



THERMOPHILIC CYANOBACTERIA: AN UNTAPPED RESERVOIR OF PHARMACOLOGICAL LEADS

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Abstract

The pharmacological leads are the characterized bioactive and natural compounds. This could be achieved by the various approaches such as conventional and combinatorial genomic methods. The developments of pharmacological leads are the first steps, which identified the possible targets against the microbial agents. However, the current pace of leads search doesn't meet the requirements of drug discovery programs due to emergence of drug resistance and new microbial pathogens.

Cyanobacteria considered the microbial fossils of the first photosynthetic organisms along with the longest evolutionary history on earth. Cyanobacteria reported and documented the varieties of natural compounds with the diverse chemical profile. However, thermophilic cyanobacterial origin compounds have been studied very least for this purpose, and considered the huge, hindered repository for the varieties of pharmacological leads. Therefore, present communication explored the untapped thermophilic cyanobacteria for the possible pharmacological leads.

Keywords: Antimicrobial agents; Bioactive compounds; Leptolyngbya; Secondary metabolites

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1. INTRODUCTION OF CYANOBACTERIA

Cyanobacteria can be defined as, “a major group of photosynthetic bacteria that are single-celled but often form colonies in the form of filaments, sheets, or spheres and are found in diverse environments (such as salt and fresh water, soils, and on rocks)”. Cyanobacteria belong to the most primitive and diverse group of photosynthetic organism found on earth that capable of oxygenic photosynthesis and found on every part of this planet (Demoulin et al., 2019). Cyanobacteria are playing crucial role in earth history and as a primary producer they have prominent role in the carbon and nitrogen cycles (Elster and Kvíderová, 2015).

Occurrence- Cyanobacteria are prominently distributed to the various habitats and environments. Cyanobacteria frequently isolated from the extreme environments such as geothermal springs, Antarctic, Arctic, alpine, hyper-saline, alkaline habitats and under high radiations, desiccation and toxicity stress. Thermophilic cyanobacteria grown with optimum temperature in between 50°-60°C near the stable temperature gradient of hot water springs (Tyagi et al., 2021; Tyagi and Singh, 2020). The thermophilic cyanobacteria lies in the range between 45-65°C while the upper temperature limits of life are 72°C (Kees et al., 2022). The hot springs provides the constant and suitable environment for the many thermophilic cyanobacterial populations. The cyanobacterial populations that thrived in these hot and humid environmental conditions developed a wide range of metabolic capabilities (Chiriac et al., 2017). The distribution patterns of the cyanobacteria principally depend by common factors like temperature, pH and water chemistry in geothermal springs (Kees et al., 2022; Ward et al., 2012). Cyanobacteria are also tolerated the cold polar and alpine environments and plays an important role in the carbon and nitrogen cycle. Cyanobacteria belonging to the *Microcoleus chthonoplastes*, *Oscillatoria limnetica*, *Synechocystis* harbor in the hyper-saline ecosystems, various species of these groups reported to tolerate the high salt concentrations (Elster and Kvíderová, 2015). Combine with these, cyanobacteria could thrive in various ecological habitats and produced a variety of secondary metabolites that may be facilitated by the extreme environment conditions like hot water springs, salt rich marine, sulfur rich and many other extreme conditions (Kultschar and Llewellyn, 2018). Cyanobacteria has been reported and enriched with the primary and secondary metabolites (Calteau et al., 2014). Primary metabolites are constantly

produced, and required during the normal growth as well as vegetative development of cyanobacteria whereas, secondary metabolites has been often produced by the response of biotic, and abiotic stress factors (Isah, 2019). Since then, secondary metabolites of cyanobacteria have been evaluated for the various therapeutic activities from the marine and freshwater cyanobacteria having the prominence role (Kultschar et al., 2019). This adaptations and occurrence had undergone several structural and functional adjustments into their genotypic and phenotypic expression (Tyagi et al., 2018; Tyagi and Singh, 2020). In results of these, cyanobacteria developed a versatile and immense range of metabolic profile (Żyska-Haberecht et al., 2019).

Diversity- Cyanobacteria described as the monophyletic group of organism but having the high diversity as compare to the other group of microorganisms (Demay et al., 2019; Rippka et al., 1979). The diversity of cyanobacteria has been not able to describe in the single magnitude. Interestingly, they belongs to bacteria domains of life but simultaneously having the plant type's photosynthetic machinery. They consist of two photo-systems, PS-I and PS-II, and well connected with the chlorophyll 'a' but heterocyst cell of cyanobacteria having only one photo-system (PS-I). Besides that, cyanobacteria display the true cell differentiation and sizes that may differ from many orders of magnitude. As comparison with the bacterial domains, cyanobacteria represented with the wide range of morphologies and traditionally they have been groups in to the five orders that principally based on the morphology and development (Elster and Kvíderová, 2015; Jiri Komarek, 2005).

2. Natural Products Of Cyanobacteria

Diversity of cyanobacteria have been accompanied their complex biosynthesis mechanisms of natural products. Cyanobacteria are proficiently biosynthesized a verity of natural compounds, they have been extensively reported as antimicrobial, anticancer, antiviral, antifungal, protease inhibition and anti-inflammation producing organism. The chemical diversity of these compounds have been studied on the basis of their molecular properties, molecular scaffolds and structural fingerprints of the pharmaceutical interests (Mariena et al 2019). Natural products (bioactive compounds) from the cyanobacterial origin have been rarely illustrated and classified for their ecological significance. However, they established and played several ecological roles in natural conditions, such as ultra-violet protection

by the mycosporine-like amino acids (MAA) (Martins et al., 2019). As the primary producers, cyanobacterial antibacterial compounds have to be more ecologically significant than the chemically synthesized compounds. Natural antibacterial compounds are more acceptable by the target cells and easily rendered and degraded.

Since the developments of genomic science from last few decades, biosynthetic gene clusters (BGC) of the natural compounds tracing the possible pharmacological leads (Albarano et al., 2020). In cyanobacteria BGC have been well documented; polyketide synthases (PKS) and non-ribosomal peptide synthases (NRPS), and they are the important routes for the natural compounds synthesis. The researchers are now screening cyanobacteria by the various methods to identify the possible pharmacological leads. The following approaches are apparently used to identification of pharmacological leads from cyanobacteria.

Conventional method- According to a recent report (Newman and Cragg, 2020), from the last four decades 162 new antibacterial chemical entities has been reported by the natural source compounds and major portions has been covered by the conventional methods. The conventional approach has been usually identified and isolated the biologically active natural products from the organisms/cyanobacteria found in natural environments. Cyanobacteria are displayed enormous chemical diversity as compared with other microbial sources. Cyanobacteria also hindered a huge repository of the natural products from the various untapped habitats. Due to low rediscovery rate, high degree of novelty, chemical diversity and wide range of biological activities of their natural products are amongst the recommended factor that cyanobacteria becomes the most conventional microbial sources for the search of pharmacological leads.

High throughput screening- Currently, the pharmaceutical industry has been shifted their interest towards the combinatorial chemistry approach and explored possible pharmacological leads (Atanasov et al., 2015). The combinatorial chemistry with the genomic annotation data have been creating the chemical libraries that used by the high-throughput screening. In cyanobacteria, certain drug targets, regulation and various process has been studied by this techniques.

Genome mining- The developments of bioinformatics branch by the deal with computational tools significantly improved the understanding about the natural products

chemistry at their genomic level. Genome mining process involved to identify the uncharacterized biosynthetic gene clusters within the genomes of sequenced organisms. Genome mining also elucidated the mechanism of action of the natural products from cyanobacteria (Dittmann et al., 2015). The genome mining capable to construct a relationship between known metabolites to its biosynthetic gene clusters that postulated the putative gene clusters amongst the cyanobacterial genomes. Genome mining together with the synthetic biology, provides the advancement in the identification of novel biosynthetic gene clusters (Nandagopal et al., 2021). However there are also a limitation lies within these as they are depends on the already genome sequenced data of particular organisms.

3. Thermophilic cyanobacteria

The distribution of cyanobacterial populations from different orders has been depends on the particular habitats conditions (Büdel, 2011). However, dominating genera of thermophilic cyanobacteria belongs to the *Stigonematales*, and *Oscillatoriales* (Singh et al., 2018). The degree of thermal adaptation involved at different levels of proteins, enzymes metabolism, heat shock proteins (HSPs) and thermo stability of the carbon fixing enzyme RuBisCO (Pedersen and Miller, 2017). *Synechococcus lividus* was reported firstly, from the hot water springs of northern hemisphere that grow well at temperatures as high as a constant 70°C (Brock and Brock, 1967; Castenholz, 1969). Since then, thermophilic cyanobacteria have been documented from the different parts of the world. Singh (2018) studied the nine different hot water springs situated in the Indian Himalayan region (Singh et al., 2018). They observed the dominance of the filamentous *Oscillatoriales* with few novel thermophilic strains. Yala et al. (2014), studied the microbial mats collected from the nine hot water springs (39-90 °C) of Algeria (Amarouche-Yala et al., 2014). Dadheech (2013) studied cyanobacterial samples from a hot springs of Lake Bogoria, Kenya (Dadheech et al., 2013). He found that prevalent phylotypes shows the high degree of endemism, and dominant members belong to the *Oscillatoriales* (*Leptolyngbya*, *Spirulina*, and *Oscillatoria*). Notably, by these few studies thermophilic cyanobacteria represent from the each corners of the earth.

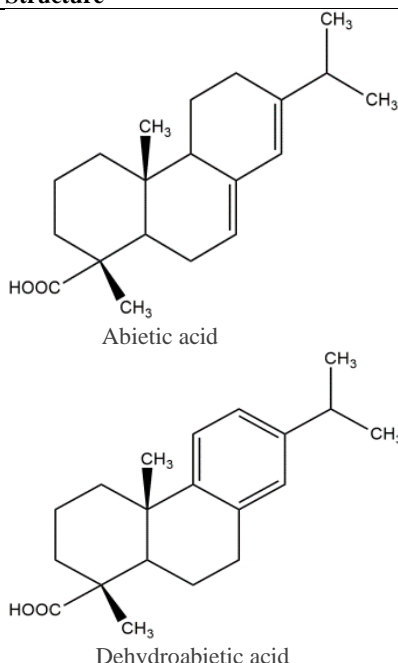
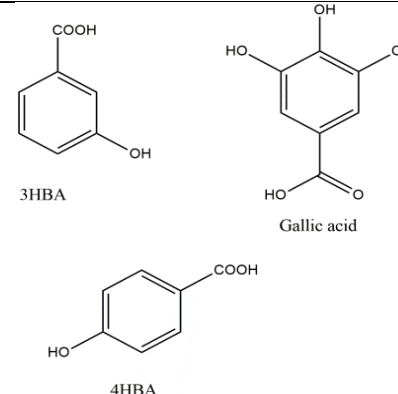
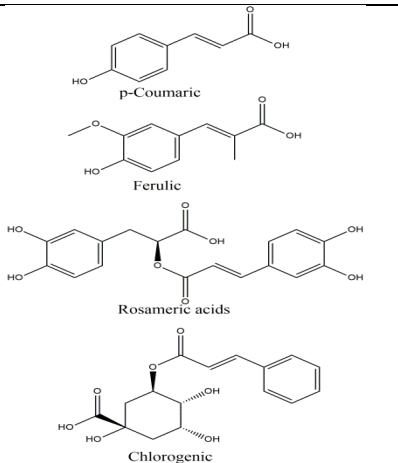
4. Pharmacological leads from thermophilic cyanobacteria

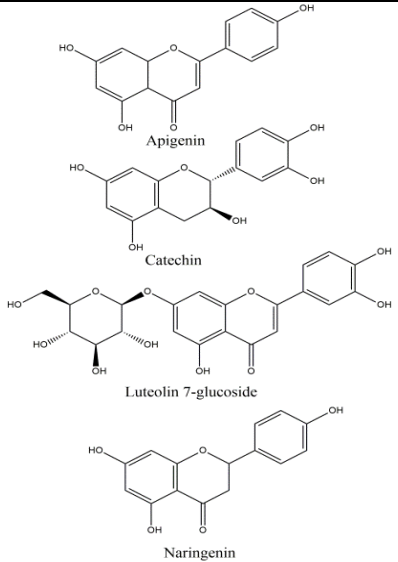
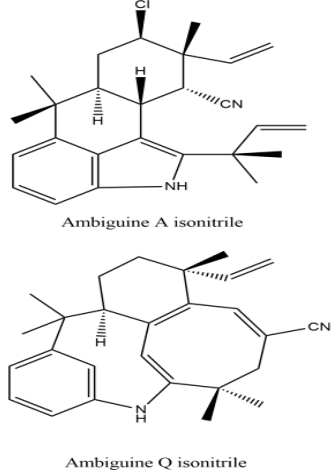
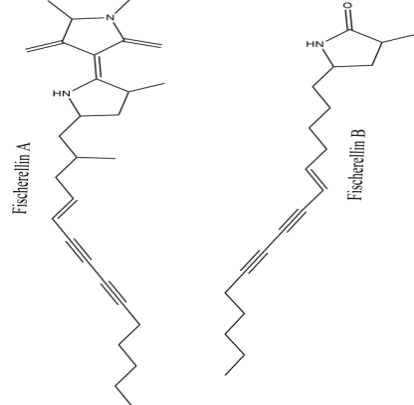
The bioactivity of thermophilic cyanobacteria studied first time by Fish and Codd (1994), while they cultivate the batch culture of thermophilic

Phormidium culture the exo-metabolites exhibited the broad-spectrum antimicrobial activity. Thermophilic cyanobacterial metabolites have been reported the diverse range of bioactivity such as; antimicrobial, anticancer, antiviral, immunosuppressant, insecticidal, anti-inflammatory to proteinase-inhibiting activities

(Abed, 2010; Luesch et al., 2001; Tidgewell et al., 2010; Wase and Wright, 2008). Dobretsov (2011) observe the significant antimicrobial activity in the thermophilic cyanobacterial mats which was obtained from a hot water springs (Dobretsov et al., 2011).

Table 1- Bioactive compounds reported from few thermophilic cyanobacterial strains.

Compound Name	Chemical classes	Activity	Cyanobacteria	Structure
Dehydroabietic and abietic acids	Terpenes	Antibacterial	<i>Leptolyngbya</i> sp.; <i>Synechococcales</i>	 <p>Abietic acid</p> <p>Dehydroabietic acid</p>
Hydroxybenzoic acids (HBA)	Phenolics	Broad spectrum	<i>Leptolyngbya</i> sp.	 <p>3HBA</p> <p>Gallic acid</p> <p>4HBA</p>
Hydroxycinnamic acids (HCA)	Phenolics	Broad spectrum	<i>Leptolyngbya</i> sp.	 <p>p-Coumaric</p> <p>Ferulic</p> <p>Rosameric acids</p> <p>Chlorogenic</p>

Flavonoids: catechin, luteolin 7-glucoside, apigenin, apigenin-7-glucoside, naringenin, luteolin, and flavon	Flavonoids	Broad spectrum	<i>Leptolyngbya</i> sp.	 <p>Apigenin</p> <p>Catechin</p> <p>Luteolin 7-glucoside</p> <p>Naringenin</p>
Ambiguine A-Q isonitrile	Alkaloids	Broad spectrum	<i>Fischerella ambigua</i> ; <i>Fischerella</i> sp	 <p>Ambiguine A isonitrile</p> <p>Ambiguine Q isonitrile</p>
Fischerellin A, B	Polyketides	Broad spectrum	<i>Fischerella</i>	 <p>Fischerellin A</p> <p>Fischerellin B</p>

They analyze the various organic extract by the GC-MS and reported several compounds. Additionally, the aqueous and ethyl acetate extracts prepared from the cyanobacterial mats (top 1-3 mm) of four hot springs were exhibited the antibacterial, and quorum-sensing inhibitory activities under natural conditions (Dobretsov et al., 2011). This study reported 74 chemical compounds from the 4 different extract that were identified by the GC-MS.

A pure culture of *Leptolyngbya* isolated from the three hot springs of Aîn Echffa, Aîn El Fakroun and Aîn Atrous, from Tunisia possesses the rich natural antioxidant compounds which may have prophylactic and therapeutic effects (Trabelsi et al., 2016). However, waste-water mat forming *Leptolyngbya* sp. strains from Egypt, reported the butylated hydroxytoluene which exhibits antimicrobial and antioxidant activities (Semary, 2012).

Filamentous *Mastigocladus* and *Microcoleus* are reported from hot water spring and their organic extracts exhibits bioactivity (Siangbood and Ramanujam, 2011). Secondary metabolites with antibacterial activity is largely reported and isolated from the cyanobacterial biomass as well as exo-metabolites (Singh et al., 2011). Cyanobacteria also reported for the excellent sources of antibacterial and antioxidants agents (Tyagi et al., 2021; Tyagi and Singh, 2020).

Recently, Demay (2019) prepared a database that contains the beneficial natural compounds of the cyanobacterial origin (Demay et al., 2019). This database arranges the 47 different metabolic families with their source information. However, this extensive study indicated that is infancy of thermophilic cyanobacteria origin of bioactive compounds (Demay et al., 2019). **Table 1** summarize the list of few compounds from the thermophilic cyanobacteria.

6. Future perspective

According to a recent study, the 157 previously known bioactive classes of cyanobacteria have been rearranged into the 55 unique bioactive classes based on their structural similarities and biological activity (Huang and Zimba, 2019). Moreover, the genome of 103 cyanobacterial species through anti-SMASH (antibiotics & Secondary Metabolite Analysis Shell) found a total of 770 biosynthetic gene cluster which arrange into 73 different types (Khumalo et al., 2020). In addition to these several other mixed gene cluster also reported from the cyanobacteria. These all bio-combinatory gene clusters are the repository of 50 % antibiotics which currently in uses (Agrawal et al., 2017).

Conclusively, thermophilic cyanobacteria have a unique evolutionary history and have been adapted according to the various thermal stress. Currently they are mostly untapped and replete source for the secondary metabolites. These metabolites could be utilized as the pharmaceutical leads and various fields of research. By the current review, admitted the importance of thermophilic cyanobacteria and in large context this section are missing previously.

AUTHOR CONTRIBUTION

AU studied, drafted and writes the manuscript, ST, AT, SA, RKS, and NS provide the scientific review and suggestion for the manuscript improvement.

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CONFLICT OF INTEREST

Not applicable

REFERENCES

1. Abed, R.M.M., 2010. Interaction between cyanobacteria and aerobic heterotrophic bacteria in the degradation of hydrocarbons. *Int. Biodeterior. Biodegrad.* <https://doi.org/10.1016/j.ibiod.2009.10.008>
2. Agrawal, S., Acharya, D., Adholeya, A., Barrow, C.J., Deshmukh, S.K., 2017. Nonribosomal Peptides from Marine Microbes and Their Antimicrobial and Anticancer Potential. *Front. Pharmacol.* 8, 1–26. <https://doi.org/10.3389/fphar.2017.00828>
3. Albarano, L., Esposito, R., Ruocco, N., Costantini, M., 2020. Genome Mining as New Challenge in Natural Products Discovery. *Mar. Drugs* 18, 199. <https://doi.org/10.3390/md18040199>
4. Amarouche-Yala, S., Benouadah, A., El Ouahab Bentabet, A., López-García, P., 2014. Morphological and phylogenetic diversity of thermophilic cyanobacteria in Algerian hot springs. *Extremophiles* 18, 1035–1047. <https://doi.org/10.1007/s00792-014-0680-7>
5. Atanasov, A.G., Waltenberger, B., Pferschy-Wenzig, E.M., Linder, T., Wawrosch, C., Uhrin, P., Temml, V., Wang, L., Schwaiger, S., Heiss, E.H., Rollinger, J.M., Schuster, D., Breuss, J.M., Bochkov, V., Mihovilovic, M.D., Kopp, B., Bauer, R., Dirsch, V.M., Stuppner, H., 2015. Discovery and resupply of pharmacologically active plant-derived natural products: A review. *Biotechnol. Adv.* 33, 1582–1614. <https://doi.org/10.1016/j.biotechadv.2015.08.001>
6. Brock, T.D., Brock, M.L., 1967. THE MEASUREMENT OF CHLOROPHYLL, PRIMARY PRODUCTIVITY, PHOTO-PHOSPHORYLATION, AND MACRO-MOLECULES IN BENTHIC ALGAL MATS. *Limnol. Oceanogr.* 12, 600–605. <https://doi.org/10.4319/lo.1967.12.4.0600>
7. Büdel, B., 2011. Cyanobacteria: Habitats and Species. pp. 11–21. https://doi.org/10.1007/978-3-642-19106-0_2
8. Burja, A.M., Banaigs, B., Abou-Mansour, E., Grant Burgess, J., Wright, P.C., 2001. Marine cyanobacteria—a prolific source of natural products. *Tetrahedron* 57, 9347–9377. [https://doi.org/10.1016/S0040-4020\(01\)00931-](https://doi.org/10.1016/S0040-4020(01)00931-)

- 0
9. Calteau, A., Fewer, D.P., Latifi, A., Coursin, T., Laurent, T., Jokela, J., Kerfeld, C.A., Sivonen, K., Piel, J., Gugger, M., 2014. Phylum-wide comparative genomics unravel the diversity of secondary metabolism in Cyanobacteria. *BMC Genomics* 15, 977. <https://doi.org/10.1186/1471-2164-15-977>
 10. Castenholz, R.W., 1969. THE THERMOPHILIC CYANOPHYTES OF ICELAND AND THE UPPER TEMPERATURE LIMIT. *J. Phycol.* 5, 360–368. <https://doi.org/10.1111/j.1529-8817.1969.tb02626.x>
 11. Chiriac, C.M., Szekeres, E., Rudi, K., Baricz, A., Hegedus, A., Dragoş, N., Coman, C., 2017. Differences in Temperature and Water Chemistry Shape Distinct Diversity Patterns in Thermophilic Microbial Communities. *Appl. Environ. Microbiol.* 83. <https://doi.org/10.1128/AEM.01363-17>
 12. Dadheech, P.K., Glöckner, G., Casper, P., Kotut, K., Mazzoni, C.J., Mbedi, S., Krienitz, L., 2013. Cyanobacterial diversity in the hot spring, pelagic and benthic habitats of a tropical soda lake. *FEMS Microbiol. Ecol.* 85, 389–401. <https://doi.org/10.1111/1574-6941.12128>
 13. Demay, J., Bernard, C., Reinhardt, A., Marie, B., 2019. Natural products from cyanobacteria: Focus on beneficial activities. *Mar. Drugs* 17, 1–49. <https://doi.org/10.3390/md17060320>
 14. Demoulin, C.F., Lara, Y.J., Cornet, L., François, C., Baurain, D., Wilmotte, A., Javaux, E.J., 2019. Cyanobacteria evolution: Insight from the fossil record. *Free Radic. Biol. Med.* 140, 206–223. <https://doi.org/10.1016/j.freeradbiomed.2019.05.007>
 15. Dittmann, E., Gugger, M., Sivonen, K., Fewer, D.P., 2015. Natural Product Biosynthetic Diversity and Comparative Genomics of the Cyanobacteria. *Trends Microbiol.* 23, 642–652. <https://doi.org/10.1016/j.tim.2015.07.008>
 16. Dobretsov, S., Abed, R.M.M.M., Al Maskari, S.M.S.S., Al Sabahi, J.N., Victor, R., 2011. Cyanobacterial mats from hot springs produce antimicrobial compounds and quorum-sensing inhibitors under natural conditions. *J. Appl. Phycol.* 23, 983–993. <https://doi.org/10.1007/s10811-010-9627-2>
 17. Elster, J., Kvíderová, J., 2015. Cyanobacteria, in: *Encyclopedia of Astrobiology*. Springer Berlin Heidelberg, Berlin, Heidelberg, pp. 590–595. https://doi.org/10.1007/978-3-662-44185-5_378
 18. Huang, I.S., Zimba, P. V., 2019. Erratum: Cyanobacterial bioactive metabolites-A review of their chemistry and biology (*Harmful algae* (2019) 83 (42-94) PII: S1568-9883(19)30058-7). *Harmful Algae* 86, 139–209. <https://doi.org/10.1016/j.hal.2019.05.001>
 19. Isah, T., 2019. Stress and defense responses in plant secondary metabolites production. *Biol. Res.* <https://doi.org/10.1186/s40659-019-0246-3>
 20. Jiri Komarek, K.A., 2005. Cyanoprokaryota 2. Teil/2ndPart: Oscillatoriales, Cyanoprokaryota: Oscillatoriales. Elsevier GmbH.
 21. Kees, E.D., Murugapiran, S.K., Bennett, A.C., Hamilton, T.L., 2022. Distribution and Genomic Variation of Thermophilic Cyanobacteria in Diverse Microbial Mats at the Upper Temperature Limits of Photosynthesis. *mSystems*. <https://doi.org/10.1128/MSYSTEMS.00317-22>
 22. Khumalo, M.J., Nzuza, N., Padayachee, T., Chen, W., Yu, J.H., Nelson, D.R., Syed, K., 2020. Comprehensive analyses of cytochrome p450 monooxygenases and secondary metabolite biosynthetic gene clusters in cyanobacteria. *Int. J. Mol. Sci.* 21. <https://doi.org/10.3390/ijms21020656>
 23. Kultschar, B., Dudley, E., Wilson, S., Llewellyn, C.A., 2019. Intracellular and Extracellular Metabolites from the Cyanobacterium *Chlorogloeopsis fritschii*, PCC 6912, During 48 Hours of UV-B Exposure. *Metabolites* 9, 74. <https://doi.org/10.3390/metabo9040074>
 24. Kultschar, B., Llewellyn, C., 2018. Secondary Metabolites in Cyanobacteria, in: *Secondary Metabolites - Sources and Applications*. <https://doi.org/10.5772/intechopen.75648>
 25. Luesch, H., Pangilinan, R., Yoshida, W.Y., Moore, R.E., Paul, V.J., 2001. Pitipectolides A and B, New Cyclodepsipeptides from the Marine Cyanobacterium *Lyngbya majuscula*. *J. Nat. Prod.* 64, 304–307. <https://doi.org/10.1021/np000456u>
 26. Martins, R., Ramos, M., Herfindal, L., Sousa, J., Skærven, K., Vasconcelos, V., 2008. Antimicrobial and Cytotoxic Assessment of Marine Cyanobacteria - *Synechocystis* and *Synechococcus*. *Mar. Drugs* 6, 1–11. <https://doi.org/10.3390/md6010001>
 27. Martins, T.P., Rouger, C., Glasser, N.R., Freitas, S., De Fraissinette, N.B., Balskus, E.P., Tasdemir, D., Leão, P.N., 2019. Chemistry, bioactivity and biosynthesis of cyanobacterial alkylresorcinols. *Nat. Prod. Rep.* 36, 1437–1461. <https://doi.org/10.1039/c8np00080h>
 28. Nandagopal, P., Steven, A.N., Chan, L.-W., Rahmat, Z., Jamaluddin, H., Mohd Noh, N.I.,

2021. Bioactive Metabolites Produced by Cyanobacteria for Growth Adaptation and Their Pharmacological Properties. *Biology* (Basel). 10, 1061.
<https://doi.org/10.3390/biology10101061>
29. Newman, D.J., Cragg, G.M., 2020. Natural Products as Sources of New Drugs over the Nearly Four Decades from 01/1981 to 09/2019. *J. Nat. Prod.* 83, 770–803.
<https://doi.org/10.1021/acs.jnatprod.9b01285>
30. Pedersen, D., Miller, S.R., 2017. Photosynthetic temperature adaptation during niche diversification of the thermophilic cyanobacterium *Synechococcus* A/B clade. *ISME J.* 11, 1053–1057.
<https://doi.org/10.1038/ismej.2016.173>
31. Rippka, E., Deruelles, J., Waterbury, N.B., 1979. Generic Assignments, Strain Histories and Properties of Pure Cultures of Cyanobacteria. *J. Gen. Microbiol.* 111, 1–61.
32. Semary, N.A. El, 2012. The characterisation of bioactive compounds from an Egyptian *Leptolyngbya* sp. strain. *Ann. Microbiol.* 62, 55–59.
<https://doi.org/10.1007/s13213-011-0226-5>
33. Siangbood, H., Ramanujam, P., 2011. A report on thermophilic Cyanophyta (Cyanobacteria) from Jakrem hot spring, Meghalaya. *Int. J. Algae.*
<https://doi.org/10.1615/InterJAlgae.v13.i2.70>
34. Singh, R.K., Tiwari, S.P., Rai, A.K., Mohapatra, T.M., 2011. Cyanobacteria: an emerging source for drug discovery. *J. Antibiot. (Tokyo)*. 64, 401–412. <https://doi.org/10.1038/ja.2011.21>
35. Singh, Y., Gulati, A., Singh, D.P., Khattar, J.I.S., 2018. Cyanobacterial community structure in hot water springs of Indian North-Western Himalayas: A morphological, molecular and ecological approach. *Algal Res.* 29, 179–192.
<https://doi.org/10.1016/j.algal.2017.11.023>
36. Tidgewell, K., Clark, B.R., Gerwick, W.H., 2010. The Natural Products Chemistry of Cyanobacteria. *Compr. Nat. Prod. II* 141–188.
<https://doi.org/10.1016/b978-008045382-8.00041-1>
37. Trabelsi, L., Mnari, A., Abdel-Daim, M.M., Abid-Essafi, S., Aleya, L., 2016. Therapeutic properties in Tunisian hot springs: first evidence of phenolic compounds in the cyanobacterium *Leptolyngbya* sp. biomass, capsular polysaccharides and releasing polysaccharides. *BMC Complement. Altern. Med.* 16, 515.
<https://doi.org/10.1186/s12906-016-1492-3>
38. Tyagi, S., Singh, P., Singh, R. kunwar, 2018. Cyanobacteria: A New Terminus for Anti-Infectious Agents, in: TRIPATHI, K. (Ed.), . Nova Science Publishers, Inc. New York, pp. 105–118.
39. Tyagi, S., Singh, R.K., 2020. Chemical profile of the antibacterial component from *Leptolyngbya* sp. HNBGU 002 isolated from a hot spring of Garhwal Himalaya. *Int J Pharm Sci Res* 11, 5225–38.
[https://doi.org/10.13040/IJPSR.0975-8232.11\(10\).5225-38](https://doi.org/10.13040/IJPSR.0975-8232.11(10).5225-38)
40. Tyagi, S., Singh, R.K., Tiwari, S.P., 2021. Anti-enterococcal and anti-oxidative potential of a thermophilic cyanobacterium, *Leptolyngbya* sp. HNBGU 003. *Saudi J. Biol. Sci.* 28, 4022–4028.
<https://doi.org/10.1016/j.sjbs.2021.04.003>
41. Ward, D.M., Castenholz, R.W., Miller, S.R., 2012. Cyanobacteria in Geothermal Habitats, in: *Ecology of Cyanobacteria II*. Springer Netherlands, Dordrecht, pp. 39–63.
https://doi.org/10.1007/978-94-007-3855-3_3
42. Wase, N. V, Wright, P.C., 2008. Systems biology of cyanobacterial secondary metabolite production and its role in drug discovery. *Expert Opin. Drug Discov.* 3, 903–929.
<https://doi.org/10.1517/17460441.3.8.903>
43. Żyszka-Haberecht, B., Niemczyk, E., Lipok, J., 2019. Metabolic relation of cyanobacteria to aromatic compounds. *Appl. Microbiol. Biotechnol.* 103, 1167–1178.
<https://doi.org/10.1007/s00253-018-9568-2>