Majeti Narasimha Vara Prasad
Sarada Devi Tetali
Catherine Bennetau-Pelissero *Editors*

Biotoxins

Biotechnological and Therapeutic Applications

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Chapter 5
Cyanotoxins: Industrial Potential

Dhammika N. Magana-Arachchi and H. M. S. A. T. Gunathilaka

Abstract Cyanotoxins are secondary metabolites produced by specific cyanobacterial species, able to grow and bloom in all aquatic and terrestrial biotas. The rationale for cyanotoxin production is still a mystery. There are many records of the adverse impacts of cyanotoxins, harming the organisms, animals, plants, and humans. However, with the continuous global research on these complex biological toxins, scientists realize their potency in industry, which benefits humans. The pharmaceutical industry is always looking for novel drugs from natural sources as most current medications cause adverse side effects, and most drugs/antibiotics have become ineffective because of the resistant nature of the infective microbes. Hence, cyanotoxins are an excellent source to be targeted. This chapter begins with an introduction to cyanobacteria, followed by a description of the diverse cyanobacterial toxins and their chemical structures. The next section will be on their bioactivity and genomics. The following section discusses the potential biomedical applications of various cyanotoxins, such as microcystins, oscillatoxins, anatoxins, and kalkitoxins, including those currently being tested and as future targets for different diseases. The following section discusses the utility of cyanotoxins in other industrial applications, including the production of algaecides, herbicides, and insecticides. The final section will include the conclusions and prospects as these cyanotoxins still need to be fully explored.

Keywords Biomedical applications of cyanotoxins · Cyanotoxin chemical structures · Cyanotoxins and cytotoxic compounds · Cylindrospermopsin · Microcystins · Nodularin · Saxitoxin

D. N. Magana-Arachchi (✉) · H. M. S. A. T. Gunathilaka
Molecular Microbiology and Human Diseases Research Programme, National Institute of Fundamental Studies, Kandy, Sri Lanka
e-mail: dhammika.ma@nifs.ac.lk

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5.1 Introduction

Natural products from microorganisms are an essential source in the pharmaceutical industry. Cyanobacteria are oxygenic phototrophic prokaryotes ubiquitous in nature and can produce diverse biologically active chemical compounds. These have been found to possess a wide range of potential antimicrobial, anticancer, antiviral, and anti-inflammatory activities. Cyanotoxins are secondary metabolites produced by several cyanobacterial species. These toxins are well-known for their harmful effects on humans and animals, and the rationale for their production is still a mystery. Cyanotoxins comprise a rich source of natural cytotoxic compounds. However, their potential in the pharmaceutical industry and the biotechnology industry as a whole has yet to be exploited. This chapter begins with an introduction to cyanobacteria, followed by a description of the diverse cyanobacterial toxins and their chemical structures. The following section will be on their bioactivity and genomics. The following section discusses the potential biomedical applications of various cyanotoxins, such as microcystins, oscillatoxins, anatoxins, and kalkitoxins, including those currently being tested and as future targets for different diseases. The next section discusses the utility of cyanotoxins in other industrial applications, including the production of algaecides, herbicides, and insecticides. The final section will include the conclusions and prospects as these cyanotoxins still need to be fully explored.

5.1.1 Cyanobacteria, Cyanotoxins, and Cytotoxic Compounds

5.1.1.1 Cyanobacteria

Cyanobacteria is one of the oldest life forms on Earth; It is evidenced by fossilized records dating back 3.5 million years. It has profoundly impacted the planet's evolutionary history. These photoautotrophic bacteria exhibit remarkable adaptability, thriving in diverse environments such as freshwater, brackish water, marine habitats, and wastewater. Cyanobacteria, recognized as pioneers of oxygenic photosynthesis, primarily obtain nutrients through photosynthesis. However, some adapt to hydrogen sulfide-rich environments by switching to anoxygenic photosynthesis, similar to bacteria. Cyanobacteria's photosynthetic machinery includes various pigments which help them adapt to changes in light intensity. Through complementary chromatic adaptation, they adjust to different light wavelengths by synthesizing phycobiliproteins, also shielding cells from harmful radiation (Sanfilippo et al. 2019). Microscopic in nature, cyanobacteria display a diverse morphology, existing in the environment as single cells, in groups, colonized, or as filamentous forms (Magana-Arachchi and Wanigatunge 2023). Many cyanobacteria live independently; some form symbiotic relationships with eukaryotes, playing crucial roles in ecosystems. They serve as natural nitrogen-fixing agents, transforming atmospheric

nitrogen into organic compounds such as ammonia, nitrite, or nitrate (Álvarez et al. 2023).

5.1.1.2 Cyanotoxins

Biotoxins originate from various living organisms, including bacteria, fungi, algae, plants, and animals. They are substances that can induce harm upon other organisms, including humans, through multiple routes of exposure, such as ingestion, inhalation, or direct contact. These toxins exhibit diverse chemical structures and biological activities, significantly contributing to ecological dynamics and human health (Still and Mohapatra 2020). Cyanobacterial toxins or cyanotoxins are a group of secondary metabolites originating from cyanobacteria. These biotoxins negatively impact aquatic ecosystems, harming aquatic life and human populations (Du et al. 2019). The favourable environmental conditions and nutrient availability boost cyanobacterial proliferation, causing blooms in waterbodies (Weralupitiya et al. 2022). Most of these blooms contain cyanobacterial species that are capable of producing cyanotoxins. Typically, these toxins are found within (intracellular) the live cells of cyanobacteria. However, both live and dead cells can release cyanotoxins into the environment (Magana-Arachchi and Wanigatunge 2023). Cyanobacterial species, such as *Cylindrospermopsis*, naturally excrete the toxin cylindrospermopsin (CYN) into water. A study reported the historical presence of the cyanotoxin CYN in sediments of hypereutrophic Lake Griffin, Florida, USA, dating back to 4700 years up to 2015 (Waters 2016).

Not all cyanobacteria produce cyanotoxins. Certain cyanobacterial species belonging to different genera are capable of producing cyanotoxins, and it is interesting to note that diverse genera can produce one particular toxin. Furthermore, a range of cyanobacterial species can produce more than one cyanotoxin, such as *Anabaena* species, which produce microcystin, cylindrospermopsin, and anatoxins (Magana-Arachchi and Wanigatunge 2023) (Fig. 5.1).

5.1.1.3 Cytotoxic Compounds from Cyanobacteria

Cytotoxic compounds of cyanobacteria refer to a broader category of bioactive substances. They exhibit toxicity towards cells, as cyanotoxins are a subset of cytotoxic compounds. This is because cyanotoxin includes compounds with cytotoxic effects, such as anticancer properties or those that disrupt cellular processes. These cytotoxic compounds may not necessarily be classified as cyanotoxins but can still harm biological systems.

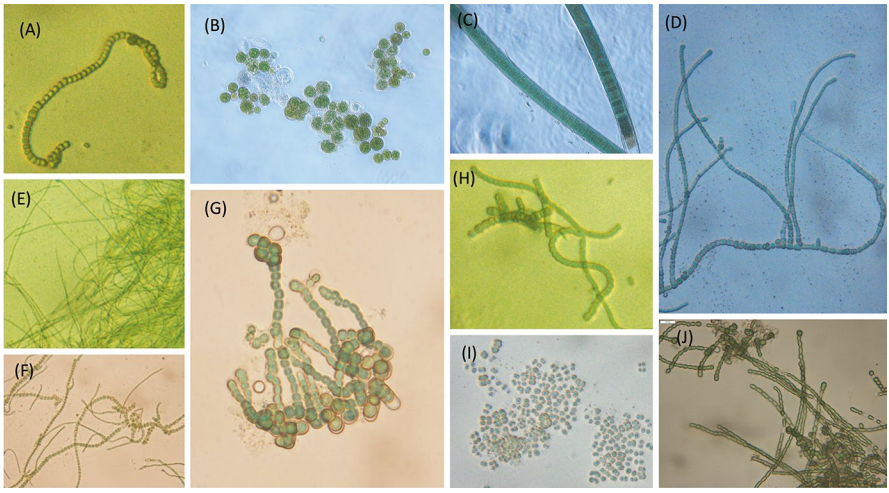

Fig. 5.1 Morphological diversity of cyanobacteria (**a**) *Nostoc* sp. (**b**) *Chroococcidiopsis* sp. (**c**) *Oscillatoria* sp. (**d**) *Anabaena* sp. (**e**) *Leptolyngbya* sp. (**f**) *Mastigocladus* sp. (**g**) *Tolypothrix* sp. (**h**) *Fischerella* sp. (**i**) *Microcystis* sp. (**j**) *Westiellopsis* sp.

5.2 Cyanobacterial Toxins and Their Chemical Structures

The mechanisms of cyanobacterial toxicity show significant diversity, including hepatotoxic, neurotoxic, and dermatotoxic effects, as well as inhibition of protein synthesis (Nugumanova et al. 2023). It is crucial to understand their chemical and physical properties to assess the risk associated with cyanotoxins, the prevalence of cyanotoxins in water sources used by humans, the regulations governing their production, and their environmental fate (Du et al. 2019).

Depending on the chemical structure, the cyanotoxins can be categorized into three groups: cyclic peptides, alkaloids, and lipopolysaccharides (LPS). Major cyanotoxins, including microcystins (MCs) and nodularins (NODs), are peptides, while cylindrospermopsin (CYN), anatoxins, lyngbyatoxins, and saxitoxins are alkaloids. Table 5.1 describes an overview of identified toxic substances originating from various genera of cyanobacteria. Additionally, the table outlines the main target organs in humans affected by these toxins**.**

5.2.1 Microcystin

Microcystins (MCs) are the most broadly studied hepatotoxins, which are cyclic peptides produced by different cyanobacterial genera such as *Microcystis*, *Planktothrix*, *Anabaena Nostoc*, etc. (Table 5.1). MCs' molecular weights are within the range of 800–1100 Da. The general structure of MC consists of

Table 5.1 The cyanotoxins detected and their corresponding taxa from which they have been isolated, along with their primary targets in mammals. *The dose needed to kill 50% of exposed animals

Toxin	Producer	LD_{50} Intraperitoneal (i.p.) Pure toxin (oral)*mouse F(Churro et al. 2012)	Primary target organ	Mechanism of action (Churro et al. 2012)
Microcystins (~280 variants) Cyclic heptapeptides	*Microcystis* sp.	~50–1000 µg/kg Bw (body weight)	Liver	Hepatotoxic Tumour promoting, inhibition of eukaryotic protein phosphatase PP1, PP2A, and phosphoprotein phosphatases PPP4, PPP5
	Planktothrix sp.			
	Dolichospermum sp.			
	Anabaenopsis sp.			
	Aphanocapsa sp.			
	Spirulina sp.			
	Snowella sp.			
	Aphanizomenon sp.			
	Oscillatoria sp.			
	Nostoc sp.			
	Phormidium sp.			
	Anabaena sp.			
	Rivularia sp.			
	Hapalosiphon sp.			
	Plectonema sp.			
Nodularin (9 variants) Cyclic pentapeptides	*Nodularia* sp.	~30–50 µg/kg Bw	Liver	Same as MCs. Inhibit the serine/thionine, protein phosphatase type 1/2a. Induce oxidative stress
	Nostoc sp. (symbiotic)			
	Spumigena sp.			
Cylidrospermopsin (4 variants) Tricyclic guanidine alkaloids	*Lyngbya* sp.	~200–2100 µg/kg Bw (24 h) 200 µg/kg Bw 5–6 days	Liver Kidneys Lung Heart	Inhibition of glutathione (GSH) and protein synthesis Inhibition of cytochrome P450 Multiple organ toxicity, neurotoxic, genotoxic, protein synthesis inhibitor
	Cylindrospermopsis sp.			
	Raphidiopsis sp.			
	Oscillatoria sp.			
	Umezakia sp.			
	Anabaena sp.			
	Aphanizomenon sp.			
Anatoxin-a (5 variants) Atropine-like alkaloid	*Anabaena* sp.	~250 µg/kg Bw/d	Post-synaptic neuromuscular junction	Agonism of muscular and neuronal nicotinic acetylcholine receptor
	Oscillatoria sp.			

(continued)

Table 5.1 (continued)

Toxin	Producer	LD_{50} Intraperitoneal (i.p.) Pure toxin (oral)*mouse F(Churro et al. 2012)	Primary target organ	Mechanism of action (Churro et al. 2012)
Homoanatoxin-A (Alkaloid)	*Anabaena* sp. *Oscillatoria* sp. *Planktothrix* sp.	~250 µg/kg Bw/d	Post-synaptic neuromuscular junction	Agonism of muscular and neuronal nicotinic acetylcholine receptor
Anatoxin-A(s) (Guanidine methyl phosphate ester)	*Anabaena* sp. *Aphanizomenon* sp. *Phormidium* sp.	~20–250 µg/kg Bw/d	Post-synaptic neuromuscular junction	Irreversible inhibition of acetylcholinesterase Neurotoxic Binds competitively at acetylcholine receptors
Saxitoxin (~60 variants) Carbamate alkaloids	*Anabaena* sp. *Lyngbya* sp. *Cylindrospermopsis* sp. *Planktothrix* sp. *Aphanizomenon* sp.	~10–30 µg/kg Bw/d	Axons	Blockage of calcium or sodium channels of the nerve axon membrane Neurotoxic Blocks voltage-gated sodium channels
Lyngbyatoxin-A (Alkaloid)	*Lyngbya* sp. *Oscillatoria* sp. *Schizothrix* sp.	~250 µg/kg Bw/d	Skin	Inflammatory agent Tumour promoting, binds to eukaryotic protein kinase C
Aplysiatoxin (Phenolic bislactone)	*Lyngbya* sp. *Planktothrix* sp.	~107–117 µg/kg Bw/d	Skin	Inflammatory agent Protein kinase c activator
Debro-moaplysiatoxin (Phenolic bislactone)	*Lyngbya* sp.	~107–117 µg/kg Bw/d	Skin	Inflammatory agent Protein kinase c activator
Kalkitoxin (Lipopolypeptide) (Shrestha et al. 2023)	*Moorea producens*	LC_{50} 3.86 nM (Morgan et al. 2015)	Neurons	Neuronal necrosis Blocks the electron transport chain complex 1 Block voltage sensitive-sodium channels

cyclo-(D-Ala[1]-X[2]-D-Masp[3]-Z[4]-Adda[5]-D-γ-Glu[6]-Mdha[7]) (Fig. 5.2a) in which X and Z are variable L-amino acids, D-Masp[3] is D-*erythro*-β-methyl-isoaspartic acid, and Mdha is *N*-methyldehydroalanine. Currently, a universal system of nomenclature is being used based on the original term microcystin-XZ, where X and Z denote the variable amino acid residues in positions 2 and 4. MCs induce haemorrhagic shock in the liver, leading to death within 45 min to a few hours and are considered tumour promoters in chronic exposures. Around 300 distinct variants of microcystins have been thoroughly characterized by 2021 (Jones et al. 2021).

5.2.2 Nodularins

Nodularins (NOD) are another type of hepatotoxic cyclic peptide. Structural variations are observed across all ten amino acids, with common alterations including the substitution of D-amino acids at positions 2 and 4, the replacement of Mdha with Dhb (dehydrobutyrine) or serine at position 7, (Fig. 5.2b) and the absence of methylation in amino acids at positions 3 and/or 7 (Brezeștean et al. 2022).

5.2.3 Cylindrospermopsin

Cylindrospermopsin (CYN) is a cyclic guanidinic alkaloid (Fig. 5.2f). It is also a hepatotoxin but functions as a protein synthesis inhibitor. CYNs are characterized by a tricyclic guanidino moiety, which is connected through a hydroxylated bridging carbon in the C7 position to uracil (WHO 2020). Four distinct structural variants of the CYNs have been identified: 7-epi-cylindrospermopsin (7-epi-CYN), 7-deoxy-cylindrospermopsin (7-deoxy-CYN), 7-deoxy-desulpho-cylindrospermopsin, and 7-deoxy-desulpho-12-acetyl cylindrospermopsin (Wimmer et al. 2014).

The hydrophilic nature of CYNs facilitates the uptake of them into the transport systems and mediates the intestinal absorption of various cell types, including hepatocytes. However, the small size of these molecules suggests limited passive diffusion through biological membranes. At low concentrations, the primary effect of CYN toxicity appears to be the inhibition of protein synthesis mediated by the parent compound (Pichardo et al. 2017).

5.2.4 Anatoxins

Neurotoxic anatoxins (ATX) are isolated from the cyanobacterial species *Anabaena*. ATX-a is a neurotoxic bicyclic alkaloid, containing 2-acetyl-9-aza bicycle (4.2.1) non-2-ene (Fig. 5.2c). ATX-a had been initially isolated from *Anabaena flos-aquae*

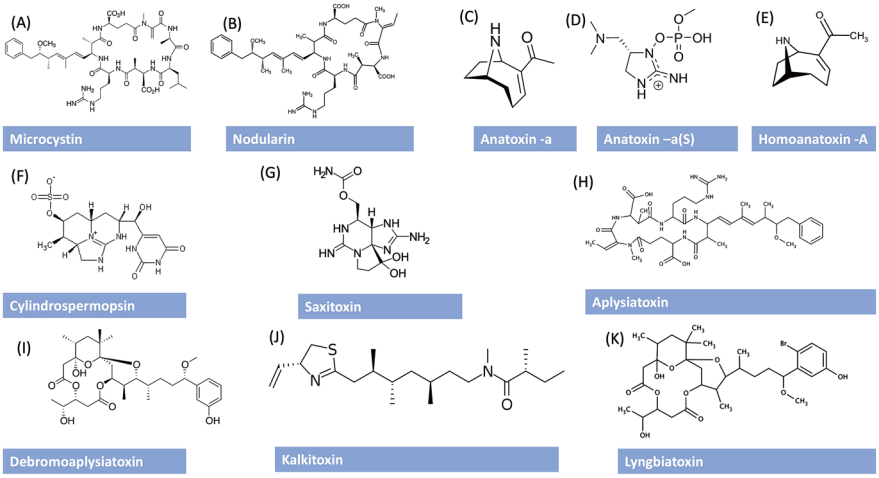

Fig. 5.2 Chemical structures of major cyanotoxins in environment

in the 1970s. Four congeners of this compound have been identified, namely; ATX-a, homoATX-a, dihydroATX-a, and dihydrohomoATX-a. According to Du et al. 2019, no analogues of ATX-a(s) (Fig. 5.2d) have been found.

Homoanatoxin-a (HTX) was isolated from a sample of *Oscillatoria* sp. HTX is a structural variant (Fig. 5.2e) differing from ATX by an ethyl group at the carbonyl-C (Colas et al. 2021). Due to its structural resemblance to ATX, HTX is produced by the same biosynthetic pathway, with the additional carbon derived from L-methionine via S-adenosyl-methionine (Plata-Calzado et al. 2022).

5.2.5 Saxitoxins

Saxitoxins (STXs), known as Paralytic Shellfish Poisons, are alkaloid neurotoxins (Oyaneder-Terrazas et al. 2022). These are primarily found in molluscs contaminated with toxic dinoflagellates. They act rapidly, blocking sodium channels in neurons, causing muscle paralysis, and leading to death within 2–30 min in mice. Saxitoxins form 57 analogues (Fig. 5.2g). They comprise a tetrahydropurine group and two guanidine subunits, representing a tricyclic perhydropurine backbone (Akbar et al. 2020).

Based on substitutions in variable positions (Functional Groups), the Saxitoxins family can be categorized into four groups: Carbamate, Decarbamoyl, N-sulfocarbamoyl, Deoxydecarbamoyl. Most known STXs are hydrophilic, except those produced by *L. wollei* in a freshwater environment (Mihali et al., 2008).

Among the roughly 200 natural products associated with tropical "*Lyngbya majuscula*", some have been identified as inducers of irritant contact dermatitis, known as dermatoxins. These include Aplysiatoxin (Nagai et al. 2019),

Debromoaplysiatoxin (Chen et al. 2023), Lyngbyatoxin A (Zhang et al. 2016), Malyngamides, Apratoxins, and Dolastatins (Brown 2022).

5.2.6 *Lyngbyatoxin*

Along with 12-epi-lyngbyatoxin, Lyngbyatoxin B and Lyngbyatoxin C, and compounds with similar chemical structures (Fig. 5.2k), had been extracted from Hawaiian specimens of "*L. majuscula*". (Pradhan et al. 2022). Lyngbyatoxin A is more lipophilic than the other lyngbyatoxins.

5.2.7 *Debromoaplysiatoxin*

Debromoaplysiatoxin was first isolated in 1977, and its structure was derived from extracts of *Lyngbya gracilis*, *Phormidium nigroviridis*, and *Schizothrix calcicola*. The phenolic bis-lactones aplysiatoxin (AT) (Fig. 5.2h) and debromoaplysiatoxin (Fig. 5.2i) (DAT) have similar structures, differing mainly in the absence of the bromine molecule on the benzene ring (Chen et al. 2023).

5.2.8 *Kalkitoxin*

Kalkitoxin (KT), a lipopeptide toxin with a molecular weight of 366.604 Da, was isolated from the marine cyanobacterium *Moorea producens*, formerly known as *Lyngbya majuscula*. According to the literature, the four methyl groups at methine chiral centres, the stereochemistry of the entire chemical structure ($C_{21}H_{38}N_2OS$), and the N–N-methyl groups are the major factors that influence kalkitoxin toxicity (Fig. 5.2j) (Shrestha et al. 2023). Studies have shown that thiazoline ring structure is a critical element of kalkitoxin's mechanism of cytotoxicity.

5.2.9 *Other Cyanotoxins and Cyanobacterial Lipopolysaccharides*

β-N-methylamino-l-alanine (BMAA) is a neurotoxin found in cyanobacteria which poses potential health hazards and, is associated with neurodegenerative diseases (Lopicic et al. 2022).

Lipopolysaccharides (LPS) are part of the outer membrane in gram-negative prokaryotes, including cyanobacteria. This has been linked to adverse health effects.

The structure of LPS generally follows highly complex core structures and variable O-polysaccharide chains. The moiety primarily responsible for toxicity is lipid A, composed of phosphorylated sugar units with linked acyl chains of varying length and saturation. Cyanobacterial LPS often lacks heptose and 3-deoxy-D-manno-octulosonic acid (or keto-deoxyoctulosonate; KDO), which are normally present in the core region of LPS in heterotrophic bacteria (Gemma et al. 2016). LPS activates toll-like receptors (TLR4), leading to a cascade of cellular reactions and the release of proinflammatory compounds. In healthy individuals, this triggers immune responses, but a massive reaction in response to LPS in the bloodstream can lead to a critical health status. LPS has been discussed as an (exogenous) hormone rather than a toxin, as its effects depend on the host response rather than its intrinsic toxic properties.

Though these cyanotoxins, with diverse mechanisms and impacts, highlight potential risks to human and animal health, structural modifications can still be made to utilize them in the industry.

5.3 Bioactivity and Genomics of Cyanotoxins

5.3.1 "mcy" and "nod" Gene Cluster

Microcystins and nodularins are synthesized through a combined nonribosomal peptide synthetase (NRPS) and polyketide synthase (PKS) pathway (Komaki and Tamura 2020). This pathway is known for synthesizing peptide antibiotics in bacteria and fungi. Cyanobacterial large multi-enzyme complexes include peptide synthetases, polyketide synthases, and tailoring enzymes. These are responsible for the production of microcystins. The genes encoding these enzymes have been characterized for various cyanobacterial species, including *Microcystis, Dolichospermum, Fischerella, Nostoc,* and *Planktothrix* (Wang et al. 2021).

The biosynthesis of nodularins is encoded by homologous genes characterized in *Nodularia.* The gene clusters for both microcystins and nodularins are approximately 50 kb pairs in size across different species, with variations in gene orders. The cyanobacterial genotypes should possess the complete gene clusters for the microcystin and nodularin production. At the same time, toxins are absent when genotypes lack essential parts of the cluster. More minor mutations in individual genes can render genotypes unable to synthesize microcystins. Several environmental factors, including temperature, light, pH, macronutrients, trace elements, and salinity, have been studied for their effects on microcystin production. These studies show an impact on microcystin content or cell quota; there is no consistent pattern in the regulation of microcystin within the cell quota. Inconsistencies can occur due to differences in culture conditions, toxin measurement methods, and the biomass proxy used for analysis (Jacinavicius et al. 2018).

5.3.2 "cyr" Gene Cluster

The complete gene cluster "cyr" responsible for the synthesis of cylindrospermopsin (CYN) was initially sequenced from *Raphidiopsis raciborskii*, spanning 43 kb and encoding 15 open reading frames (ORF). The biosynthesis involves an amidinotransferase, nonribosomal peptide/polyketide synthetases, and tailoring enzymes. A putative transporter (cyrK) is also encoded to export CYN from the cells. The presence of a putative NtcA (global nitrogen regulator) binding site within the "cyr" gene cluster suggests that CYN synthesis is influenced by nitrogen metabolism (Vico et al. 2020).

Several studies have investigated the influence of environmental factors on CYN production. Temperature, light, nutrients, and other environmental factors have been shown to influence CYN content, but the responses vary between strains and conditions. Unlike microcystins, a significant amount of cylindrospermopsins is usually found in the extracellular portion of the cells. Extracellular CYNs can constitute up to 20–40% of the total CYNs during log-phase growth, which may increase during the stationary phase.

5.3.3 "ana" Gene Cluster

Cyanobacteria produce anatoxin A (ATX). Although there are no specific studies on the stereoselectivity of the biochemical reaction towards the positive enantiomer, research has explored the biosynthesis and regulation of anatoxins. The identification of the first gene cluster coding for ATX biosynthesis (ana) was reported in *Oscillatoria* sp. PCC 6506. It mainly produces homoanatoxin (HTX). Subsequently, five other "ana" clusters were identified in various cyanobacterial strains, leading to different toxin profiles between organisms. The "ana" gene clusters share similarities in protein functions and identity in nucleotide sequences, particularly in the core genes "ana" B-G. The biosynthesis of ATX involves a polyketide synthase (PKS) family of multifunctional enzymes with a modular structural organization (Ballot et al. 2018). The adenylation domain protein "ana C" activates proline as a starter. The biosynthetic pathway includes "ana B", "ana C", and "ana D" in the initial steps, with "ana E", "ana F", "ana J", and "ana G" catalysing subsequent steps, leading to the production of HTX. The release of ATXs may involve the thioesterase "ana A", but this has not been experimentally verified. The influence of light, temperature, phosphorus, and nitrogen on cellular ATX content has been reported, but the effects seem to be strain-specific (Jin et al. 2021).

5.3.4 *"sxt" Gene Cluster*

The saxitoxin biosynthesis gene cluster "sxt" was initially characterized in *Cylindrospermopsis raciborskii* T3 and other strains, including *Dolichospermum circinale* AWQC131C, *Aphanizomenon* sp. NH-5, *Raphidiopsis brookii* D9, and *Lyngbya wollei*. The "sxt" clusters consist of biosynthetic enzymes (sxtA,sxtB, sxtD, sxtG, sxtH, sxtI sxtS, sxtT, and sxtU with diverse catalytic functions) (Geffroy et al. 2021), regulatory genes (sxtL, sxtN, and sxtX), and transporters (Moraes et al. 2021). Environmental factors, including alkalinity (pH > 8.5), high ammonia concentration (>1 mg/L), and high conductivity, have been suggested to influence STX production (Vingiani et al. 2020).

The biosynthesis of lyngbyatoxin (LTA) involves nonribosomal peptide synthetases, reduction, and prenylation steps. The core of the molecule is synthesized through these processes (Videau et al. 2016), successfully demonstrating the heterologous expression of LTA in a strain of *Anabaena* sp. (PCC 7120).

5.4 Biomedical Applications of Various Cyanotoxins

Generally, cellular metabolic processes in algae, bacteria, and plants produce valuable primary and secondary metabolites. Primary metabolites are directly involved in cellular developmental processes like cell division, growth, and reproduction. Conversely, secondary metabolites, such as hormonal compounds, antibiotics, or toxins, are not vital for primary cellular functions. The production of secondary metabolites is species-specific, and the environmental conditions around them can influence their production.

According to research, cyanobacteria grown under stress conditions are more likely to produce secondary metabolites (Filatova et al. 2021). These secondary metabolites can be transformed into value-added products, including pharmaceutical applications, allelopathic agents, biocides, etc. These secondary metabolites possess diverse properties, such as anticarcinogenic, antibiotic, antifungal, and antiviral, making them valuable for biotechnological applications (Jeong et al. 2020). During the twentieth century, numerous medical drugs emerged from several natural substances due to active human exploration of natural sources. These compounds contained antibiotics, immune suppressants, and cancer drug properties. Furthermore, cyanobacteria possess adaptations suited to various ecological niches, resulting in a vast pool of active natural substances. These substances exhibit diverse chemical structures and functions, producing numerous metabolites with anticancer, antiviral, and antifungal properties (Table 5.2).

Table 5.2 Bioactive secondary metabolites produced by various cyanobacteria against human pathogens

Medical property of metabolite	Metabolite	Chemical class	Biological target	References
Antiviral	Lectins	Protein	HIV-1 Simian immunodeficiency virus (SIV) Human herpes virus 6 (HHV-6)	(Shahid et al. 2020) (Huskens et al. 2010)
	Calcium-Spirulan (Ca-SP)	Polysaccharide	HIV-1, herpes simplex virus type 1 (HSV-1) Human cytomegalovirus (HCMV) Measles morbillivirus (MeV) Mumps virus, Influenza virus	(Carpine and Sieber 2021)
Antibacterial	Ambiguines	Alkaloid	*M. Tuberculosis*	(Nowruzi and Porzani 2021)
	Hapalindoles	Alkaloid	*S. aureus* *Pseudomonas aeruginosa* *M. tuberculosis*	(Nowruzi and Porzani 2021)
	Scytoscalarol	Terpene	*Bacillus anthracis* *S. aureus* *E. coli* *Candida albicans*	(Nowruzi and Porzani 2021)
Anticancer/ Antitumoral	Apratoxins	Cyclic depsipeptides	A549 (adenocarcinoma human alveolar basal epithelial cells) cancer cells	(Huang et al. 2016) (Robles-Bañuelos et al. 2022)
	Microcystins	Cyclic heptapeptides	Myeloma cancer cell lines Pancreatic cancer	(Shishido et al. 2019) (Kailash et al. 2022)
	Saxitoxin	Alkaloid	Interacting with site 1 of the voltage-gated Na + channel Suppresses the expression of inflammatory cytokines	(Flores-Holguín et al. 2024)
	Cryptophycins	Alkaloids	Apoptosis in cancer cells through microtubule inhibition	(Eren et al. 2021; Fanale et al. 2015)

(continued)

Table 5.2 (continued)

Medical property of metabolite	Metabolite	Chemical class	Biological target	References
Analgesic/ Anaesthetics	Neosaxitoxin	Alkaloid	Local anaesthesia	(Jeong et al. 2020)
	Gonyautoxins	Alkaloid	Pain relief in tension-type headache	(Jeong et al. 2020)
Antifungal	Laxaphycins	Cyclic heptapeptide	*Aspergillus oryzae* *Candida albicans* *Penicillium notatum* *Saccharomyces cerevisiae* *Trichophyton mentagrophytes*	(Srivastava et al. 2022a) (Bornancin et al. 2019)
	Lyngbyabellin	Lipopeptides	*Moorea* sp. *Okeania* sp. *Perforafilum* sp.	(Dahiya et al. 2020)
	Cryptophycin A	Depsipeptide	*Candida albicans* *Candida glabrata*	(Weiss et al. 2017)
	Tolytoxin	Diterpene lactone	*Saccharomyces pastorianus* *Neurospora crassa* *Candida albicans* *Pythium ultimum* *Rhizoctonia solani*	(Shishido et al. 2015)
Anti-protozoal	Aerucyclamide	Alkaloid	*P. falciparum*	(Niedermeyer and Orst 2015)
Anti-inflammatory	Aeruginosins	Fatty acids	Reduces levels of interleukin-8 (IL-8) and intercellular adhesion molecule-1 (ICAM-1)	(Tabarzad et al. 2020)

5.4.1 Anticancer Activity

5.4.1.1 Microcystin

Microcystin-LR has been identified as inducing toxic effects in the myeloma Sp2/01 cell line. The microcystin-LR delineates their potential therapeutic efficacy and modes of toxicity in myeloma cancer cell lines (Kailash et al. 2022). Consequently, it is proposed that microcystin compounds represent promising candidates for targeted drug development in cancer research and warrant thorough pharmacological evaluation, underscoring their significance in this context.

MC-LR is a model molecule for developing targeted cancer treatments that are effective against pancreatic cancer and other tumours with specific organic anion-transporting polypeptides (OATPs) expression. OATPs, particularly OATP1B1 and 1B3, enable cellular uptake. Increased levels of OATPs in pancreatic cancer show potential for new treatments (Kounnis et al. 2015). However, careful adjustment of

chemicals is necessary to prevent organ-specific side effects. Structural modifications of cyanotoxins can alter their selectivity for specific substrates, rendering them valuable for targeted cancer therapy.

5.4.1.2 Cyanotoxin Analogues

Analogues of cyanotoxins show potential as antitumor agents in biomedicine. Specific cyanotoxins exhibit strong cytotoxic effects against cancer and viral cells, making them promising candidates for antitumour therapy.

Approximately 80% of adult acute leukaemia cases in the United States are classified as acute myeloid leukaemia (AML) (Jani et al. 2023). The current treatment for the disease relies on chemotherapy and anti-leukaemic drugs. Several studies have shown that cyanotoxins contain anti-leukaemic compounds and hold the potential for natural medicines to AML. Some cyanotoxins have shown significant anti-leukaemic activity, with organic extracts displaying ≥70% effectiveness, while some toxins display the properties in hydrophilic extracts.

Cell extracts from *Nostoc* sp., *Cyanobium* sp., and *Oxynema* sp. induced apoptosis in AML cell lines. Aqueous extracts from these species, except *Nostoc* sp., also demonstrated anti-leukaemic activity, particularly at a concentration of 13.3 mg DW mL^{-1}, which exhibited a high potency in inducing cell death in human leukaemia MOLM-13 cells. Some strains of *Fischerella* spp. and *Nostoc* spp. have produced anti-leukaemic compounds with greater potency against MOLM-13 cells than normal rat kidney epithelial cells (Shishido et al. 2019).

5.4.1.2.1 Saxitoxin

Saxitoxin is a group of compounds with a basic structure of trialkyl tetrahydrofuran. This structure constitutes the two permanent guanidinium moieties characterized by NH_2 groups at positions 2 and 8 of the purine ring. The functional groups located at four positions around the purine ring divide this compound into four main categories. Within these toxins, the most potent ones fall under the carbamate division, ranked as saxitoxin (STX), neosaxitoxin (NeoSTX), and gonyautoxin (GTX1) (Flores-Holguín et al. 2024). Certain analogues of STX demonstrate significant pharmaceutical promise due to their capacity to induce anaesthesia by interacting with site 1 of the voltage-gated Na + channel (Wiese et al. 2010). Neosaxitoxin (NeoSTX) suppresses the expression of inflammatory cytokines produced by macrophages by blocking intracytoplasmic voltage-gated sodium channels. The NeoSTX potentially helps treat various conditions characterized by inflammation, such as multiple sclerosis, osteoarthritis, and cancer, as well as disorders affecting the muscles and immune system (Flores-Holguín et al. 2024).

Though cyanotoxin analogues exhibit anaesthetic properties owing to their potent neurotoxicity, showing promise for anaesthetic development, ensuring reversible nerve function suspension is essential to prevent permanent damage.

5.4.1.2.2 Apratoxins

Apratoxins are renowned for their powerful antiproliferative effects against various human cancer cell lines. These compounds are classified as cyclodepsipeptides and are extracted from marine cyanobacteria (Robles-Bañuelos et al. 2022). Apratoxin analogues enhance therapeutic efficacy by enhanced selectivity and robust antitumor activity on cancer cells. Anticancer drugs usually affect organs like the bone marrow, liver, gastrointestinal tract, and kidneys. Interestingly, the pancreas is the primary site affected by apratoxin A, which is a less frequently targeted organ. However, apratoxin A exhibited minimal toxicity in the organs commonly targeted by current therapeutic regimens. This suggests it could be a safe combination partner with standard chemotherapeutic agents. Also, Apratoxin A shows selective activity against A549 (Adenocarcinoma human alveolar basal epithelial cells) cancer cells compared to normal liver cells (Huang et al. 2016).

5.4.1.2.3 Cryptophycins

Cryptophycin-1, a cyanotoxin derived from filamentous cyanobacterium *Nostoc* sp., has been explored as a promising anticancer agent. The antitumor cryptophycins are synthetic derivatives of the cryptophycins. Cryptophycin exhibits selective antitumor properties by inducing apoptosis in cancer cells through microtubule inhibition, similar to Vinca alkaloids (Fanale et al. 2015). Cryptophycins is a depsipeptide with the attachments of four fragments; two ester and two amide linkages make cryptophycin-52 structure, which undergoes phase II clinical trials (Eren et al. 2021).

5.4.2 Antifungal Activity

5.4.2.1 Tolytoxin

Tolytoxin is a macrocyclic lactone isolated from *T. conglutinate* and is an essential antifungal metabolite. The compound demonstrates activity against various fungi, including *Saccharomyces pastorianus*, *Neurospora crassa*, *Candida albicans*, *Pythium ultimum*, *Rhizoctonia solani*, and *Sclerotinia homoeocarpa* (Karpiński 2019).

5.4.2.2 Scytophycins

Scytophycins are macrolides initially isolated from *Scytonema pseudohofmanni*. They are potent cytotoxins and fungicides. Later, Scytophycin was detected from many *Anabaena* strains, including *Anabaena* sp. HAN21/1, *Anabaena* cf. *cylindrica* PH133, *Nostoc* sp. HAN11/1, and *Scytonema* sp. HAN3/2(Karpiński 2019) (Fig. 5.3).

5.5 Cyanobacterial Cytotoxic Metabolites Other Than Cyanotoxins

5.5.1 Anticancer Activity

5.5.1.1 Dolastatin 10

Dolastatin 10 is a significant marine cyanobacterial metabolite initially isolated from sea hare *Dolabella auricularia* and later isolated from *Symploca* sp. It binds to tubulin at the rhizoxin-binding site, disrupting microtubule assembly and inducing cell death in the G2/M phase (Nandi et al. 2024). In the Phase II clinical trial for patients with hormone-refractory prostate cancer, Dolastatin 10 showed excellent tolerance, particularly among the elderly pre-treatment population (Montuori et al. 2023). Dolastatin 10 exhibited notable antiproliferative activity across four distinct human lymphoma cell lines of DB, HT, RL, and SR. Additionally, it effectively triggers apoptosis in non-Hodgkin lymphoma cells (Cragg and Pezzuto 2016).

5.5.1.2 Calothrixin A and B

These two are bioactive molecules whose structural arrangement is assembly to quinoline, quinone, and indole pharmacophores. Calothrixins have been isolated from the cyanobacterial species *Calothrix*. Calothrixin B is commonly recognized as the neutral analogue, whereas calothrixin A is identified as its N-oxide counterpart. It has considerable antiproliferative efficacy against various cell lines like human cervical cancer cells, human colon cancer cells, and human Jurkat cancer cells (Moorthy et al. 2018). Calothrixin A was found to induce cell death through apoptosis in a manner dependent on both time and concentration.

5.5.1.3 Suomilide

Sequencing the complete genome of *Nodularia sphaerocarpa* UHCC 0038 and using bioinformatic analysis of Ahmed et al. 2021 demonstrated that suomilide belongs to the aeruginosin family. Aeruginosins have a complex chemical structure

characterized by the presence of an unusual 2-carboxy-6-hydroxyoctahydroindole (Choi) moiety and the C-terminal arginine derivatives argininal, argininol, agmatine, 1-amidino-2-ethoxy-3-aminopiperidine, or more rarely the 1-amino-2-(*N*-amidino-Δ3-pyrrolinyl)-ethyl (Aeap) moiety (May et al. 2020). Studies have shown that suomilide is a potential lead for developing anti-invasive drugs; in the bigger picture, advocates that aeruginosins are an excellent source of drug leads for developing protease inhibitors (Ahmed et al. 2021).

5.5.2 Antiviral Activity

Antiviral compounds isolated from cyanobacteria typically exhibit bioactivity by blocking viral absorption or penetration and inhibiting replication stages of progeny viruses after penetration into cells. The most common antiviral compounds of cyanobacteria are lectins and carbohydrates.

5.5.2.1 Lectins

Lectins are proteins that can exist as monomers or oligomers. They can bind to carbohydrates specifically and reversibly, such as by including glycoproteins in viral envelopes. The most common cyanobacterial lectins are Cyanovirin-N, Microvirin, Scytovirin, *Microcystis viridis* lectin, and *Oscillatoria agardhii* agglutinins. These lectins are typically isolated from freshwater cyanobacterial cultures; *Nostoc ellipsosporum, Microcystis aeruginosa, Cytonema varium, Microcystis viridis,* and *Oscillatoria agardhii*, respectively (Mazur-Marzec et al. 2021).

Cyanovirin-N (CV-N)
Cyanovirin-N (CV-N) functions by blocking the interaction between the human immunodeficiency virus (HIV) gp120 protein and the CD4 T-cell receptor. In addition to that, it is effective against a range of enveloped viruses such as simian immunodeficiency virus (SIV), chimeric SIV/HIV-1 virus (SHIV89.6P), feline immunodeficiency virus (FIV) (Mazur-Marzec et al. 2021), human herpes virus 6 (HHV-6), measles virus (MeV), Ebola virus, hepatitis virus, and influenza virus. These antiviral effects are related to CV-N's interaction with N-linked high mannose oligosaccharides present on the glycoprotein components of these viruses.

Microvirin (MVN)
Microvirin (MVN) proved highly effective against different strains of HIV-1 and cell types, with IC50 values of 2–12 nM. It also prevented merging infected and uninfected cells in the T-cell line HUT-78 (Shahid et al. 2020).

Scytovirin (SVN)
Scytovirin (SVN) possesses activity against different HIV isolates as well as Zaire Ebola virus (ZEBOV).

Microcystis viridis Lectin

Microcystis viridis lectin actively inhibited the cell conjugation of HIV-I cells and HCV cells. The IC value is around 30 nM (Singh et al. 2023).

Oscillatoria Agardhii Agglutinins (OAA)

Oscillatoria agardhii agglutinins (OAA) block the viral insertion of target cells in HIV-I, HIV-I group O isolates, and HIV-2 strains. They also inhibit HIV replication in MT-4 cells.

Calcium Spirulina (Ca-SP) and Nostoflan

The most common carbohydrate antiviral compound of cyanobacteria is Calcium Spirulina (Ca-SP), isolated from *Spirulina platensis*, and nostoflan, isolated from *Nostoc flagelliforme*. Both carbohydrates are active against enveloped viruses such as HIV-1, herpes simplex virus type 1 (HSV-1), human cytomegalovirus (HCMV), measles morbillivirus (MeV), mumps virus, and influenza virus (Carpine and Sieber 2021).

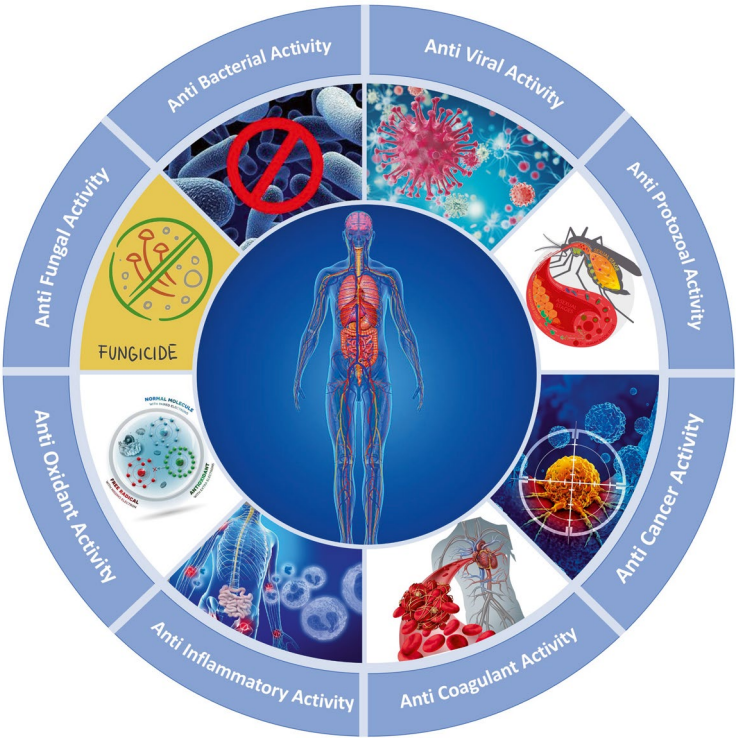

Fig. 5.3 Schematic representation of the diverse biomedical properties associated with cyanobacterial secondary metabolites, highlighting their potential applications in biomedical research

5.5.3 Antibacterial Activity

Hapalindoles
These groups are categorized as tetracyclic and tricyclic compounds. Various hapalindoles, such as Hapalindoles A, B, and T, along with epimers of hapalindoles, are derived from the *Hapalosiphon fontinalis* species. Hapalindole A is described as a chlorinated isonitrile-containing tetracyclic indole alkaloid. Hapalindole T exhibited antibacterial properties, with a MIC value of 2.5 μg/ml against *S. aureus* and 2.0 μg/ml against *Pseudomonas aeruginosa*. Additionally, at a 2.5 μg/ml concentration, Hapalindole T demonstrated activity against *M. tuberculosis* comparable to the anti-TB drug rifampicin (Nowruzi and Porzani 2021).

Ambiguines
Ambiguines were extracted from crude samples of *Fischerella ambigua*, *H. hibernica*, and *Westiellopsis prolifica*. These compounds bear a structural resemblance to hapalindoles. It features an isoprene unit attached to the C(2) position of the indole moiety. The different toxic compounds of the ambiguine group, such as Ambiguines A–F, K–O, K–N, H–J, P, and Q, are harmful. Ambiguine K isonitrile exhibited moderate activity against *M. tuberculosis*, with a minimum inhibitory concentration (MIC) value of 6.6 μM. Ambiguines H and I isonitriles showed antibacterial activity similar to antibiotics like streptomycin and puromycin (Nowruzi and Porzani 2021).

Scytoscalarol
Scytoscalarol, an antimicrobial cyano-terpene that was obtained from cultured cyanobacterium *Scytonema* sp. (UTEX 1163) through bioassay-guided fractionation. It contains a guanidinium or guanidino group. It displayed antimicrobial activity against *Bacillus anthracis, S. aureus*, *E. coli*, and *Candida albicans,* with MIC values ranging from 2 to 110 μM (Nowruzi and Porzani 2021). Furthermore, scytoscalarol demonstrated low toxicity (IC_{50} 135 μM) against green monkey kidney cells. Additionally, they indicate weak activity against *M. tuberculosis*.

5.5.3.1 Cyano Peptides

Only a few cyanobacterial peptides exhibit antibacterial properties. For instance, kawaguchi-peptins A and B, isolated from *Microcystis aeruginosa* NIES-88 strain, demonstrate similar minimum inhibitory concentration (MIC) values against *S. aureus* (Parajuli et al. 2016). Additionally, pitipeptolides A, B, C, E, and F, reported from *Lyngbya majuscula*, show activity against *M. tuberculosis* (Cock and Cheesman 2023).

5.5.3.2 Cyano Terpenes

A few terpenes from cyanobacteria have been identified for their antibacterial properties. One example is the diterpenoid noscomin, isolated from *Nostoc commune*, which shows activity against *Bacillus cereus*, *Staphylococcus epidermidis*, and *Escherichia coli* (Srivastava et al. 2022). Another antibacterial terpenoid is cybastacines A and B from *Nostoc* sp., which exhibit more significant activity against the gram-positive bacteria *Bacillus anthracis* and *S. aureus* compared to *E. coli* (Nandagopal et al. 2021a).

5.5.3.3 Cyanobacterial Lipids

Most of the cyanobacterial lipids possess quorum sensing inhibiting activity. Lyngbyoic acid, pitinoic acid A, and doscadecanamide A have been discovered to disrupt quorum sensing (QS) in *Pseudomonas aeruginosa*. The potent antibacterial γ-linolenic acid (GLA) from *Fischerella* sp. was active against *S. aureus*. Polyhalogenated compounds (PHCs) such as Ambigols A, B, C, D, and E are also produced by cyanobacteria. These compounds are effective against methicillin-resistant *S. aureus* (MRSA) (Kar et al. 2022).

5.5.3.4 Malyngolides

The first polyketide antibiotic found in cyanobacteria is malyngolide, which is isolated from *Lyngbya majuscula*. It effectively inhibits the growth of several gram-positive human pathogenic strains like *Mycobacterium smegmatis*, *Streptococcus pyogenes*, *Staphylococcus aureus*, and *Bacillus subtilis*, but is inactive against the gram-negative *Salmonella enteritidis* and *Escherichia coli*. The malyngolide disrupts the quorum sensing (QS) of two gram-negative bacteria, *Chromobacterium violaceum* CV017 and *Pseudomonas aeruginosa*. This disruption can help mitigate the development of antibiotic-resistant strains (Nandagopal et al. 2021b).

5.5.4 Antifungal Activity

According to the literature, among the secondary metabolites of cyanobacteria, nearly 106 secondary metabolites contain antifungal properties. These compounds belong to different chemical groups, including peptides, phycobiliproteins, enzymes, carbohydrates, fatty acids, alkaloids, polyketides, macrolides, phenolic compounds, terpenoids, and polymers. The hapalindole-type alkaloids were predominant among the identified antifungal compounds. The genera *Fischerella* and *Scytonema* were pivotal producers of these antifungal compounds (do Amaral et al. 2023). Initially

identified, most of the antifungal agents were later revealed to be highly potent cytotoxins.

5.5.4.1 Cyanotoxin Analogues

Laxaphycins
Laxaphycins (Laxas) are β-amino fatty acid-derived antifungal metabolites from cyanobacterium *Anabaena laxa*. They have been isolated and found to exhibit antifungal activity against various fungal species, including *Aspergillus oryzae*, *Candida albicans*, *Penicillium notatum*, *Saccharomyces cerevisiae*, and *Trichophyton mentagrophytes* (Bornancin et al. 2019).

Lyngbyabellin
Lyngbyabellin B is an antifungal compound containing two thiazole units and one chlorinated β-hydroxy acid. This compound is produced by the *Lyngbya* genus, as well as genera such as *Moorea*, *Okeani*a, and *Perforafilum*. It has been found to suppress *Candida albicans* (Dahiya et al. 2020).

Cryptophycin A
Cryptophycin A is a cyclic depsipeptide that has been documented to exhibit activity against *C. neoformans* and various other species of fungi. This compound is produced by a symbiotic cyanobacterium, *Nostoc* sp. (Weiss et al. 2017).The fungi *Candida albicans, Candida glabrata*, and a fluconazole-resistant strain of *Candida albicans* have their growth suppressed by Cryptophycin A.

Majusculamides
Four Majusculamides (Majusculamides A-D) have been identified. Majusculamides A and B are cytotoxic lipopeptides extracted from the marine cyanobacteria *Lyngbya majuscula*, exhibiting antilarval settlement activities (Du et al. 2019). Majusculamide C was previously discovered in cyanobacteria originating from the Marshall Islands and has been documented to possess antifungal properties (Barzkar et al. 2019).

Schizotrin A
Schizotrin A is an antifungal metabolite derived from the strain *Schizothrix* sp. This compound incorporates β-amino acids into its peptide chain. This compound has been found effective against various fungi, including *Fusarium oxysporum*, *Colletotrichum gloeosporioides*, *Saccharomyces cerevisiae*, *Candida albicans*, *Candida tropicalis, Rhodotorula mucilaginosa*, *Sclerotium rolfsii*, and *Rhizoctonia solani*.

Nostofungicidine is a cyclic peptide that is an antifungal compound extracted from the terrestrial cyanobacterium *Nostoc commune*. It exhibits bioactivity against the fungus *Aspergillus candidus* (Nandagopal et al. 2021).

Hassallidin A
Hassallidin A was tested against a panel of 16 Candida strains, including *C. albicans*, *C. krusei*, *C. neoformans*, and *C. parapsilosis*. This compound was extracted from the epilithic cyanobacterium *Hassallia* sp. (Nandagopal et al. 2021).

5.5.5 Anti-Protozoal Activity

Against the activity of protozoans such as *Plasmodium*, *Trypanosoma*, *Leishmania*, and *Schistosoma*, cyanobacteria produce a variety of anti-protozoal compounds, including Viridamide A, Symplocamide A, Venturamides, Dragomabin, and Ambigol C.

An alkaloid extracted from *Nostoc* sp., known as nostocarboline, exhibits activity against *Trypanosoma brucei*, *Trypanosoma cruzi*, *Leishmania donovani*, and *Plasmodium falciparum*, with IC_{50} values ranging from 0.5 to 0.194 μM (Nandagopal et al. 2021). Additionally, *Microcystis aeruginosa* releases a compound known as Aerucyclamide C, which is documented for its suppressive effects on *T. brucei* and *P. falciparum*.

5.5.5.1 Antimalarial Properties

5.5.5.1.1 Cyanotoxin Analogues

Aerucyclamide
The ribosomal cyclic peptide aerucyclamide B derived from *M. aeruginosa* is identified as the most potent antiplasmodial compound discovered in cyanobacteria. It demonstrates an IC_{50} value of 0.7 μM against *P. falciparum* with significantly lower cytotoxicity. Another promising lead compound, Balgacyclamides, is obtained from a different strain of *M. aeruginosa* and displays similar activity levels.

5.5.5.1.2 Cyanobacterial Metabolites

Lagunamides A and B
The marine cyanobacterium *L. majuscula* possesses antimalarial properties. It contains cyclodepsipeptides known as Lagunamides A and B. Lagunamide A demonstrated an IC_{50} value of 190 nM, Lagunamide B showed an IC_{50} value of 910 nM against the *P. falciparum* NF54 strain.

Lyngbyabellin
Marine cyanobacteria such as *Moorea producens*, *Moorea bouillonii*, and *Okeania* sp. are also abundant sources of depsipeptides called lyngbyabellins. These compounds exhibit significant antimalarial activities. Lyngbyabellin A, isolated from

Fijian *Moorea producens* that emerged as the most potent cyclic peptide, with an EC_{50} of 1.5 nM against the asexual stages of *P. falciparum*. Furthermore, compounds derived from antimalarial extracts of *Moorea producens* displayed moderate activity against *P. berghei* liver-stage parasites (Sweeney-Jones et al. 2020).

Cell extracts of Calothrix isolates inhibited the growth in vitro of a chloroquine-resistant strain of the malarial parasite *Plasmodium falciparum*.

5.5.6 Anticoagulant and Anti-Inflammatory Activity

Various chemicals with anti-inflammatory activity are excreted from cyanobacteria.

5.5.6.1 Cyanobacterial Metabolites

Aeruginosins
Aeruginosins are comprised of an N-terminal short fatty acid chain, L-Tyr, L-Choi, and L-argininal, and in some cases, a pentose sugar. It is notably found in *Nostoc* sp. but also structural variants in *Nodularia spumigena.* It reduces levels of interleukin-8 (IL-8) and intercellular adhesion molecule-1 (ICAM-1), both proinflammatory mediators (Tabarzad et al. 2020).

Sacran
Sacran from the *Aphanothece sacrum* exhibits anti-inflammatory activity in different animals, such as mice. Additionally, the heteroglycan compound Nc-5-s, isolated from *Nostoc commune*, significantly reduces IL-6 secretion and increases IL-10 secretion in monocytes (Tabarzad et al. 2020).

Coibacins
Coibacin B is a lactone derivative, while Coibacin A is a natural product isolated from *Oscillatoria* sp. Both are significantly affecting the gene transcription of IL-1β and iNOS cytokines (Tabarzad et al. 2020).

Furthermore, C-phycocyanins and exopolysaccharides of some cyanobacteria have significant anticoagulant activity in the human body (Barzkar et al. 2019).

5.6 Utility of Cyanotoxins in Other Industrial Applications

5.6.1 Allelopathic Agents and Biocide

Numerous secondary metabolites synthesized by cyanobacteria demonstrate inhibitory properties against the growth of diverse organisms, such as encompassing large land plants, algae, and microorganisms. Thereby presenting themselves as potential allelochemicals. Compounds such as MC-LR and MC-RR have hindered photoautotrophic organisms' growth by disrupting photosynthetic pigment synthesis. Moreover, compounds such as MC-LR and ATX-a have been found to inhibit the growth of insect larvae, including the stem borer *Chilo agamemnon* and the leaf miner *Hydrellia prosternalis.* This indicates their potential application as insecticides (Li et al. 2023). However, when developing agricultural products, it is crucial to carefully evaluate the possible adverse effects of modified natural cyanotoxins on non-target organisms. Although there is potential for creating valuable products, it is essential to ensure that cyanotoxins or secondary metabolites do not inadvertently harm the environment or non-target organisms.

5.6.1.1 Allelopathic Reactions

Microcystins have been discovered as growth-hindering molecules of numerous macrophyte species and reduce photosynthetic oxygen production. This leads to changes in pigment patterns and content in various macrophytes such as *Chara demersum*, *Myriophyllum spicatum*, and *Vallisneria natans*. Furthermore, exposure to MCs can diminish growth rates, chlorophyll-a concentration, and photosynthetic rates of specific charophyte species. They also act as allelopathic agents, with a pronounced impact on charophyte species compared to angiosperms.

Aquatic plants have an antioxidant system comprising antioxidant enzymes and glutathione (GSH) to defend against oxidative stress. Exposure to elevated levels of MCs has increased the activities of antioxidant enzymes like peroxidase (POD), superoxide dismutase (SOD), glutathione S-transferase (GST), glutathione peroxidase (GPX), and ascorbate peroxidase (APX) in diverse macrophytes. Moreover, MCs can impact GSH content, a crucial element in detoxification, through conjugation with absorbed toxins.

While most of the studies have concentrated on the allelopathic effects of cyanotoxins on aquatic plants at their high concentrations, some investigations have reported minor or detrimental effects even at environmentally relevant concentrations (Pindihama and Gitari 2017). Additionally, cyanotoxins such as cylindrospermopsin can impact aquatic plants by hindering protein and glutathione synthesis, leading to growth inhibition, modulating protease activity, and inducing changes in root histology and microtubule organization (Máthé et al. 2021).

Exposure to anatoxin-a has been associated with reduced photosynthetic oxygen production and heightened peroxidase and glutathione S-transferase activities in

floating aquatic macrophytes like *Lemna minor*. Furthermore, anatoxin-a can disturb homeostasis in submerged aquatic macrophytes such as *Ceratophyllum demersum* by triggering oxidative stress.

5.6.2 *Insecticide and Larvicide Activity*

The presence of hepatotoxic microcystins and the neurotoxic compound anatoxin-a were found to possess significant larvicidal properties against *Aedes aegypti* (Ayala et al. 2019). Additionally, when cyanobacteria were utilized as a biofertilizer, several strains demonstrated the ability to inhibit the development of mosquito larvae. Methanolic extracts from an isolate of *Westiellopsis* sp. exhibited larvicidal effects on various mosquito species (Rao et al. 1999), containing *Aedes aegypti* (a vector for Dengue Fever), *Anopheles stephensi* (a vector for malaria), and *Culex tritaeniorhynchus* and *C. quinquefasciatus* (vectors of encephalitis).

Cyanobacterial anatoxin-a specifically targets nicotine acetylcholine receptors in arthropods. Simultaneous exposure to natural toxins could impair the challenge for *Daphnia* to withstand cyanobacterial blooms, potentially reducing reproduction rates (Schwarzenberger 2022). The survival of *Daphnia magna* declined progressively over time, with microcystin-LR and other secondary metabolites playing a significant role in the negative impact of *D. magna* survival and stress response (Bojadzija Savic et al. 2021) (Fig. 5.4).

5.7 Conclusion

In conclusion, the chapter has provided an insightful exploration of cyanobacterial toxins and their multifaceted applications in therapeutic and industrial contexts. We have explored the elaborate chemistry between cyanobacteria and their toxin-producing gene clusters to uncover their medicinal uses and industrial potential

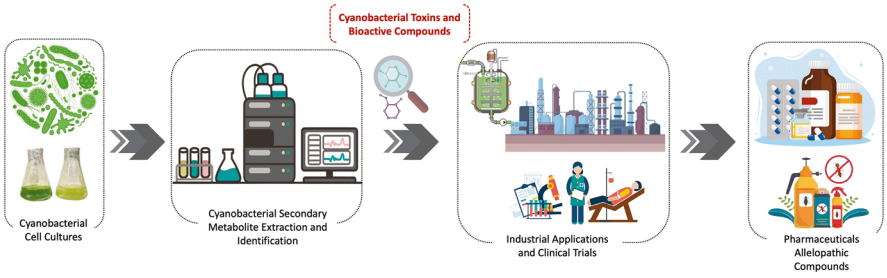

Fig. 5.4 Progression from laboratory-scale research to scaled-up industrial production of cyanobacterial metabolites, for commercially valuable pharmaceutical and other industrial applications

using a diverse array of cyanotoxins and secondary metabolites. As we unravel the mysteries of cyanobacterial toxins, there is great potential for exploiting their therapeutic benefits and industrial applications. The future holds exciting possibilities for unlocking the full potential of cyanobacterial toxins in various fields. Ongoing research and innovation are key to supporting these novel advancements and discoveries.

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