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MINI REVIEW

Cyanometabolites: molecules with immense antiviral potential

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Abstract

Cyanometabolites are active compounds derived from cyanobacteria that include small low molecular weight peptides, oligosaccharides, lectins, phenols, fatty acids, and alkaloids. Some of these compounds may pose a threat to human and environment. However, majority of them are known to have various health benefits with antiviral properties against pathogenic viruses including Human immunodeficiency virus (HIV), Ebola virus (EBOV), Herpes simplex virus (HSV), Influenza A virus (IAV) etc. Cyanometabolites classified as lectins include scytovirin (SVN), *Oscillatoria agardhii* agglutinin (OAAH), cyanovirin-N (CV-N), *Microcystis viridis* lectin (MVL), and microvirin (MVN) also possess a potent antiviral activity against viral diseases with unique properties to recognize different viral epitopes. Studies showed that a small linear peptide, microginin FR1, isolated from a water bloom of *Microcystis* species, inhibits angiotensin-converting enzyme (ACE), making it useful for the treatment of coronavirus disease 2019 (COVID-19). Our review provides an overview of the antiviral properties of cyanobacteria from the late 90s till now and emphasizes the significance of their metabolites in combating viral diseases, particularly severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which has received limited attention in previous publications. The enormous medicinal potential of cyanobacteria is also emphasized in this review, which justifies their use as a dietary supplement to fend off pandemics in future.

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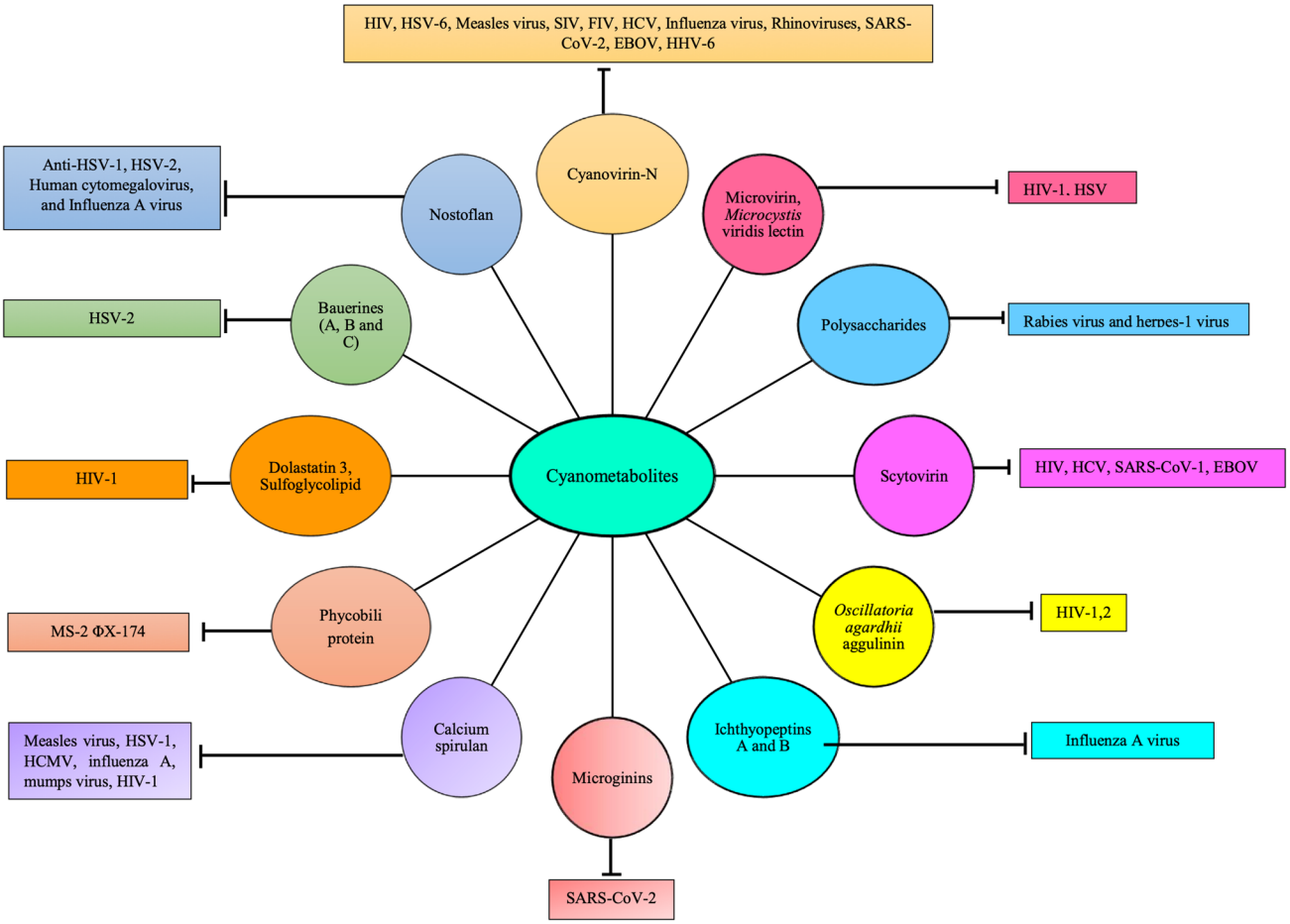
Graphical abstract



Keywords Cyanobacteria · Antiviral · Cyano-metabolites · COVID-19 · HIV · Scytovirin · Microvirin

Introduction

Viruses are obligate parasites that rely on the host for survival. They are made up of nucleic acids (DNA or RNA) enclosed in protein capsids, which are occasionally surrounded by lipid bilayers. Viruses can be categorized based on their genetic makeup and physical characteristics (enveloped or non-enveloped). Viral infections are not only prevalent in humans but also in other animals and plants. It is anticipated that there are far more viruses in the cosmos than the stars in the entire galaxy, which is close to 10^{31} (10 nonillions) (Breitbart and Rohwer 2005; Labadie et al. 2020). Although more than 200 distinct viral types have been identified as being responsible for human illnesses, some still need to be categorized (Woolhouse et al. 2012). In recent times, there has been emergence of several viral species pathogenic to human e.g., Ebola (EBOV), Zika, influenza, Middle East respiratory syndrome (MERS), Severe acute respiratory syndrome (SARS), and Nipah virus (Bloom and Cadarette 2019; Luo et al. 2020). Currently, the coronavirus disease 2019 (COVID-19) is the biggest global challenge that has resulted into 600 million infections and more than 5 million deaths worldwide till now (https://www.worldometers.info/coronavirus/) (Sundar et al. 2022). During the pandemic, herbal products had gained enormous attention among common public in India. Ayurveda, Yoga, Naturopathy, Unani, Siddha, and Homeopathy (AYUSH) had even introduced "kadha" as an immune booster for people to gain some resistance for SARS-CoV-2 (Khanal et al. 2022; Maurya and Sharma 2020). The use of Giloy (*Tinospora cordifolia*) in the daily routine of the Indian population has shown promising results in boosting immunity and fighting against COVID-19 (Kulkarni et al. 2021; Shree et al. 2022). Moreover, COVID-19 patients were also recommended to consume turmeric (*Curcuma longa*) milk along with tulsi (*Ocimum sanctum*) and ashwagandha (*Withania somnifera*)

in a hope to strengthen our immunity to fight against the virus (Khanal et al. 2022; Chopra et al. 2021). Hence, there is a pressing need to explore more herbal products that possess immuno-modulatory and anti-inflammatory potential. Cyanobacteria or blue green algae (BGA) are Gram-negative bacteria and the first organism on earth that produce oxygen through photosynthesis (Carpine et al. 2020). They dominated the Earth planet for 2 billion years (3.5 billion years ago to 1.5 billion years ago) and created oxygenic atmospheres (Mazard et al. 2016). The term "cyanobacteria" was first coined by Stanier (Stanier and Cohen-Bazire 1977). According to evolutionary theory, cyanobacteria were the first bacteria to conquer the ancient environments (Hamilton et al. 2016). A wide variety of ecological habitats can be found for BGA, including glacier, terrestrial, brackish, aerial, marine, and freshwater environments. Moreover, they can withstand a wide range of environmental conditions, including different levels of light, extreme temperatures (both high and low), varying pH levels, and salt concentrations. (Martínez-Francés and Escudero-Oñate 2018). Cyanobacteria have various health benefits that possess antiviral, antifungal, antibacterial, anti-inflammatory, anti-cancer, and antioxidant properties (Fig. 1) (Demay et al. 2019). Cyanobacteria produce various bioactive compounds that include 40% lipo-peptides, 9% amides, 5.6% amino acids, 4.2% macrolides, and 4.2% fatty acids. Lipopeptides are the important components of cyanobacteria that execute most of the cyanobacterial activities like cytotoxic (41%), anti-tumor (13%), antiviral (4%), antibiotics (12%), and the remaining 18% include anti-malarial, antimycotics, multi-drug resistance reversing agents, anti-feedant, herbicides, and immunosuppressive agents (Burja et al. 2001) A variety of biologically active compounds that are found to be promising for drug discovery, are isolated from cyanobacteria (Mazard et al. 2016; Singh et al. 2017; Lange et al. 2018; Schwarzenberger et al. 2020). *Nostoc*, *Lyngbya, Microcystis, Scytonema*, and *Spirulina* are some of the most important genera of cyanobacteria that produce biologically active compounds. Over the last two decades, more than 800 secondary metabolic compounds have been isolated from cyanobacteria. These substances can be characterized by their chemical compositions, toxicological targets, and bioassay techniques (Pearson et al. 2010). This review summarizes the antiviral properties of cyanobacterial metabolites including cyanovirin-N, *Microcystis viridis* lectin, *Oscillatoria agardhii* agglutinin, microvirin, microginins, dolastatin, sulfolipids, and some alkaloids. Furthermore, we highlight the potential of these secondary metabolites in biotechnological applications, which could greatly enhance their demand.

Antiviral cyanometabolites

Cyanobacteria produce a wide variety of antiviral cyanometabolites that are either protein, carbohydrate, lipids, or alkaloid in nature (Fig. 2). The antiviral properties of cyanometabolites are against number of different viruses like Chikungunya virus (CHIKV), Coxsackieviruses B, EBOV,

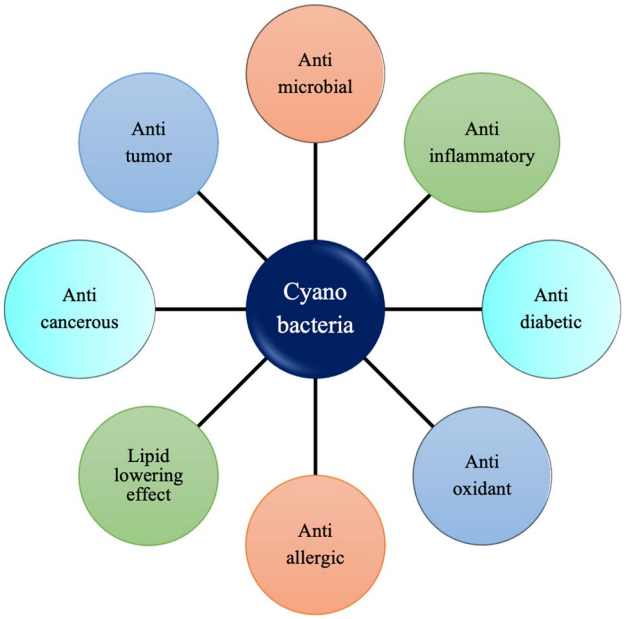


Fig. 1 Therapeutic properties of cyanobacteria. Cyanobacteria have numerous health benefits that include antimicrobial, anti-inflammatory, anti-diabetes, antioxidant, anti-allergic, lipid lowering effect, anti-cancerous, and anti-tumor in nature

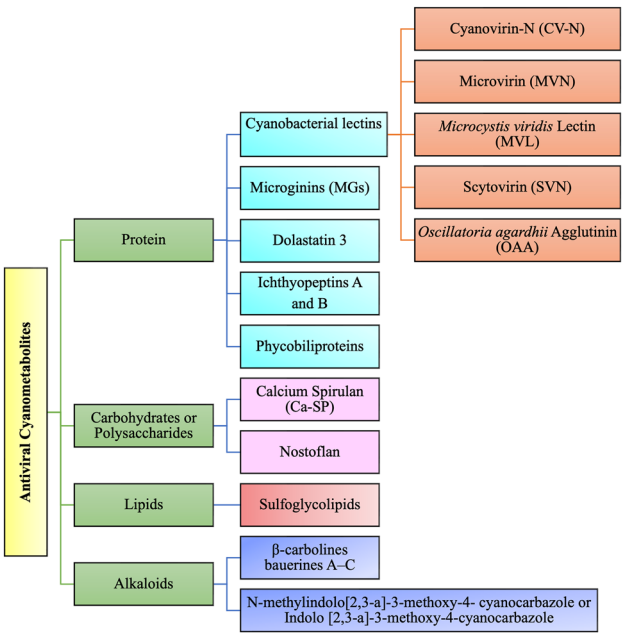


Fig. 2 Antiviral cyanometabolites from cyanobacteria. Cyanometabolites are either proteinaceous, carbohydrate, lipid, or alkaloid in nature that executes various antiviral activities

Enterivirus-71, Feline immunodeficiency virus (FIV), Human immunodeficiency virus (HIV), Hepatitis C virus (HCV), and many more viruses (Fig. 3; Table 1). Some of the key cyanometabolites, along with their respective properties, are outlined below:

Cyanobacterial proteinaceous metabolites act as antiviral agents

Cyanobacterial lectins

A lectin is a monomeric or oligomeric protein that binds carbohydrates in a reversible manner, even when found in compounds like viral envelope glycoproteins (Mitchell et al. 2017). Lectins are produced by a variety of species, including mammals, plants, fungi, protists, and microbes including bacteria, archaea, and viruses (Romero et al. 2021). Cyanobacterial lectins are highly effective against HIV and behave as a potent anti-HIV drug compared to the other lectins derived from plants. The highly effective anti-HIV properties of cyanobacterial lectins are due do their ability to directly bind to the HIV glycoprotein, gp-120. in low pico-molar to nano-molar EC_{50} values (Cheung et al. 2015). Many cyanobacterial lectins with antiviral potential may also be used in the production of microbicides due to their remarkably high affinity and specific sensitivity for carbohydrates (Lotfi et al. 2018; Mazur-Marzec et al. 2021; Chen et al. 2014; Garrison et al. 2014; Wu et al. 2015; Shahzad-ul-Hussan et al. 2011; Férir et al. 2014; Huskens and Schols 2012). Therefore, the isolated species of cyanobacteria are reliable source of novel lectins with potential medicinal applications.

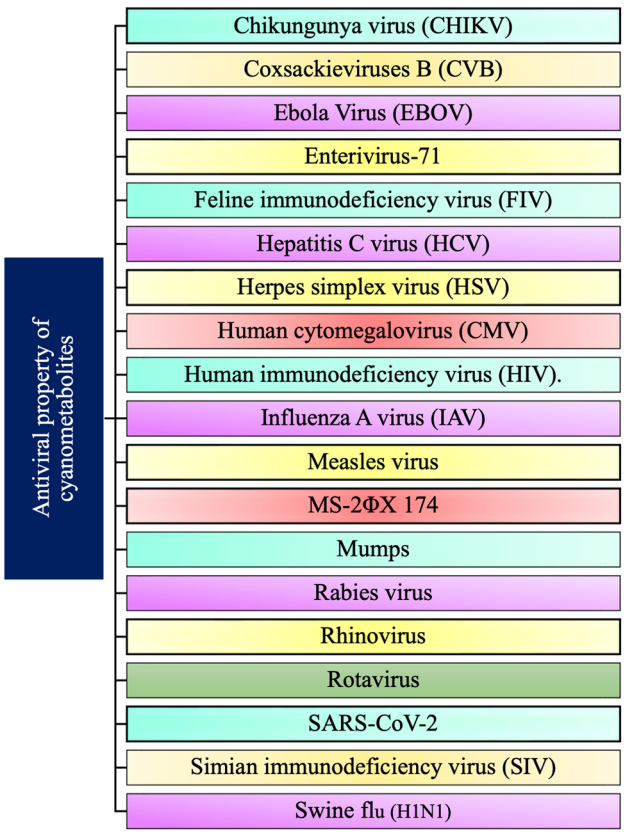


Fig. 3 Antiviral properties of cyano-metabolites on various kinds of viruses e.g., CHIKV, CVB, EBOV, Enterivirus-71, FIV, HCV, HSV, CMV, HIV, IAV, Measles virus, MS-2ΦX 174, Mumps, Rabies virus, Rhinovirus, Rotavirus, SARS-CoV-2, SIV, and H1N1

Cyanovirin-N (CV-N)

CV-N is a cyanobacterial lectin isolated from *Nostoc ellipsosporum*. It has a molecular weight of 11 kDa and consists of 101 amino acids with two intra-chains disulfide linkages formed by four cysteine residues "Cys8, Cys58, Cys22, Cys73". The CV-N structure is stabilized by these bonds that also regulate the polypeptide's antiviral activity. CV-N is considered to be an effective molecule against HIV structure, ensuring its effectiveness against HIV gp10 protein (Fig. 4). Moreover, CV-N plays a crucial role in the suppression of HIV-1 and HIV-2 by firmly binding to glycoproteins (Mannose8 or Mannose9) both *in vitro* and *in vivo* (Lotfi et al. 2018). In addition to HIV, CV-N was subsequently found to have antiviral activity against the Zaire strain of Ebola virus (ZEBOV) due to its affinity for the envelope glycoproteins of the viruses (Maier et al. 2021; Barrientos et al. 2003). The structural analysis revealed that the highest binding score of CV-N with the main protease (Mpro) and the papain-like protease (PLpro) of SARS-CoV-2 may inhibit binding of receptor-binding domain (RBD) of viral protein with human angiotensin-converting enzyme 2 (ACE-2) (Naidoo et al. 2021).

Microvirin (MVN)

Microvirin (MVN) is a carbohydrate-binding protein found in *Microcystis aeruginosa* PCC7806, a bloom forming cyanobacteria (Kehr et al. 2006). It is 33% similar to cyanovirin lectin and it has 14.3 kDa molecular weight (Lima et al. 2022). There are 108 amino acids in this monomeric protein that consists of domain A (residues 38–93) and B (residues 1–37 and 94–108). The domain A of the protein comprises the single carbohydrate-binding site, which binds with viral gp-120 glycans' terminal Man (1–2) (Shahzad-ul-Hussan et al. 2011). MVN shows anti-HIV-1 activity by inhibiting syncytium formation between HIV-1-infected HUT-78 cells and uninfected HUT-78 cells (Huskens et al. 2010). MVN stimulates pro-inflammatory cytokines secretion in peripheral blood mononuclear cells (PBMCs); however, its impact is weaker than that of CV-N (Huskens et al. 2010). The neutralizing anti-HIV mAb 2G12 antibody shows affinity

Table 1 Antiviral nature of cyanobacteria

S no.	Cyanobacterial potent for antiviral compound	Compound isolated	Natural product class	Target virus	Function	Reference
1	*Nostoc ellipsosporum*	Cyanovirin-N (CV-N)	Protein	HIV HSV-6 MV SIV FIV HCV IV RVs SARS-CoV-2 EBOV HHV-6	Anti-syncytia formation (inhibits the viral release) Inhibition of the viral entry by binding to the gp-120	Mazur-Marzec et al. (2021), Chatterjee et al. (2015), Barrientos et al. (2004), Li et al. (2022), Barrientos et al. (2003), Dey et al. (2000), O'Keefe et al. (2003), Singh et al. (2017), Smee et al. (2008, 2007)
2	*Microcystis viridis*	*M. viridis* lectin (MVL)	Protein	HIV-1 HCV	Reduction of initiation markers, such as CD69, CD25, and HLA-DR, by syncytium formation with healthy CD4 T cells	van Gremberghe et al. (2011)
3	*Microcystis aeruginosa*	Microvirin (MVN)	Protein	HIV-1 HCV	Anti-syncytia formation (Inhibit the viral release)	van Gremberghe et al. (2011)
4	*Scytonema varium*	Scytovirin (SVN)	Protein	HIV HCV SARS-CoV-1 EBOV	Binding to the viral coat proteins gp-120, gp160, and gp41 but not to cellular receptor CD4 or other tested proteins SVN inhibits the viral replication by binding to the mucin domain of the Ebola virus glycoprotein	Garrison et al. (2014)
5	*Oscillatoria agardhii*	*Oscillatoria agardhii* agglutinin (OAAH)	Protein	HIV-1 and 2	Inhibition of virus replication	Sato et al. (2007), Férir et al. (2014)
6	*Aphanothece halophytica*	Exopolysaccharide (EPS)	Exopolysaccharide	IAV	Inhibits very early step of viral replication, i.e., virus attachment and/or penetration to the host cells	Shalaby and Dubey (2018), Zheng et al. (2006)
7	*Arthrospira platensis* and *Oscillatoria sp.*	Methanol extract	NA	RV	Via binding to viral capsids preventing them from attaching to cell receptors	Deyab et al. (2020)
8	*Leptolyngbya boryana, Arthrospira platensis, Nostoc punctiforme*, *Oscillatoria* sp., *Leptolyngbya* sp.	Methanol extract	NA	CVB		Deyab et al. (2020)
9	*Microcystis*, *Nodularia*, *Oscillatoria*, *Scytonema*, *Lyngbya*, and *Calothrix*	Aqueous and methanolic extract	NA	IAV	Inhibits virus replication via inhibition of specific protease enzymes	Zainuddin et al. (2002)

Table 1 (continued)

S no.	Cyanobacterial potent for antiviral compound	Compound isolated	Natural product class	Target virus	Function	Reference
10	*Microcystis ichthyoblabe*	Ichthyopeptins A and B	Protein	IAV	Protease inhibition (inhibit virus)	Zainuddin et al. (2007)
11	*Microcystis ichthyoblabe*	Microginins	Peptides	SARS-CoV-2	Inhibitory activity against angiotensin-converting enzyme (ACE)	Mazur-Marzec et al. (2021)
12	*Scytonema* sp.	Sulfoglycolipid (Sulfoquinovosyl diacylglycerol)	Lipid	HIV-1	Inhibition of reverse transcriptase and DNA polymerases	Singh et al. (2011)
13	*Spirulina platensis*	Calcium spirulan (Ca-SP)	Sulfated polysaccharide	MV, HSV-1, HCMV, IAV, MuV, HIV-1	Blockage of viral replication by inhibiting the penetration of the virus into the host cell	Hayashi et al. (1996)
14	*Spirulina* sp.	Pure *Spirulina* extract	NA	SARS-CoV-2	Via enhancement of T cell responses T helper cells targeting the spike protein of SARS-CoV-2. The strong T cell response will suppress SARS-CoV-2 infection further arresting its proliferation	Peter (2020)
15	*Nostoc flagelliforme*	Nostoflan	Carbohydrates	HSV-1, HSV-2, CMV, and IAV	Inhibition of virus-cell interaction	Dembitsky and Řezanka (2005), Kanekiyo et al. (2005)
16	*Gloeocapsa turgidus*, *Synechococcus cedrorum*	Polysaccharides	Carbohydrates	RABV and HSV-1	Anti-protease inhibition	Shalaby and Dubey (2018), Zheng et al. (2006)
17	*Lyngbya confervoides*	Lectin	Protein	HSV-1	Inhibits plaque formation in the HSV-1 infected Vero cells	El-Fakharany et al. (2020)
18	*Dichothrix baueriana*	Bauerines (A, B and C), b-carbolines polyhalogenated aromatic compound	Indolo-quinazoline alkoloid	HSV-2	Inhibit cytopathic effect (CPE) and reduce the number of plaques formed in infected mink lung cells	Larsen et al. (1994), Vasas et al. (2010)
19	*Nostoc sphaericum*	Indolo [2,3-a]-3-methoxy-4-cyanocarbazole; N-methyl-indolo [2,3-a]-3-methoxy-4-cyano-carbazole	Alkaloids	HSV-2	Inhibits virus	Knübel et al. (1990)
20	*Lyngbya lagerhimii*, *Phormidium tenue*	Sulfolipids	Lipid	HIV	Inhibition of virus activity	Gustafson et al. (1989)

Table 1 (continued)

S no.	Cyanobacterial potent for antiviral compound	Compound isolated	Natural product class	Target virus	Function	Reference
21	*Trichodesmium erythraeum*	3-Methoxydebromoaply-siatoxin Anhydrodebro-moaply-siatoxin Debromoaplysiatoxin	NA	CHIKV	They target a step in the virus replication cycle that occurs after viral entry	Gupta et al. (2014)
22	*Arthrospira platensis*	Lipoprotein	Lipoprotein	IAV	Decreased histopathology	Pugh et al. (2015)
23	*Arthrospira platensis*	Lipoprotein	Lipoprotein	H1N1	Upregulate IL-1β, TNF-α, (IL)–8, MCP-1, MIP-1, MIP-1, IP-10, COX-2	Pugh et al. (2015), Grzanna et al. (2006)
24	*Arthrospira platensis*	*Arthrospira* crude extract	NA	HSV-1	Prevent virus adhesion to host cells	Shih et al. (2003)
25	*Lyngbya majuscula*	Dolastatin 3	Peptides	HIV-1	Anti-HIV-1 integrase (inhibit the viral replication cycle)	Kanekiyo et al. (2007)
26	*Spirulina platensis*	Phycobili-protein	Protein	MS-2 ΦX-174	Virucidal	Boyd et al. (1997)
27	*Arthrospira platensis*	Allophyco-cyanin	Protein	EV71	Prevent virus adhesion to host cells	Lee et al. (2001)
28	*Nostoc*, *Phormidium*, *Oscil-latoria*, *Chroococcus*, *Schizothrix*, *Aphanocaps*a, *Synechococcus*, *Aphan-othece*, *Xenococcus*	Cyanobacterial extracts	NA	HIV-1	Anti-RT (inhibit the viral replication cycle)	Buffa et al. (2009)

HIV Human immunodeficiency virus, *HSV-6* Human herpesvirus 6, *MV* Measles virus, *SIV* Simian immunodeficiency virus, *FIV* Feline immunodeficiency virus, *HCV* Hepatitis C virus, *IAV* Influenza A virus (IV), *RVs* Rhinoviruses, *SARS-CoV-2* Severe acute respiratory syndrome coronavirus 2, *EBOV* Ebolavirus, *HHV-6* Human herpesvirus 6, *RV* Rotavirus, *CVB* Coxsackieviruses B, *CMV* Cytomegalovirus, *MuV* Mumps virus, *RABV* Rabies virus, *HSV-2* Herpes simplex virus 2, *CHIKV* Chikungunya virus, *H1N1* swine flu virus, *EV71* Enterovirus-71, *NA* not available

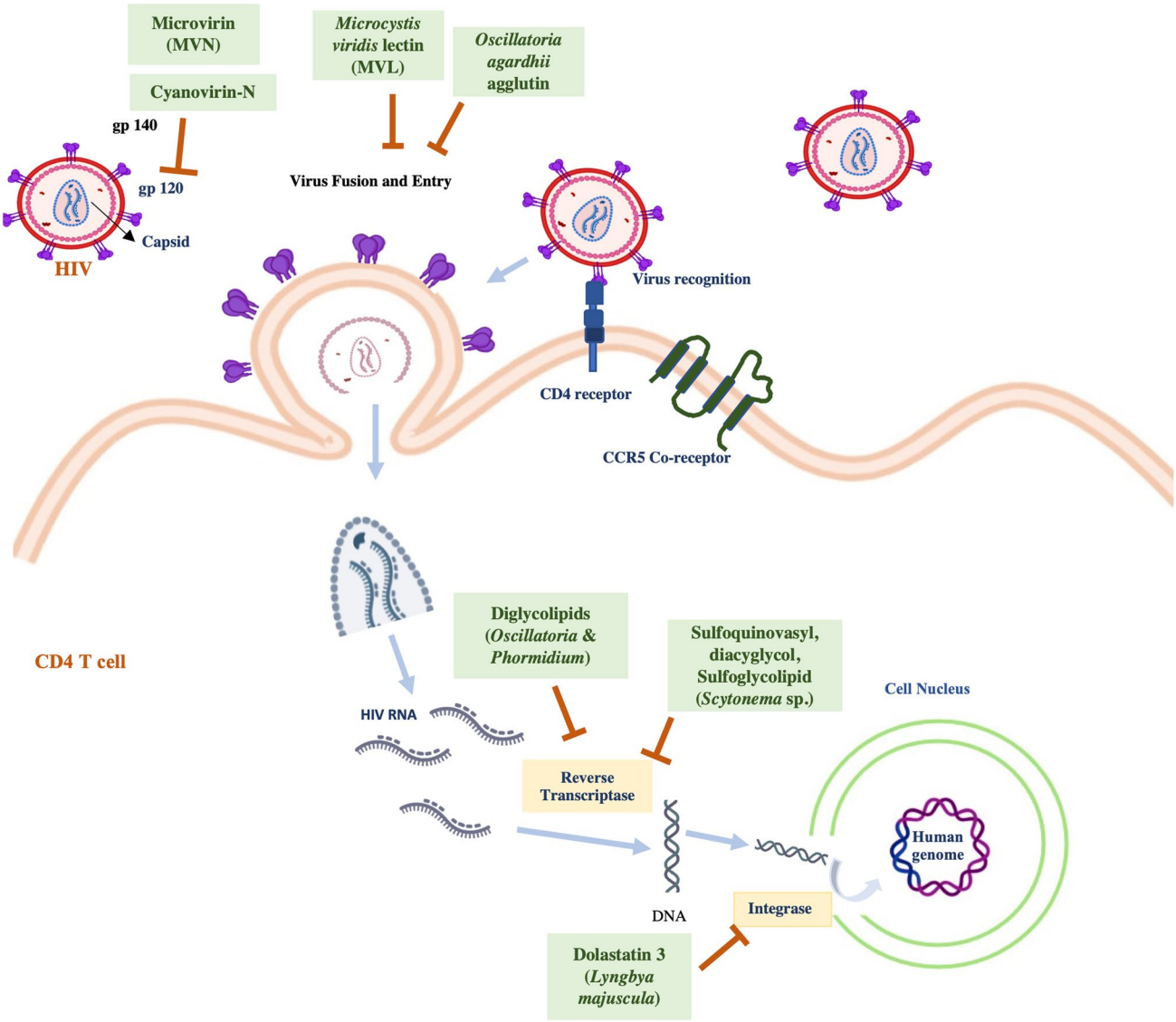


Fig. 4 The schematic illustration of the inhibitory effect of potent cyano-metabolites against HIV: MVN and CVN, inhibits the gp-120 of the HIV, thereby blocking the enveloped virus, MVL and OAA inhibit viral fusion and entry into the host cells, Di-glycolipids, Sulfoquinovasyl, Di-acyl-glycol, and Sulfoglycolipids, target the reverse transcriptase of HIV, Dolastatin 3, which inhibits the integrase enzyme, contributes to the blocking of the integration of the viral genome into the host genome

against high mannose carbohydrate of HIV gp-120. MVN has been shown to efficiently bind with gp-120 interfering with 2G12 mAb binding on HIV-1-infected cell (Huskens et al. 2010).

Microcystis viridis lectin (MVL)

Microcystis viridis Lectin (MVL) extracted from *Microcystis viridis* NIES-02, is a homodimer lectin, having 13 kDa molecular weight (Yamaguchi et al. 1999; Li et al. 2011). The monomers are made up of 113 different amino acids. The lectin blocks fusion of cells with the HCV and HIV-1 with an IC_{50} value of approximately 30 nM (Kachko et al. 2013; Bewley et al. 2004). It is noteworthy that the MVL's oligomannose binding site harbors glucosidase activity, which facilitates the hydrolysis of chitotriose, such as GlcNAcGlcAc3, into GlcNAc, GlcNAc (1–4), and GlcNAc (1–4) (Chen and Huang 2018). The cytotoxic effect of lectins develops when MVL interacts with cellular proteins. A previous study also revealed that recombinant MVL exhibits anti-cancer activity in several common cancerous cell lines, e.g., human colon (HT-29), human hepatocellular liver (HepG2), human ovarian (SK-OV-3), and stomach cells (SCG-7901) in the range of IC_{50} 40–54 g/mL (Li and Zhang 2010).

Scytovirin (SVN)

Scytovirin (SVN, 9.71 kDa) is extracted from *Scytonema varium* (Bokesch et al. 2003; Siqueira et al. 2017; Garrison et al. 2014). Scytovirin acts as a putative inhibitor of the Marburg, SARS-CoV, EBOV, and HIV viruses (Capell et al. 2020). SVN consists of a single polypeptide chain of 95-amino acid with two sequence repeats (Bokesch et al. 2003; Shahid et al. 2020). SVN contains two sites that bind to chitin and have a basic structure similar to hevein-like proteins (Mazur-Marzec et al. 2021). SVN binds to the viral envelope glycoproteins, such as Man (1–2), Man (1–6), and Man (1–6) tetra-saccharides, preferentially to glycoproteins gp-120, gp160, and less strongly to gp41 (Bokesch et al. 2003). The synthetic SVN has also been expressed in *Escherichia coli*, producing 5–10 mg/L of the lectin (Xiong et al. 2006).

Oscillatoria agardhii agglutinin (OAA)

Oscillatoria agardhii agglutinin (OAA) is a monomeric protein produced by the *Oscillatoria agardhii* NIES-204 strain that is made up of 132 amino acids (Sato et al. 2007). OAA has two carbohydrate-binding sites that are symmetrically arranged at two opposite ends of the protein. These two carbohydrate-binding sites on OAA allow the protein to bind to carbohydrates, specifically N-acetyl-galactosamine and N-acetyl-glucosamine. This binding ability is important for the role of OAA in the natural environment, where it helps the cyanobacterium to attach to surfaces and form biofilms. OAA has also been studied for its potential applications in biotechnology and medicine. Its ability to bind to carbohydrates has made it useful in the development of biosensors and as a tool for studying carbohydrate-protein interactions. Additionally, OAA has been shown to have anti-tumor and antiviral activities, making it a promising candidate for the development of new drugs. Unlike other cyanobacterial lectins (including MVL, SVN and CV-N), OAA binds to a branched central core unit of Man-9, a branching pentasaccharide glycan, Man (1–3) Man (1–3) Man (1–6) Man (Koharudin and Gronenborn 2011). In MT-4 cells, OAA has been shown to prevent HIV replication (EC_{50} = 44.5 nM) (Sato et al. 2007). *Oscillatoria agardhii* agglutinin homologue (OAAH) family lectins have been reported to be very effective against a variety of HIV clinical isolates, including HIV-1 group O, HIV-1, and HIV-2 strains (Férir et al. 2014). OAAH controls HIV replication by inhibiting virus entry into the target cell (Sato et al. 2000; Férir et al. 2014). Recently, an oscillatorial lectin from the Egyptian soil habitat of *Oscillatoria acuminate* MHM-632MK014210 was shown to have anti-cancer and antiviral properties (Saad et al. 2022b).

Microginins (MGs)

Microginins (MGs) are cyanobacterial bioactive secondary metabolites (Welker and Von Döhren 2006; Ujvárosi et al. 2020), which are isolated from bloom forming cyanobacteria i.e., *Microcystis aeruginosa* (Okino et al. 1993; Le Manach et al. 2019). They are linear pentapeptides, and their N-terminus contains 3-amino-2-hydroxy-decanoic acid (Ahda), a decanoic acid derivative (Okino et al. 1993; Zervou et al. 2020). MGs are made up of 3–6 amino acids with molecular weight ranging from 574 to 930 Da. There are several reports, which described the bioactive substances of MGs e.g., microginin FR1, microginins 770, microginins 478, T1, and T2, which block the action of ACE (Neumann et al. 1997; Okino et al. 1993; Kodani et al. 1999; Paiva et al. 2017). Therefore, their use in the treatment COVID-19 patients is thus taken into account.

Dolastatin 3

Dolastatin 3 is a compound that is isolated from the cyanobacterial metabolite of *Lyngbya majuscule*, a type of cyanobacterium. This compound has been found to have inhibitory effects on HIV-1 integrase, an enzyme that is important in the replication of the HIV virus. Specifically, it has been shown to inhibit the terminal cleavages and strand transfer reaction of HIV-1 integrase at IC50 values of 5 mM and 4.1 mM, respectively (Venkata et al. 1999; Mitchell et al. 2000). Interestingly, it has been observed that a closely related compound, homodolastatin 3, which differs from dolastatin 3 only in the substitution of an isoleucine residue for a valine residue, is unable to inhibit HIV integrase. This suggests that the valine residue plays an important role in conferring the inhibitory activity of dolastatin 3 against HIV integrase (Venkata et al. 1999). The discovery of dolastatin 3 and its inhibitory effects on HIV integrase has led to interest in the potential use of this compound and related compounds in the development of new drugs for the treatment of HIV infection. However, further research is needed to fully understand the mechanisms of action of these compounds and their potential therapeutic applications.

Ichthyopeptins A and B

Ichthyopeptins A and B are cyclic depsipeptide metabolites that are derived from the cyanobacterium *Microcystis ichthyoblabe*. These compounds have been found to possess antiviral properties, specifically against influenza A virus (IAV) (Zainuddin et al. 2007). In vitro studies conducted on the MDCK cell line, which is commonly used to study IAV, have demonstrated the efficacy of ichthyopeptins A and B against IAV (El-Fakharany et al. 2020). The antiviral activity of ichthyopeptins A and B is thought to be due to

their ability to inhibit viral replication by targeting various stages of the viral life cycle. Specifically, these compounds have been shown to interfere with viral entry into host cells, as well as with viral RNA transcription and protein synthesis. The discovery of ichthyopeptins A and B and their antiviral properties has generated interest in their potential use as therapeutic agents for the treatment of IAV infection. However, further research is needed to fully understand the mechanisms of action of these compounds and to assess their potential toxicity and efficacy in animal models and human trials.

Phycobiliproteins

Phycobiliproteins are proteins that are water-soluble and serve as auxiliary pigments for photosynthetic processes in cyanobacteria. Phycobiliproteins extracted from *Spirulina* are well recognized for their antibacterial, anti-inflammatory, and antioxidant properties. Additionally, they have antiviral quality. It has been reported in 2019 that antiviral efficacy of *Arthrospira platensis* extract was effective against X174 and MS2 bacteriophages in vitro. The single-stranded RNA virus known as MS-2 is one of the most often used models for the Hepatitis A virus (HAV), enterovirus, and human poliovirus. The single-stranded DNA virus known as ΦX174 serves as a model for the HCV, HBV, and HIV. They observed that by altering the shape of the viral capsids and impeding integration into *E. coli*, *Arthrospira platensis* extracts containing phycobiliproteins considerably altered both phages' virucidal activity (Hamid et al. 2019). Unlike many other viruses studied previously, both phages used in this experiment lacked lipid envelopes. Therefore, it seems that there is a direct interaction between the phycobiliproteins and the protein capsid in order to accomplish virucidal action. This virucidal impact stopped viral development and decreased viral titer. A new study suggests that phycobiliproteins may hold therapeutic promise for non-enveloped viruses, such as noroviruses, polioviruses, and rhinoviruses (Sami et al. 2021). In an in vivo experiment, female BALB/c mice that received 5, 12.5, or 25 mg/kg of *Spirulina* extract (*Arthrospira platensis*) orally at 4 h before H1N1 infection, followed by daily dose of 10, 25, or 50 mg/kg/day over the next 4 day, resulted in improved survival rate of 20%, 40%, and 60%, respectively (Chen et al. 2016). *Spirulina* extract contains two types of proteins, C-phycocyanin and allophycocyanin, which constitute approximately 50% and 10% of the total protein content, respectively. These proteins have been found to possess antiviral properties (Chen et al. 2016). Moreover, the virus infection with H1N1 (H1N1/WSN/33) could be prevented when mice were exposed to *Arthrospira platensis* cold water extract (Chen et al. 2016).

Cyanobacterial carbohydrates or polysaccharides metabolites act as antiviral agents

Polysaccharides are the most abundant type of natural polymers that include a variety of compounds, such as chitin, cellulose, glycogen, starch, agar, and carrageenan. Plants, animals, and microbes all have them as structural elements, and they perform a variety of different roles in their lives. Polysaccharides are also mostly used in the cosmetics, agricultural, food, and pharmaceutical industries (Dam et al. 2017). Traditional herbal and contemporary medicines have investigated their anticoagulant, antibacterial, immunomodulatory, wound healing, and anti-cancer activities (Chen et al. 2020; Chen and Huang 2018). Sulfate groups containing polysaccharides have significant antiviral actions against a wide range of viruses, including CMV (Cytomegalovirus), hepatitis virus, HIV, influenza virus, HSV, and coronavirus (Chen and Huang 2018; Chen et al. 2020).

Calcium spirulan (Ca-SP)

Spirulina platensis was the source of the first isolated calcium spirulan (Ca-SP), a sulfated polysaccharide. It was extracted from the hot water extract of *Spirulina* and shown to have inhibitory effect on HSV-1 proliferation in HeLa cells (Hayashi et al. 1993; Hayashi et al. 1996; Mader et al. 2016). Ca-SP shows selective activity toward enveloped viruses in *in vitro* experiments, including Human cytomegalovirus (HCMV), HSV-1, Mumps virus, Measles virus, HHV-6 virus, IAV, and Kaposi sarcoma-associated herpesvirus/human herpes virus 8 (KSHV/HHV-8) (Rechter et al. 2006; Mader et al. 2016; Hayashi et al. 1996). Additionally, tissue-type plasminogen activator (t-PA), which has heparin cofactor II-dependent anti-angiogenesis activity, is produced by Ca-SP in human fetal lung fibroblasts (Hayakawa et al. 1997) that blocked the tumor cells invasion and metastasis (Mishima et al. 1998). SARS-CoV-2 infection downregulates the expression of angiotensin-converting enzyme 2 (ACE-2), leading to the accumulation of angiotensin (Ang) II, which is produced by the action of angiotensin-converting enzyme (ACE) on AngI. ACE upregulation can result in pro-inflammatory cytokine release, high blood pressure, and other complications. Inhibiting ACE could be a promising approach to regulate inflammation and COVID-19 severity. Researchers have investigated the therapeutic potential of Spirulina-derived ACE inhibitor (ACEi) peptide, which may play a crucial role in controlling oxidative stress and inflammation (Ratha et al. 2021). In SARS-CoV-2 infection, the

viral spike protein (S-protein) binds to host cell ACE-2. There have been concerns that individuals with cardiac conditions who take ACE inhibitors (ACEi) may be more susceptible to viral infection. However, recent clinical trials have found no evidence to support this assumption (Hoffmann et al. 2020; Christiansen et al. 2021; Cohen et al. 2021).

Nostoflan

Nostoflan is a novel acidic polysaccharide derived from the terrestrial cyanobacterium *Nostoc flagelliforme* (Kanekiyo et al. 2005). It has high antiviral property against HSV-1. Furthermore, this molecule has potent antiviral properties against human cytomegalovirus, HSV-2, and IAV (Kanekiyo et al. 2005; 2007). Interestingly. Nostoflan lacks antiviral activity against adenovirus or coxsackie virus (Nowruzi et al. 2018). The neutral sugar in nostoflan consists of xylose (29.9%), glucose (42.8%), mannose (6.6%), glucuronic acid (13.3%), and galactose (20.7%). Nostoflan, in contrast to several sulfated polysaccharides, exhibits no antithrombin action (Kanekiyo et al. 2005). As a result, nostoflan possesses a broad antiviral range against enveloped viruses with carbohydrates as cellular receptors.

The polysaccharides derived from *Synechococcus cedrorum* and *Gloeocapsa turgidus* showed better antiviral activity against the rabies virus than the HSV-1 (Mansour et al. 2011). *Aphanothece halophytica* is responsible for the production of exopolysaccharide that is responsible for the reduction in pneumonia by 30% (Zheng et al. 2006).

Cyanobacterial lipids metabolites act as antiviral agents

Sulfoglycolipids were among the first discovered cyanometabolites to have antiviral properties (Gustafson et al. 1989). It is present in the cell wall of the heterocyst and thylakoid membrane of these microorganisms (Gupta et al. 2014). Sulfoglycolipids were isolated and identified from numerous filamentous cyanobacterial genera, including *Phormidium, Lyngbya*, *Scytonema*, *Anabaena*, *Calothrix*, and *Oscillatoria*. The long-chain fatty acids of these sulfoglycolipids are essential for their activity. Changes in fatty acid ratios (for example, 16:0, 16:1, 18:1, 18:2, 18:3), on the other hand, have a negligible influence on potency (Gustafson et al. 1989; Loya et al. 1998). The cyanobacterium *Lyngbya lagerheimii* produces type of glycerogly-colipid (Sulfolipids) containing a sulfate-group that inhibits HIV replication (Gustafson et al. 1989). These compounds, along with structurally related acylated di-glycolipids, isolated from *Phormidium* and *Oscillatoria*, inhibit the HIV-1 by inhibiting DNA polymerase activity of HIV-1 reverse transcriptase with IC50 values ranging from 24 to 2950 nM, while not affecting ribonuclease H (Gustafson et al. 1989; Reshef et al. 1997; Loya et al. 1998). Sulfoquinovosyl diacylglyceride (SQDG) and Sulfoglycolipids are effective against HIV RT when they contain sulfate groups in sugar units and fatty acid esters in side chains (Loya et al. 1998; Hielscher-Michael et al. 2016). It has been suggested that SQDG interacts with DNA polymerase through lipophilic groups.

Cyanobacterial alkaloid metabolites act as antiviral agents

β-carbolines bauerines A–C, another cyanobacterial compound, is isolated from *Dichothrix baueriana* and indolocarbazoles from cyanobacterium *Nostoc sphaericum* (Knübel et al. 1990; Niedermeyer 2015; Larsen et al. 1994; Karan and Erenler 2017). β-carbolines bauerines A–C and indolocarbazoles both are anti-HSV-2. N-methylindolo [2,3-∝]-3-methoxy-4-cyanocarbazole and Indolo [2,3-∝]-3-methoxy-4-cyanocarbazole, cyanobacterial metabolites isolated from *N*ostoc *sphaericum* EX-5–1, exhibit cytotoxicity and antiviral activities against HSV-2 (Knübel et al. 1990).

Conclusions

Viral diseases including HIV, SARS-CoV-2, and HCV are prominent viruses spread across the world's population. Despite several therapeutic drugs available in the market, there is no effective treatment available against these deadly viruses that can control chronic inflammation. Additionally, the antiviral medication currently available for these viruses has undesirable side effects. Under these conditions, it is imperative to consider new antiviral possibilities from natural sources, such as unprocessed extracts and cyanobacteria metabolites as discussed (Prabhu et al. 2022). Hence, the researchers are trying to collect different kind of the compounds such as secondary metabolites from different solvent methods (such as methanol, water, and ethanol) using cyanobacteria to find the novel candidates against the viral diseases with the least side effects and complications in the later stage of the life (Prabhu et al. 2022).

Natural products derived from biological organisms, such as plants and prokaryotes, are also commercially available for their anti-tumor and anti-infective action (Saad et al. 2022a). One of the examples is dolastatin 10 (a secondary metabolite) derived from the cyanobacteria has been approved by the food and drug administration (FDA) for the cancer chemotherapeutic pipeline (Pereira et al. 2019).

Besides, these metabolites show antioxidant action that plays a significant role in the medical field as therapeutic

agents against various chronic diseases, such as cancer, atherosclerosis, and cardiovascular disorder (Saad et al. 2022a). Because of the anti-inflammatory activity, cyanobacterial metabolites like cyanobacterial polyunsaturated fatty acid, may have role in the treatment of the chronic inflammatory disease.

The most important cyano-metabolites are phycocyanin that has become one of the important hotspots in pharmacological and medicinal industries due to their anti-cancer, anti-inflammatory effect, and from the previous reports, it is found that increase IL-4 expression and modulation of the JAK (Janus Kinase 3) pathway that promotes to the suppression of the pro-inflammatory cytokines (Saini et al. 2013). Therefore, due to enormous activities and cost-effective nature, cyano-metabolites are regarded as promising drug candidates against the deadly viral diseases although further extensive research is required to understand the immunological role of these metabolites against these viruses. Most of the above-mentioned metabolites that are classified as cyanobacterial lectins, such as MVN, CV-N, and MVL, primarily prevent viral infection at replication, entry, or fusion level.

Lectins are found to be the best inhibitors for the enveloped virus because of their properties to target the glycoprotein. Therefore, lectins can exhibit the anti-viral activity toward the enveloped virus, such as arboviruses, HAV, coronavirus, and IAV. As lectins such as mannose-binding lectins bind to glycoprotein of the host, thus inhibits the interaction with the host, furthermore it can also enhance the phagocytosis after activation of the complement pathway (lectin pathway). Given the immense antiviral potential of lectins, it is important to screen more cyanobacterial lectins that may be involved in the complement pathway to combat the viral infection. In addition to cyanobacterial lectins, cyanobacterial polysaccharide such as calcium spirulan (CA-SP) inhibits the enveloped virus infection by the induction antiviral immunity.

The above properties of metabolites suggested that cyanobacteria exhibit a broad range of anti-viral activity. Thus, it can be very advantageous to use cyano-metabolites to combat pandemic against the emerging viruses such as SARS-CoV-2. Furthermore, research is also needed to find novel cyanobacterial metabolites and study their anti-viral potential for therapeutic purposes.

There are several cyano-metabolites targeting a common virus. For example, in the case of HIV, MVN, and CV-N targets, the gp-120 protein of HIV prevents the virus from attaching to and infecting host cells. MVL and OAA inhibit HIV fusion and entry into CD4 T cells, while di-glycolipids, sulfoquinovasyl, di-acyl-glycol, and sulfoglycolipids target the reverse transcriptase enzyme, which is important for the replication of the virus. Dolastatin 3, on the other hand, inhibits the integrase enzyme, which is responsible for integrating the viral genome into the host genome. Each of these compounds targets a different aspect of the HIV life cycle, and the combination of these cyanobacterial metabolites may provide a more effective therapeutic approach for the treatment of HIV (Fig. 4). However, it is important to note that the development of any new drug requires extensive research and testing to ensure safety and efficacy in animal models and clinical trials. Therefore, the concoction of various cyano-metabolites targeting a common virus may serve as a better therapeutic approach in future studies.

Future perspectives

For many years, RNA viruses have posed a severe threat to the world's health through causing infectious diseases. Recent pandemic caused by SARS-CoV-2 virus created a havoc in the entire planet. Innovative therapeutic approaches are still required to preserve human health not withstanding immunization. Numerous bioactive metabolites found in cyanobacteria, including polyphenols, sulfated polysaccharides, and lectins have potent antiviral and immunostimulatory properties. Algae-derived compounds have been shown to possess the properties useful in the development of a range of therapeutic products. For example, these compounds can be used to develop serological test kits for the detection of viral infections. Algae-derived compounds can also be used to develop nasal sprays that can effectively deliver drugs to the respiratory system. This is particularly important for the treatment of respiratory diseases, such as asthma and chronic obstructive pulmonary disease (COPD). In addition, algae-derived compounds can be used to develop vaccines against various pathogens, including viruses. These compounds can be used to create adjuvants, which are substances that are added to vaccines to enhance the body's immune response. Algae-derived compounds can also be used to develop new antiviral drugs, such as those targeting HIV and influenza. Overall, the use of algae-derived compounds in the development of therapeutic products is a promising area of research that has the potential to lead to the development of new and effective treatments for a range of diseases (Chia et al. 2021).

The biologically active metabolites isolated from marine algae may offer a promising option to fight against COVID due to antioxidant nature of these metabolites that can reduce the oxidative stress associated with the infection (Philip et al. 2021). These bioactive compounds have also been studied and used as immunomodulators and therapeutics based on the microbiota, which can help with the treatment of SARS-CoV-2. Considering these presumptions, cyanobacterial metabolites may be a promising treatment option for COVID-19 treatment.

In a current scenario, the use of cyanobacterial products or cyano-metabolites as a supplement is a practical and environmentally friendly solution. The utilization of

nano-formulations could also greatly reduce the quantity of the active primary ingredient needed for treatment.

Eventually, the discovery of bioactive chemicals might also be used to develop innovative synthetic prototypes that could be tested in vivo and in vitro utilizing high-throughput technologies or an in silico approach.

As prevention is always preferable to treatment, well-thought-out plans are essential in the fight against new infections or future pandemics. The recombinant antigen derived from genetically engineered algae is noteworthy because dried product can be used right away, minimizing extraction and purification costs.

Despite all these efforts, it remains necessary to carry out *in vivo* animal and clinical studies to identify novel cyanobacterial products or cyano-metabolites modulator for the treatment of COVID-19 or future pandemics.

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Availability of data and materials In this investigation, all of the data analyzed are accurately cited and easy to access via their references.

Declarations

Conflict of interest The authors declare no conflict of interest.

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