al. cAC10-vcMMAE, an anti-CD30-monomethyl auristatin E conjugate with potent and selective antitumor activity. *Blood* **2003**, *102*, 1458–1465.

196. Rose, A.A.N.; Biondini, M.; Curiel, R.; Siegel, P.M. Targeting GPNMB with glembatumumab vedotin: Current developments and future opportunities for the treatment of cancer. *Pharmacol. Ther.* 2017, *179*, 127–141.

197. Barchi, J.J.; Norton, T.R.; Furusawa, E.; Patterson, G.M.L.; Moore, R.E. Identification of a cytotoxin from Tolypothrix byssoidea as tubercidin. *Phytochemistry* **1983**, *22*, 2851–2852.

198. Stewart, J.B.; Bornemann, V.; Chen, J.L.; Moore, R.E.; Caplan, F.R.; Karuso, H.; Larsen, L.K.; Patterson, G.M.L. Cytotoxic, fungicidal nucleosides from blue green algae belonging to the Scytonemataceae. *J. Antibiot. (Tokyo).* **1988**, *61*, 1048–1056.

199. Mooberry, S.L.; Stratman, K.; Moore, R.E. Tubercidin stabilizes microtubules against vinblastine-induced depolymerization, a taxol-like effect. *Cancer Lett.* **1995**, *96*, 261–266.

200. Altmann, K.-H. Microtubule-stabilizing agents: a growing class of important anticancer drugs. *Curr. Opin. Chem. Biol.* **2001**, *5*, 424–431.

201. Han, B.; Gross, H.; Goeger, D.E.; Mooberry, S.L.; Gerwick, W.H. Aurilides B and C, cancer cell toxins from a Papua New Guinea collection of the marine cyanobacterium Lyngbya majuscula. *J. Nat. Prod.* **2006**, *69*, 572–575.

202. Tripathi, A.; Puddick, J.; Prinsep, M.R.; Rottmann, M.; Tan, L.T. Lagunamides A and B: Cytotoxic and antimalarial cyclodepsipeptides from the marine cyanobacterium Lyngbya majuscula. *J. Nat. Prod.* **2010**, *73*, 1810–1814.

203. Tripathi, A.; Puddick, J.; Prinsep, M.R.; Rottmann, M.; Chan, K.P.; Chen, D.Y.K.; Tan, L.T. Lagunamide C, a cytotoxic cyclodepsipeptide from the marine cyanobacterium Lyngbya majuscula. *Phytochemistry* **2011**, *72*, 2369–2375.

204. Williams, P.G.; Yoshida, W.Y.; Quon, M.K.; Moore, R.E.; Paul, V.J. The Structure of Palau'amide, a Potent Cytotoxin from a Species of the Marine Cyanobacterium Lyngbya. *J. Nat. Prod.* **2003**, *66*, 1545–1549.

205. Andrianasolo, E.H.; Gross, H.; Goeger, D.; Musafija-Girt, M.; McPhail, K.; Leal, R.M.; Mooberry, S.L.; Gerwick, W.H. Isolation of swinholide A and related glycosylated derivatives from two field collections of marine cyanobacteria. *Org. Lett.* **2005**, *7*, 1375–1378.

206. Humisto, A.; Jokela, J.; Liu, L.; Wahlsten, M.; Wang, H.; Permi, P.; Machado, J.P.; Antunes, A.; Fewer, D.P.; Sivonen, K. The swinholide biosynthesis gene cluster from a terrestrial cyanobacterium, Nostoc sp. strain UHCC 0450. *Appl. Environ. Microbiol.* **2018**, *84*, e02321-17.

207. Tao, Y.; Li, P.; Zhang, D.; Glukhov, E.; Gerwick, L.; Zhang, C.; Murray, T.F.; Gerwick, W.H. Samholides, Swinholide-Related Metabolites from a Marine Cyanobacterium cf. Phormidium sp. *J. Org. Chem.* **2018**, *83*, 3034–3046.

208. Oftedal, L.; Myhren, L.; Jokela, J.; Gausdal, G.; Sivonen, K.; Doskeland, S.O.; Herfindal, L. The lipopeptide toxins anabaenolysin A and B target biological membranes in a cholesterol-dependent manner. *Biochim. Biophys. Acta - Biomembr.* **2012**, *1818*, 3000–3009.

209. Jokela, J.; Oftedal, L.; Herfindal, L.; Permi, P.; Wahlsten, M.; Døskeland, S.O.; Sivonen, K. Anabaenolysins, Novel Cytolytic Lipopeptides from Benthic Anabaena Cyanobacteria. *PLoS One* **2012**, *7*, e41222.

210. Rao, J.Y.; Li, N. Microfilament Actin Remodeling as a Potential Target for Cancer Drug Development. *Curr. Cancer Drug Targets* **2004**, *4*, 345–354.

211. Suenaga, K.; Mutou, T.; Shibata, T.; Itoh, T.; Fujita, T.; Takada, N.; Hayamizu, K.; Takagi, M.; Irifune, T.; Kigoshi, H.; et al. Aurilide, a cytotoxic depsipeptide from the sea hare Dolabella auricularia: Isolation, structure determination, synthesis, and biological activity. *Tetrahedron* **2004**, *60*, 8509–8527.

212. Nakao, Y.; Yoshida, W.Y.; Takada, Y.; Kimura, J.; Yang, L.; Mooberry, S.L.; Scheuer, P.J. Kulokekahilide-2, a cytotoxic depsipeptide from a cephalaspidean mollusk Philinopsis Speciosa. *J. Nat. Prod.* **2004**, *67*, 1332–1340.

213. Carmeli, S.; Kashman, Y. Structure of swinholide-a, a new macrolide from the marine sponge theonella swinhoei. *Tetrahedron Lett.* **1985**, *26*, 511–514.

214. Bubb, M.R.; Spector, I.; Bershadsky, A.D.; Korn, E.D. Swinholide A is a microfilament disrupting marine toxin that stabilizes actin dimers and severs actin filaments. *J. Biol. Chem.* **1995**, *270*, 3463–3466.

215. Trimurtulu, G.; Ohtani, I.; Patterson, G.M.L.; Moore, R.E.; Corbett, T.H.; Valeriote, F.A.; Demchik, L. Total Structures of Cryptophycins, Potent Antitumor Depsipeptides from the Blue-Green Alga Nostoc sp. Strain GSV 224. *J. Am. Chem. Soc.* **1994**, *116*, 4729–4737.

216. Stratmann, K.; Burgoyne, D.L.; Moore, R.E.; Patterson, G.M.L.; Smith, C.D. Hapalosin, a Cyanobacterial Cyclic Depsipeptide with Multidrug-Resistance Reversing Activity. *J. Org. Chem.* **1994**, *59*, 7219–7226.

217. 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. U. S. A.* **2005**, *102*, 7315–20.

218. Williams, A.B.; Jacobs, R.S. A marine natural product, patellamide D, reverses multidrug resistance in a human leukemic cell line. *Cancer Lett.* **1993**, *71*, 97–102.

219. Prinsep, M.R.; Caplan, F.R.; Moore, R.E.; Patterson, G.M.L.; Smith, C.D. Tolyporphin, a Novel Multidrug Resistance Reversing Agent from the Blue-Green Alga Tolypothrix nodosa. *J. Am. Chem. Soc.* **1992**, *114*, 385–387.

220. Prinsep, M.R.; Patterson, G.M.L.; Larsen, L.K.; Smith, C.D. Further tolyporphins from the Blue-Green alga Tolypothrix nodosa. *Tetrahedron* **1995**, *51*, 10523–10530.

221. Nanayakkara, A.K.; Follit, C.A.; Chen, G.; Williams, N.S.; Vogel, P.D.; Wise, J.G. Targeted inhibitors of P-glycoprotein increase chemotherapeutic-induced mortality of multidrug resistant tumor cells. *Sci. Rep.* **2018**, *8*, 967.

222. Ilies, M.A.; Supuran, C.T.; Scozzafava, A. Therapeutic applications of serine protease inhibitors. *Expert Opin. Ther. Pat.* **2002**, *12*, 1181–1214.

223. Drag, M.; Salvesen, G.S. Emerging principles in protease-based drug discovery. *Nat. Rev. Drug Discov.* 2010, *9*, 690–701.

224. Dey, T.; Kalita, J.; Weldon, S.; Taggart, C. Proteases and Their Inhibitors in Chronic Obstructive Pulmonary Disease. *J. Clin. Med.* **2018**, *7*, 244.

225. Guay, C.; Laviolette, M.; Tremblay, G.M. Targeting serine proteases in asthma. *Curr. Top. Med. Chem.* **2006**, *6*, 393–402.

226. Williams, M.R.; Nakatsuji, T.; Sanford, J.A.; Vrbanac, A.F.; Gallo, R.L. Staphylococcus aureus Induces Increased Serine Protease Activity in Keratinocytes. *J. Invest. Dermatol.* **2017**, *137*, 377–384.

227. Lee, H.; Ren, J.; Nocadello, S.; Rice, A.J.; Ojeda, I.; Light, S.; Minasov, G.; Vargas, J.; Nagarathnam, D.; Anderson, W.F.; et al. Identification of novel small molecule inhibitors against NS2B/NS3 serine protease from Zika virus. *Antiviral Res.* **2017**, *139*, 49–58.

228. Adams, J. The development of proteasome inhibitors as anticancer drugs. *Cancer Cell* 2004, *5*, 417–421.

229. Koblinski, J.E.; Ahram, M.; Sloane, B.F. Unraveling the role of proteases in cancer. *Clin. Chim. Acta* 2000, *291*, 113–135.

230. Kos, J.; Mitrović, A.; Mirković, B. The current stage of cathepsin B inhibitors as potential anticancer agents. *Future Med. Chem.* **2014**, *6*, 1355–1371.

231. Bian, B.; Mongrain, S.; Cagnol, S.; Langlois, M.-J.; Boulanger, J.; Bernatchez, G.; Carrier, J.C.; Boudreau, F.; Rivard, N. Cathepsin B promotes colorectal tumorigenesis, cell invasion, and metastasis. *Mol. Carcinog.* **2016**, *55*, 671–687.

232. Garcia, M.; Platet, N.; Liaudet, E.; Laurent, V.; Derocq, D.; Brouillet, J.P.; Rochefort, H. Biological and clinical significance of cathepsin D in breast cancer metastasis. *Stem Cells* 1996, *14*, 642–650.

233. Lankelma, J.M.; Voorend, D.M.; Barwari, T.; Koetsveld, J.; Van der Spek, A.H.; De Porto, A.P.N.A.; Van Rooijen, G.; Van Noorden, C.J.F. Cathepsin L, target in cancer treatment? *Life Sci.* 2010, *86*, 225–233.

234. Leto, G.; Sepporta, M.V.; Crescimanno, M.; Flandina, C.; Tumminello, F.M. Cathepsin L in metastatic bone disease: Therapeutic implications. *Biol. Chem.* 2010, *391*, 655–664.

235. Fujii, K.; Sivonen, K.; Adachi, K.; Noguchi, K.; Sano, H.; Hirayama, K.; Suzuki, M.; Harada, K. Comparative study of toxic and non-toxic cyanobacterial products: Novel peptides from toxic Nodularia spumigena AV1. *Tetrahedron Lett.* **1997**, *38*, 5525–5528.

236. Anas, A.R.J.; Kisugi, T.; Umezawa, T.; Matsuda, F.; Campitelli, M.R.; Quinn, R.J.; Okino, T. Thrombin Inhibitors from the Freshwater Cyanobacterium *Anabaena compacta*. *J. Nat. Prod.* **2012**, *75*, 1546–1552.

237. Fewer, D.P.; Jokela, J.; Rouhiainen, L.; Wahlsten, M.; Koskenniemi, K.; Stal, L.J.; Sivonen, K. The non-ribosomal assembly and frequent occurrence of the protease inhibitors spumigins in the bloom-forming cyanobacterium *Nodularia spumigena*. *Mol. Microbiol.* **2009**, *73*, 924–937.

238. Gondi, C.S.; Rao, J.S. Cathepsin B as a cancer target. *Expert Opin. Ther. Targets* 2013, *17*, 281–291.

239. Blom, J.F.; Bister, B.; Bischoff, D.; Nicholson, G.; Jung, G.; Süssmuth, R.D.; Jüttner, F. Oscillapeptin J, a new grazer toxin of the freshwater cyanobacterium Planktothrix rubescens. *J. Nat. Prod.* **2003**, *66*, 431–434.

240. Bonjouklian, R.; Smitka, T.A.; Hunt, A.H.; Occolowitz, J.L.; Perun, T.J.; Doolin, L.; Stevenson, S.; Knauss, L.; Wijayaratne, R.; Szewczyk, S.; et al. A90720A, a serine protease inhibitor isolated from a terrestrial blue-green alga Microchaete loktakensis. *Tetrahedron* **1996**, *52*, 395–404.

241. Choi, H.; Oh, S.K.; Yih, W.; Chin, J.; Kang, H.; Rho, J.-R. Cyanopeptoline CB071: a cyclic depsipeptide isolated from the freshwater cyanobacterium Aphanocapsa sp. *Chem. Pharm. Bull. (Tokyo).* **2008**, *56*, 1191–1193.

242. Elkobi-Peer, S.; Carmeli, S. New prenylated aeruginosin, microphycin, anabaenopeptin and micropeptin analogues from a Microcystis bloom material collected in Kibbutz Kfar Blum, Israel. *Mar. Drugs* **2015**, *13*, 2347–2375.

243. Fujii, K.; Sivonen, K.; Naganawa, E.; Harada, K. ichi Non-toxic peptides from toxic cyanobacteria, Oscillatoria agardhii. *Tetrahedron* **2000**, *56*, 725–733.

244. Gallegos, D.A.; Saurí, J.; Cohen, R.D.; Wan, X.; Videau, P.; Vallota-Eastman, A.O.; Shaala, L.A.; Youssef, D.T.A.; Williamson, R.T.; Martin, G.E.; et al. Jizanpeptins, Cyanobacterial Protease Inhibitors from a Symploca sp. Cyanobacterium Collected in the Red Sea. *J. Nat. Prod.* **2018**, *81*, acs.jnatprod.8b00117.

245. Grach-Pogrebinsky, O.; Sedmak, B.; Carmeli, S. Protease inhibitors from a Slovenian Lake Bled toxic waterbloom of the cyanobacterium Planktothrix rubescens. *Tetrahedron* **2003**, *59*, 8329–8336.

246. Gunasekera, S.P.; Miller, M.W.; Kwan, J.C.; Luesch, H.; Paul, V.J. Molassamide, a depsipeptide serine protease inhibitor from the marine cyanobacterium Dichothrix utahensis. *J. Nat. Prod.* **2010**, *73*, 459–462.

247. Harada, K.I.; Mayumi, T.; Shimada, T.; Fujii, K.; Kondo, F.; Park, H.D.; Watanabe, M.F. Co-production of microcystins and aeruginopeptins by natural cyanobacterial bloom. *Environ. Toxicol.* **2001**, *16*, 298–305.

248. Ishida, K.; Matsuda, H.; Murakami, M.; Yamaguchi, K. Micropeptins 478-A and -B, plasmin inhibitors from the cyanobacterium Microcystis aeruginosa. *J. Nat. Prod.* **1997**, *60*, 184–187.

249. Ishida, K.; Matsuda, H.; Murakami, M. Micropeptins 88-A to 88-F, chymotrypsin inhibitors from the cyanobacterium Microcystis aeruginosa (NIES-88). *Tetrahedron* **1998**, *54*, 5545–5556.

250. Ishida, K.; Murakami, M.; Matsuda, H.; Yamaguchi, K. Micropeptin 90, a plasmin and trypsin

inhibitor from the blue-green alga Microcystis aeruginosa (NIES-90). *Tetrahedron Lett.* **1995**, *36*, 3535–3538.

251. Itou, Y.; Ishida, K.; Shin, H.J.; Murakami, M. Oscillapeptins A to F, serine protease inhibitors from the three strains of Oscillatoria agardhii. *Tetrahedron* **1999**, *55*, 6871–6882.

252. Jakobi, C.; Oberer, L.; Quiquerez, C.; König, W.A.; Weckesser, J. Cyanopeptolin S, a sulfate-containing depsipeptide from a water bloom of Microcystis sp. *FEMS Microbiol. Lett.* **1995**, *129*, 129–133.

253. Kang, H.S.; Krunic, A.; Orjala, J. Stigonemapeptin, an Ahp-containing depsipeptide with elastase inhibitory activity from the bloom-forming freshwater cyanobacterium Stigonema sp. *J. Nat. Prod.* **2012**, *75*, 807–811.

254. Kaya, K.; Sano, T.; Beattie, K.A.; Codd, G.A. Nostocyclin, a novel 3-amino-6-hydroxy-2-piperidone-containing cyclic depsipeptide from the cyanobacterium Nostoc sp. *Tetrahedron Lett.* **1996**, *37*, 6725–6728.

255. Kodani, S.; Suzuki, S.; Ishida, K.; Murakami, M. Five new cyanobacterial peptides from water bloom materials of lake Teganuma (Japan). *FEMS Microbiol. Lett.* **1999**, *178*, 343–348.

256. Kwan, J.C.; Taori, K.; Paul, V.J.; Luesch, H. Lyngbyastatins 8-10, elastase inhibitors with cyclic depsipeptide scaffolds isolated from the marine cyanobacterium Lyngbya semiplena. *Mar. Drugs* **2009**, *7*, 528–538.

257. Lifshits, M.; Zafrir-Ilan, E.; Raveh, A.; Carmeli, S. Protease inhibitors from three fishpond water blooms of Microcystis spp. *Tetrahedron* **2011**, *67*, 4017–4024.

258. Linington, R.G.; Edwards, D.J.; Shuman, C.F.; McPhail, K.L.; Matainaho, T.; Gerwick, W.H. Symplocamide A, a potent cytotoxin and chymotrypsin inhibitor from the marine cyanobacterium Symploca sp. *J. Nat. Prod.* **2008**, *71*, 22–27.

259. Lodin-Friedman, A.; Carmeli, S. Metabolites from microcystis aeruginosa bloom material collected at a water reservoir near Kibbutz Hafetz Haim, Israel. *J. Nat. Prod.* **2013**, *76*, 1196–1200.

260. Martin, C.; Oberer, L.; Buschdtt, M.; Weckesser, J. Cyanopeptolins, new depsipeptides from the cyanobacterium Microcystis sp. PCC 7806. *J. Antibiot.* **1993**, *46*, 1550–56.

261. Matern, U.; Oberer, L.; Falchetto, R.A.; Erhard, M.; König, W.A.; Herdman, M.; Weckesser, J. Scyptolin A and B, cyclic depsipeptides from axenic cultures of Scytonema hofmanni PCC 7110. *Phytochemistry* **2001**, *58*, 1087–1095.

262. Matern, U.; Oberer, L.; Erhard, M.; Herdmand, M.; Weckesser, J. Hofmannolin, a cyanopeptolin from Scytonema hofmanni PCC 7110. *Phytochemistry* **2003**, *64*, 1061–1067.

263. Matthew, S.; Ross, C.; Paul, V.J.; Luesch, H. Pompanopeptins A and B, new cyclic peptides

from the marine cyanobacterium Lyngbya confervoides. *Tetrahedron* **2008**, *64*, 4081–4089.

264. Taori, K.; Matthew, S.; Rocca, J.R.; Paul, V.J.; Luesch, H. Lyngbyastatins 5-7, potent elastase inhibitors from Floridian marine cyanobacteria, Lyngbya spp. *J. Nat. Prod.* **2007**, *70*, 1593–1600.

265. Mehner, C.; Müller, D.; Kehraus, S.; Hautmann, S.; Gütschow, M.; König, G.M. New Peptolides from the Cyanobacterium Nostoc insulare as Selective and Potent Inhibitors of Human Leukocyte Elastase. *ChemBioChem* **2008**, *9*, 2692–2703.

266. Murakami, M.; Kodani, S.; Ishida, K.; Matsuda, H.; Yamaguchi, K. Micropeptin 103, a chymotrypsin inhibitor from the cyanobacterium Microcystis viridis (NIES-103). *Tetrahedron Lett.* **1997**, *38*, 3035–3038.

267. Okano, T.; Sano, T.; Kaya, K. Micropeptin T-20, a novel phosphate-containing cyclic depsipeptide from the cyanobacterium Microcystis aeruginosa. *Tetrahedron Lett.* **1999**, *40*, 2379–2382.

268. Okino, T.; Murakami, M.; Haraguchi, R.; Munekata, H.; Matsuda, H.; Yamaguchi, K. Micropeptins A and B, plasmin and trypsin inhibitors from the blue-green alga Microcystis aeruginosa. *Tetrahedron Lett.* **1993**, *34*, 8131–8134.

269. Okino, T.; Qi, S.; Matsuda, H.; Murakami, M.; Yamaguchi, K. Nostopeptins A and B, elastase inhibitors from the cyanobacterium Nostoc minutum. *J. Nat. Prod.* **1997**, *60*, 158–161.

270. Okumura, H.S.; Philmus, B.; Portmann, C.; Hemscheidt, T.K. Homotyrosine-containing cyanopeptolins 880 and 960 and anabaenopeptins 908 and 915 from Planktothrix agardhii CYA 126/8. *J. Nat. Prod.* **2009**, *72*, 172–176.

271. Ploutno, A.; Carmeli, S. Modified peptides from a water bloom of the cyanobacterium Nostoc sp. *Tetrahedron* **2002**, *58*, 9949–9957.

272. Ploutno, A.; Shoshan, M.; Carmeli, S. Three novel protease inhibitors from a natural bloom of the cyanobacterium Microcystis aeruginosa. *J. Nat. Prod.* **2002**, *65*, 973–978.

273. Reshef, V.; Carmeli, S. Protease inhibitors from a water bloom of the cyanobacterium Microcystis aeruginosa. *Tetrahedron* **2001**, *57*, 2885–2894.

274. Sano, T.; Kaya, K. Oscillamide-Y, a Chymotrypsin Inhibitor from Toxic Oscillatoria-Agardhii. *Tetrahedron Lett.* 1995, *36*, 5933–5936.

275. Sano, T.; Kaya, K. Oscillapeptin G, a tyrosinase inhibitor from toxic Oscillatoria agardhii. *J. Nat. Prod.* **1996**, *59*, 90–92.

276. Shin, H.J.; Murakami, M.; Matsuda, H.; Ishida, K.; Yamaguchi, K. Oscillapeptin, an elastase and chymotrypsin inhibitor from the cyanobacterium Oscillatoria agardhii (NIES-204). *Tetrahedron Lett.* **1995**, *36*, 5235–5238.

277. Stolze, S.C.; Deu, E.; Kaschani, F.; Li, N.; Florea, B.I.; Richau, K.H.; Colby, T.; Van Der Hoorn, R.A.L.; Overkleeft, H.S.; Bogyo, M.; et al. The antimalarial natural product symplostatin 4 is a nanomolar inhibitor of the food vacuole falcipains. *Chem. Biol.* **2012**, *19*, 1546–1555.

278. Taori, K.; Paul, V.J.; Luesch, H. Kempopeptins A and B, serine protease inhibitors with different selectivity profiles from a marine cyanobacterium, Lyngbya sp. *J. Nat. Prod.* **2008**, *71*, 1625–1629.

279. Thorskov Bladt, T.; Kalifa-Aviv, S.; Ostenfeld Larsen, T.; Carmeli, S. Micropeptins from Microcystis sp. collected in Kabul Reservoir, Israel. *Tetrahedron* **2014**, *70*, 936–943.

280. Tsukamoto, S.; Painuly, P.; Young, K.A.; Yang, X.; Shimizu, Y.; Cornell, L. *Journal of the American Chemical Society*. American Chemical Society November 1993, pp. 11046–11047.

281. Vegman, M.; Carmeli, S. Eight micropeptins from a Microcystis spp. bloom collected from a fishpond near Kibbutz Lehavot HaBashan, Israel. *Tetrahedron* **2013**, *69*, 10108–10115.

282. Von Elert, E.; Oberer, L.; Merkel, P.; Huhn, T.; Blom, J.F. Cyanopeptolin 954, a chlorine-containing chymotrypsin inhibitor of Microcystis aeruginosa NIVA Cya 43. *J. Nat. Prod.* **2005**, *68*, 1324–1327.

283. Zafrir-Ilan, E.; Carmeli, S. Eight novel serine proteases inhibitors from a water bloom of the cyanobacterium Microcystis sp. *Tetrahedron* **2010**, *66*, 9194–9202.

284. Fujii, K.; Sivonen, K.; Nakano, T.; Harada, K.I. Structural elucidation of cyanobacterial peptides encoded by peptide synthetase gene in Anabaena species. *Tetrahedron* **2002**, *58*, 6863–6871.

285. Adiv, S.; Ahronov-Nadborny, R.; Carmeli, S. New aeruginazoles, a group of thiazole-containing cyclic peptides from Microcystis aeruginosa blooms. *Tetrahedron* **2012**, *68*, 1376–1383.

286. Al-Awadhi, F.H.; Salvador, L.A.; Law, B.K.; Paul, V.J.; Luesch, H. Kempopeptin C, a novel marine-derived serine protease inhibitor targeting invasive breast cancer. *Mar. Drugs* **2017**, *15*, 290.

287. Banker, R.; Carmeli, S. Inhibitors of serine proteases from a waterbloom of the cyanobacterium Microcystis sp. *Tetrahedron* **1999**, *55*, 10835–10844.

288. Beresovsky, D.; Hadas, O.; Livne, A.; Sukenik, A.; Kaplan, A.; Carmeli, S. Toxins and Biologically Active Secondary Metabolites of Microcystis sp. isolated from Lake Kinneret. *Isr. J. Chem.* **2006**, *46*, 79–87.

289. Pereira, A.R.; Kale, A.J.; Fenley, A.T.; Byrum, T.; Debonsi, H.M.; Gilson, M.K.; Valeriote, F.A.; Moore, B.S.; Gerwick, W.H. The Carmaphycins: New Proteasome Inhibitors Exhibiting an α,β-Epoxyketone Warhead from a Marine Cyanobacterium. *ChemBioChem* **2012**, *13*, 810–817.

290. LaMonte, G.M.; Almaliti, J.; Bibo-Verdugo, B.; Keller, L.; Zou, B.Y.; Yang, J.; Antonova-Koch, Y.; Orjuela-Sanchez, P.; Boyle, C.A.; Vigil, E.; et al. Development of a Potent Inhibitor of the Plasmodium Proteasome with Reduced Mammalian Toxicity. *J. Med. Chem.* **2017**, *60*, 6721–6732.

291. Hirota, M.; Ohmuraya, M.; Baba, H. The role of trypsin, trypsin inhibitor, and trypsin receptor in the onset and aggravation of pancreatitis. *J. Gastroenterol.* 2006, *41*, 832–836.

292. Hilpert, K.; Ackermann, J.; Banner, D.W.; Gast, A.; Gubernator, K.; Hadvary, P.; Labler, L.; Mueller, K.; Schmid, G. Design and Synthesis of Potent and Highly Selective Thrombin Inhibitors. *J. Med. Chem.* **1994**, *37*, 3889–3901.

293. Krunic, 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 hofmanii. *J. Nat. Prod.* **2010**, *73*, 1927–1932.

294. Shim, S.H.; Chlipala, G.; Orjala, J. Isolation and structure determination of a proteasome inhibitory metabolite from a culture of Scytonema hofmanni. *J. Microbiol. Biotechnol.* **2008**, *18*, 1655–1658.

295. Almaliti, J.; Miller, B.; Pietraszkiewicz, H.; Glukhov, E.; Naman, C.B.; Kline, T.; Hanson, J.; Li, X.; Zhou, S.; Valeriote, F.A.; et al. Exploration of the carmaphycins as payloads in antibody drug conjugate anticancer agents. *Eur. J. Med. Chem.* **2018**, *161*, 416–432.

296. Salvador-Reyes, L.A.; Luesch, H. Biological targets and mechanisms of action of natural products from marine cyanobacteria. *Nat. Prod. Rep.* 2015, *32*, 478–503.

297. Bolden, J.E.; Peart, M.J.; Johnstone, R.W. Anticancer activities of histone deacetylase inhibitors. *Nat. Rev. Drug Discov.* 2006, *5*, 769–784.

298. Taori, K.; Paul, V.J.; Luesch, H. Structure and activity of largazole, a potent antiproliferative agent from the Floridian marine cyanobacterium Symploca sp. *J. Am. Chem. Soc.* **2008**, *130*, 1806–1807.

299. Liu, Y.; Salvador, L.A.; Byeon, S.; Ying, Y.; Kwan, J.C.; Law, B.K.; Hong, J.; Luesch, H. Anticolon Cancer Activity of Largazole, a Marine-Derived Tunable Histone Deacetylase Inhibitor. *J. Pharmacol. Exp. Ther.* **2010**, *335*, 351–361.

300. Wu, L.C.; Wen, Z.S.; Qiu, Y.T.; Chen, X.Q.; Chen, H. Bin; Wei, M.M.; Liu, Z.; Jiang, S.; Zhou, G.B. Largazole arrests cell cycle at g1 phase and triggers proteasomal degradation of E2F1 in lung cancer cells. *ACS Med. Chem. Lett.* **2013**, *4*, 921–926.

301. Zhou, H.; Jiang, S.; Chen, J.; Ren, X.; Jin, J.; Su, S.B. Largazole, an inhibitor of class i histone deacetylases, attenuates inflammatory corneal neovascularization. *Eur. J. Pharmacol.* **2014**, *740*, 619–626.

302. Poli, G.; Di Fabio, R.; Ferrante, L.; Summa, V.; Botta, M. Largazole Analogues as Histone

Deacetylase Inhibitors and Anticancer Agents: An Overview of Structure–Activity Relationships. *ChemMedChem* 2017, *12*, 1917–1926.

303. Ungermannova, D.; Parker, S.J.; Nasveschuk, C.G.; Wang, W.; Quade, B.; Zhang, G.; Kuchta, R.D.; Phillips, A.J.; Liu, X. Largazole and its derivatives selectively inhibit ubiquitin activating enzyme (E1). *PLoS One* **2012**, *7*, e29208.

304. Pavlik, C.M.; Wong, C.Y.B.; Ononye, S.; Lopez, D.D.; Engene, N.; McPhail, K.L.; Gerwick, W.H.; Balunas, M.J. Santacruzamate A, a potent and selective histone deacetylase inhibitor from the panamanian marine cyanobacterium cf. symploca sp. *J. Nat. Prod.* **2013**, *76*, 2026–2033.

305. Hanke, T.; Merk, D.; Steinhilber, D.; Geisslinger, G.; Schubert-Zsilavecz, M. Small molecules with anti-inflammatory properties in clinical development. *Pharmacol. Ther.* **2016**, *157*, 163–187.

306. Ridker, P.M.; Lüscher, T.F. Anti-inflammatory therapies for cardiovascular disease. *Eur. Heart J.* 2014, *35*, 1782–1791.

307. Rocha, N.P.; De Miranda, A.S.; Teixeira, A.L. Insights into neuroinflammation in Parkinson's disease: From biomarkers to anti-inflammatory based therapies. *Biomed Res. Int.* 2015, *2015*, 1–12.

308. Malloy, K.L.; Villa, F.A.; Engene, N.; Matainaho, T.; Gerwick, L.; Gerwick, W.H. Malyngamide 2, an oxidized lipopeptide with nitric oxide inhibiting activity from a Papua New Guinea marine cyanobacterium. *J. Nat. Prod.* **2011**, *74*, 95–98.

309. Stevenson, C.S.; Capper, E.A.; Roshak, A.K.; Marquez, B.; Grace, K.; Gerwick, W.H.; Jacobs, R.S.; Marshall, L.A. Scytonemin-a marine natural product inhibitor of kinases key in hyperproliferative inflammatory diseases. *Inflamm. res* **2002**, *51*, 112–114.

310. Ishida, K.; Okita, Y.; Matsuda, H.; Okino, T.; Murakami, M. Aeruginosins, protease inhibitors from the cyanobacterium Microcystis aeruginosa. *Tetrahedron* **1999**, *55*, 10971–10988.

311. Ishida, K.; Christiansen, G.; Yoshida, W.Y.; Kurmayer, R.; Welker, M.; Valls, N.; Bonjoch, J.; Hertweck, C.; Börner, T.; Hemscheidt, T.; et al. Biosynthesis and Structure of Aeruginoside 126A and 126B, Cyanobacterial Peptide Glycosides Bearing a 2-Carboxy-6-Hydroxyoctahydroindole Moiety. *Chem. Biol.* **2007**, *14*, 565–576.

312. Padrines, M.; Wolf, M.; Walz, A.; Baggiolini, M. Interleukin-8 processing by neutrophil elastase, cathepsin G and proteinase-3. *FEBS Lett.* **1994**, *352*, 231–235.

313. Wiedow, O.; Meyer-Hoffert, U. Neutrophil serine proteases: Potential key regulators of cell signalling during inflammation. *J. Intern. Med.* 2005, *257*, 319–328.

314. Pham, C.T.N. Neutrophil serine proteases: Specific regulators of inflammation. *Nat. Rev. Immunol.* 2006, *6*, 541–550.

315. Matsuda, H.; Okino, T.; Murakami, M.; Yamaguchi, K. Aeruginosins 102-A and B, New Thrombin Inhibitors from the Cyanobacterium Microcystis viridis (NIES-102). *Tetrahedron* **1996**, *96*.

316. Benedetti, S.; Benvenuti, F.; Pagliarani, S.; Francogli, S.; Scoglio, S.; Canestrari, F. Antioxidant properties of a novel phycocyanin extract from the blue-green alga Aphanizomenon flos-aquae. *Life Sci.* **2004**, *75*, 2353–2362.

317. Kuddus, M.; Singh, P.; Thomas, G.; Al-Hazimi, A. Recent developments in production and biotechnological applications of c-phycocyanin. *Biomed Res. Int.* 2013, *2013*, 742859.

318. Patel, A.; Mishra, S.; Ghosh, P.K. Antioxidant potential of C-phycocyanin isolated from cyanobacterial species Lyngbya, Phormidium and Spirulina spp. *Indian J. Biochem. Biophys.* **2006**, *43*, 25–31.

319. Garcia-Pichel, F.; Castenholz, R.W. Characterization and biological implications of scytonemin, a cyanobacterial sheath pigment. *J. Phycol.* **1991**, *27*, 395–409.

320. Proteau, P.J.; Gerwick, W.H.; Garcia-Pichel, F.; Castenholz, R. The structure of scytonemin, an ultraviolet sunscreen pigment from the sheaths of cyanobacteria. *Experientia* **1993**, *49*, 825–829.

321. Soule, T.; Stout, V.; Swingley, W.D.; Meeks, J.C.; Garcia-Pichel, F. Molecular genetics and genomic analysis of scytonemin biosynthesis in Nostoc punctiforme ATCC 29133. *J. Bacteriol.* **2007**, *189*, 4465–72.

322. Stevenson, C.S.; Capper, E.A.; Roshak, A.M.Y.K.; Marquez, B.; Eichman, C.; Jackson, J.R.; Mattern, M.; Gerwick, W.H.; Jacobs, R.S.; Marshall, L.A. The identification and characterization of the marine natural product scytonemin as a novel antiproliferative pharmacophore. *J. Pharmacol. Exp. Ther.* **2002**, *303*, 858–866.

323. Dubois, R.N.; Abramson, S.B.; Crofford, L.; Gupta, R.A.; Simon, L.S.; Van De Putte, L.B.; Lipsky, P.E. Cyclooxygenase in biology and disease. *FASEB J.* **1998**, *12*, 1063–1073.

324. Patrignani, P.; Patrono, C. Cyclooxygenase inhibitors: From pharmacology to clinical read-outs. *Biochim. Biophys. Acta - Mol. Cell Biol. Lipids* 2015, *1851*, 422–432.

325. Vane, J.R.; Botting, R.M. Anti-inflammatory drugs and their mechanism of action. *Inflamm. Res.* **1998**, *47*, 78–87.

326. Uttara, B.; Singh, A. V; Zamboni, P.; Mahajan, R.T. Oxidative stress and neurodegenerative diseases: a review of upstream and downstream antioxidant therapeutic options. *Curr. Neuropharmacol.* **2009**, *7*, 65–74.

327. Kim, G.H.; Kim, J.E.; Rhie, S.J.; Yoon, S. The Role of Oxidative Stress in Neurodegenerative Diseases. *Exp. Neurobiol.* **2015**, *24*, 325.

328. Rani, V.; Deep, G.; Singh, R.K.; Palle, K.; Yadav, U.C.S. Oxidative stress and metabolic

disorders: Pathogenesis and therapeutic strategies. *Life Sci.* 2016, *148*, 183–193.

329. Baradaran, A.; Nasri, H.; Rafieian-Kopaei, M. Oxidative stress and hypertension: Possibility of hypertension therapy with antioxidants. *J. Res. Med. Sci.* **2014**, *19*, 358–67.

330. Li, S.; Tan, H.Y.; Wang, N.; Zhang, Z.J.; Lao, L.; Wong, C.W.; Feng, Y. The role of oxidative stress and antioxidants in liver diseases. *Int. J. Mol. Sci.* 2015, *16*, 26087–26124.

331. Siti, H.N.; Kamisah, Y.; Kamsiah, J. The role of oxidative stress, antioxidants and vascular inflammation in cardiovascular disease (a review). *Vascul. Pharmacol.* 2015, *71*, 40–56.

332. Wada, N.; Sakamoto, T.; Matsugo, S. Multiple roles of photosynthetic and sunscreen pigments in cyanobacteria focusing on the oxidative stress. *Metabolites* 2013, *3*, 463–483.

333. Hirschberg, J.; Chamovitz, D. Carotenoids in Cyanobacteria BT - The Molecular Biology of Cyanobacteria. In *The Molecular Biology of Cyanobacteria*; Springer Netherlands: Dordrecht, 1994; pp. 559–579 ISBN 978-94-011-0227-8.

334. Balskus, E.P.; Walsh, C.T. The genetic and molecular basis for sunscreen biosynthesis in cyanobacteria. *Science* **2010**, *329*, 1653–6.

335. Waditee-Sirisattha, R.; Kageyama, H.; Sopun, W.; Tanaka, Y.; Takabe, T. Identification and upregulation of biosynthetic genes required for accumulation of Mycosporine-2-glycine under salt stress conditions in the halotolerant cyanobacterium Aphanothece halophytica. *Appl. Environ. Microbiol.* **2014**, *80*, 1763–9.

336. Kosourov, S.; Murukesan, G.; Jokela, J.; Allahverdiyeva, Y. Carotenoid biosynthesis in calothrix sp. 336/3: Composition of carotenoids on full medium, during diazotrophic growth and after long-term H2photoproduction. *Plant Cell Physiol.* **2016**, *57*, 2269–2282.

337. Al-Awadhi, F.H.; Law, B.K.; Paul, V.J.; Luesch, H. Grassystatins D-F, Potent Aspartic Protease Inhibitors from Marine Cyanobacteria as Potential Antimetastatic Agents Targeting Invasive Breast Cancer. *J. Nat. Prod.* **2017**, *80*, 2969–2986.

338. Al-Awadhi, F.H.; Ratnayake, R.; Paul, V.J.; Luesch, H. Tasiamide F, a potent inhibitor of cathepsins D and E from a marine cyanobacterium. *Bioorganic Med. Chem.* **2016**, *24*, 3276–3282.

339. Kwan, J.C.; Eksioglu, E.A.; Liu, C.; Paul, V.J.; Luesch, H. Grassystatins A-C from marine cyanobacteria, potent cathepsin E inhibitors that reduce antigen presentation. *J. Med. Chem.* **2009**, *52*, 5732–5747.

340. Molinski, T.F.; Reynolds, K.A.; Morinaka, B.I. Symplocin A, a linear peptide from the bahamian cyanobacterium symploca sp. configurational analysis of N, N -dimethylamino acids by chiral-phase HPLC of naphthacyl esters. *J. Nat. Prod.* **2012**, *75*, 425–431.

341. Williams, P.G.; Yoshida, W.Y.; Moore, R.E.; Paul, V.J. Tasiamide, a cytotoxic peptide from the marine cyanobacterium Symploca sp. *J. Nat. Prod.* **2002**, *65*, 1336–1339.

342. Williams, P.G.; Yoshida, W.Y.; Moore, R.E.; Paul, V.J. The isolation and structure elucidation of tasiamide B, a 4-amino-3-hydroxy-5-phenylpentanoic acid containing peptide from the marine cyanobacterium Symploca sp. *J. Nat. Prod.* **2003**, *66*, 1006–1009.

343. Mevers, E.; Haeckl, F.P.J.; Boudreau, P.D.; Byrum, T.; Dorrestein, P.C.; Valeriote, F.A.; Gerwick, W.H. Lipopeptides from the tropical marine cyanobacterium symploca sp. *J. Nat. Prod.* **2014**, *77*, 969–975.

344. Yamamoto, K.; Okamoto, K.; Tsukuba, T. Cathepsin E: An Aspartic Protease with Diverse Functions and Biomedical Implications. In *Encyclopedia of Cell Biology*; Academic Press, 2015; Vol. 1, pp. 681–690 ISBN 9780123944474.

345. Vassar, R.; Bennett, B.D.; Babu-Khan, S.; Kahn, S.; Mendiaz, E.A.; Denis, P.; Teplow, D.B.; Ross, S.; Amarante, P.; Loeloff, R.; et al. β-Secretase cleavage of Alzheimer's amyloid precursor protein by the transmembrane aspartic protease BACE. *Science (80-.).* **1999**, *286*, 735–741.

346. Sitachitta, N.; Gerwick, W.H. Grenadadiene and grenadamide, cyclopropyl-containing fatty acid metabolites from the marine cyanobacterium Lyngbya majuscula. *J. Nat. Prod.* **1998**, *61*, 681–684.

347. Han, B.; McPhail, K.L.; Ligresti, A.; Di Marzo, V.; Gerwick, W.H. Semiplenamides A-G, Fatty Acid Amides from a Papua New Guinea Collection of the Marine Cyanobacterium Lyngbya semiplena. *J. Nat. Prod.* **2003**, *66*, 1364–1368.

348. Gutiérrez, M.; Pereira, A.R.; Debonsi, H.M.; Ligresti, A.; Di Marzo, V.; Gerwick, W.H. Cannabinomimetic lipid from a marine cyanobacterium. *J. Nat. Prod.* **2011**, *74*, 2313–7.

349. Mevers, E.; Matainaho, T.; Allara', M.; Di Marzo, V.; Gerwick, W.H. Mooreamide A: A cannabinomimetic lipid from the marine cyanobacterium Moorea bouillonii. *Lipids* **2014**, *49*, 1127–1132.

350. Kleigrewe, K.; Almaliti, J.; Tian, I.Y.; Kinnel, R.B.; Korobeynikov, A.; Monroe, E.A.; Duggan, B.M.; Di Marzo, V.; Sherman, D.H.; Dorrestein, P.C.; et al. Combining Mass Spectrometric Metabolic Profiling with Genomic Analysis: A Powerful Approach for Discovering Natural Products from Cyanobacteria. *J. Nat. Prod.* **2015**, *78*, 1671–82.

351. Aizpurua-Olaizola, O.; Elezgarai, I.; Rico-Barrio, I.; Zarandona, I.; Etxebarria, N.; Usobiaga, A. Targeting the endocannabinoid system: future therapeutic strategies. *Drug Discov. Today* 2017, *22*, 105–110.

352. Patel, S.; Hill, M.N.; Cheer, J.F.; Wotjak, C.T.; Holmes, A. The endocannabinoid system as a target for novel anxiolytic drugs. *Neurosci. Biobehav. Rev.* 2017, *76*, 56–66.

353. Gaulton, A.; Hersey, A.; Nowotka, M.L.; Patricia Bento, A.; Chambers, J.; Mendez, D.; Mutowo, P.; Atkinson, F.; Bellis, L.J.; Cibrian-Uhalte, E.; et al. The ChEMBL database in 2017. *Nucleic Acids Res.* **2017**, *45*, D945–D954.