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Cyanobacterial Natural Products as Emerging Antibacterial Agents: Bioactive Compounds and Their Potential to Combat Antimicrobial Resistance

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ABSTRACT: Cyanobacteria, commonly known as blue-green algae, represent a chemically diverse group of microorganisms capable of producing a wide range of structurally diverse natural products with considerable biological activity. Their secondary metabolites include peptides, lipopeptides, alkaloids, polyketides, fatty acids, terpenoids, bromophenols, and other bioactive compounds. This review provides an integrated assessment of the phytochemical diversity and antibacterial potential of cyanobacterial natural products, with emphasis on compounds reported from different cyanobacterial genera. Species belonging to Anabaena, Calothrix, Fischerella, Lyngbya, Nostoc, Scytonema, Tolypothrix, and Oscillatoria have been reported to produce metabolites active against both Gram-positive and Gram-negative bacteria. Important antibacterial compounds include circinamide, microginin, puwainaphycin C, calophycin, fischerellins, hassallidins, muscoride A, Scytophycins C, Tolytoxin, Ambigol A, Tjipanazole D, Calothrixin A, Nostocyclyne A, Hapalindole T, and other structurally diverse metabolites. Recent studies further demonstrate antibacterial activity in both established and less-explored cyanobacterial taxa, including Arthrospira fusiformis, Lyngbya majuscula, Lyngbya martensiana, Oxynema thaianum, Oscillatoria, Cylindrospermum, and Loriellopsis. The review also discusses the chemical characteristics of cyanobacterial antibacterial compounds and possible mechanisms of action, including membrane disruption, interference with cell-envelope functions, inhibition of nucleic-acid and protein synthesis, metabolic enzyme inhibition, efflux-pump modulation, and effects on biofilm and quorum-sensing pathways. Recent advances in genome mining, metabolomics, biosynthetic gene-cluster analysis, and synthetic biology further provide

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opportunities for discovering previously inaccessible cyanobacterial metabolites. Despite this potential, antibacterial activity varies considerably with species, strain, cultivation and extraction conditions, metabolite composition, and target microorganism. Limited mechanistic, toxicity, in vivo, and large-scale production data also remain important challenges. Further bioassay-guided isolation, structural characterization, mechanism-based evaluation, toxicity assessment, and validation against clinically relevant and antimicrobial-resistant bacteria are therefore required. Cyanobacterial natural products represent a promising and expanding chemical resource for the discovery of emerging antibacterial agents and future pharmaceutical development.

1. INTRODUCTION

Antimicrobial resistance (AMR) has become a major challenge for the effective management of bacterial infections, creating a continuing need for new antibacterial agents with diverse chemical structures and biological activities. The reduced effectiveness of conventional antibiotics has increased interest in natural products as potential sources of structurally novel antimicrobial molecules. Natural products obtained from microorganisms have historically contributed substantially to drug discovery, and cyanobacteria have emerged as an important but comparatively underexplored source of bioactive secondary metabolites. Cyanobacteria, commonly referred to as blue-green algae, possess considerable metabolic diversity and produce compounds with antibacterial, antifungal, antiviral, anticancer, and other biological activities (Carpine & Sieber, 2021; Cock & Cheesman, 2023). Recent research continues to support this potential, with cyanobacterial natural products being investigated as sources of anti-infective molecules and novel chemical scaffolds relevant to drug discovery. A 2024 review of marine cyanobacteria documented more than 200 natural products with reported antibacterial, antifungal, antiviral, antiprotozoal, or other anti-infective activities, highlighting the continuing expansion of this chemical resource (Tan et al., 2024).

Cyanobacteria are widely distributed in freshwater, marine, terrestrial, and extreme environments and have developed diverse biochemical strategies for survival and competition. Their secondary metabolites are not directly required for basic cellular growth but can influence interactions with surrounding organisms and may contribute to chemical defence and ecological adaptation. The literature identifies a broad range of cyanobacterial metabolites, including hormones, antibiotics, allelochemicals, toxins, biotoxins, peptides, alkaloids, polyketides, lipopeptides, terpenoids, bromophenols, fatty acids, and polysaccharides (Carmichael, 1992; Carpine & Sieber, 2021). Recent chemical profiling further demonstrates the extensive biosynthetic capacity of cyanobacteria. Weiss et al. (2025) analysed 995 cyanobacterial natural products reported between 2010 and 2023, demonstrating substantial chemical diversity across different cyanobacterial orders and environmental sources. This chemical diversity is particularly important for antibacterial research because structurally different metabolites may provide different biological activities and chemical scaffolds for future antimicrobial development.

Phytochemical investigations of cyanobacteria have demonstrated the occurrence of several major classes of bioactive compounds. Peptides and lipopeptides represent important groups and include cyanopeptolins, anabaenopeptins, aeruginosins, cyanobactins, anabaenolysins, and hassallidins. Alkaloids such as cryptophycins, cylindrospermopsins, and nostoclides, together with polyketides such as lyngbyatoxins, curacin-related compounds, and scytonemin, further illustrate the structural diversity of cyanobacterial metabolites (Cock & Cheesman, 2023). Recent advances in cyanobacterial natural-product research have also emphasized genome mining, multi-omics approaches, biosynthetic gene-cluster analysis, and activation of cryptic pathways as strategies for discovering previously inaccessible metabolites (Baunach et al., 2024). These approaches are important because conventional culture and extraction methods may recover only a fraction of the chemical diversity encoded by cyanobacterial genomes.

The antibacterial potential of cyanobacteria has been demonstrated across a broad range of taxonomic groups. Species belonging to genera such as *Anabaena, Lyngbya, Calothrix, Spirulina, Nostoc, Hapalosiphon, Phormidium,* and *Oscillatoria* have been reported to produce antibacterial metabolites active against both Gram-positive and Gram-negative bacteria. The literature reports activity against important bacterial species including *Staphylococcus aureus, Bacillus subtilis, Streptococcus sanguinis, Pseudomonas aeruginosa, Escherichia coli, Listeria monocytogenes, Salmonella* spp., *Enterobacter aerogenes,* and *Klebsiella pneumoniae* (Kaushik & Chauhan, 2008; Chauhan et al., 2022). Recent experimental evidence has expanded this list. For example, phenolic extracts of indigenous freshwater and marine *Oscillatoria* spp. showed activity against several Gram-positive and Gram-negative bacteria associated

with fish and shellfish diseases, with filamentous *Oscillatoria* showing stronger activity than planktonic forms (Nayeem et al., 2025).

Several individual cyanobacterial compounds have received particular attention because of their reported antibacterial properties. Examples include circinamide from *Anabaena circinalis*, microginin from *Anabaena fertilisima*, puwainaphycin C from *Anabaena* sp., calophycin from *Calothrix fusca*, fischerellins from *Fischerella muscicola*, hassallidins from *Hassallia* sp., nostofungicidine from *Nostoc commune*, borophycin from *Nostoc linckia*, and muscoride A from *Nostoc muscorum*. Other structurally diverse compounds reported in Table 1 include Scytophycins C, Tolytoxin, Tolyporphin J, Ambigol A, Tjipanazole D, Kawaguchipeptin A, Tenuecyclamide A, Calothrixin A, Comnastin A, Nostocyclyne A, Scyptolin A, Pahayokolide A, Hapalindole T, Carbamidocyclophane A, Ambiguine A isonitrile, Crossbyanol A, and other metabolites. Recent research also demonstrates antibacterial activity from less extensively studied cyanobacteria. Ikhane et al. (2025) reported antibacterial activity in crude extracts of *Cylindrospermum alatosporum* and *Loriellopsis cavernicola*, further expanding the range of cyanobacterial taxa being investigated for antibacterial compounds.

Despite this promising diversity, the antibacterial potential of cyanobacterial natural products remains incompletely explored. Many reported metabolites have been investigated primarily through crude extracts or preliminary antimicrobial assays, while the biological activities and therapeutic relevance of numerous purified compounds require further investigation. Recent reviews continue to identify cyanobacteria as an underexplored resource for anti-infective drug discovery and emphasize the need for improved isolation, dereplication, genome mining, and mechanism-based evaluation (Cock & Cheesman, 2023; Baunach et al., 2024; Tan et al., 2024). Therefore, systematic evaluation of cyanobacterial natural products, their chemical diversity, antibacterial activities, and pharmaceutical relevance is important for expanding the pool of candidate antibacterial agents. This review focuses on the phytochemical diversity of cyanobacteria, reported antibacterial activities, major antibacterial compounds, and recent evidence supporting their potential as emerging antibacterial agents.

2. PHYTOCHEMICAL CONSTITUENTS OF BLUE-GREEN ALGAE

Blue-green algae (cyanobacteria) are recognized as a rich source of chemically diverse secondary metabolites with considerable biological activity. The literature reports several major groups of phytochemical constituents, particularly peptides, alkaloids, polyketides, and lipopeptides, together with fatty acids, terpenoids, bromophenols, tannins, amines, histamines, and polysaccharides. Recent chemical-diversity analyses further support this broad chemical repertoire. Weiss et al. (2025) evaluated 995 cyanobacterial natural products reported between 2010 and 2023, demonstrating substantial structural diversity across cyanobacterial taxa and environmental sources. A recent review covering 2021–2024 also reported 335 newly described cyanobacterial metabolites, showing that the discovery of new chemical constituents is continuing rapidly (Sieber & Janssen, 2026).

2.1. Peptides

Peptides represent one of the most important classes of cyanobacterial natural products. The study identifies cyanopeptolins, microcystins, anabaenopeptins, and aeruginosins among the reported cyanobacterial peptides. Recent evidence indicates that this group is expanding rapidly. Sieber and Janssen (2026) reported 253 new peptide-based metabolites between 2021 and 2024, representing approximately 75% of all newly reported cyanobacterial metabolites during this period. These included 86 cyanopeptolins, 19 microginins, 8 anabaenopeptins, 8 microcystins, and 3 microviridins. Cyanobacterial peptides arise through both non-ribosomal peptide synthetase (NRPS) pathways and ribosomally synthesized and post-translationally modified peptide (RiPP) pathways, which contribute substantially to their structural diversity. A 2025 study further identified new micropeptins, a microginin, microviridins, and ferintoic acid from a cyanobacterial bloom, demonstrating continued expansion of peptide diversity (2025).

2.2. Alkaloids

Cyanobacteria also produce structurally diverse alkaloids. Examples reported include cryptophycins, cylindrospermopsins, and nostoclides. Recent investigations continue to identify new alkaloid structures. Sieber and Janssen (2026) highlighted aetokthonotoxin, a highly brominated biindole alkaloid produced by *Aetokthonos hydrillicola*, and described the associated biosynthetic pathway responsible for its halogenation. The 2025 chemical-diversity analysis also identified numerous cyanobacterial alkaloids, including hapalindole and fischerindole derivatives with reported biological activities (Weiss et al., 2025).

2.3. Polyketides

Polyketides constitute another important group of cyanobacterial metabolites. The attached content reports lyngbyatoxins, curacin-related compounds, scytonemin, and other polyketide-derived molecules. Recent work has expanded this group through the identification of new metabolites and the activation of previously silent biosynthetic pathways. Sieber and Janssen (2026) described new polyketides including nostoclides N1 and N2, nostovalerolactone, and 9-dehydronostovalerolactone from *Nostoc punctiforme*. Their discovery demonstrates how cultivation conditions and biosynthetic gene-cluster activation can reveal previously undetected cyanobacterial metabolites.

2.4. Lipopeptides

Lipopeptides are particularly relevant to antibacterial research because several cyanobacterial examples exhibit antimicrobial properties. Cyanobactins, anabaenolysins, hassallidins, circinamide, puwainaphycin C, fischerellins, and muscoride A are among the compounds reported in the literature. Recent research has considerably expanded this class. Sieber and Janssen (2026) reported 16 new linear lipopeptides and eight new laxaphycins between 2021 and 2024, demonstrating continued structural diversification of cyanobacterial lipopeptides. Cyanobactins have also received recent attention because prenylation can influence cyclic peptide stability and biological activity, with new cyanobactins and associated prenyltransferases reported during 2021–2024 (Khan & Phan, 2025).

Thus, recent studies strongly support the view that cyanobacterial phytochemical diversity is still expanding. Advances in genome mining, metabolomics, high-resolution mass spectrometry, NMR, and activation of cryptic biosynthetic gene clusters are allowing previously inaccessible metabolites to be detected and characterized (Baunach et al., 2024; Sieber & Janssen, 2026). This expanding chemical space provides an important foundation for identifying cyanobacterial compounds with antibacterial and other pharmacological activities (Fig 1)

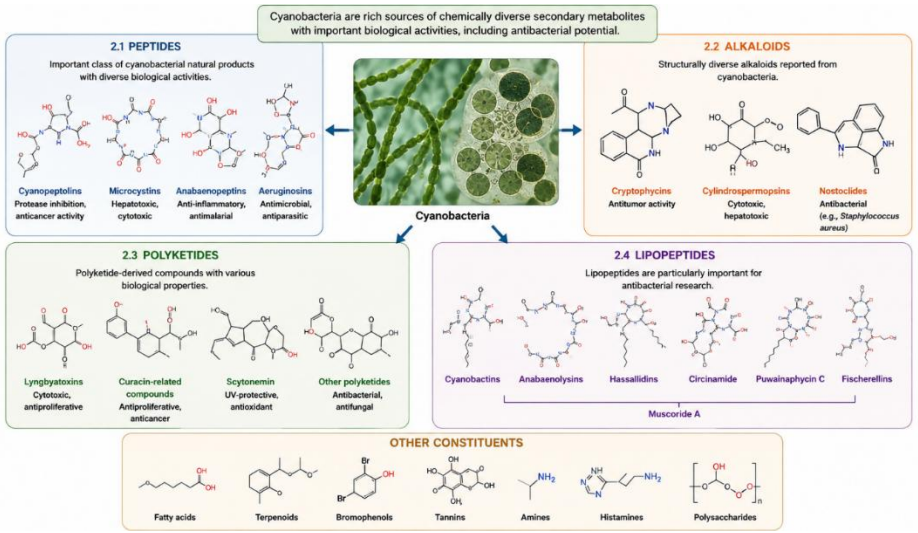


Figure 1. Major phytochemical constituents of blue-green algae (cyanobacteria), showing the principal classes of secondary metabolites, including peptides, alkaloids, polyketides, lipopeptides, fatty acids, terpenoids, bromophenols, tannins, amines, histamines, and polysaccharides, with representative compounds and their reported biological activities.

3. ANTIBACTERIAL ACTIVITY OF CYANOBACTERIA

Cyanobacteria are important producers of natural products with antibacterial activity against a broad range of microorganisms. Species belonging to genera such as *Anabaena, Lyngbya, Calothrix, Spirulina, Nostoc, Hapalosiphon, Phormidium,* and *Oscillatoria* have been investigated against both Gram-positive and Gram-negative bacteria. Reported target organisms include *Staphylococcus aureus, Bacillus subtilis, Bacillus cereus, Streptococcus sanguinis, Pseudomonas aeruginosa, Escherichia coli, Listeria monocytogenes, Salmonella* spp., *Enterobacter aerogenes,* and *Klebsiella pneumoniae* (Kaushik & Chauhan, 2008; Chauhan et al., 2022). Recent reviews continue to support cyanobacteria as an underexplored source of antibacterial and other anti-infective natural products, with more than 200 marine cyanobacterial molecules reported for antibacterial, antifungal, antiviral, antiprotozoal, or related activities (Tan et al., 2024).

The antibacterial properties of cyanobacteria are associated with diverse secondary metabolites, including peptides, lipopeptides, alkaloids, polyketides, fatty acids, and other lipid-derived compounds. Earlier investigations reported antibacterial activity in several *Anabaena* species, with active extracts subsequently examined using HPTLC to identify their chemical constituents (Kaushik et al., 2009; Chauhan et al., 2010). Extracts of *Nostoc commune* and *Lyngbya majuscula* have similarly demonstrated activity against clinically important microorganisms. The activity of cyanobacterial extracts, however, differs considerably according to species, strain, cultivation conditions, extraction solvent, and bacterial target.

Recent studies have provided further experimental evidence. In 2024, *Oscillatoria subsalsa* and *Oscillatoria flos-aquae* were investigated against biofilm-forming multidrug-resistant bacteria isolated from pharmaceutical wastewater. Both species showed significant antibacterial activity, with *O. flos-aquae* demonstrating stronger and more consistent activity, particularly against Gram-negative bacteria. Phytochemical screening detected alkaloids, flavonoids, phenols, tannins, terpenoids, sterols, quinones, and other constituents, supporting the possible contribution of multiple metabolite classes to the observed activity.

A 2025 study further demonstrated the antibacterial potential of indigenous *Oscillatoria* spp. against bacteria associated with diseases of fish and shellfish. Phenolic extracts were tested against three Gram-positive bacteria and nine Gram-negative bacteria. Filamentous *Oscillatoria* showed greater activity than planktonic forms, producing an inhibition zone of 34.06 ± 0.08 mm against *Staphylococcus* sp., whereas the planktonic form produced a lower inhibition zone of 17.11 ± 0.18 mm against *Pseudomonas* sp. The reported MIC values were 100 μg/mL for filamentous *Oscillatoria* and 150 μg/mL for planktonic *Oscillatoria*.

Ikhane et al. (2025) investigated crude extracts of the freshwater cyanobacteria *Cylindrospermum alatosporum* NR125682 and *Loriellopsis cavernicola* NR117881. The study used sequential hexane, dichloromethane, and ethanol extraction and evaluated MIC and MBC against clinical bacterial strains. The hexane extract of *L. cavernicola* showed the strongest activity, with MIC values of 0.70–1.41 mg/mL and MBC values of 1.41–2.81 mg/mL. The authors also investigated possible mechanisms involving membrane damage, efflux pumps, β-lactamase activity, DNA degradation, and interactions with conventional antibiotics.

Recent work has also expanded the geographical and taxonomic range of cyanobacterial antibacterial research. A 2025 study of Amazonian cyanobacteria identified antibacterial fractions from *Synechocystis* sp., *Desmonostoc* sp., and *Synechococcus* sp.; the most active *Synechocystis* fraction showed an MIC of 40 μg/mL and MBC of 80 μg/mL against *Salmonella typhimurium*. These findings indicate that antibacterial activity is distributed across diverse cyanobacterial taxa and environments.

Taken together, recent evidence strengthens the potential of cyanobacteria as sources of antibacterial natural products. Importantly, the activity is not uniform and depends on the producing strain, metabolite profile, extraction approach, and target microorganism. Therefore, future studies should move beyond preliminary extract screening toward bioassay-guided fractionation, compound identification, MIC/MBC determination, mechanism-of-action studies, and evaluation against multidrug-resistant bacteria. This approach can help identify cyanobacterial metabolites with genuine potential for antibacterial drug discovery.

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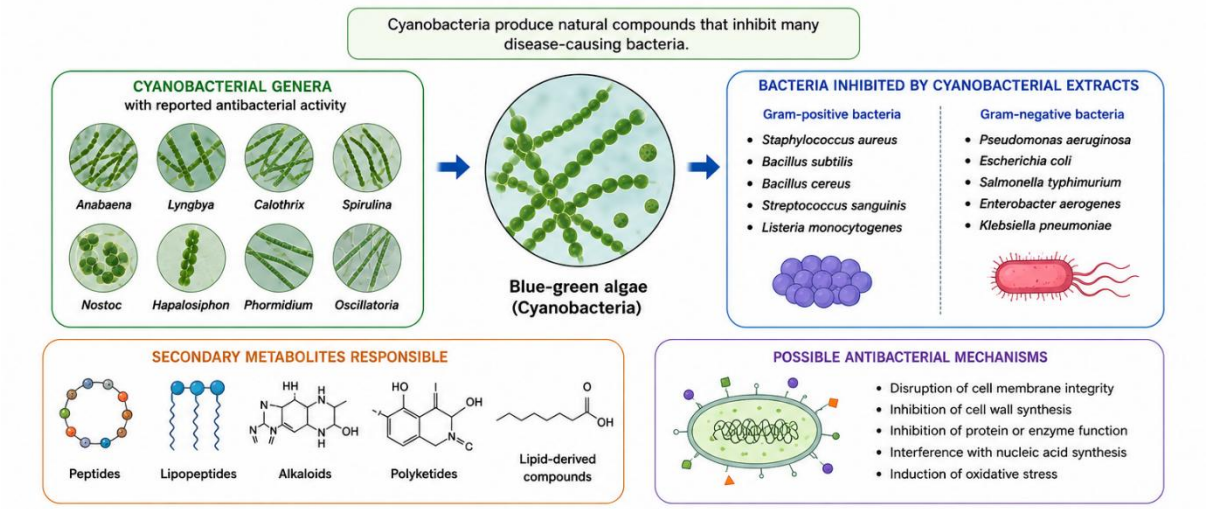


Figure 2. Antibacterial activity of blue-green algae (cyanobacteria) against Gram-positive and Gram-negative bacteria, showing major cyanobacterial genera, antibacterial metabolites

4. CYANOBACTERIAL SPECIES AND THEIR ANTIBACTERIAL COMPOUNDS

A wide range of cyanobacterial species have been investigated for the production of antibacterial compounds, with metabolites reported from freshwater, terrestrial, and marine-associated cyanobacteria. The attached literature demonstrates that antibacterial activity is distributed across several genera, particularly *Anabaena, Calothrix, Fischerella, Lyngbya, Nostoc, Scytonema, Tolypothrix,* and *Oscillatoria*. This diversity is important because different cyanobacterial taxa produce chemically distinct metabolites, providing a broad natural source for antibacterial compound discovery. Recent chemical-diversity analysis of 995 cyanobacterial natural products also demonstrates that metabolite diversity is distributed across different taxonomic groups and environmental sources (Weiss et al., 2025).

Species of *Anabaena* have yielded several antibacterial metabolites. *Anabaena circinalis* produces circinamide, a lipopeptide with antibacterial activity, while *A. fertilisima* produces microginin, a cyclic peptide with antibacterial properties. Puwainaphycin C, another antibacterial lipopeptide, has been reported from *Anabaena* sp. BQ 16-1. *Calothrix fusca* produces calophycin, a cyclic peptide reported to possess antibacterial and antifungal activities. The genus *Fischerella* is also notable for compounds such as fischerellin A and fischerellin B, both associated with antibacterial activity. Recent reviews continue to identify *Fischerella* and related cyanobacteria as important producers of structurally diverse antibacterial metabolites. In particular, fischerellins A and B have reported activity against *S. aureus, Mycobacterium tuberculosis, Mycobacterium smegmatis,* and *E. coli* (Cock & Cheesman, 2023).

Several *Nostoc* species have likewise been identified as sources of antibacterial metabolites. *Nostoc commune* produces nostofungicidine and 1,8-dihydroxy-4-methylanthraquinone, whereas *Nostoc linckia* produces borophycin and *Nostoc muscorum* produces muscoride A. Other genera have yielded structurally diverse compounds. *Scytonema pseudohofmanni* produces scytophycins C, while *Scytonema ocellatum* and *Tolypothrix conglutinata* produce tolytoxin. *Tolypothrix nodosa* produces tolyporphin J, and *Fischerella ambigua* produces ambigol A and Tjipanazole D.

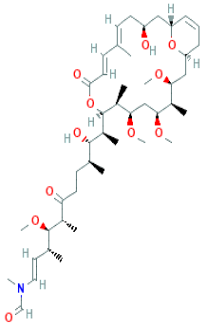
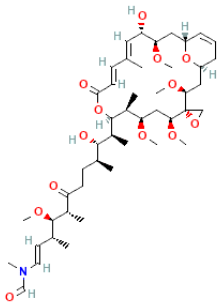
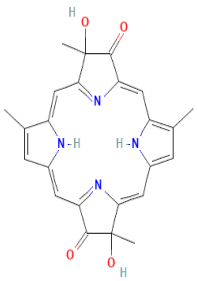
Table 1 further documents compounds from *Microcystis, Oscillatoria, Leptolyngbya, Microcoleus,* and other cyanobacteria, including Kawaguchipeptin A, Calothrixin A, Nostocyclyne A, Pahayokolide A, Hapalindole T, Carbamidocyclophane A, Ambiguine A isonitrile, and Crossbyanol A. Recent literature has expanded this species–compound relationship. A 2025 study of Amazonian cyanobacteria investigated *Synechococcus* sp. CACIAM 05, *Desmonostoc* sp. CACIAM 45, *Synechocystis* sp. CACIAM 05, and *Lyngbya* sp. CACIAM 07. A fraction of *Synechococcus* sp. showed bactericidal activity against *Bacillus subtilis* with a MIC of 40 µg/mL, while LC–MS/MS analysis identified pheophytin and phorbide derivatives among the bioactive metabolites.

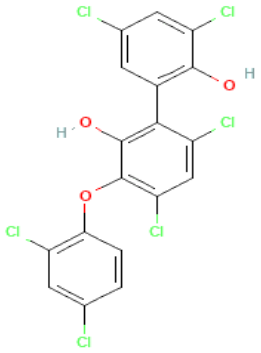
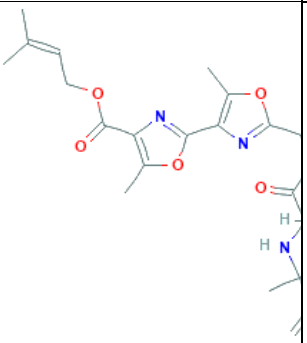
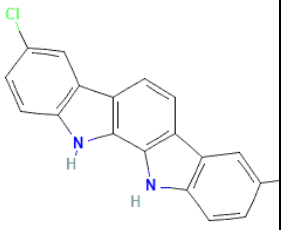
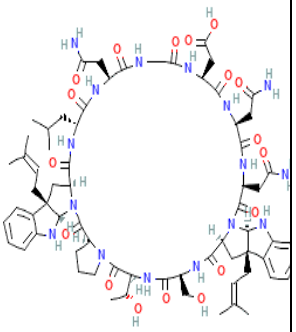
Recent studies have also identified antibacterial potential in cyanobacteria not extensively represented in earlier compound lists. Nayeem et al. (2025) reported antibacterial activity from phenolic extracts of indigenous freshwater and marine *Oscillatoria* spp. against bacterial pathogens associated with fish and shellfish diseases. Filamentous *Oscillatoria* showed greater activity than the planktonic form, with an inhibition zone of 34.06 ± 0.08 mm against *Staphylococcus* sp. A 2026 study on *Neowestiellopsis persica*

isolated from Meghalaya further demonstrated antibacterial activity of fatty acid methyl ester extracts against *E. coli, K. pneumoniae,* and *S. aureus*. The strongest activity was observed against *S. aureus*, with a zone of inhibition of 22 ± 1 mm, while *S. aureus* and *K. pneumoniae* showed MIC values of approximately 2.5 mg/mL. GC–MS analysis identified four major bioactive compounds that were subsequently investigated using molecular docking.

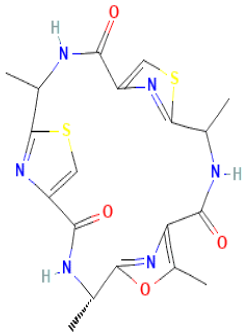
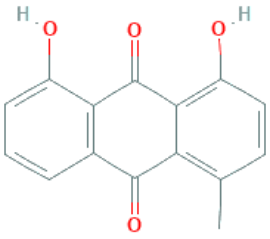
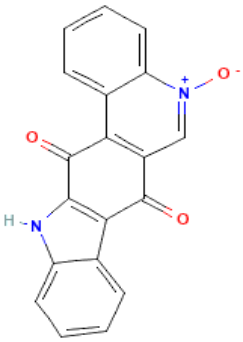
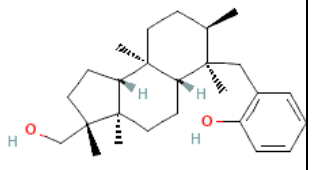
These recent findings demonstrate that antibacterial compounds are not restricted to traditionally studied genera. Instead, new cyanobacterial species, geographical regions, chemical classes, and metabolite profiles continue to expand the known antibacterial chemical space. This supports systematic screening of underexplored cyanobacteria combined with metabolomics, bioassay-guided fractionation, and molecular characterization for the discovery of new antibacterial natural products.

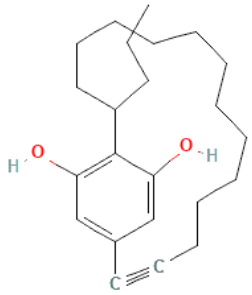
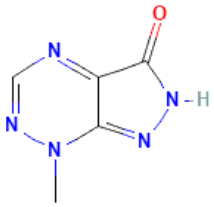
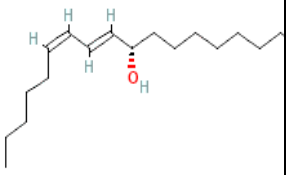
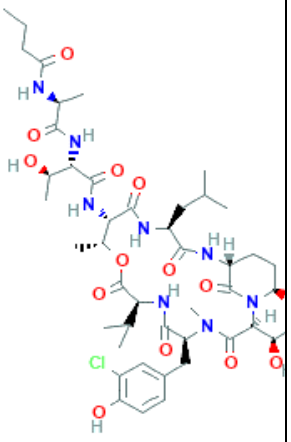
Table 1: Antibacterial compounds and chemical structures identified from Cyanobacterial species

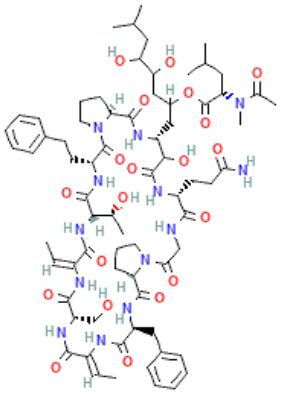
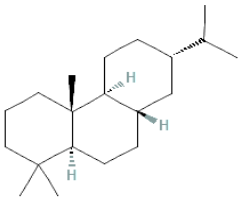
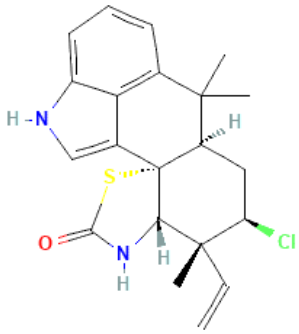
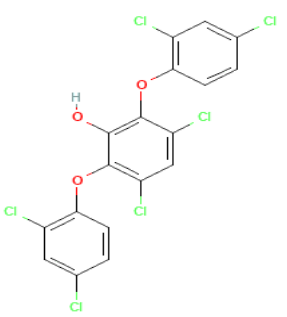
Cyanobacterial Spp.	Antibacterial Compounds	Chemical Structure	References
Scytonema pseudohofmanni	**Scytophycins C** MF: $C_{45}H_{75}NO_{11}$ MW: 806.1g/mol IUPAC Name: N-[(E,3R,4R,5R,9S,10S,11S)-10-hydroxy-11-[(1S,3S,4R,5S,7R,8S,9R,12E,14E,17S,19R)-17-hydroxy-3,5,7-trimethoxy-4,8,14-trimethyl-11-oxo-10,23-dioxabicyclo[17.3.1]tricosa-12,14,20-trien-9-yl]-4-methoxy-3,5,9-trimethyl-6-oxododec-1-enyl]-N-methylformamide		Ishibashi et al. 1986
Scytonema ocellatum, Tolypothrix conglutinate	**Tolytoxin** MF: $C_{46}H_{75}NO_{13}$ MW: 850.1g/mol IUPAC Name: N-[(E,3R,4R,5R,9S,10S,11S)-10-hydroxy-11-[(1S,3S,4S,5S,7R,8S,9R,12E,14E,16S,17R,19R)-16-hydroxy-3,5,7,17-tetramethoxy-8,14-dimethyl-11-oxospiro[10,23-dioxabicyclo[17.3.1]tricosa-12,14,20-triene-4,2'-oxirane]-9-yl]-4-methoxy-3,5,9-trimethyl-6-oxododec-1-enyl]-N-methylformamide		Moore et al. 1987
Tolypothrix nodosa	**Tolyporphin J** MF: $C_{24}H_{22}N_4O_4$ MW: 430.5g/mol IUPAC Name: 3,13-dihydroxy-3,7,13,18-tetramethyl-22,24-dihydroporphyrin-2,12-dione		Prinsep et al. 1992

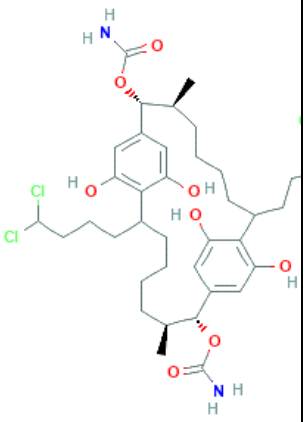
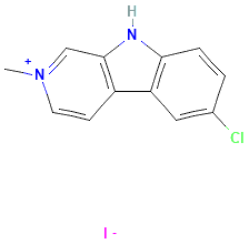
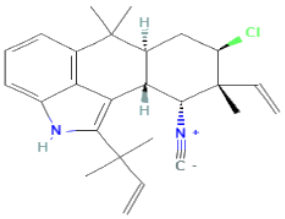
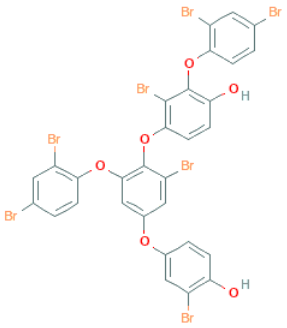
Cyanobacterial Spp.	Antibacterial Compounds	Chemical Structure	References
Fischerella ambigua	**Ambigol A** MF: $C_{18}H_8Cl_6O_3$ MW: 485g/mol IUPAC Name: 3,5-dichloro-2-(3,5-dichloro-2-hydroxyphenyl)-6-(2,4-dichlorophenoxy)phenol		Falch et al. 1995
Nostoc muscorum	**Muscoride A** MF: $C_{28}H_{40}N_4O_5$ MW: 512.6g/mol IUPAC Name: 3-methylbut-2-enyl 5-methyl-2-[5-methyl-2-[1-[3-methyl-2-(2-methylbut-3-en-2-ylamino)butanoyl]pyrrolidin-2-yl]-1,3-oxazol-4-yl]-1,3-oxazole-4-carboxylate		Nagatsu, 1995
Fischerella ambigua	**Tjipanazole D** Compound CID: 10087661 MF: $C_{18}H_{10}Cl_2N_2$ MW: 325.2g/mol IUPAC Name: 3,8-dichloro-11,12-dihydroindolo[2,3-a]carbazole		Falch et al. 1995
Microcystis aeruginosa	**Kawaguchipeptin A** MF: $C_{68}H_{92}N_{16}O_{18}$ MW: 1421.6g/mol IUPAC Name: 2-[(3S,9S,12S,15S,17S,25R,28S,31S,34S,40S,43R,46S,48S,56S)-28,31,40-tris(2-amino-2-oxoethyl)-9-[(1R)-1-hydroxyethyl]-12-(hydroxymethyl)-17,48-bis(3-methylbut-2-enyl)-43-(2-methylpropyl)-2,8,11,14,27,30,33,36,39,42,45-undecaoxo-1,7,10,13,24,26,29,32,35,38,41,44,55-tridecazaoctacyclo[44.10.0.03,7.015,26.017,25.018,23.048,56.049,54]hexapentaconta-18,20,22,49,51,53-hexaen-34-yl]acetic acid		Ishida et al. 1997

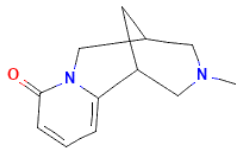
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Cyanobacterial Spp.	Antibacterial Compounds	Chemical Structure	References
Nostoc spongiaeforme var. tenue	**Tenuecyclamide A** MF: $C_{19}H_{20}N_6O_4S_2$ MW: 460.5g/mol IUPAC Name: (4S)-4,7,11,18-tetramethyl-6-oxa-13,20-dithia-3,10,17,22,23,24-hexazatetracyclo[17.2.1.15,8.112,15]tetracosa-1(21),5(24),7,12(23),14,19(22)-hexaene-2,9,16-trione		Banker and Carmeli, 1998
Nostoc commune	**1,8-dihydroxy-4-methyl anthraquinone** MF: $C_{15}H_{10}O_4$ MW: 254.24g/mol IUPAC Name: 4,5-dihydroxy-1-methylanthracene-9,10-dione		Jaki et al. 2000
Calothrix sp.	**Calothrixin A** MF: $C_{19}H_{10}N_2O_3$ MW: 314.3g/mol IUPAC Name: 20-oxido-10-aza-20-azoniapentacyclo[11.8.0.03,11.04,9.014,19]henicosa-1(13),3(11),4,6,8,14,16,18,20-nonaene-2,12-dione		Thanh et al. 2000
Nostoccommune	**Comnastin A** MF: $C_{27}H_{40}O_4$ MW: 428.6g/mol IUPAC Name: 3-[[(3R,3aR,5aS,6R,7R,9aS,9bR)-3-(hydroxymethyl)-3,3a,6,7,9a-pentamethyl-2,4,5,5a,7,8,9,9b-octahydro-1H-cyclopenta[a]naphthalen-6-yl]methyl]-4-hydroxybenzoic acid		Jaki et al. 2000

Cyanobacterial Spp.	Antibacterial Compounds	Chemical Structure	References
Nostoc sp.	**Nostocyclyne A** MF: $C_{23}H_{34}O_2$ MW: 342.5g/mol IUPAC Name: 15-propylbicyclo[14.2.2]icosa-1(19),16(20),17-trien-2-yne-17,20-diol		Ploutno and Carmeli et al. 2000
Nostoc spongiaeforme	**Nostocine A** MF: $C_5H_5N_5O$ MW: 151.13g/mol IUPAC Name: 7-methyl-2H-pyrazolo[4,3-e][1,2,4]triazin-3-one		Hirata et al. 2003
Oscillatoria redekei	**a-dimorphecolic acid** MF: $C_{18}H_{32}O_3$ MW: 296.4g/mol IUPAC Name: (9S,10E,12Z)-9-hydroxyoctadeca-10,12-dienoic acid		Mundt et al. 2003
Scytonemahofmanni PCC 7110	**Scyptolin A** MF: $C_{45}H_{69}ClN_8O_{14}$ MW: 981.5g/mol IUPAC Name: (2S,3R)-2-[[(2S)-2-(butanoylamino)propanoyl]amino]-N-[(2S,5S,8S,11R,12S,15S,18R,21R)-5-[(3-chloro-4-hydroxyphenyl)methyl]-21-hydroxy-2-[(1R)-1-hydroxyethyl]-4,11-dimethyl-15-(2-methylpropyl)-3,6,9,13,16,22-hexaoxo-8-propan-2-yl-10-oxa-1,4,7,14,17-pentazabicyclo[16.3.1]docosan-12-yl]-3-hydroxybutanamide		MacMillan and Molinski, 2005; Matern et al.

Cyanobacterial Spp.	Antibacterial Compounds	Chemical Structure	References
Lyngbya sp.	**Pahayokolide A** MF: $C_{72}H_{105}N_{13}O_{20}$ MW: 1472.7g/mol IUPAC Name: [1-[(6R,10R,13S,19R,22S,25E,28S,31Z,34S,37S)-6-(3-amino-3-oxopropyl)-34-benzyl-25,31-di(ethylidene)-9-hydroxy-22-[(1R)-1-hydroxyethyl]-28-(hydroxymethyl)-2,5,8,12,18,21,24,27,30,33,36-undecaoxo-19-(2-phenylethyl)-1,4,7,11,17,20,23,26,29,32,35-undecazatricyclo[35.3.0.013,17]tetracontan-10-yl]-4,5-dihydroxy-7-methyloctan-2-yl] (2S)-2-[acetyl(methyl)amino]-4-methylpentanoate		Berry et al. 2004
Microcoleous lacustris	**Abietane** MF: $C_{20}H_{36}$ MW: 276.5g/mol IUPAC Name: (2S,4aS,4bR,8aS,10aS)-4b,8,8-trimethyl-2-propan-2-yl-1,2,3,4,4a,5,6,7,8a,9,10,10a-dodecahydrophenanthrene		Thajuddin et al. 2005
Fischerella sp.	**Hapalindole T** MF: $C_{21}H_{23}ClN_2OS$ MW: 386.9g/mol IUPAC Name: (2S,6S,7R,8R,10R)-8-chloro-7-ethenyl-7,11,11-trimethyl-3-thia-5,17-diazapentacyclo[10.6.1.02,6.02,10.016,19]nonadeca-1(18),12(19),13,15-tetraen-4-one		Asthana et al. 2009
Fischerellaambigua	**Ambigol B** MF: $C_{18}H_8Cl_6O_3$ MW: 485g/mol IUPAC Name: 3,5-dichloro-2,6-bis(2,4-dichlorophenoxy)phenol		Raveh et al. 2007

Cyanobacterial Spp.	Antibacterial Compounds	Chemical Structure	References
Nostoc sp.	**Carbamidocyclophane A** MF: $C_{38}H_{54}Cl_4N_2O_8$ MW: 808.6g/mol IUPAC Name: [(2R,3S,13R,14S)-13-carbamoyloxy-8,19-bis(4,4-dichlorobutyl)-10,21,24,26-tetrahydroxy-3,14-dimethyl-2-tricyclo[18.2.2.29,12]hexacosa-1(22),9,11,20,23,25-hexaenyl] carbamate		Bui et al. 2007
Nostoc sp.	**Nostocarboline Hydroiodide; Nostacarboline Iodide** MF: $C_{12}H_{10}ClIN_2$ MW: 344.58g/mol IUPAC Name: 6-chloro-2-methyl-9H-pyrido[3,4-b]indol-2-ium;iodide		Becher et al. 2007
Fischerellaambigua	**Ambiguine A isonitrile** MF: $C_{26}H_{31}ClN_2$ MW: 407g/mol IUPAC Name: (2S,3R,4R,5R,7S)-5-chloro-4-ethenyl-3-isocyano-4,8,8-trimethyl-15-(2-methylbut-3-en-2-yl)-14-azatetracyclo[7.6.1.02,7.013,16]hexadeca-1(15),9(16),10,12-tetraene		Mo et al. 2009
Leptolyngbyacrosbyana	**Crossbyanol A** MF: $C_{30}H_{15}Br_7O_6$ MW: 1030.8g/mol IUPAC Name: 3-bromo-4-[2-bromo-4-(3-bromo-4-hydroxyphenoxy)-6-(2,4-dibromophenoxy)phenoxy]-2-(2,4-dibromophenoxy)phenol		Choi et al. 2010
Nostoc sp. MGL001	9-Ethyliminomethyl-12-(morpholin-4- ylmethoxy) 5, 8, 13, 16-tetraaza-hexacene-2, 3 dicarboxy-licacid (EMTAHDCA)	NA	Niveshika et al. 2016

Cyanobacterial Spp.	Antibacterial Compounds	Chemical Structure	References
Hapalosiphon Aureus	N-Methylcytisine MF: $C_{12}H_{16}N_2O$ MW: 204.27g/mol IUPAC Name: 11-methyl-7,11-diazatricyclo[7.3.1.02,7]trideca-2,4-dien-6-one		Al-Mousawi et al. 2023

NA: Not available

5. MAJOR ANTIBACTERIAL COMPOUNDS IDENTIFIED FROM CYANOBACTERIA

Cyanobacteria produce a wide range of structurally diverse compounds with reported antibacterial properties. The compounds described in the attached literature include peptides, lipopeptides, polyketides, alkaloids, aromatic compounds, and other secondary metabolites. Their structural diversity is reflected by differences in molecular formula, molecular weight, and chemical architecture, indicating the broad biosynthetic capacity of cyanobacteria. Recent reviews continue to emphasize this chemical diversity, with marine cyanobacteria alone contributing more than 200 anti-infective molecules reported up to 2024 (Tan et al., 2024).

Among the reported compounds, Scytophycins C from *Scytonema pseudohofmanni* and Tolytoxin from *Scytonema ocellatum* and *Tolypothrix conglutinata* represent structurally complex metabolites associated with antibacterial activity. *Tolypothrix nodosa* produces Tolyporphin J, while *Fischerella ambigua* produces Ambigol A and Tjipanazole D. The latter compounds demonstrate the diversity of chemical classes represented among cyanobacterial antibacterial metabolites. Hapalindole-related alkaloids also represent an important group of cyanobacterial natural products, with members of this family reported to possess antibacterial activity against diverse bacterial strains (Cock & Cheesman, 2023).

Peptide and lipopeptide compounds constitute another important group. Muscoride A, reported from *Nostoc muscorum*, is a peptide/lipopeptide with antibiotic properties. Kawaguchipeptin A from *Microcystis aeruginosa* and Tenuecyclamide A from *Nostoc spongiaeforme* var. *tenue* further demonstrate the occurrence of complex peptide metabolites. Other reported compounds include Scyptolin A from *Scytonema hofmanni* PCC 7110 and Pahayokolide A from *Lyngbya* sp. Recent studies indicate that cyanobacterial peptide chemistry continues to expand. Sieber and Janssen (2026) reported numerous newly characterized peptides, lipopeptides, and other metabolites from cyanobacteria collected or studied during 2021–2024, demonstrating that previously unexplored chemical space remains available.

A number of structurally different antibacterial metabolites have also been reported. These include 1,8-dihydroxy-4-methylanthraquinone from *Nostoc commune*, Calothrixin A from *Calothrix* sp., Comnastin A from *Nostoc commune*, and Nostocyclyne A from *Nostoc* sp. Further examples include Nostocine A, α-dimorphecolic acid, Abietane, Hapalindole T, Ambigol B, Carbamidocyclophane A, Nostocarboline hydroiodide, Ambiguine A isonitrile, and Crossbyanol A. Recent chemical-diversity studies have further demonstrated that cyanobacteria continue to yield new structural classes and analogues, particularly when metabolomics and genome-based approaches are combined with traditional isolation methods (Weiss et al., 2025).

Recent experimental studies also demonstrate that newly investigated cyanobacterial strains can yield antibacterial compounds. Amazonian cyanobacteria such as *Synechococcus* sp., *Desmonostoc* sp., *Synechocystis* sp., and *Lyngbya* sp. showed different bioactivities, with a fraction from *Synechococcus* sp. exhibiting bactericidal activity against *Bacillus subtilis* with a MIC of 40 µg/mL. LC–MS/MS analysis of the active fraction identified pheophytin and phorbide derivatives, demonstrating the value of metabolomic approaches for linking antibacterial activity with chemical constituents.

The diversity of these compounds demonstrates that antibacterial activity in cyanobacteria is not restricted to one particular chemical class. Instead, multiple structural groups contribute to the antibacterial potential of different cyanobacterial species. Recent work also emphasizes the importance of bioassay-guided fractionation, LC–MS/MS-based metabolomics, genome mining, and biosynthetic gene-cluster analysis for discovering and characterizing new cyanobacterial antibacterial compounds.

Thus, the compounds listed in Table 1 should be considered part of a much larger and continuously expanding chemical repertoire with potential relevance to antibacterial drug discovery.

6. CHEMICAL CHARACTERISTICS OF CYANOBACTERIAL ANTIBACTERIAL COMPOUNDS

Cyanobacterial antibacterial compounds show considerable chemical diversity, with structures ranging from peptides and lipopeptides to alkaloids, polyketides, aromatic compounds, fatty acid derivatives, and other cyclic metabolites. The attached literature provides molecular formulas, molecular weights, IUPAC names, and chemical structures for numerous compounds, demonstrating the wide structural variation among antibacterial metabolites reported from blue-green algae. Recent analysis of **995 cyanobacterial natural products reported between 2010 and 2023** confirmed that cyanobacterial metabolites occupy a broad chemical space and include peptides, lipopeptides, macrolides, cyclophanes, fatty acid derivatives, alkaloids, and miscellaneous structural classes (Weiss et al., 2025).

The reported compounds vary substantially in molecular size and composition. For example, **Tolyporphin J** from *Tolypothrix nodosa* has a molecular formula of $C_{24}H_{22}N_4O_4$ and molecular weight of 430.5 g/mol, whereas **Kawaguchipeptin A** from *Microcystis aeruginosa* has a considerably larger molecular formula, $C_{68}H_{92}N_{16}O_{18}$, with a molecular weight of 1421.6 g/mol. Similarly, **Pahayokolide A** from *Lyngbya* sp. has a molecular weight of 1472.7 g/mol, reflecting its highly complex peptide-derived structure. Recent chemical-diversity studies confirm that such differences in molecular size and structural complexity are characteristic of cyanobacterial natural products, particularly among peptide and lipopeptide families (Weiss et al., 2025).

Several compounds possess **halogenated structures**, which represent an important chemical feature of cyanobacterial metabolites. **Ambigol A** and **Ambigol B**, produced by *Fischerella ambigua*, have the molecular formula $C_{18}H_8Cl_6O_3$ and molecular weight of 485 g/mol. **Tjipanazole D** contains chlorine and nitrogen and has a molecular formula of $C_{18}H_{10}Cl_2N_2$. **Crossbyanol A** from *Leptolyngbya crosbyana* is another highly halogenated compound, with the molecular formula $C_{30}H_{15}Br_7O_6$ and molecular weight of 1030.8 g/mol. Recent reviews emphasize that incorporation of chlorine, bromine, and other halogens is a distinctive feature of many cyanobacterial natural products and can contribute to unusual chemical structures and biological activities (Philmus et al., 2025). Cyanobacterin provides another example of this phenomenon; recent biosynthetic research identified its halogenase-containing gene cluster and demonstrated the enzymatic basis of its chlorinated structure (Baunach et al., 2024).

Other compounds possess relatively smaller and simpler molecular frameworks. **Nostocine A** from *Nostoc spongiaeforme* has a molecular weight of 151.13 g/mol, while **1,8-dihydroxy-4-methylanthraquinone** from *Nostoc commune* has a molecular weight of 254.24 g/mol. **Calothrixin A**, reported from *Calothrix* sp., has a molecular formula of $C_{19}H_{10}N_2O_3$ and molecular weight of 314.3 g/mol. These smaller molecules occur alongside much larger peptide and lipopeptide metabolites, illustrating the broad molecular-weight range represented in cyanobacterial natural products.

Another important characteristic is the presence of **hybrid and highly functionalized molecular frameworks**. Recent analyses have identified peptide–polyketide hybrids, cyclopropane-containing fatty acid derivatives, cyclic depsipeptides, macrolides, and other unusual structures among newly reported cyanobacterial metabolites. Advances in genome mining and synthetic biology are also revealing that cyanobacteria possess numerous biosynthetic gene clusters capable of producing structurally complex compounds that remain chemically uncharacterized (Chen et al., 2025).

The chemical information presented in the attached table therefore demonstrates that cyanobacterial antibacterial metabolites encompass both relatively small molecules and highly complex peptide-based structures. This structural diversity, together with **halogenation, nitrogen-rich frameworks, lipid modifications, and hybrid biosynthetic architectures**, represents an important characteristic of cyanobacterial natural products and provides a broad chemical foundation for investigating their antibacterial potential. Recent chemical-diversity studies strongly support continued exploration of this chemical space for the discovery of new antibacterial scaffolds (Weiss et al., 2025)

7. POTENTIAL OF CYANOBACTERIAL NATURAL PRODUCTS AS ANTIBACTERIAL AGENTS

The diverse antibacterial activities reported for cyanobacteria indicate their potential as a natural source of antibacterial agents. Different cyanobacterial species produce chemically distinct metabolites, including peptides, lipopeptides, alkaloids, polyketides, cyclic compounds, and other secondary metabolites with reported activity against bacterial pathogens. The antibacterial

potential is particularly evident from studies involving both Gram-positive and Gram-negative bacteria, demonstrating that cyanobacterial extracts and isolated compounds can affect microorganisms belonging to different bacterial groups. Recent chemical-diversity studies further support this potential, showing that cyanobacteria contain a large and continuously expanding reservoir of structurally diverse natural products (Weiss et al., 2025).

The identification of specific antibacterial compounds further supports the pharmaceutical relevance of cyanobacteria. Compounds such as circinamide, microginin, puwainaphycin C, calophycin, fischerellins, hassallidins, nostofungicidine, borophycin, and muscoride A have been associated with antibacterial activity. Table 1 documents numerous structurally diverse compounds from different cyanobacterial genera, including Scytophycins C, Tolytoxin, Ambigol A, Tjipanazole D, Kawaguchipeptin A, Calothrixin A, Nostocyclyne A, Scyptolin A, Pahayokolide A, Hapalindole T, Carbamidocyclophane A, and Crossbyanol A. Recent reviews have emphasized that these compounds represent multiple biosynthetic classes and that cyanobacteria continue to yield previously uncharacterized metabolites with potential biological activities (Baunach et al., 2024; Sieber & Janssen, 2026).

Recent experimental studies further demonstrate the antibacterial potential of cyanobacterial extracts. The phycobiliprotein extract of *Arthrospira fusiformis* showed activity against selected bacterial and fungal pathogens, while extracts of *Lyngbya majuscula* and *Lyngbya martensiana* demonstrated different levels of antibacterial activity. Extracts from freshwater and rhizospheric cyanobacteria, including *Cyanothece, Synechococcus,* and *Leptolyngbya*, also demonstrated antibacterial effects, particularly against Gram-positive bacteria. More recent investigations have extended these observations to underexplored taxa. Ikhane et al. (2025) reported antibacterial activity from crude extracts of *Cylindrospermum alatosporum* and *Loriellopsis cavernicola*, with the *L. cavernicola* hexane extract showing the strongest activity and MIC values of 0.70–1.41 mg/mL against the tested bacteria. (mdpi.com) Nayeem et al. (2025) also demonstrated antibacterial activity of phenolic extracts from indigenous *Oscillatoria* spp. against bacteria associated with fish and shellfish diseases, with filamentous *Oscillatoria* showing stronger activity than planktonic forms.

The potential of cyanobacterial natural products therefore arises from their species diversity, chemical diversity, and broad spectrum of reported antibacterial activity. Recent advances in genome mining, metabolomics, biosynthetic gene-cluster analysis, and heterologous expression are also creating new opportunities to identify compounds that may not be detected through conventional extraction approaches (Baunach et al., 2024; Chen et al., 2025). (pubs.rsc.org) However, the studies also demonstrate that antibacterial effects differ among species, extracts, individual metabolites, and bacterial strains. Therefore, isolation and characterization of active compounds, followed by MIC/MBC determination and mechanism-based evaluation, remain important steps for establishing their antibacterial potential. Continued investigation of cyanobacterial natural products may therefore contribute to the identification of novel antibacterial compounds with possible pharmaceutical applications.

8. MECHANISMS OF ANTIBACTERIAL ACTION OF CYANOBACTERIAL NATURAL PRODUCTS

Cyanobacterial natural products may inhibit bacterial growth through several complementary mechanisms, depending on the chemical structure of the metabolite, producing strain, bacterial target, and concentration. Proposed mechanisms include cell-membrane disruption, interference with cell-wall functions, inhibition of DNA/RNA and protein synthesis, disruption of metabolic pathways, inhibition of efflux pumps, and interference with biofilm formation and quorum sensing. A recent review of cyanobacterial metabolites similarly identified membrane disruption, metabolic interference, inhibition of DNA/RNA/protein synthesis, and quorum-sensing inhibition among the major proposed mechanisms. However, the mechanism of action of many cyanobacterial compounds remains insufficiently established and requires compound-specific experimental validation (Kar et al., 2022; Cock & Cheesman, 2023).

One important mechanism is disruption of the bacterial cell membrane. Several cyanobacterial peptides, lipopeptides, and lipid-derived compounds can interact with bacterial membranes, resulting in increased membrane permeability, leakage of intracellular components, disturbance of ion gradients, and loss of cellular energy. This mechanism is particularly relevant for amphiphilic metabolites containing both hydrophobic and hydrophilic regions. Recent experimental evidence provides direct support for membrane-associated antibacterial activity. Ikhane et al. (2025) investigated extracts of *Cylindrospermum alatosporum* and *Loriellopsis cavernicola* and reported membrane damage together with antibacterial activity. The authors also observed synergistic effects between some cyanobacterial extracts and erythromycin, suggesting that membrane interactions may contribute to the observed antibacterial effects.

Cyanobacterial metabolites may also interfere with the bacterial cell wall and associated biosynthetic pathways. Maintenance of peptidoglycan integrity is essential for bacterial survival, particularly during cell growth and division. Some cyanobacterial metabolites may affect enzymes or cellular processes involved in cell-envelope formation, although direct experimental evidence for specific cell-wall targets remains limited. Recent reviews describe cell-wall biosynthesis as one of several bacterial processes potentially affected by cyanobacterial metabolites, but this mechanism should not be assigned to individual compounds without appropriate biochemical evidence.

Interference with protein synthesis represents another possible mechanism. Bacterial translation depends on ribosomes, tRNA, aminoacyl-tRNA synthetases, and associated factors, making these components important antibacterial targets. Cyanobacterial polyketides and alkaloids may interfere with translation through different molecular interactions. For example, earlier biochemical work demonstrated that certain cyanobacterial metabolites can directly interfere with bacterial RNA polymerase, thereby reducing RNA synthesis and consequently protein production. The alkaloid 12-epi-hapalindole E isonitrile from *Fischerella* and calothrixin A from *Calothrix* inhibited *Escherichia coli* RNA polymerase, demonstrating that cyanobacterial compounds can act directly on essential bacterial transcription machinery (Doan et al., 2001).

DNA and RNA interference can therefore represent an important antibacterial mechanism. Calothrixin A and 12-epi-hapalindole E isonitrile have been shown to interfere with RNA synthesis, while calothrixin A was also associated with inhibition of DNA replication in earlier cellular studies. More recent experimental work has provided additional evidence. Ikhane et al. (2025) found that the dichloromethane extract of *L. cavernicola* showed significant DNA-degradation activity compared with other extracts. This finding indicates that nucleic-acid damage may contribute to the antibacterial effects of some cyanobacterial metabolites, although the responsible compounds and molecular targets still require identification.

Cyanobacterial metabolites may also inhibit bacterial enzymes and metabolic pathways. Their structural diversity allows interaction with different enzyme classes and biochemical pathways. Reported mechanisms include interference with the electron-transport chain, essential metabolic enzymes, and the shikimate pathway. Some cyanobacterial compounds can also interfere with bacterial ATP generation and cellular energy metabolism. A recent review of cyanobacterial phycocompounds highlighted several possible mechanisms, including disruption of the electron-transport chain, inhibition of bacterial enzymes, interference with cell-wall biosynthesis, and inhibition of the shikimate pathway (Sabat et al., 2025).

Another mechanism particularly relevant to antimicrobial resistance is inhibition of bacterial efflux pumps. Efflux systems can remove antibiotics from bacterial cells and reduce intracellular drug concentrations. Therefore, compounds that interfere with efflux activity may potentially restore bacterial susceptibility to conventional antibiotics. Ikhane et al. (2025) provided important recent evidence by demonstrating that all tested crude extracts of *C. alatosporum* and *L. cavernicola* inhibited efflux-pump activity, although β-lactamase inhibition was comparatively weak. Some extracts also showed synergistic effects with erythromycin. These findings are particularly relevant to the development of cyanobacterial metabolites as antibiotic adjuvants rather than only as direct antibacterial agents.

Biofilm formation and quorum sensing represent another important mechanism. Biofilms protect bacterial populations from antibiotics and environmental stress, while quorum sensing coordinates processes such as virulence, motility, and biofilm development. Cyanobacterial lipids and other metabolites have previously been reported to interfere with quorum-sensing pathways. Strong recent evidence was provided by Ellis et al. (2025), who isolated two new fatty acids, anaeic acid and tumoic acid, from marine cyanobacteria. Both compounds inhibited quorum-sensing-associated virulence in *Pseudomonas aeruginosa*, reducing pyocyanin and LasB elastase production and downregulating the corresponding phzG1 and lasB genes. Importantly, the compounds did not inhibit bacterial growth under the tested conditions, indicating an anti-virulence rather than conventional bactericidal mechanism.

Recent screening also continues to demonstrate the value of cyanobacteria as sources of quorum-quenching compounds. A study screening 44 Baltic Sea cyanobacterial strains identified strains with both antibacterial and quorum-sensing inhibitory activity; bioassay-guided fractionation of *Aphanizomenon* sp. identified glycerolipids and glycolipids, including diacylglycerols and galactosyldiacylglycerols, in fractions showing quorum-quenching activity. This supports the possibility of using cyanobacterial metabolites as anti-virulence agents that interfere with bacterial communication rather than directly killing bacteria.

Taken together, current evidence indicates that cyanobacterial natural products can potentially act at multiple bacterial targets, including the membrane, cell envelope, transcription and translation machinery, DNA, metabolic enzymes, efflux systems, and

quorum-sensing pathways. Recent studies are particularly important because they have moved beyond simple inhibition-zone measurements toward membrane-damage assays, DNA-degradation studies, efflux-pump assays, gene-expression analysis, and quorum-sensing experiments. However, many reported cyanobacterial compounds still lack definitive molecular-target validation. Future work should therefore combine purified compounds with MIC/MBC determination, membrane-permeability assays, transcriptomics, proteomics, enzyme-target studies, efflux assays, biofilm models, and molecular approaches to establish precise mechanisms of action.

9. CHALLENGES, LIMITATIONS AND FUTURE PERSPECTIVES

Although cyanobacterial natural products show considerable potential as antibacterial agents, several challenges must be addressed before these metabolites can be developed into practical antibacterial drugs. A major limitation is the large variation in antibacterial activity among cyanobacterial species, strains, cultivation conditions, extraction procedures, and bacterial targets. Many studies still rely on crude extracts, making it difficult to determine which compound is responsible for the observed activity. Differences in metabolite production can also occur with changes in light, nutrients, temperature, salinity, and growth phase. Therefore, results obtained from one strain or extraction method cannot always be directly extrapolated to other cyanobacteria. Another important limitation is the low production yield and difficulty in obtaining sufficient quantities of purified compounds. A recent analysis reported that cyanobacterial natural products are commonly produced at relatively low titres, often around 0.1–0.2% of dry biomass. Cyanobacteria may also grow slowly and can be difficult to maintain as axenic cultures because of associated microorganisms. These factors can make isolation, structural characterization, pharmacological evaluation, and large-scale production difficult (Philmus et al., 2026). The large number of biosynthetic gene clusters (BGCs) represents both an opportunity and a challenge. Analysis of 326 high-quality cyanobacterial genomes identified 2,953 BGCs, including clusters associated with terpenes, ribosomally synthesized and post-translationally modified peptides (RiPPs), non-ribosomal peptides (NRPSs), polyketides (PKS), and NRPS–PKS hybrids. However, many BGCs remain uncharacterized, and their products have not yet been linked to specific chemical structures or biological activities (Philmus et al., 2026). Silent or cryptic BGCs are another major obstacle because potentially valuable metabolites may not be produced under standard laboratory cultivation conditions. Genome mining, metabolomics, transcriptomics, and other multi-omics approaches can help identify these unexplored pathways (Baunach et al., 2024). Toxicity and selectivity must also be carefully considered. Cyanobacteria produce both beneficial bioactive metabolites and potent toxins. Compounds such as microcystins and other cyanobacterial toxins demonstrate that strong biological activity does not necessarily indicate pharmaceutical suitability. Therefore, antibacterial activity should be evaluated together with cytotoxicity against mammalian cells, selectivity indices, pharmacokinetic properties, and therapeutic windows before considering further drug development. This is particularly important when crude extracts contain several metabolites with different biological activities. Another limitation is the limited mechanistic and in vivo evidence for many reported antibacterial compounds. Although inhibition zones, MIC, and MBC values provide useful preliminary information, they do not establish the molecular target or mechanism of action. Recent studies have started to address this limitation by investigating membrane damage, DNA degradation, efflux-pump activity, β-lactamase inhibition, and interactions with conventional antibiotics (Ikhane et al., 2025). More studies using purified compounds, molecular targets, bacterial transcriptomics, proteomics, and resistant clinical isolates are required. Future research should increasingly combine genome mining, LC–MS/MS metabolomics, molecular networking, artificial intelligence, and synthetic biology. Recent synthetic-biology studies have demonstrated the potential of cloning and heterologously expressing cyanobacterial BGCs in suitable microbial hosts. These approaches can overcome the low production levels and difficult cultivation of some native cyanobacteria and may provide access to metabolites that are otherwise difficult to isolate (Chen et al., 2025). The use of tools such as antiSMASH, BiG-SCAPE, CORASON, and BGC databases can further assist in prioritizing novel pathways and connecting genes with chemical products. An important future direction is the development of cyanobacterial metabolites as antibiotic adjuvants and anti-virulence agents, rather than focusing only on direct bacterial killing. Compounds capable of inhibiting efflux pumps, β-lactamases, biofilms, or quorum sensing could potentially restore antibiotic susceptibility or reduce bacterial virulence. This approach may be particularly relevant against multidrug-resistant pathogens where conventional antibiotics alone have limited effectiveness.

The future of cyanobacterial antibacterial research therefore depends on moving from crude-extract screening toward mechanism-guided discovery and translational evaluation. Bioassay-guided fractionation, structure elucidation, genome mining, multi-omics, synthetic biology, toxicity testing, and in vivo validation should be integrated into future studies. Recent perspectives recommend greater investigation of cyanobacterial BGCs, broader screening of underexplored strains, improved

data sharing, and collaboration between natural-product chemists, microbiologists, genomic scientists, and pharmacologists (Philmus et al., 2026). Such integrated approaches can help convert the considerable chemical diversity of cyanobacteria into validated antibacterial leads with realistic

9. CONCLUSIONS

Cyanobacteria represent a chemically diverse group of microorganisms capable of producing a wide range of secondary metabolites and biologically active compounds. Reported cyanobacterial metabolites include peptides, alkaloids, polyketides, lipopeptides, fatty acids, terpenoids, bromophenols, and other structurally diverse molecules. This broad chemical diversity is closely associated with the wide range of biological activities reported for cyanobacterial natural products. The antibacterial potential of cyanobacteria has been demonstrated across several genera, including *Anabaena, Calothrix, Fischerella, Lyngbya, Nostoc, Scytonema, Tolypothrix,* and *Oscillatoria*. Extracts and isolated metabolites from these cyanobacteria have shown activity against both Gram-positive and Gram-negative bacteria, including several clinically important bacterial species. Compounds such as circinamide, microginin, puwainaphycin C, calophycin, fischerellins, hassallidins, muscoride A, Calothrixin A, Scytophycins C, Tolytoxin, Ambigol A, Hapalindole T, and other metabolites further demonstrate the chemical diversity associated with cyanobacterial antibacterial activity. The reported antibacterial compounds also differ considerably in their molecular size, chemical composition, and structural organization. The occurrence of relatively small molecules together with highly complex peptides, lipopeptides, polyketides, and halogenated metabolites reflects the extensive biosynthetic capacity of cyanobacteria. Recent investigations of *Arthrospira fusiformis, Lyngbya majuscula, Lyngbya martensiana, Oxynema thaianum,* and other cyanobacteria further support the continuing importance of these organisms as sources of antibacterial metabolites. Taken together, the available evidence supports cyanobacterial natural products as a promising source of structurally diverse antibacterial compounds. The large number of producing species and the chemical diversity of their metabolites provide considerable opportunities for identifying new antibacterial candidates. However, antibacterial activity varies among species, strains, extracts, individual compounds, and target microorganisms. Further bioassay-guided isolation, structural characterization, mechanism-of-action studies, toxicity evaluation, and validation against clinically relevant bacterial strains are therefore required to establish the pharmaceutical potential of cyanobacterial metabolites and facilitate their development as natural antibacterial agents.

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