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### **Antibacterial Compounds from Heterocystous Cyanobacteria: A Review**

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#### **ABSTRACT**

Heterocystous cyanobacterial genera *Nostoc*, *Fischerella*, and *Tolypothrix* were extensively explored for antibacterial compounds. Aromatic compounds (Ambigol, 2,4-dichlorobenzoic acid), Alkaloids (Ambiguine, Ambiguine isonitrile, Ambiguine kisonitrile, Ambiguine mesonitrile, Fischambiguine, Eucapsitrione, Fischerindole, Hapalindole, Tjipanazole) and Lipopeptide (Fischerellin), Cyclophane, Diterpenoid, Cyclicdepsipeptide, Linear peptide, extracellular pigments, Polyketide, Cyclic hexapeptides, Phenol, Indane, Terpenoids, Cyclic peptides, Porphinoid, Indolophenanthridine, Cyclic depsipeptides, Macrolide, Lipopeptide, Terterpene and Indole alkaloid are antibacterial compounds isolated from heterocystous cyanobacteria. Only a few genera have been searched for antibacterial compounds. Heterocystous cyanobacteria have rich diversity, and most genera and species have not been explored for antibacterial compounds. Hence, heterocystous cyanobacteria have great potential for drug discovery.

**KEYWORDS:** Cyanobacteria, Heterocystous, *Nostoc*, *Fischerella*, *Tolypothrix*

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## INTRODUCTION

Cyanobacteria are Gram-negative, photo synthetic prokaryote. They are also known as Blue-green algae. Cyanobacteria possess properties of both prokaryote as well as eukaryote. Cyanobacteria are classified following both i.e. botanical classification system<sup>1,2</sup> and the bacteriological classification system<sup>3</sup>. Botanical classification system of cyanobacteria is based on morphological characters. All the cyanobacteria possessing specialized cells i.e., Heterocyst (Site of nitrogen fixation) are called heterocystous cyanobacteria and are clustered in two orders i.e, Nostocales and Stigonematales of Phylum Cyanophyta<sup>1</sup>. *Nostoc*, *Anabaena*, *Richelia*, *Anabaenopsis*, *Cylindrospermum*, *Aphanizomenon*, *Wollea*, *Raphidiopsis*, *Pseudanabaena*, *Homothamnion*, *Nodularia*, *Aulosira*, *Plectonema*, *Scytonema*, *Pseudoscytonema*, *Hydrocoryne*, *Scytonematopsis*, *Petalonema*, *Camptylonemopsis*, *Tolypothrix*, *Microchaete*, *Fortiea*, *Calothrix*, *Dichothrix*, *Rivularia*, *Gloeotrichia*, *Leptochaete*, *Homoeothrix*, *Stauronema*, *Mastigocoleus*, *Nostochopsis*, *Mastigocladopsis*, *Brachytrichia*, *Mastigocladus*, *Iyengariella*, *Camptylonema*, *Fischerella*, *Stigonema*, *Fischerellopsis*, *Westiella*, *Hapalosiphon* and *Westiellopsis*<sup>1</sup> are heterocystous genera. They are widely distributed from aquatic, terrestrial environment, Polar Regions to hot springs. Besides the important role in agricultural fields, cyanobacteria are of great economic importance. They produce vitamin, photosynthetic pigments, polysaccharides, sugars pharmaceutically important molecules, and other biologically active compounds. Secondary metabolites are low molecular weight organic molecules that have diverse biological activities. They are not required for normal growth and development of organisms but facilitate the survival of the organism. Antibacterial, antifungal, anticancerous, immunosuppressants, herbicidal and cholesterol-lowering properties of secondary metabolites are well established. Chemical nature of important secondary metabolites are polyketides, alkaloids, terpenoids, shikimate derived molecules and aminoglycosides. A number of cyanobacterial strains produce intracellular and extracellular metabolites with diverse biological activities including antibacterial and antifungal<sup>4,5</sup>. Cyanobacteria are the rich source of secondary metabolite with various antimicrobial activities. A large number of cyanobacteria from different habitats have shown antibacterial activity against a wide range of human pathogenic bacteria. This review article deals with the current status of the antibacterial potential of heterocystous cyanobacteria and prospects. The emergence of antibiotic-resistant bacteria is a serious problem for the whole world. Twenty-three thousand people of US died in 2013 due to infection of antibiotic resistance bacteria (CDC report 2013). Hence there is an urgent need for the discovery of new antibacterial compounds. Cyanobacteria are the rich source of secondary metabolites and have great potential for

drug discovery<sup>6,7</sup>. A score of researchers has reported a diverse group of antibacterial compounds which are listed in Table-1.

**Table-1 List of antibacterial compounds isolated from heterocystous cyanobacteria**

S.N.	Name of active compounds	Cyanobacteria/ Activity	References
1	Abietane (Diterpenoid), C <sub>20</sub> H <sub>36</sub>	<i>Microcoleus lacustris</i> Antibacterial	<sup>8</sup> Thajuddin & Subramanian, 2005
2	Ambigol A (Aromatic), C <sub>18</sub> H <sub>8</sub> C <sub>16</sub> O <sub>3</sub>	<i>Fischerella ambigua</i> Antibacterial	<sup>9</sup> Falch et al., 1995
3	Ambigol B (Aromatic), C <sub>18</sub> H <sub>8</sub> C <sub>16</sub> O <sub>3</sub> Ambiguine ( Indole alkaloid ), C <sub>28</sub> H <sub>45</sub> NO <sub>8</sub>	<i>Fischerella ambigua</i> Antibacterial and Antimycobacterial	<sup>10</sup> Raveh & Carmeli, 2007
4	Ambiguine A isonitrile ( Indole alkaloid), C <sub>26</sub> H <sub>31</sub> CIN <sub>2</sub> Ambiguine B isonitrile (Indole alkaloid) , C <sub>26</sub> H <sub>31</sub> C1 N <sub>2</sub> O Ambiguine D isonitrile( Indole alkaloid), C <sub>26</sub> H <sub>29</sub> CIN <sub>2</sub> O <sub>3</sub> Ambiguine E isonitrile ( Indole alkaloid ) C <sub>26</sub> H <sub>29</sub> CIN <sub>2</sub> O <sub>2</sub> Ambiguine F isonitrile (Indole alkaloid), C <sub>26</sub> H <sub>31</sub> C1N <sub>2</sub> O <sub>3</sub> Ambiguine H isonitrile ( Indole alkaloid ), C <sub>26</sub> H <sub>32</sub> N <sub>2</sub> Ambiguine I isonitrile ( Indole alkaloid ), C <sub>26</sub> H <sub>30</sub> N <sub>2</sub> O <sub>2</sub> Ambiguine Kisonitrile (Indole alkaloid ) C <sub>26</sub> H <sub>29</sub> CIN <sub>2</sub> O Ambiguine, Misonitrile ( Indole alkaloid ) C <sub>26</sub> H <sub>31</sub> CIN <sub>2</sub> O <sub>2</sub> Fischambiguine B (Indole alkaloid) , C <sub>26</sub> H <sub>29</sub> CIN <sub>2</sub> O <sub>2</sub> Hapalindole G (Indole alkaloid) C <sub>21</sub> H <sub>23</sub> CIN <sub>2</sub>	<i>Fischerella ambigua</i> Antibacterial and Antimycobacterial	<sup>11</sup> Mo et al., 2009
5	Borophycin ( Peptide ) C <sub>44</sub> H <sub>68</sub> BO <sub>14</sub>	<i>Nostoc linckia</i> , <i>Nostoc spongiaeforme</i> Antibacterial	<sup>12</sup> Banker & Carmeli, 1998
6	Brunsvicamides A (Cyclic peptide ) C <sub>45</sub> H <sub>64</sub> N <sub>8</sub> O <sub>8</sub> Brunsvicamides B (Cyclic peptide), C <sub>46</sub> H <sub>66</sub> N <sub>8</sub> O <sub>8</sub> Brunsvicamides C (Cyclicpeptide), C <sub>45</sub> H <sub>64</sub> N <sub>8</sub> O <sub>10</sub>	<i>Tychonema</i> sp Antimycobacterial	<sup>13</sup> Muller et al., 2006
7	Calothrixin A (Indolophenanthridine), C <sub>19</sub> H <sub>10</sub> N <sub>2</sub> O <sub>3</sub>	<i>Calothrix</i> sp. Antibacterial	<sup>14</sup> Doan et al. 2000

8	Carbamidocyclophane A (Cyclophane) C <sub>38</sub> H <sub>54</sub> Cl <sub>4</sub> N <sub>2</sub> O <sub>8</sub> , Carbamidocyclophane B (Cyclophane) C <sub>38</sub> H <sub>55</sub> Cl <sub>3</sub> N <sub>2</sub> O, Carbamidocyclophane C (Cyclophane), C <sub>38</sub> H <sub>56</sub> Cl <sub>2</sub> N <sub>2</sub> O <sub>8</sub> , Carbamidocyclophane D (Cyclophane) C <sub>38</sub> H <sub>57</sub> ClN <sub>2</sub> O <sub>8</sub> , Carbamidocyclophane E (Cyclophane) C <sub>38</sub> H <sub>58</sub> N <sub>2</sub> O <sub>8</sub>	<i>Nostoc</i> sp. CAVN Antibacterial	<sup>15</sup> Bui et al., 2007
9	Comnostins A (Diterpenoid) C <sub>27</sub> H <sub>40</sub> O <sub>4</sub> , Comnostins B (Diterpenoid) C <sub>27</sub> H <sub>38</sub> O <sub>4</sub> , Comnostins C (Diterpenoid) C <sub>27</sub> H <sub>38</sub> O <sub>5</sub> , Comnostins D (Diterpenoid) C <sub>29</sub> H <sub>44</sub> O <sub>5</sub> , Comnostins E (Diterpenoid) C <sub>27</sub> H <sub>38</sub> O <sub>4</sub> 1,8-dihydroxy-4-methyl anthraquinone (Polyketide), C <sub>15</sub> H <sub>10</sub> O <sub>4</sub> Noscomin (Diterpenoid) C <sub>27</sub> H <sub>38</sub> O <sub>4</sub>	<i>Nostoc commune</i> Antibacterial	<sup>16</sup> Jaki et al., 2000
10	Cyanobacterin (Aromatic), C <sub>23</sub> H <sub>23</sub> ClO <sub>6</sub>	<i>Scytonema hofmanni</i> Antibacterial	<sup>17</sup> Mason., 1982
11	Eucapsitrione (Alkaloid), C <sub>21</sub> H <sub>10</sub> O <sub>6</sub>	<i>Fischerella ambigua</i> Antimicobacterial	<sup>18</sup> Sturdy., 2010
13	Hapalindole A (Indole alkaloid) C <sub>21</sub> H <sub>23</sub> ClN <sub>2</sub>	<i>Nostoc CCC537, Fischerella</i> sp Antibacterial, Antimicobacterial	<sup>19</sup> Chlipala, 2011 <sup>20</sup> Asthana, 2009
15	Hapalindole T (Indole alkaloid), C <sub>21</sub> H <sub>23</sub> ClN <sub>2</sub> OS	<i>Fischerella</i> sp Antibacterial	<sup>21</sup> Asthana, 2006
16	Muscoride A (Linear peptide) C <sub>28</sub> H <sub>40</sub> N <sub>4</sub> O <sub>5</sub>	<i>Nostoc muscorum</i> Antibacterial	<sup>22</sup> Nagatsu, 1995
17	Norbietane (Diterpenoid), C <sub>19</sub> H <sub>34</sub>	<i>Microcoleus lacustris</i> Antibacterial	<sup>23</sup> Pérez Gutiérrez, 2008
18	Norharmane (Indol alkaloid) C <sub>11</sub> H <sub>8</sub> N <sub>2</sub>	<i>Nadularia harveyana</i> Antibacterial Antifungal	<sup>24</sup> Volk & Furkert, 2006
19	Nostocarboline (Alkaloid) C <sub>12</sub> H <sub>10</sub> Cl <sub>1</sub> N <sub>2</sub>	<i>Nostoc</i> sp. Antibacterial	<sup>25</sup> Becher, 2007
20	Nostocine A ( Extracellular pigment) C <sub>5</sub> H <sub>5</sub> N <sub>5</sub> O	<i>Nostoc spongiaeforme</i> Antibacterial	<sup>26</sup> Hirata et al.,2000
21	Nostoclyne (Polyketide) C <sub>23</sub> H <sub>34</sub> O <sub>2</sub>	<i>Nostoc</i> sp. Antibacterial	<sup>27</sup> Ploutno et al., 2000
23	Scyptolin A (Cyclic depsipeptides), C <sub>45</sub> H <sub>69</sub> ClN <sub>8</sub> O <sub>14</sub>	<i>Scytonema hofmanni</i> PCC 7110 Antibacterial	<sup>28</sup> MacMillan et al., 2000

24	Scytophycin A (Macrolide) C <sub>45</sub> H <sub>75</sub> N <sub>12</sub> O <sub>12</sub> , Scytophycin A (Macrolide) C <sub>47</sub> H <sub>73</sub> N <sub>12</sub> O <sub>12</sub>	<i>Scytonema pseudohofmanni</i> Antibacterial, Antifungal	<sup>29</sup> Matern et al., 2001
25	Scytonemin A (Lipopeptide), C <sub>71</sub> H <sub>106</sub> N <sub>12</sub> O <sub>21</sub>	<i>Scytonema sp.</i> Antibacterial Antifungal	<sup>30</sup> Helms et al., 1988
26	Scytophycins C (Macrolide) , C <sub>45</sub> H <sub>75</sub> N <sub>11</sub> O <sub>11</sub>	<i>Scytonema pseudohofmanni</i> Antibacterial	<sup>31</sup> Ishibashi et al., 1986
27	Scyto-scalarol (Terpene), C <sub>26</sub> H <sub>45</sub> N <sub>3</sub> O	<i>Scytonema sp</i> Antibacterial ,Antifungal, Anti mycobacterial	<sup>11</sup> Mo et al., 2009
28	Tenuocyclamide A (Cyclic hexapeptides) C <sub>19</sub> H <sub>20</sub> N <sub>6</sub> O <sub>4</sub> S <sub>2</sub> , Tenuocyclamide B (Cyclic hexapeptides) C <sub>19</sub> H <sub>20</sub> N <sub>6</sub> O <sub>4</sub> S <sub>2</sub> , Tenuocyclamide C (Cyclic hexapeptides) C <sub>20</sub> H <sub>22</sub> N <sub>6</sub> O <sub>4</sub> S <sub>3</sub> , Tenuocyclamide D (Cyclic hexapeptides) C <sub>20</sub> H <sub>22</sub> N <sub>6</sub> O <sub>5</sub> S <sub>3</sub>	<i>Nostoc spongiaeforme var. tenue</i> Antibacterial	<sup>12</sup> Banker & Carmeli, 1998
29	Tjipanazole A (Alkaloid), C <sub>24</sub> H <sub>20</sub> C <sub>12</sub> N <sub>2</sub> O <sub>4</sub>	<i>Tolypothrix tjipanasensis</i> Antibacterial and antifungal	<sup>32</sup> Bonjouklian et al., 1991
30	Tjipanazole D (Alkaloid), C <sub>18</sub> H <sub>10</sub> C <sub>12</sub> N <sub>2</sub>	<i>Fischerella ambigua</i> Antibacterial	<sup>9</sup> Falch et al., 1995
31	Tolyporphin J (Porphinoid), C <sub>24</sub> H <sub>22</sub> N <sub>4</sub> O <sub>4</sub>	<i>Tolypothrix nodosa</i> Antibacterial	<sup>33</sup> Prinsep et al., 1992
32	Tolytoxin (Macrolide), C <sub>46</sub> H <sub>75</sub> N <sub>13</sub> O	<i>Scytonema ocellatum</i> , <i>Tolypothrix conglutinate</i> Antibacterial	<sup>34</sup> Moore et al., 1986, <sup>35</sup> Patterson & Carmeli, 1992
33	12-epi-hapalindole E isonitrile (Alkaloid), C <sub>21</sub> H <sub>23</sub> Br <sub>7</sub> ClN <sub>2</sub>	<i>Fischerella</i> ATCC53239 Antibacterial	<sup>36</sup> Doan et al., 2001
34	4-4'hydroxybiphenyl (Phenol), C <sub>13</sub> H <sub>9</sub> N <sub>1</sub> O	<i>Nostoc insulare</i> Antibacterial,antifungal ,antimycobacterial	<sup>24</sup> Volk & Furkert, 2006
35	4-hydroxy-7-methyl indan-1-one (Indane), C <sub>10</sub> H <sub>10</sub> O	<i>Nostoc commune</i> Antibacterial	<sup>16</sup> Jaki et al., 2000
36	9-Ethyliminomethyl-12-(morpholin-4-ylmethoxy)-5, 8, 13, 16-tetraaza-hexacene-2, 3 dicarboxylic acid (EMTAHDCA) C <sub>32</sub> H <sub>26</sub> N <sub>6</sub> O <sub>6</sub>	<i>Nostoc sp.</i> MGL001 Antibacterial	<sup>37</sup> Niveshika et al., 2016

## DISCUSSION:

Heterocystous cyanobacteria are biological nitrogen fixers and well known for contribution in the nitrogen economy of agricultural fields. Among the heterocystous cyanobacterial genera *Nostoc*, *Fischerella*, and *Tolypothrix* were extensively explored for antibacterial compounds (Tab.-1). *Fischerella ambigua* is the most potent species among genera *Fischerella* (Tab.-1). Aromatic compounds (Ambigol, 2,4-dichlorobenzoic acid), Alkaloid (Ambiguine, Ambiguine isonitrile, Ambiguine

kisonitrile, Ambiguine mesonitrile, Fischambiguine, Eucapsitrione, Fischerindole, Hapalindole, Tjipanazole) and Lipopeptide (Fischerellin) were antibacterial compounds isolated and characterized from genus *Fischerella* and most of them from *Fischerella ambigua* (Tab.-1). Alkaloids are the most common antibiotic compounds in *Fischerella ambigua* (Tab.-1). *Nostoc linckia*, *Nostoc spongiaeforme*, *Nostoc* sp. CAVN, *Nostoc commune*, *Nostoc* sp. ATCC 53789, *Nostoc muscorum*, *Nostoc spongiaeforme* var. *tenue*, *Nostoc insulare*, *Nostoc* sp. MGL001 are some common species of genera *Nostoc* which produced antibacterial compounds (Tab.-1). Cyclophane, Diterpenoid, Cyclicdepsipeptide, Indole alkaloid, linear peptide, Diterpenoid, Alkaloid, Extracellular pigment, Polyketide, Cyclic hexapeptides, Phenol, Indane, Terpenoids and dicarboxylic acids are antibacterial compounds produced by genera *Nostoc*. Alkaloid, Cyclic peptides and Porphinoid are antibacterial compounds produced by genera *Tolypothrix* (Tab.-1). *Microcoleus lacustris* produced Diterpenoid as antibacterial compounds (Tab.-1). *Tychonema* sp produced cyclic peptides (Tab.-1). *Calothrix* sp. produced Indolophenanthridine (Tab.-1). *Scytonema* genera produced Cyclic depsipeptides, Macrolide, Lipopeptide, Terterpene and Aromatic compounds (Tab.-1). *Hapalosiphon fontinalis* produced Alkaloids (Tab.-1). *Microcoleus lacustris* produced Diterpenoid (Tab.-1). *Nadularia harveyana* produced Indol alkaloids (Tab.-1). *Hapalosiphon* produced Indole alkaloid (Tab.-1). Heterocystous cyanobacteria produced variety of antibacterial compounds. Only few heterocystous cyanobacterial strains produced variety of antibacterial compounds (Tab.-1). Most of heterocystous cyanobacterial genera have not been explored for antibacterial compounds. Each genus has a number of species with strains having worldwide distribution. So, heterocystous cyanobacterial strains may prove a potential source of future demand of antibacterial compounds.

## CONCLUSION:

Only a few heterocystous cyanobacterial strains produced a variety of antibacterial compounds (Tab.-1). Aromatic compounds (Ambigol, 2,4-dichlorobenzoic acid), Alkaloid (Ambiguine, Ambiguine isonitrile, Ambiguine kisonitrile, Ambiguine mesonitrile, Fischambiguine, Eucapsitrione, Fischerindole, Hapalindole, Tjipanazole) and Lipopeptide (Fischerellin), Cyclophane, Diterpenoid, Cyclicdepsipeptide, Indole alkaloid, Linear peptide, Diterpenoid, Extracellular pigment, Polyketide, Cyclic hexapeptides, Phenol, Indane, Terpenoids and dicarboxylic acids, Cyclic peptides and Porphinoid, Diterpenoid, Indolophenanthridine, Cyclic depsipeptides, Macrolide, Lipopeptide, Terterpene and Indole alkaloid are antibacterial compounds produced by heterocystous cyanobacteria. Heterocystous cyanobacteria have

rich diversity, and only a few genera have been searched for antibacterial compounds. Hence, heterocystous cyanobacteria have great potential for drug discovery.

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