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Letter to Editor

Importance of Bioactive Peptides Derived from Cyanobacteria

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HIGHLIGHTS

- Cyanobacteria are a valuable source of natural metabolites, including bioactive peptides.
- Cyanobacterial peptides include ribosomal synthesized and nonribosomal peptides (NRPs).
- Therapeutic applications of cyanobacterial peptides in different diseases have been reported.

ABSTRACT

Cyanobacterial peptides are a group of promising natural therapeutic agents that have been extensively studied in recent years. They can be valuable pharmaceuticals or lead compounds in developing novel therapeutics for various diseases, especially cancers, infections, and neurodegenerative diseases, which are the most important challenges of medicine today.

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Introduction

The bioactive secondary metabolites of cyanobacteria have been reported with various bioactivities and structures. Among them, oligopeptides are of great importance. The majority of known oligopeptides are of nonribosomal origin and can be divided into classes with conserved structural properties. Therefore, the overall structural diversity of cyanobacterial oligopeptides only appears to indicate the high diversity of biosynthetic pathways and corresponding genes (Welker and Von Döhren, 2006). The peptides produced by cyanobacteria can be classified into ribosomal synthesized, nonribosomal peptides (NRPs), and nonribosomal peptide synthetases (NRPSs). Some of the peptides are the peptides with posttranslational modifications. NRPs are the most abundant ones. Besides, NRPSs are a major group of cyanobacterial secondary metabolites that have been reported to have a wide range of bioactivities, such as antimicrobial activity (Slonimskiy et al., 2020).

The nonribosomal peptide biosynthetic system generally refers to nucleic acid-free proteins, in which amino acid condensation is conducted by protein templates. Through the biosynthetic steps, different protein modules are commonly required, including an adenylation domain for amino acid activation, a thiolation domain for transferring activated intermediates, and a condensation domain as the final step. Different domains of these modules are assembled at the gene level, resulting in complex gene clusters. These clusters are translated into multifunctional proteins or multi-enzyme complexes, which can be post-translationally modified by the addition of 4′-phosphopantetheine to the thiolation domain (Welker and Von Döhren, 2006).

Cyanobacterial peptides have shown a wide range of therapeutic potentials. A group of scientists in 2020 summarized the anticancer peptides derived from cyanobacteria. They stated that among the various types of bioactive metabolites, linear lipopeptides, cyclic peptides, and depsipeptides have mostly shown anticancer activity. For example, some unbranched, cyclic peptides, including Apratoxin D, Apratoxin E, Companeramides A and B, Dudawalamides A–D, Hantupeptins A–C, Itralamides A and B, Pompanopeptins A and B have been reported as a wide range anticancer agents (Ahmad et al., 2020). Moreover, Alotamide from *Lyngbya bouillonii*, Barbamide from *Lyngbya majuscule*, Biselyngbyaside from *Lyngbya* sp., Cryptophycin from *Nostoc* spp., Curacin A from *Lyngbya majuscula*, Dolastatin from *Leptolyngbya* sp., Hectochlorin from *Lyngbya majuscula*, Largazole from *Symploca* sp., Lyngbyabellin A from *Lyngbya majuscula*, Veraguamides A and Malevamide D from *Symploca hydnoides*, Nocuolin A from *Nodularia* sp., Obyanamide from *Lyngbya confervoides*, Palmyramide A from *Lyngbya majuscule*, Porphyra_334 from *Aphanothece halophytica*, Scytonemin from *Stigonema* sp., and Welwitindolinones from *Fischerella* sp. and *Hapalosiphon welwitschia* have been reported for their anticancer activities through different mechanisms resulted in apoptosis induction (Gupta et al., 2023).

Moreover, Salman Ahmed *et al.* summarized the application of cyanobacterial peptides in the treatment of neuroblastoma as the most prevalent extracranial solid tumor in children. These active peptides included cyclic depsipeptides, lipopeptides, cyclic lipopeptides, and two linear peptides (Ahmed et al., 2023).

As well, Perera et al. (2023) classified the active metabolites of cyanobacteria into those with anti-inflammatory, anticancer, hepatoprotective, anti-diabetic, anti-aging, anti-obesity, neuroprotective, antioxidant, antimicrobial, and photoprotective properties. The most prevalent application for peptides derived from cyanobacteria is based on their antimicrobial activity, which based on Perera et al. sorting, could be classified into depsipeptides, lipopeptides, cyclamides, and cyclic peptides. However, cyanobacteria peptides with anti-inflammatory, neuroprotective, and anticancer activities have also been reported (Perera et al., 2023).

Reported cyanobacterial proteins in databanks

By searching the NCBI database using "cyanobacteria", around 8605160 protein data can be found, up to the January of 2024. The most prevalent data have been reported from *Microcystis aeruginosa* (450408), *Fischerella thermalis* (188371), *Prochlorococcus marinus* (185606), *Oscillatoriales cyanobacterium* (148330), *Nostoc linckia* (108958). From these protein sequences, 1362756 cases have less than 100 amino acid lengths, most of them are the conserved domains of identified proteins.

In addition, searching PDB resulted in more than 2300 protein/peptide structures that had been recorded for cyanobacteria from 1990 up to now. Most of these structures have been discovered from *Synechocystis* sp. PCC 6803 (207), *Thermosynechococcus vestitus* BP-1 (188), *Nostoc* sp. PCC 7120 (174), *Synechococcus elongatus* PCC 7942 (140), *Synechocystis* sp. PCC 6803 substr. Kazusa (137), *Gloeobacter violaceus* PCC 7421 (82), *Gloeobacter violaceus* (51), *Nostoc punctiforme* PCC 73102 (50), *Thermostichus vulcanus* (45), *Nostoc* sp. PCC 7119 (44), and *Synechococcus elongatus* (44).

Bioactive peptides structural classification

Welker et al. (2006) reported that more than 600 cyanobacterial peptides had been identified. He and his colleagues classified the reported peptide. They stated that the peptide names commonly were chosen by the authors, which generally refer to the taxon from which the new compound had been isolated or to the geographic locality where the sample was taken from. This may include micro-, anabaeno-, kasumig-, banyas-, etc., combined with suffixes referring to structural properties (e.g., peptin, -peptilide, -cyclin, cyclamide) (Fig. 1) (Welker and Von Döhren, 2006).

Moreover, Dr. Elisabeth Janssen at the Swiss Federal Institute of Aquatic Science and Technology (Eawag) and her coworkers have developed a database named CyanoMetDB that contains 2010 compounds of cyanobacterial secondary metabolites divided into 5 major classes. These compounds included 310 microcystins, 193 cyanopeptolins (also called micropeptins), 211 other depsipeptides, 101 anabaenopeptins, 85 microginins, 67 aeruginosins, 64 cylamides, 38 cryptophycins, 38 saxitoxins, 26 spumigins, 25 microviridins, 16 nodularins, 11 anatoxins, and 5 cylindrospermopsins. Around 70% of these secondary metabolites have peptide-based structures, which composed of microcystins, cyanopeptolins, and other cyclic depsipeptides. Most of these compounds have molecular weights ≥ 900 Da, and more abundant metabolites are 1000 and 1100 Da (Jones et al., 2021).

Peptides can be derived from the enzymatic and non-enzymatic hydrolysis of proteins extracted from cyanobacteria. For example, most of the publications regarding the antimicrobial activity of cyanobacterial and microalga peptides are limited to the protein hydrolysates, such as what has been reported from *Chlorella vulgaris* (Sedighi et al., 2016), *Tetraselmis suecica* (Guzmán et al., 2019), *Desmodesmus* sp. (Ehsani et al., 2023), *Spirulina platensis* (Sun et al., 2016), and *Anabaena* sp. (Doraj et al, 2023).

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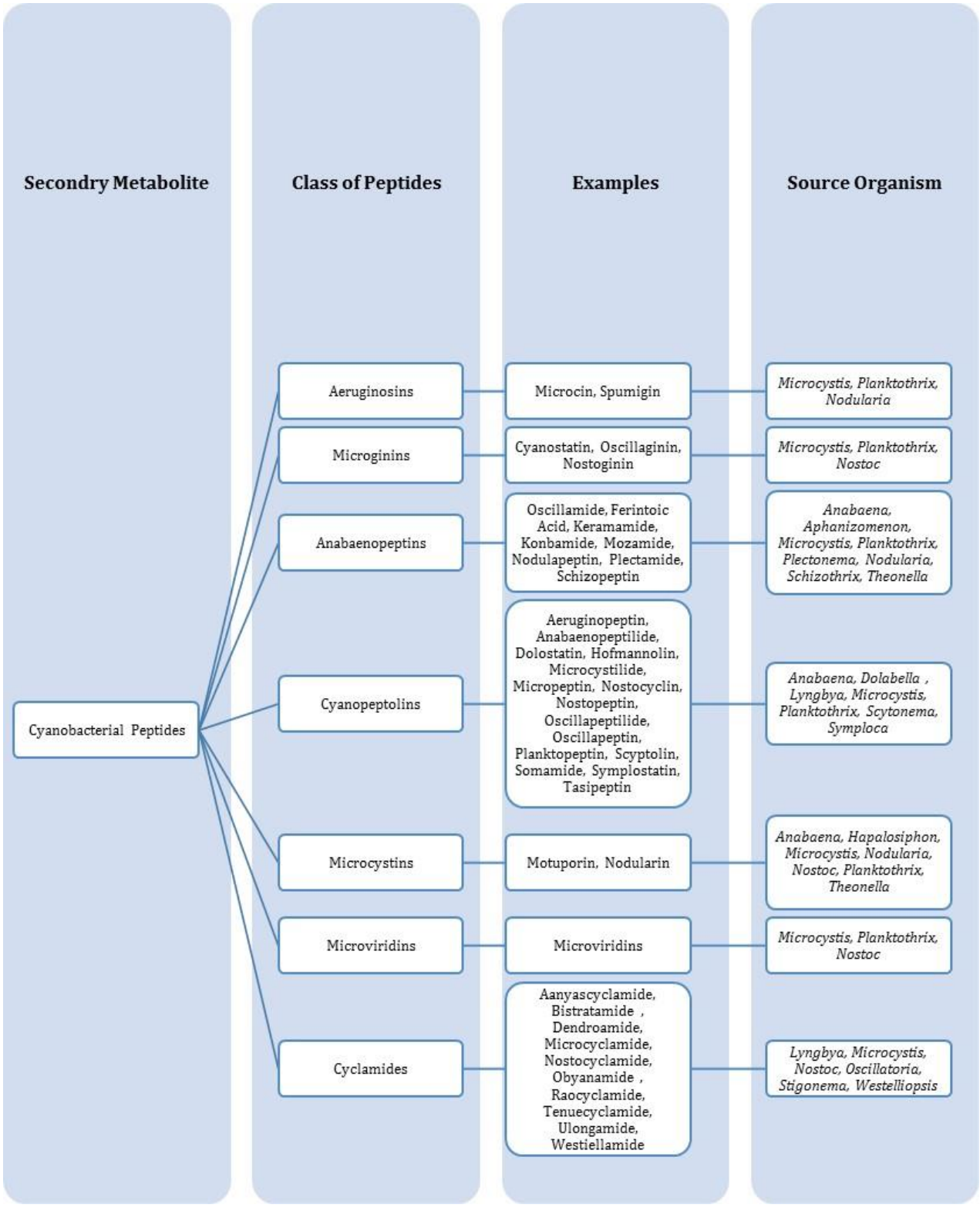

Figure 1: A type of peptide classification for cyanobacterial peptides, the related peptides reported (examples), and the related source that has produced them. The figure was drawn based on the classification of Welker *et al.* (Welker and Von Döhren 2006).

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Outlook

In recent years, using *in silico* approaches or using genomic and transcriptomic data in finding potential active metabolites from natural sources has extensively progressed. These strategies have also been used in the prediction of novel potential bioactive peptides and proteins from cyanobacteria. A group of researchers discovered novel metabolites from cyanobacteria to inhibit β-Secretase 1 through molecular dynamics simulations. This enzyme is the key enzyme involved in the development of amyloid beta peptides during Alzheimer's disease. They propose at least four potential metabolites in this regard (Kalaimathi et al., 2023). Another group studies the antibacterial activity of 24 microalgal peptides through in-silico studies. Using molecular docking, they found potential peptides that could target the proteins of lower respiratory tract infections (Raghunathan et al., 2023). A similar recent work investigated tyrosinase inhibitory peptides from allophycocyanin in *Spirulina platensis* (Yu et al., 2024). Moreover, (Nowruzi and Afshari, 2023) predicted the proteins and peptide's secondary structures and the molecular phylogeny of polypeptides synthase genes and nonribosomal peptides genes.
In general, due to the valuable medicinal potentials of cyanobacterial peptides, various *in silico*, *in vitro*, and *in vivo* attempts have been extensively performed to find potent bioactive peptides with therapeutic applications.

Ethical Statement

This work did not contain any animal or human studies performed by the authors.

Competing Interests

The authors have no conflicts of interest to declare.

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Not applicable

Authors Contribution

M. Tabarzad and B. Alizadeh contributed to the manuscript drafting. M. Tabarzad prepared the final manuscript. The final manuscript was reviewed and confirmed by both authors.

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