10-2021

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Ritu Chauhan

Abhishek Chauhan

Ashutosh Tripathi

Anuj Ranjan

Subhash C. Chauhan
The University of Texas Rio Grande Valley

See next page for additional authors

Recommended Citation

Chauhan, R., Chauhan, A., Tripathi, A., Ranjan, A., Chauhan, S., & Jindal, T. (2021). PHARMACEUTICAL POTENTIAL OF LABORATORY GROWN CULTURES OF BLUE-GREEN ALGAE: A COMPREHENSIVE REVIEW AND FUTURE POSSIBILITIES. Journal of Experimental Biology and Agricultural Sciences, 9(5), 543–751. https://doi.org/10.18006/2021.9(5).543.571

Journal of Experimental Biology and Agricultural Sciences, October - 2021; Volume – 9(5) page 543 – 571

Journal of Experimental Biology and Agricultural Sciences

http://www.jebas.org

ISSN No. 2320 – 8694

PHARMACEUTICAL POTENTIAL OF LABORATORY GROWN CULTURES OF BLUE-GREEN ALGAE: A COMPREHENSIVE REVIEW AND FUTURE POSSIBILITIES

Ritu Chauhan[1], Abhishek Chauhan[2*], Ashutosh Tripathi[1*], Anuj Ranjan[2], Subhash C. Chauhan[3], Tanu Jindal[1,2]

[1]Amity Institute of Environmental Sciences, Amity University, Sector-125, Noida, Uttar Pradesh, India
[2]Amity Institute of Environmental Toxicology, Safety and Management, Amity University, Sector-125, Noida, Uttar Pradesh, India
[3]STCECR, School of Medicine, University of Texas Rio Grande Valley, McAllen, TX 78504, USA

Received – July 26, 2021; Revision – September 29, 2021; Accepted – October 16, 2021
Available Online – October 30, 2021

DOI: http://dx.doi.org/10.18006/2021.9(5).543.571

KEYWORDS

Blue-Green Algae

Biomass

Pharmaceutically Important Compound

Biological activities

Discovery

Development

ABSTRACT

COVID-19 pandemic has taught the world researchers the urgent need for new sources and novel pharmaceuticals not only for existing diseases but also for both seasonal epidemics and future pandemics. Pharmaceutical drug discoveries for the past fifty years depended deeply on the procedure of empirical transmission of a huge number of pure bioactive compounds to provide new leads. The screening of extracts or isolating compounds is a common way to discover novel biologically active molecules. Most of the valuable Blue-Green algal metabolites are concentrated in their biomass. For existence in nature, Blue-Green algae (BGA) secrete and contain various organic substances like proteins, fatty acids, vitamins, pigments, primary and secondary metabolites, and these compounds are explored for potential biological activities such as antibacterial, antifungal, antiviral (including the anti-SARS-CoV-2 virus that causes COVID-19), anticancer, antioxidant, antidiabetic, protease inhibitory activity, anti-inflammatory activity, etc. Due to their diverse application, pharmaceutical companies have shown commercial interest in the Blue-green algal group for the discovery and development of novel molecules to combat deadly diseases for the benefit of society and mankind. The current review paper highlights and discusses the diverse pharmaceutical potential of laboratory-grown cultures of BGA along with comprehensive and current knowledge on bioactive compounds discovered by researchers globally.

* Corresponding author
E-mail: atripathi1@amity.edu (Ashutosh Tripathi); akchauhan@amity.edu (Abhishek Chauhan)

Peer review under responsibility of Journal of Experimental Biology and Agricultural Sciences.

Production and Hosting by Horizon Publisher India [HPI] (http://www.horizonpublisherindia.in/).

1 Introduction

In the extremely competitive environment of current pharmaceutical research and development of new molecules, natural products offer a unique element of molecular diversity and biological functionality, which is essential for drug discovery (Bernardini et al., 2018; Chatterjee et al., 2019; Atanasov et al., 2021). The study of secondary metabolites that organisms such as microbes including BGA and plants have evolved, largely for their survival, has historically proved of immense benefit in drug discovery and development (Petersen et al., 2020). They are providing a rich source of structurally novel bioactive molecules such as lipopeptides, amino acids, fatty acids, etc., many of which have become life-saving drugs (Singh et al., 2021a). In recent decades, pharmaceutical inventions are focused on natural sources (microbial sources such as bacterial, fungi, algal including Blue-green algae) which can deal with recent diseases. Medicinal chemistry is the backbone of lead generation in early drug invention where small molecule hits from high throughput screen (HTS), which leads to limited optimization and identification of lead compounds (Jimenez-Lopez et al., 2021). Despite these efforts, some new chemical entities have reached the market, and researchers throughout the world now are giving more attention to exploring these groups of microorganisms (including microbes from extreme environments i.e., Arctic, Antarctic) for extractions of novel compounds with diverse pharmaceutical applications.

1.1 The need for novel Pharmaceutically important compounds

The less accessibility and high cost of new generation antibiotics necessitate looking for the substances from alternative medicines with claimed antimicrobial activity. Today, most of the diseases caused by pathogens can be cured with the help of available antibiotics, but the discovery of any new antibiotic generally follows up with a course of resistance mechanism building up against it among the target organisms (Dimri et al., 2018). This phenomenon is known as 'antibiotic resistance is developing among microbial species at an appreciable rate, is a formidable complication of prudent and overuse of available antibiotics, and is imposing a serious health threat to human welfare. World Health Organization (WHO) in February 2017 published a report of antimicrobial-resistant bacteria for which new pharmaceutical compounds are urgently needed (WHO, 2017). Keeping in view the urgent requirement, the current review highlights various important aspects about the pharmaceutical potential of laboratory-grown cultures of BGA.

1.2 Blue-Green Algae

Blue-green algae are a group of extraordinary, diverse, gram-negative, oxygenic, photosynthetic prokaryotic, microscopic oldest organisms that originated 3.5 billion years ago (Kaushik et al., 2009). Blue-green algae are found all over the world, shows remarkable ecological diversity of habitats such as Freshwater (Khatoon et al., 2018; Chittapun et al., 2020), Terrestrial (Radzi et al., 2019; Riba et al., 2020), Marine (Basu et al., 2019; Uma et al., 2020), Hot spring (Tang et al., 2018; Cheng et al., 2020), etc. These BGA are also widely distributed in the polar region such as the Arctic, Antarctic, Southern Ocean, and Himalayas (Singh & Elster, 2007; Rego et al., 2019; Zaki et al., 2020). It has been estimated that about 2000 strains of freshwater and marine BGA are distributed all over the world. The capability to grow in adverse conditions and their autotrophic nature makes them an eligible candidate to grow in low nutrient-deficient lakes, ponds, and oceans which pose a serious threat to water and result in eutrophication. This may cause unpleasant tastes and odors of water through the secretion of volatile compounds. Random screening of blue-green algae will continue to play an important role in the drug discovery process for the foreseeable future. Several studies have been conducted for the isolation and identification of Blue-Green Algae from water, soil, sediments, algal mats, etc. (Figure 1-8) using advanced morphological, physiological, and molecular characterization techniques (Bellinger & Sigee, 2015; Hokmollahi et al., 2016; Radkova et al., 2020). These BGA have successfully grown on a laboratory scale using selective media i.e. BG-11, BG-13, Chu 10 (Chu, 1942; Rippka et al., 1979; Kaushik et al., 2010), Allen and Arnon Medium (Allen & Arnon, 1955), Fogg's Medium (Fogg's. 1965), Modified Bristol's Medium (Bold, 1949) and Pringsheim's Medium (Pringsheim, 1946). Blue-green algae do not require carbon or energy sources in their growth medium. Thus, they require only a basic inorganic medium, which has several logical advantages when performing the mass culture and purification of active compounds. Flask cultivation and mass cultivation for instance open pond system, hybrid system, closed photobioreactors are very well-known culturing methods used for generating biomass maintaining proper light, temperature, water, CO_2 supply, pH, nutrient supply, and proper mixing (Kaiwan-arporn et al., 2012; Troschl et al., 2017; Al-Saman et al., 2020; Jo et al., 2020). Lyophilization (freeze-drying), air drying, and sun-drying are some known popular techniques to convert biomass into powder (Smetana et al., 2017). Aqueous extraction i.e. cold and hot water extraction, organic extraction i.e. polar solvent extraction, semi-polar solvent extraction, non-polar solvent extraction, mix solvents extraction and sequential extractions, soxhlet extraction have been used extensively to isolate medicinal value active ingredients (Fatima et al., 2017; Vanlalveni et al., 2018; Yücer et al., 2018; Saurav et al., 2019). Generally, all blue-green algae vegetative cells contain carboxysomes, pseudocrystalline aggregates of the key enzymes of CO_2 fixation via the reductive pentose phosphate pathway and glycogen is a general carbohydrate reserve material of cyanobacteria. Other cellular inclusions include Poly-β-hydroxybutyrate (PHB) granules, cyanophycean granules, polyphosphate granules, carboxysomes or polyhedral bodies, and gas

vesicles (Stanier, 1988). They show notable ecological diversity. Because of extensive eutrophication of lakes, ponds and some parts of oceans BGA often forms blooms, which lead to water hygienic problems (Chorus et al., 2000; Duy et al., 2000). They may cause unpleasant tastes and odors through the excretion of volatile compounds (Jones & Korth, 1995; Liu et al., 2006).

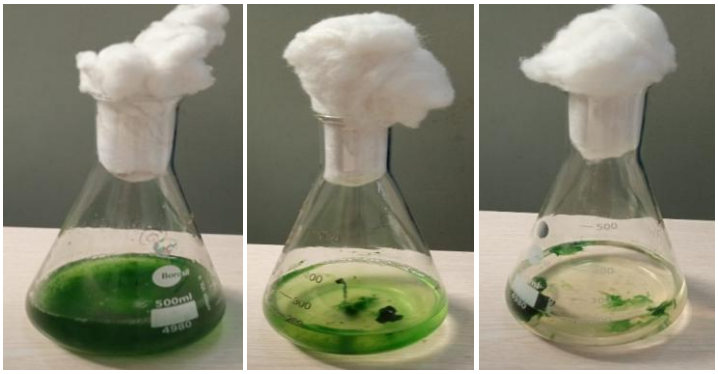


Figure 1 Laboratory Grown Culture of BGA (Medium: BG-11): A. *Calothrix* sp., B. *Spirulina* sp. C. *Oscillatoria* sp.

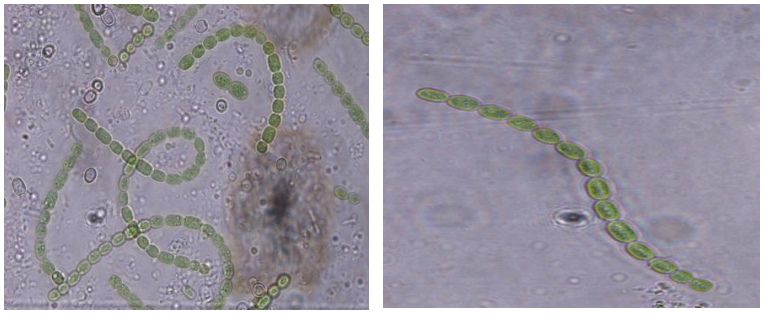


Figure 2 Microscopic images of *Anabaena* species (Chauhan & Jindal, 2020)

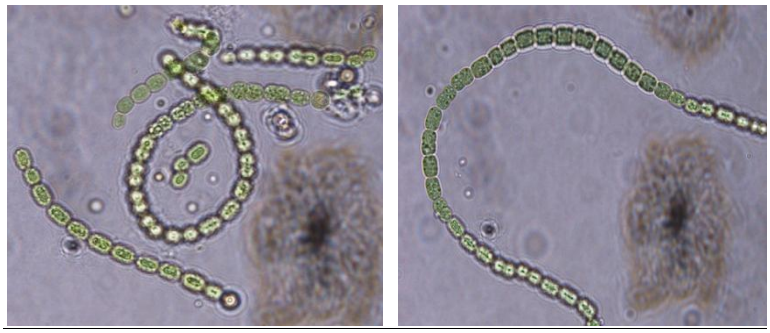


Figure 3 Microscopic images of *Nostoc* species (Chauhan & Jindal, 2020)

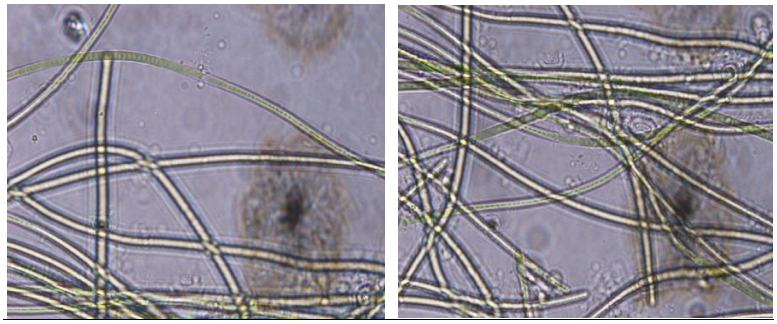


Figure 4 Microscopic images of *Calothrix* species (Chauhan & Jindal, 2020)

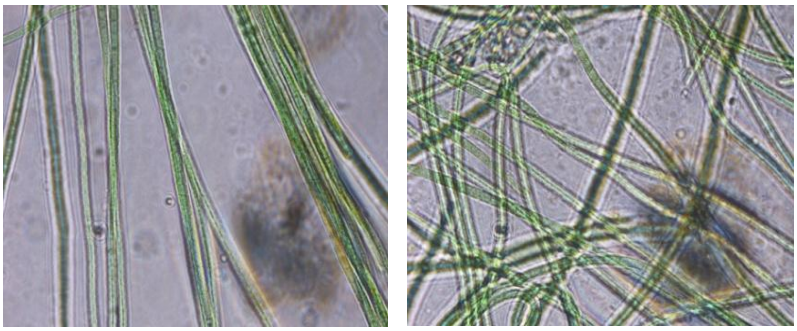


Figure 5 Microscopic images of *Oscillatoria* species (Chauhan & Jindal, 2020)

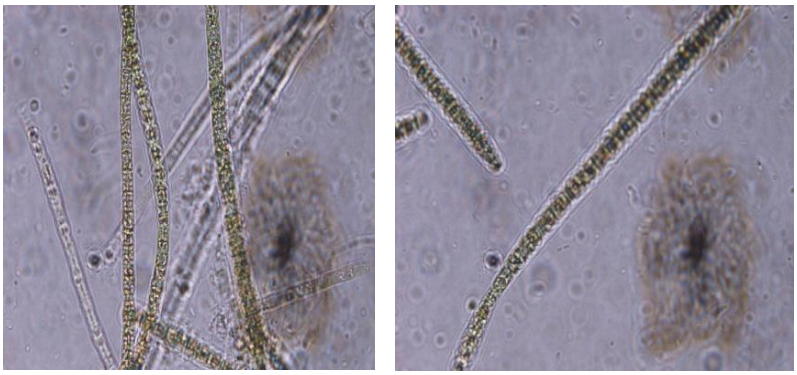


Figure 6 Microscopic images of *spirulina species* (Chauhan & Jindal, 2020)

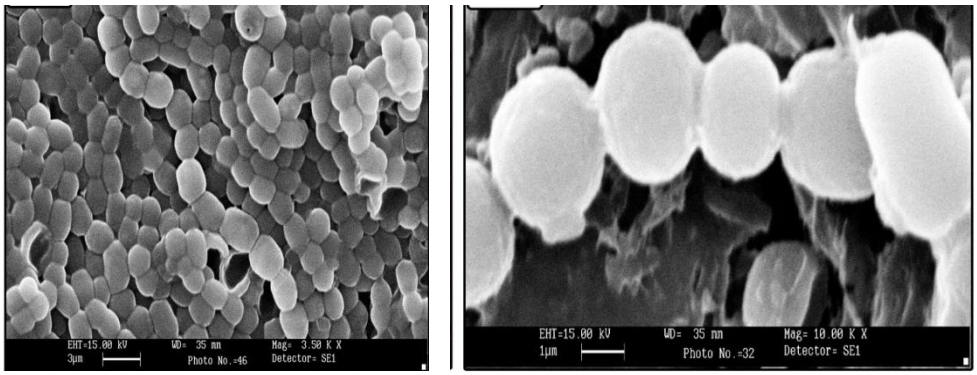


Figure 7 Scanning Electron Micrograph (SEM) image of *Anabaena* sp. (A) and *Nostoc* sp. (B) as per Kaushik & Chauhan (2008a)

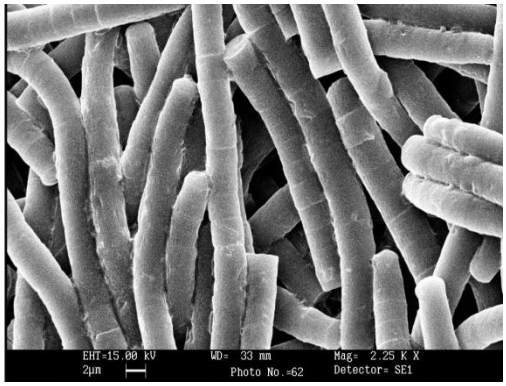


Figure 8 Scanning Electron Micrograph (SEM) image of *Spirulina platensis* (Kaushik & Chauhan, 2008b)

2 Pharmaceutical Potential of BGA

Blue-green algae are the rich source of structurally novel and biologically active metabolites with diverse antibacterial, antifungal, antiviral (including the anti-SARS-CoV-2 virus that causes COVID-19), anticancer, antioxidant, antidiabetic, protease inhibitory activity, anti-inflammatory activity, immunomodulatory activity, larvicide, and protease inhibitory activity, etc. (Figure 9) (Nainangu et al., 2020; Jafari et al., 2021). The first time before 1500 BC, medicinal and nutritional properties have been investigated for Nostoc algal species to treat gout, fistula, and cancer (Cardellina et al., 1979a; Shishido et al., 2020).

These photosynthetic microorganisms can yield proteins, carbohydrates, and lipids as a result of photosynthesis thus referred to as important biological resources having a wide range of biotechnological applications in the modern world due to their ability to grow rapidly even in harsh environmental conditions (Padmini et al., 2021). A search of these organisms for medicinal purposes has revealed important chemical prototypes for the finding of new agents, stimulating the use of refined physical techniques and new syntheses of molecules with the pharmaceutical application for human welfare. Phytochemical's constituents described from extracts of Blue-Green algae have been described by researchers (Figure 10) and are very well documented (Vasudevan et al., 2020; Nainangu et al., 2020; Gabr et al., 2020; Vasudevan et al., 2020)

2.1 Pharmaceutically important compounds isolated from BGA

Secondary metabolites refer to those compounds that are not used by the organisms for their primary metabolisms. Secondary metabolites influence other organisms in the vicinity and are thought to be of phylogenetic importance (Carpine & Sieber, 2021). Secondary metabolites include several types of compounds that may act as hormones, antibiotics, allelochemicals, toxins, and biotoxins that are found in surface supplies of fresh water (Carmichael, 1992). The ability of such compounds to kill bacteria and fungi have been well documented (Bonjouklian et al., 1988). The properties of secondary metabolites in nature are not completely understood (Metting & Pyne, 1986; Inderjit & Dakshini, 1994; Vasudevan et al., 2020).

The blue-green algae bear the characteristics to secrete vitamins, amino acids, fatty acids, carbohydrates, and various primary and secondary metabolites like amines, histamines, histidine, tannins, terpenoids, bromophenol, and polysaccharides (Figure 11). Few of these compounds are proven to be biologically active (Metting & Pyne, 1986; Padmini et al., 2021). The recent examples are cyanovirin-N secreted by *Nostoc* ellipososporum and anti-HIV glycolipids secreted by Isochyrosis and bromophenol are secreted by *Calothrix* sp. (Jaspars & Lawton 1998; Safari et al., 2020).

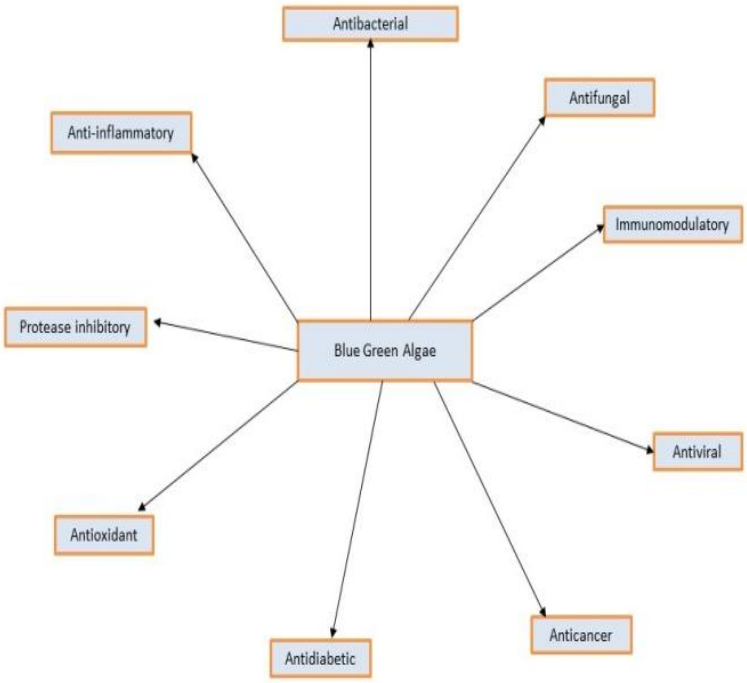


Figure 9 Pharmaceutical Potential of Blue-Green Algae

Figure 10 Major Phytochemicals constituents described from extracts of Blue-Green algae

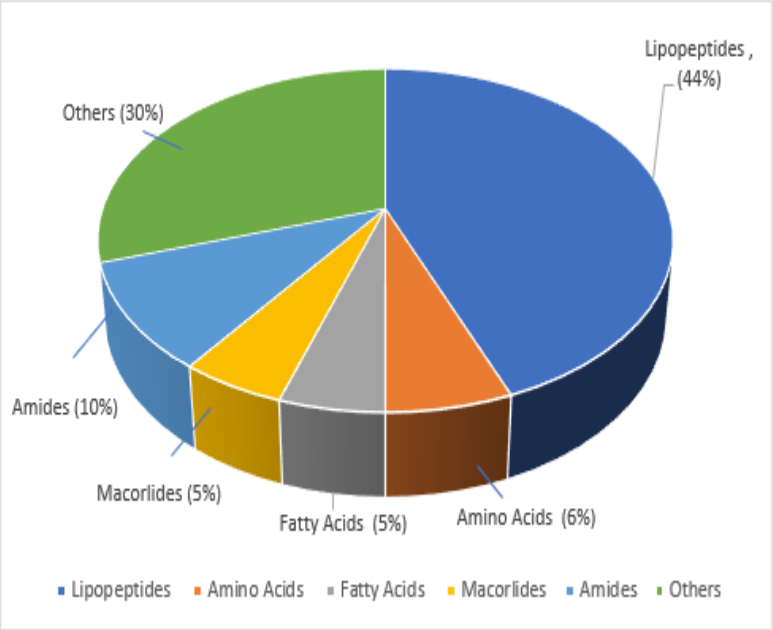


Figure 11 Pharmaceutically Important Compounds isolated from BGA

2.1.1 Antibacterial Potential of BGA

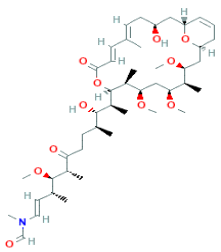
BGA are known for the secretions of antibacterial compounds with potential antibacterial activity against both Gram-positive and Gram-negative bacteria. Several strains such as *Anabaena*, *Lyngbya*, *Calothrix*, *Spirulina*, *Nostoc*, *Hapalosiphone*, *Phormidium*, and *Oscillatoria* have been identified by researchers from different habitats which can produce a wide variety of antibacterial molecules having therapeutic potentials (Chauhan et al., 2022). These organisms are even being altered genetically using biotechnological interventions for the production of various active compounds having antibacterial activity such as Bacteriocin Ambigol A, Parsiguine, Hapalindole, Hormothamnin A. *Bacillus subtilis*, *Staphylococcus aureus*, *Streptococcus sanguinis*, *Pseudomonas aeruginosa*, *Escherichia coli*, *L. monocytogenes*, *Salmonella typhimurium*, *Enterobacter aerogenes*, *Klebsiella pneumonia*, *Methicillin-resistant B. anthracis* are the examples of some gram-positive and Gram-negative bacteria which have studied for the inhibitory action of BGA (Luesch et al., 2001; Muller et al., 2006; Mo et al., 2009; Sturdy et al., 2010). The first partly identified antimicrobial compound isolated from algae were obtained from unicellular green algae particularly, *Chlorella* which contained a substance termed as '*chlorellin*' that exhibited inhibitory activity against both Gram-positive and Gram-negative bacteria, including *Staphylococcus aureus*, *Streptococcus pyogenes*, *Bacillus subtilis*, and *Pseudomonas aeruginosa* (Pratt et al., 1944). *Chlorellin* is composed of peroxides of unsaturated fatty acids (Spoehr & Milner, 1949). Kaushik & Chauhan (2008a) had reported the antibacterial activity of several species of cyanobacteria such as Anabaena, *Lyngbya*, *Calothrix*, *Spirulina*, *Nostoc*, *Hapalosiphone*, *Phormidium*, and *Oscillatoria*, etc. against both Gram-positive (*Staphylococcus aureus*, *Bacillus subtilis*, *Bacillus cereus*, etc.) and Gram-negative bacteria (*Escherichia coli*, *Pseudomonas aeruginosa*, *Salmonella typhi*, etc.). In a similar study, various species of *Anabaena* were evaluated for their antimicrobial activity and active antibacterial extracts were further screened for the presence of various chemical constituents through HPTLC techniques (Kaushik et al., 2009; Chauhan et al., 2010). Extracts of *Nostoc commune* and *Lyngbya majuscula* were studied for potent antimicrobial activity against clinically significant microorganisms (Kaushik & Chauhan, 2008a; Kaushik & Chauhan 2008b; Kaushik et al., 2009; Verma et al., 2016). HPTLC analysis were also performed to identify novel pharmaceutical compounds responsible for the activity. In a recent study, El-Sheekh et al. (2021) have evaluated the antibacterial activity of *Oscillatoria* sp. and *Spirulina* mediated silver and gold nanoparticles. Two new antibacterial molecules namely Arachidonoyl dopamine and fluocinolone recently discovered from methanolic extracts of *Arthrospira platensis*, a BGA isolated from a hypersaline lake in Rajasthan, India (Singh et al., 2021b). In another study, Antibacterial efficacy extracts of *Oxynema thaianum* have been assessed against multi-drug-resistant bacteria such as *E. coli* and *K. pneumoniae* (Padmini et al., 2021). Antibacterial compounds discovered from various species of BGA have been listed in Table 1 and Figure 12.

Table 1 Antibacterial compounds reported from BGA

BGA Sps.	Antibacterial Compounds	Detail of Chemical compounds	References
Scytonema pseudo hofmanni	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, 1982
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
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 et al., 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
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 & 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	Doan et al.,2000

BGA Sps.	Antibacterial Compounds	Detail of Chemical compounds	References
Nostoc commune	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., Jaki et al., 2000
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 & Carmeli, 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
Scytonema hofmanni 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 & Molinski, 2005; Matern et al., 2001
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 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 & Subramanian, 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
Fischerella ambigua	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 & Carmeli, 2007
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
Fischerella ambigua	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

BGA Sps.	Antibacterial Compounds	Detail of Chemical compounds	References
Fischerella ambigua	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
Leptolyngbya crosbyana	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)		Niveshika et al., 2016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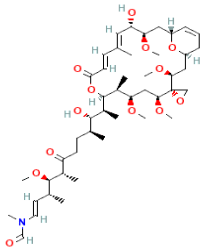
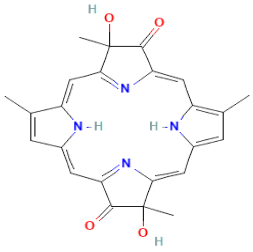

Tolytoxin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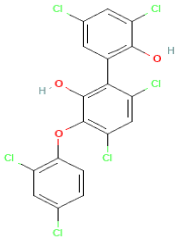
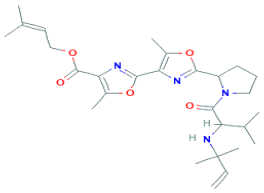
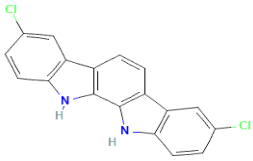
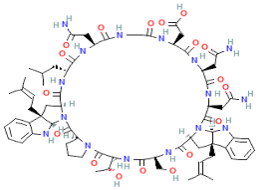
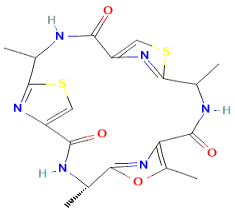

Ambigol A


Muscoride A


Tjipanazole D


Kawaguchipeptin A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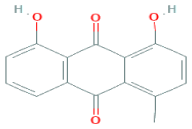
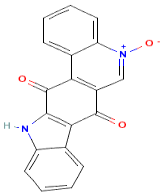
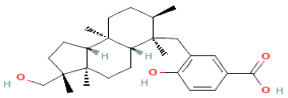
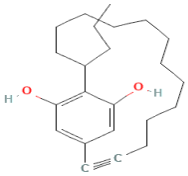
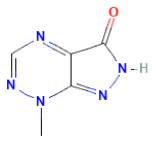
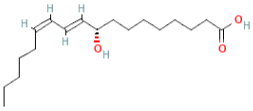

1,8-dihydroxy-4-methyl anthraquinone

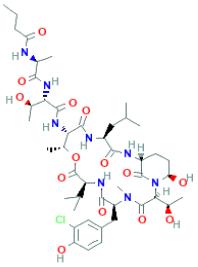

Calothrixin A

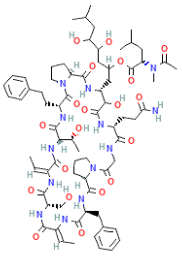

Comnastin A


Nostocyclyne A


Nostocine A


a-dimorphecolic acid


Scyptolin A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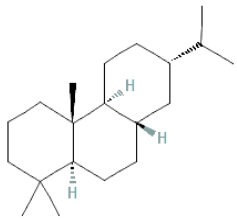
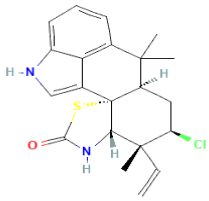
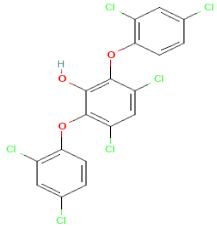


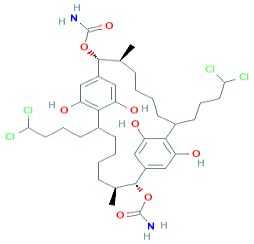
Abietane

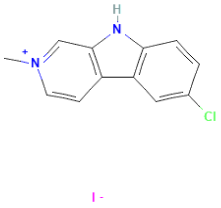


Hapalindole T

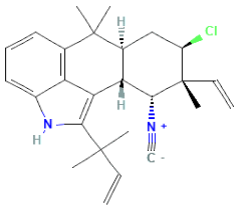


Ambigol B

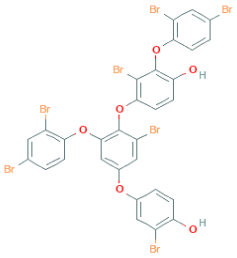




Nostocarboline Hydroiodide; Nostacarboline Iodide



Ambiguine A isonitrile



Crossbyanol A

9-Ethyliminomethyl-12-(morpholin-4- ylmethoxy) 5, 8, 13, 16-tetraaza-hexacene-2, 3 dicarboxy-licacid (EMTAHDCA)

Figure Not available

Figure 12 Chemical structures of the active ingredients isolated from various BGA and having antibacterial potential

2.1.2 Antimycobacterial potential of BGA

BGA extracts and compounds have been tested against various species of Mycobacteria. Rao et al. (2007) reported the antimycobacterial activity of different spp. of BGA *viz., Hapalosiphon sp*., *Anabaena sp. Lyngbya sp., Westeillopsis prolifica, Spirulina sp. Anabaena variabiles, Anabaena cylindrica, Oscillatoria sp.* and*Scytonema sp*. against *Mycobacterium tuberculosis ATCC 27294, M. tuberculosis MDR, M.avium, M. intracellulare,* and *M. aurum.* Other BGA species which exhibit antimycobacterial potential are *Tychonema* sp., *Fischerella ambigua* are *Lyngbyama juscule* (Muller et al., 2006; Mo et al., 2009; Sturdy et al., 2010; Luesch et al., 2001). Antimycobacterial compounds produced by these BGA strains are summarized in Table 2.

2.1.3 Antifungal potential of BGA

Antifungal properties of BGA strains have been documented globally. Fungal and yeast strains such as *Candida friedricki, Fusarium oxysporum, Aspergillus fumigatus, Alternaria alternate, A. niger, C. albicans, A. parasiticus, A. flavus, A. westerdijikia, A. ochraceus* ITAL 14, *A. carbonarius* ITAL 204, *A. steynii* IBT LKN 23096, *Penicillium verrucosum* BFE 500, *F. verticillioides* ITEM 10027, *F. proliferatum* MPVP 328 have been tested with BGA extracts and compounds (Marrez & Sultan, 2016; Vanlalveni et al., 2018; Saurav et al., 2019). Antifungal compounds reported from BGA strains have been listed in Table 3 and Figure 13**.**

2.1.4 Antioxidant potential of BGA

Blue-green algae produce large amounts of antioxidants to protect themselves from harmful stress conditions so that the cells can be protected from the effect of the reactive oxygen species (ROS) produced during stress. Hydrogen peroxide and oxygen free radicals are the two harmful reactive oxygen species formed in the cells during oxidative stress and can damage the cells (Vasudevan et al., 2020). Antioxidant properties of various extracts have been evaluated using different assay methods such as DPPH radical-scavenging Assay, $ABTS^{+}$ (2, 2-azino-bis (3-ethylbenzthiazoline-6-sulfonic acid); Nitric oxide radical scavenging Assay; Total Antioxidant capacity determination kit, and β-carotene bleaching assay (Table 5). BGA produces several antioxidants that can scavenge these free radicals. These antioxidants have been explored as a novel source of dietary supplements because the cyanobacteria are rich in phenolics, vitamins, and carotenoids, the most common being carotenoids, which can be used for alleviating oxidative stress and limiting health problems (Nainangu et al., 2020; Gabr et al., 2020). ROS are also formed in animals and humans during oxidative stress and cause damage to the biomolecules such as lipids, proteins, and DNA. Oxidative stress is associated with several diseases such as cancer, neurodegeneration, retinopathy, aging, and other diseases. Algae produce several substances that have antioxidant effects, and these substances can be used as dietary supplements by humans (Guerreiro et al., 2020; Safari et al., 2020; Li et al., 2020). Antioxidant compounds recently purified from Blue-Green Algae are summarized in Table 4.

Table 2 Antimycobacterial compounds reported from BGA

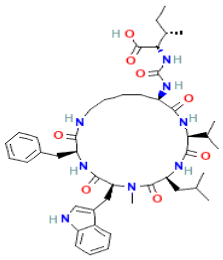
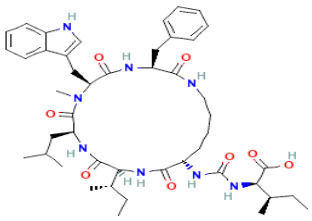
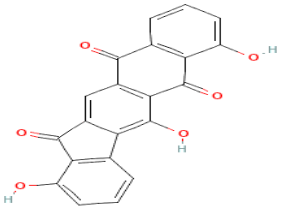
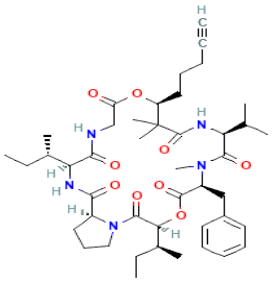
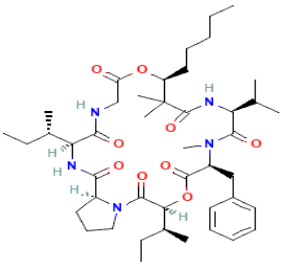
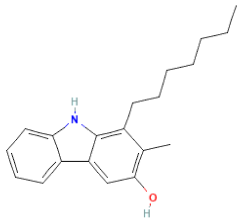
BGA Spp.	Antimycobacterial Compounds	Chemical Structure	References
Tychonema sp.	Brunsvicamide A MF: $C_{45}H_{64}N_8O_8$ MW: 845g/mol IUPAC Name: (2S)-2-[[(3S,6S,9S,12S,15S)-3-benzyl-6-(1H-indol-3-ylmethyl)-7-methyl-9-(2-methylpropyl)-2,5,8,11,14-pentaoxo-12-propan-2-yl-1,4,7,10,13-pentazacyclononadec-15-yl]carbamoylamino]-3-methylpentanoic acid		Muller et al., 2006
Tychonema sp.	Brunsvicamide B MF: $C_{46}H_{66}N_8O_8$ MW: 859.1g/mol IUPAC Name: (2S)-2-[[(3S,6S,9S,12S,15S)-3-benzyl-12-butan-2-yl-6-(1H-indol-3-ylmethyl)-7-methyl-9-(2-methylpropyl)-2,5,8,11,14-pentaoxo-1,4,7,10,13-pentazacyclononadec-15-yl]carbamoylamino]-3-methylpentanoic acid		Muller et al., 2006
Fischerella ambigua	Eucapsitrione MF: $C_{21}H_{10}O_6$ MW: 358.3g/mol IUPAC Name: 2,8,19-trihydroxypentacyclo[11.8.0.03,11.04,9.015,20]henicosa-1(13),2,4(9),5,7,11,15(20),16,18-nonaene-10,14,21-trione		Sturdy et al., 2010
Lyngbya majuscula	Pitipeptolide A MF: $C_{44}H_{65}N_5O_9$ MW: 808g/mol IUPAC Name: (3S,6S,9S,13S,19S,22S)-6-benzyl-3,19-bis[(2S)-butan-2-yl]-7,12,12-trimethyl-13-pent-4-ynyl-9-propan-2-yl-4,14-dioxa-1,7,10,17,20-pentazabicyclo[20.3.0]pentacosane-2,5,8,11,15,18,21-heptone		Luesch et al., 2001
Lyngbya majuscula	Pitipeptolides C MF: $C_{44}H_{69}N_5O_9$ MW: 812g/mol IUPAC Name: (3S,6S,9S,13S,19S,22S)-6-benzyl-3,19-bis[(2S)-butan-2-yl]-7,12,12-trimethyl-13-pentyl-9-propan-2-yl-4,14-dioxa-1,7,10,17,20-pentazabicyclo[20.3.0]pentacosane-2,5,8,11,15,18,21-heptone		Mo et al., 2009

Table 3 Antifungal compounds reported from BGA

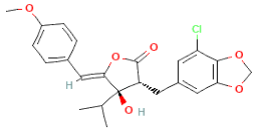
BGA Spp.	Antifungal Compounds	Detail of Chemical compounds	References
Hyella caespitosa	Carazostatin	MF: $C_{20}H_{25}NO$ MW: 295.4g/mol IUPAC Name: 1-heptyl-2-methyl-9H-carbazol-3-ol	Cardellina et al., 1979a
Scytonema hofmanni	Cyanobacterin	MF: $C_{23}H_{23}ClO_6$ MW: 430.9g/mol IUPAC Name: (5Z)-3-[(7-chloro-1,3-benzodioxol-5-yl)methyl]-4-hydroxy-5-[(4-methoxyphenyl)methylidene]-4-propan-2-yloxolan-2-one	Mason et al., 1982
Tolypothrix tenuis	Toyocamycin	MF: $C_{12}H_{13}N_5O_4$ MW: 291.26g/mol IUPAC Name: 4-amino-7-[(2R,3R,4S,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]pyrrolo[2,3-d]pyrimidine-5-carbonitrile	Moore, 1982
Tolypothrix tenuis	Tubercidin	MF: $C_{11}H_{14}N_4O_4$ MW: 266.25g/mol IUPAC Name: (2R,3R,4S,5R)-2-(4-aminopyrrolo[2,3-d]pyrimidin-7-yl)-5-(hydroxymethyl)oxolane-3,4-diol	Moore, 1982; Banker & Carmeli, 1998
Hapalosiphon fontinalis	Anhydrohaloxindole A; Anhydrohapaloxindole A	MF: $C_{21}H_{21}ClN_2O$ MW: 352.9g/mol IUPAC Name: (3R,4R,5R,7R)-5-chloro-4-ethenyl-3-isocyano-4,8,8-trimethyl-14-azatetracyclo[7.6.1.02,7.013,16]hexadeca-1,9(16),10,12-tetraen-15-one	Moore et al., 1987
Hapalosiphon fontinalis	Fontonamide	MF: $C_{20}H_{22}ClNO_2$ MW: 343.8g/mol IUPAC Name: N-[(6R,7R,10aR)-6-chloro-7-ethenyl-7,10,10-trimethyl-9-oxo-6,10a-dihydro-5H-anthracen-1-yl]formamide	Moore et al., 1987
Nostoc sp.	Nostocyclamide	MF: $C_{20}H_{22}N_6O_4S_2$ MW: 474.6g/mol IUPAC Name: (4S,18R)-4,7-dimethyl-18-propan-2-yl-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	Moore et al., 1988
Hormothamnion enteromorphoides	Hormothamnin A	MF: $C_{60}H_{97}N_{11}O_{14}$ MW: 1196.5g/mol IUPAC Name: (3Z)-28-benzyl-19,22-di(butan-2-yl)-3-ethylidene-36-hydroxy-6,31-bis(2-hydroxyethyl)-16,25-bis(2-methylpropyl)-10-pentyl-1,4,7,11,14,17,20,23,26,29,32-undecazabicyclo[32.3.0]heptatriacontane-2,5,8,12,15,18,21,24,27,30,33-undecone	Gerwick et al., 1989
Calothrix fusca	Calophycin	MF: $C_{19}H_{18}N_2O_3$ MW: 322.4g/mol IUPAC Name: (3R)-2-[(4-hydroxyphenyl)methyl]-1,3,4,9-tetrahydropyrido[3,4-b]indole-3-carboxylic acid	Moon et al., 1992
Dichothrix baueriana	Bauerine B	MF: $C_{12}H_8Cl_2N_2$ MW: 251.11g/mol IUPAC Name: 7,8-dichloro-9-methylpyrido[3,4-b]indole	Larsen et al., 1994
Nostoc sp. ATCC 53789)	Cryptophycin 1	MF: $C_{35}H_{43}ClN_2O_8$ MW: 655.2g/mol IUPAC Name: (3S,6R,10R,13E,16S)-10-[(3-chloro-4-methoxyphenyl)methyl]-6-methyl-3-(2-methylpropyl)-16-[(1S)-1-[(2R,3R)-3-phenyloxiran-2-yl]ethyl]-1,4-dioxa-8,11-diazacyclohexadec-13-ene-2,5,9,12-tetrone	Trimurtulu et al., 1994
Hapalosiphon welwitschii, *Westiella intricate*	Welwitindolinone A isonitrile	MF: $C_{21}H_{21}ClN_2O$ MW: 352.9g/mol IUPAC Name: (3S,3'S,4'R,6'R)-4'-chloro-3'-ethenyl-2'-isocyano-3',7',7'-trimethylspiro[1H-indole-3,8'-bicyclo[4.2.0]oct-1-ene]-2-one	Stratmann et al., 1994

BGA Spp.	Antifungal Compounds	Detail of Chemical compounds	References
Nostoc commune	Nostofungicidine	MF: $C_{48}H_{76}N_{10}O_{18}$ MW: 1081.2g/mol IUPAC Name: 2-[16-(2-amino-1-hydroxy-2-oxoethyl)-27-hydroxy-19-[hydroxy-(4-hydroxyphenyl)methyl]-3,22-bis(hydroxymethyl)-10-(3-hydroxypentadecyl)-2,5,8,12,15,18,21,24-octaoxo-1,4,7,11,14,17,20,23-octazabicyclo[23.3.0]octacosan-13-yl]-2-hydroxyacetamide	Kajiyama et al., 1998
Fischerella muscicola	Fischerellin B	MF: $C_{20}H_{29}NO$ MW: 299.4g/mol IUPAC Name: (3R,5S)-3-methyl-5-[(E)-pentadec-5-en-7,9-diynyl]pyrrolidin-2-one	Srivastava et al., 1999
Lyngbya majuscula	Tanikolide	MF: $C_{17}H_{32}O_3$ MW: 284.4g/mol IUPAC Name: (6R)-6-(hydroxymethyl)-6-undecyloxan-2-one	Singh et al., 1999
Scytonema pseudo hofmanni	Scytophycin A	MF: $C_{45}H_{75}NO_{12}$ MW: 822.1g/mol IUPAC Name: N-[(E,3R,4R,5S,9S,10S,11S)-6,10-dihydroxy-11-[(1S,3S,4S,5S,7R,8S,9R,12E,14E,17S,19R)-17-hydroxy-3,5,7-trimethoxy-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-trimethyldodec-1-enyl]-N-methylformamide	Matern et al., 2001
Tolypothrix byssodea	Tolybyssidin A	MF: $C_{71}H_{116}N_{16}O_{17}$ MW: 1465.8g/mol IUPAC Name: [(1R)-1-[(3S,6S,9S,12S,15S,18Z,21S,24S,27S,30S,33R,36S,39S)-21-benzyl-24,27-bis[(2S)-butan-2-yl]-36-[3-(diaminomethylideneamino)propyl]-18-ethylidene-9,30-bis[(1R)-1-hydroxyethyl]-33-(2-methylpropyl)-2,5,8,11,14,17,20,23,26,29,32,35,38-tridecaoxo-3,6,15-tri(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31,34,37-tridecazabicyclo[37.3.0]dotetracontan-12-yl]ethyl] acetate	Jaki et al., 2001
Tolypothrix byssodea	Tolybyssidin B	MF: $C_{72}H_{114}N_{16}O_{16}S$ MW: 1491.8g/mol IUPAC Name: 2-[3-[(2S,5S,8S,11S,14S,17S,20S,23S,26S,29S,32S,35S,38E)-32-benzyl-17-[(2S)-butan-2-yl]-38-ethylidene-14,20-bis[(1R)-1-hydroxyethyl]-5-[(4-hydroxyphenyl)methyl]-8-(2-methylsulfanylethyl)-3,6,9,12,15,18,21,24,27,30,33,36,39-tridecaoxo-11,23,26,29,35-penta(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31,34,37-tridecazacyclononatriacont-2-yl]propyl]guanidine	Jaki et al., 2001
Lyngbya confervoides	Lobocyclamine B	MF: $C_{65}H_{115}N_{13}O_{20}$ MW: 1398.7g/mol IUPAC Name: 3-[(3S,6R,9S,12R,15R,18S,21R,24S,28R,31S,34R,37S,39R)-9-[(2S)-butan-2-yl]-6-[(1R)-1,2-dihydroxyethyl]-28-heptyl-39-hydroxy-3,31-bis[(1R)-1-hydroxyethyl]-15,21-bis[(1S)-1-hydroxy-2-methylpropyl]-10,18-dimethyl-34-(2-methylpropyl)-2,5,8,11,14,17,20,23,26,30,33,36-dodecaoxo-24-propan-2-yl-1,4,7,10,13,16,19,22,25,29,32,35-dodecazabicyclo[35.3.0]tetracontan-12-yl]propanamide	MacMillan et al., 2002
Nostoc commune	Nostodione A	MF: $C_{18}H_{11}NO_3$ MW: 289.3g/mol IUPAC Name: (3E)-3-[(4-hydroxyphenyl)methylidene]-4H-cyclopenta[b]indole-1,2-dione	Bhadury & Wright, 2004
Hassallia sp.	Hassallidin A	MF: $C_{62}H_{99}N_{11}O_{24}$ MW: 1382.5g/mol IUPAC Name: N-[(2S,3R)-1-[[(3S,6S,12S,15Z,18S,21S,24S,25R)-3,12-bis(3-amino-3-oxopropyl)-15-ethylidene-21-[(1R)-1-hydroxyethyl]-18-[(4-hydroxyphenyl)methyl]-7,25-dimethyl-2,5,8,11,14,17,20,23-octaoxo-6-[(1R)-1-[(2R,3S,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxyethyl]-1-oxa-4,7,10,13,16,19,22-heptazacyclopentacos-24-yl]amino]-3-hydroxy-1-oxobutan-2-yl]-2,3-dihydroxytetradecanamide	Neuhof et al., 2005

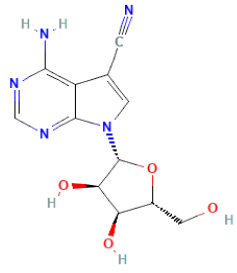
BGA Spp.	Antifungal Compounds	Detail of Chemical compounds	References
Fischerella ambigua	2,4-dichlorobenzoic acid	MF: $C_7H_4Cl_2O_2$ MW: 191.01g/mol IUPAC Name: 2,4-dichlorobenzoic acid	Wright et al., 2005
Geitlerinema sp.	Swinholide A	MF: $C_{78}H_{132}O_{20}$ MW: 1389.9g/mol IUPAC Name: (1R,3S,5E,7E,11S,12S,13R,15S,16S,17S,19S,23R,25R,27Z,29E,33S,34S,35R,37S,38S,39S,41S)-3,13,15,25,35,37-hexahydroxy-11-[(2S,3S,4R)-3-hydroxy-6-[(2S,4R,6S)-4-methoxy-6-methyloxan-2-yl]-4-methylhexan-2-yl]-33-[(2S,3S,4S)-3-hydroxy-6-[(2S,4R,6S)-4-methoxy-6-methyloxan-2-yl]-4-methylhexan-2-yl]-17,39-dimethoxy-6,12,16,28,34,38-hexamethyl-10,32,45,46-tetraoxatricyclo[39.3.1.119,23]hexatetraconta-5,7,21,27,29,43-hexaene-9,31-dione	Andrianasolo et al., 2005
Fischerella ambigua	Tjipanazole B	MF: $C_{23}H_{18}Cl_2N_2O_4$ MW: 457.3g/mol IUPAC Name: (2R,3R,4S,5R)-2-(3,8-dichloro-11H-indolo[2,3-a]carbazol-12-yl)oxane-3,4,5-triol	Wright et al., 2005
Nadularia harveyana	Norharmane	MF: $C_{11}H_8N_2$ MW: 168.19g/mol IUPAC Name: 9H-pyrido[3,4-b]indole	Volk & Furkert, 2006
Synechocystis sp.	AK-3	MF: $C_9H_{16}N_4OS$ MW: 228.32g/mol IUPAC Name: 2-(dimethylamino)-N-(5-propyl-1,3,4-thiadiazol-2-yl)acetamide	Yoon et al., 2006
Lyngbya majuscula	Hectochlorin	MF: $C_{27}H_{34}Cl_2N_2O_9S_2$ MW: 665.6g/mol IUPAC Name: [(5S,12S,13S,16S)-12-(4,4-dichloropentyl)-16-(2-hydroxypropan-2-yl)-4,4,13-trimethyl-2,10,14-trioxo-3,11,15-trioxa-7,18-dithia-20,21-diazatricyclo[15.2.1.16,9]henicosa-1(19),6(21),8,17(20)-tetraen-5-yl] acetate	Gademann & Portmann, 2008
Calothrix elenkinii	Benzoic Acid	MF: $C_7H_6O_2$ MW: 122.12g/mol IUPAC Name: benzoic acid	Natarajan et al., 2012



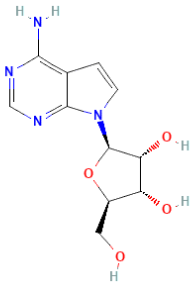
Carazostatin



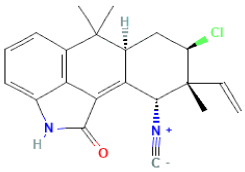
Cyanobacterin



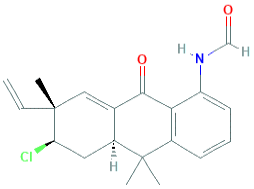
Toyocamycin



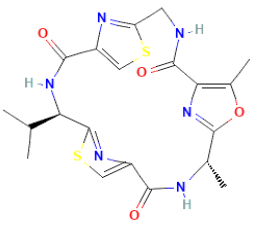
Tubercidin



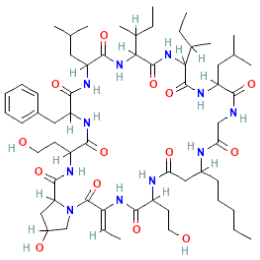
Anhydrohaloxindole A; Anhydrohapaloxindole A



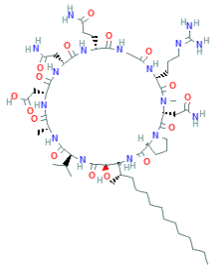
Fontonamide



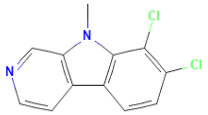
Nostocyclamide



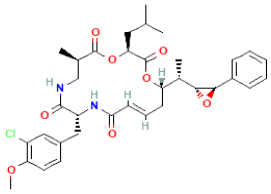
Hormothamnin A



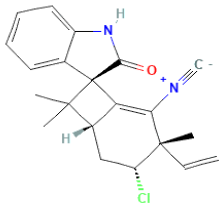
Calophycin



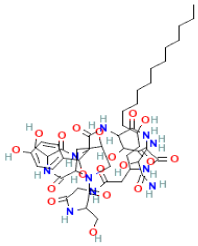
Bauerine B



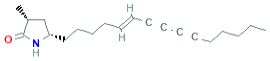
Cryptophycin 1



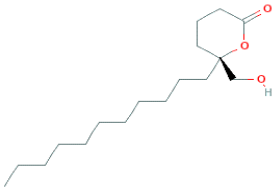
Welwitindolinone A isonitrile



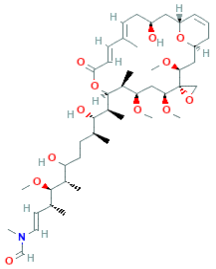
Nostofungicidine



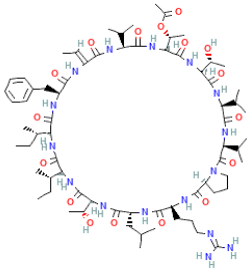
Fischerellin B



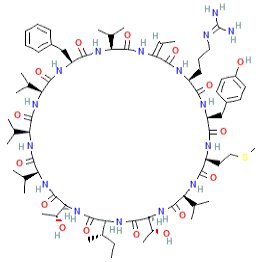
Tanikolide



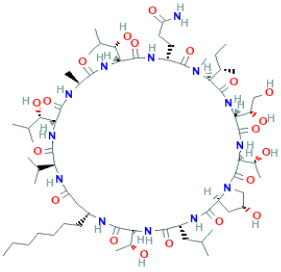
Scytophycin A



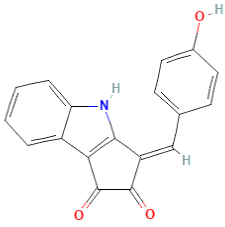
Tolybyssidin A



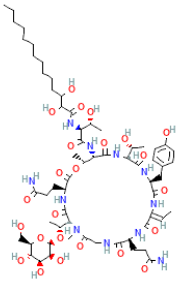
Tolybyssidin B



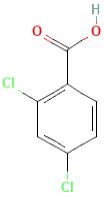
Lobocyclamine B



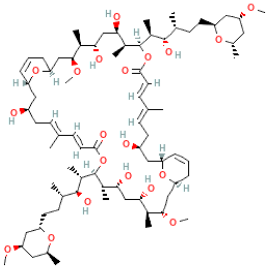
Nostodione A



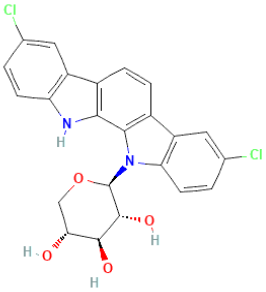
Hassallidin A



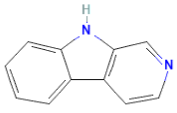
2,4-dichlorobenzoic acid



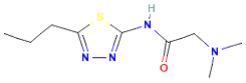
Swinholide A



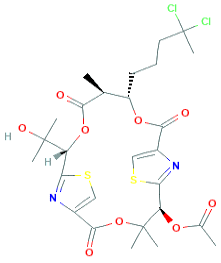
Tjipanazole B



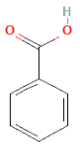
Norharmane



AK-3



Hectochlorin



Benzoic Acid

Figure 13 Chemical structures of the active ingredients isolated from various BGA and having antifungal propeties

Table 4 Antioxidants compounds recently purified from Blue-Green Algae

Antioxidants compounds	Source	References
Pyrogallol, E-Vanillic, Hespirdin	*Spirulina platensis*	Gabr et al., 2020
Benzeneacetanomide and Norvaline, n-propargyloxycarbonyl	*Microcystis aeruginosa*	Vasudevan et al., 2020
BHA, Beta tocopherol, Phytosterols	*Spirulina maxima*	Gamal et al., 2020
Caffeic acid, syringic acid, ferulic acid, p-coumaric acid, chlorogenic acid, kaempferol, quercetin and apigenin γ-linolenic acid, α-linolenic acid	*Spirulina platensis*	Bellahcen et al., 2020
Benzoic acid, 4-(1-azepinyl)azo-, ethyl ester (b) 1,6-methanonaphthalen-1(2H)-ol, octahydro-4,8a,9,9-tetramethyl, (c) Dibutyl phthalate, (d) 1,2-benzene dicarboxylic acid, (e) Hexadecanoic acid, 2-pentadecyl-1,3-dioxan-5-yl ester	*Oscillatoria sp.* SSCM01	Nainangu et al., 2020

Table 5 Types of BGA Extracts, Assay methods and their antioxidant potential

Blue-Green Algae	Type of Extract	Assay methods	Maximum Activity	References
Spirulina platensis	Ethanolic and aqueous extract	DPPH radical-scavenging Assay	96.33%	Gabr et al., 2020
Microcystis aeruginosa	Methanol Extract	Scavenging ability on 1, 1-diphenyl-2-picrylhydrazyl radicals (DPPH) Hydroxyl radical scavenging assay	54% 49%	Vasudevan et al., 2020
Spirulina maxima	-	DPPH radical-scavenging Assay	25.73 %	Gamal et al., 2020
Spirulina platensis	Ethanolic, aqueous, and lipidic extracts	Diphenyl-1-picrylhydrazyl (DPPH) Azino-bis (ethylbenzthiazoline-6-sulfonicacid (ABTS)	(IC50=449 µg/mL ± 83) (IC50=740 µg/mL ± 12)	Bellahcen et al., 2020
Oscillatoria sp. SSCM01	MeOH: CHCl3 fraction	DPPH radical scavenging assay	48%	Nainangu et al., 2020
Spirulina platensis	crude extracts	DPPH radical-scavenging activity	45.75%	Safari et al., 2020
Oscillatoria acuminate	Methanolic extract	DPPH (2, 2- diphenyl-1-picrylhydrazyl) $ABTS^{+}$ (2, 2-azino-bis (3-ethylbenzthiazoline-6-sulfonic acid)	6.58 % 34.60 %	Gheda & Ismail (2020).
Dolichospermum flos-aquae HSSASE2		DPPH radical scavenging assay Nitric oxide radical scavenging assay Anti-lipid peroxidation assay	(467.7 µg/ml) (IC50 = 28.7 ± 0.1 µg/ml) (IC50 11.9 ± 0.2 µg/ml)	Senousy et al., 2020
Anabaena sp., *Stigonaema* sp. and *Oscillatoria* sp.	Methanol Extract	Total Antioxidant capacity determination kit	0.346 (mM/L); 0.36 (mM/L) and 0.37 (mM/L)	Seddek et al., 2019
Aphanizomenon gracile (LMECYA 009), *Aphanizomenon flos-aquae* (LMECYA 088), *Nostoc* (LMECYA 291), *Plankto thrixmougeotii* (LEGE 06224)	Methanolic and ethanolic	DPPH scavenging method, β-carotene bleaching assay	10.7% 828.94 AAC	Guerreiro et al., 2019

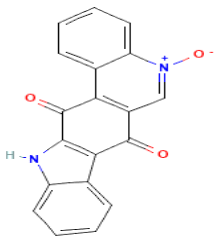
2.1.5 Anti-cancer potential of BGA

BGA extracts and compounds are known to exhibit anticancer properties (Shishido et al., 2020; Gara-Ali et al., 2021). Research by Jaspers & Lawton (1998) has focused on various biologically active compounds from BGA. The *curian A*, a novel lipid compound isolated from *Lyngbya majuscula*, is a potent inhibitor of microtubule assembly with very low IC_{50} values against L1210 leukemia cells and CD-46 Burkitt lymphoa cells, at par with those for colchicines. Cryptophycin 1 and 8, another anticancer compound was first isolated from *Nostoc sp*. by researchers at Merck. The oral supplement of *Spirulina fusiformis* is known for regression of subjects with homogenous leukolakia (Mathew et al., 1995). The extracts of *Spirulina* and *Dunaliella* inhibited the chemically induced carcinogenesis in model hamster buccal pouches (Schwartz et al., 1988). Studies have also shown that sulphated polysachharide, calcium spirulans appears to inhibit tumor invasion of melanoma cells and basement membrane (Mishima et al., 1998). *Aphanizomenon flosaquae* extract containing a high concentration of phycocyanin inhibited the *in vitro* growth of tumour cells, indicating the sensitivity of cell lines to the phycocyanin. A filamentous cyanobacterium *Phormidium tenue* contains several diacylglycerols that inhibit chemically induce tumors on mice (Tokuda et al., 1996). Similarly, cryprophycin 1 isolated from *Nostoc* sp. (ATCC 53789) is the most potent suppressor of microtubule dynamics *i.e*. it blocks all cell cycles in G2/M phase. Curacin A is isolated from *Lyngbya majuscule*. This compound is found to be a potent inhibitor of microtubule assembly. There is a need for immediate attention for more novel anticancer drugs so that carcinogenic cells are capable of resisting some drugs, like vinca alkaloids and taxanes. These drugs failed to treat cancer in a chemotherapeutic way. Cancer is known to be the major cause of mortality worldwide. Recently some new types of cancer e.g. gliobastoma are increased rapidly. Anticancer compounds reported from BGA are summarized in Table 6 Figure 14.

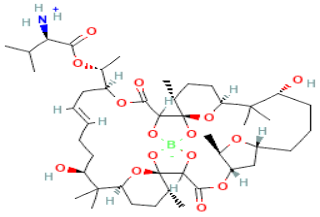
Table 6 Anticancer compounds reported from BGA

BGA Spp.	Anticancer Compounds	Chemical Structure	References
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	Cardellina et al., 1979b
Nostoc sp.	Boromycin	MF: $C_{45}H_{74}BNO_{15}$ MW: 879.9g/mol IUPAC Name: [(2R)-1-[(1R)-1-[(1R,5S,7E,11S,13S,16R,17R,24S,25R,27R,31R,33S,36R)-11,31-dihydroxy-12,12,16,25,32,32,36-heptamethyl-3,22-dioxo-4,18,20,23,26,37,38,40,41-nonaoxa-19-boranuidaheptacyclo[17.17.1.11,33.12,19.113,17.124,27.017,21]hentetracont-7-en-5-yl]ethoxy]-3-methyl-1-oxobutan-2-yl]azanium	Banker & Carmeli, 1998; Gupta, 2012
Scytonema varium	Scytovirin	MF: $C_{66}H_{91}N_{19}O_{24}S$ MW: 1566.6g/mol IUPAC Name: (4S)-4-[[(2S)-4-amino-2-[[(2S)-2-[[(2R)-2-[[(2S)-2-[[(2S,3R)-2-[[(2S)-1-[2-[[(2S)-2-[(2-aminoacetyl)amino]-3-hydroxypropanoyl]amino]acetyl]pyrrolidine-2-carbonyl]amino]-3-hydroxybutanoyl]amino]-3-(4-hydroxyphenyl)propanoyl]amino]-3-sulfanylpropanoyl]amino]-3-(1H-indol-3-yl)propanoyl]amino]-4-oxobutanoyl]amino]-5-[[(2S)-1-[[(2S)-4-amino-1-[[(2S)-4-amino-1-[(2S)-2-(carboxymethylcarbamoyl)pyrrolidin-1-yl]-1,4-dioxobutan-2-yl]amino]-1,4-dioxobutan-2-yl]amino]-1-oxopropan-2-yl]amino]-5-oxopentanoic acid	Shi et al., 1999
Symploca genus	Largazole	MF: $C_{29}H_{42}N_4O_5S_3$ MW: 622.9g/mol IUPAC Name: S-[(E)-4-[(5R,8S,11S)-5-methyl-6,9,13-trioxo-8-propan-2-yl-10-oxa-3,17-dithia-7,14,19,20-tetrazatricyclo[14.2.1.12,5]icosa-1(18),2(20),16(19)-trien-11-yl]but-3-enyl] octanethioate	Luesch et al., 2001
Nostoc sp.	Apratoxin A	MF: $C_{45}H_{69}N_5O_8S$ MW: 840.1g/mol IUPAC Name: (2S,3S,5S,7S,10S,16S,19S,22S,25E,27S)-16-[(2S)-butan-2-yl]-7-tert-butyl-3-hydroxy-22-[(4-methoxyphenyl)methyl]-2,5,17,19,20,25-hexamethyl-8-oxa-29-thia-14,17,20,23,30-pentazatricyclo[25.2.1.010,14]triaconta-1(30),25-diene-9,15,18,21,24-pentone	Grinberg et al., 2002

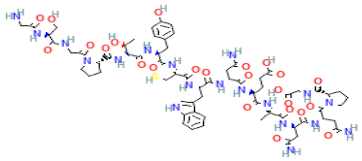
BGA Spp.	Anticancer Compounds	Chemical Structure	References
Dolabella auricularia	Dolastatin 15	MF: $C_{45}H_{68}N_6O_9$ MW: 837.1g/mol IUPAC Name: [(2S)-1-[(2S)-2-benzyl-3-methoxy-5-oxo-2H-pyrrol-1-yl]-3-methyl-1-oxobutan-2-yl] (2S)-1-[(2S)-1-[(2S)-2-[[(2S)-2-[[(2S)-2-(dimethylamino)-3-methylbutanoyl]amino]-3-methylbutanoyl]-methylamino]-3-methylbutanoyl]pyrrolidine-2-carbonyl]pyrrolidine-2-carboxylate	Stevenson et al., 2002
Cyanobacteria	Astaxanthin	-	Chen et al., 2003
Nostoc sp.	Cryptophycin	MF: $C_{35}H_{43}ClN_2O_8$ MW: 655.2g/mol IUPAC Name: (3S,6R,10R,13E,16S)-10-[(3-chloro-4-methoxyphenyl)methyl]-6-methyl-3-(2-methylpropyl)-16-[(1S)-1-[(2R,3R)-3-phenyloxiran-2-yl]ethyl]-1,4-dioxa-8,11-diazacyclohexadec-13-ene-2,5,9,12-tetrone	Back & Liang 2005; Medina et al., 2008
L. majusculata	Curacin A	MF: $C_{23}H_{35}NOS$ MW: 373.6g/mol IUPAC Name: (4R)-4-[(1Z,5E,7E,11R)-11-methoxy-8-methyltetradeca-1,5,7,13-tetraenyl]-2-[(1R,2S)-2-methylcyclopropyl]-4,5-dihydro-1,3-thiazole Isomeric SMILES: C[C@H]1C[C@H]1C2=N[C@@H](CS2)/C=C\CC/C=C/C=C(\C)/CC[C@H](CC=C)OC	Xiong et al., 2006
Lyngbya sp.	Dragonamide C	MF: $C_{33}H_{57}N_5O_6$ MW: 619.8g/mol IUPAC Name: (E)-N-[(2S)-1-[[(2S)-1-[[(2S)-1-[[(2S)-1-amino-3-methyl-1-oxobutan-2-yl]-methylamino]-3-methyl-1-oxobutan-2-yl]-methylamino]-3-methyl-1-oxobutan-2-yl]-methylamino]-3-methyl-1-oxobutan-2-yl]-3-methoxy-N-methyloct-2-en-7-ynamide	Gunasekera et al., 2008
Lyngbya sp.	Dragonamide D	MF: $C_{32}H_{55}N_5O_6$ MW: 605.8g/mol IUPAC Name: N-[(2S)-1-[[(2S)-1-[[(2S)-1-[[(2S)-1-amino-3-methyl-1-oxobutan-2-yl]-methylamino]-3-methyl-1-oxobutan-2-yl]-methylamino]-3-methyl-1-oxobutan-2-yl]-methylamino]-3-methyl-1-oxobutan-2-yl]-N-methyl-3-oxooct-7-ynamide	Gunasekera et al., 2008



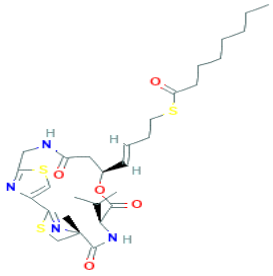
Calothrixin A



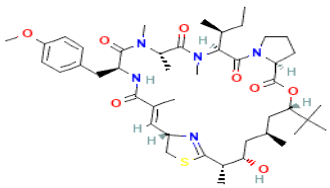
Boromycin



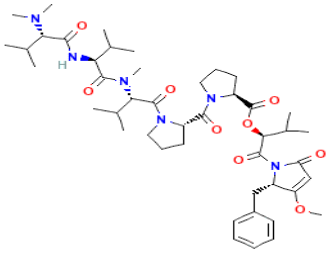
Scytovirin



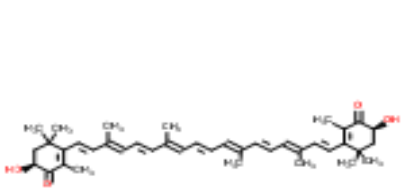
Largazole



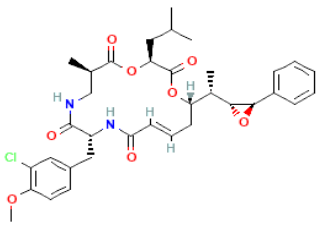
Apratoxin A



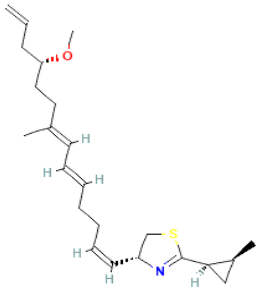
Dolastatin 15



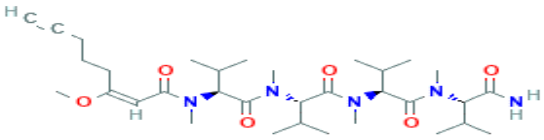
Astaxanthin



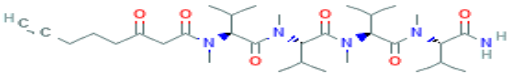
Cryptophycin



Curacin A



Dragonamide C



Dragonamide D

Figure 14 Chemical structures of the active ingredients isolated from various BGA and having anticancerous properties

2.1.6 Antiviral Potential including SARS-CoV-2

The globe is so much affected by the dreadful diseases caused by infection of viruses such as HIV-acquired immune deficiency syndrome. There is also another viral deadly disease that is dengue which may have many consequences. Despite two former major outbreaks of coronavirus infections i.e. the SARS and MERS, the world is still underprepared to effectively manage the current COVID-19 pandemic outbreak. The researchers were in search of a novel and potent drug which will be able to resist those deadly and dreadful viral infections throughout the world. Scientists have now invented novel, potent, and safe anti-viral agents that are very useful in this urgent situation. Recently there is a new scientific treatment or therapy which is named highly active antiretroviral therapy in short HAART. This is triple therapy which is very fruitful and capable in the treatment of HIV infections which is very helpful and makes control and resistance power in carcinogenic treatment. This therapy can create strong viral resistance. But this therapy cannot stop the viral agent which is causing such kinds of issues. BGA species are also known to produce substances that have been proved to be anti-HIV, therefore can be exploited in therapy against AIDS (Schaeffer & Krylov, 2000; Carpine & Sieber, 2021)

Gustafson et al. (1989) used a tetrazolum-based micro-culture to screen extracts of cultured marine cyanobacteria, *Lyngbyalager heimii*, and *Phormedium tenue*, for the inhibition of HIV-1. This led to the discovery of sulfonic acid containing glycolipids as a new class of HIV-1- inhibitory compounds. Other cyanobacteria, *Phormedium cebennse*, *Oscillatoria raciborskii*, *Scytonem aburmanicum*, *Calothrix elenkinii*, and *Anabaena variabilis*, gave extracts that inhibited HIV-1 and gave positive tests for the presence of sulfolipids.

Compounds and extracts with anti-HIV activity are also active against other retroviruses such as Herpes simplex virus (HSV) and respiratory syncytial virus, but the amount of antiviral activity varies with the compound and the virus. Most of the research has focused on sulphated homopolysaccharides and heteropolysaccharides, sulfoglycolipids, carrageenans, fucoidan, sesquiterpene hydroquinones, and other classes of compounds with an anti-HIV activity that has been isolated from algae have received less attention. Hayashi et al. (1996) isolated calcium spirulan, a sulfated polysaccharide obtained from a marine blue-green alga, *Spirulina platensis* which inhibited the Herpes simplex virus. Subsequently, Ayehunie et al. (1998) determined that an aqueous extract of *S. platensis*, at a concentration that was non-toxic to human cells, inhibited syncytium formation and HIV-1

replication in human T-cell lines, peripheral blood mononuclear cells, and Langerhans cells. The antiviral effects of polysaccharides from marine algae towards mumps virus and influenza B virus were reported by Gerber et al. (1958). Subsequently, polysaccharides fractions from extracts of red algae were found to inhibit the herpes simplex virus (HSV). Similarly, Boyd et al. (1997) isolated Cyanovirin-N from an aqueous cellular extract of cyanobacterium *Nostoc ellipsosporum* which has been proved to be antiviral. Lau et al., (1993) reported that the lipophilic and hydrophilic extracts of over 900 strains of cultured blue-green algae *in vitro* for their ability to inhibit the reverse transcriptases of avian myeloblastosis virus (Table 7)

Various compounds have been isolated from a variety of blue-green algaeBGA-derived polysaccharides that have been reported for the inhibition of SARS-CoV-2 (Sami et al., 2021). Few organizations are actively involved in developing algae-based edible vaccines for SARS-CoV-2 (Jafari et al., 2021) (Table 8)

2.1.7 Antidiabetic Potential of BGA

Blue-green algae are known to exhibit potential antidiabetic properties. In a study conducted by Priatni et al. (2016) methanol extract of marine cyanobacterial strains such as *Oscillatoria limnetica*, *Coelastrella* sp., *Oscillatoria* sp., *Chroococcus* sp., *Leptolyngbya* sp., *Pseudanabaena* sp., *Lyngbya* sp., *Aphanothece* sp., *Phormidium*sp, and *Synechococcus* sp. have potential antidiabetic potential. The metabolites of *Pseudanabaena* sp. showed the highest α-glucosidase inhibition. In another study, Egyptian Scientists evaluated extracts of *Fischerella* sp. BS1-EG for antidiabetic

Table 7 Antiviral Compounds reported from BGA

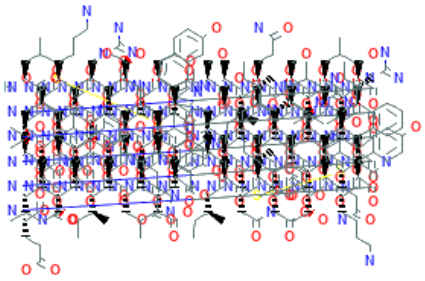
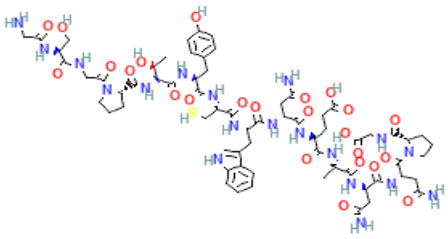
BGA Sp.	Anti Viral Compound	Chemical Structure	References
Nostoc ellipsosporum	Cyanovirin-N		Boyd et al., 1997;; Bewley, 2001
Microcystis aeruginosa	Microvirin		Kehr et al., 2006
Scytonema varium	Scytovirin MF: $C_{66}H_{91}N_{19}O_{24}S$ MW: 1566.6g/mol IUPAC Name: (4S)-4-[[(2S)-4-amino-2-[[(2S)-2-[[(2R)-2-[[(2S)-2-[[(2S,3R)-2-[[(2S)-1-[2-[[(2S)-2-[(2-aminoacetyl)amino]-3-hydroxypropanoyl]amino]acetyl]pyrrolidine-2-carbonyl]amino]-3-hydroxybutanoyl]amino]-3-(4-hydroxyphenyl)propanoyl]amino]-3-sulfanylpropanoyl]amino]-3-(1H-indol-3-yl)propanoyl]amino]-4-oxobutanoyl]amino]-5-[[(2S)-1-[[(2S)-4-amino-1-[[(2S)-4-amino-1-[(2S)-2-(carboxymethylcarbamoyl)pyrrolidin-1-yl]-1,4-dioxobutan-2-yl]amino]-1,4-dioxobutan-2-yl]amino]-1-oxopropan-2-yl]amino]-5-oxopentanoic acid		Bokesch et al., 2003
M. viridis NIES-02	Microcystis Viridis Lectin	NA	Yamaguchi et al., 1999
Arthrospira platensis	Calcium Spirulan	NA	Hayashi et al., 1996

Table 8 Anti-HIV activity of compounds from BGA

BGA strains	Compounds	References
Anabaena variabilis, Calothrix elenkinii, Lyngbya lagerheimii, Phormidium tenue, Phormedium cebennse, Oscillatoria raciborskii, Scytonema burmanicum	Extracts containing sulfolipids (sulfoquinovosyl diacylglycerols)	Gustafson et al., 1989
Spirulina platensis	activity in polysaccharide fraction	Ayehunie et al., 1998
Spirulina platensis (Marine)	Calcium spirulan, Ca-SP (sulfated polysaccharide fraction) Dextran sulfate	Hayashi et al., 1996
Nostoc ellipsosporum	Cyanovirin- N (11-k Da antiviral protein	Gustafson et al., 1996
Nostoc ellipsosporum	Cyanovirin- N (11-k Da antiviral protein	Boyd et al., 1996
900 strains	Lipophilic and Hydrophilic extracts	Lau et al., 1993
Scytonema spp.	Sulfoglycolipids	Reshef et al., 1997
Oscillatoria spp.	Acylated diglycolipids	Reshef et al., 1997
Oscillatoria raoi(TAU IL-76-12), *Syctonema spp.* (TAU SL-30-1-4), *Oscillatoria trichoides*(TAU IL 104-3-2), *Phormidium tenue* (TAU IL-144-1), *Oscillatoria limnetica, Lammermann* (TAU NG-4-1-2)	Sulfolipids, Sulfoglycolipids, hydrolysis products, synthetic derivative	Loya et al., 1998

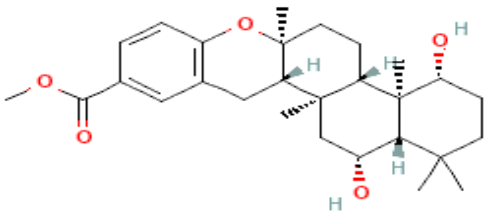


Figure 15 Chemical structure of Anti-inflammatory compounds Tolypodiol isolated from *Tolypothrix nodosa*

potential and have reported certain bioactive compounds responsible for the activity (Ahmed et al., 2018). In a recent study, Sridhar et al. (2021) have evaluated phycocyanin of *S. platensis* for its antidiabetic potential by assessing α-amylase and β-glucosidase enzyme inhibition using spectroscopy techniques. In this *in vitro* test, significant Antidiabetic activity (88%) was observed at a concentration of 250 µg/ml. In some studies, lesser antidiabetic properties have been reported, like Ghosh et al. (2016) evaluated in vitro antidiabetic properties of molecules from *Lyngbya*, *Microcoleus*, and *Synechocystis* sp. by α-amylase inhibition method and stated the lesser enzyme inhibition effect. Similarly, Xu et al. (2012) described the lowest α-amylase enzyme inhibition activity of *Phlorotannins* pigments extracted from Eckloniakurome. However, Hwang et al. (2014) reported 65 - 80% inhibitory activity at the concentration of 250 µg/ml while this was reported 51 - 67% at the dose of 200 µg/ml dose of *S. platensis* phycocyanin. Lesser enzyme inhibition even in higher concentrations was reported in a study conducted by Priatni et al. (2016).

2.1.8 Anti-inflammatory Activity of BGA

Blue-Green Algae contain a significant amount of carotenoids *i.e.* β-carotene, lycopene, lutein having antioxidant properties. By the quenching action on the reactive oxygen species, these carotenoids also have anti-inflammatory activity. This anti-inflammatory activity might be due to the presence of phycocyanin, a photo harvesting pigment. Further, the anti-inflammatory effect seemed to be the result of leucotriene formation inhibition by phycocyanin, an inflammatory metabolite of arachidonic acid (Romay et al., 1999). *Apbanizomenon flosaquae* decrease the level of arachidonic acid. Further, *A. flosaquae* and *Spirulina* contain significant amount of omega-3-alpha linolenic acid which inhibits the formation of inflammatory prostaglandins and arachidonate metabolites (Figure 15).

3 Conclusion and Future possibilities

BGA are groups of extraordinary, diverse, gram-negative, oxygenic, photosynthetic prokaryotic microscopic organisms.

Blue-green algae are found all over the world, showing remarkable ecological diversity of habitats such as freshwater, terrestrial, marine, hot spring, etc. These BGA are also widely distributed in the polar region such as the Arctic, Antarctic, Southern Ocean, and the Himalayas. Several studies have been conducted for the isolation and identification of Blue-Green algae from the water, soil, sediments, algal mats, etc. using advanced morphological, physiological, and molecular characterization techniques. Various selective media are known for their Cultivation. It has been now proven that BGA offers a great opportunity as these are considered to be one of the potential organisms useful to mankind in many ways. They exhibit diverse biological activities (Antibacterial, Antifungal, Anticancer, Antiviral Antidiabetic, and many more). Various bioactive molecules have been reported by researchers globally. In pharmaceutical companies especially in the new drug discovery research division, for the last many year's research is going on at various levels starting from extraction, purification, and identification of new compounds or drugs from various species of BGA. The major challenge in front of the current world is to fight effectively against the new emerging diseases and microbes specifically WHO priorities list of multiple antibiotic-resistant bacteria, microbial infections including SARS-CoV-2 virus and Cancer, etc., and to discover new pharmaceutical compounds for mankind and society. At the same time, there is an urgent need to think from basic to applied research to commercialize several value-added products. The use of nanomaterials to enhance biological activity could be one of the ways. Inventions of these drugs using nanotechnology can lead to the development of novel pharmaceuticals. Based on the cultures of cells, activities of enzymes, and receptors binding with ligands, various new technologies are invented to develop novel things of miniaturized screens. As a result, there is a conformational analysis, i.e., an analysis of the spatial arrangement of the component atom within a molecule that can be rotated about one or more single bonds. The known ligands result in the development of new compounds of structure-based drug design. Hence, the pharmaceutical potential of blue-green algae deserves more scientific attention and interdisciplinary research, and BGA strains from still unexplored and extreme habitats such as the Antarctic, Arctic, and the Himalayas can serve as good candidates in this regard.

Authors' contributions

All authors contributed significantly to the conception and design of the study, the interpretation of data, and the drafting and revision of the manuscript. All authors read and approved the final manuscript**.**

Acknowledgments

The authors acknowledge the support of Dr. Ashok K. Chauhan, Founder President, Amity Universe, for his constant support and encouragement. The authors also thank Dr. Atul Chauhan, Chancellor, Amity University, Uttar Pradesh, for providing all the required facilities.

Conflict of Interest

The authors hereby declare no conflict of interest.

Funding support

The authors declare that they have no funding support for this study

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