REVIEW

The paradox of cyanotoxins: from natural toxins to biotechnological resources

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Abstract

Cyanotoxins are highly toxic secondary metabolites produced by cyanobacteria that decrease water quality and exert a wide range of harmful effects on many organisms, including humans, through the food web. For many years, cyanotoxins were examined solely for their toxic effects; however, ongoing molecular biology, biochemistry, and applied biotechnology research on these metabolites has contributed to reframing them as valuable natural compounds in medicine, agriculture, and environmental biotechnology. Cyanotoxins exhibit anticancer, antimicrobial, allelopathic, and biopesticidal activities, providing promising opportunities for novel therapeutics, sustainable agriculture, and enhanced environmental remediation. Nevertheless, their high toxicity, potential harmful effects on non-target organisms, and environmental persistence necessitate comprehensive safety evaluations, environmental risk assessments, and the development of controlled application strategies. This review aims to highlight the ecological and biotechnological significance of cyanotoxins and seeks to stimulate further investigations into these natural metabolites as promising candidates for future sustainable technological developments.

Keywords: bioactivities, biotechnological applications, cyanobacteria, cyanotoxins, microcystins.

Introduction

Cyanobacteria are a diverse group of prokaryotes, occurring as unicellular, colonial, or multicellular forms, most of which are capable of photosynthesis and producing carbon and oxygen (Martínez-Burgos et al., 2024). As one of the oldest life forms on Earth, cyanobacteria played a pivotal role in the Great Oxidation Event approximately 2.1–2.4 billion years ago (Lyons, Reinhard & Planavsky,. 2014). At present, they continue to play crucial roles in the global oxygen, carbon, and nitrogen cycles (Kaštovský, 2024). Cyanobacteria exhibit a cosmopolitan distribution, including extreme habitats, and are mainly present in marine and freshwater ecosystems as planktonic members of the water column (Mehdizadeh Allaf & Peerhossaini, 2022). Although cyanobacteria constitute an essential component of the biosphere, they also pose significant risks to environmental and public health due to their ability to produce highly potent toxic secondary metabolites (Villalobos, Suárez-Isla & Garcia, 2025). These bioactive compounds, known as cyanotoxins, can cause severe intoxication in aquatic and water-associated terrestrial organisms, sometimes leading to fatal outcomes, particularly during cyanobacterial blooms (Giannuzzi et al., 2011; Metcalf et al., 2021).

Interestingly, despite their toxicity, an increasing number of studies report that cyanotoxins may have considerable potential for diverse biotechnological applications (Li et al., 2023). Within the scope of this review, a bibliometric screening of the Web of Science Core Collection database (2000–2025) was performed using “microcystins” as the search keyword and refined by the research area “Biotechnology & Applied Microbiology”. This screening indicates that approximately 5.3% (n = 353) of microcystin-related publications are biotechnology-focused. Although cyanotoxins have traditionally been examined primarily for their harmful effects, recent biotechnological developments have renewed scientific interest in their diverse biological activities. This paradox illustrates that, despite their hazardous nature, these natural metabolites can also act as valuable resources for innovative applications in medicine, agriculture, and environmental management.

This review focuses on the toxic secondary metabolites produced by cyanobacteria, summarizes their general characteristics, and discusses recent insights into their biotechnological potential. In this context, it provides a comprehensive, literature-based assessment of how cyanotoxins are being reframed from harmful compounds into valuable biotechnological resources.

General characteristics and classification of cyanotoxins

Cyanotoxins are secondary metabolites produced by cyanobacteria, comprising highly potent toxic compounds. Although not essential for vegetative growth, secondary metabolites perform adaptive functions such as mediating ecological competition, providing defense, and facilitating metal transport (Thirumurugan et al., 2018; Ndungu et al., 2025). Cyanobacterial secondary metabolites exhibit a wide range of biological activities, including antibiotic, antiviral, antialgal, antiprotozoal, antifungal, anticancer, cytotoxic, anti-inflammatory, enzyme inhibitory, and free radical scavenging properties (Pooja & Niveshika, 2022). According to a widely accepted perspective in the literature, cyanotoxins are produced as a defensive response to environmental stress, providing cyanobacteria with survival and competitive advantages within ecosystems (Ger et al., 2016; Polyak & Sukharevich, 2025). These toxins not only protect cyanobacteria from grazing pressure but also confer a competitive advantage by limiting the development of microbial competitors. Furthermore, toxin production is also regarded as a key physiological mechanism facilitating cyanobacterial adaptation to unfavorable environmental conditions. Cyanotoxins play a variety of physiological roles, including cell signalling, nutrient uptake, iron scavenging, maintenance of homeostasis, and protection against oxidative

stress (Holland & Kinnear, 2013). To date, over 3000 cyanobacterial secondary metabolites have been identified. However, the toxic properties and mechanisms of action of most remain largely unstudied (Weiss et al., 2025; Almeida et al., 2025; Marumure et al., 2025). Therefore, assuming that cyanobacterial strains that do not produce well-known cyanotoxins are entirely non-toxic would be misleading. Several studies have demonstrated that certain strains may still display toxic effects even in the absence of well-characterized toxic metabolites (Rzymski et al., 2017; Falfushynska et al., 2021).

Cyanotoxins, based on their chemical structures, are classified as cyclic peptides, alkaloids, lipopeptides, non-protein amino acids, and lipopolysaccharides (Kaebernick & Neilan, 2001; Du et al., 2019). Cyanobacterial lipopolysaccharides, which are present in all cyanobacteria, are defined as cyanotoxins owing to their dermatotoxic and pro-inflammatory properties (Bláha, Babica, & Maršálek, 2009; Durai, Batool, & Choi, 2015). Furthermore, cyanotoxins are typically categorized as hepatotoxins, neurotoxins, dermatotoxins, and cytotoxins based on their primary target organs (Fig. 1) (Kaebernick & Neilan, 2001; Rajput et al., 2024).

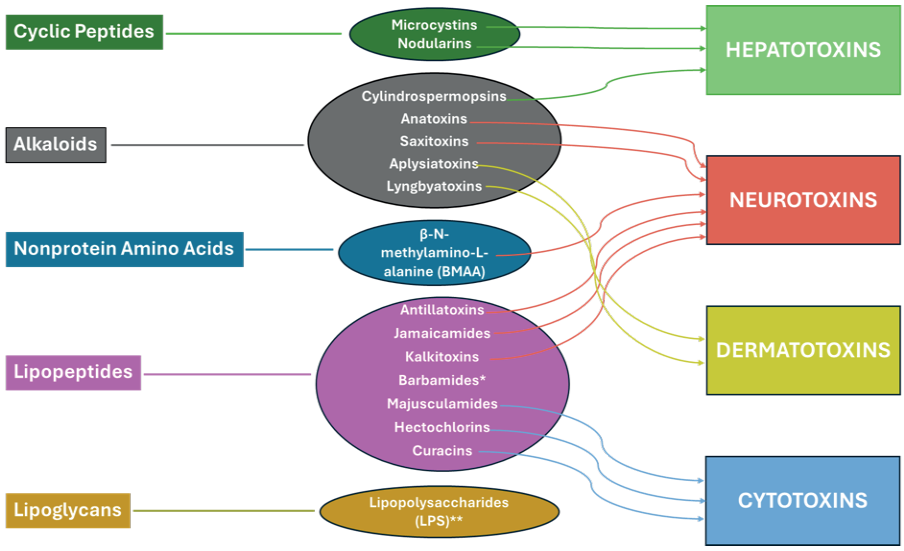

Figure 1. Chemical and functional classification of cyanotoxins (Adapted from Du et al., 2019).

*: Molluscicid,

**: Endotoxin (acts as an irritant and can trigger allergenic responses in human and animal tissues).

Cyanotoxin groups can be produced by multiple cyanobacterial genera, and a single cyanobacterial strain may have the ability to produce more than one cyanotoxin group. For example, members of the genera *Microcystis*, *Anabaena*, and *Planktothrix* can produce both neurotoxins and hepatotoxins (Table 1), and some cyanobacterial strains are capable of producing cyanotoxins from different functional groups simultaneously, such as neurotoxins and hepatotoxins (Sivonen & Jones, 1999; Kurmayer & Christiansen, 2009; Demay et al., 2019). However, there are also cyanobacterial strains that do not produce any of the currently known cyanotoxins (Magonono et al., 2018).

Table 1. Major cyanotoxins and their cyanobacterial producers (Adapted from Du et al., 2019; Villalobos et al., 2025).

1. Hepatotoxins (MC, microcystins; NOD, nodularins; CYN, cylindrospermopsins)

2. Neurotoxins (ANTX, anatoxins; ATX, antilatoxins; BMAA, β-methylamino-L-alanine; JMC, jamamicides; KTX, kalkitoxins; STX, saxitoxins)

3. Dermatoxins (APTX, aplysiatoxins; LTX, lyngbyatoxins)

4. Cytotoxins (CUR, curacins; HCT, hectochlorins; MJC, majusculamides).

5. Molluscicide (BRB, barbamides)

6. Endotoxin: (LPS, lipopolysaccharides)

Producing genera	MC[1]	NOD[1]	CYN[1]	ANTX[2]	ATX[2]	BMAA[2]	JMC[2]	KTX[2]	STX[2]	APTX[3]	LTX[3]	CUR[4]	HCT[4]	MJC[4]	BRB[5]	LPS[6]
Anabaena	✓		✓	✓		✓			✓							✓
Aphanizomenon	✓		✓	✓					✓							✓
Arthrospira				✓												✓
Calothrix						✓										✓
Chrysosporum			✓													✓
Cuspidothrix				✓					✓							✓
Cyanodictyon						✓										✓
Cylindrospermopsis			✓						✓							✓
Cylindrospermum				✓												✓
Dolichospermum	✓		✓	✓					✓							✓
Fischerella	✓								✓							✓
Geitlerinema	✓								✓							✓
Hapalosiphon	✓															✓
Iningainema		✓														✓
Leptolyngbya	✓					✓										✓
Limnothrix	✓					✓										✓
Lyngbya			✓		✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Merismopedia	✓															✓
Microcoleus				✓		✓										✓
Microcystis	✓			✓		✓										✓
Nodularia		✓				✓										✓
Nostoc	✓					✓										✓
Oscillatoria	✓		✓	✓		✓					✓					✓
Phormidium	✓			✓		✓			✓							✓
Planktothrix	✓			✓		✓			✓							✓
Pseudanabaena	✓			✓		✓										✓
Radiocystis	✓															✓
Raphidiopsis			✓	✓					✓							✓
Schizothrix											✓					✓
Scytonema						✓			✓							✓
Spirulina	✓															✓
Sphaerospermopsis			✓													✓
Synechococcus	✓					✓										✓
Tolypothrix									✓							✓
Trichodesmium	✓					✓										✓
Tychonema				✓												✓
Woronichinia	✓															✓

Cyanotoxins have been reported in a wide range of environments worldwide, from freshwater and marine systems to deserts and the Arctic, owing to the cosmopolitan distribution of cyanobacteria. A review of 468 publications on toxic cyanobacteria published up to 2018 documented a total of 1,118 major cyanotoxins in 869 freshwater ecosystems across 66 countries. The detected cyanotoxins included MCs (63%, n = 699), cylindrospermopsins (10%, n = 107), anatoxins (9%, n = 100), saxitoxins (8%, n = 93), nodularins (2%, n = 19), and cyanotoxins that were either not analyzed or unspecified (9%, n = 100). In 183 of the reported cases, humans and/or animals were affected by cyanotoxin poisonings (Svirčev et al., 2019).

Due to the significant threat posed by cyanotoxins to the environment and public health, most

studies have focused on elucidating the physiological regulation of their production and the biological functions of major toxin classes, including MCs, anatoxins, saxitoxins, and cylindrospermopsins. Additional areas of research involve the monitoring and removal of cyanotoxins from various environments, as well as the assessment of their effects on aquatic ecosystems and the health of living organisms. However, relatively few studies have explored the biotechnological applications of these toxic compounds (Ricciardelli et al., 2023). As their potential in pharmaceutical and industrial applications becomes increasingly recognized, cyanotoxins are gaining attention as innovative and functional biotechnological compounds. This transformation is important both for developing new therapeutic strategies for human health and for supporting environmental sustainability.

Biotechnological potential and applications of cyanotoxins

Cyanotoxins, with their unique chemical structures and diverse biological activities, hold significant potential for industrial and agricultural applications, including novel pharmaceuticals, allelopathic agents, and biopesticides, making them the focus of various biotechnological studies (Berry et al., 2008; Rastogi & Sinha, 2009; Vijayakumar & Menakha, 2015; Tiwari & Tiwari, 2020). These versatile biological properties render cyanotoxins valuable targets for applied biotechnology. Since the 1990s, some research groups have investigated cyanobacterial secondary metabolites to identify new biologically active sources for the development of novel and more efficient industrial products (da Silva Pinto Neto et al., 2025).

As insights into the beneficial properties of cyanotoxins continue to expand, new strategies for their effective management and utilization in water resources are emerging. For example, cyanobacterial metabolites harvested from algal blooms for environmental remediation are expected to be used as valuable bioproducts (Haque et al., 2017). Moreover, cyanobacterial peptides such as microcystins, nodularins, cylindrospermopsins, and cyanopetolins exhibit unique structural features that make them promising candidates for targeted therapies with potentially fewer side effects than conventional drugs. These metabolites also provide essential insights into cell signaling and cancer biology, positioning them as strong leads for drug discovery and development (Pandey et al., 2025). In this context, cyanotoxins represent a promising natural resource for sustainable biotechnological applications across medicine, agriculture, and environmental protection.

In this section, the biotechnological applications of cyanotoxins are examined with a focus on MCs. MCs are the best-characterized cyanotoxins in terms of both toxicological effects and biotechnological potential, supported by an extensive body of literature. Although other cyanotoxins possess structural and functional properties distinct from MCs, they exhibit comparable potential in similar biotechnological contexts. For this reason, MCs have been selected as a model for illustrating the biotechnological application potential of cyanotoxins.

MCs are cyclic heptapeptides composed of seven amino acids (cyclo-(D-alanine$_1$–X$_2$–D-MeAsp$_3$–Z$_4$–Adda$_5$–D-glutamate$_6$–Mdha$_7$)). With more than 300 identified congeners, MCs are the most widespread cyanotoxins globally (Villalobos et al., 2025). Certain cyanotoxin analogs exhibit strong cytotoxic activity against cancer and viral cells, suggesting their potential utility as antitumor agents (Li et al., 2023). MCs are one of these metabolites, and a major limitation to their use as anticancer agents is their high toxicity, particularly in hepatocytes. MCs are strong inhibitors of the protein phosphatases PP1 and PP2A, and their cellular uptake is mediated by members of the organic anion transporting polypeptide superfamily (OATPs). The most toxic congener, MC-LR (microcystin-leucine arginine), is transported into hepatocytes via the human OATP1B1 and OATP1B3, crosses

the blood–brain barrier through OATP1A2, and is not transported by OATP2B1 (Fischer et al., 2005). These transport-specific mechanisms are thought to be responsible for the organ-selective toxicity of MCs. Interestingly, certain OATPs (OATP1B1 and OATP1B3) are overexpressed in several cancer tissues, including liver, colon, and pancreatic tumors, compared with normal tissues (Abe et al., 2001; Cui et al., 2003; Lee et al., 2008). Therefore, OATPs have been proposed as a new class of therapeutic targets for the treatment of therapy-resistant metastatic cancers, and engineering MC variants with selective binding affinity for cancer-specific OATPs has been suggested as a strategy for developing novel solid-tumor therapies (Sainis et al., 2010). In one study, based on the observation that OATP1B3 is highly expressed in certain tumor tissues whereas OATP1B1 is more abundant in hepatocytes, researchers examined whether specific MC variants selectively target OATP1B3. Their findings indicated that such variants may reduce hepatic toxicity while enhancing the tumor selectivity of MCs (Niedermeyer et al., 2014). In this context, the development of optimized MC analogs for metastatic cancers that are resistant to conventional chemotherapy and that express OATPs represents a promising direction in anticancer drug development. Moreover, the strong protein phosphatase inhibitory activity of MCs represents an additional reason for their consideration as anticancer drug candidates. Since the functions of PP1 and PP2A are essential for cell growth and differentiation, and they carry no risk of inducing resistance, the inhibition of these enzymes represents a promising target in cancer research (McCluskey et al., 2002). In a study published in 2025, it was reported that derivatives generated through chemical modifications at positions 2 and 4 of MCs retained strong PP1 inhibition activity while exhibiting reduced transportability (Sallandt et al., 2025). In this way, it has been demonstrated that chemical modification of MCs can reduce hepatic toxicity while enhancing target enzyme inhibition, thus enabling development of safer and more selective anticancer drug candidates suitable as payload molecules in targeted therapies such as antibody–drug conjugates. Another study reported that MC-LR may have antitumor effects by activating the innate immune response and synergizing with chemotherapeutic agents (Li et al., 2024).

MCs are also known to exhibit antimicrobial activity. In one study, the [D-Leu^1] MC-LR variant demonstrated antimycobacterial activity against both sensitive and resistant *Mycobacterium tuberculosis* strains, as well as nontuberculous mycobacteria (*M. chelonae, M. terrae,* and *M. kansasii*). Importantly, this MC variant showed no cytotoxic activity at the concentrations that displayed antimycobacterial activity, indicating potential use in novel antimycobacterial drug development (Ramos et al., 2015). Another study found that MC levels in *Microcystis aeruginosa* increased by up to 40-fold within two days after viral infection, and that bioactive compounds produced by *M. aeruginosa* inhibited and delayed the infection of single-stranded DNA and RNA viruses (Lee et al., 2023).

Allelopathy is defined as any process involving secondary metabolites produced by bacteria, fungi, algae, or plants that affects the growth and development of biological and agricultural systems (Żak & Kosakowska, 2016). Highly toxic allelochemicals are often referred to as “toxins,” and cyanobacteria are among the most common producers of such compounds. MCs exhibit allelopathic activity against aquatic macrophytes and green algae, as well as growth-inhibitory effects on other cyanobacteria and terrestrial algae, indicating that they play a role in allelopathic interactions (Polyak & Sukharevich, 2025). Studies show that *M. aeruginosa* increases MC production when competing with green algae, interacting with other *Microcystis* species, or subjected to grazing pressure (Bittencourt-Oliveira et al., 2015; Yang et al., 2014; Bojadzija Savic et al., 2020). Although there is evidence suggesting

allelopathic properties of MCs, their allelopathic activity has not yet been conclusively demonstrated, and many more studies are required before they can be classified as confirmed allelochemicals (Polyak & Sukharevich, 2025). Additionally, the harmful effects of MCs on organisms and overall ecosystem health pose serious limitations to their use as biocontrol agents and restrict their potential for commercial application (Berry et al., 2008).

Synthetic pesticides are used globally to increase agricultural productivity, control crop pests, and protect human and animal health (Wan et al., 2025). These pesticides are primarily classified as herbicides, algicides, fungicides, miticides/acaricides, bactericides, rodenticides, termiticides, insecticides, molluscicides, and nematicides, according to their target organisms. However, synthetic pesticides have negative impacts on non-target organisms, as well as on soil and water quality. Therefore, biopesticides represent a safer and more environmentally friendly alternative (Ayilara et al., 2023). Cyanobacteria have potential as biopesticide sources due to their ability to synthesize biologically active compounds with diverse functionalities and allelochemical properties. They are regarded as a promising option for sustainable agriculture and integrated pest management strategies (Akmukhanova et al., 2023). Several studies support the biopesticidal potential of MCs. For instance, MCs exhibited fungicidal activity against *Phytophthora infestans*, the causal agent of late blight in tomatoes, and naturally grown tomato plants with partial infection showed almost complete suppression of disease symptoms (Nykyforov et al., 2021). Microcystins also demonstrated potent larvicidal activity against mosquito larvae (Kiviranta et al., 1993). In another study on cyanobacterial strains that included MC-producing strains, from the Florida Everglades and other freshwater systems, approximately 53% of isolates inhibited sympatric photoautotrophs (green algae and cyanobacteria) and about 26% inhibited mosquito larval development. According to this study, mosquito larvae exposed to *Microcystis* and *Cylindrospermopsis* isolates exhibited mortality ≥50% (Berry et al., 2008).

While synthetic biological control agents carry knowledge gaps regarding long-term ecological impacts, the natural occurrence of MCs and their well-characterized biological activities enable more realistic ecological risk assessments and support their consideration as promising biopesticide candidates. Nevertheless, thorough evaluation of the impacts of MCs and other cyanobacterial biopesticide candidates on non-target organisms, beneficial insects, and aquatic ecosystems is essential. Ensuring their safety, efficacy, and compatibility with sustainable agricultural practices will require numerous in-depth investigations (Akmukhanova et al., 2023).

To mitigate risks associated with MC-based biopesticides, bioremediation-based systems developed for pesticide-residue removal may be employed. For example, bioaugmentation technology, a leading strategy for remediating pesticide-polluted soils, has also been shown to remove MC contamination through similar biological processes (Cycoń, Mrozik, & Piotrowska-Seget, 2017; Wang et al., 2018). This demonstrates that environmental safety and control strategies can be effectively integrated into MC-based biopesticide applications. Thus, the combined use of bioremediation systems with MC-based biopesticides may represent a promising strategy for enhancing efficacy while protecting both ecosystems and human health.

In addition to MCs, other cyanotoxins are also being investigated for biotechnological use through approaches similar to those applied to microcystins. Ongoing studies highlight their potential roles in industrial, environmental, and pharmaceutical applications (Haque et al., 2017; Akmukhanova et al., 2023; Pandey et al., 2025). Existing evidence indicates that cyanotoxins can be effectively applied

in medicine, agriculture, and environmental remediation. Moreover, industrial companies developing useful products from cyanobacterial metabolites, including cyanotoxins, have been active in these sectors for many years (Figure 2).

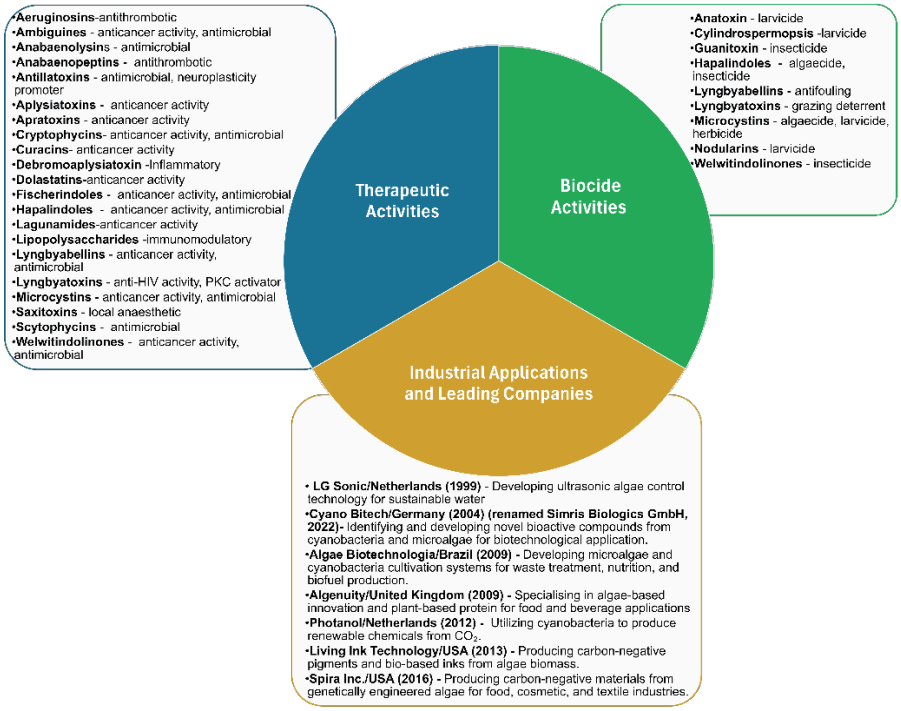

Figure 2. Major biotechnological and industrial applications associated with cyanotoxins (Adapted from Rastogi & Sinha, 2009; Haque et al., 2017; Tiwari & Tiwari, 2020; Akmukhanova et al., 2023; Cock & Cheesman, 2023; Ricciardelli et al., 2023).

Conclusions

In this review, the structural diversity, ecological functions, and biotechnological potential of cyanotoxins have been comprehensively examined. Current literature demonstrates that cyanotoxins, once viewed only as 'harmful metabolites", represent high-potential natural products that, when appropriately managed, can support the development of innovative applications in medical, agricultural, and environmental biotechnology. Cyanotoxins are strong candidate molecules that can contribute to the development of next-generation therapeutic agents through their anticancer and antimicrobial activities, while their allelopathic and biopesticidal properties support sustainable applications in agriculture and environmental management. However, due to their high toxicity and the potential harmful effects on non-target organisms, comprehensive safety assessments are critically important for the biotechnological use of these compounds.

In conclusion, assessing the biotechnological potential of cyanotoxins and translating them into beneficial products is highly significant, as they provide innovative solutions ranging from the development of new therapeutic agents and biopesticides to the enhancement of environmental remediation technologies and the advancement of sustainable agricultural practices. In this context, future research should prioritize reducing the toxicity of cyanotoxins, improving target specificity,

minimizing environmental risks, and integrating bioremediation-based strategies.

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Conflict of interest

The author declares no conflict of interest.

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Ethics committee approval

Ethics committee approval is not required for this study.

Authors' contribution statement

Study conception and design: DSK; **Data collection**: DSK; **Analysis and interpretation of results**: DSK; **Manuscript draft preparation**: DSK. The author reviewed and approved the final version of the manuscript.

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