Anabaenopeptins

Subjects: Toxicology

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Anabaenopeptins (APs) are structurally diverse peptides widely distributed in distinct ecosystems among cyanobacteria. Some structural features of these molecules are shared with other cyanotoxins, such as the presence of modified residues, exocyclic amino acids, circular structure, and amino acids in D-configuration. However, among the cyanopeptides, the ureido linkage is exclusively found in APs. Thus, these cyclic peptides demonstrate toxicity and structural diversity which will be explored in this topic, including biotechnological and ecological relevance, and their distribution.

Keywords: cyanobacteria ; peptide ; NRPS ; anabaenopeptin

1. Introduction

Cyanobacteria are photosynthetic microorganisms widely distributed in the world. They can inhabit several types of ecosystems, including aquatic and terrestrial. These microorganisms produce a great variety of bioactive compounds, which have been investigated mainly due to their biotechnological potential and environmental relevance [1][2][3]. Cyanotoxins are among the most studied compounds originated from cyanobacteria since they are capable of negatively affecting human and animal health [4][5]. These metabolites can vary drastically concerning their action mechanism and chemical structure, which include peptides, alkaloids, and lipopolysaccharides [6][7][8]. The majority of publications related to peptides from cyanobacteria have mainly focused on the class of microcystins with over 300 characterized variants [9][10]. However, cyanobacteria usually do not exclusively produce a single class of compounds, given that specific strains are co-producing different groups of secondary metabolites [11].

Other peptides beyond microcystins have been poorly explored, lacking information mainly in the environmental sciences [11]. These several metabolites are known for their potent inhibitory properties against several enzymes in nanomolar concentrations, resulting in toxic effects [12][13]. Moreover, similar to microcystins, they have been regularly detected in diverse environments [14]. In certain regions, their occurrence is more pronounceable than microcystins themselves [15]. However, information about the concentrations which are encountered is rarely reported [11]. Cyanobacteria have developed different peptides as a protection mechanism against parasites [16]. Concerning their origin, some peptides as microviridins and cyanobactins are produced via ribosomal whereas others as microginins and aeruginosins are synthesized by non-ribosomal pathways [13][17][18].

Among the most recurrent peptides encountered in the environment are anabaenopeptins (APs), a family of cyclic peptides containing six amino acid residues [19]. They have been found in an enormous variety of cyanobacteria isolated from both the aquatic and terrestrial environments, including *Anabaena* , *Nostoc* , *Microcystis* , *Planktothrix* , *Lyngbya*, and *Brasilonema* [12][20][21][22][23][24]. In their general structure is a well-conserved Lysine (Lys) residue in D-configuration, which is responsible for the ring formation and five additional variable amino acids, either proteinogenic or non-proteinogenic, resulting in 124 described AP variants from cyanobacteria (Supplementary Table 1) [19]. Besides their structural variety, molecules belonged to this group exhibit an impressive functional diversity, which includes inhibitory activity for proteases, phosphatases, and carboxypeptidases [22][25][26].

The enormous structural diversification of anabaenopeptins can be attributed to the low substrate specificity of some enzymes involved in their synthesis as well as the presence of alternative starter modules [16]. Their production is strongly influenced by environmental factors [27]. Besides that, because of their diversified bioactive properties, they exhibit an elevated biotechnological potential. This review aims at presenting the main researches on anabaenopeptins, emphasizing their general characteristics, biosynthesis as well as ecological and biotechnological relevance.

2. Structures of Anabaenopeptins

Being non-ribosomally synthesized, anabaenopeptin structures comprise a ring of five amino acids connected through an ureido linkage to an exocyclic amino acid. Thus, its general structure is represented by X 1-CO-[Lys 2-X 3-X 4-MeX 5-X 6], where the bracket represents the cyclic region of this peptide and X are variable amino acids according to their positions represented by the superscript numbers (**Figure 1**). Its ring is formed by cyclization of the C-terminal carboxyl of the amino acid at position 6 to the ε-NH 3 of the well-conserved D-lysine at position 2. Furthermore, the α-amino group of Lys is connected to the exocyclic amino acid X 1 via an ureido bridge. Due to its non-ribosomal nature, proteinogenic and non-proteinogenic amino acids are usually detected in this hexapeptide [19].

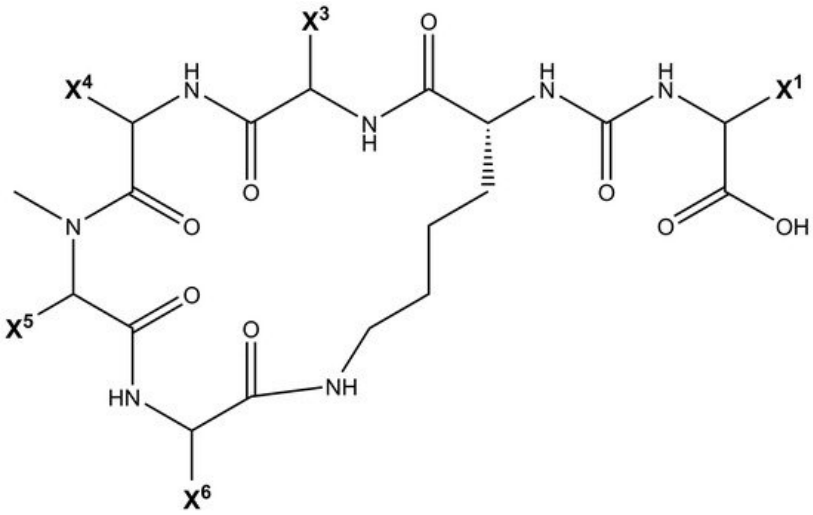

Figure 1. The general structure of the class of Anabaenopeptins. X corresponds to different amino acids in their respective positions represented by the superscript numbers.

Some of those conserved features from APs can also be visualized in other cyanopeptides. Veraguamides A-G are cyclic hexadepsipeptides, and they do not possess any exocyclic residue. Lyngbyastatin peptides demonstrate elastase, trypsin, and chymotrypsin inhibitory properties. Their structures consist of a 6-member ring coupled to a chain of 2 exocyclic residues and can bear modified and unusual residues. Also possessing a 6-member ring structure and 2 exocyclic amino acids, Tiglicamides A-C were obtained from Lyngbya confervoides [28].

Cyanopeptolins are depsipeptides containing a 6-amino acid ring bearing a side chain with 1–2 residues and modified residues, such as 3-amino-6-hydroxy-2-piperidone. Cyanopeptolin A is one example of this class of cyanopeptides and is composed by (1)-fatty acid, (2)-Arg, (3)-Ahp, (4)-Leu, (5)-methyl-Phe, (6)-Val, and (7)-Thr, in this case, the β-lacton ring is formed between Arg and Thr residues and positions 2, 4, 5 and 6 are variable. Using Anabaenopeptin A as reference (**Figure 2**), its structure is (1)-Tyr, (2)-D-Lys, (3)-Valine, (4)-Homotyrosine, (5)N-methyl-Alanine, (6)-Phenylalanine [29]. Positions 1, 3, 4, 5, and 6 are variable concerning APs (**Figure 1**) and the ureido bond is formed between 1 and 2 residues. Aerucyclamides are entirely cyclic peptides, Aerucyclamide A is composed by (1)-dehydro-Thr, (2)-Gly, (3)-thiozole, (4)-Ile, (5)-dhCys, and (6)-Ile, in this case, variations were reported in positions 2, 3, 4 and 6. Different from the cyanopeptides listed until now, Aeruginosins and Microginins are linear peptides. Aeruginosin KB 676 is formed by (1)-Hpla, (2)-Ile, (3)-Choi and (4)-Arg, only position 2 presents variation with amino acid substitution, and radical changes occur in positions 3 and 4. Finally, Microginin 713 is formed by (1)-Ahda, (2)-Ala, (3)-Val, (4)-N-methyl-Tyr, and (5)-Tyr, in this case, positions 2, 3, 4, and 5 had substitutions reported [11].

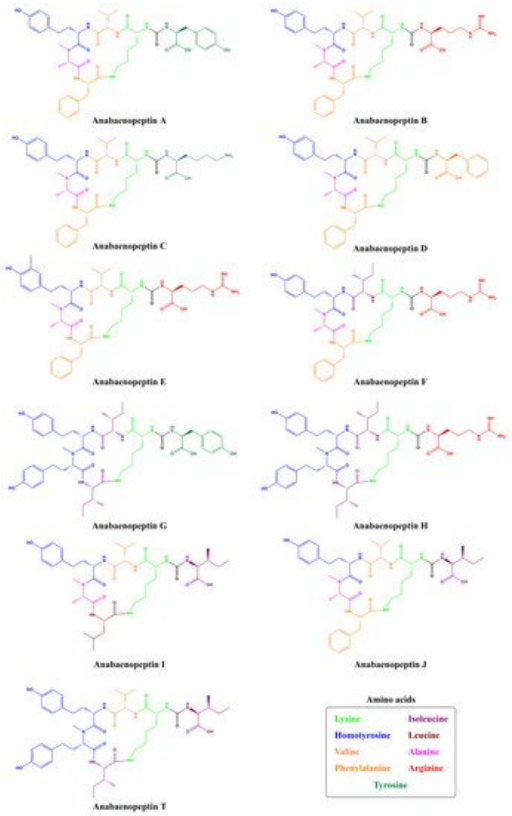

Figure 2. Structures of anabaenopeptins A–J [20][26][30][31][32] and T [33].

Structurally, despite the major amino acid variability, Microcystins, Cyanopeptolins, and Anabaenopeptins are most similar. Microcystins and Cyanopeptolins are heptapeptides and Anabaenopeptins are hexapeptides and comparting these structures, it is possible to distinguish a ring core and a linear region. Although Microcystins are technically cyclic peptides, the Adda moiety projected outside the ring may act like the fatty acid in Cyanopeptolin A or Tyrosine in Anabaenopeptin A. The Adda moiety is crucial for MCs inhibition towards phosphatases, as its long linear chain can penetrate the enzyme active site together with other side chains, having a similar role as the exocyclic residue of APs (Tyrosine from Anabaenopeptin A), as it will be further discussed in Section 7 [11][34]. This exocyclic or even protuberant residue was not observed in Aerucyclamides that only present a cyclic structure or Aeruginosins and Microginins, which are linear structures [11]. Therefore, cyclic peptides bearing exocyclic residues and unusual and D-configuration amino acids are also found in cyanobacteria, however, the ureido linkage in cyanopeptides is, so far, an exclusive characteristic of Anabaenopeptins.

3. Occurrence of Anabaenopeptins and factors involved in their expression

A total of 45, 29, and 12 cyanobacteria strains from freshwater, marine and terrestrial environment have been analyzed for AP production, respectively. As seen in **Table 1** and according to the literature [35][36][33][37][38][39][40][41][42][43][44][45][46][47], marine strains produced a total of 50 different variants of APs, in comparison to 43 and 34 variants from freshwater, and terrestrial strains, respectively (**Figure 3**). Thus, marine cyanobacteria demonstrate to produce a higher number of distinct APs variants in comparison to the remaining strains from different sources. However, APs from freshwater environments have the greatest diversity of amino acids in the majority of positions (**Figure 4**). Thus, these features could be associated with different obstacles faced in their respective environments as well as the fact that both belong to aquatic environments [48], however, this hypothesis requires further studies. Some of those APs are shared among different strains isolated from distinct environments: 2 anabaenopeptins (A and B) variants were detected in all ecosystems; in comparison, strains from both aquatic habitats had 13 APs variants in common (D, F, J, 807, NZ841, Oscillamide Y, and Nodulapeptins B, C, 855B, 871, 879, 897 and 915A) ; in contrast, only anabaenopeptin C were produced by both terrestrial and freshwater, and none Anabaenopeptin variant was shared by both terrestrial and marine strains.

Table 1. Occurrence of anabaenopeptins in different cyanobacteria genera and species.

Strains	Anabaenopeptin	Reference
Freshwater		

Strains	Anabaenopeptin	Reference
Anabaena flos-aquae 202 A 1	Anabaenopeptins B and D	[29]
Anabaena flos-aquae CYA 83/1	Anabaenopeptins B and D	[29]
Anabaena lemmermannii 202 A2/41	Anabaenopeptins B and C	[29]
Aphanizomenon flos-aquae NIES-81	Anabaenopeptins I and J	[32]
Lyngbya sp. (SAG 36.91)	Lyngbyaureamide A and B	[49]
Microcystis aeruginosa HUB 063	Anabaenopeptins B and F	[36]
Microcystis aeruginosa Kutz	Ferintoic acids A and B	[50]
Microcystis aeruginosa PCC7806	Anabaenopeptins A, B, E/F and Oscillamide Y	[51]
Microcystis aeruginosa TAU IL-342	Anabaenopeptin HU892	[52]
Microcystis sp. (MB-K)	Anabaenopeptin KT864	[53]
Microcystis sp. TAU IL-306	Anabaenopeptin F and Oscillamide Y	[52]
Microcystis sp. TAU IL-362	Anabaenopeptins MM823, MM850, MM913 and B	[52]
Microcystis spp.	Anabaenopeptin KB905, KB899, G, H, 908A, 915, HU892, MM913	[54]
Nodularia spumigena Node 2	Nodulapeptins B, C, 855B, 871, 879, 897 and 915A	[14][55]
Nodularia spumigena Nodg 3	Nodulapeptins B, C, 855B, 871, 879, 897 and 915A	[14]
Nodularia spumigena Nodh 2	Nodulapeptins B, C, 855B, 871, 879, 897 and 915A	[14]
Nodularia spumigena NSBL-05	Anabaenopeptin 807	[14]
Nodularia spumigena NSBL-06	Anabaenopeptin 807	[14]
Nodularia spumigena NSBR-01	Anabaenopeptin 807	[14]
Nodularia spumigena NSGL-01	Anabaenopeptin 807	[14]
Nodularia spumigena NSKR-07	Anabaenopeptin 807	[14]
Nodularia spumigena NSLA-01	Anabaenopeptin 807	[14]
Nodularia spumigena NSOR-02	Anabaenopeptin 807	[14]
Nodularia spumigena NSPH-02	Anabaenopeptin 807	[14]
Oscillatoria agardhii CYA 128	Anabaenopeptins A and C	[29]
Oscillatoria agardhii NIES-204	Anabaenopeptins B, E and F	[31]
Oscillatoria agardhii NIES-595	Anabaenopeptin G and H	[26]
Planktothrix agardhii CCAP 1459/11A	Anabaenopeptin F and Oscillamide B	[25]
Planktothrix agardhii CYA126/8	Anabaenopeptin 908A and 915	[56]
Planktothrix agardhii HUB 011	Anabaenopeptin G	[36]
Planktothrix agardhii NIVA CYA 15	Anabaenopeptins A and B	[57]
Planktothrix agardhii NIVA CYA 34	Anabaenopeptins A, B, F and Oscillamide Y	[57]
Planktothrix mougeotii NIVA CYA 405	Anabaenopeptins A, B, F and Oscillamide Y	[57]
Planktothrix mougeotii NIVA CYA 56/3	Anabaenopeptins C, 822 *, B, and F	[57]
Planktothrix prolifica NIVA CYA 406	Anabaenopeptins A, B, F and Oscillamide Y	[57]

Strains	Anabaenopeptin	Reference
Planktothrix prolifica NIVA CYA 540	Anabaenopeptins A, B, F and Oscillamide Y	[57]
Planktothrix prolifica NIVA CYA 98	Anabaenopeptins A, B, F and Oscillamide Y	[18][57]
Planktothrix rubescens	Anabaenopeptins A, B, F and Oscillamide Y	[58]
Planktothrix rubescens	Anabaenopeptins A, B, C, F and Oscillamide Y	[59]
Planktothrix rubescens	Anabaenopeptins B and F	[60]
Planktothrix rubescens	Anabaenopeptin A, B, and F	[61]
Planktothrix rubescens BGSD-500	Anabaenopeptins B and F	[62]
Planktothrix rubescens NIES-610	Anabaenopeptin F	[25]
Planktothrix rubescens NIVA CYA 407	Anabaenopeptins C, 822 *, B, and F	[57]
Woronichinia naegeliana	Anabaenopeptin 899	[63]
Marine		
Anabaena sp. TAU NZ-3-1	Anabaenopeptins NZ841, NZ825 and NZ857	[64]
Coelosphaeriaceae cyanobacterium 06S067	Anabaenopeptins A, B, F, 802 *, 827 *, 809 * and Oscillamide Y	[65]
Nodularia spumigena AV1	Nodulapeptins A, B, C, 871, 821, 839, 849, 855A, 863, 865, 867, 879, 881A, 881B, 883A, 897, 899A, 915A, 931	[14][66][55]
Nodularia spumigena B15a	Anabaenopeptins 841 and D	[14]
Nodularia spumigena BY1	Anabaenopeptin B and Nodulapeptins B, C, 821, 839, 855A, 855B, 871, 879, 881A, 881B, 883A, 897, 899A, 915A, 931	[14][66][55]
Nodularia spumigena CCNP 1401	Anabaenopeptins 841A and D	[14][55]
Nodularia spumigena CCNP 1423	Nodulapeptins 883B, 899B, 901, 915B, 917, 933	[14][55]
Nodularia spumigena CCNP 1424	Nodulapeptins 883B, 899B, 901, 915B, 917, 933	[14][55]
Nodularia spumigena CCNP 1425	Nodulapeptins 883B, 899B, 901, 915B, 917, 933	[14][55]
Nodularia spumigena CCNP 1402	and Nodulapeptins A, B, C, 821, 839, 855A, 855B, 871, 879, 881A, 881B, 883A, 897, 899A, 915A, 931	[14][55]
Nodularia spumigena CCNP 1403	Anabaenopeptins 841A and D	[14][55]
Nodularia spumigena CCNP 1426	Anabaenopeptins D and 841A	[55]
Nodularia spumigena CCNP 1427	Nodulapeptins B, C, 821, 855A, 855B, 871, 879, 881A, 881B, 883A, 897, 899A, 915A and 931	[55]
Nodularia spumigena CCNP 1428	Nodulapeptins 883B, 899B, 901, 915B, 917 and 933	[55]
Nodularia spumigena CCNP 1430	Anabaenopeptins D and 841A	[55]
Nodularia spumigena CCNP 1431	Nodulapeptins 883B, 885, 899B, 901, 915B, 917 and 933	[55]
Nodularia spumigena CCNP 1436	Nodulapeptins B, C, 839, 855A, 855B, 871, 879, 881A, 881B, 883A, 897, 899A, 915A, 921 and 931	[55]
Nodularia spumigena CCNP 1440	Nodulapeptins 883B, 885, 899B, 901, 915B, 917 and 933	[55]
Nodularia spumigena CCY 9414	Nodulapeptins A, B, C, 839, 855A, 855B, 871, 879, 881A, 881B, 883A, 897, 899A, 915A, 931	[14][55][67]
Nodularia spumigena KAC 11	Anabaenopeptins J and 807	[55]
Nodularia spumigena KAC 13	Anabaenopeptins D and 841A	[55]
Nodularia spumigena KAC 64	Nodulapeptins 883B, 885, 899B, 901, 915B, 917 and 933	[55]
Nodularia spumigena KAC 66	Nodulapeptins 883B, 885, 857, 899B, 901, 915B, 917 and 933	[14][55]

Strains	Anabaenopeptin	Reference
Nodularia spumigena **KAC 68**	**Nodulapeptins 883B, 885, 857, 899B, 901, 917 and 933**	[55]
Nodularia spumigena **KAC 7**	**Nodulapeptins B, C, 921, 839, 855A, 855B, 871, 879, 881A, 881B, 883A, 897, 899A, 915A and 931**	[55]
Nodularia spumigena **KAC 70**	**Nodulapeptins 807, 823, 851, 865, 867 and 883C**	[55]
Nodularia spumigena **KAC 71**	**Nodulapeptins A, B, C, 921, 823, 839, 855A, 855B, 871, 879, 881A, 881B, 883A, 897, 899A, 915A and 931**	[55]
Nodularia spumigena **KAC 87**	**Nodulapeptins 807, 823, 849, 851, 865, 867 and 883C**	[55]
Nodularia spumigena **UHCC0039**	**Nodulapeptins A, B, C, 839, 849, 855A, 863, 865, 867, 871, 879, 881A, 881B, 897, 899A, 915A and 933**	[67]
Terrestrial		
Anabaena circinalis **90**	**Anabaenopeptins A, B, and C**	[29]
Anabaena flos-aquae **NRC 525-17**	**Anabaenopeptins A and B**	[20]
Brasilonema **sp. 360**	**Anabaenopeptin 802A**	[24]
Brasilonema **sp. 382**	**Anabaenopeptin 802A**	[24]
Brasilonema **sp. CT11**	**Anabaenopeptins 788, 802A, 802B and 816**	[68]
Desmonostoc **sp. 386**	**Anabaenopeptins 848, 849, 862, 863, 877A, 877B, 891 and 905**	[24]
Nostoc **sp. 352**	**Anabaenopeptins 841B, 855, 857 and 871**	[24]
Nostoc **sp. 358**	**Anabaenopeptins 882 and 896**	[24]
Nostoc **sp. ASN_M**	**Anabaenopeptins 808 *, 828, 842 *, 844 * and 858 *,**	[69]
Nostoc **sp. ATCC 53789**	**Anabaenopeptin SA9, SA10, SA11 and SA12**	[12]
Nostoc **sp. KVJ2**	**Anabaenopeptins KVJ827, KVJ841, and KVJ811**	[21]
Schizothrix sp. **IL-208-2-2**	**Schizopeptin 791**	[70]

* Anabaenopeptin variants with non-elucidated sequence.

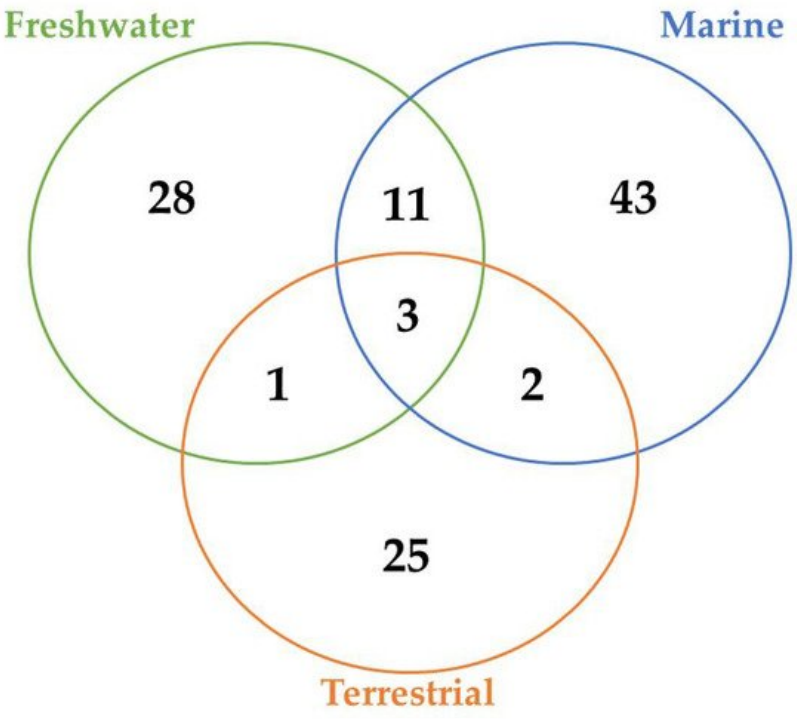

Figure 3. The number of Anabaenopeptins variants detected and shared among strains of cyanobacteria from different environments, including environmental samples.

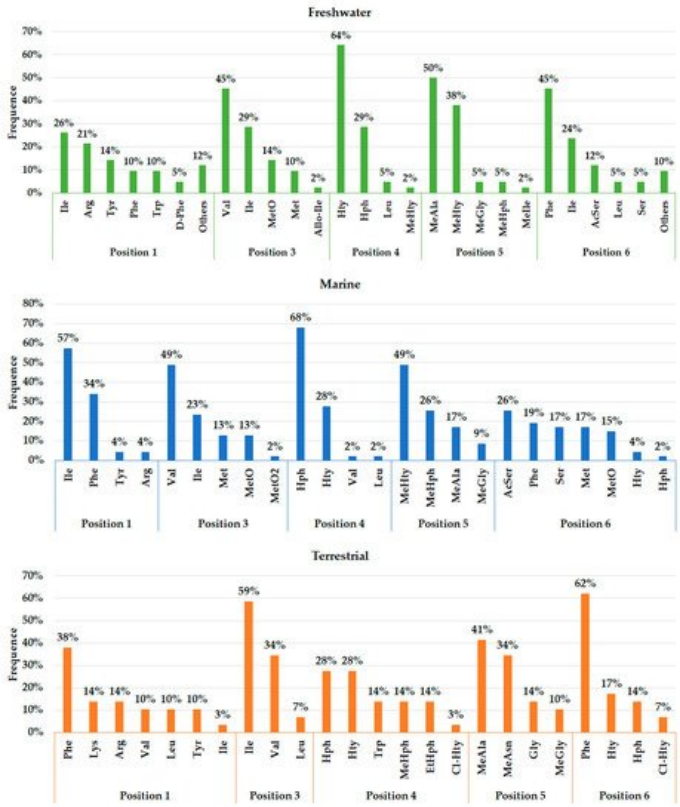

Figure 4. Relative frequency (%) of amino acids in positions 1 and 3–6 of variants of anabaenopeptins characterized according to their environment (freshwater, marine and terrestrial). The total number of variants with elucidated sequences were 42, 47 and 29 for freshwater, marine, and terrestrial environments, respectively. Position 2 was omitted as the D-Lys residue being conservated among AP variants.

According to **Table 1** and **Figure 3** , there are AP variants shared among cyanobacteria strains from different environments according to the previous discussion. Anabaenopeptins A and B are the only variants detected in all habitats analyzed, and the only difference between those variants resides at the exocyclic residue. AP B is still the most recurrent among these oligopeptides in cyanobacteria (**Table 1**), corroborating with the previously raised hypothesis that this variant was the first cyanotoxin of this class to be emerged. [71]. Furthermore, the number of common anabaenopeptins variants increases when a comparison is made among strains only from aquatic habitats (freshwater and marine): Anabaenopeptins D, F, J, 807, NZ841, Oscillamide Y, and Nodulapeptins B, C, 855B, 871, 879, 897 and 915A. Besides their production by both freshwater and marine cyanobacteria, these prevalent oligopeptides seem to be more recurrent in marine environments, given that a higher number of cyanobacteria strains from this habitat are able to produce these APs comparing to freshwater, except for Oscillamide Y, which is more recurring in the latter. Among those variants, Nodulapeptin B is the most frequent in marine microorganisms. Besides, the only difference between the AP C (produced by freshwater and terrestrial strains) and both A and B variants is the exocyclic amino acid, and the former was not detected in marine cyanobacteria.

As seen in **Figure 3** , the environment can exert a crucial role in the biosynthesis of different APs, justifying their distribution in certain locations. The presence and frequency of certain amino acids in Anabaenopeptin structures can vary according to their respective source environment. Anabaenopeptins from both aquatic environments demonstrate to have Isoleucine as the most recurrent amino acid in position 1, while this same amino acid was detected in only one AP variant in terrestrial strains (**Figure 4**). Phenylalanine was highly detected in position 1 of Anabaenopeptins isolated from terrestrial strains. Then, freshwater cyanobacteria may be promising biotechnological targets due to its highest diversity of amino acids in position 1, as the exocyclic residue is crucial for its inhibitory activity [12][35][34]. Regarding the variable position 3, Anabaenopeptins from freshwater and marine environments displayed a similar pattern of amino acid frequencies, Valine (Val) being the most frequent, followed by Ile and L-Methionine sulfone (MetO2). In contrast, terrestrial strains produce several AP variants with Ile in position 3, followed by Val and Leu, the latter being absent in this position on APs detected in aquatic environments. Homotyrosine (Hty) and Homophenylalanine (Hph) are the most found residues in position 4 among APs from all habitats analyzed, however, among terrestrial and marine strains Hph is more predominantly, while Hty is commonly observed in APs from freshwater strains. Except for Glycine (Gly) in some Anabaenopeptins from terrestrial strains, all the other residues in position 5 are N-methylated. APs from non-aquatic cyanobacteria do not harbor homoamino acids in the fifth position and, in addition, Asparagine is only detected in some of those variants in the respective position. Besides their detection in position 5, homoamino acids seem to be more

persistent in position 4 from those APs analyzed. Position 6 has the highest richness of amino acids among AP variants obtained from marine environments, having incorporated 7 different residues, while this position in variants from freshwater habitats have assimilated 9 different amino acids, being the second most diverse site. Such heterogeneity in the last position in APs from aquatic strains is not clear, as the first amino acid residue demonstrated to be important in Anabaenopeptin interaction towards its enzyme target [12][35][34]. This array of several amino acids detected in position 6 is not visualized in Anabaenopeptins from terrestrial strains, where Phe was the amino acid more detected, similar to those APs from freshwater microorganisms.

In addition to interaction with other cyanobacteria, these microorganisms are capable to establish symbiotic associations with invertebrates, such as corals, mollusks, and sponges. Both organisms can be benefited during this consortium through secondary metabolite production, for example [72]. Sponges host an enormous quantity of microorganisms belonging to diverse phyla, where cyanobacteria are mainly represented by genera *Aphanocapsa* , *Synechocystis* , *Phormidium* , and *Oscillatoria* [73]. These photosynthetic microorganisms can occupy either extra- or intracellular spaces, aiding the host in the control of the redox potential, supplying pigments and energy through carbon fixation, and in the defense mechanism by the production of secondary metabolites. Published reports have demonstrated that as a consequence of these processes, cyanobacteria have their metabolic profile altered, resulting in the production of distinct variants of natural products. The compound 2-(2’,4’-dibromophenyl)-4,6-dibromophenol is solely biosynthesized by a cyanobacterium belonging to genus Oscillatoria in association with the sponge Dysidea herbacea [74]. These factors corroborate with the hypothesis that anabaenopeptins primarily observed in sponges could be of cyanobacterial origin, as brominated APs variants were isolated only from sponges [75][76][77] and the Oscillatoria genus is known for APs production. For instance, the polyketide nosperin and some variants of oligopeptide nostopeptolide are encountered exclusively during symbiosis, which may be the same mechanism for anabaenopeptin variants production found in sponges.

4. Applications of Anabaenopeptins

Cyanopeptides such as APs have a well-demonstrated capacity of protease inhibition [78]. Protein Phosphatase 1 (PP1), Protein Phosphatase 2A, Carboxypeptidase-A (CPA), Human Serine Protease, Leucine Aminopeptidase, Trypsin, and Thrombin have already been tested against several cyanobacterial extracts and confirmed the catalysis blockage [11].

Serine/threonine protein phosphatases inhibition was also reported [22][25]. Nevertheless, several other cyanopeptides presented more effective IC 50 levels against elastase, such as some variants of lyngbyastatins, symplostatins, microvirins, and others. Concerning PP1, MCs remain the best inhibitor among all cyanopeptides [11]. IC 50 reported values to MCs and nodularins are from 1.1 to 1.9 nM as PP1 inhibitors [79]. In this case, APs remain promising candidates in Carboxypeptidase inhibition.

Cyanopeptides blooms events may present the production of different classes of cyanopeptides like MCs, APs, and cyanopeptolins. A few studies quantified cyanopeptides beyond Microcystins, even so, in 10 eutrophic lakes in the United States and Europe the cyanopeptides concentration including these 3 types of cyanopeptides were from <4 µg/L to >40 µg /L [11]. In wet weight, 2.1 mg of AP and 7.4 mg of Microcystin-LR were obtained from 1.7 kg of biomass in a water bloom of lake Teganuma (Japan) [33].

Besides some cyanopeptides presented anticancer activity, APs have been presented poor results in cytotoxic tests [80]. Anabaenopeptin B had been tested about its anticancer potential and did not demonstrate cytotoxic effects against N2a, MCF−7, and GH4 cells even at the 500 µg/mL concentration [81]. Despite anticancer activity was detected in Aliinostoc sp. CENA543 extract containing AP , it was not possible to attribute this effect exclusively to this class of oligopeptides because there were other cyanopeptides in the extract, and the exact AP was not identified [82]. No cytotoxic activity was presented by Nodulapeptins 883C, 869, 867, 865, and Anabaenopeptin 813 as well [35].

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